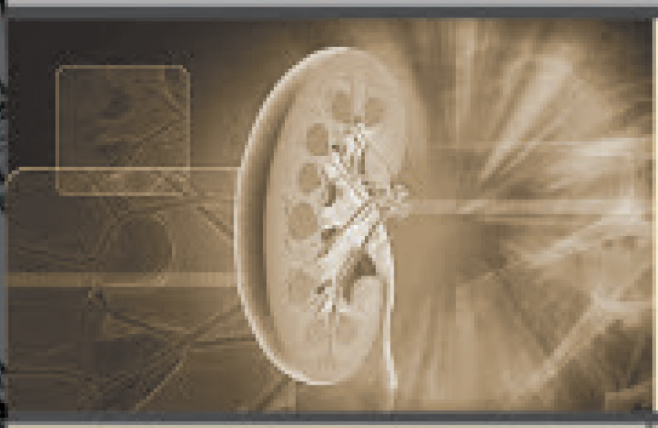
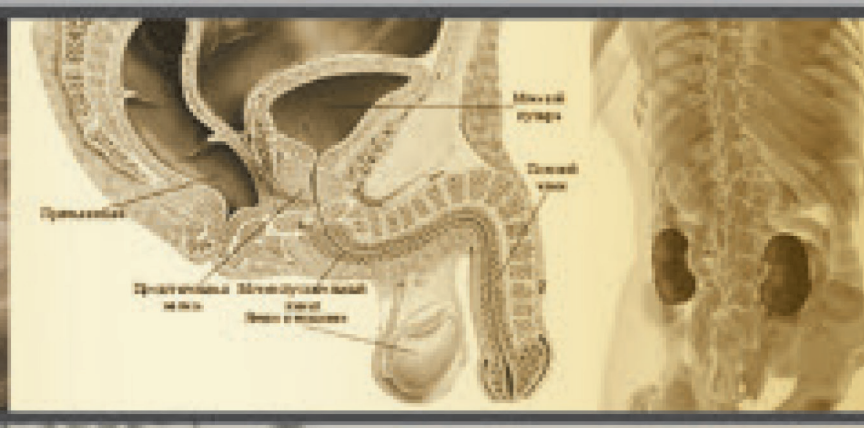
Society of Urological Surgery in Türkiye

E-ISSN 2148-9580

JOURNAL OF UROLOGICAL SURGERY

Volume 13 / Issue 3 / September 2026 www.jurolsurgery.org





galenos yayınevi

Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

EDITORIAL BOARD

Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

2010 Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

INTERNATIONAL SCIENTIFIC ADVISORY BOARD

Please refer to the journal's webpage **(https://jurolsurgery.org/)** for "Aims and Scope", "Instructions to Authors" and "Journal Policies".

The editorial and publication process of the Journal of Urological Surgery are shaped in accordance with the guidelines of ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Journal of Urological Surgery is indexed by **Web of Science-Emerging Sources Citation Index (ESCI), DOAJ, ProQuest, EBSCO, Embase, CINAHL, British Library, Gale, IdealOnline, TUBITAK/ULAKBIM Turkish Medical Database, TurkMedline, Hinari, GOALI, ARDI, OARE, AGORA, J-GATE, CNKI** and **Türkiye Citation Index**.

The journal is published electronically.

Owner: Bülent ÖNAL on Behalf of the Society of Urological Surgery

Responsible Manager: K. Fehmi Narter

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr

Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: September 2026
E-ISSN: 2148-9580
International scientific journal published quarterly.

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

Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

CONTENTS

Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

CONTENTS

REVIEW
Andrology

Doi: 10.4274/jus.galenos.2026.2026-3-5
J Urol Surg 2026;13(3):144-154

The Microbial Dimension of Male Sterility: A Pathological Review of Dysbiosis, Virulence, and the Emergent Diagnostic Imperative

Mesut Berkan Duran[1], Kürşat Küçüker[1], Aykut Akıncı[1], Yusuf Özlülerden[1], Sinan Çelen[1], Ahmet Koluman[2]

[1]Pamukkale University Faculty of Medicine, Department of Urology, Denizli, Türkiye
[2]Pamukkale University Faculty of Technology, Department of Biomedical Engineering, Denizli, Türkiye

Abstract

For decades, the male genitourinary tract was considered sterile in healthy individuals. However, advances in culture-independent molecular techniques, particularly next-generation sequencing, have revealed that semen contains a diverse microbial ecosystem known as the seminal microbiome. This paradigm shift has led to growing interest in the relationship between microbial composition and male reproductive health. Current evidence suggests that male infertility is associated not merely with the presence of bacteria in semen, but with alterations in microbial balance, termed seminal dysbiosis. Beneficial genera such as *Lactobacillus* are often associated with normal sperm parameters and genomic stability, whereas increased abundance of opportunistic and pathogenic bacteria—including *Escherichia coli, Enterococcus faecalis, Ureaplasma urealyticum,* and *Prevotella*—is associated with reduced sperm motility, abnormal morphology, and decreased sperm concentration. The pathological mechanisms underlying this relationship involve both host-mediated and pathogen-mediated pathways. Dysbiosis has been suggested to promote chronic inflammation and leukocytospermia, leading to excessive production of reactive oxygen species and consequent oxidative stress. This environment promotes lipid peroxidation and sperm deoxyribonucleic acid (DNA) fragmentation, key contributors to impaired fertilization and poor reproductive outcomes. Despite increasing recognition of the seminal microbiome's role in infertility, current diagnostic approaches remain limited. Culture-based methods frequently fail to detect viable but non-culturable microorganisms, while molecular assays cannot reliably distinguish viable pathogens from residual DNA. Improved diagnostic strategies targeting microbial viability and virulence may therefore play an important role in addressing unexplained male infertility.

Keywords: Bacteriospermia, dysbiosis, male infertility, seminal microbiome

Introduction

I. The Paradigm Shift: From Sterile Assumption to Dynamic Ecosystem

A. Deconstruction of the "Sterile" Hypothesis

For decades, male reproductive biology was framed by the assumption that the male genitourinary tract was sterile in healthy, asymptomatic individuals. This concept was shaped less by definitive evidence than by the limitations of the diagnostic methods available at the time. Conventional microbiological evaluation relied on culture-dependent techniques, which detect only organisms capable of growing on laboratory media. As a result, a large proportion of microorganisms that are difficult to culture, metabolically quiescent, or present in low abundance remained undetected (1). Consequently, bacteria isolated from semen were often dismissed as contaminants or interpreted only as overt pathogens rather than members of a resident microbial ecosystem (2).

This view has now been fundamentally overturned. With the advent of culture-independent molecular methods, particularly next-generation sequencing targeting the 16S ribosomal ribonucleic acid gene, it has become clear that semen from healthy fertile men is not sterile (2,3). Instead, it contains a diverse and relatively complex microbial community. This shift mirrors the broader transformation in microbiome research seen in the gut and other mucosal systems. The male reproductive tract is therefore better understood as a dynamic microbial ecosystem with potentially important effects on fertility, reproductive tract homeostasis, and assisted reproduction outcomes (3).

Correspondence: Mesut Berkan Duran Assoc. Prof., Pamukkale University Faculty of Medicine, Department of Urology, Denizli, Türkiye
E-mail: drberkanduran@gmail.com **ORCID-ID:** orcid.org/0000-0002-8597-2081
Received: 13.03.2026 **Accepted:** 13.04.2026 **Epub:** 10.08.2026 **Publication Date:** 01.09.2026

Cite this article as: Duran MB, Küçüker K, Akıncı A, Özlülerden Y, Çelen S, Koluman A. The microbial dimension of male sterility: a pathological review of dysbiosis, virulence, and the emergent diagnostic imperative. J Urol Surg. 2026;13(3):144-154

The clinical importance of this shift lies in the fact that male infertility can no longer be explained solely by endocrine, genetic, anatomical, or classic infectious causes. A microbial dimension must now be considered, one that lies between overt infection and health. This new framework provides a biologically plausible explanation for many cases that have historically been labeled idiopathic.

B. Characterizing the Core Seminal Microbiome and Defining Dysbiosis

The semen bacteriome, defined as the total bacterial genetic content present in semen, has become a major area of research interest (4). Studies consistently demonstrate that semen is microbiologically rich and diverse in both fertile and infertile men (5). This observation is critical because it indicates that bacteriospermia alone is not necessarily pathological. The mere presence of microorganisms is insufficient to define disease; rather, the structure, relative abundance, and functional behavior of the microbial community determine whether it is beneficial, neutral, or harmful.

This may contribute to the concept of seminal dysbiosis, which describes a disturbance in the normal microbial composition and function of the male reproductive tract (6). As in other organ systems, dysbiosis refers not simply to microbial presence, but to an imbalance that alters local metabolism, immune signaling, and tissue homeostasis. In the seminal environment, this disturbance may compromise sperm viability, motility, membrane integrity, and genomic stability.

Comparative studies between fertile and infertile men have begun to identify microbial signatures associated with eubiosis and dysbiosis. A eubiotic seminal microbiome is often characterized by predominance of genera such as *Lactobacillus*, including *Lactobacillus iners* and *Lactobacillus gasseri* (3). These organisms are generally associated with better sperm quality and deoxyribonucleic acid (DNA) integrity and may exert protective effects by maintaining ecological balance and limiting overgrowth of opportunistic pathogens (3).

By contrast, dysbiotic states are often characterized by relative overrepresentation of genera such as *Prevotella*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Enterococcus faecalis* (*E. faecalis*), *Anaerococcus*, *Corynebacterium*, *Pseudomonas*, and uropathogenic strains of *Escherichia coli* (*E. coli*) (3,5). A core group of detrimental microbes are summarized in Table 1. These organisms have been repeatedly associated with poorer semen parameters and impaired reproductive outcomes. A growing body of evidence, including systematic reviews and meta-analyses, supports a significant association between microbial dysbiosis and male infertility (6).

The important conceptual point is that the microbiological problem in male infertility is often not an acute infection but an ecological imbalance. This reframes the discussion from the presence or absence of pathogens to whether the seminal microbial community has shifted from a protective to a pathogenic configuration.

C. Broader Implications of the New Paradigm

The implications of the seminal microbiome extend beyond the male patient. Semen is not an isolated fluid; it is exchanged during intercourse and may influence the reproductive ecology of the female partner. Sexual transmission of microorganisms can alter the vaginal microbiome, supporting the concept of a "couple genital microbiota" (7,8). In this model, dysbiosis in the male partner may contribute to dysbiosis in the female reproductive tract, thereby affecting conception, implantation, and pregnancy maintenance (7,9).

This broader perspective is important because it reframes male-factor infertility as a couple-level biological interaction rather than an isolated male issue. Studies suggest that couple-level dysbiosis may impair fertility, disturb embryo implantation, and increase miscarriage risk (9). It is therefore increasingly plausible that seminal microbiome abnormalities may exert effects even when conventional semen parameters are only modestly altered.

The seminal microbiome may also influence outcomes of assisted reproductive technologies (ART). Microbial composition in semen used for in vitro fertilization or intracytoplasmic sperm injection (ICSI) may affect fertilization, embryo quality, blastocyst development, and implantation success (3). This is particularly relevant in ICSI, where sperm that appear motile may still carry profound molecular damage related to microbial-induced oxidative stress.

Another emerging implication concerns paternal programming of offspring health. Semen transmits more than paternal DNA; it also contains cytokines, metabolites, extracellular vesicles, and microbial signals (2). The seminal microbiome has therefore been proposed as a contributor to the Developmental Origins of Health and Disease framework, potentially influencing embryo development and later offspring phenotype (2).

Perhaps the most immediate clinical implication is its relevance to idiopathic infertility. A substantial proportion of male infertility, often estimated at 30-50%, remains unexplained after standard evaluation (10). The discovery of a structured and functionally relevant seminal microbiome suggests that many of these "idiopathic" cases may in fact reflect undiagnosed dysbiosis or microbial persistence that escapes routine diagnostic methods (11). This possibility fundamentally challenges current diagnostic algorithms in andrology.

Table 1. Microbial signatures of seminal dysbiosis: a comparison of genera associated with fertile and infertile states

Bacterial genus/species	Associated state	Reported impact on sperm parameters & reproductive health	Key supporting sources
Lactobacillus (e.g., *L. iners, L. gasseri*)	Beneficial	Associated with higher sperm quality and DNA integrity; appears to protect sperm quality	(3)
Prevotella	Detrimental	Opposing effect to *Lactobacillus*; associated with poor sperm quality, lower sperm counts, and motility issues	(3)
Enterococcus faecalis	Detrimental	Negatively impacts semen parameters; linked to sperm apoptosis and hyperviscosity. Commonly identified in chronic bacterial prostatitis	(3,5,15)
Ureaplasma urealyticum	Detrimental	Negatively impacts semen parameters; associated with reduced sperm motility and quality. Linked to chronic prostatitis	(3,5,6)
Mycoplasma hominis	Detrimental	Negatively impacts sperm motility and quality	(3,5)
Escherichia coli	Detrimental	Linked to acrosome damage and sperm DNA fragmentation; associated with chronic prostatitis	(3,6,15)
Pseudomonas	Detrimental	Imbalance of *Pseudomonas* relative to *Lactobacillus* is associated with excessive semen viscosity and OAT	(3,9)
Corynebacterium	Detrimental	Increased prevalence in infertile men; may reduce sperm motility and morphology	(3,15)
Anaerococcus	Detrimental	Found to be negatively correlated with sperm quality	(3)
Bacteroides	Detrimental	Systematically affects sperm morphology and DNA; can lead to mitochondrial disruption	(3)

OAT: Oligoasthenoteratozoospermia, DNA: Deoxyribonucleic acid, *L. iners: Lactobacillus iners, L. gasseri: Lactobacillus gasseri*

II. Pathologies of Seminal Dysbiosis: The Dual-mechanism Assault on Sperm

Seminal dysbiosis typically does not present as an acute symptomatic infection. Rather, it often manifests as chronic, low-grade, asymptomatic inflammation with persistent effects on spermatozoa. This pathology is especially insidious because there may be no pain, fever, or obvious urinary symptoms to trigger urologic investigation. However, sperm function may be continuously impaired through two main pathways: an indirect, host-mediated inflammatory pathway and a direct, pathogen-mediated virulence pathway.

A. Indirect Pathology: The Inflammatory-oxidative Axis

One of the clearest clinical correlates of this state is National Institute of Health category IV prostatitis, an asymptomatic inflammatory condition diagnosed by inflammatory findings in semen, prostatic secretions, or biopsy tissue (12,13). Research demonstrates that men with this condition often harbor abundant polymicrobial communities and higher total bacterial concentrations than controls (14). This provides a strong link between seminal dysbiosis and chronic subclinical reproductive tract inflammation, as further supported by the microbial patterns outlined in Table 1, where inflammation-associated species such as *E. coli* and *E. faecalis* are recurrently identified in conjunction with impaired semen parameters

A major manifestation of this inflammatory state is leukocytospermia, defined by elevated peroxidase-positive leukocytes in semen (15). These leukocytes, particularly polymorphonuclear cells, act as a major source of damage. Once activated in response to microbial signals, they produce large amounts of reactive oxygen species (ROS) through an oxidative burst intended to destroy microorganisms (16).

However, spermatozoa are highly vulnerable bystanders in this environment. Excessive ROS generation overwhelms the limited antioxidant defense capacity of seminal plasma, resulting in oxidative stress (16). This oxidative milieu damages sperm membranes, disrupts motility, alters membrane fluidity, and contributes to DNA fragmentation. ROS, therefore, represent one of the central mechanistic links between dysbiosis and infertility.

A notable feature of this system is that oxidative stress arises from two sources. Host leukocytes generate ROS as part of the inflammatory response, but pathogenic bacteria themselves also contribute to oxidative stress (17,18). For example, *E. faecalis* produces extracellular superoxide and hydrogen peroxide (19), *E. coli* generates hydrogen peroxide as a by-product of aerobic metabolism, and *Ureaplasma urealyticum* also contributes hydrogen peroxide capable of directly injuring sperm membranes (20). Thus, seminal dysbiosis produces a compounded oxidative environment in which both host and pathogen contribute to sperm damage.

Chronicity is further sustained by microbial immune modulation. *Staphylococcus aureus* (*S. aureus*), for example, produces superantigens that provoke broad, non-specific activation of

T-cells and favor a Th1/Th17-dominant inflammatory response (21-23). Instead of promoting efficient pathogen clearance, this process amplifies cytokine production and perpetuates tissue-damaging inflammation. Likewise, Gram-negative organisms such as *E. coli* activate toll-like receptor pathways through lipopolysaccharide (LPS), driving additional production of tumour necrosis factor-α, interleukin-6 (IL-6), and IL-8 (24). In this way, dysbiosis sustains a low-grade inflammatory microenvironment that is highly damaging to sperm but often clinically silent.

B. Direct Pathology: Virulence and Toxicity

In addition to indirect inflammatory injury, many bacteria within a dysbiotic seminal microbiome have evolved direct mechanisms for impairing sperm function. These effects are not merely collateral consequences of infection but, rather, represent sperm-specific or sperm-relevant virulence actions. Table 2 provides a detailed summary of these direct "sperm-centric" virulence mechanisms, demonstrating how different pathogens exert targeted molecular effects on spermatozoa. For example, *S. aureus* produces a sperm immobilization factor that inhibits Mg++ adenosine triphosphatase (ATPase) activity; *E. coli* employs fimbriae-mediated adhesion and toxin-induced membrane damage; and *Ureaplasma urealyticum* disrupts membrane phospholipids via enzymatic degradation and oxidative injury. Collectively, these findings highlight that bacterial effects on fertility are not merely indirect consequences of inflammation but also involve direct, pathogen-specific interference with sperm structure and function.

S. aureus provides one of the most striking examples. *In vitro* studies show that exposure of human spermatozoa to live *S. aureus* is linked to rapid, dose-dependent loss of motility and marked agglutination, whereas heat-killed organisms do not produce the same effect (25). This indicates an actively secreted factor rather than a passive structural interaction. That factor, termed sperm immobilization factor, is a protein of approximately 20 kilodalton that binds directly to sperm and inhibits Mg++ ATPase activity (26). Because this enzyme is essential for energy transduction involved in flagellar motion, its inhibition may contribute to sperm immobilization. The factor also interferes with acrosome reaction, further compromising fertilizing capacity (26).

Other pathogens in the dysbiotic community employ their own "weapons" to neutralize sperm, as detailed in Table 2.

E. coli affects sperm through several complementary pathways. It can attach directly to sperm via pili and flagella, particularly through interactions with mannose-containing receptors (20). This adhesion may itself reduce motility. In addition, *E. coli* secretes LPS, porins, and other factors that can damage the acrosome, impair membrane function, and is suggested to promote apoptosis (3,27). Outer membrane vesicles shed by uropathogenic *E. coli* have been shown to impair sperm function in experimental settings and to be associated with reduced semen quality. Moreover, they promote oxidative stress and DNA fragmentation (28).

E. faecalis exerts pathogenic effects through virulence factors such as hemolysin, which can disrupt membrane integrity of the sperm head, neck, and midpiece (20). Even when effects on motility are less dramatic than those caused by *S. aureus*, membrane disruption and oxidative injury may still significantly impair reproductive potential.

Ureaplasma urealyticum secretes phospholipases A and C, which directly degrade membrane phospholipids, weakening sperm

Table 2. Direct pathogenic mechanisms of sperm impairment

Pathogen	Virulence factor(s)	Mechanism of action	Consequence for sperm	Supporting sources
Staphylococcus aureus	Sperm immobilization factor (SIF)	A secreted ~20 kDa protein. Binds to a receptor on the sperm surface. Inhibits the sperm's Mg++ ATPase activity	Rapid, 100% sperm immobilization; sperm agglutination (clumping); inhibition of acrosome reaction	(25,26)
Escherichia coli	LPS, porins, fimbriae	Fimbriae/pili bind directly to mannose receptors on the sperm surface. Secreted toxins (LPS, porins) damage membranes and bind to cell receptors	Sperm immobilization/agglutination; severe acrosome damage; induction of apoptosis (programmed cell death)	(3,20,27)
Enterococcus faecalis	Hemolysin	A well-known cytotoxic virulence factor that functions as a toxin to lyse cell membranes	Direct damage to the membrane integrity of the sperm head, neck, and mid-piece	(20)
Ureaplasma urealyticum	Phospholipase A & C; H_2O_2	Secreted enzymes enzymatically degrade and "injure" the phospholipid components of the sperm membrane. H_2O_2 adds peroxidative damage	Loss of sperm membrane integrity; reduced sperm motility and morphology	(20)
Pseudomonas aeruginosa	Exotoxin A; porin	Exotoxin A specifically targets proteins in the sperm tail. Porin binds to sperm membrane receptors	Direct reduction in sperm motility; induction of apoptosis	(27)

kDA: Kilodalton, LPS: Lipopolysaccharide, ATPase: Adenosine triphosphatase

membranes and making them more susceptible to oxidative damage (20). Its production of hydrogen peroxide contributes to further chemical injury. *Pseudomonas aeruginosa* also demonstrates sperm-directed pathogenicity through exotoxins and porins that impair motility and promote apoptosis (27).

A common endpoint of these direct bacterial effects is apoptosis (20). Sperm may enter programmed cell death either as a consequence of cumulative oxidative and membrane injury or due to direct triggering by bacterial toxins (27). This contributes to a reduced number of viable sperm, reduced functional quality, and, ultimately, infertility.

Taken together, these indirect inflammatory processes and direct pathogen-mediated virulence mechanisms do not operate in isolation but converge on a shared downstream pathway of cellular injury. Persistent oxidative stress, membrane disruption, and toxin-mediated damage collectively create a molecular environment that compromises sperm integrity at its most fundamental level.

Among these downstream effects, oxidative stress-induced sperm DNA fragmentation (SDF) emerges as a central and unifying endpoint. This molecular lesion integrates the cumulative impact of both host- and pathogen-driven injury and provides a measurable link between microbial dysbiosis and impaired reproductive outcomes.

Accordingly, the following section focuses on the molecular consequences of seminal dysbiosis, with particular emphasis on oxidative stress and SDF as key mediators of infertility.

III. The Molecular Nexus of Damage: Oxidative Stress and SDF

Although seminal dysbiosis affects sperm through multiple pathways, many of these converge at one critical molecular endpoint: SDF. This lesion provides a measurable and clinically meaningful summary of the oxidative and inflammatory burden imposed by the dysbiotic reproductive tract. SDF is increasingly considered an extended functional test in the evaluation of male infertility, complementing conventional semen analysis (10).

Spermatozoa are biologically predisposed to oxidative vulnerability. Their plasma membranes contain high concentrations of polyunsaturated fatty acids, which are necessary for membrane fluidity and fertilization-related membrane dynamics (16). However, these lipids are highly susceptible to ROS-mediated lipid peroxidation. Once peroxidation begins, membrane architecture deteriorates, reducing flexibility, impairing motility, and compromising the ability of sperm to fuse with the oocyte (16,24).

Sperm have very limited intrinsic repair capacity. During maturation, spermatozoa lose most of their cytoplasm, which means they retain only restricted antioxidant defenses and limited capacity for DNA repair (16). They, unlike somatic cells, are unable to effectively repair oxidative lesions once these occur. They therefore depend heavily on extracellular antioxidant protection from seminal plasma. When ROS production from leukocytes and bacteria exceeds this protective capacity, oxidative injury becomes effectively irreversible (16,18,29).

ROS attack not only membranes but also DNA. They can oxidize DNA bases, generate lesions such as 8-hydroxy-2′-deoxyguanosine, and is suggested to promote both single- and double-strand breaks (16). In this context, SDF emerges as the downstream product of microbially induced pathology. Leukocytospermia is associated with increased oxidative stress and higher rates of DNA fragmentation (16). Likewise, bacteriospermia can induce intracellular ROS generation and trigger mitochondrial and apoptotic pathways leading to fragmented sperm DNA (30). *E. coli* outer membrane vesicles are also sufficient to produce oxidative stress and DNA damage (28).

SDF is therefore not merely an associated laboratory abnormality; it represents the integrated molecular signature of seminal microbial pathology. It captures the cumulative effects of chronic inflammation, bacterial ROS production, membrane damage, and apoptotic signaling. In men with otherwise unexplained infertility, high SDF may therefore serve as an indirect marker of hidden dysbiosis.

Clinical Impact: SDF and ART Failure

The reproductive consequences of high SDF are profound. Damaged sperm may still appear motile and be selected for use in ART, particularly during ICSI. Yet injection of a motile sperm with fragmented DNA introduces a compromised paternal genome into the oocyte (31). Although oocytes possess DNA repair mechanisms, severe SDF may exceed maternal repair capacity (32).

The clinical and statistical findings summarized in Table 3 consistently demonstrate that elevated SDF is associated with adverse reproductive outcomes across multiple ART modalities. High SDF levels are linked to reduced fertilization rates, impaired embryo quality, decreased blastocyst formation, lower implantation rates, and increased miscarriage risk. This convergence of evidence reinforces SDF's role as a clinically meaningful downstream marker of microbially induced reproductive damage and a critical determinant of ART success.

The downstream effects include impaired fertilization, poorer embryo quality, reduced blastocyst formation, embryo arrest, lower implantation rates, reduced clinical pregnancy rates, and increased miscarriage risk (32,33). Even in ICSI cycles, where mechanical sperm selection overcomes some conventional

semen deficits, high SDF remains associated with poorer reproductive outcomes (33).

Thus, the clinical relevance of microbial-induced sperm injury extends far beyond abnormal semen analysis. It affects embryo competence, implantation, and pregnancy maintenance, making dysbiosis a plausible hidden contributor to ART failure.

IV. The Diagnostic Gap: Why "Idiopathic" Infertility is Often a Failure of Detection

Current diagnostic tools in andrology remain limited in their ability to fully capture functional and molecular abnormalities, contributing to the persistence of idiopathic infertility (10). Despite the growing evidence linking seminal dysbiosis to infertility, this pathology is often missed by standard clinical diagnostics. This creates a major diagnostic gap and may explain why idiopathic male infertility remains common (11). The core problem is not necessarily the absence of pathology, but rather the failure to detect it. A central factor in this failure is the viable but non-culturable (VBNC) state.

A. The Hidden Reservoir: VBNC Pathogens

The VBNC state is a survival strategy used by many bacteria under environmental stress, including nutrient deprivation, temperature change, or antibiotic exposure (34). In this condition, bacteria remain alive, maintain cellular integrity, and often retain virulence potential, but they no longer grow on standard culture media (34,35). Importantly, these dormant organisms can later resuscitate and regain active pathogenicity when conditions improve (36).

This phenomenon is highly relevant to chronic and recurrent urogenital infection. Studies on uropathogenic *E. coli* show that after antibiotic treatment, bacteria may disappear from culture yet remain detectable by molecular assays and viability testing, indicating persistence in a VBNC state (37). These cells can act as a reservoir for relapse.

The same logic applies to male infertility. Pathogens associated with chronic prostatitis and impaired sperm quality, such as *E. faecalis*, are known to enter the VBNC state (38-40). This creates a vicious cycle: a patient receives antibiotics for a reproductive tract infection; the culture becomes negative; the patient is considered cured; yet viable, dormant organisms persist in the prostate or seminal tract, where they continue to drive low-grade inflammation, oxidative stress, and sperm damage. The result is a patient with culture-negative semen, high SDF, and infertility, subsequently labeled as idiopathic.

B. Failure of Current Diagnostic Standards

Table 4 systematically outlines the limitations of current diagnostic approaches and highlights a fundamental mismatch between microbial biology and conventional detection methods. Culture-based techniques fail to detect VBNC organisms, leading to false-negative results, whereas standard PCR detects microbial DNA without distinguishing between viable, dormant, and dead cells, resulting in clinical ambiguity and potential overtreatment. This diagnostic gap provides a compelling explanation for the persistence of "idiopathic" infertility despite apparently negative microbiological findings.

Culture-based methods fail because they depend on bacterial growth. If viable bacteria are dormant and non-culturable, the test becomes falsely negative (41). A patient may, therefore, harbor an ongoing pathogenic reservoir despite all standard cultures remaining negative.

Standard polymerase chain reaction (PCR) based methods overcome some sensitivity issues, but they create another problem: they cannot reliably distinguish DNA from live bacteria, dormant bacteria, and dead organisms (42,43). A positive PCR result may reflect an active infection, a dormant VBNC population, or only residual DNA from non-viable cells. This ambiguity limits clinical interpretation and may lead to inappropriate antibiotic use. Moreover, unnecessary antibiotics may reinforce bacterial dormancy or select for persistence.

Table 3. Clinical impact of high sperm DNA fragmentation (SDF) on assisted reproductive technology (ART) outcomes

ART modality	Measured outcome	Quantitative impact of high SDF (from systematic reviews and meta-analyses)	Key supporting sources
IVF	Fertilization rate	Reduced. High SDF (e.g., >27-30%) is associated with a significant reduction in the oocyte fertilization rate	(33)
IVF/ICSI	Embryo quality	Reduced. High SDF is significantly linked to a lower rate of high-quality embryos and altered developmental kinetics	(33)
IVF/ICSI	Blastocyst rate	Reduced. A strong negative correlation exists between SDF levels and blastulation rates. High DNA damage "promotes embryo arrest."	(32)
IVF/IUI	Clinical pregnancy rate	Reduced. High SDF is associated with a reduction in pregnancy rates in IUI and frozen embryo transfer cycles	(33)
IVF	Abortion/miscarriage rate	Increased. Patients with high sperm DNA fragmentation show an increased rate of abortion	(33)
IVF/ICSI	Implantation rate	Reduced. A reduction in implantation rate is observed in patients with high SDF	(33)

IVF: In vitro fertilization, ICSI: Intracytoplasmic sperm injection, IUI: Intrauterine insemination

Table 4. Comparative analysis of diagnostic modalities for seminal pathogen detection					
Diagnostic method	**Principle of detection**	**Ability to detect VBNC cells**	**Common clinical failure**	**Clinical consequence**	**Supporting sources**
Culture-based methods (the "Gold Standard")	Requires bacterial metabolic activity and reproduction (growth) on nutrient-rich media to form a visible colony	No. By definition, VBNC cells are non-culturable	False-negative	Fails to detect the "hidden reservoir" of viable pathogens. Leads to a "culture-negative" status and misdiagnosis of "idiopathic infertility."	(1,39,41,44)
Standard PCR (molecular)	Amplification of specific nucleic acid (DNA/RNA) sequences	Yes (detects their DNA)	False-positive/ ambiguous	Cannot differentiate between live (virulent), dormant (VBNC), and dead (non-pathogenic) cells	(42)
				Leads to clinical ambiguity and the harmful overtreatment of non-viable bacterial DNA with antibiotics	(43)
DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid, VBNC: Viable but non-culturable					

Together, these limitations explain why many men with inflammation, leukocytospermia, or high SDF remain microbiologically "negative" by routine testing. The consequence is the underdiagnosis of a potentially treatable microbial component of infertility.

V. The Future Imperative: Next-generation Diagnostics for Viability and Virulence

To address this diagnostic gap, infertility diagnostics must evolve beyond simple presence-or-absence testing. A clinically useful platform must distinguish three microbial states: dead, dormant, and metabolically active. Ideally, it should also determine whether the detected organism is actually expressing virulence traits relevant to reproductive injury (44).

A. Detecting Viability

One promising approach is viability-PCR (v-qPCR) using dyes such as propidium monoazide or ethidium monoazide (44). These agents penetrate cells with damaged membranes, bind their DNA after photoactivation, and prevent amplification during PCR. DNA from viable cells with intact membranes remains amplifiable. This allows selective detection of viable organisms while excluding signal from dead bacteria (44,45).

This approach directly addresses the false-positive limitation of standard PCR and helps determine whether detected bacteria are still biologically relevant.

B. Detecting Metabolic Activity

Viability alone does not distinguish dormant VBNC cells from metabolically active pathogens. To make this distinction, diagnostics must assess metabolic activity.

ATP bioluminescence is one of the most established approaches. ATP is a universal marker of cellular metabolism and is rapidly degraded after cell death (46). In ATP-based assays, light emission generated through luciferase activity is proportional to ATP concentration, enabling quantification of metabolic activity (46,47). In principle, dead cells yield no signal, dormant cells yield low signal, and active cells yield high signal.

Other metabolic approaches include microfluidic systems measuring oxygen consumption, fluorogenic substrates that report esterase activity, and electrochemical sensors detecting metabolic by-products or changes in medium conductance (48-50). These technologies move diagnostics from static identification toward functional assessment.

C. Detecting Virulence

The ultimate clinical question is not simply whether a bacterium is present or alive, but whether it is dangerous. Many organisms in the seminal microbiome may be commensal, context-dependent, or only weakly pathogenic (51). Thus, future diagnostics should target virulence factor expression.

This may include detection of genes or proteins encoding adhesins, toxins, hemolysins, sperm-immobilizing factors, or quorum-sensing molecules (52-54). A pathogen such as *E. coli* may be present in both commensal and virulent forms, and a useful clinical test must discriminate between them (51,52). Virulence-based sensing would offer a much more actionable assessment of fertility risk than simple taxonomic detection alone. Emerging diagnostic technologies addressing these limitations are summarized in Table 5, which illustrates a shift toward functional microbiological assessment. Platforms such as v-qPCR, ATP bioluminescence, microfluidic metabolic assays, and virulence-factor biosensors enable simultaneous evaluation of microbial viability, metabolic activity, and pathogenic potential. These innovations represent a critical transition from static detection to dynamic characterization of microbial behavior, with direct implications for precision diagnostics for male infertility.

Table 5. Advanced biosensor technologies for differentiating pathogen viability and activity

Technology	Principle of detection	Target	Clinical question answered	Supporting sources
Viability-PCR (v-qPCR)	DNA-intercalating dyes (PMA, EMA) penetrate membrane-compromised cells and covalently bind to DNA, inhibiting PCR amplification	Cellular viability (membrane integrity)	"Filters out 'noise' from dead cells. What is the total viable pathogen load?"	(44)
ATP bioluminescence	Firefly luciferin/luciferase enzymatic reaction. Light output is directly proportional to ATP concentration	Metabolic activity (intracellular ATP level)	"Is the viable population active (high ATP) or dormant/VBNC (low ATP)?"	(44,47)
Microfluidic metabolic assays	Fluorogenic substrates (e.g., Calcein AM) or oxygen-sensitive fluorophores integrated into microfluidic chips	Metabolic Activity (e.g., esterase activity, respiration)	"Are these viable cells metabolically functional and healthy?"	(48,49)
Electrochemical biosensors	Measure changes in electrical properties (impedance, conductance) as bacteria metabolize substrates	Metabolic activity (metabolic byproducts)	"Is there active metabolism occurring in this sample?"	(50)
Virulence factor (VFG) biosensors	Detect the active expression of specific genes (e.g., pap, fim), the toxins themselves (e.g., SIF), or their signaling molecules (e.g., AHLs)	Pathogenic virulence (active gene/protein expression)	"Is this viable, active population actually harmful? Is it a pathogen or a harmless commensal?"	(52-56)

ATP: Adenosine triphosphate, DNA: Deoxyribonucleic acid, AHL: N-acyl homoserine lactone, SIF: Simulated intestinal fluid, PCR: Polymerase chain reaction, PMA: Propidium monoazide, EMA: Ethidium monoazide

D. Point-of-Care Integration

The ideal endpoint of these innovations is a point-of-care platform capable of rapidly assessing the viability, activity, and virulence of microbes in semen in an infertility clinic. Advances in microfluidics, electrochemical biosensing, and smartphone-assisted diagnostics suggest that this is feasible (55-63).

A future andrology clinic could, therefore, perform a standard semen analysis alongside an integrated microbial screen, thereby yielding a practical "diagnostic triumvirate":

1. Viability: Is there a viable bacterial load?

2. Activity: Is that population dormant or metabolically active?

3. Virulence: Is it expressing fertility-damaging traits?

Such a platform would greatly improve stratification of patients currently labeled as idiopathic.

From a clinical perspective, these mechanistic insights have important implications for the diagnostic approach to male infertility. In patients with unexplained infertility or discordance between standard semen parameters and reproductive outcomes, assessment of SDF may provide additional functional information beyond conventional semen analysis (64). Furthermore, the recognition of seminal dysbiosis as a potential contributing factor suggests that negative culture results should not exclude a microbial component, particularly in the presence of leukocytospermia or elevated oxidative stress markers. In such cases, adjunctive testing strategies, including molecular assays or emerging functional diagnostics targeting microbial viability and activity, may help refine patient stratification. Although these approaches are not yet fully standardized, they highlight a shift toward a more integrated diagnostic model combining conventional semen analysis with molecular and functional assessments to better guide individualized clinical decision-making.

In selected patients, particularly those with non-obstructive azoospermia, surgical sperm retrieval techniques such as microsurgical testicular sperm extraction may influence clinical outcomes, with factors such as follicle-stimulating hormone levels and surgical approach affecting success rates (65).

Despite the growing body of evidence linking seminal microbiome alterations to male infertility, several important limitations should be acknowledged. First, there is substantial heterogeneity in study methodologies, including differences in sample collection, processing, sequencing platforms, and bioinformatic pipelines, which complicates direct comparisons across studies. Second, the lack of standardized protocols and reference frameworks limits reproducibility and hinders the translation of research findings into clinical practice. Finally, a fundamental challenge lies in distinguishing pathogenic organisms from commensal or context-dependent microbiota. Many bacterial species identified in semen may exert variable effects depending on microbial community structure, host factors, and local immune responses. While current data support an association between microbial dysbiosis and impaired reproductive outcomes, caution is warranted when interpreting these findings, and further well-designed, standardized, and longitudinal studies are needed to clarify causal relationships and clinical applicability.

Conclusion

From Pathological Review to Clinical Strategy

The evidence reviewed here supports a major transformation in the understanding of male reproductive health. Semen is not sterile but is part of a dynamic microbial ecosystem. Within this ecosystem, seminal dysbiosis may represent a clinically important driver of male infertility.

The pathological sequence is increasingly coherent. A shift from a protective, eubiotic microbiome toward a dysbiotic community dominated by opportunistic or pathogenic organisms initiates chronic, low-grade inflammation and direct, sperm-targeted toxicity. Through host leukocyte activation, bacterial ROS production, membrane injury, toxin activity, and apoptotic signaling, these microbes create a damaging reproductive microenvironment.

The principal molecular endpoint of this pathology is oxidative stress-induced SDF. This lesion is of major clinical relevance because it links hidden microbial dysfunction with poor embryo development, implantation failure, miscarriage, and ART failure. In this framework, SDF becomes not only a marker of sperm quality but also a potential indicator of otherwise undetected seminal microbial pathology.

Current diagnostics fail to adequately capture this biology. Culture-based methods miss VBNC reservoirs, while conventional PCR cannot determine whether detected organisms are alive, dormant, dead, or virulent. This mismatch between biology and diagnostics likely contributes to the persistence of the "idiopathic male infertility" category.

The field, therefore, requires a new diagnostic strategy. Future approaches should integrate conventional semen analysis with microbial assays capable of determining viability, metabolic activity, and virulence. Technologies such as v-qPCR, ATP bioluminescence, metabolic biosensors, and virulence-factor detection offer a plausible path toward that goal.

In clinical terms, this would enable a more rational triage of infertile men. Those with active virulent infections could be treated directly; those with dormant VBNC reservoirs could be managed with strategies designed to address persistence rather than simple empiric antibiotic therapy; and those without evidence of relevant microbial pathology could proceed to evaluation for endocrine, genetic, anatomical, or vascular causes. These insights support a transition from a purely descriptive diagnostic paradigm toward a more mechanism-informed and individualized approach in andrology practice.

The microbial dimension of male infertility is no longer a peripheral hypothesis. It is an increasingly evidence-based framework that links dysbiosis, inflammation, oxidative stress, SDF, and reproductive failure. While the available evidence strongly supports an association between seminal dysbiosis and male infertility, a definitive causal relationship has not yet been established; further longitudinal and mechanistic studies are required. Future progress in male infertility diagnostics will depend on acknowledging this chain and developing tools that detect not just microbial presence, but microbial behavior. Only then will a substantial fraction of so-called idiopathic infertility become biologically explainable and potentially treatable.

From a clinical perspective, two key implications emerge. First, "idiopathic" male infertility may frequently reflect undetected microbial dysbiosis and oxidative sperm DNA damage. Second, precision andrology will require diagnostic platforms that assess not only microbial presence but also biological activity and pathogenic potential.

Footnotes

Authorship Contributions

Concept: M.B.D., A.K., Design: M.B.D., K.K., A.A., A.K., Analysis or Interpretation: S.Ç., Y.Ö., Literature Search: M.B.D., A.K., Writing: M.B.D., K.K., A.A., S.Ç., Y.Ö., A.K.

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

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

References

1. Wang H, Xu A, Gong L, Chen Z, Zhang B, Li X. The microbiome, an important factor that is easily overlooked in male infertility. Front Microbiol. 2022;13:831272. [Crossref]
2. Kilama J, Dahlen CR, Reynolds LP, Amat S. Contribution of the seminal microbiome to paternal programming. Biol Reprod. 2024;111:242-268. [Crossref]
3. Chatzokou D, Tsarna E, Davouti E, Siristatidis CS, Christopoulou S, Spanakis N, Tsakris A, Christopoulos P. Semen microbiome, male infertility, and reproductive health. Int J Mol Sci. 2025;26:1446. [Crossref]
4. Hofman J, Brenerova P, Borilova Linhartova P. State-of-the-art approaches in the investigation of human seminal bacteriome using metagenomic methods. Front Reprod Health. 2025;7:1557912. [Crossref]
5. Farahani L, Tharakan T, Yap T, Ramsay JW, Jayasena CN, Minhas S. The semen microbiome and its impact on sperm function and male fertility: a systematic review and meta-analysis. Andrology. 2021;9:115-144. [Crossref]
6. Kaltsas A, Zachariou A, Markou E, Dimitriadis F, Sofikitis N, Pournaras S. Microbial dysbiosis and male infertility: understanding the impact and exploring therapeutic interventions. J Pers Med. 2023;13:1491. [Crossref]
7. Magill RG, MacDonald SM. Male infertility and the human microbiome. Front Reprod Health. 2023;5:1166201. [Crossref]
8. Grande G, Graziani A, De Toni L, Garolla A, Ferlin A. Male tract microbiota and male infertility. Cells. 2024;13:1275. [Crossref]
9. Morawiec E, Czerwiński M, Czerwińska AB, Wiczkowski A. Semen dysbiosis-just a male problem? Front Cell Infect Microbiol. 2022;12:815786. [Crossref]

10. Gül M, Russo GI, Kandil H, Boitrelle F, Saleh R, Chung E, Kavoussi P, Mostafa T, Shah R, Agarwal A. Male infertility: new developments, current challenges, and future directions. World J Mens Health. 2024;42:502-517. [Crossref]
11. Boeri L, Kandil H, Ramsay J. Idiopathic male infertility - what are we missing? Arab J Urol. 2024;23:215-229. [Crossref]
12. Murphy AB, Macejko A, Taylor A, Nadler RB. Chronic prostatitis: management strategies. Drugs. 2009;69:71-84. [Crossref]
13. Pendegast HJ, Leslie SW, Rosario DJ. Chronic prostatitis and chronic pelvic pain syndrome in men. 2024. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026. [Crossref]
14. Korrovits P, Punab M, Türk S, Mändar R. Seminal microflora in asymptomatic inflammatory (NIH IV category) prostatitis. Eur Urol. 2006;50:1338-1344; discussion 1344-1346. [Crossref]
15. Neto FTL, Viana MC, Cariati F, Conforti A, Alviggi C, Esteves SC. Effect of environmental factors on seminal microbiome and impact on sperm quality. Front Endocrinol (Lausanne). 2024;15:1348186. [Crossref]
16. Wang Y, Fu X, Li H. Mechanisms of oxidative stress-induced sperm dysfunction. Front Endocrinol (Lausanne). 2025;16:1520835. [Crossref]
17. Castleton PE, Deluao JC, Sharkey DJ, McPherson NO. Measuring reactive oxygen species in semen for male preconception care: a scientist perspective. Antioxidants (Basel). 2022;11:264. [Crossref]
18. Tvrdá E, Benko F, Ďuračka M. Oxidative stress as an underlying mechanism of bacteria-inflicted damage to male gametes. Oxygen. 2022;2:547-569. [Crossref]
19. Szemes T, Vlkova B, Minarik G, Tothova L, Drahovska H, Turna J, Celec P. On the origin of reactive oxygen species and antioxidative mechanisms in Enterococcus faecalis. Redox Rep. 2010;15:202-206. [Crossref]
20. Moretti EMoretti E, Capitani S, Figura N, Pammolli A, Federico MG, Giannerini V, Collodel G. The presence of bacteria species in semen and sperm quality. J Assist Reprod Genet. 2009;26:47-56. [Crossref]
21. Dutta S, Sengupta P, Izuka E, Menuba I, Jegasothy R, Nwagha U. Staphylococcal infections and infertility: mechanisms and management. Mol Cell Biochem. 2020;474:57-72. [Crossref]
22. Abdurrahman G, Schmiedeke F, Bachert C, Bröker BM, Holtfreter S. Allergy-a new role for t cell superantigens of *Staphylococcus aureus*? Toxins (Basel). 2020;12:176. [Crossref]
23. Tuffs SW, Haeryfar SMM, McCormick JK. Manipulation of innate and adaptive immunity by Staphylococcal superantigens. Pathogens. 2018;7:53. [Crossref]
24. Potiris A, Moustakli E, Trismpioti E, Drakaki E, Mavrogianni D, Matsas A, Zikopoulos A, Sfakianakis A, Tsakiridis I, Dagklis T, Zachariou A, Christopoulos P, Domali E, Drakakis P, Stavros S. From inflammation to infertility: how oxidative stress and infections disrupt male reproductive health. Metabolites. 2025;15:267. [Crossref]
25. Kaur S, Prabha V, Shukla G, Sarwal A. Interference of human spermatozoal motility by live Staphylococcus aureus. Am J Biomed Sci. 2010;2:91-97. [Crossref]
26. Gupta S, Prabha V. Human sperm interaction with Staphylococcus aureus: a molecular approach. J Pathog. 2012;2012:816536. [Crossref]
27. Wang S, Zhang K, Yao Y, Li J, Deng S. Bacterial infections affect male fertility: a focus on the oxidative stress-autophagy axis. Front Cell Dev Biol. 2021;9:727812. [Crossref]
28. Folliero V, Santonastaso M, Dell'Annunziata F, De Franciscis P, Boccia G, Colacurci N, De Filippis A, Galdiero M, Franci G. Impact of *Escherichia coli* outer membrane vesicles on sperm function. Pathogens. 2022;11:782. [Crossref]
29. Agarwal A, Virk G, Ong C, du Plessis SS. Effect of oxidative stress on male reproduction. World J Mens Health. 2014;32:1-17. [Crossref]
30. Henkel R. Leukocytospermia and/or bacteriospermia: impact on male infertility. J Clin Med. 2024;13:2841. [Crossref]
31. Simon L, Brunborg G, Stevenson M, Lutton D, McManus J, Lewis SE. Clinical significance of sperm DNA damage in assisted reproduction outcome. Hum Reprod. 2010;25:1594-1608. [Crossref]
32. Alvarez Sedó C, Bilinski M, Lorenzi D, Uriondo H, Noblía F, Longobucco V, Lagar EV, Nodar F. Effect of sperm DNA fragmentation on embryo development: clinical and biological aspects. JBRA Assist Reprod. 2017;21:343-350. [Crossref]
33. Lourenço ML, Moura GA, Rocha YM, Rodrigues JPV, Monteiro PB. Impact of sperm DNA fragmentation on the clinical outcome of assisted reproduction techniques: a systematic review of the last five years. JBRA Assist Reprod. 2023;27:282-291. [Crossref]
34. Göing S, Jung K. Viable but nonculturable gastrointestinal bacteria and their resuscitation. Arch Gastroenterol Res. 2021;2:55-62. [Crossref]
35. Ramamurthy T, Ghosh A, Pazhani GP, Shinoda S. Current perspectives on viable but non-culturable (VBNC) pathogenic bacteria. Front Public Health. 2014;2:103. [Crossref]
36. Pazos-Rojas LA, Cuellar-Sánchez A, Romero-Cerón AL, Rivera-Urbalejo A, Van Dillewijn P, Luna-Vital DA, Muñoz-Rojas J, Morales-García YE, Bustillos-Cristales MDR. The viable but non-culturable (VBNC) state, a poorly explored aspect of beneficial bacteria. Microorganisms. 2023;12:39. [Crossref]
37. Rivers B, Steck TR. Viable but nonculturable uropathogenic bacteria are present in the mouse urinary tract following urinary tract infection and antibiotic therapy. Urol Res. 2001;29:60-66. [Crossref]
38. Mahdizade Ari M, Scholz KJ, Cieplik F, Al-Ahmad A. Viable but non-cultivable state in oral microbiota: a critical review of an underexplored microbial survival strategy. Front Cell Infect Microbiol. 2025;15:1533768. [Crossref]
39. Xiong S, Liu X, Deng W, Zhou Z, Li Y, Tu Y, Chen L, Wang G, Fu B. Pharmacological interventions for bacterial prostatitis. Front Pharmacol. 2020;11:504. [Crossref]
40. E J, Jiang YT, Yan PF, Liang JP. Biological changes of Enterococcus faecalis in the viable but nonculturable state. Genet Mol Res. 2015;14:14790-14801. [Crossref]
41. Zhang J, Yang H, Li J, Hu J, Lin G, Tan BK, Lin S. Current perspectives on viable but non-culturable foodborne pathogenic bacteria: a review. Foods. 2023;12:1179. [Crossref]
42. Pandruvada S, Royfman R, Shah TA, Sindhwani P, Dupree JM, Schon S, Avidor-Reiss T. Lack of trusted diagnostic tools for undetermined male infertility. J Assist Reprod Genet. 2021;38:265-276. [Crossref]
43. Cangelosi GA, Meschke JS. Dead or alive: molecular assessment of microbial viability. Appl Environ Microbiol. 2014;80:5884-5891. [Crossref]
44. Trinh KTL, Lee NY. Recent methods for the viability assessment of bacterial pathogens: advances, challenges, and future perspectives. Pathogens. 2022;11:1057. [Crossref]
45. Frigoli M, Lowdon JW, Caldara M, Cleij TJ, Diliën H, Eersels K, van Grinsven B. Emerging Biomimetic Sensor Technologies for the Detection of Pathogenic Bacteria: A Commercial Viability Study. ACS Omega. 2024;9:23155-23171. [Crossref]
46. Venkateswaran K, Hattori N, La Duc MT, Kern R; New Collective Author. ATP as a biomarker of viable microorganisms in clean-room facilities. J Microbiol Methods. 2003;52:367-377. [Crossref]
47. Ayyash S, Wu WI, Selvaganapathy PR. Fast and inexpensive detection of bacterial viability and drug effectiveness through metabolic monitoring. Sensors (Basel). 2016;16:1879. [Crossref]
48. Krämer CE, Singh A, Helfrich S, Grünberger A, Wiechert W, Nöh K, Kohlheyer D. Non-invasive microbial metabolic activity sensing at single cell level by perfusion of calcein acetoxymethyl ester. PLoS One. 2015;10:e0141768. [Crossref]

49. Kulkarni MB, Ayachit NH, Aminabhavi TM. Biosensors and microfluidic biosensors: from fabrication to application. Biosensors (Basel). 2022;12:543. [Crossref]

50. Denzer L, Schroten H, Schwerk C. From gene to protein-how bacterial virulence factors manipulate host gene expression during infection. Int J Mol Sci. 2020;21:3730. [Crossref]

51. Mobley HL. Measuring Escherichia coli gene expression during human urinary tract infections. Pathogens. 2016;5:7. [Crossref]

52. Jiang L, Wang H, Luo L, Pang X, Liu T, Sun L, Zhang G. Urogenital microbiota-driven virulence factor genes associated with recurrent urinary tract infection. Front Microbiol. 2024;15:1344716. [Crossref]

53. Govindarajan DK, Kandaswamy K. Virulence factors of uropathogens and their role in host pathogen interactions. Cell Surf. 2022;8:100075. [Crossref]

54. Senturk S, Ulusoy S, Bosgelmez-Tinaz G, Yagci A. Quorum sensing and virulence of Pseudomonas aeruginosa during urinary tract infections. J Infect Dev Ctries. 2012;6:501-507. [Crossref]

55. Parihar M, W N N, Sahana, Biswas R, Dehury B, Mazumder N. Point-of-care biosensors for infectious disease diagnosis: recent updates and prospects. RSC Adv. 2025;15:29267-29283. [Crossref]

56. Tsao YT, Yang CY, Wen YC, Chang TC, Matsuura K, Chen Y, Cheng CM. Point-of-care semen analysis of patients with infertility via smartphone and colorimetric paper-based diagnostic device. Bioeng Transl Med. 2020;6:e10176. [Crossref]

57. Heidt B, Siqueira WF, Eersels K, Diliën H, van Grinsven B, Fujiwara RT, Cleij TJ. Point of care diagnostics in resource-limited settings: a review of the present and future of PoC in its most needed environment. Biosensors (Basel). 2020;10:133. [Crossref]

58. Sachdeva S, Davis RW, Saha AK. Microfluidic point-of-care testing: commercial landscape and future directions. Front Bioeng Biotechnol. 2021;8:602659. [Crossref]

59. Samuel R, Feng H, Jafek A, Despain D, Jenkins T, Gale B. Microfluidic-based sperm sorting & analysis for treatment of male infertility. Transl Androl Urol. 2018;7(Suppl 3):S336-S347. [Crossref]

60. Abbas N, Song S, Chang MS, Chun MS. Point-of-care diagnostic devices for detection of Escherichia coli O157:H7 using microfluidic systems: a focused review. Biosensors (Basel). 2023;13:741. [Crossref]

61. Liao JC, Mastali M, Gau V, Suchard MA, Møller AK, Bruckner DA, Babbitt JT, Li Y, Gornbein J, Landaw EM, McCabe ER, Churchill BM, Haake DA. Use of electrochemical DNA biosensors for rapid molecular identification of uropathogens in clinical urine specimens. J Clin Microbiol. 2006;44:561-570. [Crossref]

62. Khan MU, Rahman MM, Zahan N, Masud MK, Sarker S, Haque MH. Electrochemical biosensing for antibiotic-resistant bacteria: advances, challenges, and future directions. Micromachines (Basel). 2025;16:986. [Crossref]

63. Cesewski E, Johnson BN. Electrochemical biosensors for pathogen detection. Biosens Bioelectron. 2020;159:112214. [Crossref]

64. Farkouh A, Agarwal A, Hamoda TAA, Kavoussi P, Saleh R, Zini A, Arafa M, Harraz AM, Gul M, Karthikeyan VS, Durairajanayagam D, Rambhatla A, Boitrelle F, Chung E, Birowo P, Toprak T, Ghayda RA, Cannarella R, Phuoc NHV, Dimitriadis F, Russo GI, Sokolakis I, Mostafa T, Makarounis K, Ziouziou I, Kuroda S, Bendayan M, Kaiyal RS, Japari A, Simopoulou M, Rocco L, Garrido N, Gherabi N, Bocu K, Kahraman O, Le TV, Wyns C, Tremellen K, Sarikaya S, Lewis S, Evenson DP, Ko E, Calogero AE, Bahar F, Martinez M, Crafa A, Nguyen Q, Ambar RF, Colpi G, Bakircioglu ME, Henkel R, Kandil H, Serefoglu EC, Alarbid A, Tsujimura A, Kheradmand A, Anagnostopoulou C, Marino A, Adamyan A, Zilaitiene B, Ozer C, Pescatori E, Vogiatzi P, Busetto GM, Balercia G, Elbardisi H, Akhavizadegan H, Sajadi H, Taniguchi H, Park HJ, Maldonado Rosas I, Al-Marhoon M, Sadighi Gilani MA, Alhathal N, Pinggera GM, Kothari P, Mogharabian N, Micic S, Homa S, Darbandi S, Long TQT, Zohdy W, Atmoko W, Sabbaghian M, Ibrahim W, Smith RP, Ho CCK, de la Rosette J, El-Sakka AI, Preto M, Zenoaga-Barbăroşie C, Abumelha SM, Baser A, Aydos K, Ramirez-Dominguez L, Kumar V, Ong TA, Mierzwa TC, Adriansjah R, Banihani SA, Bowa K, Fukuhara S, Rodriguez Peña M, Moussa M, Ari UÇ, Cho CL, Tadros NN, Ugur MR, Amar E, Falcone M, Santer FR, Kalkanli A, Karna KK, Khalafalla K, Vishwakarma RB, Finocchi F, Giulioni C, Ceyhan E, Çeker G, Yazbeck C, Rajmil O, Yilmaz M, Altay B, Barrett TL, Ngoo KS, Roychoudhury S, Salvio G, Lin H, Kadioglu A, Timpano M, Avidor-Reiss T, Hakim L, Sindhwani P, Franco G, Singh R, Giacone F, Ruzaev M, Kosgi R, Sofikitis N, Palani A, Calik G, Kulaksız D, Jezek D, Al Hashmi M, Drakopoulos P, Omran H, Leonardi S, Celik-Ozenci C, Güngör ND, Ramsay J, Amano T, Sogutdelen E, Duarsa GWK, Chiba K, Jindal S, Savira M, Boeri L, Borges E, Gupte D, Gokalp F, Hebrard GH, Minhas S, Shah R; Global Andrology Forum. Controversy and consensus on the management of elevated sperm DNA fragmentation in male infertility: a global survey, current guidelines, and expert recommendations. World J Mens Health. 2023;41:809-847. [Crossref]

65. Baser A, Ozturk MI, Dogan M, Ekici M, Yaytokgil M, Baykam MM. Factors affecting TESE success in infertility treatment: preliminary results of single-center experience. Grand J Urol 2021;1:1-5. [Crossref]

ORIGINAL RESEARCH
Basic Science

Doi: 10.4274/jus.galenos.2025.2025-8-5
J Urol Surg 2026;13(3):155-159

Genitourinary Tuberculosis Diagnosis Using Urine GeneXpert: A Single-center Retrospective Study

Mohd. Hamid Shafique Ahmed, Swaroop Subbaraya, Vishnu Pratap, Ajit Sawant, Prakash Pawar, Amandeep Arora, Siddharth Nayak K, Vishwadip Bhalerao

Lokmanya Tilak Municipal Medical College and General Hospital, Department of Urology, Mumbai, India

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

Genitourinary tuberculosis (GUTB), a significant form of extrapulmonary tuberculosis accounting for 8-15% of cases, poses diagnostic challenges owing to nonspecific symptoms such as flank pain and sterile pyuria, which mimic other urological conditions and often delay treatment. Conventional diagnostics, such as acid-fast bacilli (AFB) staining and culture, suffer from low sensitivity (10-20% and 10-90%, respectively) and slow turnaround times, whereas radiological imaging (computed tomography, intravenous pyelogram, retrograde pyelography, GUTB, ultrasonography) lacks specificity. Although histopathology is definitive, it is also invasive. The GeneXpert *Mycobacterium tuberculosis*/rifampicin assay, established for rapid pulmonary tuberculosis diagnosis with up to 88% sensitivity in sputum, has poorly characterized performance in urine for GUTB diagnosis. A study conducted in a tertiary care setting in India provides a comprehensive analysis of GUTB's clinical spectrum, diagnostic approaches, and management, demonstrating that urine GeneXpert offers a sensitivity of 52-57%, comparable to AFB culture (47-52%), supporting its role as a rapid diagnostic tool. The study also highlights the high diagnostic yield of radiological imaging (82.5%), and its complementary role with GeneXpert, alongside a notable 59% nephrectomy rate, emphasizing the need for early diagnosis to prevent complications. We advocate for multicenter studies to optimize urine-based GeneXpert protocols and refine GUTB diagnostic criteria, aiming to enhance diagnostic protocols by evaluating the sensitivity of GeneXpert against traditional AFB culture methods.

Abstract

Objective: Genitourinary tuberculosis (GUTB), a prevalent form of extrapulmonary tuberculosis, is challenging to diagnose because of non-specific symptoms, and the low sensitivity of conventional diagnostic tests. The GeneXpert *Mycobacterium tuberculosis* (MTB)/rifampicin (RIF) assay offers rapid detection, however, its performance in urine for GUTB diagnosis has not been well characterized. The objective is to evaluate the clinical spectrum, diagnostic approaches, and management of GUTB and assess the sensitivity of urine GeneXpert compared to acid-fast bacilli (AFB) culture.

Materials and Methods: We conducted a retrospective analysis of 42 GUTB cases diagnosed using South Indian Consensus criteria at a tertiary care hospital in India (March 2013-March 2019). Diagnostics included urine AFB staining, GeneXpert MTB/RIF, and culture (Löwenstein-Jensen and mycobacterial growth indicator tube). The clinical features, radiological findings (computed tomography, intravenous pyelogram, retrograde pyelography, GUTB, magnetic resonance imaging), histopathology, and treatment outcomes were evaluated for each patient. The sensitivities of GeneXpert and culture were calculated with 95% confidence intervals (CIs) for all cases.

Results: Among 42 patients (male: female ratio 1.1), 38% were in their fourth decade of life. Flank pain was predominant (52%; 22/42), and 27% had a history of tuberculosis. Urine AFB was positive in 12% (5/42) of samples, GeneXpert was positive in 57% (24/42; 95% CI: 41-72%), and culture was positive in 52% (22/42; 95% CI: 37-68%). In histopathologically confirmed cases (n=19), GeneXpert sensitivity was 52.6% (10/19; 95% CI: 29-76%) and culture sensitivity was 47.4% (9/19; 95% CI: 24-71%). Radiology suggested GUTB in 82.5% (35/42) of the cases, with renal involvement being the most common finding. Nephrectomy was performed in 59% (25/42) of the patients, and no rifampicin resistance was detected.

Conclusion: The sensitivity of GeneXpert in urine samples (52-57%) is comparable to that of AFB culture, offering a rapid diagnosis of GUTB. The integration of clinical and radiological data enhances diagnostic accuracy. Multicenter studies are needed to optimize urine-based protocols.

Keywords: Genitourinary tuberculosis, GeneXpert, AFB culture, extrapulmonary tuberculosis

Correspondence: Vishnu Pratap MD, Lokmanya Tilak Municipal Medical College and General Hospital, Department of Urology, Mumbai, India
E-mail: vishnupratap1401@gmail.com **ORCID-ID:** orcid.org/0009-0001-1430-6735
Received: 09.08.2025 **Accepted:** 21.10.2025 **Epub:** 19.06.2026 **Publication Date:** 01.09.2026

Cite this article as: Ahmed MHS, Subbaraya S, Pratap V, Sawant A, Pawar P, Arora A, K SN, Bhalerao V. Genitourinary tuberculosis diagnosis using urine GeneXpert: a single-center retrospective study. J Urol Surg. 2026;13(3):155-159

Introduction

Genitourinary tuberculosis (GUTB) accounts for 8-15% of extrapulmonary tuberculosis cases globally, second only to lymph node involvement (1). Prevalent in high-burden regions, GUTB affects the kidneys, ureters, bladder, and genital organs, often leading to severe complications such as renal failure or ureteric strictures, if undiagnosed (2). Its non-spesific symptoms, such as flank pain, sterile pyuria, or hematuria, mimic urological disorders, delaying diagnosis (3). Conventional diagnostics, such as acid-fast bacilli (AFB) staining (sensitivity, 10-20%) and culture (sensitivity, 10-90%), are limited by their low sensitivity and long turnaround times (4,5). Radiological imaging techniques such as computed tomography (CT), intravenous pyelogram (IVP), retrograde pyelogram (RGP), and ultrasonography (USG) identify characteristic features such as calycectasis or putty kidney but lack specificity (6). Although histopathology is definitive, it is also invasive and resource-intensive.

The GeneXpert *Mycobacterium tuberculosis* (MTB)/rifampicin (RIF) assay, a real-time polymerase chain reaction (PCR) test, detects **Mycobacterium tuberculosis** and rifampicin resistance in <3 hours, with a sensitivity of up to 88% in sputum (7). However, its application in urine for GUTB is underexplored and potentially limited by intermittent mycobacterial shedding or urine inhibitors (8). Given the morbidity and diagnostic challenges of GUTB, the evaluation of rapid tools such as GeneXpert is critical.

Aims

To evaluate the clinical spectrum, diagnostic approaches, and management of GUTB and assess the sensitivity of urine GeneXpert compared to AFB culture.

Materials and Methods

This retrospective cohort study included 42 patients diagnosed with GUTB at a tertiary care hospital in India between March 2013 and March 2019. This study was approved by the Lokmanya Tilak Municipal Medical College and General Hospital Institutional Ethics Committee (approval number: IEC/2019/042, date: 08.06.2023). The requirement for informed consent was waived because of the retrospective nature of the study. Diagnosis adhered to the South Indian Consensus criteria (9) of requiring: one major criterion (granulomatous lesion on biopsy, an AFB in urine/tissue, or positive PCR) or two minor criteria [suggestive CT/IVP/RGP, hematuria, raised erythrocyte sedimentation rate (ESR), and prior tuberculosis history].

Data were extracted from medical records, including:

- Demographics included age and sex.
- Clinical features: Symptoms and history of tuberculosis.
- Laboratory: ESR (Westergren method).
- Urine analysis: Three early morning samples for AFB staining (Ziehl-Neelsen), GeneXpert MTB/RIF, and culture (Löwenstein-Jensen medium and mycobacterial growth indicator tube) (10).
- Imaging: CT, IVP, RGP for GUTB-specific findings (e.g., infundibular narrowing and moth-eaten ureters).
- Histopathology: Biopsy or surgical specimens of granulomatous lesions were obtained.

Patients received standard antitubercular therapy (ATT) as per the National Tuberculosis Elimination Program (11). Surgical interventions (e.g., nephrectomy and ureteric reimplantation) were also documented. Follow-up assessments were used to evaluate the treatment response and complications.

Statistical Analysis

Descriptive statistics (frequencies and percentages) were used to summarize clinical, radiological, and laboratory data. Analyses were performed using SPSS v25.0. The sensitivity of GeneXpert and AFB culture was calculated with 95% confidence intervals (CIs) using the Wilson score method for histopathologically confirmed cases of infection and all cases (clinical criteria).

Results

The cohort (22 males, 20 females; male-to-female ratio of 1.1) had a median age of 38 years (interquartile range 28-45), with 38% (16/42) in their fourth decade of life. Flank pain was the most common symptom (52%, 22/42), followed by lower urinary tract symptoms (28%, 12/42). Hematuria was rare (4.8%; 2/42). Prior tuberculosis or contact history was reported in 27% (11/42) of patients (Table 1).

Laboratory Findings

- Urine AFB staining: Positive in 12% (5/42; 95% CI: 5-25%).
- Urine GeneXpert: Positive in 57% (24/42; 95% CI: 41-72%).

Table 1. Clinical and laboratory characteristics (n=42)

Characteristic	n (%)
Flank pain	22 (52.4)
Lower urinary tract symptoms	12 (28.6)
Hematuria	2 (4.8)
Prior tuberculosis history	11 (26.2)
Sterile pyuria	20 (47.6)
Raised ESR (>20 mm/h)	20 (47.6)

ESR: Erythrocyte sedimentation rate

- Urine AFB culture: Positive in 52% (22/42; 95% CI: 37-68%).
- All AFB-positive cases (5/5) were GeneXpert-positive, showing a low mycobacterial load and no rifampicin resistance.
- ESR: Elevated (>20 mm/h) in 47.6% (20/42).

Imaging (e.g., CT/IVP/RGP/USG) suggested GUTB in 82.5% (35/42; 95% CI: 68-91%), and renal involvement was noted in 71% (30/42) (Figure 1). Common findings included infundibular narrowing (45%), pipe-stem ureters (33%), and putty kidneys (21%) (Table 2).

The diagnostic performance (sensitivity) of the urine GeneXpert MTB/RIF and the AFB culture was evaluated for GUTB diagnosis (Table 3). Among 42 patients meeting the clinical criteria (South Indian Consensus), GeneXpert detected 57.1% of cases (24/42; 95% CI: 41-72%), slightly outperforming the AFB culture, which identified 52.4% (22/42; 95% CI: 37-68%). In a subset of 19 histopathologically confirmed cases, GeneXpert's sensitivity was 52.6% (10/19; 95% CI: 29-76%), whereas it was 47.4% (9/19; 95% CI: 24-71%) for AFB culture. These findings, calculated using the Wilson score method in SPSS v25.0, indicate comparable sensitivities between the two tests, with overlapping CIs suggesting no significant differences.

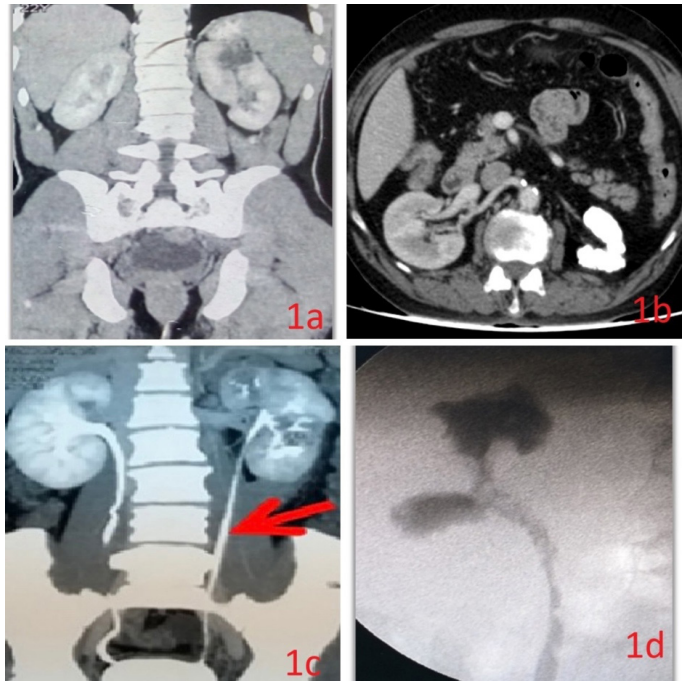


Figure 1. Imaging (CT/IVP/RGP) suggesting GUTB

1a. Left kidney showing Infundibular narrowing and calyectasis, **1b.** Putty kidney, complete calcification of left kidney, **1c.** Pipe stem ureter with dilated and irregular calyces with hiked up ureteric orifice, **1d.** Moth eaten appearance on RGP with multiple strictures in ureter

CT: Computed tomography, IVP: Intravenous pyelography, RGP: Retrograde pyelography, GUTB: Genitourinary tuberculosis

Table 2. Radiological features (CT/IVP/RGP/USG)

Radiological features (CT/IVP/RGP/USG)	Cases
Small contracted/thimble bladder	14
Non-functioning kidney	10
Pelvi ureteric junction narrowing	8
Pyelonephritis	5
Calyectasis	5
Infundibular stenosis	4
Urothelial thickening of pelvis and ureter	4
Vesico ureteric reflux	5
Ureteric stricture	2
Pipe stem ureter	2
Renal calcification/putty kidney	3
Adrenal calcification	2
Enlarged seminal vesicles	2

CT: Computed tomography, IVP: Intravenous pyelography, RGP: Retrograde pyelography, USG: Ultrasonography

Table 3. Diagnostic test performance

Test	Clinical criteria (n=42), sensitivity (95% CI)	Histopathologically (n=19), sensitivity (95% CI)
AFB staining	11.9% (5-25%)	15.8% (4-42%)
GeneXpert	57.1% (41-72%)	52.6% (29-76%)
AFB culture	52.4% (37-68%)	47.4% (24-71%)

CI: Confidence interval, AFB: Acid-fast bacilli

All patients received ATT. Nephrectomy was the most common surgery (59%; 25/42), followed by ureteric reimplantation (14%; 6/42). A novel spiral cap augmentation technique has been used in selected cases (12). Overlapping pathologies necessitated multiple procedures in 19% (8/42) of patients.

Discussion

This study elucidates the clinical, diagnostic, and management profiles of GUTB, emphasizing the role of urine GeneXpert MTB/RIF in a high-burden setting. The predominance of flank pain (52%) aligns with Krishnamoorthy et al. (6), while Kapoor et al. (13) reported lower urinary tract symptoms as primary, reflecting GUTB's variable presentation. The low hematuria rate (4.8%) challenges its utility as a minor diagnostic criterion (9), suggesting the need to refine the diagnostic frameworks. The predominance of young adults (38% in the fourth decade) and equal sex distribution (1.1 ratio) in this cohort mirrors the patterns in endemic regions (1).

The low sensitivity (12%) of AFB staining confirms its limited role, consistent with Caviedes et al. (4). AFB culture, the gold standard, achieved 52% sensitivity within the reported 10-90%

range (14); however, its 2-3-week turnaround delays treatment (4). The high yield (82.5%) of radiological imaging underscores its diagnostic value, particularly for AFB-negative cases with renal involvement (71%) and findings such as pipe-stem ureters, consistent with prior studies (6). However, the non-specificity of imaging necessitates microbiological confirmation (15).

The sensitivity of urine GeneXpert (57% clinical, 52.6% histopathological) rivaled that of culture, supporting its use as a rapid first-line test. Its performance is comparable to that of the 50-60% reported by Koul et al. (8) in urine, but is lower than that of sputum-based studies (88%) (7). This discrepancy likely stems from intermittent mycobacterial shedding or urine inhibitors, as noted by Theron et al. (16). In our study, GeneXpert samples were obtained routinely during initial evaluation of patients. All AFB-positive cases were GeneXpert-positive, suggesting high reliability for high-burden samples. The absence of rifampicin resistance aligns with the low resistance in extrapulmonary tuberculosis (17), enhancing the therapeutic guidance of GeneXpert. However, the small sample size might have an influence on this result.

GeneXpert's rapid results (<3 hours,) enable earlier ATT initiation, potentially reducing complications such as renal loss, with a nephrectomy rate of 59%. Its integration with radiology, which detected GUTB in 82.5% of cases, forms a robust diagnostic algorithm, especially in resource-limited settings where histopathology is impractical. The South Indian Consensus criteria (9) were effective, with 45% of cases being histopathologically confirmed, validating their clinical utility.

Our GeneXpert sensitivity was lower than that of lymph node aspirate studies (76-97%) (18), reflecting the GUTB-specific challenges. The variability of culture (10.7-90%) across studies highlights the dependence on sample quality and disease stage (14). The high surgical burden, particularly nephrectomy, is consistent with that reported by Gow and Barbosa (14), emphasizing the need for early diagnosis to prevent irreversible damage. The novel spiral cap technique (12) adds a unique management perspective that may be applicable to complex cases.

GeneXpert is performed at our tertiary care public hospital facility free of cost with rapid results. This adds to the feasibility of doing such tests at an early stage, which in turn helps in early diagnosis and treatment. This helps prevent disease progression and potential long-term complications.

Study Limitations

The strengths of this study include its comprehensive evaluation of clinical, radiological, and microbiological data and the use of standardized diagnostic criteria. However, the small sample size (n=42) and single-center design are limiting factors for our study. The small sample size (n=42) limits generalization of our results to a larger population. The retrospective nature of the study introduces potential selection bias, and the lack of a non-GUTB control group precludes a specific analysis. Variability in disease stage or organ involvement may influence sensitivity estimates, an aspect that has not yet been explored.

Multicenter studies with larger cohorts are essential to validate the performance of GeneXpert in urine samples and establish optimal sampling protocols. Our ongoing research investigates whether an increase in the number of urine samples (e.g., five vs. three) enhances the sensitivity. Comparative studies using advanced molecular assays (e.g., next-generation sequencing) could identify superior diagnostic methods. Cost-effectiveness analyses would inform the scalability of GeneXpert in low-resource settings. Integrating artificial intelligence with imaging and microbiological data may improve diagnostic precision and address the current limitations.

Conclusion

GUTB diagnosis requires a multifaceted approach that combines clinical suspicion, radiological evaluation, and microbiological confirmation. Urine GeneXpert (with 52-57% sensitivity comparable to AFB culture) offers rapid, actionable results, supporting its role as a first-line diagnostic tool. Early diagnosis with such tests can prevent potential complications occurring at a later stage of the disease, such as end-stage renal disease requiring nephrectomy. Its integration into clinical practice, along with imaging and standardized criteria, enhances diagnostic accuracy. Large-scale studies are needed to optimize urine-based protocols and reduce morbidity associated with GUTB in endemic regions.

Ethics

Ethics Committee Approval: This study was approved by the Lokmanya Tilak Municipal Medical College and General Hospital Institutional Ethics Committee (approval number: IEC/2019/042, date: 08.06.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.H.S.A., S.S., V.P., A.S., P.P., A.A., S.N.K., V.B., Concept: S.S., Design: V.P., Data Collection or Processing: S.N.K., V.B., Analysis or Interpretation: A.S., P.P., Literature Search: A.A., Writing: M.H.S.A.

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

Financial Disclosure: The authors declared that this study

received no financial support.

References

1. Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res. 2004;120:316-353. [Crossref]
2. Chattopadhyay A, Bhatnagar V, Agarwala S, Mitra DK. Genitourinary tuberculosis in pediatric surgical practice. J Pediatr Surg. 1997;32:1283-1286. [Crossref]
3. Figueiredo AA, Lucon AM. Urogenital tuberculosis: update and review of 8961 cases from the world literature. Rev Urol. 2008;10:207-217. [Crossref]
4. Caviedes L, Lee TS, Gilman RH, Sheen P, Spellman E, Lee EH, Berg DE, Montenegro-James S. Rapid, efficient detection and drug susceptibility testing of Mycobacterium tuberculosis in sputum by microscopic observation of broth cultures. The Tuberculosis Working Group in Peru. J Clin Microbiol. 2000;38:1203-1208. [Crossref]
5. Muneer A, Macrae B, Krishnamoorthy S, Zumla A. Urogenital tuberculosis - epidemiology, pathogenesis and clinical features. Nat Rev Urol. 2019;16:573-598. [Crossref]
6. Krishnamoorthy S, Palaniyandi V, Kumaresan N, Govindaraju S, Rajasekaran J, Murugappan I, Ramanan V, Krishnan MN. Aspects of evolving genito urinary tuberculosis-a profile of genito urinary tuberculosis (GUTB) in 110 patients. J Clin Diagn Res. 2017;11:PC01-PC05. [Crossref]
7. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R, Rustomjee R, Milovic A, Jones M, O'Brien SM, Persing DH, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C, Alland D, Perkins MD. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010;363:1005-1015. [Crossref]
8. Koul AN, Kassana BA, Rather AR. Utility of GeneXpert in the diagnosis, reliance on urine microscopy and clinical characteristics of genitourinary tuberculosis at a tertiary care hospital. Indian J Med Microbiol. 2018;36:93-96. [Crossref]
9. Venugopal PP, Pillai BS, Moorthy DK; Association of Southern Urologists. South Indian consensus on the diagnosis and management of genitourinary tuberculosis [Internet]. South Zone Urological Society of India; 2015. [Crossref]
10. Roddy K, Tobin EH, Leslie SW, Rathish B. Genitourinary tuberculosis. [Updated 2024 Aug 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. [Crossref]
11. Central TB Division. National Tuberculosis Elimination Programme [Internet]. New Delhi: Directorate General of Health Services, Ministry of Health and Family Welfare; [n.d.]. [Crossref]
12. Sawant SA, Tamhankar AS, Kumar V, Prakash WP, Gaurav VK, Bansal S. "Spiral-Cap" ileocystoplasty for bladder augmentation and ureteric reimplant. Urol Ann. 2016;8:464-467. [Crossref]
13. Kapoor R, Ansari MS, Mandhani A, Gulia A. Clinical presentation and diagnostic approach in cases of genitourinary tuberculosis. Indian J Urol. 2008;24:401-405. [Crossref]
14. Gow JG, Barbosa S. Genitourinary tuberculosis. A study of 1117 cases over a period of 34 years. Br J Urol. 1984;56:449-455. [Crossref]
15. Keric N, Kalasauskas D, Freyschlag CF, Gempt J, Misch M, Poplawski A, Lange N, Ayyad A, Thomé C, Vajkoczy P, Meyer B, Ringel F. Impact of postoperative radiotherapy on recurrence of primary intracranial atypical meningiomas. J Neurooncol. 2020;146:347-355. [Crossref]
16. Theron G, Peter J, Calligaro G, Meldau R, Hanrahan C, Khalfey H, Matinyenya B, Muchinga T, Smith L, Pandie S, Lenders L, Patel V, Mayosi BM, Dheda K. Determinants of PCR performance (Xpert MTB/RIF), including bacterial load and inhibition, for TB diagnosis using specimens from different body compartments. Sci Rep. 2014;4:5658. [Crossref]
17. Bulaj G, Zhang MM, Green BR, Fiedler B, Layer RT, Wei S, Nielsen JS, Low SJ, Klein BD, Wagstaff JD, Chicoine L, Harty TP, Terlau H, Yoshikami D, Olivera BM. Synthetic muO-conotoxin MrVIB blocks TTX-resistant sodium channel NaV1.8 and has a long-lasting analgesic activity. Biochemistry. 2006;45:7404-7414. [Crossref]
18. World Health Organization (WHO). Policy update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance [Internet]. Geneva: World Health Organization; 2013 [cited 2025 Jun 3]. [Crossref]

ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2025.2025-7-9
J Urol Surg 2026;13(3):160-166

Uroflowmetry Derived Index: A New Novel Metric in BPE Evaluation and Treatment Planning

Gautam Shubhankar[1], Pooja Nigade[2]

[1]Keshav Memorial Charitable Trust Medical College & Hospital, Clinic of Urology, Uttar Pradesh, India
[2]Keshav Memorial Charitable Trust Medical College & Hospital, Clinic of Physiology, Uttar Pradesh, India

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

Uroflowmetry and international prostate symptom score (IPSS) commonly used in benign prostatic enlargement (BPE) assessment. Diagnostic ambiguity often due to mismatch between symptom scores and flow rates. Urodynamic studies are considered the gold standard; however, they are invasive and less accessible. Guidelines recommend combining symptom scores with objective parameters for accurate evaluation. Isolated flow metrics insufficient for predicting treatment outcomes reliably. Introduction of the flow-derived bladder outlet efficiency (FDBOE) index as a novel, non-invasive parameter; integration of voiding efficiency and dynamic flow parameters into a single composite metric. Demonstration of strong inverse correlation between FDBOE and IPSS. Stratification of patients using FDBOE grading to predict treatment response and surgical need; provision of a simple, reproducible, and resource-friendly tool for clinical decision-making in BPE.

Abstract

Objective: Benign prostatic enlargement (BPE) causes lower urinary tract symptoms (LUTS) in ageing men. While conventional diagnostic tools like the international prostate symptom score (IPSS) and uroflowmetry are routinely used, they often yield equivocal findings. Urodynamic studies, though definitive, are invasive and less accessible. This study aimed to evaluate the clinical utility of a novel, non-invasive uroflowmetry-derived parameter—flow-derived bladder outlet efficiency (FDBOE)—in assessing symptom severity and predicting treatment outcomes in BPE.

Materials and Methods: A prospective observational study was conducted over four months involving 51 male patients aged >45 years presenting with LUTS due to BPE. After exclusion of confounding urological conditions, baseline IPSS and uroflowmetry assessments were performed. FDBOE was calculated using the formula: Voiding efficiency × Q_{avg} × (flow time/total voiding time). All patients were started on silodosin (8 mg daily) and reassessed after four weeks.

Results: FDBOE values ranged from 0.51 to 7.76 mL/sec, with a mean of 3.49±1.70 mL/sec. A strong inverse correlation between FDBOE and IPSS ($r=-0.832$, $p<0.001$) was observed. Sensitivity analysis using an FDBOE threshold of ≤3.3 mL/sec yielded a sensitivity of 92.6% for detecting severe LUTS. Post-treatment analysis revealed that 95% of grade I patients, 35% of grade II patients, and none of the grade III patients required surgical intervention.

Conclusion: FDBOE is a simple, reproducible, non-invasive parameter that correlates strongly with LUTS severity, and predicts treatment outcomes in BPE. It offers practical utility in clinical decision-making, especially in resource-limited settings.

Keywords: BPE, uroflowmetry, IPSS, voiding efficiency

Introduction

Benign prostatic enlargement (BPE) leads to lower urinary tract symptoms (LUTS) in nearly 50% of men over 50 years old (1). Workup in these patients begins with an international prostatic symptom score (IPSS) calculation. Uroflowmetry, a common non-invasive test, is routinely done as an extension of the clinical examination. All these tests aim to assess the severity of

Correspondence: Gautam Shubhankar MD, Keshav Memorial Charitable Trust Medical College & Hospital, Clinic of Urology, Uttar Pradesh, India
E-mail: shubhankar2006@gmail.com **ORCID-ID:** orcid.org/0000-0003-2397-1160
Received: 21.07.2025 **Accepted:** 24.10.2025 **Epub:** 11.06.2026 **Publication Date:** 01.09.2026

Cite this article as: Shubhankar G, Nigade P. Uroflowmetry derived index: a new novel metric in BPE evaluation and treatment planning. J Urol Surg. 2026;13(3):160-166

the disease at the time of diagnosis to start the treatment. They also warn patients about the future risk of worsening symptoms or the likelihood of failure of medical therapy.

However, many times, equivocal findings on uroflowmetry raise questions about the future progression of the disease. Also, sometimes the IPSSs do not correlate with uroflowmetry findings. Patients with high symptom scores may exhibit normal flow rates, and vice versa, complicating the diagnostic process (2). Many clinicians opt for a urodynamic study (UDS) in such cases to decide the further management plan. But unfortunately, urodynamic studies are not available everywhere, especially in remote areas where medical facilities are not very adequate. Furthermore, the invasive nature of the UDS reduces the number of patients opting for it. As such, there arises a need to obtain more concrete answers using non-invasive tests.

In light of the same, we conducted a prospective study to determine whether uroflowmetry values could be useful, especially in equivocal results, to assess the severity of the disease and predict the outcome of the medical management. Through this study, we attempted to derive a flow-derived index using routinely available uroflowmetry variables such as voiding efficiency (VE), average flow rate (Q_{avg}), flow time and total voiding time. The main idea behind the index derivation was to provide a more holistic representation of voiding dynamics to predict symptom severity and treatment response more accurately. To our knowledge, this is the first observational study to explore the utility of a flow-derived index as a predictive tool for symptom burden and medical treatment outcomes in men with BPE and LUTS. This is the first prospective observational study on such a topic.

Materials and Methods

It was a prospective observational study carried out over 4 months at our institute. Ethical approval was obtained from the KMC Medical College and Hospital Institutional Ethics Committee (approval number: IEC/KMC/2025/0487, date: 04.02.2025) was obtained before commencing the study. The study population included male patients with BPE, aged >45 years, who came to the outpatient department with LUTS. Patients with indwelling catheters, underlying urinary tract infections, gross haematuria, urethral stricture disease or neurogenic bladder were excluded from the study. Proper informed consent was taken from all the patients before enrolling them in the study.

The IPSSs of all the included patients were calculated. Following this, they all underwent uroflowmetry testing. Voided volume, post-void residual volume (PVR), VE, maximum flow rate (Q_{max}), average flow rate (Q_{avg}), flow time (time during which the urine flow occurred) and total voiding time (total time taken from the command to void to the end of flow) were all calculated and analysed. Ultrasound of kidneys, urinary bladder and prostate, urine routine examination, urine culture, complete blood count, kidney function test, and serum prostate-specific antigen were also done as a part of the routine workup for BPE.

Using the uroflowmetry parameters, a product of VE x Q_{avg} x flowtime/total voiding time was calculated for all the patients at the initial presentation. This product was labeled the flow-derived bladder outlet efficiency (FDBOE). Patients were then administered medical management with the same alpha blocker (tablet silodosin 8 mg), and 4 weeks later, they were reassessed with IPSS, voiding satisfaction, and Uroflowmetry. The FDBOE calculated on the initial presentation was correlated with the IPSS, voiding satisfaction, and uroflowmetry findings after 4 weeks of medical management. The results were analysed (Figure 1).

In the FDBOE calculation—VE × Q_{avg} × (flow time/total voiding time)—, each variable adheres to standard urodynamic units. VE is expressed as a fraction (not a percentage), derived from the ratio of voided volume to total bladder volume (voided volume + post-void residual); hence, it is unitless. Q_{avg}, or average flow rate, is measured in millilitres per second (mL/s), which is the conventional unit reported in uroflowmetry. Both flow time and total voiding time are recorded in seconds, rendering their ratio dimensionless. Therefore, the final FDBOE value retains the unit of mL/sec, effectively reflecting a modified flow efficiency metric. This unit consistency allows for meaningful comparisons across patients and over time, and ensures that the index can be seamlessly integrated into routine clinical uroflowmetry assessments.

Statistical Analysis

As this was the first such prospective study, a convenience sample of at least 30 patients was taken as the sample size. However,

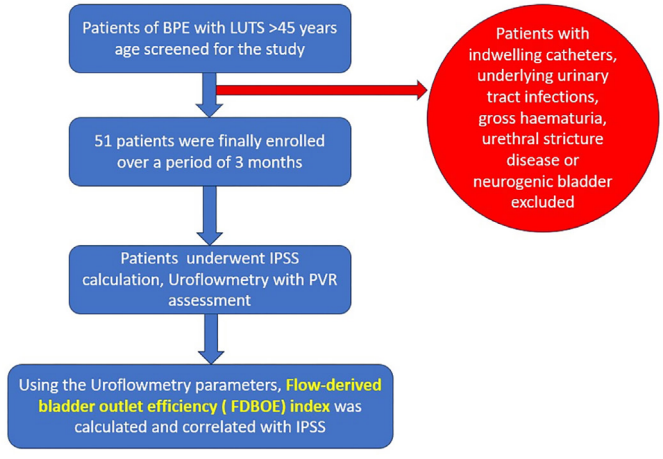


Figure 1. Showing study algorithm

IPSS: International prostate symptom score, LUTS: Lower urinary tract symptoms, PVR: Post-void residual volume

all the patients meeting the inclusion criteria within the study period were included. Statistical analysis was done using SPSS software version 28. Pearson's correlation coefficient was used to determine the correlation between the different parameters.

Results

In this prospective observational study, 51 male patients with BPE were enrolled. The mean age of the cohort was 62.3 years, with ages ranging from 48 to 78 years. Based on their baseline IPSS, 27 patients (52.9%) presented with severe LUTS (IPSS ≥20), while the remaining 24 patients (47.1%) were categorised as having moderate LUTS (IPSS 8-19). None of the patients presented with mild LUTS.

The calculated FDBOE index ranged from 0.51 to 7.76 mL/sec, with a mean value of 3.49±1.70 mL/sec across the cohort. This helped in understanding the data spread and natural clustering of patients. Patients with FDBOE values significantly below the mean consistently exhibited severe symptoms and poor voiding dynamics. In contrast, those with values significantly above the mean displayed milder symptoms and efficient bladder emptying. To formalize this, sensitivity analysis was performed using IPSS ≥20 as a marker for severe LUTS, leading to the identification of an optimized FDBOE threshold of ≤3.3 mL/sec, which correctly identified nearly 90% of severe cases. Thus, patients with FDBOE values, <2.9 mL/sec, slightly below the threshold to maintain higher specificity, were classified as grade I (low efficiency). The middle range, between 2.9 and 4.5 mL/sec, was defined as grade II (moderate efficiency), representing patients with mixed symptom profiles and intermediate voiding dynamics. Grade III (high efficiency) included those with FDBOE values >4.5 mL/sec, where patients consistently exhibited efficient bladder outlet function and lower symptom burden. This stratification logically transforms the continuous FDBOE data into clinically actionable categories, aligning statistical observations with meaningful clinical outcomes for practical application in patient management. Grade I (low efficiency) with FDBOE <2.9 mL/sec included 20 patients (39.2%); grade II (moderate efficiency) with FDBOE values between 2.9 and 4.5 mL/sec comprised 17 patients (33.3%); and grade III (high efficiency) with FDBOE >4.5 mL/sec encompassed 14 patients (27.5%).

Patients in grade I predominantly demonstrated severe LUTS, with 17 out of 20 patients (85%) in this group having IPSS ≥20. The mean IPSS in this subset was notably high at 21.8, accompanied by lower average flow rates and elevated PVR volumes. Particularly patients with FDBOE <1.5 mL/sec represented the most clinically significant subgroup, with uniformly severe symptoms and markedly impaired voiding parameters. This suggests that FDBOE values below this threshold may serve as a "red flag" indicator of significant bladder outlet inefficiency. Conversely, patients in grade III predominantly had moderate LUTS, with only one patient showing severe symptoms. Their mean IPSS was significantly lower at 14.3, reflecting milder symptomatology and efficient bladder emptying.

Correlation analysis underscored the clinical relevance of the FDBOE index. A strong inverse correlation was observed between FDBOE and IPSS ($r=-0.832$, $p<0.001$), indicating that higher FDBOE values were consistently associated with lower symptom scores. In contrast, conventional uroflowmetry parameters displayed weaker associations: the average flow rate (Q_{avg}) showed a moderate inverse correlation ($r=-0.664$, $p<0.001$), and PVR exhibited a moderate positive correlation ($r=+0.552$, $p<0.001$) with IPSS. This confirms that FDBOE, as a composite metric, reflects symptom burden more robustly than single uroflowmetry measures.

A sensitivity analysis further validated the clinical utility of the FDBOE index. Using FDBOE <2.9 mL/sec as a threshold for defining low outlet efficiency, the index correctly identified 23 of 27 patients with severe LUTS, yielding a sensitivity of 85.2%. Additionally, when focusing on patients with FDBOE <1.5 mL/sec, the index exhibited a perfect correlation with severe symptoms, albeit, in a smaller subset, suggesting that this stricter threshold may serve as a highly specific predictor of advanced bladder outlet obstruction (BOO). Using IPSS ≥20 as the reference standard for severe LUTS, the diagnostic performance of the FDBOE index was evaluated at two thresholds. At a cut-off of ≤3.3 mL/sec, FDBOE demonstrated excellent sensitivity (100%) and negative predictive value (100%), ensuring that no patients with severe LUTS were missed. However, specificity was modest at 62.9%, with a positive predictive value of 55.2% and an overall accuracy of 74.5%, reflecting a higher rate of false positives. In contrast, applying a stricter threshold of <2.9 mL/sec improved the balance of diagnostic metrics, yielding a sensitivity of 93.8%, specificity of 82.9%, positive predictive value of 71.4%, negative predictive value of 96.7%, and accuracy of 86.3%. These findings suggest that while the 3.3 mL/sec cut-off is optimal for ruling out severe LUTS, the 2.9 mL/sec threshold offers superior overall diagnostic performance and may be more clinically useful in stratifying patients.

After 4 weeks of follow-up, it was found that the clinical significance of FDBOE-based stratification was strongly reflected in treatment outcomes. In grade I, of the 20 patients, 19 (95%) ultimately required surgical intervention due to failure of medical therapy, underscoring the predictive value of low FDBOE scores in identifying patients with refractory BOO. In grade II, out of 17 patients, 6 (35%) required surgery after failing to respond adequately to alpha-blocker therapy, highlighting the variable treatment trajectory in this intermediate group. Notably, in grade III, which included 14 patients, none (0%)

progressed to surgical intervention, indicating that patients with high FDBOE values reliably benefited from conservative medical management. These outcome patterns validate the FDBOE grading as not only a reflection of baseline VE but also a predictive marker for clinical decision-making. Patients with lower FDBOE values are more likely to fail medical therapy and require early surgical referral, while those with higher efficiency scores can be confidently managed with pharmacotherapy alone. This reinforces the practical utility of the FDBOE index as a non-invasive, outcome-oriented tool in the management of BPE.

The results substantiate the FDBOE index as a superior, integrative uroflowmetry-derived parameter. Patients with FDBOE <2.9 mL/sec should be considered at risk for severe LUTS and suboptimal response to medical therapy alone, potentially benefiting from closer monitoring or earlier surgical consideration. Conversely, FDBOE >4.5 mL/sec appears predictive of good bladder outlet efficiency, milder symptom burden, and better responsiveness to pharmacotherapy.

The results suggest a strong inverse correlation between FDBOE and IPSS, supporting the use of FDBOE as a valuable, non-invasive predictor of symptom severity and treatment response in BPE. Unlike traditional uroflowmetry metrics, which may present ambiguous or conflicting information when considered in isolation, FDBOE integrates multiple functional dimensions into a single quantifiable value. This makes it a particularly useful tool in settings where urodynamic studies are unavailable or infeasible. Furthermore, it holds promise for identifying patients who may require closer follow-up or early surgical referral compared to those likely to benefit from conservative medical therapy alone.

It is important to clarify that this study was intentionally designed as a pilot prospective observational investigation, with the primary objective of introducing and preliminarily validating the FDBOE index as a novel, non-invasive metric derived from standard uroflowmetry variables. The sample size of 51 patients, though modest, was sufficient to demonstrate statistically significant correlations, most notably, a strong inverse relationship between FDBOE and IPSS. This provides early evidence of the index's potential clinical relevance. The absence of a control group reflects the fact that this was not an interventional or comparative study, but rather a hypothesis-generating analysis focused on correlating a new parameter with established clinical markers. Furthermore, the 4-week follow-up was deliberately chosen to assess the initial symptomatic response to alpha-blocker therapy, which is known to manifest early improvements in LUTS. While a longer follow-up period would be essential to establish the predictive durability of FDBOE, and a control group would strengthen the generalisability of results, this preliminary study was not intended to draw definitive conclusions but to lay the groundwork for larger, more robust prospective trials.

Discussion

BPE is a leading cause of LUTS in ageing males and can significantly impact quality of life. The standard evaluation of BPE includes symptom assessment using the IPSS and objective testing such as uroflowmetry. However, in many clinical scenarios, IPSS and uroflowmetry findings do not correlate well, leading to diagnostic ambiguity. In such cases, UDS are often recommended but are invasive, costly, and not always feasible in routine outpatient or rural settings (3). In response to this diagnostic gap, our study introduced the FDBOE index, a novel, non-invasive parameter derived from standard uroflowmetry components, aiming to offer a more integrated and clinically useful assessment of bladder outlet function.

The FDBOE index is calculated as VE × average flow rate (Q_{avg}) × flow time/total voiding time. This formula captures multiple aspects of voiding physiology, unlike traditional single-parameter measures. Q_{avg} was deliberately chosen for the FDBOE formula because it reflects the overall voiding dynamics across the entire flow period, whereas Q_{max} captures only a single peak moment that is highly variable, and effort-dependent. Given the objective of FDBOE to represent sustained outlet efficiency rather than transient flow peaks, Q_{avg} was considered the more reliable parameter for incorporation into the composite index. Our study found a strong inverse correlation between FDBOE and IPSS, with patients showing low FDBOE values (<2.5) having significantly higher IPSSs (severe LUTS); those with high FDBOE values (>4.5) exhibited mild symptoms. For example, such as patients 12 and 47 had the highest FDBOE values (7.4 and 7.76, respectively) and the lowest IPSSs, suggesting efficient bladder emptying. Conversely, patients with low FDBOE (e.g., patient 8 with a value of 0.81) presented with an IPSS of 24 and a PVR of 125 mL, indicating severe obstruction. This trend is consistent with earlier findings that support the value of combining VE and flow rates for better assessment of bladder outlet performance.

Existing guidelines and expert consensus underscore the limitations of traditional uroflowmetry parameters in reliably diagnosing BOO and predicting treatment outcomes. The European Association of Urology (EAU) Guidelines highlight that parameters such as Q_{max} and PVR often fail to capture the full spectrum of voiding dysfunction, especially in cases where symptom severity does not align with flow rates or prostate size. Similarly, Oelke et al. (4) recommend the use of more integrative assessment tools that combine symptom scores

with objective measures, recognizing that reliance on isolated flow metrics can lead to diagnostic uncertainty in benign prostatic obstruction. Furthermore, Abrams et al. (5) through the International Continence Society, have underscored the necessity for standardisation in lower urinary tract terminology, and evaluation metrics to ensure consistency and clinical relevance in practice. Homma et al. (6) and Park and Lee (7) further emphasise the need for objective, non-invasive metrics that correlate meaningfully with patient-reported symptoms, given the observed inconsistencies between symptom scores and conventional flow rates in LUTS evaluation. In this context, our study introduces the FDBOE index as a clinically practical, non-invasive alternative that integrates VE with dynamic flow parameters to overcome these diagnostic gaps. The strong inverse correlation observed between FDBOE and IPSS in our cohort directly addresses the disconnect highlighted in prior literature, offering a reproducible metric that not only reflects symptom burden more accurately but also predicts treatment response, thus aligning with the call for improved diagnostic tools in current guidelines.

Our data also show that FDBOE could be a practical tool for treatment planning and monitoring. Patients with higher baseline FDBOE values responded more favourably to medical therapy (silodosin 8 mg) over four weeks, as evidenced by improved IPSSs and subjective voiding satisfaction. These findings echo those of Gacci et al. (8) and Lepor et al. (9), who observed that improvements in flow parameters often translate into symptomatic relief when patients are treated with alpha-blockers. By providing a quantifiable and reproducible measure of outlet efficiency, FDBOE may assist clinicians in stratifying patients for medical versus surgical management, particularly when traditional uroflowmetry results are inconclusive or conflicting with clinical symptoms.

Furthermore, the FDBOE index is calculated using non-invasive, widely available data, making it an ideal tool for resource-limited settings where invasive diagnostics like UDS are impractical. Its ease of use, reproducibility, and strong correlation with IPSS make it highly suitable for widespread adoption in primary and secondary care. As supported by studies from Zwergel et al. (10), el Din et al. (11), and Roehrborn et al. (12), integrating flow parameters with symptom scores significantly improves diagnostic accuracy and patient outcomes. In conclusion, FDBOE represents a clinically valuable, non-invasive, and cost-effective addition to the BPE diagnostic toolkit. It offers improved interpretability of uroflowmetry results and may serve as a reliable predictor of treatment response, bridging the gap between subjective symptoms and objective findings in BPE evaluation.

Although this study positions FDBOE as a practical, non-invasive alternative to invasive UDS, it is important to recognize that UDS remains the gold standard for the assessment of BOO. For a novel index such as FDBOE to be considered a strong predictor or a potential surrogate for UDS, direct comparison with established urodynamic parameters is essential. Indices like the BOO index (BOOI) and bladder contractility index (BCI), derived from pressure-flow studies, provide objective insights into outlet resistance and detrusor contractility, which cannot be fully inferred from uroflowmetry alone. While the current study demonstrates a robust correlation between FDBOE and symptom burden, future research should include a subset of patients undergoing UDS to validate FDBOE against this gold standard metric. Such correlation would not only confirm the physiological accuracy of FDBOE in reflecting outlet function, but also significantly strengthen its clinical credibility as a reliable, non-invasive tool for diagnosis and treatment planning in a BPE.

The primary focus of this study was to introduce the FDBOE index as a novel, non-invasive parameter derived from routine uroflowmetry variables, and to assess its correlation with symptom severity in BPE. While the uniqueness of the index was highlighted, we acknowledge that a more comprehensive review of existing composite indices—such as the BOOI, BCI, and other urodynamic-based scoring systems—would provide greater scientific context. These existing indices, although informative, rely on invasive pressure-flow studies, which are not always feasible in routine outpatient or resource-limited settings. FDBOE, by contrast, offers a practical, non-invasive alternative that incorporates VE, flow rate, and time dynamics into a single metric. Furthermore, integrating the EAU 2024 Guidelines, which underscore the limitations of standard uroflowmetry and advocate for improved, accessible diagnostic tools, would strengthen the manuscript. A more detailed comparison with such guidelines and the current literature landscape will be incorporated in future iterations, to better delineate the position of FDBOE within established clinical frameworks. This will highlight the specific diagnostic gap it aims to address.

We acknowledge the concerns regarding the complexity of Table 1 and broader methodological limitations. The detailed presentation was intended to maintain transparency and allow for granular analysis of individual patient parameters in relation to the novel FDBOE index. However, we agree that summarising the data into clinically meaningful groupings—such as FDBOE grades with corresponding mean IPSS, Q_{avg}, and PVR—would enhance clarity and clinical relevance. As this was a pilot feasibility study, the modest sample size, short follow-up, and absence of a control group reflect the preliminary nature of the work rather than definitive conclusions.

Table 1. Showing uroflowmetry parameters and FDBOE index calculation

	IPSSs	Voided volume (mL)	PVR (mL)	Voiding efficiency [voided volume / (voided volume + PVR)]	Q_{avg} (mL/sec)	Flow time (sec)	Total voiding time (sec)	Flow-based bladder outlet efficiency index (voiding efficiency x Q_{avg} x flowtime/total voiding time)
1.	20/35	157	83	0.65	4.9	32	35	2.88
2.	14/35	247	25	0.90	8.1	27	33	5.83
3.	16/35	102	45	0.69	5.3	24	30	2.92
4.	15/35	82	21	0.79	4.0	21	24	2.84
5.	17/35	162	32	0.83	6.8	28	32	4.93
6.	22/35	45	54	0.45	3.6	13	15	1.45
7.	19/35	153	36	0.80	4.7	32	38	3.16
8.	24/35	110	125	0.46	2.1	44	54	0.81
9.	20/35	125	78	0.61	5.8	34	39	3.08
10.	16/35	152	86	0.63	6.1	31	40	3.17
11.	21/35	148	75	0.66	5.9	29	39	2.8
12.	12/35	223	25	0.90	9.2	18	20	7.4
13.	20/35	50	3	0.94	3.0	15	18	2.35
14.	14/35	78	15	0.83	2.5	31	31	2.07
15.	13/35	219	75	0.74	3.4	60	64	2.35
16.	14/35	103	35	0.74	4.3	19	24	2.51
17.	18/35	206	68	0.74	5.1	26	29	3.41
18.	23/35	145	95	0.60	4.2	22	26	2.13
19.	17/35	165	72	0.69	4.9	27	30	3.07
20.	16/35	193	59	0.79	4.3	24	28	2.93
21.	22/35	100	90	0.53	3.8	28	34	1.64
22.	18/35	175	55	0.761	5.2	30	35	3.39
23.	13/35	230	25	0.902	6.5	20	23	5.10
24.	15/35	198	52	0.792	5.6	25	28	3.96
25.	24/35	98	105	0.483	2.9	35	43	1.14
26.	20/35	142	65	0.686	4.7	32	36	2.87
27.	12/35	250	18	0.933	8.5	22	24	7.26
28.	16/35	190	48	0.798	5.9	30	33	4.28
29.	19/35	130	90	0.591	4.2	33	38	2.15
30.	14/35	210	35	0.857	6.7	28	31	5.20
31.	15/35	161	75	0.68	4.7	19	23	2.64
32.	13/35	216	45	0.79	6.1	24	26	4.48
33.	21/35	155	110	0.58	3.9	28	33	1.93
34.	22/35	80	65	0.55	2.8	20	60	0.51
35.	15/35	156	54	0.74	6.2	31	34	4.12
36.	18/35	126	68	0.64	5.8	29	31	3.47
37.	17/35	110	55	0.66	5.9	28	30	3.63
38.	16/35	130	53	0.71	6.1	33	35	4.08
39.	21/35	86	62	0.58	3.8	34	39	1.92
40.	20/35	78	45	0.63	3.9	32	35	2.2
41.	17/35	146	54	0.73	5.5	29	31	3.75
42.	14/35	210	45	0.82	8.9	24	25	6.03
43.	15/35	180	54	0.76	6.0	29	31	4.26
44.	18/35	179	82	0.68	5.1	33	36	3.17
45.	20/35	110	76	0.59	4.2	32	35	2.26
46.	16/35	156	67	0.69	5.8	30	33	3.63
47.	12/35	245	45	0.84	9.6	26	27	7.76
48.	19/35	156	75	0.67	5.0	28	30	3.14
49.	22/35	74	67	0.52	2.6	39	44	1.19
50.	13/35	218	46	0.82	6.2	23	25	4.67
51.	17/35	141	58	0.70	5.3	28	31	3.35

PVR: Post-void residual volume, IPSS: International prostate symptom score, FDBOE: Flow-derived bladder outlet efficiency

Study Limitations

The primary aim was to introduce and explore the utility of FDBOE, and despite the limitations, a strong inverse correlation with IPSS was observed, suggesting potential clinical value. While the current form may not fully meet the standards of high-level evidence, the originality of the approach, and the need for non-invasive, accessible diagnostic tools in BPE support the rationale for further research with larger, methodologically rigorous studies.

Conclusion

In conclusion, the FDBOE index demonstrates strong potential as a non-invasive, integrative marker for assessing bladder outlet function in patients with BPE. A clear inverse relationship was observed between FDBOE and IPSS, with lower FDBOE values correlating with more severe urinary symptoms. This index, combining multiple uroflowmetry parameters, provides a more comprehensive assessment than individual metrics alone. FDBOE may be especially useful in cases with inconclusive uroflowmetry results or where invasive urodynamic studies are impractical. Its clinical utility lies in aiding diagnosis, predicting treatment response, and guiding management decisions in men with LUTS.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the KMC Medical College and Hospital Institutional Ethics Committee (approval number: IEC/KMC/2025/0487, date: 04.02.2025).

Informed Consent: Patient consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.S., P.N., Concept: G.S., P.N., Design: G.S., P.N., Data Collection or Processing: G.S., P.N., Analysis or Interpretation: G.S., P.N., Literature Search: G.S., P.N., Writing: G.S., P.N.

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

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

References

1. Rosier PFWM, Schaefer W, Lose G, Goldman HB, Guralnick M, Eustice S, Dickinson T, Hashim H. International continence society good urodynamic practices and terms 2016: urodynamics, uroflowmetry, cystometry, and pressure-flow study. Neurourol Urodyn. 2017;36:1243-1260. [Crossref]
2. Eckhardt MD, van Venrooij GE, Boon TA. Symptoms, prostate volume, and uroflowmetry in the diagnosis of BPH: the role of ultrasound. Br J Urol. 2001;87:575-580. [Crossref]
3. Roehrborn CG. Benign prostatic hyperplasia: an overview. Rev Urol. 2005;7(Suppl 9):S3-S14. [Crossref]
4. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, N'dow J, Nordling J, de la Rosette JJ; European Association of Urology. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol. 2013;64:118-140. [Crossref]
5. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A; Standardisation Sub-committee of the International Continence Society. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21:167-178. [Crossref]
6. Homma Y, Gotoh M, Kawauchi A, Kojima Y, Masumori N, Nagai A, Saitoh T, Sakai H, Takahashi S, Ukimura O, Yamanishi T, Yokoyama O, Yoshida M, Maeda K. Clinical guidelines for male lower urinary tract symptoms and benign prostatic hyperplasia. Int J Urol. 2017;24:716-729. [Crossref]
7. Park YW, Lee JH. Correlation between the visual prostate symptom score and international prostate symptom score in patients with lower urinary tract symptoms. Int Neurourol J. 2014;18:37-41. [Crossref]
8. Gacci M, Ficarra V, Sebastianelli A, Corona G, Serni S, Shariat SF, Maggi M, Zattoni F, Carini M, Novara G. Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. J Sex Med. 2014;11:1554-1566. [Crossref]
9. Lepor H, Williford WO, Barry MJ, Brawer MK, Dixon CM, Gormley G, Haakenson C, Machi M, Narayan P, Padley RJ. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans affairs cooperative studies benign prostatic hyperplasia study group. N Engl J Med. 1996;335:533-539. [Crossref]
10. Zwergel U, Wullich B, Lindenmeir U, Rohde V, Zwergel T. Long-term results following transurethral resection of the prostate. Eur Urol. 1998;33:476-480. [Crossref]
11. el Din KE, Kiemeney LA, de Wildt MJ, Rosier PF, Debruyne FM, de la Rosette JJ. The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol. 1996;156:1020-1025. [Crossref]
12. Roehrborn CG, Siami P, Barkin J, Damião R, Major-Walker K, Nandy I, Morrill BB, Gagnier RP, Montorsi F; CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol. 2010;57:123-131. [Crossref]

ORIGINAL RESEARCH
Endourology

Doi: 10.4274/jus.galenos.2025.2025-10-1
J Urol Surg 2026;13(3):167-171

Prognostic Factors Affecting Recurrence After Internal Urethrotomy in Primary Short-segment Urethral Strictures

Mustafa Serdar Çağlayan[1], Cemil Aydın[1], Mustafa Kestel[2], Musa Ekici[1], Muhammet İhsan Öztürk[1], Metin Kızgın[1], Mehmet Murat Baykam[1]

[1]Hitit University Faculty of Medicine, Department of Urology, Çorum, Türkiye
[2]Hitit University Erol Olçok Training and Research Hospital, Department of Urology, Çorum, Türkiye

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

Internal urethrotomy (IU) is the most common first-line treatment for short-segment urethral strictures. Despite its simplicity and minimal invasiveness, IU has high recurrence rates reported in the literature. Various patient and stricture-related factors have been studied to predict recurrence after IU, but results remain inconsistent. Identifies advanced age, diabetes mellitus, coronary artery disease, and postoperative complications as independent risk factors for recurrence after IU. Provides evidence that stricture length, etiology, and location are not significant predictors of recurrence. Supports individualized management strategies and early surgical planning for high-risk patients.

Abstract

Objective: This study aimed to identify prognostic factors affecting recurrence after internal urethrotomy (IU) performed without adjuvant therapy in patients with urethral strictures shorter than 2 cm.

Materials and Methods: We retrospectively analyzed the records of 263 patients who underwent IU for the first time between January 2018 and June 2024. Patient characteristics, including age, comorbidities, stricture length, etiology, location, postoperative complications (hematuria, urinary tract infection), and catheterization duration were recorded. Recurrence was defined as the need for re-intervention within the first year. Statistical analyses were performed using chi-square, Fisher's exact, Student's t-test, Mann-Whitney U, and Kruskal-Wallis tests.

Results: The mean patient age was 68.2±18.9 years. Recurrence rates were 29.6% at 3 months and 64.2% at 1 year. Advanced age, diabetes mellitus (DM), coronary artery disease (CAD), and postoperative complications (hematuria, urinary tract infection) significantly increased the risk of recurrence (all $p<0.001$). No significant association was observed between recurrence and stricture length, etiology, location, or catheterization duration.

Conclusion: Advanced age, DM, CAD, and postoperative complications (hematuria, urinary tract infection) are independent risk factors for recurrence after IU. Evaluation of these parameters may aid in planning early surgical strategies for high-risk patients. This study was retrospectively conducted and was not registered in a clinical trial registry as it did not meet the criteria for prospective registration.

Keywords: Urethral stricture, internal urethrotomy, recurrence, risk factors, prognostic factors

Introduction

Urethral stricture is characterized by narrowing of the urethral lumen due to fibrosis affecting the urethral epithelium and the underlying corpus spongiosum (1). Patients typically present with obstructive voiding symptoms, recurrent urinary tract infections, or urinary retention (2). Urethral strictures are considered one of the most challenging problems in urology due to diagnostic complexity, treatment difficulties, recurrence tendency, and the need for long-term postoperative follow-up. In developed countries, the prevalence of urethral stricture has been reported to range between 0.6% and 1.2% (3). Iatrogenic,

Correspondence: Mustafa Serdar Çağlayan MD, Hitit University Faculty of Medicine, Department of Urology, Çorum, Türkiye
E-mail: serdar.09.09@hotmail.com **ORCID-ID:** orcid.org/0000-0002-5086-8671
Received: 11.10.2025 **Accepted:** 24.10.2025 **Epub:** 19.06.2026 **Publication Date:** 01.09.2026

Cite this article as: Çağlayan MS, Aydın C, Kestel M, Ekici M, Öztürk Mİ, Kızgın M, Baykam MM. Prognostic factors affecting recurrence after internal urethrotomy in primary short-segment urethral strictures. J Urol Surg. 2026;13(3):167-171

traumatic, inflammatory, and idiopathic causes are the most common etiological factors (2).

Diagnostic evaluation includes uroflowmetry, retrograde urethrography, and urethrocystoscopy (4). While a low Qmax value and plateau-shaped flow curve on uroflowmetry suggest the presence of a stricture, retrograde urethrography provides information about the location and length of the stricture. Cystoscopy, which can be easily performed in outpatient settings, allows for rapid confirmation of the diagnosis, immediate interventions such as dilatation, and precise determination of the distal location of the stricture (4).

Treatment of urethral stricture depends on the length, location, and etiology of the stenosis. The technique of visual internal urethrotomy (IU), first described by Sachse (5) in 1974, is currently the most commonly used first-line treatment option, especially for short (<2 cm), uncomplicated strictures in the bulbar and membranous urethra (6). However, long-term recurrence rates after IU have been reported to range from 35% to 70% (7), raising concerns regarding its long-term efficacy. Several adjuvant intralesional therapies such as Mitomycin-C, paclitaxel, triamcinolone, platelet-rich plasma (PRP), and erythropoietin have been investigated to reduce recurrence rates, but the results have been inconclusive (6).

In our study, only primary, uncomplicated strictures shorter than 2 cm were included, and therefore, more invasive surgical options such as urethroplasty were not planned. The literature suggests that IU is recommended as the initial treatment for short-segment strictures, whereas urethroplasty is reserved for recurrent or long-segment (>2 cm) strictures (6). For this reason, IU was preferred in patients without an indication for urethroplasty or in those refusing more invasive surgical approaches.

The aim of this study was to evaluate the factors affecting treatment success after IU performed without adjuvant therapy in patients with primary urethral strictures shorter than 2 cm.

Materials and Methods

This retrospective study was approved by the Institutional Review Board of Hitit University Clinical Research Ethics Committee (approval number: 2024/88; date: 15.10.2024) and conducted in accordance with the principles of the Declaration of Helsinki and informed consent was obtained from all participants.

The medical records of 263 patients aged 18-90 years who underwent IU for the first time between January 2018 and June 2024 due to urethral strictures of various etiologies (e.g., transurethral resection for bladder tumor or prostate, traffic accidents, ureterorenoscopy, radical prostatectomy, traumatic catheterization, idiopathic causes) were retrospectively analyzed.

Preoperative evaluation included uroflowmetry for all patients, and those with a stricture pattern, and Qmax ≤10 mL/sec underwent routine retrograde urethrography to assess stricture length and location (Figure 1). Intraoperatively, the location and length of the stricture were also recorded. Patients with a history of neurogenic bladder, recurrent strictures, or receipt of adjuvant therapies (e.g., Mitomycin-C, PRP, steroids) were excluded from the study.

All procedures were performed using Sachse's (5) technique, involving a single cold-knife incision at the 12 o'clock position, utilizing a 21F urethrotome. Following the incision, urethrocystoscopy was performed in all patients, and a 16-20F Foley catheter appropriate for the urethral diameter was inserted. In our series, the urethral catheter was routinely removed on the 3rd to 5th postoperative day in uncomplicated cases once local edema had subsided. A retrograde urethrogram was subsequently performed immediately after catheter removal to verify urethral patency and to rule out extravasation prior to resumption of spontaneous voiding.

Postoperatively, patients were followed up at 3-month intervals during the first year. Uroflowmetry and if necessary, retrograde urethrography (for Qmax <10 mL/sec) were performed at each visit (Figure 2). The need for repeated surgical intervention within the first year was defined as recurrence.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Differences between categorical variables were assessed using the chi-square test or Fisher's exact test where appropriate. For comparisons between two groups, Student's t-test was used for parametric continuous variables, and the Mann-Whitney U test was used for non-parametric

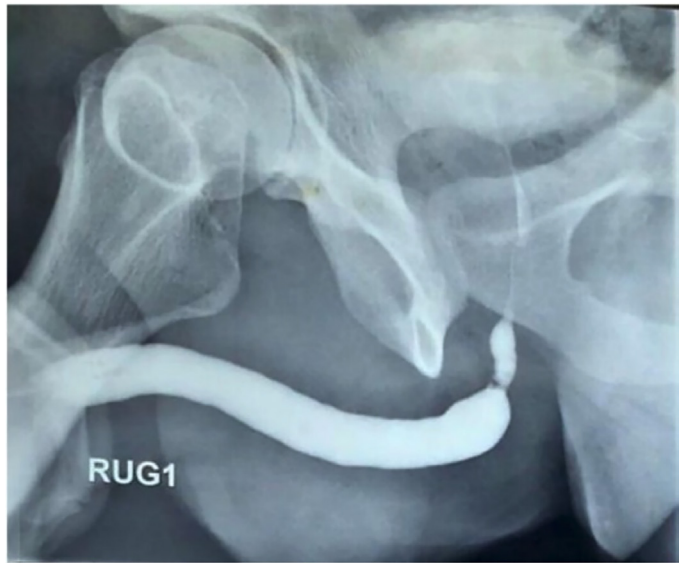


Figure 1. Preoperative retrograde urethrography

continuous variables. Comparisons among three or more groups were performed using the Kruskal-Wallis analysis of variance. A p-value <0.05 was considered statistically significant for all tests.

Results

A total of 263 patients were included in the study, with a mean age of 68.2±18.9 years (range: 20-91). Among them, 70 patients (26.6%) had diabetes mellitus (DM), 54 (20.5%) had hypertension, and 61 (23.1%) had coronary artery disease (CAD), while 46 patients (17.5%) had no comorbidities. The mean follow-up duration was 42.1±11.2 months (range: 5-63).

At the 3-month follow-up, recurrence was observed in 78 patients (29.6%), whereas 185 patients (70.4%) had no recurrence. By the end of the first year, the recurrence rate increased to 64.2% (n=169), with a mean time to recurrence of 6.9 months.

The mean stricture length was 1.4±0.43 cm (range: 0.5-2), and the majority of strictures (73%) were located in the bulbar urethra. Functional outcomes showed that the mean preoperative Qmax was 6.75±1.41 mL/sec, which improved to 14.3±4.96 mL/sec postoperatively. The mean catheterization duration was 4.94±1.26 days (range: 2-10). Postoperatively, hematuria occurred in 2 patients, and urinary tract infection occurred in 1 patient. The urinary tract infection was managed with antibiotic therapy and observation.

Risk factor analysis demonstrated that advanced age significantly increased the risk of recurrence (71.4±19.1 years in the recurrence group vs. 66.4±13.4 years in the non-recurrence group; p<0.001). The presence of DM and CAD also significantly elevated recurrence risk (both p<0.001). Patients with postoperative complications had a significantly higher risk of recurrence (p<0.001) and prolonged catheterization times (p=0.012). In contrast, no significant association was found between recurrence and stricture length, etiology, location, or catheterization duration (all p>0.05) (Table 1).

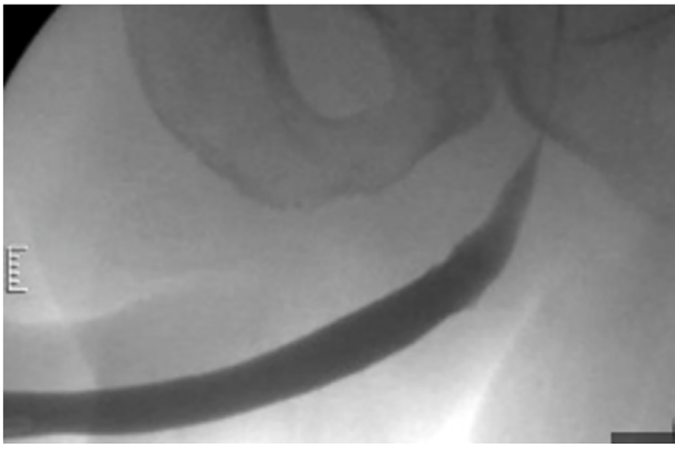


Figure 2. Postoperative retrograde urethrography

Discussion

Urethral stricture is a common and challenging condition encountered in daily urological practice (1). Its etiology includes transurethral interventions, trauma, catheterization, infections, and in some cases, idiopathic (2). The fact that the etiological distribution in our study aligns with the existing literature increases the generalizability of our findings.

Although the pathogenesis of urethral stricture has long been understood, there is still no consensus on the optimal treatment approach. IU, first described by Sachse (5) in 1974, is widely used as a first-line treatment for primary, isolated strictures shorter than 2 cm due to its simplicity, reliability, and minimally invasive nature. However, the high long-term recurrence rates reported in the literature, ranging from 35-70%, raise concerns regarding its long-term efficacy (7). Moreover, repeated IU procedures have been shown to decrease success rates and negatively impact the outcomes of subsequent reconstructive surgeries such as urethroplasty (8). Kessler et al. (8) also reported

Table 1. Factors associated with recurrence after internal urethrotomy

Variable	Recurrence (n)	No recurrence (n)	p-value
Age (years)	71.4±19.1	66.4±13.4	<0.001[a]
Diabetes mellitus			
Yes	24	46	<0.001[b]
No	54	139	
Coronary artery disease			
Yes	20	41	<0.001[b]
No	58	144	
Postoperative complications (hematuria, UTI)			
Yes	3	0	<0.001[b]
No	75	185	
Stricture length (cm)	1.6±0.27	1.3±0.12	0.125[a]
Stricture etiology			
Iatrogenic	56	136	0.198[b]
Trauma	15	37	
Idiopathic	7	12	
Stricture location			
Membranous	15	41	0.073[c]
Bulbar	57	133	
Penile	8	11	
Catheterization time (days) (mean)	5.89±1.62	4.59±1.71	0.249[a]

[a]: Mann-Whitney U test, [b]: Chi-square test, [c]: Kruskal-Wallis test, UTI: Urinary tract infection

significantly lower urethroplasty success rates in patients with two or more prior IU procedures. Therefore, identifying risk factors for recurrence is essential for optimizing clinical decision-making.

The relatively high success rate in our study may be attributed to the inclusion of only primary, short-segment strictures, the predominance of bulbar urethral strictures, and the definition of success as the absence of re-intervention. Nevertheless, prospective, multicenter studies with longer follow-up periods are required to validate these findings.

Our results demonstrated that advanced age, DM, CAD, and postoperative complications (hematuria, urinary tract infection, etc.) significantly increased the risk of recurrence after IU. Yahşi et al. (9) reported that urethral strictures in elderly patients are associated with vascular insufficiency and decreased tissue perfusion. Similarly, Mondal et al. (10) emphasized that low serum testosterone levels were associated with longer strictures and higher recurrence rates. Consistent with these findings, our data confirmed a significant association between increasing age and recurrence risk.

The negative impact of diabetes and aging on wound healing has been well established in previous studies (11,12). Additionally, components of the metabolic syndrome have been linked to adverse urologic outcomes and may influence stricture biology (13).

In line with this, our study also demonstrated a significantly higher recurrence risk among patients with DM. Likewise, CAD plays a key role not only in the development of urethral strictures but also in recurrence risk. Yildiz et al. (14) reported a positive correlation between CAD severity and urethral stricture formation while Meyer et al. (15) found that CAD significantly increased recurrence rates after urethroplasty. Our findings also support a significant association between CAD and recurrence after IU.

Regarding etiology, iatrogenic causes predominate in developed countries, whereas traumatic and infectious causes are more frequent in developing regions (16). Sawyer et al. (17) reported a limited impact of postoperative infections and hematomas on early recurrence, whereas in our study, all patients with postoperative complications experienced early recurrence, suggesting a stronger association in our cohort.

Although some studies have suggested that stricture length and catheterization duration may affect recurrence risk (18,19), we found no significant association between these variables and recurrence in our analysis.

Study Limitations

The main limitations of our study include its retrospective design, single-center setting, limited long-term follow-up data, and the fact that procedures were performed by different surgeons.

Future prospective, multicenter studies with standardized surgical techniques and longer follow-up periods are warranted to confirm our findings.

Conclusion

IU is a simple, minimally invasive procedure that is safely applied in selected patients; however, advanced age, DM, CAD, and postoperative complications significantly increase the recurrence risk. Identifying these risk factors may help in selecting high-risk patients who could benefit from early consideration of alternative surgical options such as urethroplasty.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Institutional Review Board of Hitit University Clinical Research Ethics Committee (approval number: 2024/88; date: 15.10.2024) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.S.Ç., C.A., M.K., M.E., M.İ.Ö., Me.K., M.M.B., Concept: M.S.Ç., C.A., M.K., M.E., M.İ.Ö., Me.K., M.M.B., Design: M.S.Ç., C.A., M.K., M.E., M.İ.Ö., Me.K., M.M.B., Data Collection or Processing: M.S.Ç., C.A., M.K., M.E., M.İ.Ö., Me.K., M.M.B., Analysis or Interpretation: M.S.Ç., C.A., M.K., M.E., M.İ.Ö., Me.K., M.M.B., Literature Search: M.S.Ç., C.A., M.K., M.E., M.İ.Ö., Me.K., M.M.B., Writing: M.S.Ç., C.A., M.K., M.E., M.İ.Ö., Me.K., M.M.B.

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

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

References

1. Pal DK, Kumar S, Ghosh B. Direct visual internal urethrotomy: is it a durable treatment option? Urol Ann. 2017;9:18-22. [Crossref]
2. Abdeen BM, Leslie SW, Badreldin AM. Urethral strictures. 2024 Oct 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. [Crossref]
3. Mershon JP, Baradaran N. Recurrent anterior urethral stricture: challenges and solutions. Res Rep Urol. 2021;13:237-249. [Crossref]
4. Hillary CJ, Osman NI, Chapple CR. Current trends in urethral stricture management. Asian J Urol. 2014;1:46-54. [Crossref]
5. Sachse H. Zur Behandlung der Harnröhrenstriktur: Die transurethrale Schlitzung unter Sicht mit scharfem Schnitt [Treatment of urethral stricture: transurethral slit in view using sharp section]. Fortschr Med. 1974;92:12-15. German. [Crossref]

6. Hughes M, Blakely S, Nikolavsky D. Advancements in transurethral management of urethral stricture disease. Curr Opin Urol. 2021;31:504-510. [Crossref]
7. Li X, Xu C, Ji X, Zhu Z, Cai T, Guo Z, Lin J. Balloon dilation for the treatment of male urethral strictures: a systematic review and meta-analysis. BMJ Open. 2024;14:e071923. [Crossref]
8. Kessler TM, Schreiter F, Kralidis G, Heitz M, Olianas R, Fisch M. Long-term results of surgery for urethral stricture: a statistical analysis. J Urol. 2003;170:840-844. [Crossref]
9. Yahşi S, Ceylan C, Öztürk O, Ceviz K. İdiopatik üretra darlığında nüksü öngörmede inflamatuar belirteçlerin klinik önemi. Fırat Tıp Dergisi. 2023;28:51-55. [Crossref]
10. Mondal S, Jana A, Sarkar D. Low serum testosterone as a poor prognostic marker in urethral stricture: a single-center prospective longitudinal study. Cureus. 2024;16:e58895. [Crossref]
11. Wilkinson HN, Hardman MJ. Wound healing: cellular mechanisms and pathological outcomes. Open Biol. 2020;10:200223. [Crossref]
12. Wilkinson HN, Clowes C, Banyard KL, Matteuci P, Mace KA, Hardman MJ. Elevated local senescence in diabetic wound healing is linked to pathological repair via CXCR2. J Invest Dermatol. 2019;139:1171-1181.e6. [Crossref]
13. Gorbachinsky I, Akpinar H, Assimos DG. Metabolic syndrome and urologic diseases. Rev Urol. 2010;12:e157-e180. [Crossref]
14. Yildiz I, Gokalp F, Burak C, Karazindiyanoglu S, Yildiz PO, Rencuzogullari I, Karabag Y, Cagdas M. Relationship between the severity of coronary artery disease and catheter-associated urethral stricture in patients with acute coronary syndrome. J Tehran Heart Cent. 2020;15:113-118. [Crossref]
15. Meyer CP, Lamp J, Vetterlein MW, Soave A, Engel O, Dahlem R, Fisch M, Kluth LA. Impact of cardiovascular and metabolic risk factors on stricture recurrence after anterior one-stage buccal mucosal graft urethroplasty. Urology. 2020;146:253-259. [Crossref]
16. Stein DM, Thum DJ, Barbagli G, Kulkarni S, Sansalone S, Pardeshi A, Gonzalez CM. A geographic analysis of male urethral stricture aetiology and location. BJU Int. 2013;112:830-834. [Crossref]
17. Sawyer KN, Cofield SS, Selph JP. Race as a predictor of recurrence and complications after urethroplasty in men with urethral stricture disease. Urology. 2022;163:69-75. [Crossref]
18. Yürük E, Yentur S, Çakır ÖO, Ertaş K, Şerefoğlu EC, Semercioöz A. Catheter dwell time and diameter affect the recurrence rates after internal urethrotomy. Turk J Urol. 2016;42:184-189. [Crossref]
19. Hernández-Hernández D, Ortega-González MY, Padilla-Fernández B, Díaz-González I, Climent-González J, Hess-Medler S. Direct vision internal urethrotomy in the management of bulbar urethral strictures: long-term follow-up and factors predicting treatment failure. Urol Int. 2025:1-6. [Crossref]

ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2025.2025-9-6
J Urol Surg 2026;13(3):172-177

TRK Expression in Urothelial Bladder Cancer: A Single-center Cohort Study

Emre Akar[1], Halil Fırat Baytekin[2], Öykü Dila Gemci[2], Selçuk Şahin[3], Serdar Altınay[2], Kanay Yararbaş[4], Deniz Tural[5]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Hematology, Tekirdağ, Türkiye
[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Pathology, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, İstanbul, Türkiye
[4]Demiroğlu Bilim University Faculty of Medicine, Department of Genetics, İstanbul, Türkiye
[5]Koç University Faculty of Medicine, Department of Medical Oncology, İstanbul, Türkiye

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

Neurotrophic receptor tyrosine kinase (NTRK) gene fusions represent rare but actionable alterations across solid tumors, with tropomyosin receptor kinase (TRK) inhibitors showing high efficacy in fusion-positive cases. However, the prevalence and clinical impact of TRK expression and NTRK fusions in bladder cancer are poorly defined, with existing reports providing inconsistent results. This study demonstrates that TRK expression is very uncommon and that NTRK fusions are absent in a cohort with metastatic urothelial carcinoma. These findings suggest limited relevance of TRK-targeted therapies in unselected bladder cancer populations, while underscoring the importance of systematic molecular profiling.

Abstract

Objective: Urothelial carcinoma is an aggressive malignancy with limited therapeutic options in the metastatic setting. Neurotrophic receptor tyrosine kinase (NTRK) gene fusions are actionable alterations in several solid tumors; however, their prevalence and clinical relevance in bladder cancer remain unclear.

Materials and Methods: A retrospective analysis was performed on cystectomy specimens from 60 patients with metastatic urothelial carcinoma who were treated between 2009 and 2021 at a single tertiary center. Tropomyosin receptor kinase (TRK) protein expression was evaluated by immunohistochemistry using a pan-TRK antibody. Positive cases were further analyzed for NTRK1/2/3 fusions using a real-time polymerase chain reaction assay detecting 109 known variants. Clinicopathological parameters and survival outcomes were reviewed.

Results: The cohort included 55 males (91.7%) and 5 females (8.3%), with a median age of 62 years. At cystectomy, all tumors were high-grade, with pathological stages ranging from pT1 to pT4a. Median overall survival was 49.5 months, and median survival after progression to metastatic disease was 19.5 months. Pan-TRK positivity was observed in 2 of 60 cases (3.3%). Molecular analyses of these samples revealed no NTRK fusions, indicating isolated TRK protein overexpression without gene rearrangements.

Conclusion: TRK expression was rare, and NTRK fusions were absent in this cohort with metastatic urothelial carcinoma. These results suggest that TRK-targeted therapies are unlikely to benefit unselected bladder cancer populations. Nonetheless, systematic molecular profiling remains essential for identifying patients with rare targetable alterations, while TRK signaling does not appear to represent a major oncogenic driver in urothelial carcinoma.

Keywords: Bladder cancer, urothelial carcinoma, tropomyosin receptor kinase, TRK

Correspondence: Emre Akar MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Hematology, Tekirdağ, Türkiye
E-mail: dr.emreakar@gmail.com **ORCID-ID:** orcid.org/0000-0002-9834-7488
Received: 18.09.2025 **Accepted:** 28.10.2025 **Epub:** 19.06.2026 **Publication Date:** 01.09.2026

Cite this article as: Akar E, Baytekin HF, Gemci ÖD, Şahin S, Altınay S, Yararbaş K, Tural D. TRK expression in urothelial bladder cancer: a single-center cohort study. J Urol Surg. 2026;13(3):172-177

Introduction

Urothelial carcinoma is the ninth most common cancer worldwide (1). Although only 5% of patients present with metastatic disease at diagnosis, approximately 40% of those initially diagnosed at an early stage eventually progress to metastatic disease during the course of their disease (2). Platinum-based chemotherapy remains the standard first-line treatment for stage IV bladder cancer, with a median overall survival (OS) of approximately 15 months (3). Among patients who experience disease progression after initial chemotherapy, the expected survival is markedly poor, ranging from 5 to 7 months (4). In recent years, the introduction of immune checkpoint inhibitors into routine clinical practice has expanded treatment options in both the first- and second-line settings for stage IV bladder cancer. Particularly among patients who achieve a response, these agents have been associated with durable remissions and prolonged survival (5). However, the objective response rates (ORRs) observed in clinical trials of immunotherapeutics have been relatively modest, ranging from 17% to 28% (6-9). Consequently, elucidating alternative molecular mechanisms in patients who do not respond to checkpoint inhibition or develop secondary resistance is essential for developing new therapeutic strategies (10). The tropomyosin receptor kinase (TRK) family (TRKA, TRKB, and TRKC) comprises neurotrophin receptors that play key roles in neural development, but they also function as oncogenic proteins implicated in carcinogenesis. Genetic alterations, most notably neurotrophic receptor tyrosine kinase (NTRK) gene fusions, lead to ligand-independent activation of TRK receptors, thereby promoting cellular proliferation and survival (11). Clinical trials investigating TRK-targeted tyrosine kinase inhibitors, such as larotrectinib and entrectinib, have demonstrated striking response rates (ORR approximately 75%) in tumors harboring NTRK fusions (12). The prevalence and biological relevance of NTRK fusions and TRK expression in bladder cancer remain poorly characterized. In one study evaluating TRK expression in bladder cancer, TRKB positivity was observed at relatively high frequencies, ranging from 46.7% to 76.9% (13). Another study of upper tract urothelial carcinoma reported TRKC expression in 54.2% of cases (14). In light of these data, the present study aimed to investigate TRK expression and NTRK gene fusions in cystectomy specimens from patients with metastatic (stage IV) bladder cancer.

Materials and Methods

Patients

This study used archived cystectomy specimens from patients diagnosed with metastatic bladder cancer who were followed at the Medical Oncology Department of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital between January 1, 2009, and January 1, 2021. Demographic and clinical data were obtained by reviewing patient files and digital medical records.

Immunohistochemistry and Pathological Evaluation

Archived formalin-fixed paraffin-embedded (FFPE) tumor tissues and slides from cystectomy specimens were re-evaluated to confirm the diagnosis, the pathological T-stage, and the histological grade. All histopathological and immunohistochemical evaluations were performed independently by two pathologists blinded to clinical data. For each patient, the paraffin block that best represented the morphological characteristics of the tumor and had the highest T-stage was selected. 4-µm-thick sections were cut, mounted on lysine-coated slides, and processed for immunohistochemistry (Figure 1). All immunohistochemical procedures were performed using the fully automated Ventana Benchmark XT system (Ventana Medical Systems, Tucson, AZ, USA). Following standard deparaffinization, rehydration, and antigen retrieval (CCV1 antigen retrieval solution, 64 minutes at 100 °C), sections were incubated for 1 hour at 37 °C with a recombinant immunoglobulin G anti-pan-TRK antibody (ab181560, clone EPR17341, Abcam, Cambridge, MA, USA) at a 1:500 dilution. Detection was performed using the OptiView DAB Immunohistochemistry Detection Kit (Roche Diagnostics/Ventana Medical Systems, Tucson, AZ, USA) for 10 minutes, followed by amplification with the OptiView Amplification Kit (Roche Diagnostics/Ventana Medical Systems, Tucson, AZ, USA) for 30 minutes. Slides were then counterstained with hematoxylin, dehydrated through graded alcohols and xylene, and mounted for microscopic evaluation. The immunohistochemical staining results were independently assessed by two pathologists blinded to clinical data. An external positive control was established using cerebellar tissue, whereas an internal positive control was verified using ganglion cells.

NTRK Fusion Analysis

The presence of NTRK gene fusions in tumor tissue was assessed using the AmoyDx® NTRK Gene Fusions Detection Kit (Amoy Diagnostics Co., Ltd., Xiamen, China). Analyses were performed on total RNA isolated from FFPE tumor samples, using kits optimized for FFPE material, in accordance with the manufacturer's instructions. Extracted RNA was reverse transcribed into cDNA during the kit's reverse transcription step. Real-time polymerase chain reaction amplification was subsequently carried out using specific primers and fluorescent probes targeting 109 known fusion variants of NTRK1, NTRK2, and NTRK3. Reactions were performed in a 40 µL volume under the manufacturer's recommended conditions (initial denaturation at 95 °C followed by 47 three-step cycles).

Each run included manufacturer-supplied positive controls and no-template controls. Amplification curves were analyzed using fusion-specific signal and reference gene signal fluorescence channels. Samples with Ct ≤25 were considered positive for the corresponding NTRK fusion, whereas samples with Ct >25 were classified as negative or below the limit of detection. RNA quality was verified through amplification of the internal control gene provided in the kit.

Ethical Approval and Funding

The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2019-18, date: 16.09.2019). The budget for the study was covered by the institution's budget in accordance with the approval decisions of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (meeting no: 13, decision number: 5, meeting date: 20.11.2019, and meeting no: 10, decision number: 6, date: 12.11.2020).

Statistical Analysis

Descriptive statistics and frequency analyses were performed. Survival analyses, including OS and progression-free survival (PFS), were conducted using the Kaplan-Meier method. Statistical analyses were performed using SPSS version 23.0 (IBM Inc.). Two-sided p-values <0.05 were considered statistically significant.

Results

A total of 60 patients were included in the study, comprising 55 men (91.7%) and 5 women (8.3%). The median age at diagnosis was 62 years (range: 35-81). Based on the initial transurethral resection (TUR), the pathological stage was pTa in 8 patients (13.3%), pT1 in 23 patients (38.3%), pT2a in 18 patients (30%), and pT2b in 11 patients (18.3%). At diagnosis, 14 patients (23.3%) had low-grade tumors, whereas 46 (76.7%) had high-grade disease. Cystectomy was performed for different clinical indications. These included palliative or salvage surgery (7 patients, 11.7%), invasive disease detected at diagnostic TUR (28 patients, 46.7%), radiologically identified invasive tumors, ≥pT2 (5 patients, 8.3%), and progression to invasive disease during TUR follow-up (20 patients, 33.3%). Pathological evaluation of cystectomy specimens revealed pT1 in 4 patients (6.7%), pT2a in 3 patients (5%), pT2b in 7 patients (11.7%), pT3a in 10 patients (16.7%), pT3b in 9 patients (15%), and pT4a in 27 patients (45%). All cystectomy specimens demonstrated high-grade tumors. Sites of recurrence or metastasis included pelvic masses in 9 patients (15%), lymph node metastases in 7 patients (11.7%), bone metastases in 21 patients (35%), lung metastases in 24 patients (40%), liver metastases in 15 patients (25%), and intracranial lesions in 3 patients (5%). Clinical and pathological characteristics of the patients are summarized in Table 1. The median OS for the entire cohort was 49.5 months. In patients who underwent cystectomy for reasons other than primary metastatic disease (excluding those who underwent palliative or salvage surgery), the median PFS was 19 months (range: 1-81 months). After progression to metastatic disease, the median OS was 19.5 months. Immunohistochemical evaluation with the anti-pan-TRK antibody revealed no staining in 58 patients (96.7%), while positive staining was observed in 2 patients (3.3%) (Figures 1c and d). Both positively stained specimens exhibited a cytoplasmic staining pattern; one showed approximately 1% positivity, while the other showed 5% positivity. Non-neoplastic urothelium, T and B lymphocytes, stroma, and muscle tissue were negative for TRK expression. Subsequent NTRK fusion analysis of tumor samples from the two patients with immunohistochemically positive TRK expression did not reveal any NTRK fusions. Therefore, these cases were considered to have TRK protein overexpression without NTRK gene fusions.

Discussion

In advanced or metastatic bladder cancer, treatment options are limited for patients who progress after cisplatin-based chemotherapy or immune checkpoint inhibitor therapy. Given the aggressive nature of the disease and its dismal prognosis, molecular profiling and personalized therapeutic approaches are becoming increasingly important (15). TRK proteins, encoded by the NTRK genes, are receptor tyrosine kinases that acquire oncogenic potential through genetic alterations, most notably gene fusions. These alterations activate intracellular signaling pathways such as the mitogen-activated protein kinase and protein kinase B pathways, thereby promoting cellular proliferation and carcinogenesis (11). Clinical trials investigating anti-TRK tyrosine kinase inhibitors (particularly larotrectinib and entrectinib) in solid tumors harboring NTRK fusions have demonstrated remarkable ORRs and durable survival benefits (16,17). NTRK fusions are relatively rare in adult tumors, with an overall prevalence of approximately 0.31% (18). In a large-scale study conducted at Memorial Sloan Kettering Cancer Center (MSKCC), NTRK fusions were detected in 87 of 33,997 patients. The highest frequencies were observed in salivary gland carcinoma (5.08%), thyroid carcinoma (2.28%), sarcomas (0.68%), colorectal cancer (0.31%), lung adenocarcinoma (0.23%), pancreatic adenocarcinoma (0.34%), cholangiocarcinoma (0.25%), breast cancer (0.13%), and melanoma (0.36%) (19). In contrast, urothelial bladder cancer has not been reported to be NTRK fusion-positive in most molecular studies. However, these studies often lack detailed information regarding the

Table 1. Clinical and pathological characteristics of the patients		
Variable	**n**	**%**
Sex		
Male	55	91.7
Female	5	8.3
Age		
<65	36	60.0
≥65	24	40.0
Pathological T-stage at diagnosis (TUR)		
pTa	8	13.3
pT1	23	38.3
pT2a	18	30.0
pT2b	11	18.3
Grade at diagnosis		
Low grade	14	23.3
High grade	46	76.7
Indication for cystectomy		
Palliative/salvage	7	11.7
Invasive tumor at TUR	28	46.7
Invasive tumor on imaging	5	8.3
Progression during follow-up	20	33.3
Pathological T-stage at cystectomy		
pT1	4	6.7
pT2a	3	5.0
pT2b	7	11.7
pT3a	10	16.7
pT3b	9	15.0
pT4a	27	45.0
Pathological grade at cystectomy		
High grade	60	100
Nodal stage at cystectomy		
N0	41	68.3
N1	6	10.0
N2	12	20.0
N3	1	1.7
Sites of recurrence/metastasis		
Pelvic mass	9	15.0
Distant lymph node	7	11.7
Bone	21	35.0
Lung	24	40.0
Liver	15	25.0
Intracranial	3	5.0
TUR: Transurethral resection		

proportion of bladder cancer cases included in their cohorts (19,20). Consequently, the prevalence of TRK expression and NTRK fusions in bladder cancer remains poorly defined. In the only available report, Lai et al. (13) demonstrated immunohistochemical positivity for TRKB in commercially obtained bladder cancer specimens, with positivity rates of 76.9%, 46.7%, and 63.6% in grades I, II, and III, respectively. However, these findings were inconsistent with the broader literature, and the authors themselves suggested potential artifacts related to tissue preparation or antibody cross-reactivity. Similarly, Lim et al. (14) reported TRKC expression in 54.2% of upper tract urothelial carcinoma cases, although fusion analysis was not performed to validate these results. In our study, TRK expression was detected immunohistochemically in 3.3% of cases (2/60), but no NTRK fusions were identified by molecular analysis. These findings are consistent with the results of large-scale molecular studies, further supporting the rarity of NTRK fusions in bladder cancer. For detecting NTRK fusions, next-generation sequencing (NGS) platforms that analyze DNA or RNA are generally recommended as the gold standard. Nevertheless, due to the high cost and time required for molecular testing, pan-TRK immunohistochemistry has been suggested as a practical screening tool in patients with advanced cancer (21). Several studies have evaluated the sensitivity and specificity of pan-TRK immunohistochemistry. Hechtman et al. (22) reported immunohistochemical positivity in 20 of 21 NTRK fusion-positive cases. Rudzinski et al. (23) demonstrated a sensitivity of 97% and a specificity of 98% for pan-TRK staining in pediatric mesenchymal tumors. In the MSKCC series, the sensitivity of immunohistochemistry was 96.2% for NTRK1/2 fusions but only 79.4% for NTRK3 fusions, while specificity across all tumor types was 81.1%. Specificity was particularly high (100%) in cancers not typically associated with TRK expression, such as colorectal cancer, lung cancer, pancreatobiliary tumors, and melanoma. Conversely, in tumors of neuronal origin, such as gliomas and neuroblastomas, strong background staining in normal tissue occasionally resulted in false-positive interpretations (19).

Study Limitations

Thus, pan-TRK immunohistochemistry may serve as a useful screening method, with positive cases requiring confirmatory molecular testing by NGS to verify the presence of NTRK fusions (24). Our study demonstrated that TRK expression is exceedingly rare in urothelial bladder cancer, in line with findings from other common tumor types. Limitations of our study include the relatively small sample size, retrospective design, and reliance on archived pathology specimens.

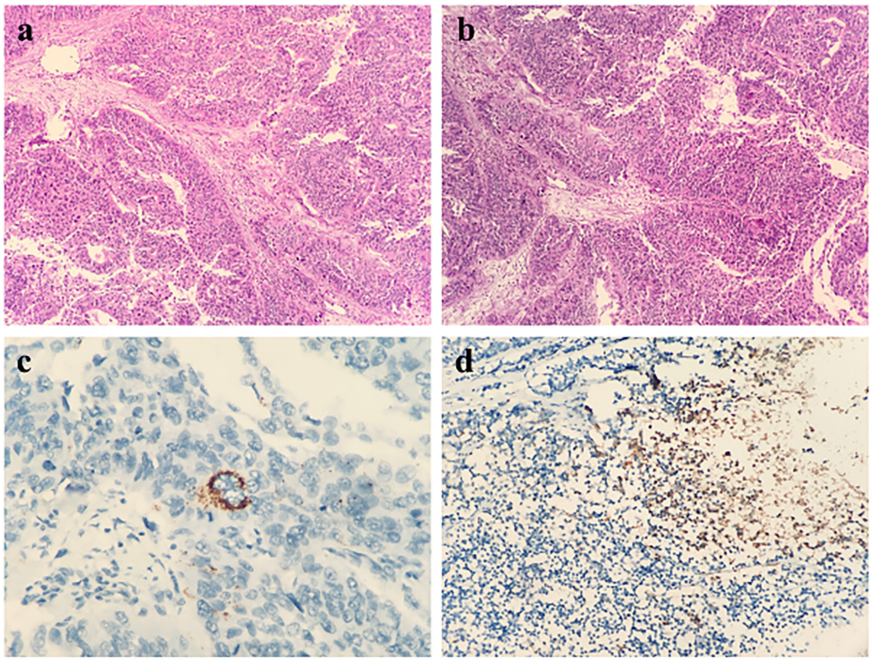


Figure 1. a, b: Representative cystectomy specimen and hematoxylin and eosin staining, **c, d:** Immunohistochemical staining with anti-pan tropomyosin receptor kinase antibody (c: negative and d: positive cases)

Conclusion

These findings suggest that TRK-targeted therapies are unlikely to represent a meaningful treatment strategy in unselected bladder cancer populations. Nevertheless, systematic evaluation of TRK expression and NTRK fusions remains warranted, as identifying patients harboring these rare alterations could enable the use of highly effective targeted therapies. Moreover, the negative findings in this study contribute to refining precision oncology approaches by ruling out TRK signaling as a major oncogenic driver in bladder cancer.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2019-18, date: 16.09.2019).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

Financial Disclosure: The budget for the study was covered by the institution's budget in accordance with the approval decisions of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (meeting no: 13, decision number: 5, meeting date: 20.11.2019, and meeting no: 10, decision number: 6, date: 12.11.2020).

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424. [Crossref]
2. SEER*Explorer: an interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Last access date: 23.04.2021]. [Crossref]
3. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A, Arning M. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005;23:4602-4608. [Crossref]
4. Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, Caty A, Carles J, Jagiello-Gruszfeld A, Karyakin O, Delgado FM, Hurteloup P, Winquist E, Morsli N, Salhi Y, Culine S, von der Maase H. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009;27:4454-4461. Erratum in: J Clin Oncol. 2010;28:182. Winquist, Eric [added]. [Crossref]
5. Fradet Y, Bellmunt J, Vaughn DJ, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Nam K, Frenkl TL, Perini RF, de Wit R, Bajorin DF. Randomized

phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. Ann Oncol. 2019;30:970-976. [Crossref]

6. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, Loriot Y, Necchi A, Hoffman-Censits J, Perez-Gracia JL, Dawson NA, van der Heijden MS, Dreicer R, Srinivas S, Retz MM, Joseph RW, Drakaki A, Vaishampayan UN, Sridhar SS, Quinn DI, Durán I, Shaffer DR, Eigl BJ, Grivas PD, Yu EY, Li S, Kadel EE 3rd, Boyd Z, Bourgon R, Hegde PS, Mariathasan S, Thåström A, Abidoye OO, Fine GD, Bajorin DF; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389:67-76. Erratum in: Lancet. 2017;390:848. [Crossref]
7. Patel MR, Ellerton J, Infante JR, Agrawal M, Gordon M, Aljumaily R, Britten CD, Dirix L, Lee KW, Taylor M, Schöffski P, Wang D, Ravaud A, Gelb AB, Xiong J, Rosen G, Gulley JL, Apolo AB. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN solid tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol. 2018;19:51-64. Erratum in: Lancet Oncol. 2018;19:e335. [Crossref]
8. Sharma P, Siefker-Radtke A, de Braud F, Basso U, Calvo E, Bono P, Morse MA, Ascierto PA, Lopez-Martin J, Brossart P, Rohrberg K, Mellado B, Fischer BS, Meadows-Shropshire S, Abdel Saci, Callahan MK, Rosenberg J. Nivolumab alone and with ipilimumab in previously treated metastatic urothelial carcinoma: checkmate 032 nivolumab 1 mg/kg plus ipilimumab 3 mg/kg expansion cohort results. J Clin Oncol. 2019;37:1608-1616. Erratum in: J Clin Oncol. 2019;37:2094. [Crossref]
9. Tural D, Ölmez ÖF, Sümbül AT, Artaç M, Özhan N, Akar E, Çakar B, Köstek O, Ekenel M, Erman M, Coşkun HŞ, Selçukbiricik F, Keskin Ö, Türköz FP, Oruç K, Bayram S, Yılmaz U, Bilgetekin İ, Yıldız B, Şendur MAN, Paksoy N, Dirican A, Erdem D, Selam M, Tanrıverdi Ö, Paydaş S, Urakçı Z, Atağ E, Güncan S, Ürün Y, Alkan A, Kaya AO, Özyükseler DT, Taşkaynatan H, Yıldırım M, Sönmez M, Başoğlu T, Gündüz Ş, Kılıçkap S. Atezolizumab in patients with metastatic urothelial carcinoma who have progressed after first-line chemotherapy: results of real-life experiences. Eur Urol Focus. 2021;7:1061-1066. [Crossref]
10. Wang Z, Wu X. Study and analysis of antitumor resistance mechanism of PD1/PD-L1 immune checkpoint blocker. Cancer Med. 2020;9:8086-8121. [Crossref]
11. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018;15:731-747. [Crossref]
12. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, Nathenson M, Doebele RC, Farago AF, Pappo AS, Turpin B, Dowlati A, Brose MS, Mascarenhas L, Federman N, Berlin J, El-Deiry WS, Baik C, Deeken J, Boni V, Nagasubramanian R, Taylor M, Rudzinski ER, Meric-Bernstam F, Sohal DPS, Ma PC, Raez LE, Hechtman JF, Benayed R, Ladanyi M, Tuch BB, Ebata K, Cruickshank S, Ku NC, Cox MC, Hawkins DS, Hong DS, Hyman DM. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378:731-739. [Crossref]
13. Lai PC, Chiu TH, Huang YT. Overexpression of BDNF and TrkB in human bladder cancer specimens. Oncol Rep. 2010;24:1265-1270. [Crossref]
14. Lim LM, Lee YC, Lin TW, Hong ZX, Hsu WC, Ke HL, Hwang DY, Chung WY, Li WM, Lin HH, Kuo HT, Huang AM. NTRK3 exhibits a pro-oncogenic function in upper tract urothelial carcinomas. Kaohsiung J Med Sci. 2024;40:445-455. [Crossref]
15. Guercio BJ, Iyer G, Rosenberg JE. Developing precision medicine for bladder cancer. Hematol Oncol Clin North Am. 2021;35:633-653. [Crossref]
16. Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM, Rohrberg KS, van Tilburg CM, Nagasubramanian R, Berlin JD, Federman N, Mascarenhas L, Geoerger B, Dowlati A, Pappo AS, Bielack S, Doz F, McDermott R, Patel JD, Schilder RJ, Tahara M, Pfister SM, Witt O, Ladanyi M, Rudzinski ER, Nanda S, Childs BH, Laetsch TW, Hyman DM, Drilon A. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 2020;21:531-540. [Crossref]
17. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, Blakely CM, Seto T, Cho BC, Tosi D, Besse B, Chawla SP, Bazhenova L, Krauss JC, Chae YK, Barve M, Garrido-Laguna I, Liu SV, Conkling P, John T, Fakih M, Sigal D, Loong HH, Buchschacher GL Jr, Garrido P, Nieva J, Steuer C, Overbeck TR, Bowles DW, Fox E, Riehl T, Chow-Maneval E, Simmons B, Cui N, Johnson A, Eng S, Wilson TR, Demetri GD; trial investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21:271-282. Erratum in: Lancet Oncol. 2020;21:e70. Erratum in: Lancet Oncol. 2020;21:e341. Erratum in: Lancet Oncol. 2020;21:e372. Erratum in: Lancet Oncol. 2021;22:e428. [Crossref]
18. Okamura R, Boichard A, Kato S, Sicklick JK, Bazhenova L, Kurzrock R. Analysis of NTRK alterations in pan-cancer adult and pediatric malignancies: implications for NTRK-targeted therapeutics. JCO Precis Oncol. 2018;2018:PO.18.00183. [Crossref]
19. Solomon JP, Linkov I, Rosado A, Mullaney K, Rosen EY, Frosina D, Jungbluth AA, Zehir A, Benayed R, Drilon A, Hyman DM, Ladanyi M, Sireci AN, Hechtman JF. NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. Mod Pathol. 2020;33:38-46. [Crossref]
20. Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol. 2019;32:147-153. [Crossref]
21. Marchiò C, Scaltriti M, Ladanyi M, Iafrate AJ, Bibeau F, Dietel M, Hechtman JF, Troiani T, López-Rios F, Douillard JY, Andrè F, Reis-Filho JS. ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. Ann Oncol. 2019;30:1417-1427. [Crossref]
22. Hechtman JF, Benayed R, Hyman DM, Drilon A, Zehir A, Frosina D, Arcila ME, Dogan S, Klimstra DS, Ladanyi M, Jungbluth AA. Pan-Trk immunohistochemistry is an efficient and reliable screen for the detection of NTRK fusions. Am J Surg Pathol. 2017;41:1547-1551. [Crossref]
23. Rudzinski ER, Lockwood CM, Stohr BA, Vargas SO, Sheridan R, Black JO, Rajaram V, Laetsch TW, Davis JL. Pan-Trk immunohistochemistry identifies NTRK rearrangements in pediatric mesenchymal tumors. Am J Surg Pathol. 2018;42:927-935. [Crossref]
24. Weiss LM, Funari VA. NTRK fusions and Trk proteins: what are they and how to test for them. Hum Pathol. 2021;112:59-69. [Crossref]

ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2025.2025-9-18
J Urol Surg 2026;13(3):178-185

Consultation Potential of Artificial Intelligence Chatbots in Prostatitis Management: An Evaluation of Quality, Reliability and Readability

Halil Demirçakan[1], Burak Köseoğlu[2], Taha Numan Yıkılmaz[3]

[1]Çumra State Hospital, Clinic of Urology, Konya, Türkiye
[2]Polatlı Duatepe State Hospital, Clinic of Urology, Ankara, Türkiye
[3]Private Egekent Hospital, Clinic of Urology, Denizli, Türkiye

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

Prostatitis is a common condition with complex management, especially in chronic forms. Patients often seek online information beyond medical consultation. artificial intelligence chatbots are increasingly used in healthcare, but concerns exist regarding the quality, reliability, and readability of their responses. This study is the first to compare ChatGPT-4, Gemini Pro, and Llama 3.1 Large with respect to prostatitis. Gemini Pro provided higher-quality responses, Llama 3.1 Large offered more reliable answers, and ChatGPT-4 demonstrated the highest readability, although all exceeded the recommended reading level.

Abstract

Objective: This study aimed to assess the responses of three artificial intelligence (AI) chatbots (ChatGPT-4, Gemini Pro, Llama 3.1 Large) on prostatitis using quality, reliability, readability scales and examine their role in disease management.

Materials and Methods: Keywords related to prostatitis were identified using Google Trends and Semrush platforms. The search volume and regional distribution of these terms over the past five years were analyzed, leading to the selection of 25 questions. The core question set was categorized into six subgroups: general information, symptoms, diagnostic methods, treatment methods, complications, and myths. The responses generated by the AI chatbots were assessed for readability using the Flesch-Kincaid Grade Level (FKGL) and Flesch Reading Ease (FRES) scores. Quality and reliability were evaluated using the Educational Quality of Information for Patients (EQIP) score and the Modified DISCERN score.

Results: No significant difference was observed among AI chatbots in mean FKGL scores (p=0.354). However, ChatGPT-4 had a significantly higher mean FRES score than Gemini Pro and Llama 3.1 Large (p=0.016 and p=0.003, respectively). Gemini Pro had the highest mean EQIP score, significantly surpassing Llama 3.1 Large and ChatGPT-4 (p<0.001); Llama 3.1 Large had the highest median Modified DISCERN score (p<0.001). Across all subgroup analyses, Gemini Pro yielded the highest mean EQIP score, while Llama 3.1 Large had the highest median Modified DISCERN score.

Conclusion: The findings of this study suggest that Llama 3.1 Large provides more reliable responses to questions about prostatitis, whereas Gemini Pro delivers higher-quality responses. However, the readability levels of all AI chatbots exceeded the recommended 6th-grade level, indicating that their responses may be challenging for general audiences.

Keywords: Prostatitis, artificial intelligence, ChatGPT-4, Gemini Pro, Llama 3.1 large

Introduction

Prostatitis is a condition characterized by symptoms such as chronic pelvic pain, dysuria, and pain during ejaculation. It has a high prevalence, with an overall prevalence of 8% among adult men, making it a common reason for urological consultations (1). Unlike other prostate-related conditions such as benign prostatic hyperplasia and prostate cancer, which are more prevalent in older men, prostatitis affects men of all ages, with a higher incidence in middle-aged men (2). The treatment of prostatitis is determined by the disease type. Acute prostatitis is typically caused by a bacterial infection; since its etiological

Correspondence: Halil Demirçakan MD, Çumra State Hospital, Clinic of Urology, Konya, Türkiye
E-mail: drhalildemircakan@gmail.com **ORCID-ID:** orcid.org/0000-0003-2376-580X
Received: 03.10.2025 **Accepted:** 04.11.2025 **Epub:** 11.06.2026 **Publication Date:** 01.09.2026

Cite this article as: Demirçakan H, Köseoğlu B, Yıkılmaz TN. Consultation potential of artificial intelligence chatbots in prostatitis management: an evaluation of quality, reliability and readability. J Urol Surg. 2026;13(3):178-185

well defined, its treatment follows a standardized, specific antibiotic therapy protocol. In contrast, chronic prostatitis is a multifactorial condition in which, besides infection, neurological, immunological, inflammatory, and psychosocial factors play a significant role. As a result, its treatment must be more individualized and multidisciplinary, making the management process more complex (3). Despite various treatment options, success rates for chronic prostatitis remain low, with a recurrence rate of approximately 50% (4,5). This leads patients to seek alternative sources of information outside conventional medical resources, particularly online sources that are readily accessible (6).

Artificial intelligence (AI) refers to computer systems designed to mimic human intelligence and perform complex tasks such as problem-solving, learning, decision-making, and language processing. AI systems are designed to acquire information from their environment, process the collected data, and make informed decisions (7). AI chatbots have rapidly emerged as valuable tools in healthcare, offering innovative applications ranging from diagnosis and treatment to patient management and optimization of operational processes. AI-based systems stand out due to their ability to provide rapid access to information, analyze patient data, and offer clinical guidance. However, concerns remain regarding the quality, accuracy, and readability of the content generated by AI chatbots (8).

To the best of our knowledge, no study has compared the responses provided by AI chatbots regarding prostatitis. This study aims to evaluate and compare the quality and readability of information on prostatitis provided by different AI chatbots.

Materials and Methods

In this study, responses provided by three AI chatbots (ChatGPT-4, Gemini Pro, and Llama 3.1 Large) to frequently asked questions about prostatitis were evaluated for quality, reliability, and readability. Since the study did not involve human participants and the data were obtained from publicly available sources, ethics committee approval was not required.

Evaluation Parameters

Reliability refers to the degree of accuracy, impartiality, and trustworthiness of the information provided by the chatbots. In this context, the evaluation assessed whether the purpose of the information was clearly stated, whether it was supported by reliable sources, whether the content was presented in a balanced and unbiased manner, whether additional sources of information were provided, and whether the scientific uncertainties or limitations of the available evidence related to the topic were explicitly acknowledged (9).

Quality refers to the educational value, comprehensiveness, and presentation of the content. Rather than focusing solely on factual accuracy, this parameter evaluates how clearly, objectively, and instructively information is presented to patients, and how up to date that information is. It includes elements such as whether the content states its purpose clearly, follows a logical structure, explains treatment options with associated risks and benefits, and provides references to additional sources of information (10).

Readability refers to how easily a text can be understood and followed by the reader. It is measured based on linguistic features such as sentence structure, word length, syntactic complexity, and overall grammatical composition (11).

Data Collection and Analysis

In the first stage, online search trends related to "prostatitis" were determined using Google Trends (http://trends.google.com/) and Semrush (http://www.semrush.com/). The search volume and regional distribution of terms over the past five years were analyzed, and 25 questions were formulated. The core set of questions was categorized into four subgroups: general information (six questions), symptoms and diagnostic methods (eight questions), treatment methods (seven questions), and complications and myths (four questions). The comprehensive list of these 25 queries directed to the AI chatbots is presented in Table 1, while representative chatbot responses are provided in Supplementary Appendix 1. In the second stage, the 25 selected questions were presented to three AI chatbots (ChatGPT-4, Gemini Pro, and Llama 3.1 Large), and responses from each were recorded in Microsoft Word. All prompts were entered on the same date and under identical default configurations for each AI chatbot to ensure methodological consistency and fairness across models.

The collected data were analyzed for word count (WS), sentence count, and syllable count (SYC). To assess text readability, the average Flesch Reading Ease (FRES) score and average Flesch-Kincaid Grade Level (FKGL) score were calculated. The readability level based on the FRES score was classified as follows: "easy" for scores above 70, "moderate" for scores between 60 and 70, and "difficult" for scores below 60 (12). The FRES score is calculated using the following formula:

$$206.835 - 1.015\left(\frac{total\ words}{total\ sentences}\right) - 84.6\left(\frac{total\ syllabes}{total\ words}\right)$$

The FKGL score indicates the readability level of a text, with a score of <6 corresponding to an elementary school level and a score of >13 indicating a graduate-level comprehension (13). The FKGL formula is as follows:

$$0.39\left(\frac{total\ words}{total\ sentences}\right) + 11.8\left(\frac{total\ syllabes}{total\ words}\right) - 15.59$$

Table 1. Comprehensive list of queries directed to ChatGPT-4, Gemini Pro, and Llama 3.1 large (by category)
General information
What is prostatitis and who is more likely to have it?
What are the different types of prostatitis and how are they classified?
What are the differences between acute and chronic prostatitis?
What are the causes of chronic prostatitis and how can it be prevented?
Can prostatitis be associated with stress?
What are the current studies on the relationship between the microbiome and prostatitis?
Symptoms and diagnostic methods
What tests are performed for the diagnosis of prostatitis?
What is the importance of microbial analyses in the treatment of chronic prostatitis?
Is the PSA test a reliable method for diagnosing prostatitis?
What imaging methods are used in the diagnosis of prostatitis?
What are the differences between chronic and acute prostatitis, and which symptoms help distinguish them?
Can prostatitis cause sexual dysfunction?
What is the relationship between prostatitis and urinary tract infections?
How does chronic prostatitis affect work and social life?
Treatment methods
What medications are used to treat prostatitis and how do they work?
Which natural supplements may help prevent prostate inflammation?
Is there scientific evidence supporting the use of herbal supplements such as saw palmetto for chronic prostatitis symptoms?
Is prostate massage truly beneficial in the treatment of chronic prostatitis, or is it a weakly supported practice?
Can stress management, meditation, or cognitive behavioral therapy help control chronic prostatitis pain?
How effective are pelvic floor muscle exercises in managing chronic prostatitis?
When is surgical intervention necessary for prostatitis?
Complications and myths
What are the ways to improve quality of life in patients with chronic prostatitis?
Can prostate inflammation turn into cancer?
What urological complications can occur if chronic prostatitis treatment is delayed?
Is chronic prostatitis likely to recur, and what measures can be taken to prevent recurrence in the long term?

The quality, reliability, and adequacy of the content were evaluated using the Patient Education Quality Information (EQIP) score (0-100 points) and the Modified DISCERN score (0-5 points). The EQIP scoring system is based on 20 questions, each of which can be answered as "yes," "partially," "no," or "not applicable." A "yes" response scores 1 point, a "partially" response scores 0.5 points, and a "no" response scores 0 points. The average score is calculated by dividing the sum of points by the number of questions answered. "Not applicable" responses are excluded from this calculation. The resulting value is then multiplied by 100, providing an EQIP score expressed as a percentage (14). An EQIP score of 0-25% indicates "serious quality issues," 26-50% indicates "significant quality issues," 51-75% indicates "good quality with minor issues," and 76-100% indicates "high quality" (15). The Modified DISCERN score comprises five questions, each scored 0 or 1 depending on whether its criterion is met. The scores for both scales were obtained by averaging the evaluations of two independent clinicians who were highly knowledgeable about prostatitis.

Statistical Analysis

The dataset was imported into IBM SPSS Statistics 27. Descriptive statistics were presented as the median [interquartile range (IQR)] for non-parametric data and as the mean ± standard deviation for parametric data. The normality of data distribution was assessed using the Shapiro-Wilk test. One-way ANOVA was used for normally distributed variables, while the Kruskal-Wallis test was applied to non-parametric or ordinal data. In cases where a significant difference was identified, pairwise comparisons were conducted using the Bonferroni correction. Non-parametric methods were prioritized when subgroup sample sizes were small. A p-value of <0.05 was considered statistically significant.

Results

The mean number of sentences per response was 12.72±6.31 for ChatGPT-4, 19.40±5.70 for Gemini Pro, and 11.96±4.92 for Llama 3.1 Large. A statistically significant difference was observed among the AI chatbots regarding the average number of sentences per response (p<0.001). Pairwise comparisons revealed that Gemini Pro had a significantly higher number of sentences than both ChatGPT-4 and Llama 3.1 Large (p<0.001 for both). However, no statistically significant difference was found between ChatGPT-4 and Llama 3.1 Large (p>0.05).

A statistically significant difference was also observed among the AI chatbots in the number of words per response (p<0.001). Pairwise comparisons demonstrated that Gemini Pro had a significantly higher WS than both ChatGPT-4 and Llama 3.1 Large (p<0.001 and p=0.001, respectively). Additionally, Llama 3.1 Large had a significantly higher WS than ChatGPT-4 (p=0.002).

The mean FKGL scores were 22.9±2.9 for ChatGPT-4, 23.7±2.5 for Gemini Pro, and 24.1±2.6 for Llama 3.1 Large, with no statistically significant differences observed among the AI chatbots (p=0.354). The mean FRES scores were 36.2±11.6 for ChatGPT-4, 27.4±11.1 for Gemini Pro, and 25.6±9.4 for Llama 3.1 Large, indicating a statistically significant difference among the AI chatbots (p=0.002). Pairwise comparisons showed that ChatGPT-4 had a significantly higher mean FRES score than Gemini Pro and Llama 3.1 Large (p=0.016 and p=0.003, respectively), while no significant difference was found between Gemini Pro and Llama 3.1 Large (p>0.05).

Mean EQIP scores were 68.2±1.1 for Gemini Pro, 56.7±2.5 for ChatGPT-4, and 57.2±2.0 for Llama 3.1 Large. A statistically significant difference in mean EQIP score was observed among the AI chatbots (p<0.001). Pairwise comparisons indicated that Gemini Pro had a significantly higher mean EQIP score than both Llama 3.1 Large and ChatGPT-4 (p<0.001 for both), while no significant difference was observed between Llama 3.1 Large and ChatGPT-4 (p>0.05).

The median (IQR) Modified DISCERN scores were 2 (1) for Gemini Pro, 2 (1) for ChatGPT-4, and 4 (0) for Llama 3.1 Large (p<0.001). The median Modified DISCERN score was significantly higher for Llama 3.1 Large than for Gemini Pro and ChatGPT-4 (p<0.001 for both comparisons). However, no significant differences were observed among the other AI chatbots (p=0.608; Table 2).

In all subgroup analyses, Gemini Pro had a significantly higher mean EQIP score than both Llama 3.1 Large and ChatGPT-4 (Figure 1), while the median Modified DISCERN score was significantly higher for Llama 3.1 Large than for Gemini Pro and ChatGPT-4 (Figure 2).

Discussion

Chronic prostatitis is a recurrent condition that remains difficult to manage despite the availability of various treatment options (4). This challenge often leads patients to seek alternative sources of health information outside traditional medical channels, such as easily accessible online platforms (6). Therefore, evaluating how accurately and clearly AI chatbots convey health-related information is of clinical importance. To the best of our knowledge, this is the first study to assess the readability, reliability, and quality of AI chatbot responses to frequently asked questions about prostatitis. The findings revealed notable differences among the evaluated models. Specifically, Gemini Pro provided more comprehensive and higher-quality information; Llama 3.1 Large generated the most reliable responses; and ChatGPT-4 achieved the highest readability scores.

Readability is defined in the literature as a fundamental component of health literacy, ensuring the comprehensibility of documents (16). Gül et al. (17) assessed the content provided by three AI chatbots (ChatGPT-4, Bard, and Perplexity) about subdural hematoma and reported that the responses did not meet recommended reading levels and that the average reader would not be able to fully benefit from these sources. In the same study, it was noted that while Google Bard provided more

Table 2. Comparison of the FKRE, FKGL, EQIP and Modified DISCERN scores of the three different AI chatbots

	ChatGPT	Gemini	Llama	p-value
FKRE Mean ± SD	36.2±11.6	27.4±11.1	25.6±9.4	0.002[a]
FKGL Mean ± SD	22.9±2.9	23.7±2.5	24.1±2.6	0.354
EQIP score Mean ± SD	56.7±2.5	68.2±1.1	57.2±2.0	<0.001[b]
Modified DISCERN score Median (IQR)	2 (1)	2 (1)	4 (0)	<0.001[c]

[a]: Difference between ChatGPT and other, [b]: Difference between Gemini and other, [c]: Difference between Llama and other, FKRE: FLesch kincaid reading ease, FKGL: Flesch kincaid grade level, EQIP: Educational quality of information for patients, AI: Artificial intelligence, SD: Standard deviation, IQR: Interquartile range

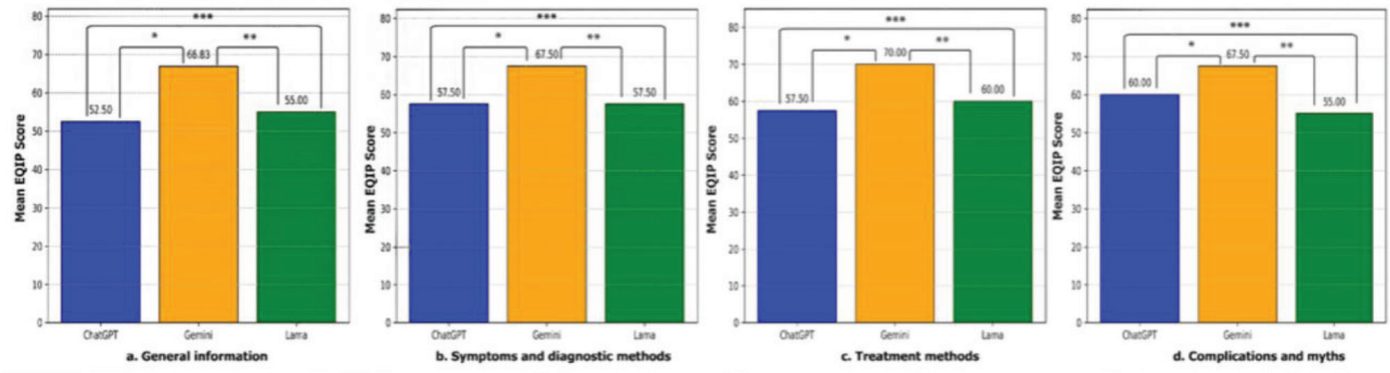


Figure 1. Comparison of the EQIP scores of three different AI chatbots for all subgroups

a. *p<0.001, **p<0.001, ***p=0.189

b. *p<0.001, **p<0.001, ***p>0.05

c. *p<0.001, **p<0.001, ***p<0.001

d. *p=0.005, **p<0.001, ***p=0.046

EQIP: Educational quality of information for patients, AI: Artificial intelligence

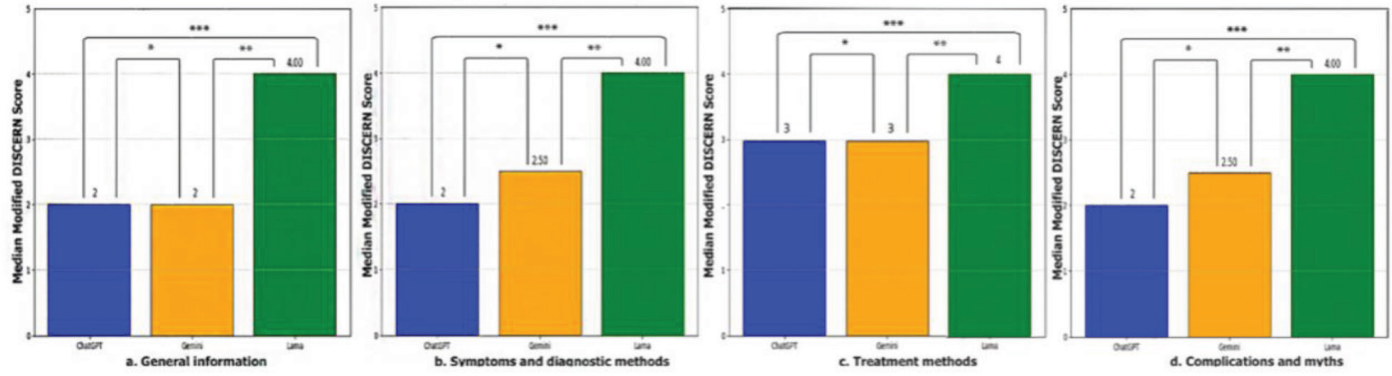


Figure 2. Comparison of the modified DISCERN scores of three different artificial intelligence chatbots for all subgroups

a. *p=0.725, **p=0.001, ***p=0.003

b. *p=0.765, **p=0.001, ***p<0.001

c. *p=0.75, **p=0.001, ***p<0.001

d. *p=0.392, **p=0.032, ***p=0.003

readable responses, ChatGPT-4's responses were more difficult to understand than those of the other chatbots. Similarly, Şahin et al. (18) demonstrated that AI chatbots' responses to questions about erectile dysfunction did not meet readability requirements. In this study, ChatGPT-4 was reported to generate content that was more difficult to understand than content produced by other AI chatbots. Another study examining the readability and quality of responses from five AI chatbots regarding palliative care information found that all five provided content exceeding a sixth-grade reading level. The study also indicated that Gemini Pro generated content that was significantly more difficult to read than content generated by ChatGPT-4 (19). In our study, although the three AI chatbots had similar FKGL scores, ChatGPT-4 had a significantly higher FRES score than the other two, indicating superior readability and comprehensibility. However, all three AI models had FRES scores below 60 and FKGL scores above 6, indicating that their responses exceeded the 6th-grade reading level recommended by the National Institutes of Health and the American Medical Association for health information, which makes them difficult to read (20,21). Poor readability of AI chatbot responses may limit their usability for patients. Additionally, the greater complexity of medical terminology relative to lay language may have contributed to the evaluated AI chatbots' inability to generate comprehensible responses for the general public.

In today's digital landscape, reliable online health information is critically important for patients (22). The inclusion of citations and references is essential for assessing the credibility of health-related information. In a study by Dursun and Bilici Geçer (12) that evaluated responses generated by ChatGPT-3.5, ChatGPT-4, Gemini Pro, and Copilot regarding orthodontic clear aligners, all AI chatbots were reported to produce responses of moderate reliability. The study found that Copilot provided the most reliable responses, followed by Gemini Pro, ChatGPT-4, and ChatGPT-3.5. The lower reliability of ChatGPT-3.5 and ChatGPT-4 compared to other chatbots was attributed to their inability to provide references or citations for the information they generated. In contrast, a study evaluating the recommendations of Bard, BingAI, and ChatGPT-4 regarding melanoma management found that ChatGPT-4 provided more reliable, evidence-based clinical recommendations than Bard and BingAI, achieving higher scores across all reliability scales (23). In our study, responses from Llama 3.1 Large were the most reliable. This was attributed to Llama 3.1 Large's ability to cite scientific publications and its superior organization of textual content. In contrast, Gemini Pro and ChatGPT-4 lacked reference materials and had unclear response origins, resulting in lower reliability compared with Llama 3.1 Large. The variability in reliability findings across studies may be explained by differences in question content and scoring systems.

The EQIP score, developed by healthcare professionals and patient information specialists, is used to assess the quality of health information sources such as websites and patient brochures (14). In a study evaluating the quality of responses provided by ChatGPT-4 on osteoporosis, the mean EQIP score was 48.7, and significant concerns were raised regarding the quality of the generated responses (24). Another study examining ChatGPT-4's responses to frequently asked questions about spinal cord injuries found that the EQIP scores averaged 43.02±6.37, raising concerns about the quality of the responses (25). A study investigating responses from five different chatbots to questions about erectile dysfunction reported EQIP scores as follows: ChatGPT-4 (40.0±4.2), Bing (39.5±3.1), Bard (32.1±30.4), Ernie Bot (53.1±20.6), and Copilot (63.5±12.7). The study concluded that ChatGPT-4, Bing Chat, and Copilot provided "acceptable quality with minor issues," whereas Ernie Bot and Bard exhibited "significant quality issues" (18). In our study, the mean EQIP scores for Gemini Pro, ChatGPT-4, and Llama 3.1 Large were found to be 68.2±1.1, 56.7±2.5, and 57.2±2.0, respectively. The responses provided by all chatbots were categorized as "good quality with minor issues." The variations in mean EQIP scores across studies can be attributed to differences in methodological approaches and evaluators' expertise.

In a study by Durmaz Engin et al. (26), responses of AI models (ChatGPT-4, Bing AI, and Gemini Pro) to categorized questions about retinopathy of prematurity (ROP) were evaluated using the DISCERN and EQIP instruments and three readability scales. All responses from each AI chatbot were analyzed collectively to obtain a single composite score for each model. The study found no significant differences in median scores among the three AI chatbots in the "general information" category, which can be attributed to the standardized and well-established nature of disease definitions. In contrast, ChatGPT-4 outperformed other AI chatbots in the screening, diagnosis, treatment, and prognosis subcategories. The variability in diagnostic criteria and treatment methods, and the impact of these factors on prognosis, were cited as explanations for differences among AI chatbots. In our study, across all subgroups, Llama 3.1 Large provided more reliable responses, while Gemini Pro generated higher-quality responses. The higher reliability scores for Llama 3.1 Large can be explained by its inclusion of citations to scientific publications and the use of evidence-based statements, such as clinical classifications and prevalence data. Gemini Pro, in contrast, presented information more simply, more comprehensibly, and in a patient-oriented manner, avoiding unnecessary technical details. Moreover, by organizing the content in a logical sequence that allows readers to follow the topic step by step, Gemini Pro demonstrated superior content coherence and educational value compared to Llama 3.1 Large. We believe that these differences may also be attributable to structural variations in the models' training data sources and text-generation strategies.

Nevertheless, the classification of the set of questions used in our study into four main categories — general information, symptoms and diagnostic methods, treatment methods, and complications and myths — demonstrates that AI chatbots may play roles at different stages of healthcare delivery. AI chatbots can perform functions such as providing general health information via clear, accessible explanations and supporting patients in recognizing their symptoms and seeking appropriate medical care. Our findings indicate that, at present, AI should be used only as a complementary tool in the education, awareness, diagnosis, and treatment phases of healthcare and cannot substitute for professional medical evaluation or physician examination.

Study Limitations

One of the strengths of our study is that the AI chatbot's responses were evaluated by two clinicians with extensive expertise in prostatitis. However, our study has some notable limitations. First, the study was conducted in English, and AI search results were limited to English. This limitation prevented an evaluation of the quality and readability of responses in other languages. Additionally, each question was posed to the AI chatbots only once, meaning that different responses might have been obtained if the same questions had been posed at different times or repeated. Furthermore, the scores were

obtained by averaging the evaluations of two independent clinicians, but since individual scores were not recorded separately, statistical analysis of interrater agreement could not be performed. Finally, the scoring systems used in this study were not specifically designed for AI chatbots, which may have introduced certain limitations in the evaluations.

Conclusion

AI chatbot models have generally provided high-quality, moderately reliable responses to questions about prostatitis. Among these models, the Gemini Pro model has generated the highest-quality responses, whereas the Llama 3.1 Large model has offered the most reliable responses. A significant limitation of ChatGPT-4 and Gemini Pro is their inability to provide references or citations to support their answers. Additionally, all chatbot models have produced content that exceeds the recommended sixth-grade reading level, which may limit their accessibility to a broader audience. These findings indicate that AI models should be enhanced with more evidence-based information and improved readability. Future research should therefore focus on increasing the accessibility of AI-based information sources and optimizing the role of these models in patient education and disease management.

Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Not necessary.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.D., B.K., T.N.Y., Concept: H.D., B.K., T.N.Y., Design: H.D., B.K., T.N.Y., Data Collection or Processing: H.D., B.K., T.N.Y., Analysis or Interpretation: H.D., B.K., T.N.Y., Literature Search: H.D., B.K., T.N.Y., Writing: H.D., B.K., T.N.Y.

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

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

Supplementary Appendix 1. https://d2v96fxpocvxx.cloudfront.net/bb2eeae3-0e60-42a4-acea-81e4a349912c/content-images/d2a8f682-3776-4ec2-83af-17a5b4cc247c.pdf

References

1. Guimaraes CTS, Sauer LJ, Romano RFT, Pacheco EO, Bittencourt LK. Prostate benign diseases. Top Magn Reson Imaging. 2020;29:1-16. [Crossref]
2. Nickel JC, Downey J, Hunter D, Clark J. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. J Urol. 2001;165:842-845. [Crossref]
3. Magri V, Boltri M, Cai T, Colombo R, Cuzzocrea S, De Visschere P, Giuberti R, Granatieri CM, Latino MA, Larganà G, Leli C, Maierna G, Marchese V, Massa E, Matteelli A, Montanari E, Morgia G, Naber KG, Papadouli V, Perletti G, Rekleiti N, Russo GI, Sensini A, Stamatiou K, Trinchieri A, Wagenlehner FME. Multidisciplinary approach to prostatitis. Arch Ital Urol Androl. 2019;90:227-248. [Crossref]
4. Nickel JC, Shoskes DA, Wagenlehner FM. Management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): the studies, the evidence, and the impact. World J Urol. 2013;31:747-753. [Crossref]
5. Resim S. Akut ve bakteriyel prostatit olgularında tedavi yaklaşımları. Androl Bul. 2020;22:113-123. [Crossref]
6. Aktas BK, Demirel D, Celikkaleli F, et al. YouTube™ as a source of information on prostatitis: a quality and reliability analysis. Int J Impot Res. 2024;36:242-247. [Crossref]
7. Deng J, Lin Y. The benefits and challenges of ChatGPT: an overview. Front Comput Intell Syst. 2023;2:81-83. [Crossref]
8. Xu L, Sanders L, Li K, Chow JCL. Chatbot for health care and oncology applications using artificial intelligence and machine learning: systematic review. JMIR Cancer. 2021;7:e27850. [Crossref]
9. Uzun O. Assessment of reliability and quality of videos on medial epicondylitis shared on YouTube. Cureus. 2023;15:e37250. [Crossref]
10. Hu M, Zou P, Li T, Wang Y. Evaluating the quality of ChatGPT-generated medical information on major ophthalmic conditions: a comparative assessment against the EQIP tool and guidelines. PLoS One. 2025;20:e0334250. [Crossref]
11. Erkin Y, Hanci V, Ozduran E. Evaluating the readability, quality and reliability of online patient education materials on transcutaneuous electrical nerve stimulation (TENS). Medicine (Baltimore). 2023;102:e33529. [Crossref]
12. Dursun D, Bilici Geçer R. Can artificial intelligence models serve as patient information consultants in orthodontics? BMC Med Inform Decis Mak. 2024;24:211. [Crossref]
13. Kincaid JP, Fishburne RP Jr, Rogers RL, Chissom BS. Derivation of new readability formulas: automated readability index, fog count and Flesch reading ease formula. Orlando (FL): Institute for Simulation and Training; 1975. Accessed November 1, 2023. [Crossref]
14. Moult B, Franck LS, Brady H. Ensuring quality information for patients: development and preliminary validation of a new instrument to improve the quality of written health care information. Health Expect. 2004;7:165-175. [Crossref]
15. Hain T. Improving the quality of health information: the contribution of C-H-i-Q. Health Expect. 2002;5:270-273. [Crossref]
16. Meade MJ, Dreyer CW. Orthodontic treatment consent forms: a readability analysis. J Orthod. 2022;49:32-38. [Crossref]
17. Gül Ş, Erdemir İ, Hanci V, Aydoğmuş E, Erkoç YS. How artificial intelligence can provide information about subdural hematoma: assessment of readability, reliability, and quality of ChatGPT, BARD, and perplexity responses. Medicine (Baltimore). 2024;103:e38009. [Crossref]
18. Şahin MF, Ateş H, Keleş A, Özcan R, Doğan Ç, Akgül M, Yazıcı CM. Responses of five different artificial ıntelligence chatbots to the top searched queries about erectile dysfunction: a comparative analysis. J Med Syst. 2024;48:38. [Crossref]
19. Hancı V, Ergün B, Gül Ş, Uzun Ö, Erdemir İ, Hancı FB. Assessment of readability, reliability, and quality of ChatGPT®, BARD®, Gemini®, Copilot®, Perplexity® responses on palliative care. Medicine (Baltimore). 2024;103:e39305. [Crossref]
20. Weis BD. Health literacy: a manual for clinicians. American Medical Association Foundation and American Medical Association; 2003. [Crossref]

21. National Institute of Health. How to write easy-to-read health materials. [Crossref]
22. Whiles BB, Bird VG, Canales BK, DiBianco JM, Terry RS. Caution! AI bot has entered the patient chat: ChatGPT has limitations in providing accurate urologic healthcare advice. Urology. 2023;180:278-284. [Crossref]
23. Mu X, Lim B, Seth I, Xie Y, Cevik J, Sofiadellis F, Hunter-Smith DJ, Rozen WM. Comparison of large language models in management advice for melanoma: Google's AI BARD, BingAI and ChatGPT. Skin Health Dis. 2023;4:e313. [Crossref]
24. Erden Y, Temel MH, Bağcıer F. Artificial intelligence insights into osteoporosis: assessing ChatGPT's information quality and readability. Arch Osteoporos. 2024;19:17. [Crossref]
25. Temel MH, Erden Y, Bağcıer F. Information quality and readability: ChatGPT's responses to the most common questions about spinal cord injury. World Neurosurg. 2024;181:e1138-e1144. [Crossref]
26. Durmaz Engin C, Karatas E, Ozturk T. Exploring the role of ChatGPT-4, BingAI, and Gemini as virtual consultants to educate families about retinopathy of prematurity. Children (Basel). 2024;11:750. [Crossref]

ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2025.2025-9-4
J Urol Surg 2026;13(3):186-198

RAD51, *BRCA1*, and *BRCA2*: Can be Promising Prognostic Factors and New Therapy Targets for Clear Cell Renal Cell Carcinoma Patients?

Amira M. Abd El Maged[1], Heba Mahmoud Abdelgeleel[2], Eslam G. Abozaid[3], Amira H. Hanna[4], Hanan Lotfy Mohammed[5]

[1]Menoufia University Faculty of Medicine, Shebin El Kom, Egypt
[2]Zagazig University Faculty of Medicine, Department of Pathology, Zagazig, Egypt
[3]Zagazig University Surgical Oncology Unit, Department of General Surgery, Zagazig, Egypt
[4]Zagazig University Faculty of Medicine, Department of Clinical Oncology and Nuclear Medicine, Zagazig, Egypt
[5]Zagazig University Faculty of Medicine, Zagazig, Egypt and Ibn Sina National College for Medical Studies (ISNC), Department of Pathology, Jeddah, Saudi Arabia

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

RAD51 showed increased immunohistochemical (IHC) expression in clear cell renal cell carcinoma (ccRCC), while *BRCA1* and *BRCA2* show reduced IHC expression, suggesting impaired homologous recombination (HR) repair mechanisms in ccRCCs. High *RAD51* expression is associated with poor prognostic factors of ccRCC patients. High *BRCA1/BRCA2* expression is linked to good prognostic factors of ccRCC patients. Expression of these DNA repair proteins may serve as prognostic markers for ccRCC patients, helping to predict cancer aggressiveness and metastasis and detect outcomes. Targeting HR-proficient /deficient ccRCC with DNA repair-targeting therapies, *RAD51* inhibitors or PARP inhibitors could be a promising treatment approach.

Abstract

Objective: Clear cell renal cell carcinoma (ccRCC) is the predominant form of renal cell carcinoma, distinguished by its genetic alterations that affects the tumor's progression and response to treatment. *RAD51*, *BRCA1*, and *BRCA2* are fundamental components of the homologous recombination (HR) DNA repair system, which is vital for preserving genomic stability. Yet, data regarding their expression pattern and potential role in ccRCC development and progression remain unclear. The aim of this work was to study the immunohistochemical expression of *RAD51*, *BRCA1*, and *BRCA2* in ccRCC and to investigate the correlation between their expression levels and the clinical outcomes of patients with ccRCC.

Materials and Methods: Across-sectional study has been performed at Zagazig University's Faculty of Medicine using data from the Pathology Department archives between January 2020 and December 2023 through analyzing 76 ccRCC specimens who underwent either a total (56 cases) or partial nephrectomy (20 cases) to determine the *RAD51*, *BRCA1*, and *BRCA2* immunohistochemical expressions and comparing these with clinicopathologic parameters and survival.

Results: High nuclear expression of *RAD51* was detected in 42.1% of cases and was significantly associated with poor prognostic indicators, including advanced tumor stage, lymphatic spread, distant metastasis, and recurrence. High nuclear expression of *BRCA1*, *BRCA2*, and both proteins was detected in 51.3%, 35.5%, and 27% of cases, respectively, and their immune expression was significantly correlated with favorable prognostic indicators, including early tumor stage and absence of lymphatic spread. High *RAD51* expression showed significant indirect correlations with *BRCA1* expression and with the co-expression of *BRCA1* and *BRCA2*. Using Kaplan-Meier analysis, patients with high *RAD51* and low *BRCA1* expression had shorter disease-free survival and overall survival.

Conclusion: This research emphasizes the significance of *RAD51*, *BRCA1*, and *BRCA2* in the progression of ccRCC. Elevated *RAD51* levels alongside reduced *BRCA1* and *BRCA2* expression are associated with more aggressive tumors, suggesting their potential as immunohistochemical prognostic indicators and providing insights into novel therapeutic approaches for patients with ccRCC.

Keywords: *RAD51*, *BRCA1*, *BRCA2*, clear cell renal cell carcinoma, immunohistochemistry, homologous recombination, prognosis

Correspondence: Heba Mahmoud Abdelgeleel MD, Zagazig University Faculty of Medicine, Department of Pathology, Zagazig, Egypt
E-mail: HMAbduljalil@medicine.zu.edu.eg **ORCID-ID:** orcid.org/0000-0002-2508-1770
Received: 08.09.2025 **Accepted:** 04.11.2025 **Epub:** 13.07.2026 **Publication Date:** 01.09.2026

Cite this article as: Abd El Maged AM, Abdelgeleel HM, Abozaid EG, Hanna AH, Mohammed HL. *RAD51*, *BRCA1*, and *BRCA2*: can be promising prognostic factors and new therapy targets for clear cell renal cell carcinoma patients? J Urol Surg. 2026;13(3):186-198

Introduction

Renal cell carcinoma (RCC) is a highly prevalent malignancy of the urinary system and one of the ten most frequently diagnosed solid tumors (1). Clear cell renal cell carcinoma (ccRCC) is the predominant histopathological subtype, constituting more than 80% of RCCs (2). While ccRCC generally has a good prognosis when treated in its early stages, up to one-third of cases will metastasize, and 2040% of cases will experience a post-nephrectomy recurrence. ccRCC is notably resistant to chemotherapy, and once recurrence occurs, no further management is effective (3).

Deletion of chromosome 3p and mutations in the *Von Hippel-Lindau (VHL)* gene are prevalent in most ccRCC patients, leading to loss of various tumor suppressor genes, which further enhances genomic instability (4). Moreover, a deficiency in homologous recombination (HR) significantly contributes to genomic instability (5).

HR is recognized as a precise process for the repair of DNA double-strand breaks (DSBs), and any defect in this process can lead to tumorigenesis by enabling the accumulation of chromosomal abnormalities and mutations. In numerous instances, aggressive tumors are characterized by reduced expression of HR proteins, but these tumors also show increased responsiveness to therapeutic interventions, including chemotherapy and radiotherapy. The HR pathway involves important proteins encoded by the *RAD51*, *BRCA1*, and *BRCA2* genes (6).

The *RAD51* gene on human chromosome 15q15.1 encodes the essential HR protein *RAD51*. It has a significant role in DSBs by creating nucleoprotein filaments on single-stranded DNA, enabling strand exchange between single- and double-stranded DNA, and facilitating homologous pairing. When DNA damage occurs, *RAD51* relocates to nuclear foci, where it is believed to recognize and facilitate the repair of broken replication forks (7). Recent research has demonstrated that *RAD51* is a potential prognostic biomarker for various tumors, such as colorectal cancer (8), non-small cell lung cancer (9), and breast cancer (10). Nonetheless, there is a lack of evidence demonstrating the link between *RAD51* and ccRCC, which was the rationale for selecting this marker to be investigated in the current study.

The tumor suppressor gene, *BRCA1*, plays a crucial role in maintaining genome stability. It is frequently impaired in several types of cancer, including breast, ovarian, and pancreatic cancers, leading to the accumulation of genetic defects (11). *BRCA1* forms a complex with *BARD1* to aid DSB repair through HR. The complex formed by *BRCA1-BARD1* interacts directly with *RAD51*, boosting its ability to facilitate recombination. Mutations in *BRCA1* that disrupted the *RAD51* interaction hinder DNA strand invasion and compromise HR (12). Therefore, *BRCA1* serves as a crucial prognostic and therapeutic target for advancing cancer treatment approaches.

BRCA2 protein promotes HR-mediated repair of DSBs by facilitating *RAD51*-dependent DNA strand invasion, pairing, and exchange. The C-terminal recombinase binding (CTRB) domain of *BRCA2* is responsible for loading *RAD51* onto and binding *RAD51* to single-stranded DNA (ssDNA). CTRB alone significantly increases the DNA strand-exchange activity of *RAD51* and enables it to use ssDNA for this activity (13). In human cells, *BRCA2* deficiency leads to HR abnormality, genetic instability, inhibited formation of *RAD51* foci in response to DNA damage, and altered responsiveness to chemotherapy agents (14).

This study is the first to analyze immunohistochemical (IHC) expression of *RAD51*, *BRCA1*, and *BRCA2* in ccRCC and to investigate correlations between their expression levels and the clinicopathological features and clinical outcomes in patients with ccRCC. This research may help identify additional prognostic indicators for ccRCC and inform the development of novel anticancer strategies.

Materials and Methods

This cross-sectional study was conducted at Zagazig University's Faculty of Medicine using data from the Pathology Department archives collected from January 2020 to December 2023. The study included 76 sections from formalin-settled paraffin-inserted tissue blocks diagnosed as primary ccRCC who underwent either a total (56 cases) or partial nephrectomy (20 cases). Patients was selected consecutively. Clinicopathologic information, histopathology reports, and hematoxylin and eosin-stained slides from ccRCC cases were reviewed to confirm the diagnosis. Exclusion criteria were: a history of synchronous or metachronous malignancies; prior antitumor therapy; histological types other than the clear-cell variant; or insufficient tissue for IHC analysis. This work was conducted in agreement with the Helsinki Declaration and written consent was obtained from each member. Moreover, the current study was permitted by the Ethical Committee of Zagazig University according to the Egyptian Ethical Guidelines (approval number: ZU-IRB#11335, date: 12.03.2024).

Immunohistochemistry

The immunostaining method employed a streptavidin-biotin amplification system. The slides were subjected to consecutive steps of deparaffinization, rehydration, and blocking of endogenous peroxidase activity. Antigen recovery was performed by boiling in citrate-buffered saline (pH 6), followed by cooling at room temperature. The slides were then stained with primary antibodies against *RAD51* (rabbit monoclonal Ab; Catalog # EPR4030(3); 1:300 dilution; Abcam, Cambridge, UK), *BRCA1* (rabbit monoclonal Ab; Catalog # EPR19433; 1:400 dilution; Abcam, Cambridge, UK), and *BRCA2* (rabbit polyclonal Ab; Catalog # ab216972; 1:400 dilution; Abcam, Cambridge, UK). The

primary antibody was incubated overnight at room temperature, and then the secondary antibody was applied; diaminobenzidine was used as the chromogen, followed by counterstaining with Mayer's hematoxylin. The *RAD51* positive-control slide used germ cells from healthy testicular tissue. The positive control for *BRCA1* and *BRCA2* was tissue from invasive ductal carcinoma of the breast. Negative control slides were treated without the addition of primary antibodies.

Immunohistochemical Evaluation Criteria

Two independent investigators examined all stained sections by light microscopy; interobserver agreement was achieved. They specifically focused on assessing the nuclear expression of *RAD51*, *BRCA1*, and *BRCA2*. During the pathological annotation process, the assessment involved determining the percentage of positive cells, categorized as follows: 0 for less than 5%, 1 for 5-25%, 2 for 25-50%, 3 for 50-75%, and 4 for 75-100%. Additionally, the intensity of staining was evaluated on a scale where 0 indicates negative, 1 represents weak, 2 denotes moderate, and 3 signifies strong staining. The overall score was derived by multiplying the intensity score by the percentage score. Samples were subsequently classified as either "high expression" or "low expression" based on a cut-off score of 6 (15).

Analysis of Survival Data

For 76 patients with ccRCC between January 2020 and December 2023, the overall survival (OS) time was determined by reviewing the patients' files. Disease-free survival (DFS) and OS were analyzed using the Kaplan-Meier method, and differences among the survival curves were assessed by a log-rank test. A multivariate Cox proportional hazards analysis was employed to determine the independent risk factors influencing survival time.

Statistical Analysis

SPSS 22.0 for Windows and MedCalc Windows were used to perform all analyses. The Mann-Whitney U test was employed to compare two groups of non-normally distributed variables, whereas the Kruskal-Wallis test was utilized for comparisons involving more than two groups of non-normally distributed variables. The proportions of categorical variables were compared using Fisher's exact test or Pearson's chi-square test, as appropriate. A p-value ≤0.05 was considered statistically significant.

Results

Patients' Characteristics

This study included 76 patients with ccRCC. Patients' ages ranged from 48-80 years, with a mean age of 58.66±7.561 years (Table 1). There were 45 (59.2%) male patients and 31 (40.8%) female patients. Tumor size exceeded 7 cm in 54 cases (71.1%). Thirty-nine (51.3%) cases were high grade, while 37 (48.7%) were low grade. Necrosis was detected in 31 (40.8%) cases, while lymphovascular invasion was present in 19 (25%) cases. Seventeen of these 76 patients (22.4%) had stage I disease. On the other hand, 20 ccRCC patients (26.3%) presented with stage IV disease. Nodal metastasis was recorded preoperatively in 25 (32.9%) and distant metastasis in 23 (30.3%) cases as well. The average duration of follow-up was 27.4 months (range: 10-36 months), during which 40 patients (52.6%) remained disease-free. Recurrence occurred in 36 patients (47.4%), while 28 patients (36.8%) died during the follow-up period. The clinicopathological features of the 76 ccRCC patients are detailed in Table 1.

Pattern of *RAD51* Expression in ccRCC and Association with Clinicopathological Parameters

In ccRCC patients, nuclear staining of tumor cells was considered *RAD51*-positive (Figure 1). High *RAD51* expression was observed in 32 patients (42.1%), while 44 patients (57.9%) showed low expression (Table 1). In adjacent non-tumor tissue, no immunostaining for *RAD51* was observed.

Table 1. Clinicopathologic parameters of 76 ccRCC cases

Variable	No (%)
Gender	
Male	45 (59.2)
Female	31 (40.8)
Age	
Mean ± standard deviation	58.66±7.561
Median	57
Range	32
Age	
<50	20 (26.3)
≥50	56 (73.7)
Tumor size	
<7	22 (28.9)
≥7	54 (71.1)
The WHO/ISUP grade	
Grade I-II	37 (48.7)
Grade III-IV	39 (51.3)
Vascular invasion	
Present	19 (25)
Absent	57 (75)
Necrosis	
Present	31 (40.8)
Absent	45 (59.2)
Tumor stage	
T1	17 (22.4)
T2	23 (30.3)

Table 1. Continued

Variable	No (%)
T3	16 (21.1)
T4	20 (26.3)
Tumor stage grouping	
Early stage	40 (52.6)
Advanced stage	36 (47.4)
Nodal stage	
N0	51 (67.1)
N1	25 (32.9)
Distant metastasis	
M0	53 (69.7)
M1	23 (30.3)
Relapse	
Absent	40 (52.6)
Present	36 (47.4)
Death	
Alive	48 (63.2)
Dead	28 (36.8)
RAD51	
Low expression	44 (57.9)
High expression	32 (42.1)
BRCA1	
Low expression	37 (48.7)
High expression	39 (51.3)
BRCA2	
Low expression	49 (64.5)
High expression	27 (35.5)
High co-expression of *BRCA1* and *BRCA2*	
Positive	21 (27.6)
Negative	55 (72.4)

ISUP: International Society of Urologic Pathologists, WHO: World Health Organization, ccRCC: Clear cell renal cell carcinoma

High *RAD51* expression was significantly correlated with higher tumor stage, with high expression observed in 4 (23.5%) stage I, 6 (26.1%) stage II, 8 (50%) stage III, and 14 (70%) stage IV ccRCC cases (p=0.009); the correlation was significant (p=0.001). Moreover, high *RAD51* was significantly associated with tumor lymphatic spread (p<0.001 and p=0.000), distant spread (p<0.001 and p=0.000), and tumor recurrence (p=0.024 and p=0.02) (Table 2, Figure 1).

Pattern of *BRCA1* and *BRCA2* Expression in ccRCC and Association with Clinicopathological Parameters

BRCA1 and *BRCA2* showed nuclear staining in cancer cells, with negative immunostaining in the adjacent non-tumor tissue (Figure 2). High immunohistochemical (IHC) expression of *BRCA1*, *BRCA2*, and both proteins were observed in 39 (51.3%), 27 (35.5%), and 21 (27.6%) cases, respectively (Table 1).

BRCA1 immune expression was significantly correlated with early stages of ccRCC, with higher expression observed in 14 (82.4%) stage I cases compared with 8 (40%) stage IV cases (p=0.017); the correlation was significant (p=0.006). Additionally, *BRCA1* expression was significantly associated with cases without lymphatic spread (p=0.028). Similarly, co-expression of *BRCA1* and *BRCA2* was significantly associated with early stages of ccRCC patients (p=0.004; p=0.002), and lack of nodal metastasis (p=0.032; p=0.01). However, *BRCA2* expression is significantly correlated with the early tumor stage (p=0.008) and with the correlation coefficient (p=0.005) (Table 3; Figure 2).

Association Between *RAD51*, *BRCA1*, and *BRCA2* Expression

A significant correlation was detected between positive *RAD51* expression and negative *BRCA1* expression: 30 (68.2%) cases with high *BRCA1* expression showed low *RAD51* expression, whereas 9 (28.1%) of the high *BRCA1* expression cases showed high *RAD51* immunostaining (p=0.001; correlation coefficient p=0.000). No significant correlation was found between *RAD51* and *BRCA2* immune expression (p=0.507); however, co-expression of *BRCA1* and *BRCA2* showed a significant inverse association with *RAD51*. In the correlation between *BRCA1* and *BRCA2*, a significant positive association was detected (p=0.001); 21 cases (27.6%) with high *BRCA2* expression also showed high *BRCA1* expression, and the correlation coefficient was significant (p<0.001) (Figure 3).

Univariate Survival Analysis for Predicting Overall & Disease-free Survival

Univariate analysis of OS and DFS in 76 ccRCC patients using the Kaplan-Meier method (Figure 4) revealed that high tumor grade (p=0.001 and 0.001), advanced stage (p=0.043 and 0.016), presence of nodal metastasis (p=0.004 and 0.003), distant metastasis (p=0.02 and 0.008), and tumor recurrence (p<0.001 and <0.001) were associated with shorter OS and DFS, respectively (Table 4).

High expression of *RAD51* was associated with shorter OS and DFS (p=0.02 and p=0.014, respectively). Cases with a mean OS of 30.93 months exhibited high *RAD51* immunostaining, whereas cases with a longer mean OS of 32.04 months displayed lower *RAD51* expression levels. Conversely, *BRCA1* expression was significantly associated with longer OS and DFS (p=0.04 and p=0.009, respectively). However, *BRCA2* showed no significant correlation with patient survival (Figure 4, Table 5).

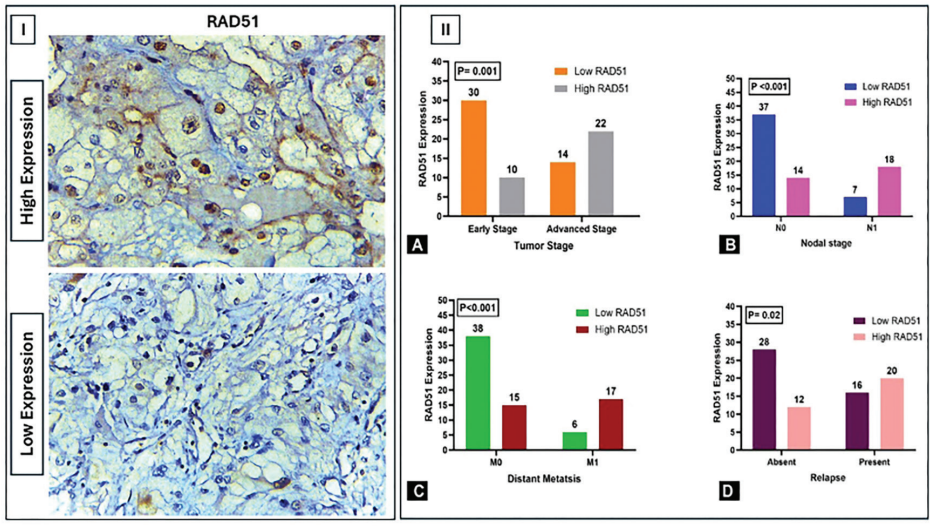


Figure 1. I) High and low *RAD51* immunohistochemical expression in clear cell renal cell carcinoma cases (magnified x400). **II)** High *RAD51* showed a significant association with advanced tumor stage (A), nodal involvement (B), distant metastasis (C), and tumor relapse (D)

Table 2. Correlation between *RAD51* with clinicopathologic parameters of 76 ccRCC cases

Variable	*RAD51* expression		p-value
	Low expression No (%)	High expression No (%)	
Gender			
Male	(28) 62.2%	(17) 37.8%	0.357
Female	(16) 51.6%	(15) 48.4%	
Age			
<50	(13) 65.0%	(7) 35.0%	0.453
≥50	(31) 55.4%	(25) 44.6%	
Tumor size			
<7	(12) 54.5%	(10) 45.5%	0.706
≥7	(32) 59.3%	(22) 40.7%	
WHO/ISUP grade			
Grade I-II	(24) 64.9%	(13) 35.1%	0.231
Grade III-IV	(20) 51.3%	(19) 48.7%	
Vascular invasion			
Present	(10) 52.6%	(9) 47.4%	0.592
Absent	(34) 59.6%	(23) 40.4%	
Necrosis			
Present	(15) 48.4%	(16) 51.6%	0.164
Absent	(29) 64.4%	(16) 35.6%	
Tumor stage			
T1	(13) 76.5%	(4) 23.5%	
T2	(17) 73.9%	(6) 26.1%	**0.009***
T3	(8) 50%	(8) 50%	
T4	(6) 30%	(14) 70%	
Tumor stage grouping			
Early stage	(30) 75%	(10) 25%	**0.001***
Advanced stage	(14) 38.9%	(22) 61.1%	
Nodal stage			
N0	(37) 72.5%	(14) 27.5%	**<0.001***
N1	(7) 28%	(18) 72%	

Table 2. Continued

Variable	*RAD51* expression		p-value
	Low expression No (%)	High expression No (%)	
Distant metastasis			
M0	(38) 71.7%	(15) 28.3%	**<0.001***
M1	(6) 26.1%	(17) 53.1%	
Relapse			
Absent	(28) 70%	(12) 30%	**0.024***
Present	(16) 44.4%	(20) 55.6%	
BRCA1			
Low expression	(14) 37.8%	(23) 62.2%	**0.001***
High expression	(30) 76.9%	(9) 23.1%	
BRCA2			
Low expression	(27) 55.1%	(22) 44.9%	0.507
High expression	(17) 63%	(10) 37%	
High co-expression of *BRCA1* and *BRCA2*			
Positive	(17) 81%	(4) 19%	**0.018***
Negative	(27) 49.1%	(28) 50.9%	

*: Significant, ISUP: International Society of Urologic Pathologists, WHO: World Health Organization, ccRCC: Clear cell renal cell carcinoma

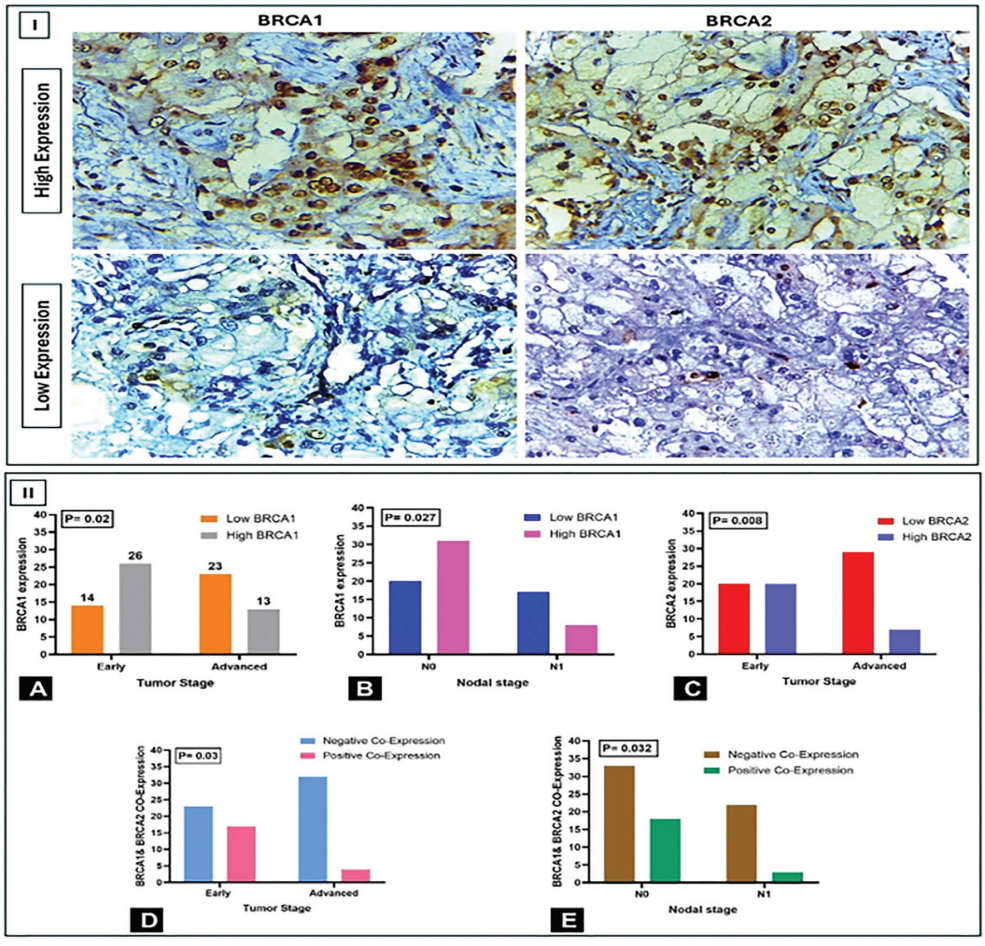


Figure 2. I) High and low *BRCA1* and *BRCA2* immunohistochemical expression in clear cell renal cell carcinoma cases (magnified x400). **II)** High *BRCA1* showed significant associations with early tumor stage (A) and with presence of nodal stage (B); *BRCA2* showed significant association with early tumor stage (C). Co-expression of both showed significant association with early tumor stage (D), and presence of nodal stage (E)

Table 3. Correlation between *BRCA1*, *BRCA2*, and co-expression of both with clinicopathologic parameters of 76 ccRCC cases

Variable	*BRCA1* expression		p-value	*BRCA2* expression		p-value	Co-expression		p-value
	Low expression No (%)	High expression No (%)		Low expression No (%)	High expression No (%)		Negative expression No (%)	Positive expression No (%)	
Gender									
Male	(21) 46.7%	(24) 53.3%	0.672	(26) 57.8%	(19) 42.2%	0.142	(29) 64.4%	(16) 35.6%	0.07
Female	(16) 51.6%	(15) 48.4%		(23) 74.2%	(8) 25.8%		(26) 83.9%	(5) 16.1%	
Age									
<50	(9) 45.0%	(11) 55.0%	0.701	(11) 55%	(9) 45%	0.302	(14) 70%	(6) 30%	0.78
≥50	(28) 50%	(28) 50%		(38) 67.9%	(18) 32.1%		(41) 73.2%	(15) 26.8%	
Tumor size									
<7	(9) 40.9%	(13) 59.1%	0.387	(12) 54.5%	(10) 45.5%	0.248	(15) 68.2%	(7) 31.8%	0.60
≥7	(28) 51.9%	(26) 48.1%		(37) 68.5%	(17) 31.5%		(40) 74.1%	(14) 25.9%	
WHO/ISUP grade									
Grade I-II	(15) 40.5%	(22) 59.5%	0.167	(21) 56.8%	(16) 43.2%	0.171	(24) 64.9%	(13) 35.1%	0.15
Grade III-IV	(22) 56.4%	(17) 43.6%		(28) 71.8%	(11) 28.2%		(31) 79.5%	(8) 20.5%	
Vascular invasion									
Present	(10) 52.6%	(9) 47.4%	0.691	(15) 78.9%	(4) 21.1%	0.128	(17) 89.5%	(2) 10.5%	0.076
Absent	(27) 47.4%	(30) 52.6%		(34) 59.6%	(23) 40.4%		(38) 66.7%	(19) 33.3%	
Necrosis									
Present	(17) 54.8%	(14) 45.2%	0.373	(22) 71%	(9) 29%	0.326	(24) 77.4%	(7) 22.6%	0.41
Absent	(20) 44.4%	(25) 55.6%		(27) 60%	(18) 40%		(31) 68.9%	(14) 31.1%	
Tumor stage									
T1	(3) 17.6%	(14) 82.4%		(7) 41.2%	(10) 58.8%		(10) 58.8%	(7) 41.2%	
T2	(11) 47.8%	(12) 52.2%	**0.017***	(13) 56.5%	(10) 43.5%	**0.03***	(13) 56.5%	(10) 43.5%	**0.021***
T3	(11) 68.8%	(5) 31.2%		(13) 81.2%	(3) 18.8%		(15) 93.8%	(1) 6.2%	
T4	(12) 60%	(8) 40%		(16) 80%	(4) 20%		(17) 85%	(3) 15%	
Tumor stage grouping									
Early	(14) 35%	(26) 65%	**0.021***	(20) 50%	(20) 50%	**0.008***	(23) 57.5%	(17) 42.5%	**0.004***
Advanced	(23) 63.9%	(13) 36.1%		(29) 80.6%	(7) 19.4%		(32) 88.9%	(4) 11.1%	
Nodal stage									
N0	(20) 39.2%	(31) 60.8%	**0.028***	(29) 56.9%	(22) 43.1%	0.07	(33) 64.7%	(18) 35.3%	**0.032***
N1	(17) 68%	(8) 32%		(20) 80%	(5) 20%		(22) 88%	(3) 12%	
Distal metastasis									
M0	(22) 41.5%	(31) 58.5%	0.080	(27) 50.0%	(27) 50.0%	0.098	(35) 66%	(18) 34%	0.09
M1	(15) 65.2%	(8) 34.8%		(10) 45.5%	(12) 54.5%		(20) 87%	(3) 13%	
Relapse									
Absent	(18) 45%	(22) 55%	0.498	(27) 67.5%	(13) 32.5%	0.561	(30) 75%	(10) 25%	0.58
Present	(19) 52.8%	(17) 47.2%		(22) 61.1%	(14) 38.9%		(25) 69.4%	(11) 30.6%	
RAD51									
Low expression	(14) 31.8%	(30) 68.2%	**0.001***	(27) 61.4%	(17) 38.6%	0.507	(27) 61.4%	(17) 38.6%	**0.018**
High expression	(23) 71.9%	(9) 28.1%		(22) 68.8%	(10) 31.2%		(28) 87.5%	(4) 12.5%	

ISUP: International Society of Urologic Pathologists, WHO: World Health Organization, ccRCC: Clear cell renal cell carcinoma

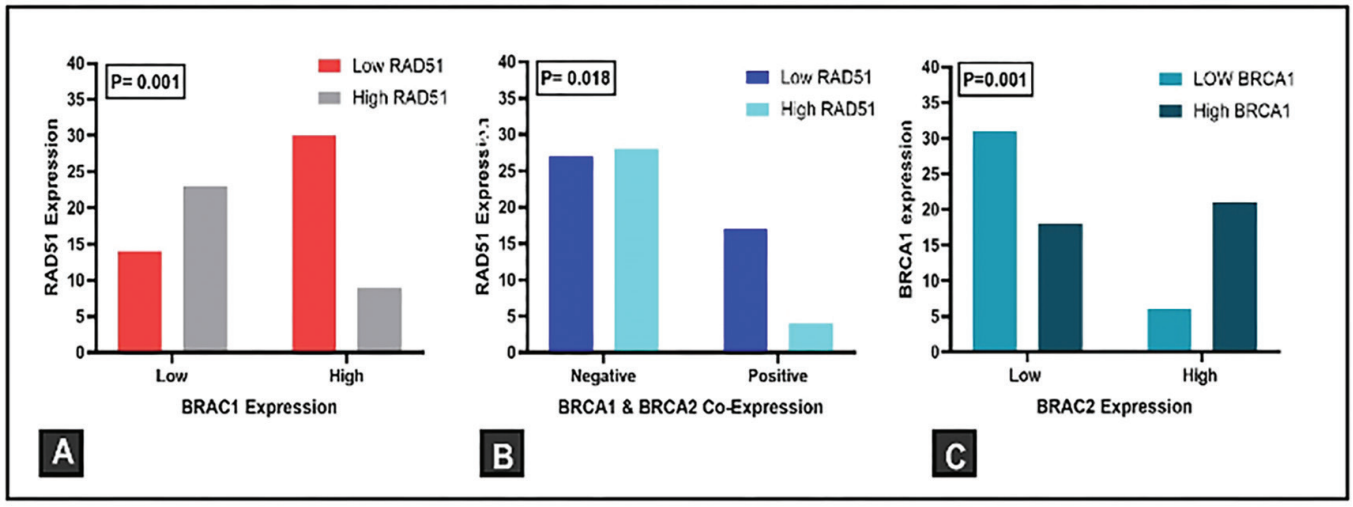


Figure 3. *RAD51* expression showed significantly inverse association with *BRCA1* (A), and co-expression of *BRCA1* & *BRCA2* (B). Direct significant association between *BRCA1* and *BRCA2* (C)

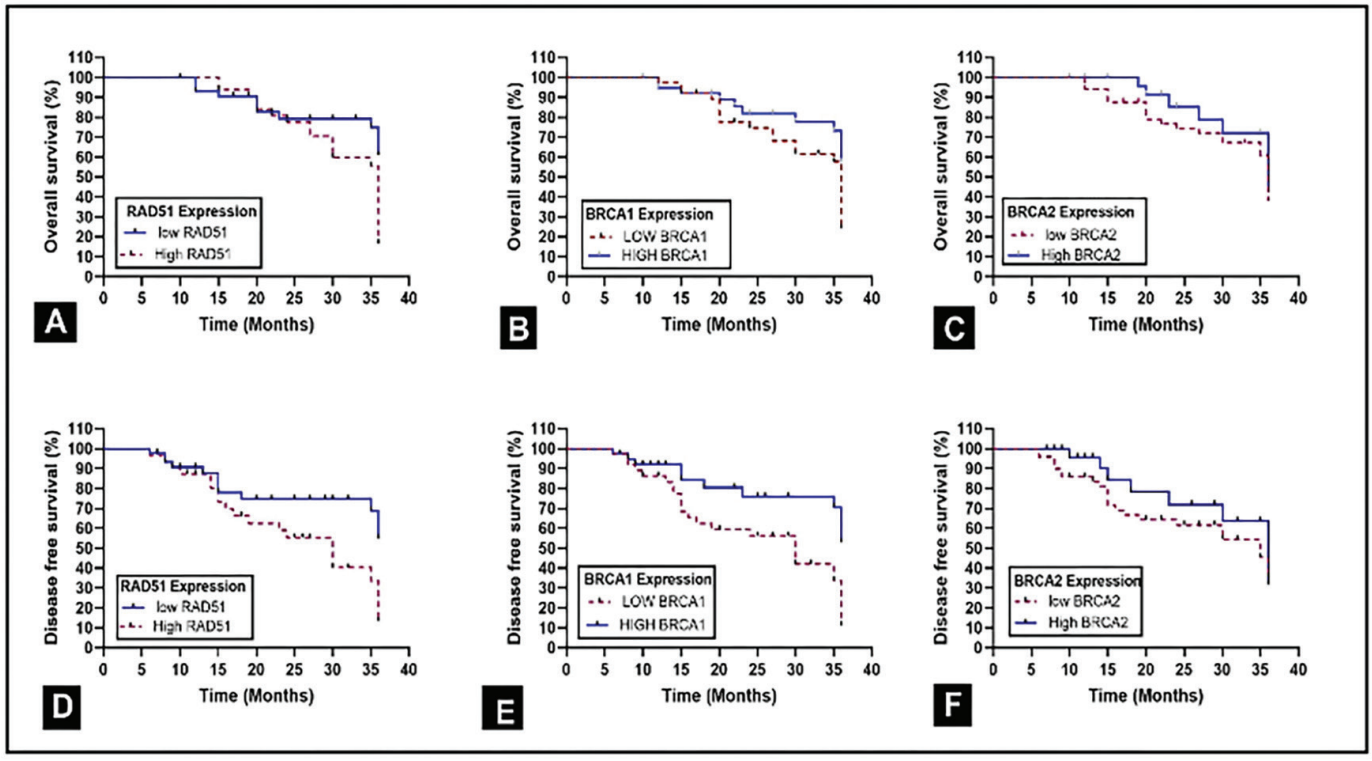


Figure 4. Kaplan-Meier plot, upper panel: Overall survival, lower panel: Disease free survival. (A&F) all studied patient: (A&D) stratified by *RAD51*, (B&E) stratified by *BRCA1*, and (C&F) stratified by *BRCA2*

Table 4. Univariate survival analysis for predicting overall & disease-free survival

Variable	OS			DFS		
	Mean (CI 95%)	Log-rank	p-value	Mean (CI 95%)	Log-rank	p-value
Tumor size						
<7	30.24 (26.09-34.39)	0.132	0.716	27.92 (22.23-33.61)	0.002	0.965
≥7	31.81 (29.79-33.83)			27.80 (24.76-30.84)		
WHO/ISUP grade						
Grade I-II	33.77 (31.58-35.96)	10.78	**0.001***	32.21 (29.17-35.25)	11.46	0.001*
Grade III-IV	29.58 (26.87-32.29)			24.59 (20.87-28.30)		
Vascular invasion						
Present	29.32 (24.57-34.06)	0.668	0.414	26.72 (20.25-33.18)	0.44	0.504
Absent	32.17 (30.34-34.00)			28.28 (25.38-31.17)		
Necrosis						
Present	29.80 (26.76-32.85)	2.8	0.094	24.45 (20.08-28.82)	3.45	0.063
Absent	32.74 (30.58-34.91)			30.39 (27.21-33.57)		
Tumor stage						
T1	31.84 (27.68-36.01)	8.14	**0.043***	29.74 (23.46-36.03)	10.38	**0.016***
T2	33.75 (31.04-36.46)			32.20 (28.42-35.98)		
T3	31.2 (27.49-34.91)			27.46 (21.66-33.29)		
T4	28.92 (24.87-32.98)			22.36 (17.25-27.47)		
Tumor stage grouping						
Early stage	33.10 (30.80-35.40)	7.172	**0.007***	31.37 (28.05-34.70)	8.77	**0.003***
Advanced stage	29.96 (27.22-32.70)			24.74 (20.91-28.57)		
Nodal stage						
N0	32.71 (30.69-34.73)	8.16	**0.004***	30.61 (27.64-33.57)	9.06	**0.003***
N1	29.23 (25.79-32.68)			23.15 (18.62-27.67)		
Distal metastasis						
M0	32.48 (30.47-34.49)	5.35	**0.02***	30.28 (27.33-33.277)	7.01	**0.008***
M1	29.42 (25.79-33.05)			22.97 (18.17-27.78)		
Relapse						
Absent	33.45 (31.26-35.64)	16.05	**<0.001***	32.10 (29.25-34.95)	17.26	**<0.001***
Present	29.30 (26.44-32.16)			23.28 (19.31-27.25)		
RAD51						
Low expression	32.04 (29.49-34.60)	5.27	**0.02***	29.96 (26.40-33.52)	6.02	**0.014***
High expression	30.93 (28.41-33.46)			25.57 (21.67-29.46)		
BRCA1						
Low expression	30.52 (27.91-33.12)	3.93	**0.04***	25.30 (21.56-29.05)	6.86	**0.009***
High expression	32.40 (29.85-34.96)			30.79 (27.23-34.35)		
BRCA2						
Low expression	30.66 (28.25-33.07)	0.72	0.39	26.71 (23.35-30.08)	0.65	0.41
High expression	32.79 (30.12-35.45)			30.03 (25.66-34.41)		
High co-expression of *BRCA1* and *BRCA2*						
Positive	33.56 (30.69-36.44)	2.70	0.10	32.00 (27.49-36.50)	3.46	0.06
Negative	30.67 (28.46-32.93)			26.399 (23.20-29.59)		

OS: Overall survival, DFS: Disease free survival, CI: Confidence interval, *: Significant, ISUP: International Society of Urologic Pathologists, WHO: World Health Organization, ccRCC: Clear cell renal cell carcinoma

Table 5. Multivariate COX-regression analysis for detection of the most independent prognostic factor affecting patient overall survival

Variable	Multivariate	
	HR (LL-UL CI 95%)	**p-value**
WHO/ISUP grade	0.38 (0.104-1.44)	0.158
Tumor stage	0.069 (0.009-0.52)	0.82
Nodal stage	1.13 (0.37-3.39)	**0.01***
Distal metastasis	13.12 (1.96-87.68)	**0.008***
Relapse	1.32 (0.52-3.33)	0.058
RAD51	0.78 (0.32-1.90)	0.59
BRCA1	0.30 (0.09-1.03)	0.56

HR: Homologous recombination, CI: Confidence interval, LL: Lower limit, UL: Upper limit, *: Significant, ISUP: International Society of Urologic Pathologists, WHO: World Health Organization

Multivariate COX-regression Analysis for Detection of the Most Independent Prognostic Factor Affecting Patient Overall Survival

Nodal metastasis (p=0.01) and distant metastasis (p=0.008) emerged as the most significant independent prognostic factors affecting OS in ccRCC patients in multivariate Cox proportional-hazards analysis.

Discussion

Genomic instability contributes to tumor initiation and advancement, often resulting from defects in DNA damage repair (DDR) (16). HR, a key DDR pathway, maintains genome stability by repairing DNA DSBs. Due to its role in maintaining genome stability, HR is generally considered a pathway that suppresses tumors. In line with this concept, mutations or deficiencies that result in loss of HR function can also lead to genomic instability and tumor initiation (17).

RAD51, *BRCA1*, and *BRCA2* are crucial proteins in the HR pathway (6), and their relevance to ccRCC has received growing attention as understanding of ccRCC genetics and molecular mechanisms advances. Additionally, their function in DNA repair and cancer development is becoming clearer.

RAD51, a crucial participant in HR, is directly responsible for preserving the stability of the genome. *RAD51* encircles a single broken DNA strand with the assistance of auxiliary proteins, then captures the complementary copy of DNA, aligning it with the sequence of the broken strand (18). Since *RAD51* is essential for maintaining genome stability, *RAD51* expression must be tightly regulated in human cells. Inadequate *RAD51* expression could result in accumulation of DNA breaks. Conversely, an increase in *RAD51* expression could stimulate hyper-recombination, which could cause genomic instability (19).

Studies have reported conflicting findings regarding the prognostic significance of *RAD51* across different cancer types. In breast cancer (20) and non-small cell lung cancer (21), low *RAD51* expression has been correlated with an unfavorable prognosis. Conversely, high *RAD51* expression has been linked to a poor prognosis in colon cancer (8), breast cancer (10), and non-small-cell lung cancer (9).

This study focused on *RAD51* IHC expression in ccRCC and revealed *RAD51* overexpression in tumor cells. High nuclear *RAD51* expression was observed in a considerable proportion (42.1%) of cases and was significantly associated with advanced tumor stages, nodal metastasis, distant metastasis, and disease recurrence. Survival analysis revealed an association between high *RAD51* expression and shorter OS and DFS in patients with ccRCC. These findings support the tumor-promoting role of *RAD51* and its potential as a novel predictive biomarker in ccRCC patients.

Consistent with our results, *RAD51* overexpression has been consistently observed in multiple cancer types across several studies and has been linked to aggressive proliferation and increased metastatic potential. In a study involving 70 neuroblastoma cases, *RAD51* expression was notably elevated in stage IV tumors compared with stages I and II, particularly in cases with bone marrow metastases (22). A previous study reported an association between high expression of *RAD51* and breast cancer with lymph node metastases (23). Furthermore, Qiao et al. (9) established *RAD51* expression as a potential prognostic indicator in lung cancer, showing that high *RAD51* expression in tumors predicts poor patient survival.

Lu et al. (18) analyzed *RAD51* expression in various cancers, including ccRCC. They found that the expression of *RAD51* was notably elevated in cancerous cells compared with adjacent tissues. Furthermore, the research indicated a strong association between *RAD51* expression and both advanced pathological stages and DFS. Moreover, the study suggested that the expression of *RAD51* was linked to several important immune checkpoints and immunosuppressive genes, indicating its potential impact on controlling the immune response in tumors through regulation of immune checkpoint activity.

RAD51, despite its vital function in the repair of damaged DNA and its possible role as a tumor suppressor, has been linked to genomic instability and the onset of cancer when overexpressed. Increased *RAD51* expression can lead to accumulation of genotoxic *RAD51* on undamaged chromatin, resulting in reduced HR efficiency (24). Additionally, *RAD51* overexpression can positively regulate cell proliferation, decrease intracellular reactive oxygen species production, and regulate aerobic glycolysis by targeting hypoxia-inducible factor 1α, ultimately contributing to tumor progression (25). *RAD51* is also known to increase the activity of transcription factors, thereby promoting epithelial-mesenchymal transition and production of metalloproteinases (26).

Overexpression of *RAD51* in malignant tissue is linked to a marked rise in HR activity, enhancing tumor cell genetic flexibility. Furthermore, it is believed that it improves the ability to repair DNA breaks, thereby protecting cells from DNA-damaging treatments and conferring resistance to conventional cancer therapies. Consequently, inhibiting *RAD51* to render HR-proficient tumor cells HR-deficient may sensitize them to chemotherapeutic agents. Indeed, some *RAD51* inhibitors have proven effective against certain cancers (27). In ccRCC Liu and Weng (28), 2022 stated that patients with low *RAD51* expression were found to be more likely to respond to immune checkpoint blockade immunotherapy. These findings indicate that *RAD51* protein may serve as a poor prognostic indicator and a potential target for developing anti-tumor strategies for ccRCC patients, necessitating further investigation.

BRCA1 and *BRCA2* are recognized as important tumor suppressor genes that help to prevent tumors by maintaining the stability of the genome. They perform complex tasks in the repair of DNA damage (29). *BRCA1* functions early in HR by detecting DNA damage and facilitating end resection, allowing ssDNA to bind replication protein A (RPA) before RAD51 replaces RPA on the ssDNA. *BRCA2*, aided by *BRCA1* and *PALB2*, displaces RPA and loads *RAD51* onto the resected DNA, forming a *RAD51*-ssDNA filament that is essential for HR and for blocking the detrimental single-strand annealing pathway (30).

Although *BRCA1* and *BRCA2* mutations are mainly linked to ovarian and breast carcinomas (31,32), research on their role in ccRCC remains under active investigation. Understanding these associations could offer valuable insights for improved risk assessment, targeted therapies, and monitoring strategies for affected individuals.

In this study, high IHC expression of *BRCA1*, *BRCA2*, and co-expression of *BRCA1* and *BRCA2* in ccRCC patients were 51.3%, 35.5%, and 27.6%, respectively, and their expression was significantly associated with several favorable prognostic factors, including early tumor stage and absence of lymphatic spread. Furthermore, survival analysis demonstrated an association between high *BRCA1* expression and longer OS and DFS in ccRCC patients. These findings indicate that *BRCA1* and *BRCA2* may play a role in suppressing progression of ccRCC and could be good prognostic indicators for patients with ccRCC.

In 2011, the first report documented a *BRCA1* germline mutation in a Pakistani patient with an aggressive form of ccRCC (33). In the Chinese population, inherited mutations in DDR-related genes, including *BRCA1*, have also been reported in RCC patients (34). A previous study reported a significant association between *BRCA1* alterations and the aggressiveness of ccRCC (35). In contrast, another study found no evidence that *BRCA1* mutations play a role in the development of kidney cancer in Polish individuals (36).

Recognizing VHL as a tumor suppressor gene in RCC (4), Scanlon et al. (37) reported that VHL-deficient cells in RCC had a decreased ability to carry out HR and reduced levels of specific HR genes, such as *BRCA1*. Additionally, VHL loss increased ER-α, which can bind to *BRCA1*, reduce *BRCA1* expression, block *BRCA1-RAD51* interaction, and induce γ-tubulin expression, which is strongly linked to resistance to microtubule-targeted therapy such as Taxol. This may represent a mechanism of drug resistance observed in both RCC and *BRCA1*-deficient cancers.

Diez-Calzadilla et al. (35) found that changes in *BRCA2* were linked to the development of RCC and were strongly associated with aggressive tumors, including higher Fuhrman grades and an increased risk of distant metastasis. Liu et al. (38) suggested that *BRCA2* may be linked to colorectal cancer, ovarian cancer, and RCC by interacting with downregulated BCCIP.

Souza's et al. (39) and Kong et al., (40) indicate that in certain RCCs with a particular morphology, a *BRCA2* mutation may serve as a key mutation. *BRCA2* mutations may contribute to tumor aggressiveness and progression to high-grade RCCs in RCC subtypes such as ccRCC and papillary RCC. Moreover, the chromosomal region containing *BRCA2* is often deleted in sarcomatoid RCC. These findings contradict the conclusions of Złowocka-Perłowska et al. (36), who stated that *BRCA2* does not appear to be associated with the development of kidney cancer. Because of the contradictory information on the involvement of *BRCA2* in RCC.

Mutations in *BRCA1/2* could increase the risk of developing RCC and may have contributed to genomic instability in ccRCC patients; further investigation is required to determine the impact of *BRCA1/2* mutations on ccRCC development.

From a therapeutic standpoint, tumors that harbor *BRCA1/2* germline mutations exhibit biological characteristics resulting in genomic instability, which may make them responsive to DNA-damaging therapies such as platinum-based chemotherapy

and poly (ADP-ribose) polymerase inhibitors (PARPi) (41). It will be interesting to investigate whether patients with ccRCC and *BRCA1/2* mutations could similarly benefit from these treatments.

In this research, we examined the role of *BRCA1* and *BRCA2* as cofactors for *RAD51* and found a significant indirect association between *RAD51* and *BRCA1* expression, suggesting the presence of unknown compensatory mechanisms that allow the maintenance or restoration of *RAD51* recruitment to DNA lesions even when either *BRCA1* or *BRCA2* is absent. Therefore, *RAD51* has a crucial role in the DNA repair mechanisms of most malignant tumors, regardless of whether they have normal or abnormal *BRCA* status (proficient or deficient) (19).

Study Limitations

Median follow-up is 27.4 months, which may be considered relatively short for metastatic ccRCC.

Conclusion

This study highlights the importance of HR proteins, namely *RAD51*, *BRCA1*, and *BRCA2*, in the development and progression of ccRCC. Increased *RAD51* expression and lower expression of *BRCA1* and *BRCA2* are linked to more aggressive tumors and shorter OS and DFS, indicating their potential as significant prognostic markers in IHC analyses and providing insights into novel treatment strategies for ccRCC patients.

Ethics

Ethics Committee Approval: The current study was permitted by the Ethical Committee of Zagazig University according to the Egyptian Ethical Guidelines (approval number: ZU-IRB#11335, date: 12.03.2024).

Informed Consent: Written consent was obtained from each member.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.A.E.M., H.M.A., E.G.A., A.H.H., H.L.M., Concept: A.M.A.E.M., Design: A.M.A.E.M., Data Collection or Processing: A.H.H., H.L.M., Analysis or Interpretation: H.M.A., Literature Search: H.M.A., Writing: A.M.A.E.M., H.M.A., H.L.M.

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

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

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12-49. Erratum in: CA Cancer J Clin. 2024;74:203. [Crossref]
2. Lobo J, Ohashi R, Amin MB, Berney DM, Compérat EM, Cree IA, Gill AJ, Hartmann A, Menon S, Netto GJ, Raspollini MR, Rubin MA, Tan PH, Tickoo SK, Tsuzuki T, Turajlic S, Zhou M, Srigley JR, Moch H. WHO 2022 landscape of papillary and chromophobe renal cell carcinoma. Histopathology. 2022;81:426-438. [Crossref]
3. Makhov P, Joshi S, Ghatalia P, Kutikov A, Uzzo RG, Kolenko VM. Resistance to systemic therapies in clear cell renal cell carcinoma: mechanisms and management strategies. Mol Cancer Ther. 2018;17:1355-1364. [Crossref]
4. de Cubas AA, Rathmell WK. Epigenetic modifiers: activities in renal cell carcinoma. Nat Rev Urol. 2018;15:599-614. [Crossref]
5. Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. Eur J Cancer. 2016;60:49-58. [Crossref]
6. Pádua JDB, Mariano CFA, Fabro AT, Tirapelli DPDC, Sankarankutty AK, Dos Santos JS, Brunaldi MO. Prognostic value of the immunohistochemical expression of RAD51 and BRCA2 in gastric adenocarcinoma. J Histochem Cytochem. 2022;70:199-210. [Crossref]
7. Gachechiladze M, Škarda J, Soltermann A, Joerger M. RAD51 as a potential surrogate marker for DNA repair capacity in solid malignancies. Int J Cancer. 2017;141:1286-1294. [Crossref]
8. Li Y, Wang WY, Xiao JH, Xu F, Liao DY, Xie L, Wang J, Luo F. Overexpression of Rad51 predicts poor prognosis in colorectal cancer: our experience with 54 patients. PLoS One. 2017;12:e0167868. Retraction in: PLoS One. 2018;13:e0206398. [Crossref]
9. Qiao GB, Wu YL, Yang XN, Zhong WZ, Xie D, Guan XY, Fischer D, Kolberg HC, Kruger S, Stuerzbecher HW. High-level expression of Rad51 is an independent prognostic marker of survival in non-small-cell lung cancer patients. Br J Cancer. 2005;93:137-143. [Crossref]
10. Maacke H, Opitz S, Jost K, Hamdorf W, Henning W, Krüger S, Feller AC, Lopens A, Diedrich K, Schwinger E, Stürzbecher HW. Over-expression of wild-type Rad51 correlates with histological grading of invasive ductal breast cancer. Int J Cancer. 2000;88:907-913. [Crossref]
11. Inoue K, Fry EA. Haploinsufficient tumor suppressor genes. Adv Med Biol. 2017 1st Quarter;118:83-122. [Crossref]
12. Zhao W, Steinfeld JB, Liang F, Chen X, Maranon DG, Jian Ma C, Kwon Y, Rao T, Wang W, Sheng C, Song X, Deng Y, Jimenez-Sainz J, Lu L, Jensen RB, Xiong Y, Kupfer GM, Wiese C, Greene EC, Sung P. BRCA1-BARD1 promotes RAD51-mediated homologous DNA pairing. Nature. 2017 Oct 19;550(7676):360-365. [Crossref]
13. Kwon Y, Rösner H, Zhao W, Selemenakis P, He Z, Kawale AS, Katz JN, Rogers CM, Neal FE, Badamchi Shabestari A, Petrosius V, Singh AK, Joel MZ, Lu L, Holloway SP, Burma S, Mukherjee B, Hromas R, Mazin A, Wiese C, Sørensen CS, Sung P. DNA binding and RAD51 engagement by the BRCA2 C-terminus orchestrate DNA repair and replication fork preservation. Nat Commun. 2023;14:432. [Crossref]
14. Abul-Husn NS, Soper ER, Odgis JA, Cullina S, Bobo D, Moscati A, Rodriguez JE; CBIPM Genomics Team; Regeneron Genetics Center; Loos RJF, Cho JH, Belbin GM, Suckiel SA, Kenny EE. Exome sequencing reveals a high prevalence of BRCA1 and BRCA2 founder variants in a diverse population-based biobank. Genome Med. 2020;12:2. [Crossref]
15. Du C, Peng Y, He Y, Chen G, Chen H. Low levels of BRCA1 protein expression predict a worse prognosis in stage I-II colon cancer. Int J Biol Markers. 2021;36:47-53. [Crossref]
16. Jiang M, Jia K, Wang L, Li W, Chen B, Liu Y, Wang H, Zhao S, He Y, Zhou C. Alterations of DNA damage response pathway: biomarker and therapeutic strategy for cancer immunotherapy. Acta Pharm Sin B. 2021;11:2983-2994. [Crossref]

17. Matos-Rodrigues G, Guirouilh-Barbat J, Martini E, Lopez BS. Homologous recombination, cancer and the 'RAD51 paradox'. NAR Cancer. 2021;3:zcab016. [Crossref]
18. Lu H, Li Z, Liu L, Tao Y, Zhou Y, Mao X, Zhu A, Wu H, Zheng X. A pan-cancer analysis of the oncogenic roles of RAD51 in human tumors. Advanced Gut & Microbiome Research. 2022:1-28. [Crossref]
19. Orhan E, Velazquez C, Tabet I, Sardet C, Theillet C. Regulation of RAD51 at the transcriptional and functional levels: what prospects for cancer therapy? Cancers (Basel). 2021;13:2930. [Crossref]
20. Alshareeda AT, Negm OH, Aleskandarany MA, Green AR, Nolan C, TigHhe PJ, Madhusudan S, Ellis IO, Rakha EA. Clinical and biological significance of RAD51 expression in breast cancer: a key DNA damage response protein. Breast Cancer Res Treat. 2016;159:41-53. [Crossref]
21. Gachechiladze M, Škarda J, Kolek V, Grygárková I, Langová K, Bouchal J, Kolář Z, Baty F, Stahel R, Weder W, Soltermann A, Joerger M. Prognostic and predictive value of loss of nuclear RAD51 immunoreactivity in resected non-small cell lung cancer patients. Lung Cancer. 2017;105:31-38. [Crossref]
22. Xu Y, Chen K, Cai Y, Cheng C, Zhang Z, Xu G. Overexpression of Rad51 predicts poor prognosis and silencing of Rad51 increases chemo-sensitivity to doxorubicin in neuroblastoma. Am J Transl Res. 2019;11:5788-5799. [Crossref]
23. Wu R, Patel A, Tokumaru Y, Asaoka M, Oshi M, Yan L, Ishikawa T, Takabe K. High RAD51 gene expression is associated with aggressive biology and with poor survival in breast cancer. Breast Cancer Res Treat. 2022;193:49-63. [Crossref]
24. Kim PM, Allen C, Wagener BM, Shen Z, Nickoloff JA. Overexpression of human RAD51 and RAD52 reduces double-strand break-induced homologous recombination in mammalian cells. Nucleic Acids Res. 2001;29:4352-4360. [Crossref]
25. Zhang X, Ma N, Yao W, Li S, Ren Z. RAD51 is a potential marker for prognosis and regulates cell proliferation in pancreatic cancer. Cancer Cell Int. 2019;19:356. [Crossref]
26. Wiegmans AP, Al-Ejeh F, Chee N, Yap PY, Gorski JJ, Da Silva L, Bolderson E, Chenevix-Trench G, Anderson R, Simpson PT, Lakhani SR, Khanna KK. Rad51 supports triple negative breast cancer metastasis. Oncotarget. 2014;5:3261-3272. [Crossref]
27. Grundy MK, Buckanovich RJ, Bernstein KA. Regulation and pharmacological targeting of RAD51 in cancer. NAR Cancer. 2020;2:zcaa024. [Crossref]
28. Liu H, Weng J. A pan-cancer bioinformatic analysis of RAD51 regarding the values for diagnosis, prognosis, and therapeutic prediction. Front Oncol. 2022;12:858756. [Crossref]
29. Jeggo PA, Pearl LH, Carr AM. DNA repair, genome stability and cancer: a historical perspective. Nat Rev Cancer. 2016;16:35-42. [Crossref]
30. Yang H, Li Q, Fan J, Holloman WK, Pavletich NP. The BRCA2 homologue Brh2 nucleates RAD51 filament formation at a dsDNA-ssDNA junction. Nature. 2005;433:653-657. [Crossref]
31. Kechin AA, Boyarskikh UA, Ermolenko NA, Tyulyandina AS, Lazareva DG, Avdalyan AM, Tyulyandin SA, Kushlinskii NE, Filipenko ML. Loss of heterozygosity in BRCA1 and BRCA2 genes in patients with ovarian cancer and probability of its use for clinical classification of variations. Bull Exp Biol Med. 2018;165:94-100. [Crossref]
32. Semmler L, Reiter-Brennan C, Klein A. BRCA1 and breast cancer: a review of the underlying mechanisms resulting in the tissue-specific tumorigenesis in mutation carriers. J Breast Cancer. 2019;22:1-14. [Crossref]
33. Rashid MU, Gull S, Faisal S, Khaliq S, Asghar K, Siddiqui N, Amin A, Hamann U. Identification of the deleterious 2080insA BRCA1 mutation in a male renal cell carcinoma patient from a family with multiple cancer diagnoses from Pakistan. Fam Cancer. 2011;10:709-712. [Crossref]
34. Kong W, Yang T, Wen X, Mu Z, Zhao C, Han S, Tian J, Zhang X, Zhou T, Zhang Y, Lou F, Cao S, Wang H, Zhang J. Germline mutation landscape and associated clinical characteristics in Chinese patients with renal cell carcinoma. Front Oncol. 2021;11:737547. [Crossref]
35. Diez-Calzadilla NA, Noguera Salvá R, Soriano Sarrió P, Martínez-Jabaloyas JM. Genetic profile and immunohistochemical study of clear cell renal carcinoma: pathological-anatomical correlation and prognosis. Cancer Treat Res Commun. 2021;27:100374. [Crossref]
36. Złowocka-Perłowska E, Tołoczko-Grabarek A, Narod SA, Lubiński J. Germline BRCA1 and BRCA2 mutations and the risk of bladder or kidney cancer in Poland. Hered Cancer Clin Pract. 2022;20:13. [Crossref]
37. Scanlon SE, Hegan DC, Sulkowski PL, Glazer PM. Suppression of homology-dependent DNA double-strand break repair induces PARP inhibitor sensitivity in VHL -deficient human renal cell carcinoma. Oncotarget. 2018;9:4647-4660. [Crossref]
38. Liu X, Cao L, Ni J, Liu N, Zhao X, Wang Y, Zhu L, Wang L, Wang J, Yue Y, Cai Y, Jin J. Differential BCCIP gene expression in primary human ovarian cancer, renal cell carcinoma and colorectal cancer tissues. Int J Oncol. 2013;43:1925-1934. [Crossref]
39. Souza VC, de Freitas Vinhas C, Miguel D, Athanazio DA, Trpkov K. Renal cell carcinoma morphologically similar to fumarate hydratase-deficient RCC in a patient with BRCA2 germline mutation. Pathol Int. 2018;68:541-542. [Crossref]
40. Kong Q, Gagan J, Zhou M. A high-grade renal cell carcinoma with somatic BRCA2 mutation. Pathol Int. 2019;69:432-433. [Crossref]
41. Nientiedt C, Tolstov Y, Volckmar AL, Endris V, Bonekamp D, Haberkorn U, Jäger D, Sültmann H, Stenzinger A, Hohenfellner M, Grüllich C, Duensing S. PARP inhibition in BRCA2-mutated prostate cancer. Ann Oncol. 2017;28:189-191. [Crossref]

ORIGINAL RESEARCH
Functional Urology

Doi: 10.4274/jus.galenos.2025.2025-9-7
J Urol Surg 2026;13(3):199-206

Long-term Outcomes of Trans Obturator Mid-urethral Sling Procedure in the Treatment of Female Stress Urinary Incontinence: The Same Surgeon, Surgical Technique, and Material

Ersin Köseoğlu[1], Kayhan Tarım[1], Ömer Acar[1,2], Tufan Tarcan[1,3]

[1]Koç University Faculty of Medicine, Department of Urology, İstanbul, Türkiye
[2]University of Illinois College of Medicine, Department of Urology, Chicago, United States of America
[3]Marmara University Faculty of Medicine, Department of Urology, İstanbul, Türkiye

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

Transobturator mid-urethral sling (TO-MUS) is widely used for female stress urinary incontinence, but long-term data remain limited. Prior studies are often heterogeneous with respect to surgical technique, surgeon experience, and sling material, which limits their generalizability. This study provides long-term outcomes (median follow-up of 125 months) of TO-MUS performed by a single surgeon, using a uniform technique and material. High treatment success (83.3%) and patient satisfaction (92.8%), with no mesh-related complications, demonstrate the durability and safety of TO-MUS under standardized conditions.

Abstract

Objective: To evaluate the long-term outcomes of the transobturator mid-urethral sling (TO-MUS) procedure for the treatment of female stress urinary incontinence (SUI) when performed by a single surgeon using a standardized surgical technique and the same material.

Materials and Methods: Patients (n=42) who underwent TO-MUS between 2006 and 2023 were retrospectively analyzed. Inclusion criteria were a diagnosis of urodynamic SUI confirmed by the International Continence Society Uniform Cough Stress Test and a minimum follow-up duration of 12 months. Treatment success was defined as no pad use and a negative response to item 6 of the International Consultation on Incontinence Questionnaire-Short Form. Patient satisfaction was assessed via structured telephone interviews. The treatment success and patient satisfaction rates were compared between patients with follow-up periods above and below ten years. Group 1 comprises patients with follow-up durations ranging from 12 to 120 months, while Group 2 consists of patients with follow-up durations of 121 months or more.

Results: With a median follow-up of 125 months (range: 12-204). Group 1 (n=24) had a median follow-up duration of 69.5 months, while Group 2 (n=18) had a median follow-up duration of 154 months. TO-MUS was the primary intervention in 92.9% of patients. Across all patients, treatment success and patient satisfaction rates were 83.3% (35/42) and 92.8% (39/42), respectively. No statistically significant differences were observed between the two groups. *De novo* urgency was reported in 16.6% of patients; one patient experienced persistent voiding difficulty. Three patients (7.1%) required reoperation. No mesh-related complications were observed.

Conclusion: This study presents one of the longest follow-up periods (more than 10 years) among single-surgeon, single-center TO-MUS case series. High long-term treatment success and satisfaction rates, together with low complication and reoperation rates support the durability and safety of the TO-MUS procedure in carefully selected patients when it is performed by experienced surgeons using standardized techniques and surgical materials.

Keywords: Complication, female, mesh, stress urinary incontinence, TOT, urodynamics

Correspondence: Tufan Tarcan Prof. MD, Koç University Faculty of Medicine; Marmara University Faculty of Medicine, Department of Urology, İstanbul, Türkiye
E-mail: bilgi@tufantarcan.com **ORCID-ID:** orcid.org/0000-0002-3387-3524
Received: 15.09.2025 **Accepted:** 16.12.2025 **Epub:** 29.06.2026 **Publication Date:** 01.09.2026

Cite this article as: Köseoğlu E, Tarım K, Acar Ö, Tarcan T. Long-term outcomes of trans obturator mid-urethral sling procedure in the treatment of female stress urinary incontinence: the same surgeon, surgical technique, and material. J Urol Surg. 2026;13(3):199-206

Introduction

Mid-urethral sling (MUS) procedures have become the gold-standard surgical treatment for stress urinary incontinence (SUI) in women, owing to their minimally invasive nature and favorable short- to mid-term outcomes. Among these, the transobturator MUS (TO-MUS) is widely adopted due to its lower risk of bladder injury and shorter operative time than the retropubic (RP) approach (1,2). However, long-term data on TO-MUS procedures, particularly those performed by the same surgeon whose surgical technique and choice of mesh material remained unchanged over the study period, are scarce. Another limitation in many prior studies has been heterogeneity in surgical techniques, surgeon experience, and patient selection. Moreover, few studies have assessed both objective and subjective measures of success, together with long-term safety, under standardized conditions. In addition to outcome variability, there is increasing concern about procedure-related complications, such as mesh exposure, *de novo* urgency, and voiding dysfunction, all of which may contribute to patient dissatisfaction. The TO-MUS procedure has been increasingly de-emphasized in certain guidelines and has even been prohibited in some countries (3). However, the growing negative climate surrounding TO-MUS lacks evidence-based support from data obtained in long-term studies conducted in standardized clinical settings. This study aims to address this gap by presenting long-term outcomes of TO-MUS procedures performed using a uniform surgical technique and mesh material in a well-defined patient cohort.

Materials and Methods

Study Design and Patient Selection

Following the institutional review board approval from Koç University Ethics Committee (approval number: 2025.339.IRB2.161, date: 31.07.2025), the medical records of all female patients who underwent TO-MUS using the same surgical technique and material (Boston Scientific Obtryx II Transobturator Mid-urethral Sling System®) between 2006 and 2023 were retrospectively reviewed. Eligible patients had received TO-MUS as primary or secondary treatment for SUI and had a minimum postoperative follow-up of 12 months.

Patients with morbid obesity (body mass index ≥30) and/or those who could not be reached by telephone or were lost to follow-up were excluded. It should be noted that the early years of the study (2006-2015) relied on paper-based records, and accessing archived files posed difficulties. Some patient files were incomplete or could not be retrieved due to archival limitations, contributing to the number of unreachable patients. No patient was excluded based on clinical outcome; the only reason for exclusion was the absence of sufficient follow-up information.

Preoperative Assessment

All patients underwent a standardized preoperative evaluation, which included pelvic examination for the assessment of pelvic organ prolapse (POP), graded according to the Baden-Walker system, and assessment of urethral mobility using the Q-tip test. Urethral hypermobility was defined as a Q-tip excursion >300. The evaluation also incorporated the International Continence Society Cough Stress Test (ICS-Uniform CST) and invasive urodynamic studies (UDS) to confirm the diagnosis of SUI (4-7). Although the ICS-Uniform CST was formally introduced in 2018, the same standardized CST protocol—consistent with the currently accepted ICS method—had been routinely used in our clinic throughout the study period. UDS was performed after manual reduction of POP in patients with POP greater than grade 2. When POP of grade 3 or higher was identified, concomitant POP surgery (anterior and/or posterior vaginal wall repairs) was performed.

Surgical Material

The TO sling system used in this study incorporated a halo-type trocar specifically designed to facilitate passage of the device through the obturator foramen. The trocar-tip length was optimized for efficient TO insertion, and the integrated association loop enabled secure trocar engagement and straightforward removal. The system featured thin dilator legs intended to create a minimal delivery tract, thereby allowing smooth passage of the sling with reduced tissue disruption. The suburethral segment of the mesh was left unsleeved to enhance visualization and ensure precise positioning beneath the urethra. A blue centering tab marked the midpoint of the mesh, enabling equal distribution on either side of the urethra and allowing direct visualization of tension and centering during positioning and sleeve removal. The mesh consisted of de-tanged polypropylene designed to maintain structural integrity during tensioning and potentially reduce irritation of the urethral wall (8).

Surgical Technique

All procedures were performed by the same surgeon on an inpatient basis under general anesthesia, in the lithotomy position. The patient was positioned in the lithotomy position with the hips hyperflexed. A 2 cm incision was made on the anterior vaginal wall at the level of the mid-urethra. Blunt dissection was carried out laterally until the index finger contacted the inner surface of the ischiopubic ramus and the obturator foramen. Bilateral horizontal lines were drawn from the clitoral level to the inguinofemoral sulcus. A 1 cm vertical skin incision was made at each intersection of the lines with the sulcus. Sling's halo trocars were used to perforate the obturator membrane and then directed medially, guided by a finger inserted through the vaginal incision, to emerge into

the vaginal canal. The tape was mounted on the trocar and then pulled through the skin incision on each side. Tension was adjusted to ensure that the dissecting scissors could lie flat between the tape and the urethra without resistance (9,10). A cystoscopy was performed immediately after trocar insertion to assess for any inadvertent intravesical placement of the mesh and to verify bilateral ureteral patency by confirming clear efflux from both ureteral orifices. The incisions were closed using absorbable sutures. The Foley catheter was removed 12-24 hours after surgery.

In cases where concomitant POP surgery was performed, vaginal wall repair was always carried out through a separate incision, rather than using the same incision as the TO-MUS procedure.

Follow-up and Outcome Measures

Although a structured early postoperative follow-up protocol (at 1 week, 3 months, and 12 months) was routinely performed in our clinic, these visits were not included in the analysis due to inconsistent documentation over the long study period. Long-term outcomes were therefore based on standardized telephone interviews administered uniformly to all patients. Patients' current condition was assessed via structured telephone interviews conducted by the same urologist; the interviews consisted of six standardized questions evaluating continence status International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF item 6), pad use, patient satisfaction, *de novo* urgency, voiding difficulty, and any pain or symptoms suggestive of mesh-related complications. Treatment success was defined as absence of pad use and a negative response to the sixth item of the ICIQ-SF, indicating no current SUI. Patient satisfaction was defined as a self-reported improvement in urinary symptoms and an affirmative response to the question "Would you recommend this procedure to a friend with similar complaints?"

To assess whether treatment outcomes differed between patients with follow-up durations of up to 10 years and those with longer follow-up, outcomes were compared between two groups defined by follow-up duration:

- Group 1: 12 to 120 months,
- Group 2: 121 months and above.

In addition to success and satisfaction rates, any postoperative complications requiring surgical intervention were recorded, as were *de novo* urinary symptoms such as urgency or voiding difficulty.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians with corresponding ranges, given the non-parametric distribution of the data. Categorical variables were summarized as frequencies and percentages. Comparisons between groups were conducted using the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. A p-value less than 0.05 was considered statistically significant.

Results

During the study period (2006-2023), a total of 59 TO-MUS procedures were performed using the same standardized technique and sling material. Among these, 42 patients were successfully reached for long-term follow-up and were included in the analysis. Seventeen patients were excluded due to the inability to contact them despite multiple attempts. The median age was 53 years (range, 34-69 years). TO-MUS was performed as the primary treatment in 39 patients (92.9%) and as a secondary intervention in 3 patients (7.1%) with a history of SUI surgery. All patients had increased urethral mobility, a positive ICS-Uniform CST, and invasive UDS demonstrating SUI. The overall median follow-up duration was 125 months (range, 12-204). The overall treatment success rate was 83.3% (35/42), while the patient satisfaction rate was 92.8% (39/42). Concomitant POP surgeries were performed in 5 patients: 3 anterior wall repair, 1 posterior wall repair, and 1 anterior and posterior wall repair. Regarding safety, 92.8% (39/42) of patients did not require additional intervention for TO-MUS related complications. However, 7 patients (16.6%) developed *de novo* urgency, and 1 patient (2.3%) reported persistent voiding difficulty. Patients who developed *de novo* urgency were managed with oral pharmacotherapy. The patient with persistent voiding difficulty underwent a tape-cut procedure.

A total of 3 patients (7.1%) underwent reoperation. None of those were in the concomitant POP surgery group. All patients reported symptom resolution following the revision procedure and reported no further issues:

- Two patients underwent tape-cut (1 groin pain, 1 difficult micturition),
- One patient underwent re-TO-MUS procedure due to persistent SUI.

Group 1 (n=24, 57.1%) had a median follow-up duration of 69.5 months, while Group 2 (n=18, 42.9%) had a median follow-up duration of 154 months. Outcomes stratified by follow-up duration are presented in Figure 1. There were no statistically significant differences between the two groups in treatment success rates and patient satisfaction rates. The baseline characteristics, perioperative findings, and long-term outcomes

for the entire cohort, with separate columns for each group, are presented in Table 1.

Figures 2 and 3 were constructed using data extracted from previously published studies with ≥5 years of follow-up and outcomes from our own cohort, which were included for direct comparison.

Discussion

MUS were widely regarded as the gold standard for the surgical treatment of female SUI. However, following a 2019 communication from the U.S. Food and Drug Administration (11), the safety and long-term efficacy of these procedures have come under increased scrutiny. Additionally, the National

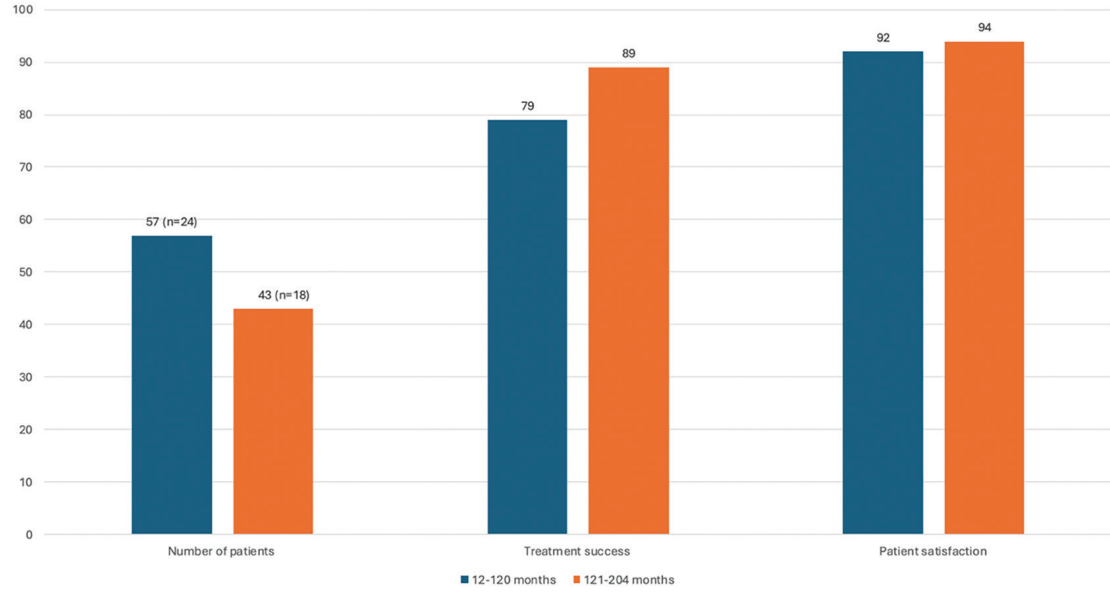


Figure 1. Number of patients (%, n), treatment success (%), and patient satisfaction (%) rates with respect to follow-up duration

Table 1. The baseline characteristics, perioperative findings, and long-term outcomes of the entire cohort, including separate columns for Groups 1 and 2

Parameter	Overall (n=42)	Group 1 (12-120 months, n=24)	Group 2 (≥121 months, n=18)
Baseline characteristics			
Age, median (range), years	53 (34-69)	53.5 (34-66)	50 (34-69)
Urethral hypermobility (%)	100%	100%	100%
Prior SUI surgery (%)	7.1% (3/42)	4.8% (2/42)	2.3% (1/42)
Perioperative features			
Concomitant POP surgery	11.9% (5/42)	3/42	2/42
Intraoperative complications	0	0	0
TO-MUS material	Obtryx II (uniform)	Same	Same
Surgical technique	Standardized (uniform)	Same	Same
Outcomes			
Median follow-up, months	125 (12-204)	69.5 (12-119)	154 (125-204)
Treatment success (%)	83.3% (35/42)	79.2% (19/24)	88.9% (16/18)
Patient satisfaction (%)	92.8% (39/42)	91.7% (22/24)	94.4% (17/18)
De novo urgency (%)	16.6% (7/42)	7.1% (3/42)	9.5% (4/42)
Voiding difficulty (%)	2.3% (1/42)	2.3% (1/42)	0
Reoperation (%)	7.1% (3/42)	4.6% (2/42)	2.3% (1/42)
Mesh-related complications (erosion, extrusion)	0	0	0

TO-MUS: Trans obturator mid-urethral sling, SUI: Stress urinary incontinence, POP: Pelvic organ prolapse

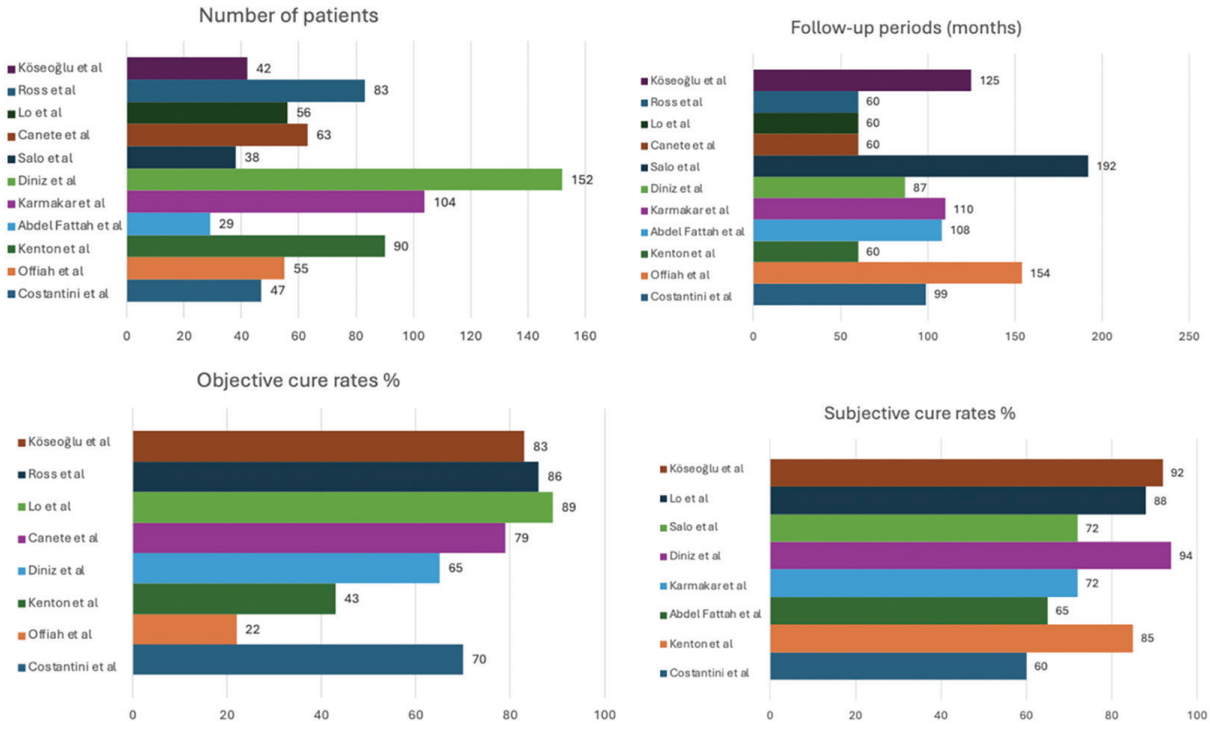


Figure 2. Cohort size (n), median follow-up duration (months), and success rates (%) in selected mid-urethral sling (retropubic and trans obturator) series with follow-up longer than 5 years. The figure includes data extracted from previously published studies as well as the outcomes of the present cohort, incorporated for direct comparison

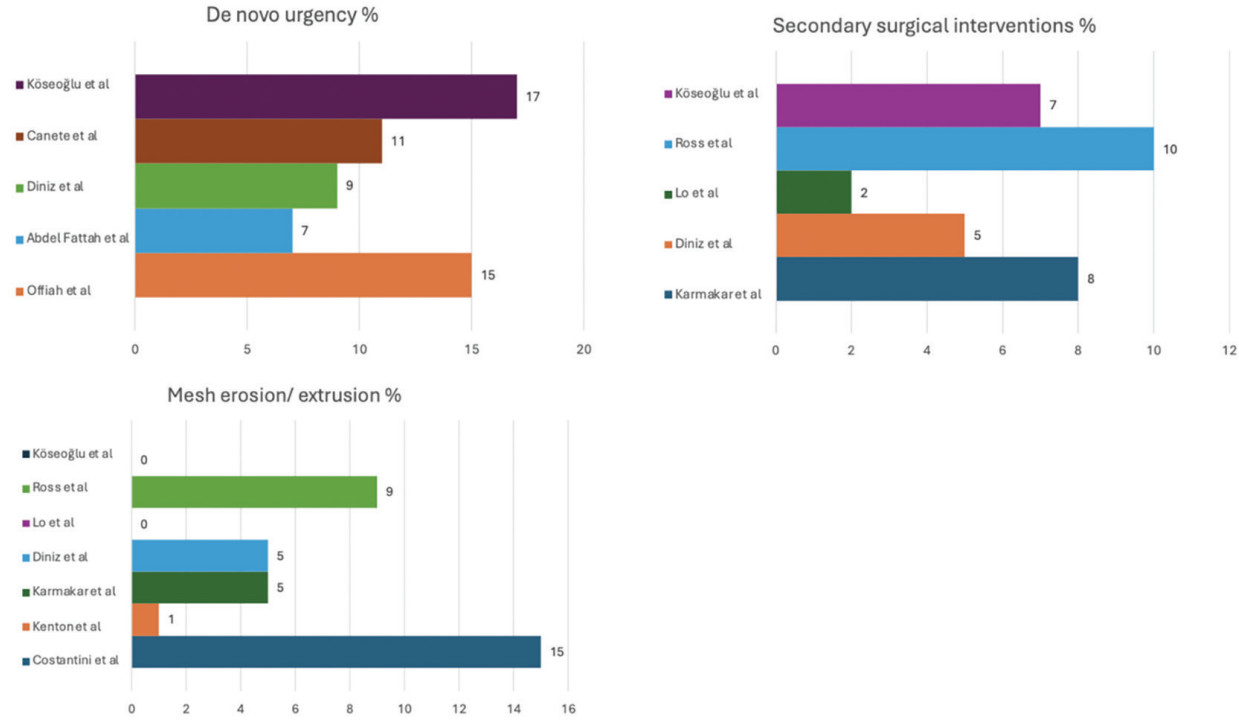


Figure 3. Rates of *de novo* urgency (%), mesh-related complications (%), and reoperation (%) in selected transobturator mid-urethral sling series with follow-up longer than 5 years. This figure displays both literature-derived data and the corresponding outcomes of the current study to allow comparison

Institute for Health and Care Excellence guidelines (3) excluded the TO approach from the recommended surgical options for female SUI. This recommendation was primarily based on findings from the ester systematic review (12), which suggested a higher incidence of mesh exposure associated with the TO route than the RP approach. Nevertheless, the review lacked clarity regarding the consistent use of terminology such as "erosion," "extrusion," and "exposure" across the included studies. Furthermore, most studies had relatively short follow-up durations, typically less than two years. The authors concluded that although MUS procedures appear to be more effective than alternative surgical options, there remains a significant need for robust long-term outcome data. Despite these changes, a recent survey by Karsenty (13), involving 57 urologists from 19 European countries, revealed a contrasting perspective. Of these respondents, 71% specialized in functional urology and 82% were affiliated with academic institutions. Notably, 82% of the participants reported that the TO-MUS remains their preferred surgical technique for treating female SUI (13). This finding highlights the continued clinical favorability and perceived utility of the trans obturator approach among experienced European urologists, despite evolving regulatory guidance. In this context, our study offers valuable insight by providing standardized, long-term follow-up data for TO-MUS procedures with no mesh-related complications. This finding may be explained by the uniform use of a standardized surgical technique and material combined with the expertise of the surgeon who performed all procedures, which together reduced the impact of the learning curve on clinical outcomes.

Our long-term outcomes demonstrate a success rate of 83.3% and a patient satisfaction rate of 92.8%. Objective and subjective success rates for MUS vary based on the duration of follow-up, the criteria used to define success, and the assessment tools employed, such as validated questionnaires, pad tests, or UDS. In most studies, the primary outcomes were objective treatment success and patient-reported satisfaction, commonly referred to as subjective success rates. Leone Roberti Maggiore et al. (14) conducted a systematic review and meta-analysis to evaluate the long-term effectiveness and safety of MUS procedures for SUI based on data from randomized controlled trials and non-randomized studies. Cumulative objective and subjective success rates were 61.6% and 76.5% for RP-MUS and 64.4% and 81.3% for the TO technique, demonstrating similar long-term effectiveness. In the literature, the objective and subjective success rates for all MUS among studies with a follow-up duration of more than 5 years ranged from 22% to 89% and from 64% to 97%, respectively (15-23). The wide variability in reported success rates may be attributed to the heterogeneous criteria used to define treatment success across studies. Offiah et al. (15) reported one of the lowest success rates for MUS procedures: 22% for TO-MUS and 41% for RP-MUS. In their study, treatment success was defined by a particularly stringent criterion: a response of "never" to item 9a of the ICIQ Female Lower Urinary Tract Symptoms questionnaire, which asks, "does urine leak before you can get to the toilet?". Additionally, unlike many other studies, their long-term data included patients with mixed urinary incontinence. These methodological differences underscore the lack of standardized outcome measures in the existing body of literature (Figure 2). The strict definition of treatment success used in our study (no pad use and no leakage on ICIQ-SF Q6) may underestimate clinically meaningful improvement in some patients. While this approach ensures methodological consistency and comparability with prior MUS studies using strict cure criteria, it does not capture partial improvement, which remains clinically important. Patient satisfaction outcomes were therefore reported separately to complement the primary success measure.

To maintain standardization and ensure material reliability, a single type of MUS was used across all our cases. The mesh was selected based on its long-standing clinical use, demonstrated consistent quality, and widespread availability in our country. Locally manufactured or homemade alternatives were not utilized, as they lack comparable long-term reliability and clinical validation. This selection was made to reduce variability associated with implant characteristics and did not reflect any commercial affiliation or bias. Braga et al. (24) demonstrated the importance of using a standard technique and sling material in their prospective study. They similarly demonstrated the long-term efficacy and safety of the TO approach when a standardized surgical technique and a consistent sling material (Monarch tape) were used. In their study, which included only patients with pure SUI treated by a single surgeon, objective and subjective success rates were reported as 80% and 81.4%, respectively, over a 17-year follow-up period. These outcomes are comparable to ours, reinforcing the long-term durability and reliability of the TO-MUS when performed under consistent surgical conditions. Our results are further supported by the study of Salo et al. (23), which compared the long-term outcomes of 34 RP-MUS and 38 TO-MUS procedures over a 16-year follow-up period. All procedures were performed by a single surgeon, utilizing the same type of sling material-gynecare tape for the tension-free vaginal tape group and Monarch tape for the TO-MUS group. The overall subjective success rate was 72%, with similar outcomes observed between the two surgical approaches. The standardized use of sling materials and consistent surgical technique across all cases, as in our study, underscore the importance of reducing procedural variability when assessing the long-term effectiveness of MUS.

In our cohort, *de novo* urgency was observed in 17% of patients, a rate that is consistent with the literature. Among the studies

with at least 5 years of follow-up, the incidence of *de novo* urgency ranged from 2% to 23%, whereas studies focusing exclusively on TO-MUS procedures reported rates of 7%-17% (Figure 3) (3,15,17,18,25). The interpretation of urgency symptoms in long-term follow-up remains challenging, as it is often difficult to determine whether such symptoms are directly attributable to the MUS procedure, attributable to aging, or attributable to the progression of a pre-existing condition (26).

The literature reports that the incidence of mesh-related complications associated with MUS procedures ranges from 0% to 15% (Figure 3) (17,19-21). In our study, no mesh-related complications were identified. Similarly, Lo et al. (19) reported no mesh-related complications among 56 women who underwent TO-MUS procedures, with a five-year follow-up. The absence of mesh-related complications in our cohort may be attributed to the fact that all surgeries were performed by an experienced surgeon using the same standardized technique and material. The relatively small number of TO-MUS procedures analyzed in our study does not reflect the surgeon's overall surgical volume, but rather the highly selective nature of our cohort and the institutional preference toward RP-MUS during the early and mid-2000s. The surgeon who performed all procedures is highly experienced in female and functional urology with more than 500 total procedures performed during the study period.

Study Limitations

The retrospective design, the relatively small sample size, the absence of preoperative ICIQ-SF scores, and the lack of assessment of patient satisfaction using a validated tool should be considered when interpreting the results. Another limitation of our study is that long-term outcomes were based on subjective measures, including self-reported continence status and patient satisfaction, without objective reassessment through repeat physical examination, cough stress test, pad testing, or postoperative urodynamics. Therefore, the results should be interpreted with caution, recognizing that subjective measures may either overestimate or underestimate true continence outcomes. No mesh-related complications were reported by patients during the structured telephone interview; however, since no routine postoperative physical or endoscopic examinations were performed, asymptomatic mesh exposures or erosions cannot be entirely ruled out.

Conclusion

To our knowledge, the present study is among the few that report long-term outcomes of the TO-MUS procedure in a well-defined patient population with SUI confirmed by physical examination, ICS-Uniform CST, and UDS. Homogeneity and extended follow-up strengthen our findings. The standardized technique and the use of a uniform sling material, combined with the surgeon's extensive experience in female and functional urology, likely contributed to the favorable long-term outcomes observed in this highly selected cohort. Prospective multicenter studies with larger cohorts are warranted to validate these findings and to further establish the long-term efficacy and safety of TO-MUS procedures.

Ethics

Ethics Committee Approval: The institutional review board has been approved from Koç University Ethics Committee (approval number: 2025.339.IRB2.161, date: 31.07.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K., T.T., Concept: Ö.A., T.T., Design: E.K., Ö.A., T.T., Data Collection or Processing: E.K., K.T., Analysis or Interpretation: E.K., K.T., Literature Search: E.K., K.T., Writing: E.K., Ö.A.

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

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

References

1. Ford AA, Rogerson L, Cody JD, Aluko P, Ogah JA. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2017;7:CD006375. [Crossref]
2. Nager CW. Midurethral slings: evidence-based medicine vs the medicolegal system. Am J Obstet Gynecol. 2016;214:708.e1-e5. [Crossref]
3. Lau HH, Davila GW, Chen YY, Sartori MGF, Jármy-Di Bella ZIK, Tsai JM, Liu YM, Su TH; FIGO Urogynecology and Pelvic Floor Committee. FIGO recommendations: use of midurethral slings for the treatment of stress urinary incontinence. Int J Gynaecol Obstet. 2023;161:367-385. [Crossref]
4. Guralnick ML, Fritel X, Tarcan T, Espuna-Pons M, Rosier PFWM. ICS Educational Module: cough stress test in the evaluation of female urinary incontinence: introducing the ICS-Uniform Cough Stress Test. Neurourol Urodyn. 2018;37:1849-1855. [Crossref]
5. Rosier PFWM, Schaefer W, Lose G, Goldman HB, Guralnick M, Eustice S, Dickinson T, Hashim H. International Continence Society Good Urodynamic Practices and Terms 2016: urodynamics, uroflowmetry, cystometry, and pressure-flow study. Neurourol Urodyn. 2017;36:1243-1260. [Crossref]
6. Bergman A, McCarthy TA, Ballard CA, Yanai J. Role of the Q-tip test in evaluating stress urinary incontinence. J Reprod Med. 1987;32:273-275. [Crossref]
7. Baden WF, Walker TA. Physical diagnosis in the evaluation of vaginal relaxation. Clin Obstet Gynecol. 1972;15:1055-1069. [Crossref]
8. White AB, Kahn BS, Gonzalez RR, Rosamilia A, Anger JT, Eilber KS, Schaffer JI. Prospective study of a single-incision sling versus a transobturator sling in women with stress urinary incontinence: 3-year results. Am J Obstet Gynecol. 2020;223:545.e1-545.e11. [Crossref]

9. Delorme E. La bandelette trans-obturatrice: un procédé mini-invasif pour traiter l'incontinence urinaire d'effort de la femme [Transobturator urethral suspension: mini-invasive procedure in the treatment of stress urinary incontinence in women]. Prog Urol. 2001;11:1306-1313. [Crossref]
10. de Leval J. Novel surgical technique for the treatment of female stress urinary incontinence: transobturator vaginal tape inside-out. Eur Urol. 2003;44:724-730. [Crossref]
11. U.S. Food and Drug Administration. Urogynecologic surgical mesh implants. Silver Spring (MD): FDA; 2021. [Crossref]
12. Brazzelli M, Javanbakht M, Imamura M, Hudson J, Moloney E, Becker F, Wallace S, Omar MI, Shimonovich M, MacLennan G, Ternent L, Vale L, Montgomery I, Mackie P, Saraswat L, Monga A, Craig D. Surgical treatments for women with stress urinary incontinence: the ESTER systematic review and economic evaluation. Health Technol Assess. 2019;23:1-306. [Crossref]
13. Karsenty G. Current use of synthetic slings in European countries. European Association of Urology; 2022. [Crossref]
14. Leone Roberti Maggiore U, Finazzi Agrò E, Soligo M, Li Marzi V, Digesu A, Serati M. Long-term outcomes of TOT and TVT procedures for the treatment of female stress urinary incontinence: a systematic review and meta-analysis. Int Urogynecol J. 2017;28:1119-1130. [Crossref]
15. Offiah I, Freeman R; MONARC™ study group. Long-term efficacy and complications of a multicentre randomised controlled trial comparing retropubic and transobturator mid-urethral slings: a prospective observational study. BJOG. 2021;128:2191-2199. [Crossref]
16. Kenton K, Stoddard AM, Zyczynski H, Albo M, Rickey L, Norton P, Wai C, Kraus SR, Sirls LT, Kusek JW, Litman HJ, Chang RP, Richter HE. 5-year longitudinal followup after retropubic and transobturator mid urethral slings. J Urol. 2015;193:203-210. [Crossref]
17. Diniz MB, Diniz LCB, Lopes da Silva GF, Filho ALDS, Reis ZSN, Monteiro MVC. Five-year follow-up of transobturator sling: 152 cases with the same surgeon. Rev Bras Ginecol Obstet. 2018;40:614-619. [Crossref]
18. Cañete P, Ortiz E, Domingo S, Cano A. Transobturator suburethral tape in the treatment of stress urinary incontinence: efficacy and quality of life after 5 year follow up. Maturitas. 2013;74:166-171. [Crossref]
19. Lo TS, Jaili S, Tan YL, Wu PY. Five-year follow-up study of Monarc transobturator tape for surgical treatment of primary stress urinary incontinence. Int Urogynecol J. 2016;27:1653-1659. [Crossref]
20. Ross S, Tang S, Eliasziw M, Lier D, Girard I, Brennand E, Dederer L, Jacobs P, Robert M. Transobturator tape versus retropubic tension-free vaginal tape for stress urinary incontinence: 5-year safety and effectiveness outcomes following a randomised trial. Int Urogynecol J. 2016;27:879-886. [Crossref]
21. Karmakar D, Mostafa A, Abdel-Fattah M. Long-term outcomes of transobturator tapes in women with stress urinary incontinence: E-TOT randomised controlled trial. BJOG. 2017;124:973-981. [Crossref]
22. Costantini E, Kocjancic E, Lazzeri M, Giannantoni A, Zucchi A, Carbone A, Bini V, Palleschi G, Pastore AL, Porena M. Long-term efficacy of the transobturator and retropubic mid-urethral slings for stress urinary incontinence: update from a randomized clinical trial. World J Urol. 2016;34:585-593. [Crossref]
23. Salo H, Sova H, Laru J, Talvensaari-Mattila A, Nyyssönen V, Santala M, Piltonen T, Koivurova S, Rossi HR. Long-term results of a prospective randomized trial comparing tension-free vaginal tape versus transobturator tape in stress urinary incontinence. Int Urogynecol J. 2023;34:2249-2256. [Crossref]
24. Braga A, Papadia A, Gamarra E, Caccia G, Campitiello MR, Torella M, Mesiano G, Fiorani M, Scancarello C, Cimmino C, Serati M. Long-term outcomes of tension-free vaginal tape obturator: efficacy and safety at long-term follow-up. J Clin Med. 2024;13:5699. [Crossref]
25. Abdel-Fattah M, Cao G, Mostafa A. Long-term outcomes for transobturator tension-free vaginal tapes in women with urodynamic mixed urinary incontinence. Neurourol Urodyn. 2017;36:902-908. [Crossref]
26. Jahanlu D, Hunskaar S. Type and severity of new-onset urinary incontinence in middle-aged women: the Hordaland Women's Cohort. Neurourol Urodyn. 2011;30:87-92. [Crossref]

ORIGINAL RESEARCH
Endourology

Doi: 10.4274/jus.galenos.2025.2025-6-9
J Urol Surg 2026;13(3):207-211

Does Ureteral Pre-stenting Influence Post-RIRS Residual Fragment Rate? A Prospective Analysis

Krushnadevsinh Jadeja, Kshitij Raghuvanshi, Rajeev Choudhary

Ruby Hall Clinic, Department of Urology, Pune, India

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

Ureteral pre-stenting is commonly used to facilitate access during retrograde intrarenal surgery (RIRS); it is known to increase ureteral compliance and aid ureteral access sheath (UAS) insertion, but its effect on stone clearance remains uncertain. This prospective study confirms that while pre-stenting improves UAS insertion success and reduces operative time, it does not significantly influence residual fragment rates post-RIRS, highlighting the need for selective rather than routine use of pre-stenting.

Abstract

Objective: Retrograde intrarenal surgery (RIRS) is an established treatment modality for renal calculi ≤2 cm. Preoperative ureteral stenting is often employed to facilitate access, but its influence on residual fragment rates remains controversial. This prospective study aimed to evaluate the impact of ureteral pre-stenting on residual stone fragments following RIRS.

Materials and Methods: A prospective observational study was conducted at a tertiary care center from July 2023 to December 2024, involving 180 patients with renal calculi. Participants were randomized into two groups: pre-stented (n=90) and non-stented (n=90). All patients underwent RIRS according to standardized protocols and had a non-contrast computed tomography kidney, ureter, and bladder on postoperative day 90. Residual fragments ≥3 mm were considered significant. Baseline demographics, stone parameters, intraoperative data, and postoperative outcomes were analyzed. Statistical significance was set at $p<0.05$.

Results: Baseline characteristics, including age, body mass index, stone size, volume, and density, were comparable between groups. Ureteric access sheath (UAS) insertion was significantly more successful in the pre-stented group (100%) than in the non-stented group (86.66%, p=0.037). The mean operative time was shorter in the pre-stented group (79.70±18.83 min vs. 89.33±16.02 min, p=0.036). However, the residual fragment rate was identical in both groups (2 patients per group, 6.6%, p=1.000). Postoperative complications, including fever and urinary tract infection, did not differ significantly.

Conclusion: Preoperative ureteral stenting improved the success of UAS insertion and reduced operative time during RIRS but did not influence the rate of residual stone fragments. Pre-stenting may be beneficial in optimizing surgical access, but does not appear to directly enhance stone clearance outcomes.

Keywords: Retrograde intrarenal surgery, ureteral stenting, residual stone fragments, ureteral access sheath, renal calculi

Introduction

The global prevalence of renal stone disease is around 12% (1). According to current guidelines, retrograde intrarenal surgery (RIRS) has become an established standard for the treatment of renal stones up to 2 cm, owing to advances in surgical techniques and instrumentation (2). The introduction of high-resolution flexible ureteroscopes and the development of low-caliber, high-efficiency laser systems have significantly enhanced the safety and efficacy of this approach for managing upper urinary tract calculi. The stone-free rate is one of the primary treatment objectives for renal stone disease. Reported stone-free rates for RIRS vary from 54% to 96% for renal stones smaller than 2 cm (3).

Correspondence: Krushnadevsinh Jadeja MD, Ruby Hall Clinic, Department of Urology, Pune, India
E-mail: krjadeja17@gmail.com **ORCID-ID:** orcid.org/0009-0005-2450-2413
Received: 23.06.2025 **Accepted:** 18.12.2025 **Epub:** 06.08.2026 **Publication Date:** 01.09.2026

Cite this article as: Jadeja K, Raghuvanshi K, Choudhary R. Does ureteral pre-stenting influence post-RIRS residual fragment rate? A prospective analysis. J Urol Surg. 2026;13(3):207-211

In clinical practice, ureteral double-J (DJ) stents are commonly inserted following RIRS procedures to prevent ureteral obstruction and facilitate postoperative drainage (4). In certain situations, such as obstructive uropathy, active infection, or compromised renal function, stent placement before RIRS is also considered (5). Additionally, pre-stenting may be used to facilitate access in cases where the ureteric orifice is too narrow to accommodate the ureteric access sheath (UAS) (5).

While the guidelines do not mandate routine preoperative stenting for RIRS, emerging evidence suggests that preoperative stenting may influence procedural outcomes (5). Several studies have indicated that pre-stenting can improve intraoperative access, reduce ureteral trauma, and potentially enhance stone clearance (5). However, its impact on residual fragment rates following RIRS remains a subject of debate. This study aims to evaluate the impact of placing a ureteral DJ stent before RIRS on rates of residual stone fragments, with the goal of improving treatment approaches for kidney stones.

Material and Methods

A prospective observational study was conducted at our institute over an 18-month period, from July 2023 to December 2024. A total of 180 patients were enrolled during this period. Ethical and scientific approvals were obtained from the Institutional Ethic Committee of Ruby Hall Clinic (decision no: RHC/BIOPMRFIEC/2022/443, date: 20.07.2023) prior to study initiation. The cohort comprised individuals diagnosed with renal calculi who subsequently underwent RIRS after providing written informed consent to participate in the study. Patients presenting with anatomical variations such as crossed renal ectopia, duplicated collecting systems, or pelvic kidneys were excluded from the study.

Upon presentation to the urology department with a clinical suspicion of nephrolithiasis, patients underwent a comprehensive evaluation, including a detailed medical history and a systemic physical examination. Demographic variables such as age, sex, and body mass index were documented. As part of the preoperative assessment, all patients underwent non-contrast computed tomography kidney, ureter, and bladder (NCCT KUB). Imaging findings were systematically analyzed, including stone characteristics such as size, number, total stone volume, anatomical location, laterality, and radiodensity (measured in Hounsfield units). Following initial evaluation and confirmation of eligibility, all 180 patients were randomly allocated, using a simple randomization technique, into two equal groups: (1) pre-stented and (2) non-stented. A lottery method was employed for simple randomization, i.e., patients were allocated to two groups after randomly drawing their names for stenting or non-stenting to prevent any bias. All patients allocated to the pre-stented group underwent insertion of a 5 Fr/26 cm DJ ureteral stent on the side of the renal stone. RIRS was subsequently performed seven days after stent placement to allow for passive ureteral dilation. In contrast, patients assigned to the non-stented group proceeded directly to RIRS following completion of the preoperative assessment. During RIRS, standard operative procedures were followed, with all intraoperative parameters kept constant, including a 35 Watt thulium fiber laser (IPG Photonics), a 200 µm laser fiber, and a standard UAS sheath (9.5/11.5 Fr). After laser lithotripsy, each calyx was checked for complete dusting of the stone. A DJ stent was placed in all patients after endoscopy, and the stent was removed 3 to 4 weeks postoperatively, when we were certain that the bypass was no longer necessary. All intra-operative and post-operative complications, both major and minor, were considered, along with total operative time. Postoperatively, the stone clearance rate was documented on NCCT KUB on postoperative day 90. Residual fragments ≥3 mm were considered significant.

Statistical Analysis

Data were recorded using a predesigned pro forma and analyzed using Microsoft Excel and IBM SPSS Statistics for Windows, version 25. Descriptive statistics included mean ± standard deviation for quantitative variables and frequencies (percentages) for categorical variables. Normality was assessed using the Shapiro-Wilk test. The chi-square test evaluated associations between qualitative variables, while the Mann-Whitney U test compared quantitative variables. Logistic regression was used for predictive analysis. A p-value of <0.05 was considered statistically significant.

Results

A total of 180 patients were enrolled in the present study and equally allocated to two groups: pre-stented (n=90) and non-stented (n=90). Comprehensive baseline comparisons were conducted to ensure homogeneity between the two cohorts (Table 1).

Discussion

In this prospective analysis, we investigated whether preoperative ureteral stenting influences residual fragment rates following RIRS. Our findings revealed that the number of patients with residual fragments was identical in both the pre-stented and non-stented groups (6 patients in each group), indicating no significant difference in stone-free outcomes. These results suggest that pre-stenting may not play a direct role in improving stone clearance post-RIRS. The stone-related parameters—including number, volume, size, density, and location—were comparable between the two groups, thereby

Table 1. Impact of pre-stenting on residual fragments post RIRS			
Variables	**Presented group**	**Non-stented group**	**p-values**
Patients (n)	90	90	
Age	36.94±7.78	38.04±7.59	0.581
Gender			
Male	48	54	0.602
Female	42	36	
BMI	22.98±2.09	23.33±1.51	0.465
Laterality of stone			
Right	36	48	0.301
Left	54	42	
Number of stones	1.67±0.64	1.83±0.41	0.26
Stone volume (mm^3)	945.96±385.51	968.83±214.49	0.78
Stone size (mm)	14.58±3.8	16±2.28	0.096
Stone density (HU)	1046.33±114.1	999.84±178.62	0.235
Stone location			
lower pole	42	51	0.44
non lower pole	48	39	
UAS insetion successful, n (%)	90 (100%)	78 (86.66%)	0.037
Intraoperative complication			0.313
Intra op. bleeding	0	3	
Post-operative complication			
Post op fever	3	3	>0.999
Post op UTI	6	3	0.554
Surgical duration (min)	79.70±18.83	89.33±16.02	0.036
Number of patients with residual fragments	6	6	>0.999

BMI: Body mass index, HU: Hounsfield unit, UAS: Ureteral access sheath, UTI: Urinary tract infection, min: Minimum, RIRS: Retrograde intrarenal surgery

minimizing potential confounding factors. This balanced distribution supports the reliability of comparing residual fragment outcomes between groups. While some researchers, such as Rubenstein et al. (6), have reported a significant association between stent placement and improved stone-free rates, others have found no such correlation. For instance, Fabrizio et al. (7) observed that although pre-stenting facilitated ureteral dilation and improved access during surgery, it did not significantly influence the final stone clearance outcomes.

In our study, we observed a significantly higher success rate of UAS insertion in patients who underwent preoperative DJ stenting; i.e., all 90 (100%) patients in the prestented group had successful UAS insertion, compared with 78 patients (86.6%) who did not undergo prestenting. The use of a UAS has become integral to RIRS, offering advantages such as reducing intrarenal pressure, improving endoscopic visibility, preventing pyelovenous reflux, and facilitating multiple re-entries into the collecting system during the procedure. However, UAS placement is not universally successful and may be limited by anatomical constraints such as narrow ureters or tight ureteral orifices. The native ureter typically measures 6-9 Fr in diameter, whereas commonly used UASs have outer diameters ranging from 9.5 to 11.5 Fr, often exceeding the ureter's natural caliber and posing a challenge for direct insertion. The successful insertion of UAS in the pre-stented group is attributed to passive ureteral dilation induced by the indwelling stent; this dilation increases ureteral compliance, straightens ureteral kinks, and enlarges the ureteral orifice, thereby facilitating smoother insertion of larger-caliber sheaths. Mogilevkin et al. (8) prospectively evaluated the ability to insert a 14 Fr UAS and analyzed possible predictors of successful insertion. The failure rate for UAS placement was approximately 15%, and pre-stenting appeared to be a positive predictor of UAS placement in his study. Perlmutter et al. (9) observed that preoperative ureteral stenting contributed to passive dilation of the ureter, which in turn influenced the procedural outcomes of RIRS.

Moreover, the duration of surgery was significantly shorter in the pre-stented group than in the non-stented group. This suggests that, although pre-stenting may not directly

improve stone-free rates, it can enhance procedural efficiency, possibly by facilitating navigation within the urinary tract.

In our prospective study, we also evaluated the influence of preoperative ureteral stenting on intraoperative and postoperative complications of RIRS. The results indicated no statistically significant difference in complication rates between the pre-stented and non-stented groups. These results are consistent with previous literature, indicating that while ureteral stents can facilitate access during RIRS, they do not appear to markedly reduce complication rates. Prolonged stent dwell time is sometimes associated with increased irritative symptoms and an increased risk of infection. However, in our study, where stenting was applied selectively and in a controlled manner, no such increase in postoperative morbidity was observed.

In our study, although pre-stenting conferred procedural advantages—higher UAS insertion success rate and shorter operative time—there was no significant difference in the residual fragment rate between the pre-stented and non-stented groups. This supports the notion that while preoperative stenting may optimize surgical conditions, its impact on overall stone clearance remains limited. These contrasting findings in the literature highlight the need for a more individualized approach, where the decision to pre-stent is based on patient anatomy, stone complexity, and anticipated technical challenges rather than a routine protocol.

Our study offers several strengths. It is a prospective observational study assessing the impact of preoperative ureteral stenting on residual fragment rates and perioperative outcomes following RIRS. All patients were evaluated using NCCT KUB, which remains the gold standard for stone assessment and ensures high diagnostic accuracy. Imaging was interpreted by a senior radiologist who was blinded to surgical outcomes and who employed standardized techniques, including magnification and bone-window settings, to minimize bias. To maintain procedural consistency, all surgeries were performed by experienced endourologists using the same model of flexible ureteroscope and identical disposable instruments.

Study Limitations

Our findings, from a study conducted at a high-volume tertiary care center with uniform surgical protocols and imaging quality, reflect outcomes under optimized clinical conditions. However, external validation across centers with different levels of expertise, equipment availability, and procedural variation is essential to establish the broader relevance of the results.

Conclusion

This prospective study demonstrated that preoperative ureteral stenting significantly improved the success rate of UAS placement and reduced operative time during RIRS. However, pre-stenting did not significantly affect the incidence of residual stone fragments or of intraoperative or postoperative complications.

Ethics

Ethics Committee Approval: Ethical and scientific approvals were obtained from the Institutional Ethic Committee of Ruby Hall Clinic (decision no: RHC/BIOPMRFIEC/2022/443, date: 20.07.2023) prior to study initiation.

Informed Consent: The cohort comprised individuals diagnosed with renal calculi who subsequently underwent RIRS after providing written informed consent to participate in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.J., K.R., R.C., Concept: K.J., K.R., R.C., Design: K.J., K.R., R.C., Data Collection or Processing: K.J., K.R., R.C., Analysis or Interpretation: K.J., K.R., R.C., Literature Search: K.J., K.R., R.C., Writing: K.J., K.R., R.C.

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

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

References

1. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010;12:e86-e96. [Crossref]
2. Zeng G, Zhao Z, Mazzon G, Pearle M, Choong S, Skolarikos A, Denstedt J, Seitz C, Olvera Pasada D, Fiori C, Bosio A, Papatsoris A, Méndez Probst CE, Perez Fentes D, Ann Git K, Wu Q, Wiseman O, Emiliani E, Farahat Y, Ilker Gökce M, Giannakopoulos S, Goumas Kartalas I, Somani B, Knoll T, de la Rosette J, Zhong J, Vinicius Maroccolo M, Saltirov L, Chew B, Wang K, Lahme S, Giusti G, Ferretti S, Yong Cho S, Geavlete P, Cansino R, Kamphuis GM, Smith D, Matlaga BR, Ghani KD, Bernardo N, Silva AD, Ng ACF, Yang S, Gao X, Traxer O, Miernik A, Liatsikos E, Priyakant Parikh K, Duvdevani M, Celia A, Yasui T, Aquino A, Alomar M, Choonhaklai V, Erkurt B, Glass J, Sriprasad S, Osther PJ, Keeley FX Jr, Preminger GM, Cepeda Delgado M, Beltran Suarez E, Ye Z, Sarica K. European Association of Urology Section of Urolithiasis and International Alliance of Urolithiasis Joint Consensus on retrograde intrarenal surgery for the management of renal stones. Eur Urol Focus. 2022;8:1461-1468. [Crossref]
3. Schoenthaler M, Wilhelm K, Katzenwadel A, Ardelt P, Wetterauer U, Traxer O, Miernik A. Retrograde intrarenal surgery in treatment of nephrolithiasis: is a 100% stone-free rate achievable? J Endourol. 2012;26:489-493. [Crossref]
4. Ozyuvali E, Resorlu B, Oguz U, Yildiz Y, Sahin T, Senocak C, Bozkurt OF, Damar E, Yildirim M, Unsal A. Is routine ureteral stenting really necessary

after retrograde intrarenal surgery? Arch Ital Urol Androl. 2015;87:72-75. [Crossref]

5. Yuk HD, Park J, Cho SY, Sung LH, Jeong CW. The effect of preoperative ureteral stenting in retrograde Intrarenal surgery: a multicenter, propensity score-matched study. BMC Urol. 2020;20:147. [Crossref]
6. Rubenstein RA, Zhao LC, Loeb S, Shore DM, Nadler RB. Prestenting improves ureteroscopic stone-free rates. J Endourol. 2007;21:1277-1280. [Crossref]
7. Fabrizio MD, Behari A, Bagley DH. Ureteroscopic management of intrarenal calculi. J Urol. 1998;159:1139-1143. [Crossref]
8. Mogilevkin Y, Sofer M, Margel D, Greenstein A, Lifshitz D. Predicting an effective ureteral access sheath insertion: a bicenter prospective study. J Endourol. 2014;28:1414-1417. [Crossref]
9. Perlmutter AE, Talug C, Tarry WF, Zaslau S, Mohseni H, Kandzari SJ. Impact of stone location on success rates of endoscopic lithotripsy for nephrolithiasis. Urology. 2008;71:214-217. [Crossref]

ORIGINAL RESEARCH
Endourology

Doi: 10.4274/jus.galenos.2026.2026-1-7
J Urol Surg 2026;13(3):212-219

Impact of Lithotripsy Technology on Mini-PCNL Outcomes: A Comparative Study of Holmium and Thulium Laser

Ersin Gökmen[1], Türker Altuntaş[2], Abdul Vahap Bakır[2], Kaan Derici[2], Günal Özgür[1], Tarık Emre Şener[2]

[1]Marmara University, Pendik Training and Research Hospital, Department of Urology, İstanbul, Türkiye
[2]Marmara University School of Medicine, Department of Urology, İstanbul, Türkiye

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

Mini-percutaneous nephrolithotomy (PCNL) is a well-established minimally invasive technique for the management of renal stones. Holmium:YAG laser is the traditional and most widely used lithotripsy energy source in mini-PCNL. Thulium fiber laser has recently emerged as an alternative, with potential advantages in stone dusting efficiency and radiation reduction, but clinical data in mini-PCNL are limited. This study provides a comparison of holmium:YAG and thulium fiber laser in mini-PCNL performed by a single surgeon, reducing procedural variability. According to our results both laser systems demonstrate comparable safety, efficacy, and stone-free rates. Thulium fiber laser is associated with reduced radiation exposure in patients with smaller stone burdens, supporting its role as a reliable modern alternative to holmium:YAG in mini-PCNL.

Abstract

Objective: To evaluate outcomes of mini-percutaneous nephrolithotomy (PCNL) performed with holmium:YAG (Ho:YAG) versus thulium fiber laser (TFL).

Materials and Methods: This retrospective study included adult patients who underwent mini-PCNL with either Ho:YAG or TFL between January 2024-2025. Demographic features, stone characteristics, operative parameters, and postoperative outcomes were analysed. All surgeries were performed by a single surgeon using the modified supine position. Residual fragments were assessed on postoperative day 1, and stones ≥4 mm were considered significant. Patients were divided into two groups based on the laser system, and outcomes were compared across clinical, perioperative, and postoperative variables.

Results: Eighty-six patients underwent mini-PCNL (44 Ho:YAG, 42 TFL). Of the 86 patients included in the study, 64 (74.4%) were male and 22 (25.6%) were female. The median age was 52.5 years (range: 27-76). Baseline and operative parameters were comparable between groups. Stone-free rates were similar (81.4% vs. 88.1%). The thulium group showed lower radiation exposure in stones <3 cm (p=0.028) but a slightly higher postoperative creatinine change (p=0.033). Both lasers demonstrated equivalent efficacy and safety.

Conclusion: Ho:YAG and TFL demonstrate comparable safety and efficacy in mini-PCNL. TFL may offer a technical advantage by reducing radiation exposure, particularly in patients with smaller stone burdens, while overall outcomes remain similar. These results support TFL as a reliable, modern alternative to Ho:YAG, with both lasers providing safe and effective energy options for mini-PCNL.

Keywords: Basic science, endourology, functional urology

Introduction

The prevalence rates for urinary stones vary from 1% to 20% (1). The aetiology of urolithiasis is multifactorial; metabolic abnormalities, low fluid intake, dietary habits, urinary obstruction, and infections all play a critical role in stone formation. For large or complex renal stones, or those refractory to extracorporeal modalities, surgical intervention is often required (2).

Correspondence: Türker Altuntaş MD, FEBU, Marmara University School of Medicine, Department of Urology, İstanbul, Türkiye
E-mail: turkeraltuntas@hotmail.com **ORCID-ID:** orcid.org/0000-0001-9387-250X
Received: 14.01.2026 **Accepted:** 20.04.2026 **Epub:** 12.08.2026 **Publication Date:** 01.09.2026

Cite this article as: Gökmen E, Altuntaş T, Bakır AV, Derici K, Özgür G, Şener TE. Impact of lithotripsy technology on mini-PCNL outcomes: a comparative study of holmium and thulium laser. J Urol Surg. 2026;13(3):212-219

Currently, indications for active treatment of renal stones are primarily guided by stone size, stone location, and anatomical or stone-related characteristics that influence the effectiveness of stone fragmentation or extraction. According to the European Association of Urology (EAU) guidelines, percutaneous nephrolithotomy (PCNL) is recommended as the first-line treatment for stones larger than 2 cm. For stones measuring 10-20 mm, PCNL, ureteroscopy (URS), and shock wave lithotripsy (SWL) share a similar level of recommendation, whereas for stones smaller than 10 mm, SWL and URS are preferred treatment options, with PCNL reserved for selected circumstances (2).

The development of miniaturized instruments has led to the emergence of mini-PCNL, typically employing a tract size ≤24 Fr. This approach provides reduced blood loss, shorter hospital stay, and lower complication rates while maintaining high stone clearance efficacy (3).

Laser lithotripsy has revolutionized endourological stone management. The Holmium:YAG (Ho:YAG) laser has long been considered the standard energy source due to its versatility, reliability, and tissue safety (4). However, limitations such as stone retropulsion, inefficient energy transfer, and prolonged lasing times have led to the development of more efficient alternatives. The thulium fiber laser (TFL), a newer technology operating at 1940 nm compared with the 2100 nm Ho:YAG laser, offers lower pulse energy, higher frequencies, minimal retropulsion, and greater ablation efficiency (5). Early evidence indicates that TFL may enable shorter lasing times, smoother dusting, and reduced radiation exposure (6,7).

Despite its increasing use, comparative data between Ho:YAG and TFL in mini-PCNL are still limited. In this study, we aimed to present our experience comparing the outcomes of mini-PCNL cases performed in our clinic using both laser types.

Materials and Methods

This retrospective study was performed at our tertiary care referral centre. Ethical approval was obtained from the Marmara University Faculty of Medicine, Drug and Non-Medical Device Research Ethics Committee (approval number: 09.2025.25-0732, date: 05.09.2025). The study was conducted in accordance with the declaration of Helsinki and designed and reported in line with the STROBE guidelines for observational studies.

Patients who underwent mini-PCNL using either Ho:YAG or TFL at our institution between January 2024 and January 2025 were included in the study and initially reviewed. Patients over 18 years of age who underwent mini-PCNL and had complete preoperative and postoperative clinical data were included. Our exclusion criteria were as follows: patients with incomplete data, abnormal renal anatomy, pregnancy, concomitant surgical interventions, bilateral renal stones, multiple stones, or prior stone surgery.

Demographic parameters (age, sex, body mass index), comorbidities (Charlson Comorbidity Index), and stone characteristics (size, location, and Hounsfield units) were recorded. Intraoperative variables, including operative duration, lasing time, total laser energy delivered, fluoroscopy time (recorded in seconds), and radiation exposure parameters, including dose-area product (DAP, expressed in $Gy.cm^2$), were obtained directly from the fluoroscopy unit and used as standardized indicators of radiation exposure. Postoperative outcomes comprised haemoglobin drop, change in serum creatinine, transfusion requirement, length of hospital stay, and complications graded according to the Clavien-Dindo system (8). Serum creatinine levels were measured at the postoperative 1 month follow-up, whereas other laboratory parameters were assessed on postoperative day 1.

All procedures were performed under general anaesthesia in the Galdakao-modified supine Valdivia position (9). The procedures were performed by a single experienced endourologist. Percutaneous access to the renal collecting system was obtained under fluoroscopic guidance. The tract was dilated using 16/20 Fr Amplatz dilators. Stone fragmentation was performed using Ho:YAG and TFL devices, including the 60-W Quanta CyberHo system and the Fiber Dust® Thulium Fiber Laser (Quanta System). Laser settings were adjusted intraoperatively according to stone hardness, as different compositions require distinct energy profiles for optimal fragmentation. Collectively, these tailored laser settings ensured efficient and controlled fragmentation across varying stone types.

Residual stone status was assessed on postoperative day 1 by abdominal X-ray. Patients with a suspicious opacity on the abdominal radiograph or who were symptomatic underwent non-contrast computed tomography in accordance with EAU guidelines. Stones ≥4 mm were considered residual stones (2).

In this study, patients were stratified into two groups based on the laser type used during mini-PCNL (Ho:YAG or TFL). The primary objective was to compare perioperative performance and postoperative outcomes between the two laser modalities, including operative parameters, complication rates, length of hospital stay, and stone-free rates, while ensuring comparable baseline demographics and stone-related characteristics between the groups.

Statistical Analysis

Statistical analyses were carried out using IBM SPSS 25.0. Because the data were not normally distributed (Kolmogorov-Smirnov test), non-parametric tests were applied. Numerical data were presented as median and interquartile range, and categorical data as counts and percentages. Categorical data were analyzed

using the chi-square test or Fisher's exact test, as appropriate; group comparisons were performed with the Mann-Whitney U test. A p-value <0.05 was considered statistically significant.

Results

A total of 86 patients who underwent mini-PCNL were included in the study. Forty-four patients were treated with the Ho:YAG laser (Group 1) and forty-two patients were treated with the TFL (Group 2). Of the 86 patients included in the study, 64 (74.4%) were male and 22 (25.6%) were female. The median age was 52.5 years (range: 27-76).

The median age of the patients was similar between the two groups (53 vs. 51 years, p=0.477). The male-to-female ratio did not differ significantly (77.3% vs. 71.4%, p=0.535). Similarly, no statistically significant differences were observed between the groups regarding body mass index, Charlson Comorbidity Index, or stone diameter. The majority of stones were located in the renal pelvis (59.1% in Group 1 and 61.9% in Group 2), with similar distributions across other calyceal locations. The mean stone density, was comparable between groups. Laser time, total laser energy used, radiation exposure, and operation time showed no statistically significant differences between the two groups. The median operation time was 120 minutes in both groups. Postoperative outcomes, including decreases in haemoglobin levels, hospital stays, transfusion requirements, and intensive care unit admissions, were also similar. However, there was a statistically significant difference in the change of serum creatinine levels [ΔCreatinine=0.005 (-0.08-0.08) vs. 0.06 (0.01-1.6), p=0.033], indicating a slightly higher postoperative creatinine rise in the thulium group. The overall stone-free rate was 81.4% in the holmium group and 88.1% in the thulium group (p=0.391). Postoperative complications, classified according to the Clavien-Dindo system, were distributed similarly between the groups, and most were minor (Grade I-II) (Table 1).

Table 1. Comparison of holmium and thulium laser for all patients

	Group 1 (n=44)	**Group 2 (n=42)**	**p-value**
Age (years), median (IQR)	53 (45.5-65.5)	51 (39.5-63)	0.477
Sex (male/female), n (%)	34/10 (77.3/22.7)	30/12 (71.4/28.6)	0.535
BMI (kg/m^2), median (IQR)	25.91 (24.42-28.3)	27.53 (25.99-30.4)	0.137
CCI, median (IQR)	0 (0-1)	0 (0-2)	0.564
Stone diameter (mm), median (IQR)	23.5 (17.25-28)	20.5 (16-30)	0.525
Stone location, n (%)			
Renal pelvis	26 (59.1)	26 (61.9)	0.572
Upper pole	1 (2.3)	3 (7.1)	
Middle pole	6 (13.6)	3 (7.1)	
Lower pole	11 (25)	10 (23.9)	
Stone density (Hounsfield unit), median (IQR)	1268 (960-1420)	1232.5 (959.75-1470)	0.651
Lasing time (sec), median (IQR)	1810 (1237-2980)	1647.5 (1023.75-2951)	0.554
Lasing energy (Joule), median (IQR)	45.73 (20.06-89.1)	47.36 (16.33-74.96)	0.881
Radiation time (sec), median (IQR)	75 (46.5-120)	72 (30.75-104)	0.435
Fluoroscopy energy (mGy), median (IQR)	21.01 (10-69.2)	23.48 (8-49.62)	0.659
Fluoroscopy energy (DAP), median (IQR)	6 (2.64-12.51)	2.89 (1.26-6.02)	0.077
Operation time (min), median (IQR)	120 (100-180)	120 (94.25-150)	0.324
Exit strategy (DJ/Nephrostomy), n (%)	41/3 (93.2/6.8)	38/4 (90.5/9.5)	0.474
ΔHaemoglobin, median (IQR)	0.8 (0.3-1.5)	0.5 (0-1.6)	0.582
ΔCreatinine, median (IQR)	0.005 (-0.08-0.08)	0.06 (0.01-1.6)	**0.033**
Stone-free rate, n (%)	35 (81.4)	37 (88.1)	0.391
Blood Transfusion, n (%)	3 (6.8)	3 (7.1)	0.953
Intensive care unit necessary, n (%)	2 (4.5)	1 (2.4)	0.518
Clavien-Dindo classification, n (%)			
Grade 1	1 (2.3)	1 (2.4)	0.431
Grade 2	3 (6.8)	6 (14.3)	
Grade 3	1 (2.3)	4 (9.5)	
Grade 4	2 (4.5)	1 (2.4)	
Hospital stay (day), median (IQR)	2 (1-3)	2 (1.75-7.25)	0.4

Bold values indicate statistically significant results
BMI: Body mass index, CCI: Charlson comorbidity index, DAP: Dose-area product, DJ: Double-J stent, IQR: Interquartile range, mGy: Milligray, min: Minute, mm: Milimeter, sec: Second

In the subgroup analysis of patients with stones <3 cm (Table 2), 35 patients were in the holmium group and 31 were in the thulium group. Demographic characteristics such as age, sex, BMI, and comorbidities were comparable. The median stone size was 20 mm in both groups, and the distribution of stone locations did not differ significantly (p=0.238). Intraoperative parameters, including laser time, total laser energy, radiation time, and operation duration, were similar. However, the thulium group exhibited a significantly lower fluoroscopy DAP [1.48 (1.07-4.82) vs. 6 (1.71-13.84) Gy.cm^2, p=0.028], indicating reduced radiation exposure. Postoperative changes in serum creatinine were again significantly higher in the thulium group (p=0.02). The median hospital stay was 2 days in both groups, and the stone-free rates were 76.5% and 83.9% for holmium and thulium, respectively (p=0.456). The complication profile was similar, with most events classified as Clavien-Dindo Grade II, and no Grade V complications were recorded.

Among patients with stones >3 cm (Table 3), 9 were in the holmium group and 11 were in the thulium group. Both groups had similar demographic and preoperative characteristics. The median stone diameter and density did not differ significantly. Intraoperative outcomes, including laser and radiation parameters as well as operation time, were comparable. The median operative duration was 140 minutes in Group 1 and 150 minutes in Group 2 (p=0.818). All patients in both groups achieved complete stone clearance (100% stone-free rate). Postoperative haemoglobin drops, creatinine changes, and length of hospital stay were similar in the two groups. No statistically significant differences were found in complication rates, and no major adverse events or mortality were observed.

Table 2. Comparison of holmium and thulium laser for >3 cm stones

	Group 1 (n=35)	**Group 2 (n=31)**	**p-value**
Age (years), median (IQR)	51 (42-62)	48.5 (39.5-63)	0.67
Sex (male/female), n (%)	27/8 (77.1/22.9)	24/7 (77.4/22.6)	0.979
BMI (kg/m^2), median (IQR)	25.71 (24.1-28.56)	27.17 (25.25-29.18)	0.28
CCI, median (IQR)	0 (0-1)	0 (0-1)	0.768
Stone diameter (mm), median (IQR)	20 (15-25)	20 (15-23)	0.138
Stone location, n (%)			
Renal pelvis	22 (62.9)	18 (58.1)	0.238
Upper pole	0	3 (9.7)	
Middle pole	3 (8.6)	1 (3.2)	
Lower pole	10 (28.6)	9 (29)	
Stone density (Hounsfield unit), median (IQR)	1234 (955.25-1405)	1242 (1014-1488)	0.4
Lasing time (sec), median (IQR)	1780 (1170-3011)	1647.5 (1023.75-2559.5)	0.887
Lasing energy (Joule), median (IQR)	30.64 (19.25-75.16)	37.67 (14.7-55.25)	0.719
Radiation time (sec), median (IQR)	75 (46.5-119.5)	65.5 (26.25-97.5)	0.332
Fluoroscopy energy (mGy), median (IQR)	28.52 (10-75.6)	20 (7.9-49.33)	0.53
Fluoroscopy energy (DAP), median (IQR)	6 (1.71-13.84)	1.48 (1.07-4.82)	**0.028**
Operation time (min), median (IQR)	120 (100-180)	110 (90-130)	0.292
Exit strategy (DJ/nephrostomy), n (%)	32/3 (91.4/8.6)	29/2 (93.5/6.5)	0.558
ΔHaemoglobin, median (IQR)	0.9 (0.3-1.42)	0.45 (0.2-1.37)	0.142
ΔCreatinine, median (IQR)	0 (-0.08-0.08)	0.07 (0-0.18)	**0.02**
Stone-free rate, n (%)	26 (76.5)	26 (83.9)	0.456
Blood transfusion, n (%)	3 (8.6)	2 (6.5)	0.558
Intensive care unit necessary, n (%)	2 (5.7)	0	0.277
Clavien-Dindo classification, n (%)			
Grade 1	1 (2.9)	1 (3.2)	0.133
Grade 2	3 (8.6)	6 (19.4)	
Grade 3	0	3 (9.7)	
Grade 4	2 (5.7)	0	
Hospital stay (day) median (IQR)	2 (1-3)	2 (1-8)	0.335

Bold values indicate statistically significant results
BMI: Body mass index, CCI: Charlson comorbidity index, DAP: Dose-area product, DJ: Double-J stent, IQR: Interquartile range, mGy: Milligray, min: Minute, mm: Milimeter, sec: Second

Table 3. Comparison of holmium and thulium laser for <3 cm stones			
	Group 1 (n=9)	**Group 2 (n=11)**	**p-value**
Age (years), median (IQR)	59 (50.5-69.5)	53 (39-66)	0.268
Sex (male/female), n (%)	7/2 (77.8/22.2)	6/5 (54.5/45.5)	0.272
BMI (kg/m^2), median (IQR)	26.88 (24.41-29.86)	27.68 (26.54-35.26)	0.427
CCI, median (IQR)	0 (0-1)	2 (0-2)	0.189
Stone diameter (mm), median (IQR)	35 (31-40)	32 (31-35)	0.376
Stone location, n (%)			
Renal pelvis	4 (44.4)	8 (72.7)	0.502
Upper pole	1 (11.1)	0	
Middle pole	3 (33.3)	2 (18.2)	
Lower pole	1 (11.1)	1 (9.1)	
Stone density (Hounsfield unit), median (IQR)	1300 (971.5-1584.5)	1216 (935-1440)	0.47
Lasing time (sec), median (IQR)	2156.5 (1741-2675.5)	1683.5 (934.25-2951)	0.438
Lasing energy (Joule), median (IQR)	81.25 (54.7-122.21)	95.5 (57.5-147)	0.657
Radiation time (sec), median (IQR)	123.5 (37.5-164.5)	93 (58.75-110.75)	0.83
Fluoroscopy energy (mGy), median (IQR)	20.5 (9.75-37.75)	39.01 (9.5-54.25)	0.451
Fluoroscopy energy (DAP), median (IQR)	5.8 (4.2-21.25)	7.38 (2.88-10.25)	0.667
Operation time (min), median (IQR)	140 (120-190)	150 (120-176)	0.818
Exit strategy (DJ/nephrostomy), n (%)	9/0 (100/0)	9/2 (81.8/18.2)	0.289
ΔHaemoglobin, median (IQR)	0.4 (0-2.45)	1.5 (0.3-2.4)	0.403
ΔCreatinine, median (IQR)	0.01 (-0.065-0.085)	0.02 (-0.16-0.11)	0.76
Stone-free rate, n (%)	9 (100)	11 (100)	-
Blood transfusion, n (%)	0	1 (9.1)	0.55
Intensive care unit necessary, n (%)	0	1 (9.1)	0.55
Clavien-Dindo classification, n (%)			
Grade 1	0	0	0.648
Grade 2	0	0	
Grade 3	1 (11.1)	1 (9.1)	
Grade 4	0	1 (9.1)	
Hospital stay (day), median (IQR)	2 (2-3)	2 (2-5)	0.901

BMI: Body mass index, CCI: Charlson comorbidity index, DAP: Dose-area product, DJ: Double-J stent, IQR: Interquartile range, mGy: Milligray, min: Minute, mm: Milimeter, sec: Second

Overall, both Ho:YAG and TFL lithotripsy demonstrated comparable efficacy and safety in mini-PCNL procedures. The TFL was associated with a slightly lower radiation exposure in smaller stones and a marginally higher postoperative creatinine increase, but without a clinically significant difference in outcomes.

Discussion

In the present study, we compared the efficacy and safety of the Ho:YAG and TFL systems in patients undergoing mini-PCNL. Both modalities demonstrated comparable operative durations, laser times, haemoglobin decreases, lengths of hospital stay, and complication rates. The stone-free rate did not differ significantly between the groups. However, a statistically significant yet clinically minor postoperative increase in serum creatinine was observed in the TFL group. Although the absolute change was small and clinically insignificant, several mechanisms may explain this finding. We believe that differences in irrigation dynamics and intrarenal pressure during lithotripsy may play a role. TFL is typically used with higher frequencies and longer lasing durations, which may require sustained irrigation and potentially lead to transient increases in intrarenal pressure. Elevated intrarenal pressure has been associated with temporary impairment in renal function due to pyelovenous and pyelolymphatic backflow. In addition, the higher ablation efficiency and finer dusting characteristics of TFL may increase particulate load within the collecting system, potentially causing transient tubular stress or micro-level obstruction.

Therefore, the observed difference in our cohort is more likely to reflect procedural and perioperative factors rather than a direct detrimental effect of the TFL itself. Future studies incorporating real-time intrarenal pressure monitoring and standardized laser settings would be valuable to better elucidate this association.

In the subgroup analysis of stones <3 cm, the TFL group exhibited significantly lower fluoroscopy DAP, suggesting that TFL may reduce radiation exposure during procedures for smaller stones. In the subgroup of patients with stones <3 cm, stone-free rates were higher in the TFL group, although the difference was not statistically significant. Several factors may explain this finding. First, the relatively small sample size in this subgroup limits the statistical power to detect modest differences between the two laser modalities. Second, while TFL has been shown in previous studies to provide superior dusting and reduced retropulsion, these technical advantages may be more pronounced during ureteroscopic procedures than during PCNL, in which active fragment extraction plays a major role. This may explain why, despite its theoretical advantages, TFL did not translate into a significantly higher stone-free rate in our cohort. Finally, variability in stone composition and hardness, which was not systematically analysed in our study, may also have influenced fragmentation efficiency and final clearance rates. These findings are consistent with existing literature suggesting comparable clinical success rates between Ho:YAG and TFL despite differences in laser physics and fragmentation characteristics. In light of these results, we believe that both laser platforms can be safely and effectively used in mini-PCNL for small and large stone burdens, with broadly similar surgical outcomes and postoperative complication profiles.

A review of the existing literature identified several studies that, as in our work compare different lithotripsy modalities with respect to efficacy and complication rates in mini-PCNL and other endourological procedures. Shubham et al. (10) conducted a large comparative mini-PCNL study in which patients were treated with Ho:YAG, TFL, or a pneumatic lithotripter, and reported comparable stone-free and complication rates between all three groups, with a tendency toward shorter operative time in the TFL arm. Similar to our findings, they showed that both Ho:YAG and TFL are safe and effective options in a mini-PCNL setting. In contrast to our findings, TFL in their cohort was associated with a more pronounced reduction in operative time. This discrepancy may be related to differences in sample size and study design. Shubham et al. (10) analysed a larger population and included a third treatment arm (pneumatic lithotripsy), which may have increased the power to detect modest differences in efficiency. Furthermore, their results may reflect centres with greater experience in optimizing TFL settings, where reduced retropulsion, higher ablation rates, and thinner fibres could facilitate faster stone clearance. In our series, the absence of a significant difference in operative time between lasers may, in part, be explained by the relatively limited sample size, heterogeneity in stone characteristics, and potential variability in surgeon experience with TFL.

In a prospective randomized trial specifically designed to compare TFL and Ho:YAG in the mini-PCNL setting, Mahajan and Mahajan (11) reported that TFL achieved significantly shorter stone disintegration times while maintaining similar overall operative times, stone-free rates, and complication profiles compared with Ho:YAG. In line with our results, their study supports the view that both lasers are clinically equivalent in terms of safety and success, but that TFL may offer technical advantages with respect to stone fragmentation. Unlike our retrospective design, their randomized methodology and larger sample size allowed a more detailed analysis of laser-efficiency endpoints, such as pure disintegration time. The lack of a measurable operative-time advantage for TFL in our cohort, despite similar technological properties, may therefore be attributable to non-laser factors that contribute substantially to total procedure duration in mini-PCNL (e.g., access creation, tract dilation) and could overshadow modest differences in lithotripsy speed.

From a broader endourological perspective, several ureteroscopic series have also compared TFL with Ho:YAG. Ulvik et al. (12) and subsequent prospective studies have shown that TFL can achieve higher or at least non-inferior stone-free rates, shorter laser activation times, and comparable or lower complication rates during ureteroscopic treatment of ureteral and renal stones. These URS data, consistent with our findings in mini-PCNL, suggest that TFL does not compromise safety and may improve lithotripsy efficiency. In contrast to some of these studies, we did not demonstrate a clear superiority of TFL in terms of stone-free rates, which may again be attributable to differences in stone burden, access route, and the relative contribution of non-lithotripsy steps to total operative time in mini-PCNL. Nevertheless, the comparable stone-free and complication rates observed in our study reinforce the concept that, in terms of clinical outcomes, both Ho:YAG and TFL are appropriate energy sources in contemporary endourological practice.

Our finding of a significantly lower DAP in the TFL group for stones <3 cm is noteworthy, as it aligns with the growing emphasis on radiation reduction strategies in stone surgery. Prior work has demonstrated that modifications such as pulsed fluoroscopy, ultrasound-guided access, and protocol optimization can substantially decrease radiation exposure during URS and PCNL (13). Some ureteroscopic series have suggested that more efficient lithotripsy techniques, including TFL-based protocols, may indirectly shorten fluoroscopy time and reduce dose (5,13). In our cohort, the lower DAP observed for small stones treated with TFL may similarly reflect faster

fragmentation, a reduced need for repeated fluoroscopic checks, or greater operator confidence in endoscopic rather than fluoroscopic guidance. Although we did not record surgeon radiation exposure or fluoroscopy time separately, the reduction in DAP is relevant to the "as low as reasonably achievable" principle and suggests that TFL could contribute to radiation-sparing mini-PCNL strategies, particularly in patients with limited stone burden.

The modest but statistically significant postoperative change in creatinine in the TFL group in our study warrants comment. Prior multicentre analyses of mini-PCNL have generally reported only minor and transient changes in renal function, irrespective of the energy source used (14). Our data are in line with this overall pattern, and the absolute magnitude of creatinine change remains small and clinically negligible. Although our study cannot definitively attribute this difference to the laser type, it is conceivable that subtle variations in intrarenal pressure, irrigation flow, or thermal profile between systems could contribute to transient changes in renal function. Future studies incorporating standardised intraoperative pressure monitoring, detailed documentation of laser settings, and longer-term renal follow-up would help clarify whether the observed difference is purely statistical or physiologically relevant.

Beyond laser technology itself, recent work has increasingly focused on integrating artificial intelligence (AI) and machine learning (ML) approaches into PCNL to predict stone-free status, complications, and operative time based on preoperative imaging and clinical variables (15,16). Several groups have developed ML models that outperform traditional scoring systems such as Guy's Stone Score and the S.T.O.N.E. score in predicting stone-free outcomes, whereas others have created algorithms to estimate complication risk and hospitalisation needs after PCNL (17). Although these models do not yet routinely incorporate laser type as an input variable, they illustrate an emerging paradigm in which individualised risk prediction and procedural planning may be enhanced by AI. In this context, future studies could explore whether the choice between Ho:YAG and TFL, combined with detailed stone and patient characteristics, can be integrated into predictive models to refine patient selection for mini-PCNL and optimise perioperative management.

Study Limitations

The present study has several limitations. Its retrospective design may have introduced selection bias, and the single-centre setting may limit the generalisability of our findings. The sample size, particularly for patients with stones >3 cm, was relatively small, reducing the statistical power of subgroup analyses. Furthermore, stone composition and long-term recurrence data were not evaluated, and intraoperative parameters such as intrarenal pressure and detailed laser settings were not systematically recorded. Prospective, multicentre studies with larger patient populations, standardised laser protocols, and extended functional follow-up are needed to confirm our results and better define the impact of laser type on long-term renal outcomes.

Conclusion

Both Ho:YAG and TFL demonstrate comparable safety and efficacy in mini-PCNL, with similar stone-free and complication rates. TFL may reduce radiation exposure for smaller stones, while showing a statistically significant but clinically negligible increase in postoperative creatinine. Overall, both energy sources can be safely used in mini-PCNL, and the choice of laser may be guided by institutional availability and surgeon preference.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Marmara University Faculty of Medicine, Drug and Non-Medical Device Research Ethics Committee (approval number: 09.2025.25-0732, date: 05.09.2025).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.G., Concept: E.G., G.Ö., T.E.Ş., Design: E.G., G.Ö., T.E.Ş., Data Collection or Processing: E.G., T.A., A.V.B., K.D., Analysis or Interpretation: E.G., T.A., A.V.B., K.D., Literature Search: E.G., T.A., Writing: E.G., T.A., A.V.B., K.D., G.Ö., T.E.Ş.

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

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

References

1. Sorokin I, Mamoulakis C, Miyazawa K, Rodgers A, Talati J, Lotan Y. Epidemiology of stone disease across the world. World J Urol. 2017;35:1301-1320. [Crossref]
2. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T. EAU Guidelines on interventional treatment for urolithiasis. Eur Urol. 2016;69:475-482. [Crossref]
3. Knoll T, Buchholz N, Wendt-Nordahl G. Extracorporeal shockwave lithotripsy vs. percutaneous nephrolithotomy vs. flexible ureterorenoscopy for lower-pole stones. Arab J Urol. 2012;10:336-341. [Crossref]
4. Candela L, Keller EX, Pietropaolo A, Esperto F, Juliebø-Jones P, Emiliani E, De Coninck V, Tailly T, Talso M, Tonyali S, Sener ET, Hameed BMZ, Tzelves L, Mykoniatis I, Tsaturyan A, Salonia A, Ventimiglia E. New technologies in

endourology and laser lithotripsy: the need for evidence in comprehensive clinical settings. J Clin Med. 2023;12:5709. [Crossref]

5. Taratkin M, Azilgareeva C, Petov V, Morozov A, Ali S, Babaevskaya D, De Coninck V, Korolev D, Akopyan G, Scoffone CM, Chinenov D, Androsov A, Fajkovic H, Lifshitz D, Traxer O, Enikeev D. Thulium fiber laser vs Ho:YAG in RIRS: a prospective randomized clinical trial assessing the efficacy of lasers and different fiber diameters (150 µm and 200 µm). World J Urol. 2023;41:3705-3711. [Crossref]
6. Chua ME, Bobrowski A, Ahmad I, Kim JK, Silangcruz JM, Rickard M, Lorenzo A, Lee JY. Thulium fibre laser vs holmium: yttrium-aluminium-garnet laser lithotripsy for urolithiasis: meta-analysis of clinical studies. BJU Int. 2023;131:383-394. [Crossref]
7. Kozubaev B, Oguz Demirdogen S, Aksakalli T, Ozkaya F, Adanur S. Comparison of thulium fiber laser and holmium:YAG laser lithotripsy in retrograde intrarenal surgery for kidney stone treatment: a randomized prospective study. Actas Urol Esp (Engl Ed). 2025;49:501808. English, Spanish. [Crossref]
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-213. [Crossref]
9. Ozgur G, Gokmen E, Tanidir Y, Cam K, Sener TE. Surgical success and predictive factors for residual stones following supine percutaneous nephrolithotomy in the Galdakao-modified Valdivia position. Medeni Med J. 2025;40:217-225. [Crossref]
10. Shubham N, Kumar U, Singh Y, Trivedi S, Kumar L, Srivastava A, Data S, Baliyan A, Gopal Bhardwaj M. Comparative analysis of the thulium fiber laser, holmium: YAG laser, and pneumatic lithotripter in mini-percutaneous nephrolithotomy: a tertiary care center experience. Cureus. 2025;17:e93209. [Crossref]
11. Mahajan AD, Mahajan SA. Thulium fiber laser versus holmium:yttrium aluminum garnet laser for stone lithotripsy during mini-percutaneous nephrolithotomy: a prospective randomized trial. Indian J Urol. 2022;38:42-47. [Crossref]
12. Ulvik Ø, Æsøy MS, Juliebø-Jones P, Gjengstø P, Beisland C. Thulium fibre laser versus holmium:YAG for ureteroscopic lithotripsy: outcomes from a prospective randomised clinical trial. Eur Urol. 2022;82:73-79. [Crossref]
13. Gan Q, Li J, Zhai G, Liu B, Qin Y, Tan S, Wang W, Zeng Q. Expanding urolithiasis treatment: comparison of super pulsed thulium laser and holmium:YAG laser for ureteral stone management. Eur J Med Res. 2025;30:379. [Crossref]
14. Jones P, Beisland C, Ulvik Ø. Current status of thulium fibre laser lithotripsy: an up-to-date review. BJU Int. 2021;128:531-538. [Crossref]
15. Zhao H, Li W, Li J, Li L, Wang H, Guo J. Predicting the stone-free status of percutaneous nephrolithotomy with the machine learning system: comparative analysis with Guy's stone score and the S.T.O.N.E score system. Front Mol Biosci. 2022;9:880291. [Crossref]
16. Zou XC, Luo CW, Yuan RM, Jin MN, Zeng T, Chao HC. Develop a radiomics-based machine learning model to predict the stone-free rate post-percutaneous nephrolithotomy. Urolithiasis. 2024;52:64. [Crossref]
17. Ali M, Nzekwue C, Moseley E, Singh S, Vinoo A, Ajzajian J. A comparative evaluation of holmium:YAG and thulium fiber lasers in urinary stone treatment. Cureus. 2025;17:e89491. [Crossref]

ORIGINAL RESEARCH
Transplantation and Vascular Surgery

Doi: 10.4274/jus.galenos.2026.2026-3-8
J Urol Surg 2026;13(3):220-226

Harvesting Model in Rats: Investigation of the Protective Effect of Ozone in Cold Ischemic Renal Injury and the Evaluation of the Damage

Hüseyin Uğur Özkaya[1], Hasan Anıl Kurt[2], Yasemen Adalı Ruşen[3], Emre Onur Güven[4], Karolin Yanar[5], Pınar Atukeren[5], Cabir Alan[2]

[1]Ordu State Hospital, Clinic of Urology, Ordu, Türkiye
[2]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Urology, Çanakkale, Türkiye
[3]İzmir Democracy University Faculty of Medicine, Department of Pathology, İzmir, Türkiye
[4]Gölhisar State Hospital, Clinic of Urology, Burdur, Türkiye
[5]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Medical Biochemistry, İstanbul, Türkiye

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

Cold ischemia causes oxidative and structural damage in harvested kidneys, which negatively affects graft quality. Preservation solutions, including the University of Wisconsin Solution, are routinely used to reduce ischemic injury; however, oxidative stress remains a major challenge during organ preservation. This experimental rat harvesting model demonstrates that intraperitoneal ozone administration before organ removal may reduce oxidative damage and histopathological injury during cold ischemia, suggesting a novel protective strategy to improve kidney preservation.

Abstract

Objective: We aim to investigate cold ischemic injury in the kidney harvested from rats and the protective effect of ozone (O_3) on cold ischemia damage.

Materials and Methods: Thirty Wistar albino male rats were randomly assigned to three groups. Group 1 received isotonic sodium chloride (n=10; I), Group 2 received the University of Wisconsin Solution (n=10; UW), from the aorta during the procedure. Group 3 (n=10; IP + UW) was given O_3-oxygen mixture at a dose of 0.7 mg/kg (50 µg/mL) intraperitoneally 30 minutes before the procedure, in addition to the UW Solution. The organs were excised and stored in the given solutions for 12 hours. Thereafter, the kidneys were removed for examination.

Results: The biochemical evaluation revealed significantly lower levels of advanced oxidation protein products and protein carbonyl groups in the IP + UW group than in the I group. Statistically, these general protein oxidation indicators were also lower in the IP + UW group compared to the UW group. Superoxide dismutase levels were significantly higher in the IP + UW group than in the UW group. Histopathologically, the number of degenerated or necrotic tubules (D/NT), the number of tubules exhibiting brush border loss (BBT), and the number of tubular cast structures were significantly higher in group I than the UW and IP + UW groups. Comparison of the UW and IP + UW groups showed that the D/NT and the BBT counts were significantly higher in the UW group.

Conclusion: Intraperitoneal O_3 therapy, together with UW Solution, effectively attenuated cold ischemic injury in rat kidneys.

Keywords: Organ harvesting, intraperitoneal injections, ozone, rats, cold ischemia

Correspondence: Hüseyin Uğur Özkaya MD, Ordu State Hospital, Clinic of Urology, Ordu, Türkiye
E-mail: ozkayaumd@gmail.com **ORCID-ID:** orcid.org/0000-0001-7311-5739
Received: 17.03.2026 **Accepted:** 15.05.2026 **Epub:** 20.08.2026 **Publication Date:** 01.09.2026

Cite this article as: Özkaya HU, Kurt HA, Adalı Ruşen Y, Güven EO, Yanar K, Atukeren P, Alan C. Harvesting model in rats: investigation of the protective effect of ozone in cold ischemic renal injury and the evaluation of the damage. J Urol Surg. 2026;13(3):220-226

Introduction

Chronic kidney disease (CKD) is a multifactorial pathophysiological condition characterized by a gradual and irreversible decline in nephron number and function, frequently progressing to end-stage kidney disease (ESKD). Following CKD, many patients eventually develop ESKD, a stage in which intrinsic renal function is permanently lost. This life-threatening condition necessitates renal replacement therapies, including long-term dialysis or kidney transplantation, to prevent uremic complications (1). Kidney transplantation remains the most effective therapeutic option for ESKD patients requiring dialysis (2).

The preservation of the excised organ in protective solutions until transplantation (cold ischemia) and the potential injury caused by inadequate nutrient supply during this period represent critical factors that can negatively affect transplantation outcomes (3). Ozone (O_3) therapy consists of delivering a controlled mixture of O_3 and oxygen (O_2) into the body (4). Research indicates that O_3 therapy may enhance the activity of the antioxidant system, thereby mitigating damage induced by oxidative stress (5). O_3 therapy has been reported to provide beneficial effects on renal ischemia-reperfusion (I/R) injury (6).

In this study, renal cold ischemic injury following organ procurement in rats and the potential protective role of O_3 against ischemia-related damage were evaluated.

Materials and Methods

30 male Wistar albino rats (350-400 g) were housed in specialized cages under standard feeding conditions for the duration of the study. All rats underwent clinical evaluation, including behavioral, respiratory, and cardiovascular assessments, and were subsequently included in the study because no adverse events were observed. During the study period, every rat was provided with a standard chow diet and free access to water. Each rat was maintained in an environment set at 21±2 °C, under a 12:12-hour light-dark cycle. The rats were individually housed in cages within a clean-air environment. Food was provided ad libitum, except during an 8 hours fasting period prior to anesthesia.

The experimental rats were randomly allocated to three groups of ten animals each. All subjects received anesthesia. A midline incision was made to access the rats' abdominal cavities (Figure 1). Cannulation of the aortas was performed caudal to the renal arteries in all rats, and the aortas were ligated cranial to the renal arteries. During the procedure, Group 1 was administered isotonic sodium chloride (NaCl) (n=10; I) via the aorta. Group 2 received the University of Wisconsin Solution (n=10, UW), which is routinely employed for organ retrieval from the aorta (Figure 2). In addition to the UW Solution administered from the aorta, Group 3 (n=10; IP + UW) received an intraperitoneal O_3-O_2 mixture at a dose of 0.7 mg/kg (50 µg/mL) 30 minutes before the procedure to allow sufficient time for O_3-induced oxidative preconditioning and activation of endogenous antioxidant defense mechanisms prior to ischemia, as previously described in experimental studies (6,7). The organs from all three groups were harvested according to standard procedure, and the rats were euthanized upon its completion. After 12 hours of storage in the designated preservation solutions at 4 °C, the harvested organs were collected for biochemical and histopathological analyses. The experimental procedure was then concluded.

At the end of the experiment, the harvested kidney tissues were divided into two portions. The first portion of each kidney was stored in either isotonic NaCl or UW solution for 12 hours. It was

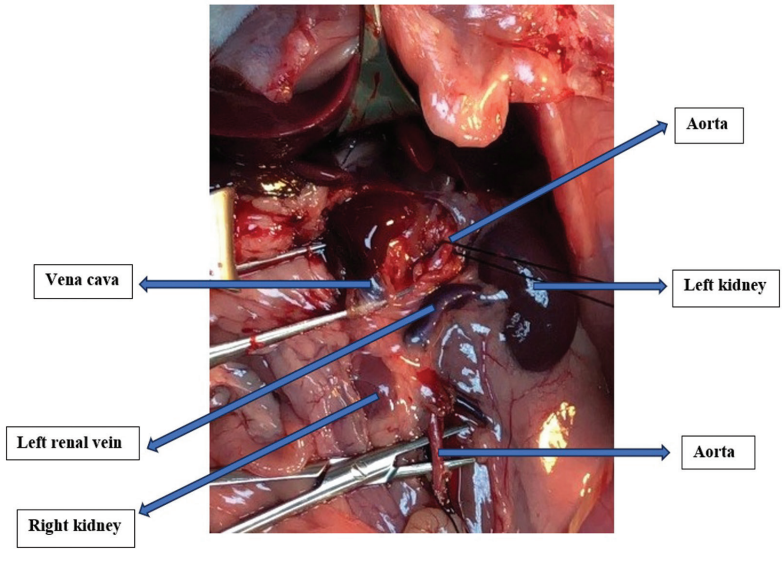


Figure 1. Exposure of the aorta, vena cava, and renal veins

then aseptically dried and preserved at -86 °C until biochemical analyses. These analyses included advanced glycation end products, advanced oxidation protein products (AOPP), and protein carbonyl groups (PCO). Malondialdehyde, kynurenine (KYN), lipid hydroperoxides, N-formyl KYN, superoxide dismutase (SOD), and total thiol fractions were also quantified. The second portion of each kidney was stored in either isotonic NaCl or UW Solution for 12 hours, after which it was transferred to formalin for histopathological evaluation.

Biochemical Method

Biochemical analyses were conducted by an experienced biochemist unaware of the group assignments. The tissues were maintained at -86 °C. Before analysis, they were removed from the freezer. Kidney tissue specimens were rinsed in chilled 0.9% NaCl and placed on an ice-cold plate. After dissection, their masses were determined. The specimens were promptly frozen in liquid nitrogen and stored until homogenization. Next, they were manually homogenized in a buffer (100 mM KH_2PO_4-K_2HPO_4) to prepare 10% homogenates. Homogenization was performed on ice using a tissue grinder equipped with a Teflon pestle. The homogenates were sonicated twice on ice at 30 seconds intervals. In this step, a MSE sonicator with a power output of 38 W was used. The homogenates were centrifuged at 15,000 g for 15 minutes. The obtained supernatant was collected for further analysis. Throughout the aliquoting process, the supernatant samples were kept at 4 °C under low-light conditions. The supernatant samples were aliquoted. Each aliquot was designated for a specific assay. The samples were stored at -80 °C for no longer than two weeks prior to biochemical analyses (8-15).

Histopathological Method

An experienced pathologist, unaware of the treatment allocation, performed the morphological evaluation. Kidney samples collected from the subjects were fixed in 10% buffered formalin and individually placed into cassettes for morphological analysis. The kidney tissues were processed using an automated tissue processor (Leica TP 1020) and embedded in paraffin. Kidney tissues were sectioned into 4-µm-thick slices. The sections were stained using hematoxylin and eosin (H&E). A light microscope (Leica DM2500) was used to observe the morphological features. Microscopic assessment was performed following the method described by Pegues et al. (16), without employing an imaging software. The numbers of degenerated or necrotic tubules (D/NT), of tubules exhibiting brush border loss (BBT) without evident cellular injury, and of tubules containing cast formations (TCT) were quantified. D/NT and BBT evaluations were obtained by averaging the counts of tubules exhibiting each injury across 10 random high-magnification fields at the cortex and cortex-medulla junction. TCT assessment was obtained by averaging the number of tubules containing tubular cast structures across 10 randomly selected high-magnification fields at the corticomedullary junction and in the medullary area. Areas with edge and section artifacts were not included in the evaluation.

Ethics Statement

All experimental procedures were performed at the Experimental Research Application and Research Center of Çanakkale Onsekiz Mart University (ÇOMÜ) following approval from the Animal Experiments Local Ethics Committee of ÇOMÜ (approval number: 2020/07-02, date: 24.08.2020). It was conducted in accordance

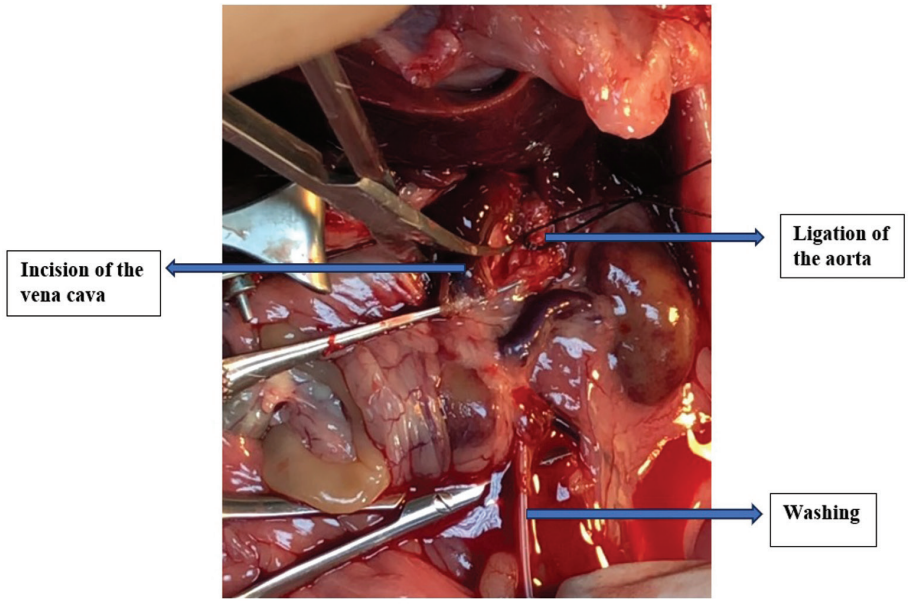


Figure 2. Ligation of the aorta, initiation of washing from the cannulated aortic section, and incision of the vena cava

with the United Kingdom Animals (Scientific Procedures) Act 1986 and its associated guidelines, and with the European Union (EU) Directive 2010/63/EU for animal experiments.

Statistical Analysis

Data analysis was conducted using IBM SPSS version 25 (SPSS Inc., Chicago, IL, USA). A p-value of less than 0.05 was regarded as statistically significant for all analyses. All values are reported as means accompanied by their standard deviations (SD). Following verification of normality using the Shapiro-Wilk test, normally distributed data were analyzed with a parametric one-way analysis of variance. For parameters showing significant differences, group comparisons were performed using a post-hoc test. Non-normally distributed parameters were analyzed using the Kruskal-Wallis test. Pairwise comparisons of significant parameters were performed using a post-hoc test.

Results

Biochemistry

Levels of AOPP and PCO, recognized as indicators of general protein oxidation, were significantly reduced in the IP + UW group versus the I group ($p<0.05$). Though the UW group demonstrated a downward trend, the change did not reach statistical significance. A more marked reduction in general protein oxidation markers occurred in the IP + UW group relative to the UW group ($p<0.05$).

SOD activity exhibited a modest, non-significant rise in the IP + UW group compared with the I group ($p>0.05$); however, SOD activity levels were markedly greater than in the UW group ($p<0.05$), suggesting a possible antioxidant response. In the UW group, SOD levels declined compared with levels in the I group; however, this difference failed to achieve statistical significance ($p>0.05$) (Table 1).

Histopathology

Light microscopy revealed clear, diffuse signs of acute tubular injury in the I group, whereas the UW and IP + UW groups displayed milder tubular damage than the I group. Images of the H&E-stained sections are presented in Figures 3 and 4. Table 2 presents the mean, minimum, and maximum values, along with SDs, of the parameters assessed across the groups.

Table 1. Comparison of oxidative stress parameters of I, UW and IP + UW groups (n=10 per group)

		KYN	N-FKYN	AOPP	PCO	LHPs	MDA	AGEs	T-SH	Cu, Zn-SOD activity
		(FU/mg protein)	(FU/mg protein)	(µmol/L)*	(nmol/mg protein)	(µmol/mg protein)	(nmol/mg protein)	(FU/mg protein)	(nmol/mg protein)	(U/mg protein)
I	Mean	658.65	527.62	55.87	4.61	0.67	3.50	490.13	9.57	2.78
	SD	194.13	118.51	14.37	1.05	0.09	0.86	89.28	1.35	1.91
UW	Mean	674.72	535.82	50.73	4.26	0.66	5.50	506.55	9.48	1.71
	SD	102.32	44.94	8.66	0.42	0.11	0.96	65.94	0.65	0.64
IP + UW	Mean	806.01	604.50	32.13	2.73	0.62	5.24	584.47	10.36	3.08
	SD	71.23	51.72	6.78	1.10	0.10	0.86	18.90	1.31	0.65

*Values are expressed as Chloramine-T equivalents
SD: Standard deviation, KYN: Kynurenine, N-FKYN: N-formyl KYN, AOPP: Advanced oxidation protein products, PCO: Protein carbonyl groups, LHP: Lipid hydroperoxide, MDA: Malondialdehyde, AGE: Advanced glycation end product, T-SH: Total thiol fractions, Cu, Zn-SOD: Superoxide dismutase, I: Isotonic sodium chloride group, UW: University of Wisconsin Solution group, IP + UW: Intraperitoneal O_3 + University of Wisconsin Solution group

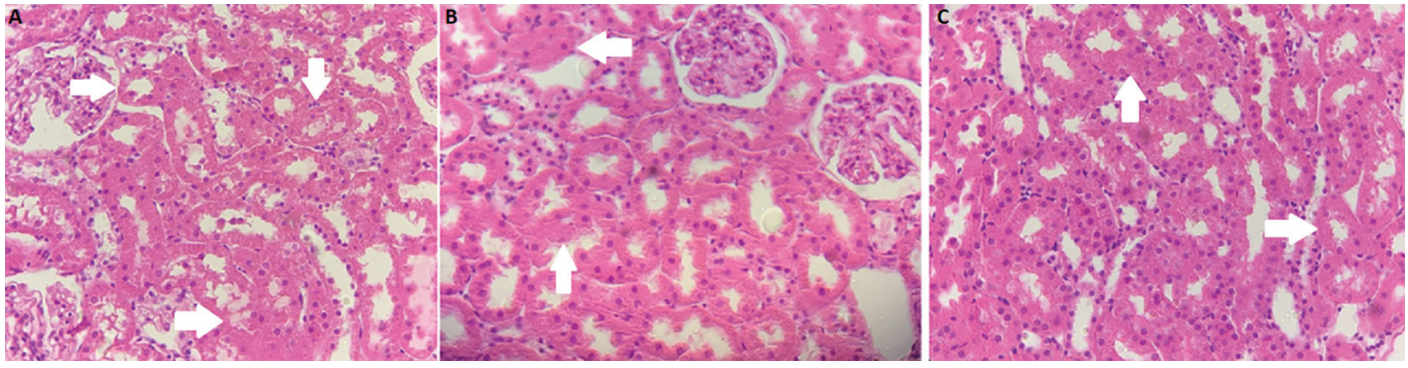


Figure 3. Degenerated/necrotic tubules marked with white arrows in kidney tissues belonging to I, UW and IP+UW groups, from left to right, at low magnification (H&E, 400x)

H&E: Hematoxylin and eosin, I: Isotonic sodium chloride group, UW: University of Wisconsin Solution group, IP + UW: Intraperitoneal O_3 + University of Wisconsin Solution group

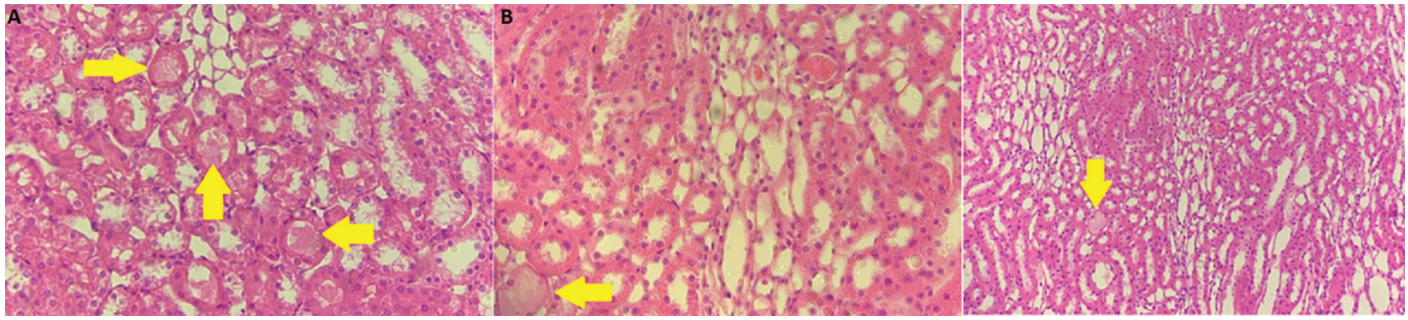


Figure 4. Cast-containing tubules marked with yellow arrows in kidney tissues belonging to I, UW (H&E, 400x) and IP + UW groups, from left to right, at low magnification (H&E, 200x)

H&E: Hematoxylin and eosin, I: Isotonic sodium chloride group, UW: University of Wisconsin Solution group, IP + UW: Intraperitoneal O_3 + University of Wisconsin Solution group

Table 2. Minimum, maximum and mean values and standard deviations of D/NT count, BBT count and TCT count in I, UW and IP + UW groups

Values	I	UW	IP + UW
D/NT count			
Minimum-maximum	55-82	22-39	18-26
Mean-standard deviation	66.7+9.2	32.7+5.9	22.1+2.6
BBT count			
Minimum-maximum	7-19	42-53	49-63
Mean-standard deviation	16.6+3.8	47.2+3.8	57.1+4.3
TCT count			
Minimum-maximum	2-8	1-2	1-2
Mean-standard deviation	4.4+1.8	1.3+0.5	1.2+0.4

D/NT: Degenerated or necrotic tubules, BBT: Tubules exhibiting brush border loss, TCT: Tubules containing cast formations, I: Isotonic sodium chloride group, UW: University of Wisconsin Solution group, IP + UW: Intraperitoneal O_3 + University of Wisconsin Solution group

Statistical analysis showed that the numbers of D/NT, BBT, and TCT in the I group exceeded those noted in the UW group ($p<0.001$ for all comparisons). Similarly, the numbers of D/NT, BBT, and TCT were significantly greater in the I group than in the IP + UW group ($p<0.001$ for all comparisons). The number of tubules observed within a microscopic field falls within a defined range. The tubules observed in this field represent the total of those categorized as D/NT and as BBT. As shown in Table 2, the BBT count was lower in group I than in the other groups. This was attributed to the higher number of D/NT in the I group than in BBT. To summarize the data presented in Table 2, the lower BBT count in the I group was primarily due to a high degree of damage, i.e., an increased number of D/NT.

A comparison of the UW and IP + UW groups indicated that D/NT ($p=0.001$) and BBT ($p=0.001$) counts were significantly higher in the UW group, whereas TCT counts showed no significant difference between groups.

Discussion

Renal transplantation is influenced by multiple perioperative variables that may compromise graft function. Among these, cold ischemia and subsequent reperfusion represent major sources of allograft injury. Reactive O_2 species (ROS) and proinflammatory mediators are considered key contributors during the reperfusion phase (17). Accordingly, strategies aimed at limiting ROS generation and attenuating inflammatory mediator release may contribute to improved graft performance and prolonged allograft viability. Our findings demonstrate that O_3 preconditioning significantly attenuates oxidative stress markers and histopathological injury in rat kidneys, suggesting a protective effect.

Previous studies have demonstrated the protective effects of O_3 against I/R injury across different tissues and organs. Chen et al. (6) evaluated the protective effects of O_3 on renal I/R injury in their post-reperfusion observation studies. Recently, a study in a spinal cord I/R injury model specifically investigating different administration routes (intrathecal, intraperitoneal, and rectal) reported that O_3 could control the adverse effects of I/R injury on renal tissue by regulating cellular oxidative stress mechanisms (7).

AOPP levels, mainly derived from albumin, reflect the degree of protein oxidation. Previous studies have shown that ischemia induces structural changes in serum albumin, leading to the identification of a novel serum marker. Tusat et al. (18) investigated the protective effects of intraperitoneally administered O_3 in preventing testicular I/R injury and found that serum ischemia-modified albumin levels were lower in the O_3 group. Jamel et al. (19) showed that plasma PCO measurement might be useful as an oxidative stress biomarker in intestinal I/R injury. Our study revealed that AOPP and PCO levels, indicators of protein oxidation, were significantly reduced in the IP+UW group compared with those in the I group. A downward trend was observed in the UW group; nonetheless, the change was

not significant. The reduction in general protein oxidation parameters was notably larger in the IP + UW group than in the UW group; this difference reached statistical significance. This shows the protective effect of O_3 in terms of general protein oxidation markers. Our study uniquely demonstrates these protective effects in a cold ischemic renal harvesting model.

SOD activity is upregulated as part of the endogenous antioxidant response to oxidative stress induced by I/R injury (20). In a rat model of ovarian torsion-associated I/R injury, Sayar et al. (21) observed a significant increase in SOD activity following ischemic insult, whereas intraperitoneal O_3 administration mitigated this response, indicating a potential regulatory influence on oxidative stress-mediated antioxidant activation. In two separate experimental models evaluating the protective roles of O_3 and hyperbaric O_2 in skeletal muscle and bone I/R injury, Koca et al. (22,23) reported reduced SOD activity following I/R induction, whereas intraperitoneal O_3 administration significantly enhanced SOD levels. The literature further suggests that SOD activity does not uniformly rise after therapeutic intervention; in some experimental settings, enzyme levels have been reported to remain low despite treatment, highlighting the complex regulation of oxidative stress responses (24). In our study, SOD levels were significantly higher in the IP + UW group than those in the UW group. These findings suggest that O_3 may augment the intrinsic antioxidant defense capacity. This study expands knowledge by suggesting that intraperitoneal O_3 may confer renal protection during cold ischemia by enhancing SOD-mediated antioxidant defenses.

The experimental study of Qiu et al. (25) showed that transrectal administration of O_3 could reduce the rate of oxidative stress damage-induced apoptosis in renal tubular epithelial cells of rats during the renal transplantation process. In the experimental study of Wang et al. (3), the number of tubules with BBT, D/NT, and enlargement was lower in the O_3-administered rat group compared to other groups. The recent spinal cord I/R study similarly provided histopathological evidence, showing that tubular dilatation and lymphocyte infiltration were statistically reduced in the O_3-administered rat groups relative to the I/R group. However, that study observed that glomerular vacuolization, vascular vacuolization and hypertrophy, and Bowman capsule dilation were significantly higher in the intrathecal and intraperitoneal groups in relation to the I/R group, indicating that the route of administration may affect specific histological structures differently (7). The histopathological examinations in our study revealed marked increases in D/NT, BBT, and TCT in the I group compared with the UW group. Mirroring prior experimental results, the I group exhibited significantly elevated D/NT, BBT, and TCT counts compared to the IP + UW group in our study. A comparison between the UW and IP + UW groups revealed significantly higher D/NT and BBT counts in the UW group, whereas TCT counts did not differ significantly. Unlike previous studies investigating rectal O_3 administration in kidney transplant models or other O_3 administration routes in I/R models, our study provides evidence for the histopathological protective effects of intraperitoneal O_3 in a kidney harvesting model under cold ischemia.

Study Limitations

This study has several limitations. It was conducted in a rat model, and the results may not fully translate to human renal harvesting and transplantation scenarios. O_3 was administered intraperitoneally at a single dose, and alternative dosages or administration routes were not explored, which could influence its protective effects. Proinflammatory mediators, including interleukin-6 (IL-6), tumor necrosis factor-alpha, IL-18, and interferon, were not evaluated, limiting the understanding of the inflammatory mechanisms involved. Future studies are required to address these limitations and clarify the mechanistic effects of O_3 in cold ischemic kidney injury.

Conclusion

Intraperitoneal administration of O_3 prior to the renal harvesting procedure significantly reduced general protein oxidation and increased SOD levels, indicating enhanced endogenous antioxidant defense. Histopathological examination suggested that intraperitoneal O_3 administration before the procedure appeared to improve most parameters compared to other groups, except the TCT number compared to the UW group. These results support a potential protective effect of intraperitoneal O_3 in a renal harvesting model under cold ischemia in rats. To enable future clinical translation, additional experimental work is required to elucidate the protective mechanisms underlying intraperitoneal O_3 administration and to determine the most effective dosing strategy.

Ethics

Ethics Committee Approval: All experimental procedures were performed at the Experimental Research Application and Research Center of Çanakkale Onsekiz Mart University (ÇOMÜ) following approval from the Animal Experiments Local Ethics Committee of ÇOMÜ (approval number: 2020/07-02, date: 24.08.2020).

Informed Consent: Not applicable.

Footnotes

The manuscript was originally written in Turkish, and then professionally translated and edited into English by protranslate.net Translation Services at the authors' own expense.

Authorship Contributions

Surgical and Medical Practices: H.U.Ö., H.A.K., E.O.G., C.A., Concept: H.U.Ö., H.A.K., C.A., Design: H.U.Ö., H.A.K., C.A., Data Collection or Processing: H.U.Ö., H.A.K., Y.A.R., E.O.G., K.Y., P.A., Analysis or Interpretation: H.U.Ö., Y.A.R., K.Y., P.A., Literature Search: H.U.Ö., Y.A.R., E.O.G., K.Y., P.A., Writing: H.U.Ö., H.A.K.

Conflict of Interest: Cabir Alan Prof. MD is Section Editor in Journal of Urological Surgery. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review. The other authors declared no conflict of interest.

Financial Disclosure: This research was supported by Çanakkale Onsekiz Mart University Scientific Research Projects Management Unit (project number: TTU-2020-3433).

References

1. Jungers P, Joly D, Barbey F, Choukroun G, Daudon M. Insuffisance rénale terminale d'origine lithiasique : fréquence, causes et prévention [Nephrolithiasis-induced ESRD: frequency, causes and prevention]. Nephrol Ther. 2005;1:301-310. French. [Crossref]
2. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341:1725-1730. [Crossref]
3. Wang Z, Han Q, Guo YL, Liu XH, Qiu T. Effect of ozone oxidative preconditioning on inflammation and oxidative stress injury in rat model of renal transplantation. Acta Cir Bras. 2018;33:238-249. [Crossref]
4. Sagai M, Bocci V. Mechanisms of action involved in ozone therapy: is healing induced via a mild oxidative stress? Med Gas Res. 2011;1:29. [Crossref]
5. Guven A, Gundogdu G, Sadir S, Topal T, Erdogan E, Korkmaz A, Surer I, Ozturk H. The efficacy of ozone therapy in experimental caustic esophageal burn. J Pediatr Surg. 2008;43:1679-1684. [Crossref]
6. Chen H, Xing B, Liu X, Zhan B, Zhou J, Zhu H, Chen Z. Ozone oxidative preconditioning protects the rat kidney from reperfusion injury: the role of nitric oxide. J Surg Res. 2008;149:287-295. [Crossref]
7. Köksal Z, Şengel N, Küçük A, Sezen ŞC, Güneş I, Atlı M, Kip G, Gökgöz Acar S, Özer A, Kavutcu M, Arslan M. Effects of intrathecal, intraperitoneal, and rectal ozone application routes on kidney tissue in rats with spinal cord ischemia–reperfusion injury. Bratisl Med J. 2025;126:3428-3439. [Crossref]
8. Reznick AZ, Packer L. Oxidative damage to proteins: spectrophotometric method for carbonyl assay. Methods Enzymol. 1994;233:357-363. [Crossref]
9. Hanasand M, Omdal R, Norheim KB, Gøransson LG, Brede C, Jonsson G. Improved detection of advanced oxidation protein products in plasma. Clin Chim Acta. 2012;413:901-906. [Crossref]
10. Sadowska-Bartosz I, Galiniak S, Bartosz G, Rachel M. Oxidative modification of proteins in pediatric cystic fibrosis with bacterial infections. Oxid Med Cell Longev. 2014;2014:389629. [Crossref]
11. Wolff SP. Ferrous ion oxidation in presence of ferric ion indicator xylenol orange for measurement of hydroperoxides. Methods Enzymol. 1994;233:182-189. [Crossref]
12. Buege JA, Aust SD. Microsomal lipid peroxidation. Methods Enzymol. 1978;52:302-310. [Crossref]
13. Sedlak J, Lindsay RH. Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal Biochem. 1968;25:192-205. [Crossref]
14. Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. Clin Chem. 1988;34:497-500. [Crossref]
15. Smith PK, Krohn RI, Hermanson GT, Mallia AK, Gartner FH, Provenzano MD, Fujimoto EK, Goeke NM, Olson BJ, Klenk DC. Measurement of protein using bicinchoninic acid. Anal Biochem. 1985;150:76-85. Erratum in: Anal Biochem 1987;163:279. [Crossref]
16. Pegues MA, McWilliams IL, Szalai AJ. C-reactive protein exacerbates renal ischemia-reperfusion injury: are myeloid-derived suppressor cells to blame? Am J Physiol Renal Physiol. 2016;311:F176-F181. [Crossref]
17. Li YW, Zhang Y, Zhang L, Li X, Yu JB, Zhang HT, Tan BB, Jiang LH, Wang YX, Liang Y, Zhang XS, Wang WS, Liu HG. Protective effect of tea polyphenols on renal ischemia/reperfusion injury via suppressing the activation of TLR4/NF-κB p65 signal pathway. Gene. 2014;542:46-51. [Crossref]
18. Tusat M, Mentese A, Demir S, Alver A, Imamoglu M. Medical ozone therapy reduces oxidative stress and testicular damage in an experimental model of testicular torsion in rats. Int Braz J Urol. 2017;43:1160-1166. [Crossref]
19. Jamel MJ, Pereira Lde P, Mello NB, Eleuthério EC, Schanaider A. Blood carbonyl protein measurement as a specific oxidative stress biomarker after intestinal reperfusion in rats. Acta Cir Bras. 2010;25:59-62. [Crossref]
20. McCord JM, Edeas MA. SOD, oxidative stress and human pathologies: a brief history and a future vision. Biomed Pharmacother. 2005;59:139-142. [Crossref]
21. Sayar I, Bicer S, Gursul C, Gürbüzel M, Peker K, Işik A. Protective effects of ellagic acid and ozone on rat ovaries with an ischemia/reperfusion injury. J Obstet Gynaecol Res. 2016;42:52-58. [Crossref]
22. Koca K, Yurttaş Y, Yıldız C, Caycı T, Uysal B, Korkmaz A. Effect of hyperbaric oxygen and ozone preconditioning on oxidative/nitrosative stress induced by tourniquet ischemia/reperfusion in rat skeletal muscle. Acta Orthop Traumatol Turc. 2010;44:476-483. [Crossref]
23. Koca K, Yurttas Y, Bilgic S, Cayci T, Topal T, Durusu M, Kaldirim U, Akgul EO, Ozkan H, Yanmis I, Oguz E, Tunay S, Korkmaz A, Basbozkurt M. Effect of preconditioned hyperbaric oxygen and ozone on ischemia-reperfusion induced tourniquet in skeletal bone of rats. J Surg Res. 2010;164:e83-e89. [Crossref]
24. Erdogan H, Fadillioglu E, Yagmurca M, Uçar M, Irmak MK. Protein oxidation and lipid peroxidation after renal ischemia-reperfusion injury: protective effects of erdosteine and N-acetylcysteine. Urol Res. 2006;34:41-46. [Crossref]
25. Qiu T, Wang ZS, Liu XH, Chen H, Zhou JQ, Chen ZY, Wang M, Jiang GJ, Wang L, Yu G, Zhang L, Shen Y, Zhang L, He L, Wang HX, Zhang WJ. Effect of ozone oxidative preconditioning on oxidative stress injury in a rat model of kidney transplantation. Exp Ther Med. 2017;13:1948-1955. [Crossref]

ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2026.2026-3-3
J Urol Surg 2026;13(3):227-233

Comparison of Laparoscopic and Open Radical Prostatectomy in Terms of Surgical Efficacy and Safety of Initial Cases: A Single-center Retrospective Study

Yusuf Şenoğlu, Murat Kars, Abdul Vahap Bakır, Günal Özgür, Kamil Çam

Marmara University Faculty of Medicine, Department of Urology, İstanbul, Türkiye

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

Laparoscopic radical prostatectomy has been shown to provide perioperative benefits compared to open radical prostatectomy, especially in terms of reduced blood loss, lower transfusion rates, and shorter hospital stays; however, its steep learning curve can affect early perioperative and functional results. This study contributes to the literature by demonstrating that even during surgeons' initial radical prostatectomy cases, the laparoscopic approach was associated with more favorable perioperative outcomes and improved early urinary continence, while achieving similar early oncological outcomes, including positive surgical margins and short-term prostate-specific antigen recurrence rates, compared to the open approach.

Abstract

Objective: Surgeons aiming to adopt minimally invasive techniques may initiate laparoscopic radical prostatectomy (LRP) either after performing a certain number of open procedures or even without prior open surgical experience. This study aimed to evaluate the feasibility, safety, and efficacy of LRP performed without previous open radical prostatectomy (ORP) experience.

Materials and Methods: This retrospective analysis included the initial ORP and LRP cases performed by two surgeons who had no prior experience with either approach before completing their residency training. Demographic, perioperative, pathological, and postoperative functional outcomes at 12 months were compared between the two groups.

Results: Sixty patients were analyzed (ORP: 30, LRP: 30). Baseline characteristics were similar (p>0.05). Operative time was comparable (p=0.849). Intraoperative blood loss was significantly lower in the LRP group (200 mL vs. 950 mL, p=0.001). Hospital stay was shorter for LRP (5 vs. 6 days, p=0.004). Continence rates favored LRP (100% vs. 60% continent; <0.001), whereas erectile function recovery was comparable. Minor complications occurred in 18% overall, with no major complications (Clavien ≥III). Positive surgical margin rates were 20% for ORP and 17% for LRP (p>0.99). Biochemical recurrence at 12 months (prostate-specific antigen >0.2 ng/mL) was observed in 10% of patients in both groups (p>0.99).

Conclusion: LRP, even when performed by surgeons without prior ORP experience, achieved superior perioperative outcomes and better early continence recovery while maintaining early oncological control. In centers with limited access to robotic surgery due to high costs and restricted availability of trained surgeons, laparoscopy remains a safe and effective alternative for radical prostatectomy.

Keywords: Radical prostatectomy, open surgery, laparoscopy

Introduction

Prostate cancer is the world's second most frequently diagnosed malignancy in men and continues to be a leading cause of cancer-related death, particularly in developed countries. Radical prostatectomy represents a standard curative treatment for patients with clinically localized prostate cancer, providing excellent long-term oncological control in appropriately selected cases (1).

Correspondence: Yusuf Şenoğlu MD, FEBU, Marmara University Faculty of Medicine, Department of Urology, İstanbul, Türkiye
E-mail: ysenoglu@yahoo.com, yusuf.senoglu@marmara.edu.tr **ORCID-ID:** orcid.org/0000-0002-3072-9252
Received: 09.03.2026 **Accepted:** 10.07.2026 **Epub:** 18.08.2026 **Publication Date:** 01.09.2026

Cite this article as: Şenoğlu Y, Kars M, Bakır AV, Özgür G, Çam K. Comparison of laparoscopic and open radical prostatectomy in terms of surgical efficacy and safety of initial cases: a single-center retrospective study. J Urol Surg. 2026;13(3):227-233

Historically, open radical prostatectomy (ORP) has been widely performed and has served as an established surgical approach for localized prostate cancer. However, the development and widespread adoption of minimally invasive surgical techniques have led to increased use of laparoscopic radical prostatectomy (LRP), which may offer several advantages, such as reduced blood loss, shorter hospitalization, and reduced postoperative pain (2).

Despite these potential benefits, the laparoscopic approach is technically demanding, characterized by a long learning curve that can influence oncological results, especially during the surgeon's initial experience (3). Previous studies, comparing ORP and LRP, have reported mixed results; differences in perioperative morbidity, operative time, oncological outcomes, and functional results often vary depending on surgeon expertise, institutional experience, and patient characteristics (4-6).

In this retrospective analysis, we sought to compare the preoperative, intraoperative, and postoperative outcomes of patients undergoing open and LRP at our center, performed by two surgeons who had no prior experience with the procedure. By evaluating objective clinical data, we aimed to clarify the safety, efficacy, and feasibility of both surgical techniques for initial cases in routine practice.

Materials and Methods

Study Design and Setting

This single-center, retrospective, comparative cohort study, conducted in the Department of Urology of Marmara University Training and Research Hospital, included patients who underwent radical prostatectomy for localized prostate cancer between March 2021 and May 2024. The study was approved by Marmara University Faculty of Medicine Non-Drug and Non-Medical Device Research Ethics Committee (approval number: 09.2025.25-0501, date: 20.06.2025). Written informed consent was obtained from all participants.

Patient Selection and Grouping

Patients were divided into two groups based on the initial surgical approach, which was performed by two different surgeons: Group 1 (ORP) and Group 2 (LRP).

Eligible patients were identified from the institution's surgical database. The inclusion criteria were: histopathologically confirmed prostate adenocarcinoma; treatment by either open or LRP; availability of complete perioperative and follow-up data; and a minimum follow-up period of twelve months. Patients were excluded if they had a history of pelvic surgery or radiotherapy, evidence of metastatic disease at diagnosis, prior neoadjuvant therapy, or incomplete clinical records.

Surgical Techniques

ORP was performed through a lower midline extraperitoneal retropubic approach. Nerve-sparing and pelvic lymph node dissection (PLND) were selectively performed based on the preoperative the European Association of Urology (EAU) risk assessment and intraoperative factors, including surgical exposure, anatomical difficulty, comorbidity status, and the surgeon's assessment of technical feasibility for both approaches.

LRP was performed via a transperitoneal five-port technique. Standard steps included seminal vesicle dissection at the posterior aspect of the prostate, anterior mobilization of the prostate, ligation of the dorsal venous complex, bladder neck transection, preservation of the neurovascular bundles when feasible, and urethrovesical anastomosis.

The surgeries were performed by two surgeons, each with 5 years of urology training. The surgeon performing the open surgery had prior experience in other open oncologic procedures, while the surgeon performing the laparoscopic surgery had extensive experience in other laparoscopic procedures.

Data Collection and Variables

Demographic, clinical, and surgical data were obtained retrospectively from the hospital information management system and surgical records. The following parameters were recorded:

Preoperative Variables

Age, preoperative prostate-specific antigen (PSA) level, digital rectal examination findings (benign vs. malignant), prostate volume, and biopsy International Society of Urological Pathology (ISUP) grade, preoperative urinary continence and erectile function (the ability to achieve penetration with or without the use of phosphodiesterase-5 inhibitors). Patients were preoperatively classified as low-, intermediate-, or high-risk according to EAU risk stratification.

Perioperative Variables

Surgical approach (ORP vs. LRP), PLND (yes/no), nerve-sparing status (categorized as performed or not performed), operative duration, estimated blood loss, and need for intraoperative transfusion.

Postoperative Variables

Hospital stay, duration of catheterization, need for postoperative transfusion, complications (classified according to Clavien-Dindo), positive surgical margin (PSM) status, final pathological ISUP grade and stage, serum PSA level, urinary incontinence status (patients using no pads or only one safety pad per day were considered continent, whereas those requiring more than one pad per day were considered incontinent), and erectile

function status (presence or absence of erections sufficient for penetration, with or without medication).

Follow-up Protocol

Postoperative follow-up visits were conducted at 10-14 days (for catheter removal and wound evaluation) and at 1, 3, 6, 9, and 12 months. Serum PSA levels were routinely assessed from the third postoperative month onward and at each subsequent follow-up visit. Persistent PSA was defined as a PSA level of ≥0.2 ng/mL at the first postoperative PSA assessment, whereas biochemical recurrence was defined as a subsequent detectable or rising PSA level of ≥0.2 ng/mL confirmed on two separate measurements after having achieved an undetectable postoperative PSA level. Urinary continence and erectile function outcomes were assessed clinically and documented by patient self-report at 12 months.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was evaluated visually (histograms and probability plots) and with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables that do not conform to a normal distribution are reported as the median and interquartile range (IQR). The Mann-Whitney U test was used to compare two independent groups for non-parametric continuous and ordinal data. Categorical variables are presented as frequencies (%) and contingency tables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. ISUP grade distributions across groups were analyzed using the chi-square test. A p-value <0.05 was considered statistically significant.

Results

A total of 60 patients who underwent radical prostatectomy were included in the study, of whom 30 had ORP and 30 had LRP. The mean age was slightly higher in the LRP group (67.6±7.4 years) compared to the ORP group (65±6.3 years), although this difference was not statistically significant (p=0.212). The preoperative median PSA level was 7.6 ng/mL (IQR: 5.5-9.6) in the ORP group and 5.8 ng/mL (IQR: 4.6-10.6) in the LRP group (p=0.25). Digital rectal examination findings were comparable between the groups (benign findings: 60.0% in the ORP group vs. 50.0% in the LRP group, p=0.604).

No significant differences were observed between the groups for preoperative prostate volume (median 44.5 mL in ORP vs. 41 mL in LRP, p=0.968) or the biopsy ISUP grade distribution (p=0.486). Risk classification was similar between groups, with low-, intermediate-, and high-risk disease observed in 40.0%, 43.3%, and 16.7% of patients in the ORP group in and in 36.7%, 56.7%, and 6.7% of patients in the LRP group, respectively (p=0.394). All patients were continent preoperatively. Furthermore, all patients reported erections sufficient for penetration, with or without the use of phosphodiesterase-5 inhibitors. All comparative outcomes are shown in Table 1.

Perioperative Outcomes

The median operative time was similar between the groups: 253 minutes (IQR: 231.3-301.5) for ORP and 240 minutes (IQR: 240-270) for LRP (p=0.849). In contrast, estimated intraoperative blood loss was significantly greater in the ORP group (median 950 mL, IQR: 700-1625) than in the LRP group (median 200 mL, IQR: 150-300) (p=0.001). Likewise, the requirement for intraoperative transfusion was substantially higher in the open surgery cohort (60% vs. 0%, p<0.001). Nerve-sparing status (performed vs. not performed) differed significantly between the groups, with a higher rate in the LRP group (66.7% vs. 26.7%, p=0.004). PLND was performed significantly more often in the ORP group (47%) than in the LRP group (17%) (p=0.025).

Postoperative Outcomes

The median hospital stay was significantly longer in the ORP group (6 days, IQR: 5-7) than in the LRP group (5 days, IQR: 4-5.8) (p=0.004). Overall complication rates did not differ significantly between the groups (p>0.999). All complications observed in both groups were minor (Clavien-Dindo grade I-II), such as transient fever, and minor wound-related problems. No major complications were recorded in either group. PSM rates (20% ORP vs. 17% LRP, p>0.999), and postoperative pathologic ISUP grade distribution (p=0.329) were similar in both groups. All patients achieved undetectable PSA levels (<0.2 ng/mL) in the early postoperative period. Detectable PSA (>0.2 ng/mL) at 12 months was observed in 10% of patients in both groups, consistent with biochemical recurrence (Table 2).

Functional Outcomes

Postoperative urinary continence outcomes differed significantly between groups: continence (no pad or one safety pad) was achieved in 60% of ORP patients compared with 100% of LRP patients; and incontinence (≥2 pads/day) in 40% vs. 0%, respectively (p<0.001). Recovery of erectile function was observed in 30% of ORP patients and 37% of LRP patients, with no significant difference between the groups (p=0.780) (Table 2).

Table 1. Comparative pre- and perioperative outcomes of ORP and LRP			
Variable	**ORP (n=30)**	**LRP (n=30)**	**p-value**
Age, years (mean ± SD)	65±6.3	67.6±7.4	0.212
Preoperative PSA, ng/mL (median, IQR)	7.6 (5.5-9.6)	5.8 (4.6-10.6)	0.25
Prostate volume, mL (median, IQR)	44.5 (24-66)	41 (32-64)	0.968
Digital rectal examination			
Benign	18, 60%	15, 50%	0.604
Malign	12, 40%	15, 50%	
ISUP grade, Bx (n, %)			
1	14, 47%	18, 60%	
2	8, 27%	8, 27%	0.486
3	4, 13%	3, 10%	
4	4, 13%	1, 3%	
5	0	0	
Risk group			
Low	12, 40%	11, 37%	0.394
Intermediate	13, 43%	17, 56%	
High	5, 17%	2, 7%	
Nerve-sparing			
Performed	8, 26.7%	20, 66.7%	0.004
Not performed	22, 73.3%	10, 33.3%	
PLND (n,%)	14, 47%	5, 17%	0.025
Operative time, min (median, IQR)	253 (231-301)	240 (240-270)	0.849
Estimated blood loss, mL (median, IQR)	950 (700-1625)	200 (150-300)	0.001
Intraoperative transfusion (n,%)	18, 60%	0, 0%	<0.001

Chi-square test was used for variables with more than two categories; Fisher's exact test was used for 2×2 categorical variables
ORP: Open radical prostatectomy, LRP: Laparoscopic radical prostatectomy, SD: Standard deviation, IQR: Interquartile range, PSA: Prostate-specific antigen, Bx: Prostate biopsy, ISUP: International Society of Urological Pathology, PLND: Pelvic lymph node dissection

Table 2. Post-operative and functional outcomes			
Variable	**ORP (n=30)**	**LRP (n=30)**	**p-value**
Hospital stay, days (median, IQR)	6 (5-7)	5 (4-5.8)	0.004
Overall complication rate (%)	6, 20%	5, 17%	>0.99
ISUP grade, RP (n, %)			
1	3, 10%	5, 17%	
2	18, 60%	16, 53%	0.329
3	6, 20%	3, 10%	
4	3, 10%	3, 10%	
5	0	3, 10%	
Positive surgical margins (%)	6, 20%	5, 17%	>0.99
PSA recurrence (n,%)	3, 10%	3, 10%	>0.99
Continence (n, %)	18, 60%	30, 100%	<0.001
Erectile function recovery (n, %)	9, 30%	11, 37%	0.780

ORP: Open radical prostatectomy, LRP: Laparoscopic radical prostatectomy, SD: Standard deviation, IQR: Interquartile range, PSA: Prostate-specific antigen, RP: Radical prostatectomy, ISUP: International Society of Urological Pathology

Discussion

This study compared the outcomes of open retropubic and LRP performed during the surgeons' initial learning phases. Notably, the surgeon performing the laparoscopic procedures lacked prior experience with ORP, which could have influenced perioperative performance and the progression of the learning curve.

Recent evidence suggests that minimally invasive radical prostatectomy, including laparoscopic and robot-assisted approaches, offers perioperative advantages over open surgery, such as lower estimated blood loss, reduced transfusion requirements, and shorter hospital stays (2,5). A study comparing minimally invasive and open techniques found that minimally invasive approaches were associated with approximately a 83% reduction in transfusion risk and a 1.18-day reduction in hospital stay (2). Although enhanced visualization in minimally invasive surgery may offer technical advantages for functional preservation, the available literature generally suggests that continence outcomes are broadly comparable between minimally invasive and ORP (5,7). In line with these reports, our findings showed that LRP was associated with significantly reduced intraoperative blood loss and transfusion requirements, shorter hospitalization, and improved early continence, while maintaining comparable operative times and oncological outcomes. These results support the existing evidence highlighting the perioperative advantages of minimally invasive techniques, particularly in reducing morbidity and promoting faster recovery.

Radical prostatectomy is a technically challenging procedure that requires delicate dissection because of the complex pelvic anatomy and the need for both functional preservation and oncologic control. Numerous studies have evaluated the learning curve and reported significant variation in the number of cases needed to achieve surgical proficiency. While perioperative parameters such as operative time, complication rates, and hospital stay may improve within the early phase of the learning curve, oncologic and functional outcomes, including continence and surgical margin status, generally require greater surgical experience to stabilize (6,8,9). In their analysis of 4,702 laparoscopic radical prostatectomies, Vickers et al. (3) showed that the risk of recurrence continued to decline with increasing surgical experience, even up to 750 prior cases, indicating a prolonged learning curve for oncologic outcomes. Similarly, Secin et al. (10) reported that the learning curve for PSMs in LRP was prolonged, with improvement continuing up to approximately 200-250 cases, and appeared less rapid than that reported for open surgery.

Despite this challenging learning curve, minimally invasive approaches—even during the early learning period—have demonstrated perioperative advantages, including lower blood loss, reduced transfusion requirements, and shorter hospital stays, while producing comparable oncologic outcomes when performed by experienced surgeons. A meta-analysis by Cao et al. (2) showed that minimally invasive radical prostatectomy, including laparoscopic and robot-assisted approaches significantly reduced blood loss (mean difference ≈749 mL) and transfusion risk (odds ratio ≈0.17) compared with open surgery, with no significant difference between groups in PSMs or biochemical recurrence rates.

Bhayani et al. (11) found that LRP was associated with substantially lower blood loss (533 mL vs. 1,473 mL) and quicker recovery compared with open retropubic prostatectomy, albeit with longer operative time during the initial experience (5.8 hours vs. 2.8 hours). Likewise, a recent randomized clinical study by Guan et al. (12) confirmed that LRP achieved less intraoperative bleeding, shorter hospitalization, faster recovery, and better early continence than open surgery in localized prostate cancer. In our series, despite the surgeons being in their early learning phase, LRP showed clear perioperative benefits over open surgery-markedly lower intraoperative blood loss (~200 mL vs. ~950 mL), no transfusions, and shorter hospital stay. The relatively high transfusion rate in the ORP group should be interpreted in light of transfusion decisions being based on intraoperative clinical judgment rather than on a predefined blood-loss cut-off. Additionally, since these cases were performed during the surgeon's initial learning phase, a lower threshold for transfusion may have been adopted for some patients to improve perioperative safety. Early recovery of urinary continence was also superior in the LRP group. Our results are consistent with previous studies showing that LRP can reduce perioperative morbidity without compromising oncological safety.

The superiority of LRP in these aspects stems from several technical and physiological advantages inherent to the minimally invasive approach. These perioperative advantages may be partly explained by the magnified operative view and the tamponade effect of pneumoperitoneum, which can facilitate dissection and hemostasis (13,14). Minimal access reduces wound trauma, postoperative pain, and systemic inflammatory response, resulting in earlier mobilization and shorter hospitalization. Moreover, enhanced magnification may facilitate more precise preservation of periurethral and sphincteric structures, which could contribute to functional recovery (15). More broadly, when performed by adequately trained surgeons, the perioperative advantages of LRP may be achieved without a clear compromise in oncologic outcomes, as comparative studies have generally reported comparable PSM and biochemical recurrence results between minimally invasive and open techniques (5,16).

In our study, PLND was performed significantly less often in the LRP group than in the ORP group. Although differences in preoperative risk distribution may have contributed to this imbalance, the discrepancy cannot be explained solely by risk stratification. It is also likely to reflect surgeon- and technique-related factors during the early learning phase, including the greater technical complexity of laparoscopic PLND, limited tactile feedback, restricted instrument mobility, and a tendency to avoid more demanding adjunctive procedures during that phase. Therefore, the lower PLND rate in the LRP group should be interpreted as multifactorial rather than as a difference solely attributable to the patient risk profile. Similar patterns have been reported in early laparoscopic series. In the large series by Stolzenburg et al. (17), pelvic lymph node dissection was not performed in all patients. Similarly, the prolonged learning curve reported for LRP may indirectly reflect the technical burden of the procedure during early experience; however, this evidence does not specifically address PLND rates (10). Therefore, the lower PLND rate in our LRP cohort most likely represents a learning-phase phenomenon rather than an inherent limitation of the minimally invasive technique. This difference should also be taken into account when interpreting perioperative outcomes, as the lower PLND rate in the LRP group may have contributed, at least in part, to the observed differences in blood loss, transfusion requirements, operative time, and complication profiles.

In our cohort, postoperative recovery of erectile function was similar in the open and laparoscopic groups (30% vs. 37%, p=0.78). Although the difference did not reach statistical significance, the slightly higher rate observed in the LRP group may be attributable to improved dissection of the neurovascular bundles achieved with laparoscopic magnification. Stolzenburg et al. (17) reported that the magnified laparoscopic view and improved hemostasis may facilitate more precise identification and preservation of the neurovascular bundles in selected patients, which may support postoperative sexual function recovery.

Compared with conventional laparoscopy, robotic surgery may facilitate adoption because of wristed instrumentation, three-dimensional visualization, and improved ergonomics; however, reported learning-curve estimates vary substantially depending on the outcome assessed (15,18). However, particularly in resource-limited settings, use of robot-assisted radical prostatectomy remains limited for several reasons. Beyond the high installation and ongoing maintenance costs of robotic systems, limited access to training and a shortage of experienced robotic surgeons—particularly in developing or resource-limited healthcare settings—continue to be major obstacles (19,20). Therefore, in regions where robotic technology remains inaccessible or financially impractical, conventional LRP continues to play a crucial role as a safe, effective, and sustainable treatment option. Consistent with these observations, our findings further support the clinical feasibility and safety of LRP as a durable, minimally invasive alternative in resource-limited settings.

Study Limitations

The retrospective design and single-center setting of our study may have introduced selection bias, limiting the generalizability of the results. The small sample size made it difficult to demonstrate small differences statistically, particularly in functional and oncologic outcomes. Due to the limited follow-up period, long-term continence, potency, and oncologic control could not be assessed. Moreover, both surgeons were at the beginning of their respective learning curves. Therefore, it is difficult to distinguish outcomes related to the intrinsic characteristics of the surgical technique from those associated with the surgeon's level of proficiency, which may have been an important confounding factor in comparisons between groups. Another important limitation is that urinary continence and erectile function outcomes were based on patients' self-reports rather than on validated questionnaires or objective assessment tools, which may have introduced reporting and recall biases. In addition, the significant difference in PLND rates between the groups may have acted as a confounding factor, as it may have affected perioperative outcomes, including blood loss, transfusion requirements, operative time, and complications. Despite these limitations, we believe that this study makes a significant contribution to the feasibility and safety of LRP in patients with no prior experience of open surgery, especially in clinics with limited access to robotic technology.

With appropriate training and structured mentorship, safe and reproducible outcomes can be achieved in radical prostatectomy, even during the surgeon's early experience. The literature suggests that early LRP experience supported by structured mentorship may provide acceptable perioperative and functional outcomes during the initial learning phase, while large high-volume series have shown that favorable outcomes can be achieved with increasing experience (9,14). However, prior experience with basic laparoscopic urogenital procedures may facilitate the transition to more complex operations, such as LRP (21). Therefore, our findings support the notion that under proper supervision and after sufficient laparoscopic experience, surgeons completing urology residency may safely begin their learning curve in performing LRP.

Conclusion

This retrospective analysis indicates that LRP provides superior perioperative outcomes, including reduced blood loss, fewer transfusions, shorter hospital stays, and improved early urinary

continence. Moreover, it maintains early oncologic safety compared with ORP, even during the initial learning curve. Larger prospective studies are necessary to confirm these findings and to further assess long-term functional and oncological results.

Ethics

Ethics Committee Approval: The study was approved by Marmara University School of Medicine Non-Drug and Non-Medical Device Research Ethics Committee (approval number: 09.2025.25-0501, date: 20.06.2025).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.Ş., M.K., Concept: Y.Ş., M.K., G.Ö., K.Ç., Design: Y.Ş., A.V.B., K.Ç., Data Collection or Processing: A.V.B., G.Ö., Analysis or Interpretation: A.V.B., G.Ö., Literature Search: A.V.B., Writing: Y.Ş., M.K., K.Ç.

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

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

References

1. Cornford P, van den Bergh RCN, Briers E, Chiu P, Eberli D, Epure A, Farolfi A, Fonteyne V, Gandaglia G, Gillessen S, Grivas N, Henry AM, van Leenders GJLH, Espinos EL, Matsen B, Oldenburg J, van Oort IM, Oprea-Lager DE, Roberts MJ, Rouvière O, Sachdeva A, Santis M, Schoots IG, Smith EJ, Stranne J, Wiegel T, Tilki D. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer-2026 update. Part I: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2026:S0302-2838(26)02114-7. [Crossref]
2. Cao L, Yang Z, Qi L, Chen M. Robot-assisted and laparoscopic vs open radical prostatectomy in clinically localized prostate cancer: perioperative, functional, and oncological outcomes: a systematic review and meta-analysis. Medicine (Baltimore). 2019;98:e15770. [Crossref]
3. Vickers AJ, Savage CJ, Hruza M, Tuerk I, Koenig P, Martínez-Piñeiro L, Janetschek G, Guillonneau B. The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. Lancet Oncol. 2009;10:475-480. [Crossref]
4. von Ahlen C, Geissler A, Vogel J. Comparison of the effectiveness of open, laparoscopic, and robotic-assisted radical prostatectomies based on complication rates: a retrospective observational study with administrative data from Switzerland. BMC Urol. 2024;24:215. [Crossref]
5. Matalani CFA, Costa MSS, Rocha MRD, Lopes RI, Talizin TB, Bessa Júnior J, Nahas WC, Ribeiro-Filho LA, Suartz CV. Minimally invasive radical prostatectomy versus open radical prostatectomy: a systematic review and meta-analysis of randomized control trials. Clinics (Sao Paulo). 2025;80:100636. [Crossref]
6. Ficarra V, Novara G, Artibani W, Cestari A, Galfano A, Graefen M, Guazzoni G, Guillonneau B, Menon M, Montorsi F, Patel V, Rassweiler J, Van Poppel H. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. Eur Urol. 2009;55:1037-1063. [Crossref]
7. Roumeguere T, Bollens R, Vanden Bossche M, Rochet D, Bialek D, Hoffman P, Quackels T, Damoun A, Wespes E, Schulman CC, Zlotta AR. Radical prostatectomy: a prospective comparison of oncological and functional results between open and laparoscopic approaches. World J Urol. 2003;20:360-366. [Crossref]
8. Barnaś A, Milecki T, Ida A, Kasperczak M, Lipski A, Antczak A, Cieślikowski WA. Learning curve for laparoscopic radical prostatectomy. Wideochir Inne Tech Maloinwazyjne. 2025;20:69-75. [Crossref]
9. Fabrizio MD, Tuerk I, Schellhammer PF. Laparoscopic radical prostatectomy: decreasing the learning curve using a mentor initiated approach. J Urol. 2003;169:2063-2065. [Crossref]
10. Secin FP, Savage C, Abbou C, de La Taille A, Salomon L, Rassweiler J, Hruza M, Rozet F, Cathelineau X, Janetschek G, Nassar F, Turk I, Vanni AJ, Gill IS, Koenig P, Kaouk JH, Martinez Pineiro L, Pansadoro V, Emiliozzi P, Bjartell A, Jiborn T, Eden C, Richards AJ, Van Velthoven R, Stolzenburg JU, Rabenalt R, Su LM, Pavlovich CP, Levinson AW, Touijer KA, Vickers A, Guillonneau B. The learning curve for laparoscopic radical prostatectomy: an international multicenter study. J Urol. 2010;184:2291-2296. [Crossref]
11. Bhayani SB, Pavlovich CP, Hsu TS, Sullivan W, Su Li. Prospective comparison of short-term convalescence: laparoscopic radical prostatectomy versus open radical retropubic prostatectomy. Urology. 2003;61:612-616. [Crossref]
12. Guan Y, Tan C, Zhu H, Li H, Liu H, Hu W, Song H, Xiao F. Clinical effects of laparoscopic versus open radical prostatectomy in the treatment of early prostate cancer. Afr J Reprod Health. 2025;29:106-112. [Crossref]
13. Jo SB, Kim JW. Recent advances in radical prostatectomy: a narrative review of surgical ınnovations and outcomes. Cancers (Basel). 2025;17:902. [Crossref]
14. Stolzenburg JU, Rabenalt R, Do M, Kallidonis P, Liatsikos EN. Endoscopic extraperitoneal radical prostatectomy: the University of Leipzig experience of 2000 cases. J Endourol. 2008;22:2319-2325. [Crossref]
15. Lau HM, Qu LG, Woon DTS. Advances in techniques in radical prostatectomy. Medicina (Kaunas). 2025;61:1222. [Crossref]
16. Kim DK, Moon YJ, Chung DY, Jung HD, Jeon SH, Kang SH, Paick S, Lee JY; Korean Society of Endourology and Robotics (KSER) Research Committee. Comparison of robot-assisted, laparoscopic, and open radical prostatectomy outcomes: a systematic review and network meta-analysis from KSER update series. Medicina (Kaunas). 2025;61:61. [Crossref]
17. Stolzenburg JU, Rabenalt R, DO M, Ho K, Dorschner W, Waldkirch E, Jonas U, Schütz A, Horn L, Truss MC. Endoscopic extraperitoneal radical prostatectomy: oncological and functional results after 700 procedures. J Urol. 2005;174:1271-1275; discussion 1275. [Crossref]
18. Tokas T, Mavridis C, Bouchalakis A, Nakou CM, Mamoulakis C. Learning curves in robotic urological oncological surgery: has anything changed during the last five years? Cancers (Basel). 2025;17:1334. [Crossref]
19. Barbash GI, Glied SA. New technology and health care costs--the case of robot-assisted surgery. N Engl J Med. 2010;363:701-704. [Crossref]
20. Falola AF, Singh S, Das U, Oluwagbemi A, Etta R, Adeyeye A. Barriers and recommendations for the implementation of robot-assisted minimally invasive surgery in Africa. J Robot Surg. 2024;19:16. [Crossref]
21. Bollens R, Sandhu S, Roumeguere T, Quackels T, Schulman C. Laparoscopic radical prostatectomy: the learning curve. Curr Opin Urol. 2005;15:79-82. [Crossref]

ORIGINAL RESEARCH
Pediatric Urology

Doi: 10.4274/jus.galenos.2026.2026-6-9
J Urol Surg 2026;13(3):234-240

Screen-related Behavioral Patterns and Toilet Postponement are Associated with Lower Urinary Tract Symptoms: A Cross-sectional Survey Study

Engin Denizhan Demirkıran[1], Onur Baki Çavuş[2], Arkın Arıcı[2], Bedirhan Esin[2], Ezgi Çetin[2], Ayşegül Karakaş[2], Nidanur Akpınar[2], İsmail Cunedioğlu[2], Cansel Deveci[2], Burcu Oturak[2], Fatma Sude Şentürk[2], Tuna Yılmaz[2], Ayşe Gökçe[2], Janset Beyza Çifçi[2], Ceylin Naz Aksoy[2]

[1]*Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Urology, Zonguldak, Türkiye*
[2]*Zonguldak Bülent Ecevit University Faculty of Medicine, Zonguldak, Türkiye*

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

Excessive screen exposure has been linked to sedentary behavior and other adverse health outcomes, while maladaptive toileting behaviors are associated with lower urinary tract symptoms (LUTS). However, the interaction between screen-related behaviors, toilet postponement, and LUTS remains unclear. This study shows that digital behavior and toilet postponement scores are independently associated with LUTS burden, whereas screen exposure duration alone is not. These findings suggest that behavioral patterns accompanying screen use, rather than screen time itself, may be more relevant to urinary health.

Abstract

Objective: To investigate the relationship between screen-related behavioral patterns, toilet postponement behavior, and lower urinary tract symptoms (LUTS) in young adults.

Materials and Methods: This university campus-based cross-sectional survey included participants aged ≥18 years recruited through face-to-face interviews between May 1 and May 30, 2026. The questionnaire assessed demographic characteristics, screen use habits, toilet postponement behavior, and LUTS. Study-specific composite digital behavior score (DBS), toilet postponement score (TPS), and LUTS scores were calculated. Correlation and multivariable linear regression analyses were performed.

Results: A total of 478 participants were included (mean age: 26.05±11.7 years; 62.1% female). DBS was positively correlated with TPS (rho=0.445, p<0.001), LUTS total score (rho=0.268, p<0.001), LUTS storage score (rho=0.140, p=0.002), and LUTS voiding score (rho=0.308, p<0.001). TPS was also associated with LUTS total score (rho=0.344, p<0.001). Participants reporting longer daily screen exposure had significantly higher DBS and TPS values (both p<0.01). In multivariable regression analysis, DBS (β=0.439, p=0.002), TPS (β=0.656, p<0.001), and tea/coffee consumption (β=1.125, p<0.001) remained independently associated with higher LUTS total scores, whereas screen exposure duration was not associated (p=0.771).

Conclusion: Screen-related behavioral patterns and toilet postponement behavior were independently associated with greater LUTS burden, whereas screen exposure duration alone was not associated with greater LUTS burden. Behavioral factors accompanying digital lifestyles may have a greater impact on urinary health than screen time itself.

Keywords: Lower urinary tract symptoms, digital behavior, toilet postponement, screen exposure, voiding behavior

Correspondence: Engin Denizhan Demirkıran MD, FEBU, Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Urology, Zonguldak, Türkiye
E-mail: eddemirkiran@gmail.com **ORCID-ID:** orcid.org/0000-0002-0021-5402
Received: 17.06.2026 **Accepted:** 17.07.2026 **Publication Date:** 01.09.2026

Cite this article as: Demirkıran ED, Çavuş OB, Arıcı A, Esin B, Çetin E, Karakaş A, Akpınar N, Cunedioğlu İ, Deveci C, Oturak B, Şentürk FS, Yılmaz T, Gökçe A, Çifçi JB, Aksoy CN. Screen-related Behavioral patterns and toilet postponement are associated with lower urinary tract symptoms: a cross-sectional survey study. J Urol Surg. 2026;13(3):234-240

Introduction

The widespread use of smartphones, tablets, computers, and other digital devices has substantially transformed daily life over the last decade. Screen-based activities have become an integral part of work, education, entertainment, and social interaction, resulting in prolonged sedentary behavior and extended periods of uninterrupted screen exposure. Recent evidence suggests that excessive screen time is associated with various adverse health outcomes, including obesity, musculoskeletal disorders, sleep disturbances, and mental health problems (1-3).

Healthy bladder function depends on regular voiding habits and timely responses to bladder filling sensations. However, individuals engaged in prolonged periods of work, studying, gaming, or social media use may intentionally delay voiding despite urinary urgency. This behavior, commonly referred to as delayed voiding or toilet postponement, has emerged as a potentially modifiable risk factor for lower urinary tract dysfunction (4-6).

Previous studies have demonstrated significant associations between maladaptive toileting behaviors and lower urinary tract symptoms (LUTS), including urinary frequency, urgency, urinary incontinence, and voiding dysfunction (5,7,8). In addition, healthy bladder initiatives have emphasized the importance of appropriate toileting practices to prevent bladder disorders (9).

Despite growing evidence linking excessive screen exposure to adverse health outcomes, and maladaptive toileting behaviors to LUTS, the potential interplay between screen use, toilet-postponement behavior, and LUTS remains largely unexplored. Given the rapid expansion of screen-based lifestyles worldwide, clarifying this relationship may have important implications for bladder health and preventive behavioral interventions. We hypothesized that prolonged screen use and screen-related behavioral patterns are associated with increased toilet postponement and a higher burden of LUTS. Therefore, this study aimed to investigate the relationship between screen-use habits, toilet-postponement behavior, and LUTS in a campus-based, cross-sectional survey conducted at a university.

Materials and Methods

Study Design and Participants

This university campus-based cross-sectional questionnaire survey was conducted between May 1 and May 30, 2026. The study was conducted as part of a social responsibility project organized by university students. Participants were recruited through face-to-face interviews conducted on Zonguldak Bülent Ecevit University campus. Although the majority of participants were university students, members of the general community present on campus during the study period were also invited to participate.

Individuals aged 18 years or older who voluntarily agreed to complete the questionnaire were eligible for inclusion. Participants younger than 18 years of age and those with incomplete questionnaire data were excluded. All responses were collected anonymously, and no personally identifiable information was recorded.

Survey Instrument and Score Definitions

The questionnaire consisted of five sections. The first section collected demographic data, including age, sex, marital status, parental status, occupation, height, weight, daily screen exposure duration, and primary purpose of screen use.

Screen-related behavior was assessed using five Likert-type items evaluating loss of time awareness during screen use, postponement of toileting due to screen use, difficulty reducing screen use, forgetting to drink water during screen use, and family warnings about screen duration. Each item was scored from 1 to 5, with higher scores indicating greater screen-related behavioral involvement. A digital behavior score (DBS) was calculated by summing these five items, resulting in a total score range of 5-25. The DBS is a study-specific composite score developed for this study and has not undergone formal external validation.

Toilet postponement behavior was assessed using two Likert-type items that evaluated intentional delay of voiding and prolonged urine holding. Each item was scored from 1 to 5. The toilet postponement score (TPS) was calculated as the sum of these two items, resulting in a total score range of 2-10, with higher scores indicating greater toilet-postponement behavior. The TPS was also a study-specific composite score and has not undergone formal external validation.

LUTS were assessed using symptom items adapted from the International Consultation on Incontinence Questionnaire female LUTS (ICIQ-FLUTS) and ICIQ male LUTS (ICIQ-MLUTS) questionnaires (10,11). LUTS domain scores were generated to enable analysis across the entire study population. The LUTS storage score was calculated using five items assessing daytime urinary frequency, nocturia, urgency, urgency urinary incontinence, and bladder pain. The LUTS voiding score was calculated using six items assessing hesitancy, straining, intermittency, weak urinary stream, incomplete bladder emptying, and post-micturition dribbling. The LUTS total score was calculated as the sum of the storage score, the voiding score, and four items assessing overall urinary incontinence, stress urinary incontinence, unexplained leakage, and nocturnal enuresis.

Sex-specific ICIQ-FLUTS and ICIQ-MLUTS scores were calculated for female and male participants and used for subgroup analyses.

Outcome Measures

The primary outcome was the association between screen-related behavior and total LUTS burden. Secondary outcomes included associations between screen-related behavior and toilet postponement behavior; between toilet postponement behavior and LUTS domain scores; and between screen exposure duration and LUTS severity. The primary analyses were performed using harmonized LUTS scores to allow combined evaluation of both sexes, whereas sex-specific ICIQ-FLUTS and ICIQ-MLUTS scores were analyzed as secondary outcomes.

Ethical Considerations

The study protocol was approved by the Zonguldak Bülent Ecevit University Non-Interventional Research Ethics Committee (approval number: 2026/06, date: 01.04.2026). All participants provided informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and informed consent was obtained from all participants.

Statistical Analysis

Statistical analyses were performed using Jamovi software version 2.3.28 (Jamovi Project, Sydney, Australia). Continuous variables were expressed as mean ± standard deviation or median and interquartile range, depending on data distribution. Categorical variables were presented as frequencies and percentages. The normality of continuous variables was assessed using visual methods and the Shapiro-Wilk test.

Comparisons between groups were performed using the independent samples t-test or Mann-Whitney U test for two-group comparisons and one-way analysis of variance or Kruskal-Wallis test for comparisons among more than two groups, as appropriate. Categorical variables were compared using the chi-square test. Internal consistency was evaluated using Cronbach's alpha (α). Correlations between DBS, TPS, LUTS total score, LUTS storage score, and LUTS voiding score were evaluated using Spearman's rank correlation.

Multivariable linear regression analysis was performed to identify independent predictors of the LUTS total score. Clinically relevant variables, including age, sex, body mass index, daily screen exposure duration, daily fluid intake, tea/coffee consumption category, DBS, and TPS, were considered for inclusion in the model. A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 478 participants were included in the final analysis. The mean age of the study population was 26.05±11.7 years, and 297 participants (62.1%) were female. Most participants reported daily screen exposure exceeding 4 hours (62.1%). Baseline demographic and clinical characteristics are summarized in Table 1.

The mean DBS was 12.64±4.14, while the mean TPS was 4.62±2.39. The mean LUTS storage score, LUTS voiding score, and LUTS total score were 3.36±2.73, 3.35±3.62, and 7.74±7.44, respectively. Internal consistency analysis demonstrated acceptable reliability for DBS (Cronbach's α=0.716) and good reliability for TPS (Cronbach's α=0.846). The LUTS Total Score demonstrated excellent internal consistency (Cronbach's α=0.881) (Table 2).

Table 1. Baseline characteristics of the study population (n=478)

Variable	Value
Age, years	26.05±11.71
BMI, kg/m²	24.04±3.99
Underweight	28 (5.9%)
Normal weight	268 (56.1%)
Overweight	148 (31.0%)
Obese	34 (7.1%)
Gender	
Female	297 (62.1%)
Male	181 (37.9%)
Marital status	
Single	389 (81.4%)
Married	77 (16.1%)
Divorced/widowed	12 (2.5%)
Daily screen time	
<1 hour	5 (1.0%)
1-2 hours	40 (8.4%)
2-4 hours	136 (28.5%)
>4 hours	297 (62.1%)
Most commonly used screen content	
Game	54 (11.3%)
Social media	20 (4.2%)
Work/education	30 (6.3%)
TV series/movie	314 (65.7%)
Other	60 (12.6%)
Daily fluid intake	
<1 L	76 (15.9%)
1-2 L	225 (47.1%)
2-2.5 L	110 (23.0%)
>2.5 L	67 (14.0%)
Tea/coffee consumption	
1 cup/day	135 (28.2%)
2 cups/day	131 (27.4%)
3 cups/day	100 (20.9%)
≥4 cups/day	112 (23.4%)

Data are presented as mean ± standard deviation or n (%)
BMI: Body mass index, TV: Television, L: Liter

Table 2. Distribution and internal consistency of the study scores				
Score	**Possible range**	**Mean ± SD**	**Median (IQR)**	**Cronbach's α**
DBS	5-25	12.64±4.14	12 (10-15)	0.716
TPS	2-10	4.62±2.39	4 (2-6)	0.846
LUTS storage score	0-20	3.36±2.73	3 (2-4.75)	0.666
LUTS voiding Score	0-24	3.35±3.62	2 (1-5)	0.792
LUTS total score	0-60	7.74±7.44	6 (3-10)	0.881
DBS: Digital behavior score, TPS: Toilet postponement score, IQR Interquartile range, SD: Standard deviation, LUTS: Lower urinary tract symptoms				

When participants were stratified according to daily screen exposure duration, significant differences were observed in DBS, TPS, and LUTS voiding scores. Participants with screen exposure exceeding 4 hours per day demonstrated higher DBS and TPS values compared with those reporting shorter screen exposure (p<0.001 and p=0.002). Similarly, LUTS Voiding Scores increased significantly with longer screen exposure duration (p=0.009). In contrast, no significant differences were observed in LUTS storage scores or LUTS total scores among screen-time groups (Table 3).

Correlation analysis demonstrated a moderate positive association between DBS and TPS (rho=0.445, p<0.001). Higher DBS values were also associated with higher LUTS total scores (rho=0.268, p<0.001), LUTS storage scores (rho=0.140, p=0.002), and LUTS voiding scores (rho=0.308, p<0.001). TPS was positively correlated with LUTS total score (rho=0.344, p<0.001) (Table 4).

Multivariable linear regression analysis was performed to identify independent predictors of LUTS burden. After adjustment for age, sex, body mass index, daily screen time, daily fluid intake, and tea and coffee consumption, both DBS [β=0.439, 95% confidence interval (CI): 0.163-0.715, p=0.002] and TPS (β=0.656, 95% CI: 0.334-0.978, p<0.001) remained independently associated with higher LUTS total scores. In addition, higher tea/coffee consumption was independently associated with increased LUTS burden (β=1.125, 95% CI: 0.524-1.727, p<0.001). Daily screen exposure duration was not an independent predictor of LUTS severity after adjustment for behavioral factors (p=0.771) (Table 5). Sex-specific analyses using the validated ICIQ-FLUTS and ICIQ-MLUTS questionnaires, stratified by screen exposure duration, are summarized in Supplementary Tables 1 and 2; these subgroup analyses were broadly consistent with the primary analyses based on harmonized LUTS scores.

Discussion

In the present study, we investigated the relationship between screen use habits, toilet postponement behavior, and LUTS in a relatively young adult population. The principal findings were threefold. First, greater screen-related behavioral involvement was associated with increased LUTS burden. Second, toilet postponement behavior demonstrated a significant positive association with LUTS severity. Third, although prolonged daily screen exposure was associated with higher digital behavior and TPSs, screen duration itself was not an independent predictor of LUTS after adjustment for behavioral factors. These findings suggest that behavioral patterns accompanying screen use may be more relevant to urinary health than screen exposure duration alone.

Excessive screen use has become an important public health concern because of its associations with sedentary behavior, sleep disturbances, obesity, and adverse mental health outcomes (12,13). However, little is known regarding its potential relationship with lower urinary tract function. In our study, higher DBSs were associated with a greater LUTS burden, including storage and voiding symptoms. This finding suggests that the behavioral consequences of intensive screen engagement, rather than screen exposure itself, may be associated with urinary symptom burden. Notably, the items that comprise the DBS—loss of time awareness, difficulty reducing use, and family complaints about screen time—closely parallel the core

Table 3. Comparison of symptom scores according to daily screen exposure duration						
Daily screen time	**n**	**DBS**	**TPS**	**LUTS storage score**	**LUTS voiding score**	**LUTS total score**
<1 hour	5	7 (5-10)	2 (2-4)	5 (3-6)	3 (3-3)	9 (6-10)
1-2 hours	40	10 (8-13)	3 (2-4)	3 (2-4)	1 (0-4)	6 (3-9)
2-4 hours	136	11 (8-14)	4 (2-6)	3 (1-4)	2 (0-4)	5 (3-9)
>4 hours	297	14 (11-16)	4 (3-7)	3 (2-5)	3 (1-5)	6 (4-10)
p-value	–	<0.001	0.002	0.118	0.009	0.076
Data are presented as median (interquartile range). P-values were calculated using the Kruskal-Wallis test DBS: Digital behavior score, TPS: Toilet postponement score, LUTS: Lower urinary tract symptoms						

Table 4. Spearman correlation analysis between digital behavior, toilet postponement, and LUTS scores

Variable 1	Variable 2	Spearman's rho	p-value
DBS	TPS	0.445	<0.001
DBS	LUTS total score	0.268	<0.001
DBS	LUTS storage score	0.140	0.002
DBS	LUTS voiding score	0.308	<0.001
TPS	LUTS total score	0.344	<0.001

DBS: Digital behavior score, TPS: Toilet postponement score, LUTS: Lower urinary tract symptoms

Table 5. Multivariable linear regression analysis predicting LUTS total score

Predictor	β coefficient	95% CI	p-value
Age	0.026	-0.029 to 0.081	0.362
Male gender	-1.234	-2.656 to 0.187	0.089
BMI	0.134	-0.023 to 0.290	0.094
Daily screen time category	0.140	-0.804 to 1.083	0.771
Daily fluid intake category	0.524	-0.360 to 1.409	0.245
Tea/coffee consumption category	1.125	0.524 to 1.727	<0.001
DBS	0.439	0.163 to 0.715	0.002
TPS	0.656	0.334 to 0.978	<0.001

DBS: Digital behavior score, TPS: Toilet postponement score, LUTS: Lower urinary tract symptoms, CI: Confidence interval, BMI: Body mass index

dimensions of problematic smartphone use (PSU), a behavioral construct typically characterized by salience, loss of control, and negative life consequences (14). This conceptual overlap is further supported by evidence that PSU itself is associated with greater screen exposure, reduced physical activity, and adverse physical health outcomes such as fatigue and obesity, lending construct validity to a behavior-based score rather than relying on screen duration alone (15). Individuals who become highly immersed in screen-based activities may be prone to ignoring physiological signals, postponing basic bodily needs, and reporting unhealthy voiding habits. To our knowledge, this is among the first studies to demonstrate a significant relationship between screen-related behavioral patterns and LUTS.

A particularly important finding was the strong association between toilet postponement behavior and LUTS severity. This observation is consistent with previous studies demonstrating that maladaptive toileting behaviors are associated with urinary urgency, urinary incontinence, overactive bladder symptoms, and voiding dysfunction (4,7,8,16). Notably, this association is not confined to women or children; comparable patterns have been reported in mixed occupational settings where task demands enforce postponement irrespective of sex, such as among nurses, in whom delayed voiding was the most frequently reported unhealthy toileting behavior and was linked to a high prevalence of urge and stress incontinence (17). This parallel suggests that screen-driven postponement may represent a discretionary, non-occupational analogue of the same underlying behavioral mechanism. Healthy bladder function depends on regular voiding habits and timely responses to bladder filling sensations (6,7,9). Habitual postponement of micturition has been proposed to be associated with altered bladder sensation, increased bladder storage pressures, dysfunctional voiding patterns, and worsening urinary symptoms (4). Our findings further support the growing body of evidence suggesting that toilet postponement represents a potentially modifiable behavioral factor associated with LUTS.

Interestingly, daily screen exposure duration was not independently associated with LUTS severity after adjustment for digital behavior and TPSs. This finding may explain why studies evaluating screen time alone have often produced inconsistent health-related outcomes (1,2). The observed association between digital lifestyles and LUTS may therefore be better explained by accompanying behavioral patterns rather than exposure duration itself. Spending several hours in front of a screen may not be associated with greater symptom burden if healthy hydration and voiding behaviors are maintained. Conversely, individuals with maladaptive screen-related behaviors may experience greater urinary symptom burden regardless of total screen exposure time.

Another notable finding was an independent association between higher consumption of tea and coffee and greater LUTS burden. Caffeine has long been recognized as a potential contributor to urinary urgency, frequency, and overactive bladder symptoms via both diuretic and bladder-stimulatory effects (18,19). Our findings are consistent with previous reports and support current recommendations encouraging moderation of caffeine intake in individuals experiencing bothersome urinary symptoms.

The clinical implications of our findings deserve consideration. Modern lifestyles increasingly involve prolonged engagement with smartphones, computers, and other digital devices. Educational interventions targeting healthy voiding behaviors, adequate hydration, and awareness of toilet postponement may therefore represent simple and cost-effective approaches for addressing LUTS burden in young adults. Because toilet-postponement behavior appears modifiable, behavioral counseling may be particularly valuable for individuals reporting intensive screen-related activities (9,20).

Study Limitations

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes any conclusions regarding causality. Second, all information was self-reported

and may therefore be subject to recall bias. Third, the study population predominantly comprised young adults recruited from a university, which may limit generalizability to older populations. Fourth, the smallest screen-time category (<1 hour/day) included relatively few participants, and comparisons involving this subgroup should therefore be interpreted with caution. Fifth, although several questionnaire items were adapted from validated ICIQ instruments, the DBS and TPS were study-specific composite measures and have not undergone formal psychometric validation. Although both demonstrated acceptable internal consistency, further validation in independent populations is warranted.

Despite these limitations, this study provides novel evidence regarding the relationship among digital behavior, toilet postponement, and LUTS. To our knowledge, this is one of the first studies to investigate these factors simultaneously within a single analytical framework. Prospective studies are needed to clarify temporal relationships and determine whether behavioral interventions targeting screen-related habits are associated with changes in LUTS burden.

Conclusion

Screen-related behavioral patterns and toilet postponement behavior were independently associated with greater LUTS burden, whereas daily screen exposure duration alone was not associated. These findings suggest that behavioral adaptations accompanying digital lifestyles may be more closely related to urinary health than to screen time itself. Promoting healthy voiding habits and reducing toilet postponement may represent practical strategies for addressing LUTS among individuals with intensive screen use.

Ethics

Ethics Committee Approval: The study protocol was approved by the Zonguldak Bülent Ecevit University Non-Interventional Research Ethics Committee (approval number: 2026/06, date: 01.04.2026).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: E.D.D., Design: E.D.D., Data Collection or Processing: O.B.Ç., A.A., B.E., E.Ç., A.K., N.K., İ.C., C.D., B.O., F.S.Ş., T.Y., J.B.Ç., C.N.A., Analysis or Interpretation: E.D.D., Literature Search: E.D.D., O.B.Ç., A.A., B.E., E.Ç., A.K., N.K., İ.C., C.D., B.O., F.S.Ş., T.Y., J.B.Ç., C.N.A., Writing: E.D.D.

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

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

AI Disclosure Statement: The manuscript's language and structure were enhanced with support from artificial intelligence (ChatGPT 5.5, OpenAI). The authors have thoroughly checked and validated the content, taking full responsibility for ensuring the scientific accuracy and integrity of the final document.

Supplementary Tables Link: https://d2v96fxpocvxx.cloudfront.net/68ab204c-182b-49da-b227-bc7efe058632/content-images/0f470bf3-5d23-4864-ba12-42213176aa72.pdf

References

1. Devi KA, Singh SK. The hazards of excessive screen time: Impacts on physical health, mental health, and overall well-being. J Educ Health Promot. 2023;12:413. [Crossref]
2. Stiglic N, Viner RM. Effects of screentime on the health and well-being of children and adolescents: a systematic review of reviews. BMJ Open. 2019;9:e023191. [Crossref]
3. Haug E. Adolescents' screen-based media use and the relationship with moderate-to-vigorous physical activity, sports club participation and active commuting. Scand J Public Health. 2025;53(Suppl 1):42-51. [Crossref]
4. Wu C, Xue K, Palmer MH. Toileting behaviors related to urination in women: a scoping review. Int J Environ Res Public Health. 2019;16:4000. [Crossref]
5. Newman DK, Burgio KL, Cain C, Hebert-Beirne J, Low LK, Palmer MH, Smith AL, Rickey L, Rudser K, Gahagan S, Harlow BL, James AS, Lacoursiere DY, Hardacker CT, Wyman JF; Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium. Toileting behaviors and lower urinary tract symptoms: a cross-sectional study of diverse women in the United States. Int J Nurs Stud Adv. 2021;3:100052. [Crossref]
6. Kowalik CG, Daily A, Delpe S, Kaufman MR, Fowke J, Dmochowski RR, Reynolds WS. Toileting Behaviors of Women-What is Healthy? J Urol. 2019;201:129-134. [Crossref]
7. O'Connell KA, Nicholas TB, Palmer MH. Toileting behaviors, urinary cues, overactive bladder, and urinary incontinence in older women. Int Urogynecol J. 2023;34:707-716. [Crossref]
8. Perlow A, Joyce CJ, Bennis S, Mueller ER, Fitzgerald CM. Toileting behaviors and lower urinary tract symptoms among female physicians and medical students. Urogynecology (Phila). 2023;29:678-686. [Crossref]
9. Lukacz ES, Sampselle C, Gray M, Macdiarmid S, Rosenberg M, Ellsworth P, Palmer MH. A healthy bladder: a consensus statement. Int J Clin Pract. 2011;65:1026-1036. [Crossref]
10. Gungor Uğurlucan F, Yasa C, Yuksel Ozgor B, Ayvacikli G, Gunaydin C, Balci BK, Yalcin O. Validation of the Turkish version of the ICIQ-FLUTS, ICIQ-FLUTS long-form, ICIQ-LUTS quality-of-life, and ICIQ-FLUTS sexual functions. Neurourol Urodyn. 2020;39:962-968. [Crossref]
11. Mertoğlu O, Üçer O, Ceylan Y, Bozkurt O, Günlüsoy B, Albaz AC, Demir Ö; Aegean Study Group of Society of Urological Surgery. Reliability and validity of the Turkish language version of the International Consultation on Incontinence Questionnaire - male lower urinary tract symptoms. Int Neurourol J. 2016;20:159-163. [Crossref]

12. Twenge JM, Campbell WK. Associations between screen time and lower psychological well-being among children and adolescents: evidence from a population-based study. Prev Med Rep. 2018;12:271-283. [Crossref]

13. Teague S, Somoray K, Shatte A, Miller D, Moss K, Crawford A, Wildman H, Kayal D, Hutchinson D. Digital media use and child health and development: a systematic review and meta-analysis. JAMA Pediatr. 2026;180:510-517. [Crossref]

14. Park E, Noh JW. Towards a valid and reliable smartphone overdependence scale: factor analysis, and measurement invariance testing. Psychiatry Res. 2025;352:116663. [Crossref]

15. Yaakoubi M, Ghorbel A, Abdelkafi H, Masmoudi L, Gharbi A, Trabelsi O. Screen time, fatigue, obesity and physical inactivity: health correlates of problematic smartphone use in adolescents. Child Care Health Dev. 2026;52:e70237. [Crossref]

16. von Gontard A, Niemczyk J, Wagner C, Equit M. Voiding postponement in children-a systematic review. Eur Child Adolesc Psychiatry. 2016;25:809-820. [Crossref]

17. Allen E, Ackerson K. Stressors and bathroom behaviors associated with urinary incontinence in nurses working during the COVID-19 pandemic: a mixed-methods study. Nurs Manage. 2024;55:38-47. [Crossref]

18. Hashim H, Abrams P. How should patients with an overactive bladder manipulate their fluid intake? BJU Int. 2008;102:62-66. [Crossref]

19. Cameron AP, Chung DE, Dielubanza EJ, Enemchukwu E, Ginsberg DA, Helfand BT, Linder BJ, Reynolds WS, Rovner ES, Souter L, Suskind AM, Takacs E, Welk B, Smith AL. The AUA/SUFU guideline on the diagnosis and treatment of idiopathic overactive bladder. J Urol. 2024;212:11-20. [Crossref]

20. Doumouchtsis SK, de Tayrac R, Lee J, Daly O, Melendez-Munoz J, Lindo FM, Cross A, White A, Cichowski S, Falconi G, Haylen B. An International Continence Society (ICS)/ International Urogynecological Association (IUGA) joint report on the terminology for the assessment and management of obstetric pelvic floor disorders. Int Urogynecol J. 2023;34:1-42. Erratum in: Int Urogynecol J. 2023;34:1137. [Crossref]

ORIGINAL RESEARCH
Pediatric Urology

Doi: 10.4274/jus.galenos.2026.2026-6-12
J Urol Surg 2026;13(3):241-248

Lower Urinary Tract Symptoms in Adolescents with Allergic Rhinitis: The Role of Disease Duration and Severity

Figen Çelebi Çelik[1], Anıl Eker[2]

[1]University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Department of Pediatrics, Division of Allergy and Immunology, İzmir, Türkiye
[2]University of Health Sciences Türkiye, İzmir City Hospital, Department of Urology, İzmir, Türkiye

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

Previous studies have reported associations between allergic diseases and pediatric lower urinary tract symptoms, mainly by assessing allergic disease as present or absent. This study finds that among adolescents with allergic rhinitis, urinary symptom burden is more closely associated with the duration and severity of allergic disease.

Abstract

Objective: Allergic respiratory diseases may be associated with lower urinary tract symptoms (LUTS), but whether the allergic disease burden is related to the severity of urinary symptoms remains unclear. This study aimed to evaluate LUTS in adolescents with allergic rhinitis (AR) and to test the hypothesis that allergic disease burden is associated with higher Dysfunctional Voiding and Incontinence Symptom Score (DVISS).

Materials and Methods: This single-center, cross-sectional observational study included children aged 12-18 years with physician-diagnosed AR. AR severity was categorized as mild or moderate-to-severe according to the Allergic Rhinitis and its Impact on Asthma classification. Disease duration, visual analogue scale score, medication score, laboratory markers of atopy, aeroallergen sensitization profile, and DVISS were recorded. Group comparisons, Spearman correlation analysis, and multivariable linear regression analysis were performed.

Results: Of the 111 adolescents, 55 had AR alone and 56 had AR with asthma. The total DVISS score did not differ significantly between the groups. Total DVISS score was weakly positively correlated with disease duration, disease severity, and visual analogue scale score. In multivariable analysis, longer disease duration and greater disease severity were weak-to-modest factors associated with higher DVISS scores after adjustment for age, sex, and medication score; however, the explanatory power of the model was limited. Storage symptoms, particularly daytime urinary frequency, nocturia, and urgency, showed more consistent associations with allergic disease burden than voiding symptoms.

Conclusion: In adolescents with AR, longer disease duration and greater disease severity were weak-to-modest factors associated with a higher burden of LUTS. These findings support considering LUTS in adolescents with chronic or severe allergic respiratory disease; however, further prospective studies are required before routine clinical recommendations can be made.

Keywords: Allergic rhinitis, asthma, adolescent, lower urinary tract symptoms, dysfunctional voiding

Introduction

Allergic rhinitis (AR) and asthma are among the most common chronic inflammatory diseases in childhood and adolescence, affecting quality of life, school performance, and healthcare utilization worldwide (1). These conditions frequently coexist as manifestations of a unified airway disease and share common immunological mechanisms characterized by type 2 inflammation, eosinophilic infiltration, mast cell activation, and increased production of inflammatory mediators. Owing to

Correspondence: Figen Çelebi Çelik MD, University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Department of Pediatrics, Division of Allergy and Immunology, İzmir, Türkiye
E-mail: figencelebicelik@gmail.com **ORCID-ID:** orcid.org/0000-0002-1100-4117
Received: 30.06.2026 **Accepted:** 21.07.2026 **Publication Date:** 01.09.2026

Cite this article as: Çelebi Çelik F, Eker A. Lower urinary tract symptoms in adolescents with allergic rhinitis: the role of disease duration and severity. J Urol Surg. 2026;13(3):241-248

their chronic nature, both diseases may exert systemic effects extending beyond the respiratory tract (2,3).

Accumulating evidence suggests that allergic diseases may be associated with lower urinary tract function and urinary symptom burden in children (4,5). Experimental and clinical studies have demonstrated that mast cell activation, eosinophilic inflammation, neuroimmune interactions, and increased sensory nerve excitability may contribute to bladder hypersensitivity and lower urinary tract symptoms (LUTS) (6,7). These mechanisms have been proposed to explain storage symptoms such as increased daytime urinary frequency, urgency, nocturia, and urinary incontinence in selected pediatric populations. However, the underlying mechanisms remain incompletely understood, and the available evidence is limited.

Previous studies investigating the relationship between allergic diseases and pediatric LUTS have primarily focused on the presence of allergic conditions (8,9). In contrast, little attention has been paid to whether the clinical burden of allergic disease—including disease duration, symptom severity, treatment intensity, and laboratory markers of atopy—is associated with urinary symptom severity. Furthermore, comparative data between children with AR alone and those with concomitant asthma remain scarce.

The present study aimed to evaluate LUTS in adolescents with AR, with or without concomitant asthma, using the Dysfunctional Voiding and Incontinence Symptom Score (DVISS). In addition to comparing urinary symptoms between disease phenotypes, we investigated the relationships between urinary symptom severity and clinical characteristics of allergic disease, including disease duration, disease severity, visual analogue scale (VAS) score, medication score, laboratory parameters, and aeroallergen sensitization profile. We hypothesized that the clinical burden of allergic respiratory disease, rather than disease phenotype alone, would be associated with higher urinary symptom burden within this allergic population.

Materials and Methods

This study was reported in accordance with the STROBE guidelines for cross-sectional studies.

Study Design and Participants

This single-center, cross-sectional, observational study was conducted at the Pediatric Allergy and Immunology outpatient clinic of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital.The study included adolescents aged 12-18 years with a diagnosis of AR, with or without concomitant asthma.

Patients were eligible if they had a physician-confirmed diagnosis of AR, with or without concomitant asthma, had attended a routine outpatient visit, and had complete clinical and questionnaire data available for analysis. Patients with known neurological disease, neurogenic bladder, structural urinary tract abnormalities, active urinary tract infection, previous urological surgery, chronic kidney disease, use of medications that could directly affect voiding function, or incomplete questionnaire data were excluded. After applying the inclusion and exclusion criteria, 111 adolescents (aged 12-18 years) with allergic respiratory disease were included in the final analysis. All included patients had complete clinical, laboratory, and questionnaire data; therefore, no patient was excluded because of missing data.

A sample size calculation was performed based on the primary hypothesis that allergic disease burden would be associated with the total DVISS/*İşeme Bozuklukları Semptom Skoru* (İBSS) score. Because no directly comparable previous study was available, a weak-to-moderate expected correlation coefficient of 0.30 was considered clinically relevant. Using a two-tailed correlation model with an alpha error probability of 0.05 and 80% power, the minimum required sample size was calculated to be 84 participants. Therefore, the final sample size of 111 adolescents was considered sufficient for the primary correlation analysis.

The study protocol was approved by the University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Disease and Surgery Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: GOA-386, date: 04.06.2026). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants, and assent was obtained from adolescents when appropriate.

All data were collected using a standardized case report form. The recorded variables included demographic characteristics, type of allergic respiratory disease, disease duration, clinical severity, medication use, asthma treatment status, VAS score, laboratory parameters, aeroallergen sensitization profile, and LUTS scores.

Assessment of Allergic Respiratory Diseases

AR was diagnosed by a pediatric allergist based on compatible nasal symptoms, including rhinorrhea, nasal obstruction, sneezing, and/or nasal itching, together with clinical evaluation and evidence of allergic sensitization when available, in accordance with the Allergic Rhinitis and its Impact on Asthma (ARIA) approach (10). AR severity was classified as mild or moderate-to-severe according to the ARIA classification, based on symptom burden and its impact on daily activities, sleep, school performance, and quality of life. Disease duration was recorded separately as the number of years since diagnosis and

did not represent the ARIA intermittent/persistent classification. Patients were classified as having AR alone or as having AR with concomitant asthma.

Asthma was diagnosed according to current Global Initiative for Asthma (GINA)-based clinical principles, using recurrent respiratory symptoms, physician assessment, treatment history, and objective lung function findings when available (11). Current asthma treatment was recorded as a binary variable. Disease duration was recorded in years.

Medication Score

Medication use was evaluated using a modified, study-defined medication score (MS), structured on the medication-use component of the Combined Symptom and Medication Score framework proposed by the European Academy of Allergy and Clinical Immunology (EAACI) (12). The MS was scored from 0 to 3 according to the highest medication category recorded for each patient: 0, no medication; 1, oral and/or topical non-sedating H1-antihistamines; 2, intranasal corticosteroids with or without H1-antihistamines; and 3, leukotriene receptor antagonist therapy, specifically montelukast, with or without other medications. Since none of the patients in this cohort received oral corticosteroids during the study period, montelukast use was categorized as the highest medication step in this study-defined scoring approach. Scores were not cumulative; when more than one medication category was used, only the highest applicable score was recorded.

VAS Assessment

The severity of allergic respiratory symptoms was assessed using a 10 cm VAS, a simple quantitative tool commonly used to evaluate AR symptom burden (13). Patients were asked to rate their overall allergic respiratory symptom severity from 0, indicating no symptoms, to 10, indicating the most severe symptoms imaginable. Higher VAS scores reflected greater perceived symptom burden.

Assessment of LUTS

LUTS were evaluated using the DVISS, recorded in Turkish as the "İBSS" (14). The questionnaire assessed urinary frequency, nocturia/enuresis, urgency, urinary incontinence, intermittent voiding, straining or hesitancy during voiding, post-void symptoms, holding maneuvers, constipation, and quality of life. Item scores were summed to obtain the total DVISS score, with higher scores indicating more severe voiding symptoms (15,16). In addition to the total score, individual symptom components were recorded separately for analysis.

Laboratory Parameters and Allergic Sensitization

Routine laboratory values obtained during clinical follow-up were extracted from patient records. These included eosinophil percentage, absolute eosinophil count, total serum immunoglobulin E (IgE) level, neutrophil count, lymphocyte count, and platelet count.

Aeroallergen sensitization was evaluated using available skin-prick test results and/or serum-specific IgE results obtained during routine allergy assessment. Sensitization to house dust mite, grass pollen, olive pollen, animal dander, and mold allergens was recorded. Skin prick test results were interpreted according to standard procedures, and sensitization was considered present when a clinically relevant positive response was documented (17). Aeroallergen sensitization was further categorized according to allergen source. Sensitization to house dust mite, animal dander, and mold allergens was classified as indoor allergen sensitization, whereas sensitization to grass pollen and olive pollen was classified as outdoor allergen sensitization. Patients sensitized to both indoor and outdoor allergens were considered to have mixed sensitization. This classification was used for exploratory comparisons of LUTS scores according to aeroallergen sensitization profile.

Statistical Analysis

Statistical analyses were performed using appropriate statistical software. Continuous variables were assessed for normality by visual inspection and by statistical normality tests. Normally distributed variables were presented as mean ± standard deviation, whereas non-normally distributed variables were presented as median and interquartile range or minimum-maximum values, as appropriate. Categorical variables were summarized as numbers and percentages.

Comparisons between groups, such as AR alone versus AR with asthma, were performed using the Mann-Whitney U test for continuous variables according to the distribution of the data. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Correlations among clinical scores, laboratory parameters, disease duration, and medication, VAS, and DVISS scores were evaluated using Spearman correlation analysis. Confidence intervals (CIs) for Spearman correlation coefficients were calculated using Fisher's z transformation. Multivariable regression analysis, adjusted for potential confounders such as age and sex, was planned to identify independent factors associated with LUTS severity. A p-value <0.05 was considered statistically significant.

Results

A total of 111 adolescents with allergic respiratory disease were included in the study. Of these, 55 (49.5%) had AR alone and 56 (50.5%) had concomitant AR and asthma. The mean age of the study population was 14.93±2.05 years, and 78 participants (70.3%) were male.

Table 1. Comparison of demographic, allergic disease-related, and lower urinary tract symptom characteristics between the groups					
		AR	AR + asthma	p-value	Effect sizes
Age, years, median (IQR)		16 (14-17)	14 (13-16.75)	0.006$^{\Sigma}$	r=0.26
Sex	Boy	33 (60%)	45 (80.4%)	0.019$^{\alpha}$	V=0.22
	Girl	22 (40%)	11 (19.6%)		
Disease duration, years, median (IQR)		3 (2-5)	7 (2.25-9)	<0.001$^{\Sigma}$	r=0.35
Disease severity	Mild	18 (32.7%)	18 (32.1%)	0.948$^{\alpha}$	
	Moderate-to-severe	37 (67.3%)	38 (67.9%)		
Medication score	0	4	4	0.505$^{\beta}$	
	1	9	8		
	2	23	17		
	3	19	27		
VAS score, median (IQR)		5 (4-6)	5 (3.25-6)	0.872$^{\Sigma}$	
Daytime urinary frequency, median (IQR)		5 (4-7)	5 (4-8)	0.266$^{\Sigma}$	
Nocturia	Absent	42 (76.4%)	46 (82.1%)	0.453$^{\alpha}$	
	Present	13 (23.6%)	10 (17.9%)		
Urgency	Absent	42 (76.4%)	43 (76.8%)	0.958$^{\alpha}$	
	Present	13 (23.6%)	13 (23.2%)		
Urinary incontinence	Absent	54 (98.2%)	50 (89.3%)	0.113$^{\beta}$	
	Present	1 (1.8%)	6 (10.7%)		
Interrupted urinary stream	Absent	50 (90.9%)	51 (91.1%)	0.976$^{\beta}$	
	Present	5 (9.1%)	5 (8.9%)		
Hesitancy/straining	Absent	52 (94.5%)	54 (96.4%)	0.679$^{\beta}$	
	Present	3 (5.5%)	2 (3.6%)		
Sensation of incomplete bladder emptying	Absent	46 (83.6%)	42 (75%)	0.262$^{\alpha}$	
	Present	9 (16.4%)	14 (25%)		
Constipation	Absent	49 (89.1%)	51 (91.1%)	0.727$^{\alpha}$	
	Present	6 (10.9%)	5 (8.9%)		
Total DVISS/IBSS score, median (IQR)		0 (0-2)	1 (0-2)	0.346$^{\Sigma}$	
DVISS/IBSS QoL item	No effect	48 (87.3%)	47 (83.9%)	0.606$^{\beta}$	
	Mild effect	6 (10.9%)	6 (10.7%)		
	Moderate effect	1 (1.8%)	3 (5.4%)		
	Severe effect	0 (0%)	0 (0%)		

Effect sizes were reported as r for Mann-Whitney U tests and Cramér's V (V) for categorical comparisons
AR: Allergic rhinitis, DVISS: Dysfunctional Voiding and Incontinence Symptom Score, İBSS: *İşeme Bozuklukları Semptom Skoru*, VAS: Visual analogue scale, IQR: Interquartile range, $^{\Sigma}$: Mann-Whitney U test, $^{\alpha}$: Chi-square test, $^{\beta}$: Fisher's exact test

The comparison of demographic characteristics, clinical features, and LUTS between the study groups is presented in Table 1. Patients with concomitant asthma were significantly younger than those with AR alone (p=0.006), and a significantly higher proportion of males was observed in the AR plus asthma group (p=0.019). Disease duration was also significantly longer in patients with concomitant asthma (p<0.001). However, disease severity, medication score, and VAS score were comparable between the groups (p>0.05).

No significant differences were observed between the AR and AR plus asthma groups regarding daytime urinary frequency, nocturia, urgency, urinary incontinence, interrupted urinary stream, hesitancy, sensation of incomplete bladder emptying, total DVISS score, or quality-of-life item (p>0.05). Likewise, separate analyses of each DVISS item demonstrated no statistically significant differences between the two groups. Urinary incontinence was numerically more frequent in the AR plus asthma group than in the AR group; however, this difference did not reach statistical significance. Given the small number of incontinence events, this comparison should be interpreted cautiously.

Correlation analysis demonstrated statistically significant positive correlations between total DVISS score and disease severity (ρ=0.229, 95% CI: 0.045-0.398, p=0.016), disease

duration (ρ=0.293, 95% CI: 0.113-0.455, p=0.002), and VAS score (ρ=0.247, 95% CI: 0.064-0.414, p=0.009). In contrast, medication score, eosinophil percentage, absolute eosinophil count, total serum IgE level, and aeroallergen sensitization profiles were not significantly correlated with total DVISS score (p>0.05).

Multivariable linear regression analysis identified disease duration (B=0.135, 95% CI: 0.010-0.259, β=0.196, p=0.034) and disease severity (B=1.012, 95% CI: 0.006-2.017, β=0.190, p=0.049) as weak-to-modest independent factors associated with higher DVISS scores after adjustment for age, sex, and MS. Age, sex, and MS were not independently associated with the DVISS score. Although VAS score was significantly correlated with total DVISS score, it was not included in the final multivariable model because it reflects subjective allergic symptom burden and is closely related to disease severity; including both variables in the same model could have increased collinearity and overfitting given the modest sample size. For transparency, constipation was reported as an individual DVISS component in Table 1. However, it was not included as an independent covariate in the multivariable regression model because it is already part of the total DVISS score; including it as a predictor of total DVISS would have resulted in circular adjustment. The overall regression model was statistically significant but explained a limited proportion of the variance in DVISS scores (R^2=0.135, adjusted R^2=0.094, p=0.009).

Using the previously suggested DVISS/IBSS threshold for clinically significant voiding dysfunction (≥9), only 3 patients (2.7%) exceeded this cut-off in the overall cohort. Clinically significant DVISS/IBSS scores were observed in 2 patients (3.6%) in the AR group and in 1 patient (1.8%) in the AR plus asthma group; there was no significant difference between groups (p=0.618).

Correlation analyses of individual LUTS are summarized in Table 2. Among storage symptoms, disease duration was positively correlated with daytime urinary frequency (ρ=0.245, 95% CI: 0.061-0.413, p=0.010) and nocturia (ρ=0.198, 95% CI: 0.012-0.371, p=0.037), whereas disease severity was positively correlated with urgency (ρ=0.247, 95% CI: 0.064-0.414, p=0.009), nocturia (ρ=0.212, 95% CI: 0.027-0.383, p=0.026), and daytime urinary frequency (ρ=0.186, 95% CI: 0.000-0.360, p=0.049). No significant correlations were identified between urinary incontinence and either disease duration or disease severity. Regarding voiding symptoms, disease duration showed a weak but statistically significant positive correlation with the sensation of incomplete bladder emptying (ρ=0.187, 95% CI: 0.001-0.361, p=0.049), whereas no significant correlations were observed with interrupted urinary stream or hesitancy. Disease severity was not significantly correlated with any voiding symptom, including interrupted urinary stream, hesitancy, or sensation of incomplete bladder emptying.

In the exploratory analysis, stratified by aeroallergen sensitization profile and performed without correction for multiple comparisons, children sensitized to outdoor allergens had higher total DVISS scores than those sensitized to indoor allergens (p=0.039). Among individual urinary symptoms, urgency was more frequent in the outdoor-sensitization group (p=0.031), whereas no significant differences were observed for the other storage or voiding symptoms. These exploratory findings should be interpreted cautiously.

Discussion

The present study investigated the relationship between allergic respiratory diseases and LUTS in adolescents with AR, with or without concomitant asthma. Although the coexistence of asthma did not result in significantly higher LUTS scores than those for AR alone, several clinically relevant findings emerged. First, disease duration, disease severity, and VAS score were positively correlated with overall symptom severity. Second, disease duration and disease severity remained independently associated with higher DVISS scores in multivariable analysis. Storage symptoms, particularly daytime urinary frequency, nocturia, and urgency, were more strongly associated with allergic disease burden than voiding symptoms. These findings

Table 2. Correlation between allergic disease characteristics and lower urinary tract symptoms

Symptom		Disease duration (ρ)	p-value	95% CI	Disease severity (ρ)	p-value	95% CI
Storage symptoms	Daytime urinary frequency	0.245	**0.010**	0.061-0.413	0.186	**0.049**	0.000-0.360
	Nocturia	0.198	**0.037**	0.012-0.371	0.212	**0.026**	0.027-0.383
	Urgency	0.134	0.161		0.247	**0.009**	0.064-0.414
	Urinary incontinence	0.091	0.345		0.101	0.294	
Voiding symptoms	Interrupted urinary stream	0.044	0.649		0.151	0.114	
	Hesitancy	0.077	0.420		0.058	0.548	
	Sensation of incomplete bladder emptying	0.187	**0.049**	0.001-0.361	0.117	0.222	

Bold values indicate statistically significant results (p<0.05)
ρ: Spearman's correlation coefficient, CI: Confidence interval

suggest that within an allergic adolescent population, the clinical burden of allergic respiratory disease may be more strongly associated with urinary symptom burden than with disease phenotype alone. Overall, DVISS scores were low in both groups, suggesting a possible floor effect. Consistent with this, only a very small proportion of patients exceeded the suggested threshold for clinically significant voiding dysfunction. In addition, the observed correlations were weak to modest, and the multivariable model explained only a limited proportion of the variance in urinary symptom burden. Therefore, disease duration and severity should be interpreted as two clinical factors associated with DVISS scores rather than as dominant determinants of LUTS.

Previous studies have consistently reported an association between allergic diseases and pediatric LUTS. Children with AR, asthma, eczema, and other atopic disorders have been shown to have a higher prevalence of overactive bladder, urinary urgency, and voiding dysfunction than healthy controls. However, most previous investigations primarily evaluated allergic diseases as dichotomous variables (present or absent), whereas relatively little attention has been given to the impact of disease burden on urinary symptoms (4,5,8,9,18). Importantly, the present study did not include a healthy, non-allergic control group, and therefore cannot determine whether adolescents with AR have a higher prevalence or greater severity of LUTS than non-allergic adolescents. Rather, our findings indicate that disease duration and clinical severity are more closely associated with LUTS than asthma itself. This observation suggests that chronic inflammatory activity and cumulative symptom burden may have greater clinical relevance than disease phenotype alone.

The mechanisms linking allergic respiratory diseases and LUTS are likely multifactorial. Experimental and clinical studies have demonstrated that mast cell activation, eosinophilic inflammation, and neuroimmune interactions contribute to bladder hypersensitivity through the release of inflammatory mediators, including histamine, leukotrienes, nerve growth factor, and various neuropeptides. These mediators increase the excitability of bladder afferent nerves and promote sensory dysfunction, potentially leading to urgency, increased daytime urinary frequency, and nocturia (4,7,19,20). The predominance of storage symptoms observed in our cohort is consistent with this proposed pathophysiological framework and may suggest a relationship between allergic disease burden and bladder sensory symptoms rather than voiding-phase dysfunction.

Laboratory markers of atopy, including peripheral eosinophil count, eosinophil percentage, and total serum IgE levels, were not significantly associated with urinary symptom burden. Although these biomarkers are commonly used to characterize type 2 inflammation and atopic status in allergic airway disease, their ability to reflect local inflammatory processes in non-respiratory target organs may be limited (21,22,23). These findings suggest that systemic biomarkers may not adequately reflect the local inflammatory and neuroimmune processes involved in bladder dysfunction. Instead, clinical indicators of disease activity, such as disease duration, symptom severity, and patient-reported symptom burden, may better represent the cumulative inflammatory exposure influencing lower urinary tract function.

In the exploratory aeroallergen analysis, outdoor allergen sensitization was associated with higher total DVISS scores and a higher frequency of urgency. This finding may be biologically plausible, as outdoor allergens, particularly pollen, can be associated with seasonal increases in allergic symptoms and systemic inflammatory burden, potentially amplifying bladder sensory symptoms. Supporting this hypothesis, previous data from patients with urologic chronic pelvic pain syndrome suggested that elevated pollen levels may be linked to symptom flares, especially among individuals with allergies, possibly through mast cell activation and histamine release (24). However, this evidence comes from adults with chronic pelvic pain and cannot be directly extrapolated to adolescents with AR. Moreover, because our aeroallergen analysis was exploratory, subgroup sizes were limited, and no correction for multiple comparisons was applied, the observed association between outdoor sensitization and urgency should be interpreted cautiously and considered hypothesis-generating, rather than confirmatory.

The present study has several strengths. To our knowledge, this is one of the few studies to evaluate the relationship between the clinical burden of allergic respiratory disease and LUTS using both symptom-based and multivariable analytical approaches. In addition to comparing AR alone to AR accompanied by asthma, we assessed disease duration, disease severity, VAS and MS, laboratory parameters, aeroallergen sensitization profiles, and individual LUTS components. This comprehensive evaluation allowed us to examine clinical factors associated with urinary symptom severity beyond the disease phenotype.

Study Limitations

Nevertheless, several limitations should be acknowledged. First, the cross-sectional design precludes any causal inference between allergic disease and LUTS. Second, this was a single-center study with a relatively modest sample size, which may limit the generalizability of the findings. Because all participants were recruited from a pediatric allergy and immunology outpatient clinic, selection bias is possible; this referral-based setting may have enriched the cohort with adolescents who had more symptomatic, persistent, or treatment-requiring allergic disease. Therefore, our findings may not be directly generalizable

to adolescents with milder AR in the general population. In addition, the lack of a non-allergic healthy control group prevented us from determining whether adolescents with AR have a higher prevalence or greater severity of LUTS than non-allergic adolescents.

Several methodological limitations should also be considered. The low median DVISS scores observed in both groups may indicate a floor effect, and the modest correlation coefficients and the limited explanatory power of the regression model should be considered when interpreting the clinical relevance of the findings. Correction for multiple comparisons was not applied; therefore, borderline statistically significant findings should be interpreted cautiously and considered exploratory. Although the DVISS is a validated pediatric instrument, its validation specifically for adolescents aged 12-18 years is limited. Objective functional assessments, such as uroflowmetry or urodynamic studies, were not performed; potential confounders, including body mass index, pubertal stage, detailed control status for asthma and AR, and fluid intake, were not available. The study-defined MS has not been externally validated. Finally, histopathological evaluation of bladder tissue was not available; therefore, potential local inflammatory changes, such as mast cell or eosinophilic infiltration, could not be assessed despite their proposed role in bladder hypersensitivity and LUTS-like presentations (4,23,25). Longitudinal studies are warranted to determine whether changes in allergic disease control over time are associated with changes in LUTS.

Conclusion

Among adolescents with allergic respiratory diseases, the coexistence of asthma was not associated with a greater burden of LUTS than AR alone. However, longer disease duration and greater disease severity were weak to modest factors associated with a higher urinary symptom burden, particularly storage symptoms, such as daytime urinary frequency, urgency, and nocturia. These findings suggest that the clinical burden of allergic respiratory disease, rather than disease phenotype alone, may be associated with greater LUTS burden. These findings support consideration of LUTS in adolescents with chronic or more severe allergic respiratory disease; however, further prospective studies are required before routine clinical recommendations can be made. Further prospective studies incorporating objective urological assessments and investigations of bladder inflammatory mechanisms are warranted to clarify the underlying pathophysiological pathways.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Disease and Surgery Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: GOA-386, date: 04.06.2026).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of all participants, and assent was obtained from adolescents when appropriate.

Footnotes

Authorship Contributions

Concept: F.Ç.Ç., Design: F.Ç.Ç., A.E., Data Collection or Processing: F.Ç.Ç., Analysis or Interpretation: A.E., Literature Search: F.Ç.Ç., A.E., Writing: F.Ç.Ç., AE.

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

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

References

1. Sureshkumar P, Mohandas S, M Rose B, Sreedevi A. Prevalence of asthma and allergic rhinitis and their association with chronotype among adolescents in Ernakulam district: a school-based cross-sectional study. Cureus. 2025;17:e89928. [Crossref]
2. Zhang X, Zhang Z, Peng Q, Huang X, Liu M, Bai D, Yang R, Zhang Y, Yang C. The immunogenetic landscape of allergic rhinitis: from cellular effectors to gene regulation and targeted therapies. Int J Biol Sci. 2026;22:1322-1345. [Crossref]
3. Cheng L, Sun L. The major role of type 2 inflammation in asthma: from the perspective of immunological mechanism. Biomed Res Int. 2026;2026:5663596. [Crossref]
4. Zheng Y, Yin L, Wang X, Zhao C, Du Y. Prevalence and allergy-related risk factors of overactive bladder in children in Northeast China. Front Public Health. 2024;12:1415833. [Crossref]
5. Yin L, Zhang Z, Zheng Y, Hou L, Zhao CG, Wang XL, Jiang KL, Du Y. Clinical correlation between overactive bladder and allergy in children. Front Pediatr. 2022;9:813161. [Crossref]
6. Grundy L, Caldwell A, Brierley SM. Mechanisms underlying overactive bladder and ınterstitial cystitis/painful bladder syndrome. Front Neurosci. 2018;12:931. [Crossref]
7. Akaihata H, Matsuoka K, Hata J, Harigane Y, Yaginuma K, Endo Y, Imai H, Matsuoka Y, Onagi A, Tanji R, Honda-Takinami R, Hoshi S, Koguchi T, Sato Y, Kataoka M, Uemura M, Igawa Y, Kojima Y. Involvement of mast-cell-tryptase- and protease-activated receptor 2-mediated signaling and urothelial barrier dysfunction with reduced uroplakin II expression in bladder hyperactivity ınduced by chronic bladder ıschemia in the rat. Int J Mol Sci. 2023;24:3982. [Crossref]
8. Zheng Y, Zhang Z, Hou L, Wang X, Jiang K, Zhang S, Du Y. Clinical observation of the correlation between overactive bladder and atopic constitution in children. Front Pediatr. 2021;9:646118. [Crossref]
9. Ozkaya E, Aydın SC, Yazıcı M, Dundaröz R. Enuresis Nocturna in children with asthma: prevalence and associated risk factors. Ital J Pediatr. 2016;42:59. [Crossref]
10. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, Brignardello-Petersen R, Canonica GW, Casale T, Chavannes NH, Correia de Sousa J, Cruz AA, Cuello-Garcia CA, Demoly P, Dykewicz M, Etxeandia-Ikobaltzeta I, Florez ID, Fokkens W, Fonseca J, Hellings PW, Klimek L,

Kowalski S, Kuna P, Laisaar KT, Larenas-Linnemann DE, Lødrup Carlsen KC, Manning PJ, Meltzer E, Mullol J, Muraro A, O'Hehir R, Ohta K, Panzner P, Papadopoulos N, Park HS, Passalacqua G, Pawankar R, Price D, Riva JJ, Roldán Y, Ryan D, Sadeghirad B, Samolinski B, Schmid-Grendelmeier P, Sheikh A, Togias A, Valero A, Valiulis A, Valovirta E, Ventresca M, Wallace D, Waserman S, Wickman M, Wiercioch W, Yepes-Nuñez JJ, Zhang L, Zhang Y, Zidarn M, Zuberbier T, Schünemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017;140:950-958. [Crossref]

11. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2025. Global Initiative for Asthma; 2025. [Crossref]
12. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, Durham SR, Jacobsen L, Malling HJ, Mösges R, Papadopoulos NG, Rak S, Rodriguez del Rio P, Valovirta E, Wahn U, Calderon MA; European Academy of Allergy and Clinical Immunology. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. 2014;69:854-867. [Crossref]
13. Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, Bousquet J. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy. 2007;62:367-372. [Crossref]
14. Akbal C, Genc Y, Burgu B, Ozden E, Tekgul S. Dysfunctional voiding and incontinence scoring system: quantitative evaluation of incontinence symptoms in pediatric population. J Urol. 2005;173:969-973. [Crossref]
15. Farhat W, Bägli DJ, Capolicchio G, O'Reilly S, Merguerian PA, Khoury A, McLorie GA. The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol. 2000;164:1011-1015. [Crossref]
16. Altan M, Çitamak B, Bozaci AC, Mammadov E, Doğan HS, Tekgül S. Is there any difference between questionnaires on pediatric lower urinary tract dysfunction? Urology. 2017;103:204-208. [Crossref]
17. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, Durham S, Fokkens W, Gjomarkaj M, Haahtela T, Bom AT, Wöhrl S, Maibach H, Lockey R. The skin prick test - European standards. Clin Transl Allergy. 2013;3:3. [Crossref]
18. Dahan P, de Bessa J Jr, de Oliveira DM, Gomes CC, Cardoso JC, Macedo IT, de Almeida Belo M, de Figueiredo AA, Netto JM. Association between asthma and primary nocturnal enuresis in children. J Urol. 2016;195:1221-1226. [Crossref]
19. Jones BM, Tykocki NR. New direct evidence that histamine augments bladder sensory outflow during filling is nothing to sneeze at. Am J Physiol Renal Physiol. 2020;318:F455-F456. [Crossref]
20. Kwon J, Kim DY, Cho KJ, Hashimoto M, Matsuoka K, Kamijo T, Wang Z, Karnup S, Robertson AM, Tyagi P, Yoshimura N. Pathophysiology of overactive bladder and pharmacologic treatments including β3-adrenoceptor agonists -basic research perspectives. Int Neurourol J. 2024;28(Suppl 1):12-33. [Crossref]
21. Guida G, Bagnasco D, Carriero V, Bertolini F, Ricciardolo FLM, Nicola S, Brussino L, Nappi E, Paoletti G, Canonica GW, Heffler E. Critical evaluation of asthma biomarkers in clinical practice. Front Med (Lausanne). 2022;9:969243. [Crossref]
22. Sánchez-García S, Habernau Mena A, Quirce S. Biomarkers in inflammometry pediatric asthma: utility in daily clinical practice. Eur Clin Respir J. 2017;4:1356160. [Crossref]
23. Hasan A, Abdel-Al I, Nafie K, Rashad MF, Abozied H, Elhussiny MEA, Rabie A, Rabaan AA, Abd Elnabi MK, Abdelwahed MS, Ahmed MA, Mohammed Y. Clinicopathological characteristics and outcomes of eosinophilic cystitis: a retrospective study. Ann Med Surg (Lond). 2021;68:102626. [Crossref]
24. Javed I, Yu T, Li J, Pakpahan R, Milbrandt M, Andriole GL, Lowder JL, Lai HH, Colditz GA, Sutcliffe S. Does pollen trigger urological chronic pelvic pain syndrome flares? A case-crossover analysis in the multidisciplinary approach to the study of chronic pelvic pain research network. J Urol. 2021;205:1133-1138. [Crossref]
25. Mosholt KS, Dahl C, Azawi NH. Eosinophilic cystitis: three cases, and a review over 10 years. BMJ Case Rep. 2014;2014:bcr2014205708. [Crossref]

VIDEO ARTICLE
Urooncology

Doi: 10.4274/jus.galenos.2025.2025-6-2
J Urol Surg 2026;13(3):249-251

Intraoperative Risks Associated with Non-absorbable Polymer Ligation Clips in Laparoscopic Radical Nephrectomy: A Case-based Video Report

Ekrem Başaran, Emre Ediz, Ali İbrahim İzula, Dursun Baba, Ahmet Yıldırım Balık, Arda Taşkın Taşkıran

Düzce University Faculty of Medicine, Department of Urology, Düzce, Türkiye

Abstract

Laparoscopic nephrectomy is a widely performed urologic surgical procedure in which non-absorbable polymer ligation (NPL) clips are frequently used for vascular control. We present a case involving a 64-year-old male scheduled for laparoscopic radical nephrectomy due to renal cell carcinoma, during which two Hem-o-lok clips applied to the renal artery unexpectedly reopened intraoperatively. Even when applied by experienced surgeons in accordance with standard protocols, the risk of malfunction remains and must be considered during laparoscopic renal surgery. NPL clips are frequently used to achieve secure vascular control. Although generally considered reliable, these clips may occasionally malfunction leading to potentially life-threatening complications.

Keywords: Laparoscopic nephrectomy, Hem-o-lok, polymer clip failure, renal hilum, intraoperative complication

Introduction

Laparoscopic techniques have become an integral part of modern urologic surgery. Procedures such as adrenalectomy, simple nephrectomy, radical nephrectomy, and nephroureterectomy exemplify minimally invasive approaches. The first laparoscopic nephrectomy, a milestone in renal surgery, was reported by Clayman et al. (1) in 1991.

Renal vascular dissection and ligation represent one of the most technically demanding and complication-prone stages of urologic procedures. Common methods for achieving secure hilar control laparoscopically include endovascular staplers, conventional titanium clips, and non-absorbable polymer ligation (NPL) clips (Hem-o-lok, Weck Closure Systems, Research Triangle Park, NC). Despite their widespread use and general reliability, all mechanical devices carry a risk of malfunction (2).

NPL clips are widely accepted for renal vascular control during laparoscopic nephrectomy. Numerous studies have demonstrated their clinical reliability and applicability, supporting their routine use in minimally invasive urologic procedures (3,4). However, technical failures have also been reported, occasionally necessitating conversion to open surgery. The U.S. Food and Drug Administration's (FDA) Manufacturer and User Facility Device Experience (MAUDE) database includes significant reports documenting such complications (5).

In this video case report, we present a rare but serious intraoperative complication in which NPL clips applied to the renal artery reopened (Video 1).

Case Presentation

A 64-year-old male patient with no comorbidities, regular medications, or prior surgical history presented with lower urinary tract symptoms. Contrast-enhanced computed tomography revealed a 61×58×72 mm right renal mass, which was diagnosed as renal cell carcinoma. Laparoscopic radical nephrectomy was planned.

Under general anesthesia, the patient was placed in a 45° lateral decubitus position. Pneumoperitoneum was established using a Veress needle. A 10 mm camera port and two additional trocars were then placed under direct vision in a triangular configuration.

Correspondence: Emre Ediz MD, Düzce University Faculty of Medicine, Department of Urology, Düzce, Türkiye
E-mail: dr.emreediz@gmail.com **ORCID-ID:** orcid.org/0000-0003-2532-6114
Received: 09.06.2025 **Accepted:** 17.10.2025 **Epub:** 19.06.2026 **Publication Date:** 01.09.2026

Cite this article as: Başaran E, Ediz E, İzula Aİ, Baba D, Balık AY, Taşkıran AT. Intraoperative risks associated with non-absorbable polymer ligation clips in laparoscopic radical nephrectomy: a case-based video report. J Urol Surg. 2026;13(3):249-251

Renal pedicle dissection identified two veins and one artery. Following our standard protocol, a total of three NPL clips were applied to the artery and proximal renal vein (two on the patient side and one on the specimen side).

During re-dissection of the previously clipped renal artery, the first applied clip was found to have reopened. The failed clip was removed, and a new one was applied. Subsequently, another clip was placed between the artery and kidney, but previously applied clip was also found to have reopened and was replaced. The NPL clips used in this case were supplied through the State Supply Office and were manufactured by a China-based local company.

Ultimately, the renal artery was secured with three clips (two on the patient side), while the renal vein was divided using three clips (two on the patient side). The kidney was retrieved using an endobag. Total operative time was 220 minutes, with an estimated blood loss of 150 mL.

Histopathological evaluation revealed type 2 papillary renal cell carcinoma, stage pT1b, with negative surgical margins.

Discussion

Despite the increasing adoption of laparoscopic nephrectomy, complication rates remain significantly high and associated with hilar control (6). There are three main alternative techniques for renal hilar control: endovascular staplers, titanium clips, and NPL clips (7). Each device carries risks of complications such as hemorrhage, transfusion, conversion to open surgery, and, albeit rarely, mortality.

Endovascular staplers, for example, demonstrated low malfunction rates (1-1.7%) in institutional studies such as that by Chan et al. (8). However, according to FDA MAUDE database reports, laparoscopic hemostatic devices account for 63% of failures. The most common issues are staple line malformation (47%) and device locking (29%). These malfunctions led to conversion to open surgery in 27-35% of patients, blood transfusion in 10-15%, and mortality in 1-4%. In addition, operator errors such as misfiring or firing over pre-existing clips were commonly reported (9).

Titanium clips account for 23-33% of hemostatic device failures. Frequent problems include jamming, or feeding difficulties (27%), and closure, shearing issues (26%). Dislodgement or slippage from the vessel was also reported in 6-14% of cases (7).

NPL clips account for 5-13% of hemostatic device failures in the FDA MAUDE database. The most frequently reported complication is clip dislodgement (44% postoperative, 25% intraoperative). Associated outcomes include reoperation (58%) and mortality (17%) (7,10). Furthermore, one study reported 12 cases of NPL clip malfunction during laparoscopic donor nephrectomy, two of which were fatal (10). Sun et al. (11) also described Hem-o-lok clip migration into the renal pelvis following laparoscopic partial nephrectomy, leading to stone formation and necessitating percutaneous nephrolithotomy. This highlights that each technique may present unique and unexpected complications, underscoring the need for vigilance on the part of surgeons.

Recent studies have provided additional insights into the safety of NPL clips. Ordon et al. (12) reported in a large-scale study that the use of three titanium clips on the renal artery and two polymer ligation clips on the renal vein during left laparoscopic donor nephrectomy was safe, with no major bleeding complications in 503 consecutive cases. More recently, Lachkar et al. (13) published a comprehensive systematic review addressing the "clip versus stapler" debate in laparoscopic live donor nephrectomy, providing updated evidence on their comparative safety profiles. In line with this, Fallatah et al. (14) compared donor nephrectomy performed with different approaches and concluded that Hem-o-lok clips remain a reliable method of vascular control across all techniques when appropriately applied.

In our institution, various brands of NPL clips and their compatible appliers—including Click'aV® (Grena®), Click'aV Plus® (Grena), Hem-o-lok® (Weck®, Teleflex®), Lookmed®, and multiple Chinese brands supplied through the state supply office—are routinely used in procedures such as radical prostatectomy, nephrectomy, and cystectomy. In the present case, 11 NPL clips were applied, with two intraoperative failures observed. Prompt recognition and appropriate intervention prevented adverse outcomes, though such failures could otherwise have been fatal.

As large-scale randomized controlled trials are lacking, the choice of hilar control method largely depends on the surgeon's preference and experience. Because all these devices have potential failure mechanisms, careful application by experienced surgeons and awareness of device-specific risks are essential to minimize complications.

Preventive strategies include using certified, high-quality clips and compatible appliers, confirming their functionality preoperatively, and avoiding uncertified or off-brand products. Additional technical precautions include applying multiple clips, leaving a 1-2 mm vascular cuff, preventing tissue entrapment in the locking mechanism, visually confirming full engagement, and selecting appropriately sized clips (10,15,16). Nevertheless, as demonstrated in this case, malfunctions can occur despite adherence to these precautions.

Conclusion

Although NPL clips are widely used and generally considered safe in laparoscopic surgery, meticulous surgical technique and intraoperative vigilance are essential. Even experienced surgeons must remain prepared for device malfunction and adopt preventive strategies to minimize the risk of severe complications.

Video 1. https://www.youtube.com/watch?v=rvbWLyYYOIA

Ethics

Informed Consent: Prior to submission, all relevant data were fully anonymized, and written informed consent for publication was obtained.

Footnotes

Authorship Contributions

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

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

Financial Disclosure: The authors declare that they received no financial support for this study.

References

1. Clayman RV, Kavoussi LR, Soper NJ, Dierks SM, Merety KS, Darcy MD, Long SR, Roemer FD, Pingleton ED, Thomson PG. Laparoscopic nephrectomy. N Engl J Med. 1991;324:1370-1371. [Crossref]
2. Deng DY, Meng MV, Nguyen HT, Bellman GC, Stoller ML. Laparoscopic linear cutting stapler failure. Urology. 2002;60:415-419; discussion 419-420. [Crossref]
3. Baumert H, Ballaro A, Arroyo C, Kaisary AV, Mulders PF, Knipscheer BC. The use of polymer (Hem-o-lok) clips for management of the renal hilum during laparoscopic nephrectomy. Eur Urol. 2006;49:816-819. [Crossref]
4. Kapoor R, Singh KJ, Suri A, Dubey D, Mandhani A, Srivastava A, Kumar A. Hem-o-lok clips for vascular control during laparoscopic ablative nephrectomy: a single-center experience. J Endourol. 2006;20:202-204. [Crossref]
5. Meng MV. Reported failures of the polymer self-locking (Hem-o-lok) clip: review of data from the food and drug administration. J Endourol. 2006;20:1054-1057. [Crossref]
6. Wille AH, Roigas J, Deger S, Tüllmann M, Türk I, Loening SA. Laparoscopic radical nephrectomy: techniques, results and oncological outcome in 125 consecutive cases. Eur Urol. 2004;45:483-488; discussion 488-489. [Crossref]
7. Hsi RS, Saint-Elie DT, Zimmerman GJ, Baldwin DD. Mechanisms of hemostatic failure during laparoscopic nephrectomy: review of food and drug administration database. Urology. 2007;70:888-892. [Crossref]
8. Chan D, Bishoff JT, Ratner L, Kavoussi LR, Jarrett TW. Endovascular gastrointestinal stapler device malfunction during laparoscopic nephrectomy: early recognition and management. J Urol. 2000;164:319-321. [Crossref]
9. Food and Drug Administration (FDA). Medical Device Reporting for Manufacturers; Guidance for Industry and Food and Drug Administration Staff [guidance document]. Rockville (MD): U.S. Food and Drug Administration; 2016 (original draft 2013). [Crossref]
10. Hsi RS, Ojogho ON, Baldwin DD. Analysis of techniques to secure the renal hilum during laparoscopic donor nephrectomy: review of the FDA database. Urology. 2009;74:142-147. [Crossref]
11. Sun J, Zhao LW, Wang XL, Huang JG, Fan Y. Migration of a Hem-o-Lok clip to the renal pelvis after laparoscopic partial nephrectomy: a case report. World J Clin Cases. 2022;10:3188-3193. [Crossref]
12. Ordon M, Sowerby RJ, Ghiculete D, Djuimo M, Kroczak T, Lee JY, Honey RJD, Pace KT. Clips can be safely used for vascular control of the renal vessels during laparoscopic donor nephrectomy. Urology. 2021;147:150-154. [Crossref]
13. Lachkar S, Boualaoui I, Ibrahimi A, El Sayegh H, Nouini Y. Clip or staple in laparoscopic live donor nephrectomy? A systematic literature review. Fr J Urol. 2024;34:102656. [Crossref]
14. Fallatah M, Aldughiman AW, Binjawhar AS, Melaibary BA, El-Tholoth HS, Al-Gadheeb AS, Alzahrani AY, Zahrani TM, Alakrash HS. Renal pedicle control in laparoscopic donor nephrectomy: evaluation of a single-center experience. Urol Ann. 2022;14:152-155. [Crossref]
15. Saki Z, Kallidonis P, Noureldin Y, Kotsiris D, Ntasiotis P, Adamou C, Vagionis A, Liatsikos E. Experimental studies of nonabsorbable polymeric surgical clips for use in urologic laparoscopy. J Endourol. 2019;33:730-735. [Crossref]
16. Grigore N, Pirvut V, Mihai I, Mitariu SIC, Sava M, Hasegan A. Polymer ligating clips in urologic laparoscopic surgery. Mater Plast. 2017;54:295-297. [Crossref]

CASE REPORT
Urooncology

Doi: 10.4274/jus.galenos.2025.2025-1-3
J Urol Surg 2026;13(3):252-254

Transvaginal Evisceration Six Months After Sex Sparing Robotic Cystectomy: A Case Report

Giorgio Cerrelli, Eleonora Rosato, Francesco Di Rocco, Enrico Finazzi Agrò, Simone Albisinni

Tor Vergata University of Rome, Department of Urology, Rome, Italy

Abstract

Transvaginal evisceration is a rare yet serious complication following pelvic surgery. This report presents the case of a 69-year-old woman with high-grade bladder carcinoma, unresponsive to Bacillus Calmette-Guérin, who underwent sex-sparing robotic-assisted radical cystectomy (RARC), with intracorporeal ileal conduit reconstruction. The procedure involved complete preservation of the vagina, uterus, fallopian tubes and ovaries. Seven months postoperatively, the patient presented with transvaginal evisceration of the omentum and bowel, requiring emergent surgical repair. To the best of our knowledge, this is the first report of such a rare late complication after sex-sparing RARC.

Keywords: General urology, reconstructive urology, urooncology

Introduction

Robotic-assisted radical cystectomy (RARC) is a preferred approach for high-grade, muscle-invasive, and Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder carcinoma, offering enhanced precision, reduced blood loss, and shorter recovery times compared to open techniques (1,2). However, RARC in female patients poses unique postoperative risks, notably pelvic floor complications. Sex sparing radical cystectomy in the female is expanding its indications, particularly in cases where the preservation of sexual and urinary function is prioritized without compromising oncological outcomes. Data indicate that organ- and nerve-sparing techniques contribute to improved quality of life outcomes by maintaining enhanced urinary continence rates, reducing the frequency of intermittent catheterization, and preserving sexual function postoperatively (3). Vaginal wall dehiscence is a rare and serious complication that significantly increases the risk of transvaginal evisceration, a critical complication characterized by herniation of intra-abdominal viscera through the vaginal canal (4,5). Postoperative vaginal dehiscence represents a significant surgical complication, as it results in a loss of anatomical integrity of the pelvic floor, exposing the patient to a markedly increased risk of delayed transvaginal evisceration.

We present the case of a 69-year-old woman with high-grade bladder cancer unresponsive to BCG who underwent sex-sparing RARC with intracorporeal ileal conduit urinary diversion. Six months after surgery, the patient developed vaginal wall dehiscence and subsequent transvaginal evisceration, necessitating emergency surgical repair. This case highlights the critical need for individualized intraoperative management and stringent postoperative surveillance to mitigate risks associated with delayed pelvic floor complications in similar patients.

Case Presentation

A 69-year-old female patient with high-grade non-muscle-invasive bladder carcinoma, unresponsive to BCG therapy, presented with recurrent high-grade bladder tumors. The patient underwent multiple transurethral resection of bladder tumors (TURBTs) in 2023 for persistent high-grade lesions. In December, cystoscopy revealed multifocal tumors at the bladder neck and trigone, with left ureteral involvement, and a final TURBT confirmed recurrent high-grade carcinoma. Further diagnostic workup included a contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis, which confirmed bladder wall thickening and suspicious lesions in the posterior bladder wall and trigone, suggestive of extensive disease.

Correspondence: Simone Albisinni Prof. MD, Tor Vergata University of Rome, Department of Urology, Rome, Italy
E-mail: simone.albisinni@ptvonline.it **ORCID-ID:** orcid.org/0000-0001-5529-3064
Received: 21.01.2025 **Accepted:** 27.05.2025 **Epub:** 10.06.2025 **Publication Date:** 01.09.2026

Cite this article as: Cerrelli G, Rosato E, Di Rocco F, Agrò EF, Albisinni S. Transvaginal evisceration six months after sex sparing robotic cystectomy: a case report. J Urol Surg. 2026;13(3):252-254

Given the failure of conservative approaches and the high risk of progression, a multidisciplinary team recommended proceeding with RARC.

Surgical Technique

Sex sparing RARC was performed in February 2024. As the patient was sexually active, a complete sex sparing approach with preservation of the ovaries, fallopian tubes, uterus, and anterior vaginal wall was performed. Following demoltion, an intracorporeal urinary diversion with an ileal conduit was performed, following extensive informed discussion with the patient in the preoperative setting, the procedure was uneventful with a console time of 200 min and total operative time of 250 min. Estimated blood loss was 100 mL, and no intraoperative complications were observed.

Postoperative Course and Follow-up

The patient's immediate postoperative course was marked by the displacement of one ureteral stent, with a consequent acute renal insufficiency and paralytic ileus. The complication responded to removal of the displaced stent and medical therapy (Clavien II). The patient was discharged in good health on 11th post-operative day. Final pathologic analysis revealed pT1N0 sec. The American Joint Committee on Cancer 8th edition. A follow-up CT scan showed no abnormalities at 3 months after surgery.

Although not having begun vaginal sexual activity, the patient was admitted to the ER seven months after surgery for vaginal discharge. Physical examination revealed complete evisceration of the omentum, confirmed by abdominal CT scan (Figure 1). Emergent surgical resection of the omentum, reduction of the evisceration, and transvaginal repair of the defect were performed. The vaginal defect was closed with a two-layer Vicryl 2/0 suture.

The patient recovered well and post-operative controls at 4 and 8 weeks confirmed adequate consolidation of the vaginal defect.

Discussion

The sex-sparing approach in RARC is designed to optimize oncologic control while preserving pelvic structures, which is particularly important in carefully selected patients with high-grade, BCG-unresponsive bladder cancer who have tumors confined to the bladder without involvement of the bladder neck or trigone. This approach is indicated for younger patients who are sexually active or have a strong preference for maintaining pelvic function. The main advantage of the sex-sparing RARC is the preservation of the anterior vaginal wall, uterus, ovaries, and neurovascular structures, which helps maintain both urinary continence and sexual function. Investigators have reported that this approach leads to high continence rates (over 90% for both daytime and nighttime) and allows a significant proportion of patients to remain sexually active at one year postoperatively (6,7).

Despite these benefits, the sex-sparing technique is not without its challenges. The preservation of pelvic organs can increase the risk of specific vaginal complications, including dehiscence and transvaginal evisceration, although the latter is rare. Vaginal dehiscence can compromise the structural integrity of the pelvic floor and, if left undetected or untreated, may lead to severe complications such as the evisceration of abdominal organs. This case is unique because the evisceration occurred seven months postoperatively, which is a delayed presentation compared to the typical early postoperative period (6,7). We are unable to identify a single factor that contributed to the evisceration presented by our patient. The minimal incision of

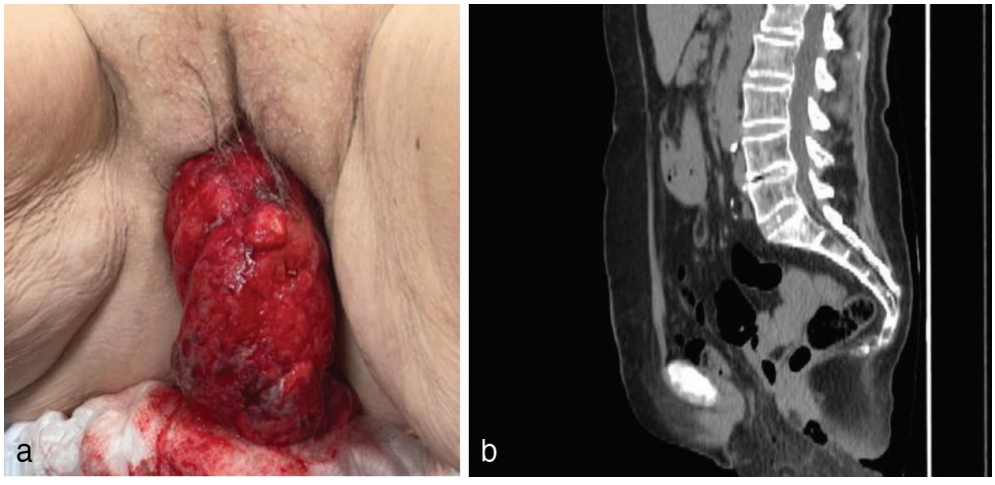


Figure 1. (a) Small bowel protrusion through the vagina on physical examination, **(b)** computed tomography image showing small bowel herniation through the vagina (sagittal slice)

the vagina, sutured perioperatively as seen in the Video 1, is unlikely to have caused a massive dehiscence after 7 months. Possibly, a reduction in blood flow to the vaginal wall may have contributed, although the tissues did not appear necrotic or ischemic during surgical repair. Our patient denied sexual trauma.

The rarity of this case highlights the importance of individualized surgical planning and vigilant long-term follow-up in patients undergoing sex-sparing RARC. While preserving pelvic structures can enhance postoperative quality of life, it is crucial to balance this with the risk of late-onset complications. This case suggests that transvaginal evisceration presents as a delayed complication, highlighting the need for continuous monitoring and timely surgical intervention when necessary to prevent life-threatening outcomes (5,6).

Conclusion

This case report demonstrates a rare late complication of sex-sparing RARC in the female. Although infrequent, this serious complication demands attention by the clinician and should be suspected in cases of vaginal discharge after RARC, even months after full surgical recovery. To the best of our knowledge, the present case is the first documented case of such a complication in sex-sparing RARC.

Video 1. https://www.youtube.com/watch?v=GUTqrrjg_f0

Ethics

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

Footnotes

Authorship Contributions

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

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

Financial Disclosure: The authors declare that they received no financial support for this study.

References

1. Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, Weizer AZ, Konety BR, Tollefson M, Krupski TL, Smith ND, Shabsigh A, Barocas DA, Quek ML, Dash A, Kibel AS, Shemanski L, Pruthi RS, Montgomery JS, Weight CJ, Sharp DS, Chang SS, Cookson MS, Gupta GN, Gorbonos A, Uchio EM, Skinner E, Venkatramani V, Soodana-Prakash N, Kendrick K, Smith JA Jr, Thompson IM. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet. 2018;391:2525-2536. [Crossref]
2. Hussein AA, Elsayed AS, Aldhaam NA, Jing Z, Osei J, Kaouk J, Redorta JP, Menon M, Peabody J, Dasgupta P, Khan MS, Mottrie A, Stöckle M, Hemal A, Richstone L, Hosseini A, Wiklund P, Schanne F, Kim E, Ho Rha K, Guru KA. Ten-year oncologic outcomes following robot-assisted radical cystectomy: results from the international robotic cystectomy consortium. J Urol. 2019;202:927-935. [Crossref]
3. Laukhtina E, von Deimling M, Pradere B, Yanagisawa T, Rajwa P, Kawada T, Quhal F, Pallauf M, Bianchi A, Majdoub M, Mostafaei H, Sari Motlagh R, Mori K, Enikeev D, Fisch M, Moschini M, D'Andrea D, Soria F, Albisinni S, Fajkovic H, Rink M, Teoh JY, Gontero P, Shariat SF; European Association of Urology-Young Academic Urologists (EAU-YAU): Urothelial Carcinoma Working Group. Urinary function in female patients after traditional, organ-sparing and nerve-sparing radical cystectomy for bladder cancer: a systematic review and pooled analysis. BJU Int. 2024;133:246-258. [Crossref]
4. Lin FC, Medendorp A, Van Kuiken M, Mills SA, Tarnay CM. Vaginal dehiscence and evisceration after robotic-assisted radical cystectomy: a case series and review of the literature. Urology. 2019;134:90-96. [Crossref]
5. Chopra S, Dharmaraja A, Djaladat H, Aron M. Transvaginal bowel evisceration following robot-assisted radical cystectomy. Indian J Urol. 2016;32:320-322. [Crossref]
6. Tuderti G, Mastroianni R, Flammia S, Ferriero M, Leonardo C, Anceschi U, Brassetti A, Guaglianone S, Gallucci M, Simone G. Sex-sparing robot-assisted radical cystectomy with intracorporeal padua ileal neobladder in female: surgical technique, perioperative, oncologic and functional outcomes. J Clin Med. 2020;9:577. [Crossref]
7. Richter LA, Egan J, Alagha EC, Handa VL. Vaginal complications after radical cystectomy for bladder cancer: a systematic review. Urology. 2021;156:e20-e29. [Crossref]

CASE REPORT
Urooncology

Doi: 10.4274/jus.galenos.2025.2025-1-6
J Urol Surg 2026;13(3):255-258

Total Pelvic Exenteration for Huge Rectal Gastrointestinal Stromal Tumour with Concurrent Urinary and Intestinal Reconstruction

Haiyang Zhou, Yilei Liu, Peng Zhang

Navy Medical University, Changzheng Hospital, Department of Colorectal Surgery, Shanghai, China

Abstract

A 67-year-old female presented to our hospital with a 12-month history of abdominal pain. Preoperative pelvic magnetic resonance imaging revealed a large pelvic mass arising from the anterior wall of the rectum invading the bladder and uterus, with suspected lymph node metastases. To eradicate the tumor, total pelvic exenteration was carried out. An end-to-end colorectal anastomosis was performed. A Y-shaped uretero-ureteral anastomosis coupled with ureterovesical reimplantation was used for urinary reconstruction. Pathology showed the lesion was a high-risk gastrointestinal stromal tumor (GIST). The patient was treated with imatinib for 6 months following the operation, without tumor recurrence. In conclusion, total pelvic exenteration for huge rectal GISTs with concurrent urinary and intestinal reconstruction is technically feasible. However, whenever a preoperative biopsy and pathological diagnosis is available, neoadjuvant imatinib should be prescribed for large rectal GISTs, as it significantly decreases both tumour size and mitotic activity, thereby permitting less radical and sphincter-preserving surgery.

Keywords: Pelvic exenteration, gastrointestinal stromal tumour, urinary reconstruction, intestinal reconstruction

Introduction

Gastrointestinal stromal tumours (GISTs) represent the most common mesenchymal soft tissue tumours of the gastrointestinal tract (1). Approximately 5% of GISTs originate from the rectum, and often require radical surgery to achieve a complete resection (2). Despite the use of neoadjuvant imatinib for rectal GISTs significantly decreases the tumour size and permits less radical sphincter-preserving surgery (3), accurate preoperative pathological diagnosis of GISTs was not always possible due to the unusual imaging manifestations (4). Here we present a case report of total pelvic exenteration for a large rectal GIST with a concurrent urinary and intestinal reconstruction. The written informed consent was obtained from the patient.

Case Presentation

A 67-year-old female presented to our hospital with the symptom of abdominal pain for 12 months. Preoperative pelvic magnetic resonance imaging revealed a large pelvic mass arising (12.7 cm at its largest diameter) from the anterior wall of rectum invading the bladder and uterus with suspectable lymph node metastases in the mesorectum (Figure 1). After a multidisciplinary team discussion, a computed tomography (CT) or endoscopic ultrasound (EUS) guided biopsy was recommended. However, the patient refused the advice of biopsy and insisted on getting surgery. To eradicate the tumor, total pelvic exenteration was carried out after obtaining written informed consent.

The patient was placed in the lithotomy Trendelenburg position. The invaded ileum was first resected. The sigmoid colon was then mobilized. The inferior mesenteric artery and vein were ligated and divided. Then, the ovarian vessels were ligated and cut. The ureters were identified. The internal iliac artery was divided at the distal location (after branching off the superior gluteal artery). The internal iliac veins were transected with linear staplers. The para-vesical spaces were dissected. The lateral pelvic lymph nodes were removed with the obturator nerves preserved. The left ureter was transected near the bladder. The right ureter was transected at the level of sacral promontory because the distal part seemed to be invaded by the tumour. A partial cystectomy was performed because the bladder neck was not infiltrated by the tumour. Total hysterectomy was performed. The vaginal stump was closed with a 2-0 monofilament,

Correspondence: Prof. Haiyang Zhou MD, Navy Medical University, Changzheng Hospital, Clinic of Colorectal Surgery, Shanghai, China
E-mail: haiyang1985_1@aliyun.com **ORCID-ID:** orcid.org/0000-0003-2782-1821
Received: 09.02.2025 **Accepted:** 18.07.2025 **Epub:** 16.03.2026**Publication Date:** 01.09.2026

Cite this article as: Zhou H, Liu Y, Zhang P. Total pelvic exenteration for huge rectal gastrointestinal stromal tumour with concurrent urinary and intestinal reconstruction. J Urol Surg. 2026;13(3):255-258

absorbable suture. The rectum was mobilized and transected at 5 cm distal to the tumour with a linear stapler. Then the specimen was removed (Figure 2a). The distal margin of rectal resection was 5 cm from the anal verge. A straight end-to-end colorectal anastomosis was performed with a circular stapler. Then, a cystoplasty was performed, and a Y-shaped uretero-ureteral anastomosis coupled with ureterovesical reimplantation was used for urinary reconstruction (Figure 2b). A modified Lich-Gregoir reimplantation technique was applied for the ureterovesical anastomosis (5). The postoperative bladder capacity was about 180 mL. A greater omental pedicle was prepared and transplanted into the pelvic cavity. Drainage tubes were placed appropriately. The pelvic floor was reconstructed with a biologic mesh (Figure 2c) (6). The operative time was 420 minutes. The estimated blood loss was 600 mL. The specimen was completely intact with a wide resection margin (Figure 2d). The postoperative course was uneventful and the patient was discharged 12 days after surgery. Pathology report showed the lesion was a high-risk GIST, with mitotic rate of 15/50 high power field, involving rectal wall, uterine, bladder,

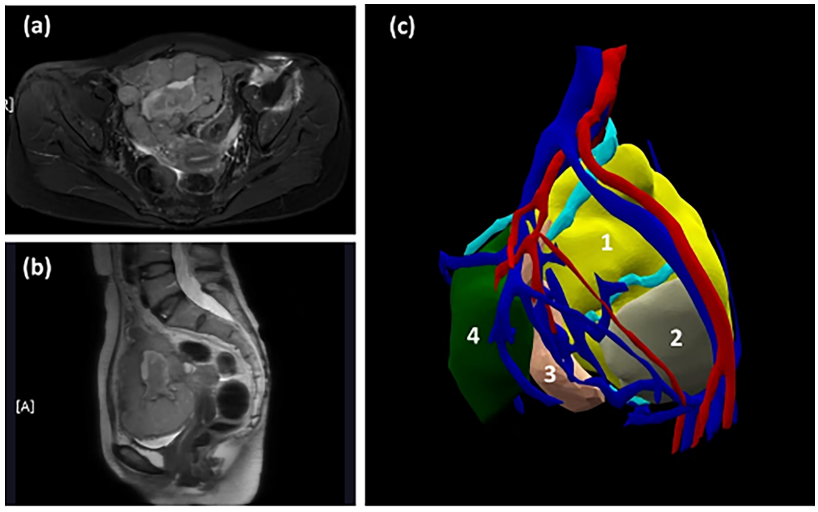


Figure 1. (a) Transverse section of MRI; (b) Sagittal section of MRI; (c) 3D reconstruction of MRI

MRI: Magnetic resonance imaging, 3D: Three-dimensional

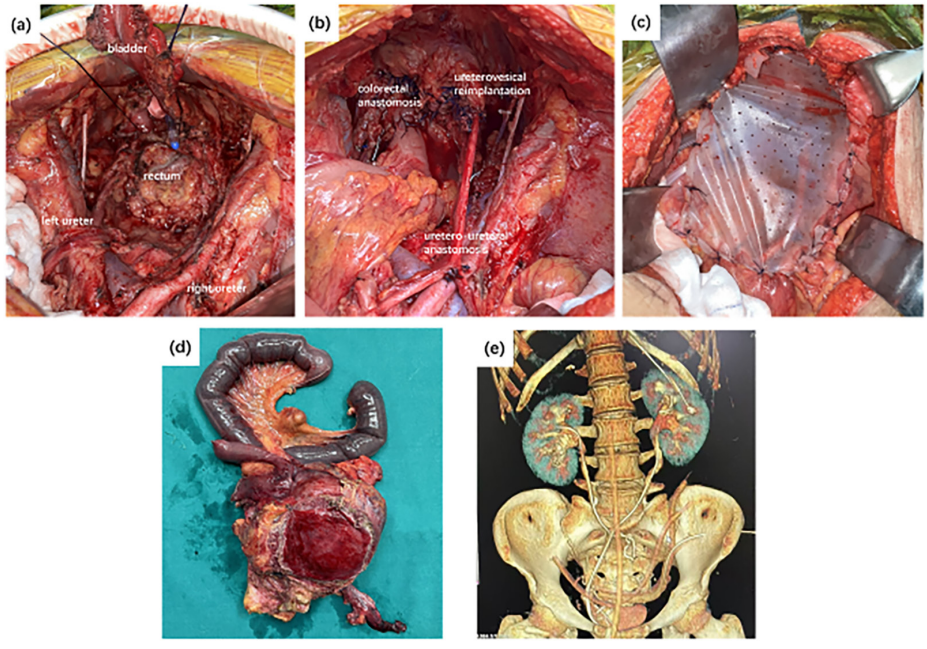


Figure 2. (a) Intraoperative photograph after removing the specimen and before reconstruction; (b) A Y-shaped uretero-ureteral anastomosis coupled with ureterovesical reimplantation for urinary reconstruction and an end-to-end colorectal anastomosis for intestinal reconstruction; (c) Pelvic reconstruction with a biological mesh; (d) Resected specimen; (e) Postoperative CTU showed the reconstructed urinary tract

CTU: Computed tomography urography

ureters and ileum, with no (0/43) lymph node involvement. A postoperative CT urography was performed one month after surgery, showing no urinary fistula or stricture (Figue 2e). Double J catheters were inserted intraoperatively and removed 3 months after surgery. No hydronephrosis occurred after their withdrawal. The patient was treated with imatinib for 6 months following the operation without tumor recurrence.

Discussion

Here we report a case of large rectal GIST treated with total pelvic exenteration. We believed this top-level case had an educational value for both urologists and colorectal surgeons.

Firstly, a multidisciplinary approach was particularly important in the case of rectal GIST. It should be noted that the imaging manifestations of GISTs were quite variable, so the surgeons would not necessarily be aware of the disease preoperatively (4). Nevertheless, it was preferable to obtain a preoperative diagnosis to exclude differential diagnoses including prostate cancer, leiomyosarcoma, germ cell tumours, lymphoma, neurogenic tumours, and desmoid tumours, as these pathologies may require different treatment strategies (7-9). A CT or EUS, guided biopsy should be considered before the surgery whenever possible. The benefits of neoadjuvant imatinib treatment in patients with high-risk GISTs arising from the rectum have been proven, including tumour down-sizing, reduction in mitotic activity, and a reduced risk of recurrence (3,10). The European Society for Medical Oncology (ESMO) guidelines recommended considering neoadjuvant imatinib treatment if R0 tumour resection is not feasible, and if resection can be achieved by less mutilating surgery, or if the operation can be made safer, for instance by decreased blood loss and risk of tumour rupture (11).

Secondly, if neoadjuvant treatment with imatinib was planned, it was essential to confirm the diagnosis of GISTs by histological and molecular tests, as there may be a small number of tumours with platelet-derived growth factor receptor alpha mutations or a wild-type that does not respond well to imatinib (11). Preoperative treatment should be continued until best response, which typically occurred after 6-9 months (9). After surgery, patients at high risk of recurrence or distant relapse should receive 3 years of adjuvant imatinib, if their tumour was not likely to be resistant to therapy (11).

Lastly, surgery should be considered for all rectal GIST cases, regardless of size. Surgery for GISTs must achieve a complete removal (full layer) of the tumor-bearing rectal wall because GISTs originate from the muscularis propria and not the mucosa. Surgical strategy needed to be tailored to the anatomic site, the size of the tumour, and the relation to the adjacent organs and sphincter complex. The approach should be carefully considered, as rectal GISTs may be accessed and resected via transabdominal, transanal, pararectal approaches, and minimally invasive approaches (12,13). When possible, an organ-preserving approach should be considered. However, with large rectal GISTs as in this case, it was sometimes difficult to preserve the adjacent organs despite neoadjuvant imatinib therapy, and extended operations such as total pelvic exenteration should be selected, if necessary, to achieve R0 resection (13). Besides performing a pelvic exenteration, we carried out a complex urinary reconstruction and an end-to-end intestinal reconstruction. The advantage was that it led to a good quality of life. However, complex reconstruction was technically challenging and might need more re-interventions (14). Our center performs more than 200 pelvic exenteration surgeries annually. The use of the greater omentum pedicle and a biological mesh was our standard approach for pelvic reconstruction. In our experience, the combined use of greater omental pedicle and biological mesh promoted neovascularization, hemostasis, tissue healing, and regeneration, which led to faster and more effective recovery (6).

Conclusion

Total pelvic exenteration for large rectal GISTs with concurrent urinary and intestinal reconstruction is technically feasible. However, whenever preoperative biopsy and pathological diagnosis is available, neoadjuvant imatinib should be prescribed for large rectal GISTs, as it significantly decreases both tumour size and mitotic activity, which may permit less radical and sphincter-preserving surgery.

Ethics

Informed Consent: The written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Z., Y.L., Concept: H.Z., Design: H.Z., Data Collection or Processing: H.Z., Y.L., P.Z., Analysis or Interpretation: H.Z., Literature Search: H.Z., Y.L., P.Z., Writing: H.Z., Y.L., P.Z.

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

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

References

1. Søreide K, Sandvik OM, Søreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. Cancer Epidemiol. 2016;40:39-46. [Crossref]
2. Cavnar MJ, Wang L, Balachandran VP, Antonescu CR, Tap WD, Keohan M, Singer S, Temple L, Nash GM, Weiser MR, Guillem JG, Aguilar JG, DeMatteo RP, Paty PB. Rectal gastrointestinal stromal tumor (GIST) in the era of imatinib: organ preservation and improved oncologic outcome. Ann Surg Oncol. 2017;24:3972-3980. [Crossref]
3. Wilkinson MJ, Fitzgerald JE, Strauss DC, Hayes AJ, Thomas JM, Messiou C, Fisher C, Benson C, Tekkis PP, Judson I. Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. Br J Surg. 2015;102:965-971. [Crossref]
4. Kim SW, Kim HC, Yang DM, Won KY. Gastrointestinal stromal tumours (GISTs) with a thousand faces: atypical manifestations and causes of misdiagnosis on imaging. Clin Radiol. 2016;71:e130-e142. [Crossref]
5. Wang A, Zhang P, Bian C, Chen M, Zhou H. Laparoscopic total mesorectal excision with combined resection of the ureter and ureterovesical reimplantation for recurrent cervical adenocarcinoma. Dis Colon Rectum. 2024;67:e1540-e1541. [Crossref]
6. Wang A, Zhang P, Zang J, Zhang X, Zhang J, Zhou H. Total pelvic exenteration with presacral fascia and pelvic musculature excision for pelvic recurrence of rectal cancer. Ann Surg Oncol. 2025;32:2308-2309. [Crossref]
7. Ghobadi A, Kabbani W, Barker B, Dowell JE. Rectal GI stromal tumor mimicking a prostate mass. J Clin Oncol. 2007;25:5827-5828. [Crossref]
8. Wang A, Wang A, Xu X, Chen M, Zhou H. Simultaneous robotic sphincter-preserving rectal resection and prostatectomy for rectal gastrointestinal stromal tumor and prostatic cancer. Ann Surg Oncol. 2024;31:7796-7797. [Crossref]
9. Judson I, Jones RL, Wong NACS, Dileo P, Bulusu R, Smith M, Almond M. Gastrointestinal stromal tumour (GIST): British Sarcoma Group clinical practice guidelines. Br J Cancer. 2025;132:1-10. [Crossref]
10. IJzerman NS, Mohammadi M, Tzanis D, Gelderblom H, Fiore M, Fumagalli E, Rutkowski P, Bylina E, Zavrakidis I, Steeghs N, Bonenkamp HJ, van Etten B, Grünhagen DJ, Rasheed S, Tekkis P, Honoré C, van Houdt W, van der Hage J, Bonvalot S, Schrage Y, Smith M. Quality of treatment and surgical approach for rectal gastrointestinal stromal tumour (GIST) in a large European cohort. Eur J Surg Oncol. 2020;46:1124-1130. [Crossref]
11. Casali PG, Blay JY, Abecassis N, Bajpai J, Bauer S, Biagini R, Bielack S, Bonvalot S, Boukovinas I, Bovee JVMG, Boye K, Brodowicz T, Buonadonna A, De Álava E, Dei Tos AP, Del Muro XG, Dufresne A, Eriksson M, Fedenko A, Ferraresi V, Ferrari A, Frezza AM, Gasperoni S, Gelderblom H, Gouin F, Grignani G, Haas R, Hassan AB, Hindi N, Hohenberger P, Joensuu H, Jones RL, Jungels C, Jutte P, Kasper B, Kawai A, Kopeckova K, Krákorová DA, Le Cesne A, Le Grange F, Legius E, Leithner A, Lopez-Pousa A, Martin-Broto J, Merimsky O, Messiou C, Miah AB, Mir O, Montemurro M, Morosi C, Palmerini E, Pantaleo MA, Piana R, Piperno-Neumann S, Reichardt P, Rutkowski P, Safwat AA, Sangalli C, Sbaraglia M, Scheipl S, Schöffski P, Sleijfer S, Strauss D, Strauss SJ, Hall KS, Trama A, Unk M, van de Sande MAJ, van der Graaf WTA, van Houdt WJ, Frebourg T, Gronchi A, Stacchiotti S; ESMO Guidelines Committee, EURACAN and GENTURIS. Electronic address: clinicalguidelines@esmo.org. Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022;33:20-33. [Crossref]
12. Tsukamoto S, Honma Y, Shoji H, Hirano H, Inoue M, Takamizawa Y, Moritani K, Imaizumi J, Kanemitsu Y. Clinical outcomes of surgical and imatinib treatment for rectal gastrointestinal stromal tumours: retrospective cohort study. BJS Open. 2022;6:zrac067. [Crossref]
13. Emoto S, Akiyoshi T, Mukai T, Yamaguchi T, Nagasaki T, Konishi T, Fukunaga Y. Surgical outcomes of rectal gastrointestinal stromal tumor in the era of imatinib. J Gastrointest Surg. 2021;25:2963-2965. [Crossref]
14. Palma CA, van Kessel CS, Solomon MJ, Leslie S, Jeffery N, Lee PJ, Austin KKS. Bladder preservation or complete cystectomy during pelvic exenteration of patients with locally advanced or recurrent rectal cancer, what should we do? Eur J Surg Oncol. 2023;49:1250-1257. [Crossref]