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Figure 2 - Examples of virtual reality through the coronal axis, depicting venous, arterial and collecting systems, parenchyma and the tumors: 2a keeps the parenchyma, evidencing in an anterior view only the exophytic portions of the tumors; in 2b the parenchyma was removed, evidencing the endophytic portions and its relation to vessels and collecting system; 2c has the same purpose of 2b, but through a posterior view. *e20250463*

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The use of Silodosin in Ureterolithiasis is the Hot Topic in this Number of International Brazilian Journal of Urology

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The March-April number of International Brazilian Journal of Urology presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Artificial Intelligence, BPH, Endourology, Kidney cancer, Basic Research, Infertility, Bladder Cancer, Micropenis, Prostate Cancer and Reconstructive Urology. The papers came from many different countries such as Brazil, Italy, China, Denmark, Colombia, United Kingdom and Germany, and as usual the editor´s comment highlights some of them. The editor in chief would like to highlight the works about Silodosin.

Dr. Godinho and collegues from Brazil, presented in page e20250355 (1) a nice systematic review about the "Impact of preoperative Silodosin on ureteroscopy outcomes for ureterolithiasis". The paper shows important aspects about the α-adrenergic receptor antagonists and their capacity to optimize preoperative conditions during ureteroscopy. Ureteroscopy (URS) is one of the most important modalities for the management of ureteral stones (2-6). Silodosin is a selective alpha-1A adrenergic receptor blocker has at least one registered product approved for commercialization in Brazil by ANVISA in 2025.

In the present paper the authors concluded that the use of silodosin as a preoperative treatment in the URS approach for ureterolithiasis improves both the safety and efficiency of the procedure compared to no preoperative therapy. Future research should prioritize randomized controlled trials that incorporate stratification based on stone location while also focusing on standardizing the definition of tone-free rate, ensuring proper follow-up, and optimizing preoperative Silodosin treatment duration

The Editor-in-chief expects everyone to enjoy reading.

CONFLICT OF INTEREST

None declared.

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EDITORIAL

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Bladder Cancer Immunotherapy in 2025: ALBAN, CREST, POTOMAC, and the Winner Is BCG!

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COMMENT

Immune checkpoint inhibition (ICI) has transformed treatment paradigms in metastatic and muscle-invasive bladder cancer over the past decade. The integration of ICIs into earlier stages of urothelial cancer has long been viewed as an inevitable evolution in bladder cancer therapeutics. In 2025, this assumption faces its first major test in BCG-naïve high-risk non-muscle-invasive bladder cancer (HR-NMIBC) with the publication of the POTOMAC and CREST trials. These Phase III studies, which are large, rigorously conducted, and use induction plus 2 years maintenance BCG in their control arms, allow a critical reassessment of whether systemic (1 year) or subcutaneous (2 years) checkpoint blockade meaningfully enhances outcomes beyond BCG monotherapy (1, 2).

While POTOMAC and CREST reached statistical significance for their primary endpoints, the absolute magnitude of benefit demands careful interpretation. Both studies met their primary endpoints, showing improvements in disease-free or event-free survival. Yet, when placed in a clinical context, these results challenge rather than confirm the expectation that systemic or injectable checkpoint inhibition should be added to frontline BCG for all patients. Here, we critically examine what these trials have taught us scientifically, clinically, and pragmatically, and why BCG remains the backbone of NMIBC immunotherapy despite the biological elegance of checkpoint inhibition.

The results are clear and consistent: while the addition of ICIs produces a statistically significant improvement in disease-free survival (DFS) or event-free survival (EFS), the absolute benefit is modest, toxicity increases substantially, and there is no clue for improvement in the endpoints that matter most, progression, metastasis, bladder preservation, and survival.

Considering therapy-related adverse effects (TRAE) grade ≥3 at 36 months, and EFS/DFS, the number needed to harm (NNH) was 4 and 6, and the number needed to treat (NNT) was 23 and 14, for Sasanlimab and Durvalumab, respectively. These endpoints represent the outcomes of the highest value to patients and health systems, raising the critical question of clinical meaningfulness, particularly when the marginal gains come at the cost of significant toxicity and financial burden (3).

MIBC and/or metastatic disease was 4.7% in durvalumad + BCG vs. 4.4% in BCG alone and 2.8% in sasanlimab + BCG vs. 3.9% in BCG alone. Moreover, historically, most NMIBC-related deaths arise from progression to

muscle-invasive disease. The failure of checkpoint intensification to influence this trajectory should temper enthusiasm for broad adoption and refocus the field toward precision immuno-oncology rather than universal escalation.

Immune-related adverse events, including hepatotoxicity, endocrine dysfunction, and gastrointestinal or pulmonary inflammation, often require corticosteroids, specialist care, and sometimes lead to irreversible morbidity. Additionally, ICI therapy imposes a significant economic burden due to drug acquisition costs, infusion or administration infrastructure, monitoring and immunotoxicity management, as well as increased imaging and laboratory surveillance.

Most importantly, POTOMAC and CREST reaffirm the foundation upon which NMIBC care has rested for decades: BCG alone, when administered with induction and maintenance, remains a potent and reliable immunotherapy. The 36- and 24-month EFS/DFS rates in the BCG-only arm, with full induction and maintenance, were 74.8% and 79.9% in CREST, and 77.4% and 81.6% in POTOMAC, respectively. Additionally, the optimized conditions in contemporary clinical trials resulted in a higher-than-expected complete response rate at any time and unusually low grade 3-4 adverse events for the BCG alone group, with rates of 93% and 4% in the POTOMAC trial and 85.2% and 6% in the CREST trial, respectively, significantly superior to the historical series (1, 2, 4).

Given the safety and strong performance of BCG alone, the absolute gain on disease/event free survival in 36 and 24 months was 4.4 and 4.9% in POTOMAC (durvalumab 1y 13cycles + BCG, with 17% absolute increase in Grade ≥3 TRAE) and 7.3 and 4.8% in CREST (sasanlimab 2y 25cycles + BCG, with 23% absolute increase in Grade ≥3 TRAE), respectively (1, 2).

Importantly, a third arm (ICI + BCG induction only) in both the CREST and POTOMAC trials failed to outperform the complete 2-year BCG induction-plus-maintenance schedule, confirming that BCG monotherapy, when adequately offered, maintains an exceptional therapeutic index, high efficacy, and minimal severe toxicity, setting a high bar for any combination strategy. This finding aligns with the randomized phase III ALBAN trial, which offered 1 year of BCG maintenance and did not demonstrate an improvement in EFS compared to BCG alone in BCG-naive high-risk NMIBC patients (1, 2, 5).

While endpoint definitions and censoring rules for EFS (e.g., upper tract tumors, low-grade recurrences) vary across studies, limiting direct comparisons, other important factors, such as patient mix, geographic distribution, and BCG strain availability, may also influence the results. While the POTOMAC and CREST trials (1, 2) recruited patients with significant previous BCG vaccine and tuberculosis exposures (i.e., Russia), the ALBAN trial (5) limited its recruitment to areas with no or minimal previous BCG/tuberculosis exposure (France, Belgium, and Spain) (6).

In the future, we may need to optimize patient selection based on biomarkers that predict their immune responses and on both BCG-related and unrelated immunogenicity, making the BCG naïve definition more comprehensive, considering any previous BCG priming beyond intravesical BCG. A major challenge is predicting the immunogenic potential of immunotherapies (BCG and beyond) and how it varies with environmental factors (high vs. low-income countries), comorbidities, and age, as it influences not only treatment response but also toxicity (7). For better results, we may evolve into a system of "immune staging" for a more individualized approach, complementing the current tumoricentric and immune-blind approach.

Even patients treated with BCG alone conceal inherent heterogeneities. Based on current knowledge, realistic strategies to potentially enhance the already robust BCG alone results include higher rates of treatment completion and the extension of BCG maintenance for up to 3 years (8, 9). Even in the CREST and POTOMAC trials, BCG treatment completion rates were limited to 53% to 54%. Additionally, 65 to 78% of patients received BCG strains other than TICE, each containing a wide variation of 1 to 8×10^8 colony-forming units (1, 2).

In 2025 trials (1, 2, 5) also highlight a significant limitation in bladder cancer immunotherapy research: the lack of reliable predictive biomarkers. PD-L1 expres-

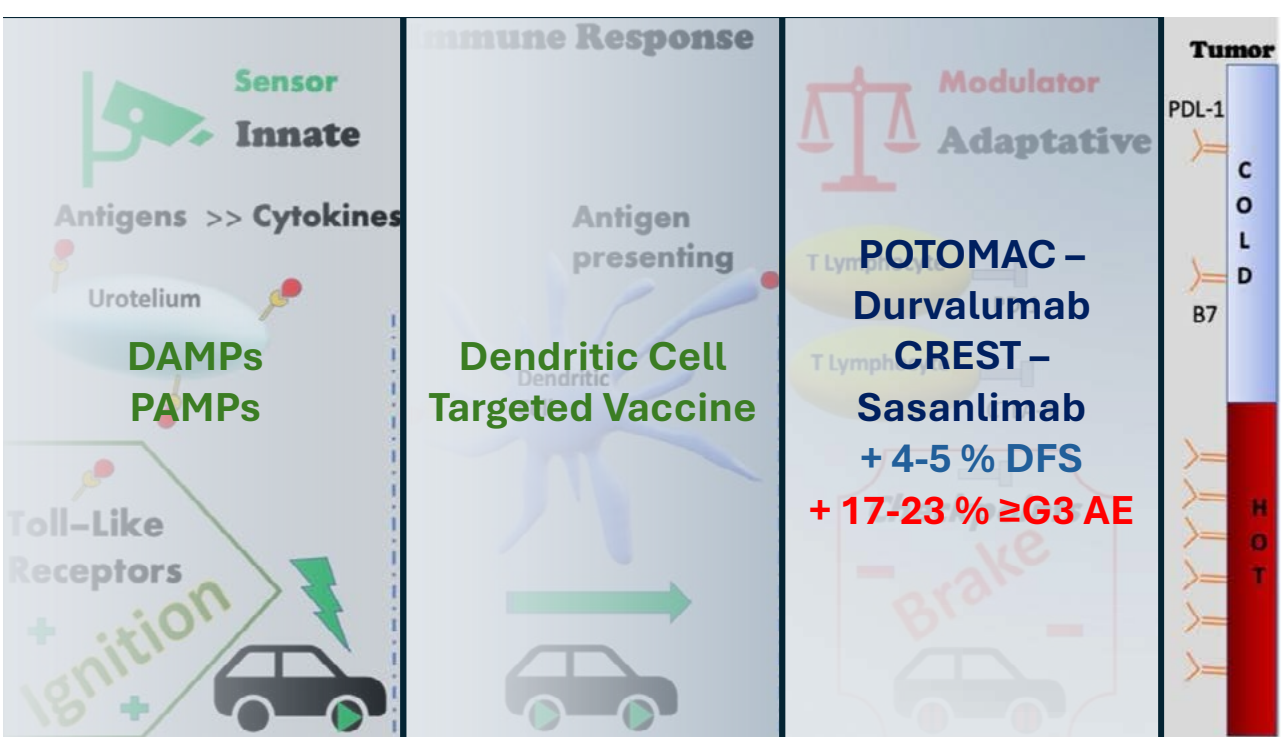
sion remains insufficient to guide treatment selection. No validated genomic signature or immune profiling strategy emerged. Translational correlatives released so far do not clarify who benefits most from systemic therapy. Without meaningful biomarkers, systemic immunotherapy in NMIBC becomes an unguided escalation strategy, exposing many patients to toxicity without assured benefit.

The ongoing KEYNOTE-676 trial will present results of BCG induction, followed by 3 years of maintenance, both with and without intravenous pembrolizumab (administered for 2 years), in patients with recurrent or persistent high-risk NMIBC (9). Future trials on immunotherapy must be robustly designed with strategies for identifying biomarkers and understanding immunological profiles ("immuno-score") that predict clinically significant outcomes (bladder preservation, progression, metastasis, survival), and serious side effects.

Future clinical and research implications

BCG monotherapy should remain the standard of care for BCG-naïve HR-NMIBC. Checkpoint inhibitors should not be universally integrated into first-line NMIBC treatment. Patient selection must be prioritized, with shared decision-making that transparently weighs modest benefits against toxicity and cost. Future research must be biomarker-driven, incorporating immune profiling, genomic classifiers, and spatial immunology. Mechanistic studies should elucidate why BCG remains so effective and to early detect which patients truly require treatment beyond BCG. Alternative immuno-oncologic strategies, such as intravesical cytokine engineering, oncolytic vectors, or localized immune modulation, may offer superior therapeutic ratios compared with systemic ICIs. Only through such approaches can we deliver meaningful advances in bladder preservation, progression prevention, and survival.

Figure 1 - Co-dependency diagram of innate ("ignition", TLR) and adaptive ("brake", checkpoint) immune responses as a multi-targeted immunotherapy strategy (developed by the author).



DAMPs = Damage-Associated Molecular Patterns; PAMPs = Pathogen-Associated Molecular Patterns; DFS = disease-free survival (increment); G3 AE = grade 3 adverse effect (increment)

CONCLUSIONS

One of the most important insights from both positive trials is the high efficacy of contemporary BCG when delivered with full induction and maintenance, consistent with international guideline standards. Checkpoint inhibitors are expensive and potentially toxic; deploying them empirically, without biomarker guidance, is no longer acceptable in modern immuno-oncology. Precision strategies, immune profiling, molecular subtyping, spatial immunophenotyping, and circulating biomarkers must become central in future NMIBC trials.

In high-income settings, these costs strain oncology budgets. In middle-income countries, including Brazil, where bladder cancer incidence is rising, and access to immunotherapy remains uneven, such regimens risk exacerbating disparities (10). Without clear evidence of improved progression or survival, the cost-effectiveness of adding ICIs to BCG is questionable. Health-policy considerations, particularly in universal health systems, require that incremental benefits justify broad public investment.

BCG should remain the foundation of care, and systemic ICIs should be used sparingly, thoughtfully, and, ideally, guided by biomarkers that do not yet exist. The field must now pivot from empiric combination toward precision immunology and rational patient selection.

The "winner" is therefore not a single drug, but the strategy that centers on BCG as the necessary immunologic partner, unlocking an era of bladder-sparing precision immunotherapy. This approach will include a more individualized treatment, where, beyond tumor characterization, understanding the patient's "immune staging" will play a crucial role for treatment efficacy and safety.

CONFLICT OF INTEREST

None declared.

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Nota par os autores: Citar a tabela 3 no texto; Citar as referências 23 e 36 no texto.

REVIEW ARTICLE

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Micropenis in Children and Adolescents: A Narrative Review

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ABSTRACT

Purpose: To summarize current evidence on the etiology, diagnostic approach, management strategies, and outcomes of micropenis in children and adolescents.

Materials and Methods: A narrative review was performed using PubMed/MEDLINE (October 2025) with the search terms (Micropenis OR Microphallus OR "Small Penis") AND (Children OR Youth OR Adolescents). From 707 records screened, 36 studies were selected based on methodological quality and relevance to clinical practice.

Results: Micropenis is a clinical sign frequently associated with underlying endocrinopathies, particularly Congenital Hypogonadotropic Hypogonadism (CHH). Accurate diagnosis relies on standardized Stretched Penile Length (SPL) assessment, recently optimized by the Stretched Penile Length INdicator Technique (SPLINT). Use of population-specific SPL nomograms is critical for diagnostic reliability. Testosterone therapy remains the primary treatment modality and demonstrates greatest efficacy in early infancy, promoting significant penile growth and generally favorable functional outcomes. Spontaneous catch-up growth during puberty has been reported in select cases. Current evidence supporting surgical interventions in children and adolescents is limited, heterogeneous, and associated with inconsistent long-term results; thus, surgery should not be considered first-line therapy. High-quality long-term outcome data and randomized placebo-controlled trials are lacking.

Conclusions: Standardized SPL measurement and appropriate nomogram use are essential for accurate diagnosis. Early hormonal therapy, especially in CHH-associated micropenis, appears to yield optimal functional and psychosocial outcomes. Expectant management may be appropriate in selected clinical scenarios. Surgical techniques remain controversial, with insufficient evidence to recommend routine use. Further well-designed prospective studies, including randomized placebo-controlled trials, are needed to define long-term outcomes and guide clinical decision-making.

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INTRODUCTION

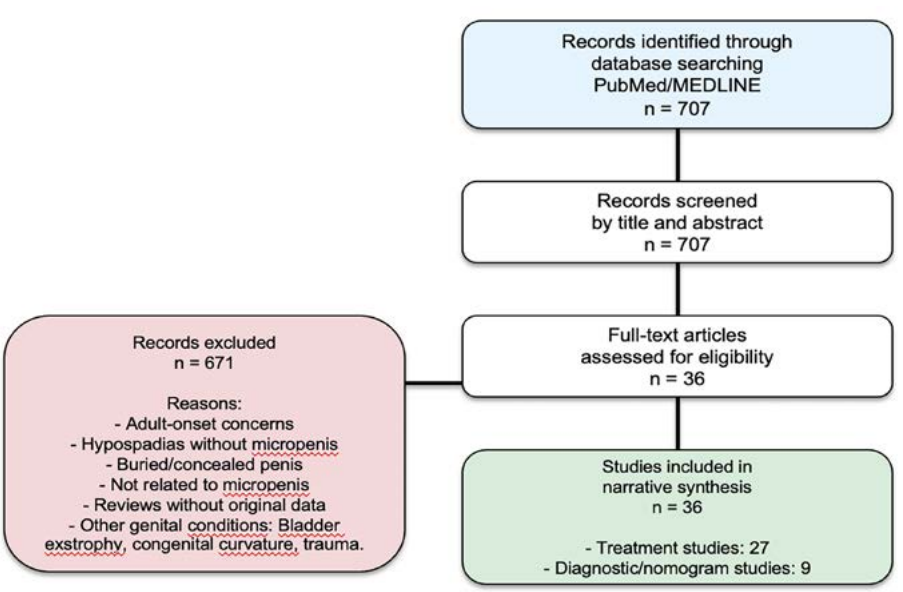
Micropenis is a clinical diagnosis characterized by a structurally normal, albeit small, penis (1). The condition is defined by a Stretched Penile Length (SPL) that falls 2.5 standard deviations (SD) or more below the mean in a chart for a patient's age and level of sexual development (2). The identification of micropenis in infancy or childhood is of paramount importance, as it is frequently the presenting sign of a significant underlying congenital or acquired endocrinopathy (3, 4). The clinical relevance of micropenis extends beyond its physical manifestation. The diagnosis can cause considerable anxiety for parents, significant psychosocial distress, body image issues, self-esteem problems, concerns about future sexual function and loss of Quality of Life (5). Historically, the management of micropenis has been a subject of controversy, with past recommendations even including the now-obsolete consideration of gender reassignment for the most severe cases (6). However, cumulative evidence from follow-up studies, albeit with persisting knowledge gaps, has considerably advanced our understanding, especially in the context of hormonal therapy. (7). This narrative review aims to provide a comprehensive overview of the current state of knowledge regarding micropenis in the pediatric and adolescent population. The relevance of the topic, the diagnostic process with a comparison of the principal growth charts used globally, the mainstays of treatment, and the reported outcomes based on contemporary scientific evidence will be covered.

MATERIALS AND METHODS

A comprehensive literature search was conducted on PubMed/MEDLINE in October 2025. The search strategy employed Medical Subject Headings (MeSH) and free-text terms: (Micropenis OR Microphallus OR "Small Penis") AND (Children OR youth OR adolescents), unrestricted by date or language, with a focus on articles published in English.

Initial results were screened by title and abstract for pediatric/adolescent relevance. Inclusion criteria: articles discussing etiology, diagnosis, treatment, or outcomes. Exclusion criteria: adult-onset concerns, hypospadias, epispadias, bladder exstrophy, buried/concealed penis unrelated to shaft length deficiency or other genital abnormalities. A total of 707 articles were identified. Of these, 36 key articles were selected for this review based on their relevance, study design, and contribution, with a focus on studies reporting penile growth charts and treatment results. Reviews and articles that did not mention diagnosis or treatment results were also excluded (Figure-1).

Figure 1 - PRISMA flowchart of the study selection process.



RESULTS

a. Relevance of the Topic in Pediatric Urology

Micropenis is a relevant topic in pediatric urology and endocrinology primarily because it serves as a critical physical marker for underlying systemic diseases. The precise global prevalence is unknown, but data suggest an incidence of approximately 1 in 300 male births, with a reported incidence in North America of approximately 1.5 per 10,000 male newborns (8). The condition is most often a consequence of insufficient androgen stimulation for penile growth during a critical window of fetal development, specifically from 12 weeks of gestation through the postnatal "mini-puberty" in the first six months of life.

The most common underlying known cause is Congenital Hypogonadotropic Hypogonadism (CHH), a failure of the testosterone axis (9). Furthermore, micropenis can be a feature of numerous genetic syndromes, such as Prader-Willi, Kallmann, and Klinefelter syndrome, making its recognition a key step in a broader diagnostic workup (10). A full medical evaluation is essential not only to address the penile size itself but also to diagnose and manage potentially life-threatening associated conditions, such as hypoglycemia in cases of panhypopituitarism (Table-1).

Table 1 - Surgical Approaches for Micropenis.

Reference Number and Year	Technique Description	Outcomes & Complications	Author's Remarks / Goals
Hinman 1971 (33)	**Two-Stage Elongation and Burial: Stage 1:** Corporal bodies are dissected to their base for maximal length and then buried in subcutaneous 2. **Stage 2 (3-4 months later):** The penis is liberated, and skin coverage with thick scrotal flaps.	Outcomes not quantitatively reported.	Aims to allow for vascular adaptation and shaft elongation before providing skin coverage.
Gilbert et al. 1993 (34)	**One-Stage Microsurgical Free Flap Phalloplasty (Radial Forearm):** Radial forearm free flap to create a neophallus. Vascular anastomoses are made to epigastric vessels, and nerve coaptation is performed with the pudendal nerve for sensation.	**Success Rate:** 91%. **Complications:** Urethral fistulas (5 cases), strictures (3 cases). **Sensory Outcomes:** All patients with nerve coaptation regained protective and erogenous sensation.	Goals are to achieve voiding while standing, preserve sensation, create a phallus suitable for a prosthesis.
Perović et al. 1995 (35)	**Extended Pedicle Island Groin Flap:** A flap from the groin and lower abdomen, based on superficial iliac and epigastric vessels, is used. It is designed in three parts to create a neourethra and neophallus.	All patients achieved a cosmetically and functionally satisfactory neophallus. **Complications:** Partial flap necrosis (2 cases), urethral fistula (2 cases), anastomotic stenosis (1 case). **Sensitivity:** Generally mild to moderate.	The technique aims to create a complete neophallus with a neourethra in a single stage, with glans sculpting performed later.

b. Diagnosis and Comparison of Growth Charts

The diagnosis of micropenis is clinical, based on an accurate measurement of SPL. A 2024 systematic review (11) highlighted significant heterogeneity in measurement methodologies across 145 studies. This review identified several factors that influence the accuracy of SPL measurements. To address these inconsistencies, the authors proposed a standardized protocol named the Stretched Penile Length INdicator Technique (SPLINT) – (Figure-2).

A cornerstone of diagnosis is the use of penile length nomograms. These charts provide the mean and standard deviations for SPL across different ages. However, there is a significant finding in the literature about the well-documented variation in penile size across different ethnic and geographic populations. This has led to the development of numerous population-specific nomograms. A comparison of the most widely used charts is presented in Table-2.

As the table illustrates, there are just few anthropometric pediatric populations sampling around the World. Therefore, clinicians should use the most relevant, up-to-date, and population-specific data available to accurately diagnose micropenis and local data record charts are undoubtedly the best way to diagnosis micropenis.

c. Treatment

The initial objectives of micropenis management are counseling, investigation of underlying endocrinological causes (as often as possible) and hormonal therapy, with the goal to stimulate penile growth to achieve a length that is within the normal range for age. Surgical options are reserved for cases where hormonal therapy fails to achieve adequate penile length, or in the presence of anatomical abnormalities.

Figure 2 - SPLINT (Stretched Penile Length INdicator Technique). Note the private ambient room, supine position, foreskin retraction (for those who doesn`t have phimosis), use of rigid ruler with zero-error correction and the compression over the suprapubic fat. The penis is stretched vertically to the point of resistance without causing discomfort. At least two (preferably three) measurements are obtained to ensure reproducibility. *Figure Source: The Author.*

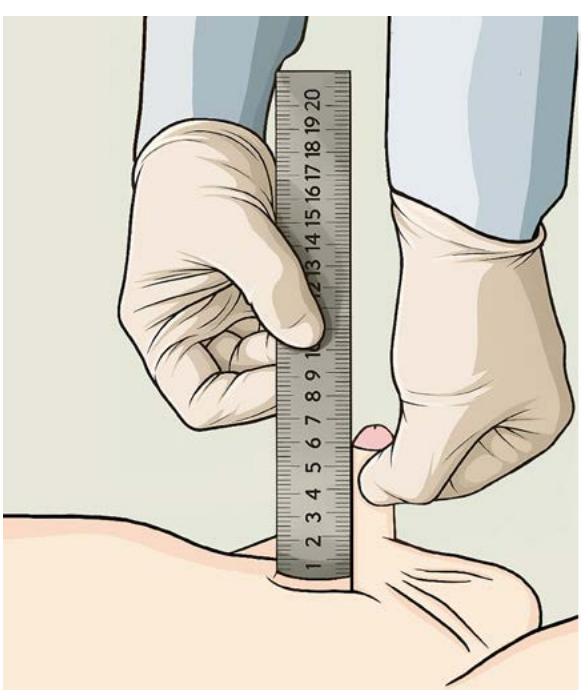


Table 2 - Review of SPL Nomograms.

Reference Number	Year	Population	Key Characteristics
Teckchandani and N, Bajpai (12)	2014	Indian	200 patients (0-10y); two measures in supine position by the same observer. Excluded endocrine and genetic syndromes.
Ishii et al. (13)	2015	Japanese	1628 patients (0-7y); multicentric cohort. Absence of genital anomalies, endocrine disorders or major malformations.
Gul et al. (14)	2021	Turkish	948 healthy, uncircumcised boys; single center, one examiner. Excluded genital/ congenital abnormalities.
Ibrahim et al. (15)	2023	Egyptian	1500 prepubertal patients (5-9y); single center, single observer. Excluded chronic illness, abnormal growth, and uncircumcised boys.
Krämmer et al. (16)	2025	Brazilian	140 Preterm male newborns; measures within 72h of life, repeated weekly. Single examiner.
Gabrich et al. (17)	2007	Brazilian	2,010 participants (0-18y); heterogeneous cohort. Three examiners. Dual classification by age and Tanner stage.
Wang et al. (18)	2018	Chinese	2,974 healthy urban boys (0-17y); two trained examiners.
Tomova et al. (19)	2010	Bulgarian	6,200 healthy white boys (0-19y); single endocrinologist. Included testicular volume and penile circumference.

c.1. Hormonal Therapy

The most widely accepted and effective treatment for micropenis, which can be particularly effective in cases of CHH, is hormonal therapy, but some patients may not reach normal adult penile size, especially in cases of severe hypogonadotropic hypogonadism (20). Monitoring for side effects such as premature virilization and elevated serum testosterone is recommended, particularly with topical therapy. There are no large, placebo controlled, long-term studies and evidence-based guidelines directly addressing testosterone therapy for micropenis, and further research is needed to optimize treatment timing and assess long-term outcomes.

According to medical literature, the optimal timing for testosterone therapy to achieve the best response in penile growth for patients with micropenis is during infancy or early childhood, including the period of mini puberty. Early initiation of therapy is associated with greater penile growth, and initial penile dimensions – particularly glans width – are strong predictors of response (21-23). Table-3 summarizes the main study results with testosterone for micropenis.

c.2 Surgical Treatment

Surgical intervention, as documented in medical literature, is not a first-line treatment for micropenis in children. Surgical techniques are complex and include procedures like the release of the suspensory ligament (31) and neo phalloplasty. The outcomes of these surgeries in the pediatric population are not well-documented, and they carry significant risks, making hormonal therapy the preferred initial approach. The Brazilian Federal Medical Council, under Resolution 1.478/1997, considers penile lengthening surgery for sexual dysfunction to be experimental and restricts its performance to rigorously controlled human research protocols (32).

DISCUSSION

Micropenis is clinically significant because it frequently reflects underlying disruptions in androgen endocrinologic axis, with Congenital Hypogonadotropic Hypogonadism (CHH) being the most common identifiable etiology. Its presence may also indicate broader syndromic conditions, emphasizing the role of micropenis as an early diagnostic marker within multidisciplinary evaluations (36).

Table 3 - Hormonal Management of Micropenis.

Reference Number	Study type, Substance(s), Patient Cohort	Posology	Key Outcomes & Remarks
Ishii et al. 2004 (24)	Prospective, Testosterone Enanthate (TE), 53 Japanese prepubertal boys.	25mg IM every 4 weeks, up to 4 times.	**Effective:** Median SPL increment of 0.6cm, independent of age or gene polymorphisms.
Karrou et al. 2023 (25)	Prospective, Transdermal Dihydrotestosterone (DHT) vs. TE, 49 boys without hypogonadism or genetic syndromes.	**DHT:** 5mg daily for 5 weeks (renewed 1-2 times). **TE:** 50mg IM monthly (renewed once).	**DHT Superiority:** Mean growth DHT +2.37 cm vs. TE +1.82 cm (p=0.008). **No Side Effects Critique:** Small sample size, no genetic testing.
Bin-Abbas et al. 1999 (26)	Retrospective,Testosterone Enanthate (TE), 8 males (18-27y) with CHH.	25-50mg IM every 4 weeks for 3 months (1-2 courses), then dose increased to adult regimen.	**Long-Term Success:** No significant difference between early (infancy) vs. late (childhood) treatment.
Nerli et al. 2013 (27)	Retrospective, TE vs. hCG, 25 boys with isolated non-syndromic micropenis.	**TE (<11y):** 25mg IM monthly for 3 months. **hCG (>11y):** 1,500-2,000 IU IM weekly for 6 weeks.	**Significant Growth:** >100% increase in SPL in both groups. No adverse effects reported.
Becker et al. 2016 (28)	Retrospective, hCG, 20 patients with CHH.	1,500-2,000 IU IM, 3x/week for 8 weeks.	**Effective for IHH:** Mean SPL increased 2.31 cm. Safe and well-tolerated.
Arisaka et al. 2001 (29)	Prospective, Topical Testosterone, 50 prepubertal boys (5mo-8y).	5% cream (10mg) applied daily for 30 days.	**Significant Growth:** Mean SPL increased ~44%,. **Minimal Side Effects:** Mild, transient local hyperpigmentation/eczema. No skeletal effects.
Xu et al. 2017 (30)	Open Prospective, DHT Gel, 23 boys (9mo-11y) with normal karyotype.	2.5% gel (0.1-0.2 mg/kg/day) applied daily for up to 6 months.	**High Success Rate:** 61% achieved normal SPL (> -2.5 SD). 26% clinically improved. **Safe:** No bone age acceleration or systemic side effects.

Accurate diagnosis depends on correct use of standardized Stretched Penile Length (SPL) measurement protocols. The literature demonstrates substantial heterogeneity in measurement techniques, increasing the risk of misclassification. The recently proposed Stretched Penile Length Indicator Technique (SPLINT) offers a reproducible method designed to mitigate these discrepancies, although further validation across diverse populations is required. Given the documented ethnic and regional variability in penile length, the use of population-specific nomograms remains essential for diagnostic reliability.

Testosterone therapy remains the most effective and widely accepted treatment. Studies consistently demonstrate significant penile growth, particularly when initiated in infancy or early childhood, corresponding to periods of heightened androgen sensitivity. While short-term outcomes are favorable, long-term data are limited,

and randomized placebo-controlled trials are lacking. Factors such as baseline penile size may influence treatment response, but standardized predictive markers have not yet been established.

Emerging evidence suggests that many untreated patients may achieve normalization of penile size during puberty, supporting expectant management in selected cases. However, methodological limitations - particularly high attrition rates - restrict the generalizability of this approach. Any expectant strategy must be individualized and accompanied by structured clinical and psychosocial follow-up.

Surgical management remains controversial. The available evidence is scarce, heterogeneous, and limited by small cohorts and inconsistent outcome reporting. Procedures such as suspensory ligament release or phalloplasty are reserved for exceptional situations and should not be considered first-line interventions.

Significant knowledge gaps persist, including the optimal timing and duration of hormonal therapy, long-term functional and psychosocial outcomes, and predictors of spontaneous pubertal growth. Future progress will depend on well-designed prospective studies capable of addressing these limitations.

CONCLUSIONS

The management of micropenis in children and adolescents relies fundamentally on accurate diagnosis using standardized SPL measurement techniques and population-specific nomograms. Hormonal therapy, particularly in cases related to CHH, remains the cornerstone of treatment and generally yields favorable functional and psychosocial outcomes when initiated early. Emerging evidence suggests that expectant management may be appropriate in select individuals due to the potential for spontaneous pubertal catch-up growth, although further validation is required. Surgical interventions lack robust evidence, show inconsistent outcomes and high morbidity, and should not be considered first-line therapy in this population. High-quality prospective studies, including randomized placebo-controlled trials, are needed to define long-term outcomes, refine patient selection, and guide evidence-based management strategies.

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ABBREVIATIONS

BMI = Body Mass Index
CHH = Congenital Hypogonadotropic Hypogonadism
DHT = Dihydrotestosterone
GnRH = Gonadotropin-Releasing Hormone
HPG = Hypothalamic-Pituitary-Gonadal
LH = Luteinizing Hormone
FSH = Follicle-Stimulating Hormone
SD = Standard Deviation
SPL = Stretched Penile Length
SPLINT = Stretched Penile Length INdicator Technique
TE = Testosterone Enanthate

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Impact of Preoperative Silodosin on Ureteroscopy Outcomes for Ureterolithiasis: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: To perform a systematic review and meta-analysis evaluating the efficacy and safety of preoperative silodosin in improving ureteroscopy (URS) outcomes for ureterolithiasis.

Materials and Methods: PubMed, EMBASE and Cochrane Central were systematically searched for studies comparing preoperative silodosin with placebo or 'no preoperative silodosin' in patients undergoing URS for ureteral stones. Primary outcomes included ureteral wall injury, analgesia use, fever, haematuria, stone-free rate (SFR), operative time, and complications. Statistical analysis was performed using Review Manager 5.1.7. Study quality and risk of bias were assessed per Cochrane guidelines.

Results: Nine studies, including eight randomized clinical trials, including 960 patients were analysed; 450 (46.8%) received silodosin. Compared to controls, silodosin significantly reduced ureteral injuries (RR 0.30; 95% CI: 0.18–0.49; p < 0.00001) and operative time (MD -17.72 minutes; 95% CI: -24.72 to -10.72; p < 0.00001). It also lowered analgesia needs (RR 0.35; 95% CI: 0.16–0.75; p = 0.007), with trends toward reduced fever (RR 0.67; 95% CI: 0.36–1.22; p = 0.19) and haematuria (RR 0.57; 95% CI: 0.32–1.02; p = 0.06). In studies with ≥10 days of preoperative use, silodosin significantly improved SFR (RR 1.17; 95% CI: 1.10–1.26; p < 0.00001).

Conclusions: Preoperative silodosin reduces ureteral injuries, operative time, and complications, supporting its use to improve safety and efficiency of URS for ureterolithiasis.

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INTRODUCTION

Ureterolithiasis, defined as the presence of calculi within the ureter, represents a common urological condition associated with significant clinical morbidity, including acute pain, urinary tract obstruction, and other complications necessitating timely intervention (1, 2). Ureteroscopy (URS) has emerged as a cornerstone modality for the management of ureteral stones, offering high stone-free rates and broad applicability. Despite its efficacy, URS is not without technical challenges; it is frequently associated with prolonged operative times, the need for ureteral dilation, and procedural complications that may adversely affect patient outcomes and recovery (1).

In an effort to address these challenges, pharmacological adjuncts, most notably α-adrenergic receptor antagonists, have been explored for their capacity to optimize preoperative conditions. Among these, silodosin, a highly selective α1A-adrenergic receptor blocker, has garnered increasing attention for its potential to improve ureteroscopic outcomes, particularly in comparison to tamsulosin in the context of distal ureteral calculi (3). Silodosin's greater selectivity for α1A receptors, as opposed to tamsulosin's broader affinity for both α1A and α1D subtypes, may enhance its efficacy in promoting ureteral smooth muscle relaxation and facilitating stone passage (3). These pharmacodynamic properties have led to the conduction of several randomized controlled trials (RCTs) evaluating silodosin's role in the preoperative setting.

Accordingly, we conducted a systematic review and meta-analysis to assess the impact of preoperative silodosin on the safety and efficacy of URS for ureterolithiasis. Specifically, this study evaluates outcomes including ureteral wall injury, stone-free rate (SFR), operative time, analgesic requirement, and perioperative complications. By synthesizing current evidence, it seeks to clarify silodosin's role in optimizing ureteroscopic procedures and to provide high-quality data to support clinical decision-making in urological practice.

MATERIALS AND METHODS

Protocol and Registration

This systematic review and meta-analysis followed the Cochrane Handbook and PRISMA guidelines (4, 5). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (protocol: CRD42025633316).

Inclusion and Exclusion Criteria

Studies were included if they: (I) compared preoperative silodosin with a control; (II) involved patients undergoing ureteroscopy (URS); and (III) addressed ureterolithiasis. The control groups included no treatment or placebo, defined as an inert substance mimicking silodosin without pharmacologic effects. These comparators served to isolate silodosin's specific impact on surgical outcomes.

Conversely, studies were excluded if they were animal studies, case reports, or case series, as well as those that did not align with the PICOT framework. Specifically: (P) Population – patients with ureterolithiasis scheduled for URS; (I) Intervention – preoperative use of silodosin; (C) Comparison – no alpha-blockers or placebo; (O) Outcomes – intraoperative dilation, SFR, operative time, hospital stay, ureteral navigation, and complications; and (T) Type of studies – primary studies only, thereby excluding animal studies and case reports or series.

Search Strategy

Searches were conducted in PubMed, Embase, and Cochrane databases for studies published between 2014 and 2024. No language or sample size restrictions were applied. The search strategy is detailed in Supplementary Table-S1 (see material supplementary).

Study Selection and Data Extraction

Two reviewers independently screened studies using Rayyan software (6), resolving discrepancies by consensus. Data were extracted by one reviewer and cross-checked by the other. Extracted

variables included study design, sample size, age, BMI, stone location, stone size, and outcomes. All data were stored in a standardized database.

Endpoints and Definitions

The endpoints of interest were categorized as intraoperative and postoperative. Intraoperative endpoints included operative time, ureteral wall injury, and need for dilation (defined as requiring dilation if the ureteroscope could not pass the ureterovesical junction). Postoperative endpoints included SFR (residual fragments < 4 mm), need for analgesia, fever (≥ 38º C), and haematuria. Follow-up timing and imaging varied by study protocol. Only studies with comparable definitions were included in outcome-specific syntheses.

Quality Assessment

Quality assessment of included studies was conducted using Cochrane tools.: RoB 2 for RCTs (7) and ROBINS-I for non-randomized studies (8), ensuring reliability and transparency of findings.

Statistical analysis

Meta-analyses were conducted using Review Manager 5.4 (Copenhagen) (9). For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated, whereas continuous outcomes were analysed using mean differences (MDs). Moreover, a random-effects model was employed, as variations in study populations and protocols were anticipated.

In addition, heterogeneity was assessed via Cochran's Q and I^2 statistics, with $p < 0.10$ and $I^2 > 25\%$ considered significant. To further address heterogeneity, sensitivity analyses were performed. Furthermore, subgroup analyses were conducted based on study type (RCT vs. non-RCT) and duration of silodosin use (<10 vs. ≥10 days). Finally, when only medians and interquartile ranges were reported, means and standard deviations were estimated using the method proposed by Wan et al. (10).

RESULTS

Selected Studies and Baseline Characteristics

A total of 313 articles were identified through PubMed, Embase, and Cochrane. After removing 151 duplicates, 162 records were screened, and 12 underwent full-text review. Four conference abstracts were excluded. Additional studies identified via backward snowballing brought the final number to nine included in the meta-analysis. The selection process is detailed in the PRISMA flow diagram (Figure-1), with the full checklist in the supplementary material (Figures S12–S14) (see material supplementary).

Nine studies (eight RCTs) with 960 patients were analysed (1, 2, 11-17). Of these, 450 (46.8%) received 8 mg/day of silodosin for 3–14 days before URS. Follow-up ranged from 1 to 3 months. Additionally, 613 patients were male (63.8%) and 145 (55.9%) had lower ureteral stones. Baseline characteristics are summarized in Table-1 and Table-S2 (see material supplementary).

Quality Assessment

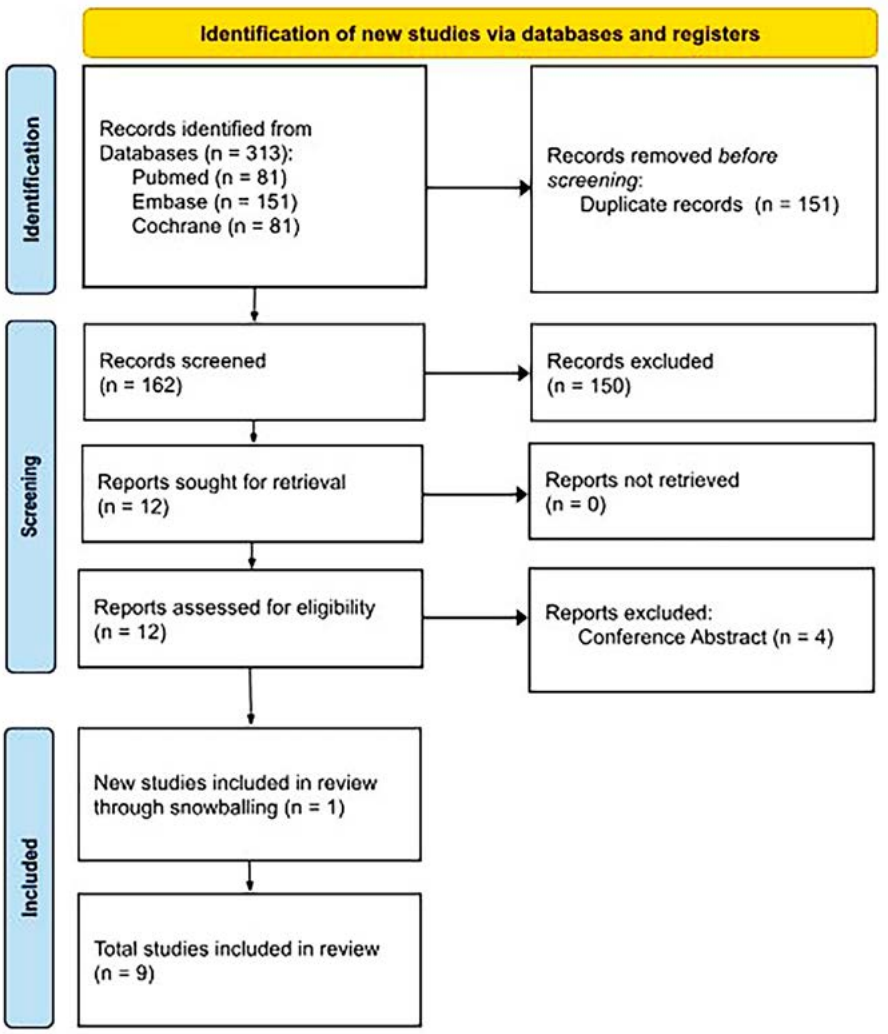
Two reviewers independently appraised the quality of individual studies. Notably, two RCTs raised some bias concerns: Aydin et al. (2), due to differences in ureteroscope use, and Goyal et al. (15), due to unclear blinding. Furthermore, Alaridy et al. (2) was rated as having moderate risk of bias per ROBINS-I, owing to unadjusted confounders and missing data.

Endpoints Pooled Analysis

A meta-analysis showed that preoperative silodosin significantly improved 6 outcomes. It reduced ureteral injury (RR 0.31; 95% CI: 0.20–0.49; $p < 0.00001$; $I^2 = 0\%$; Figure-2A) and shortened operative time by 14.17 minutes (95% CI: -19.37 to -8.97; $p < 0.000001$; $I^2 = 96\%$; Figure-2B).

The SFR showed no significant difference between the silodosin and control groups (RR 1.13; 95% CI 0.97 – 1.31; $p = 0.12$; $I^2 = 91\%$; Figure-2C). However, it is important to note that the timing and method of postoperative imaging to assess stone-free sta-

Figure 1 - PRISMA flow diagram of study screening and selection.



tus varied considerably across the included studies. Some trials performed evaluations as early as 1 week after surgery, whereas others waited up to 3 months. Additionally, the imaging modalities used were not standardized, further contributing to the observed heterogeneity. Despite these variations in follow-up protocols, the requirement for ureteral dilation was significantly lower in the silodosin group (RR 0.37; 95% CI 0.27 – 0.51; p < 0.00001; I^2 = 31%; Figure-2D), and silodosin-treated patients required less post-operative analgesia than controls (RR 0.46; 95% CI 0.25–0.82; p = 0.009; I^2 = 0%; Figure-S2) (see material supplementary).

Subgroup Analyses

Subgroup Analysis of RCTs

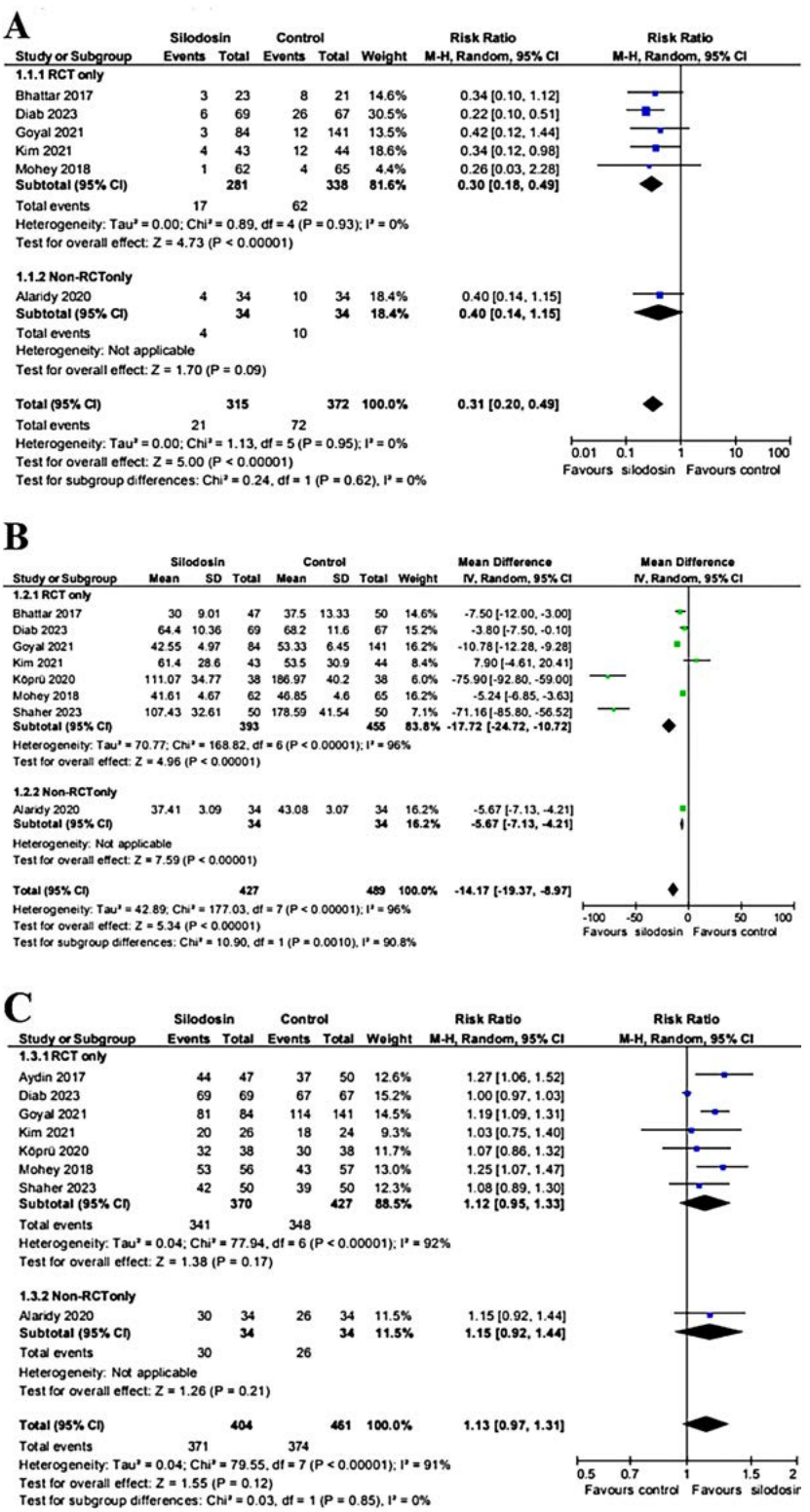
In the subgroup analyses limited to RCTs, the previously observed outcomes remained consistent in both direction and statistical significance. The incidence of ureteral wall injury (RR 0.30; 95% CI 0.18 - 0.49; p < 0.00001; I^2 = 0%; Figure-2A), reduction in operative time (MD -17.72; 95% CI -24.72 to -10.72; p < 0.00001; I^2 = 96%; Figure-2B), lower requirement for ureteral dilation (RR 0.31; 95% CI 0.23 - 0.43; p < 0.00001; I^2 = 0%; Figure-2D), reduced need for post-operative analgesia (RR 0.35; CI 0.16 - 0.75; p = 0.007; I^2 = 0%; Figure-S2) (see material supplementary), as

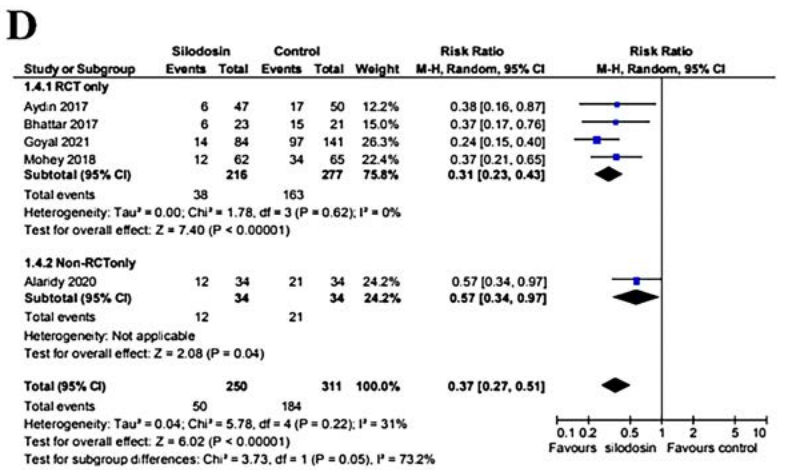
Table 1 - Baseline characteristics of the included studies.

Study, year	Study Design	Type of Control	Follow-up (months)	Time of therapy (dways)	Baseline Population Size, No. Silodosin Control	Age, years (mean ± SD) Silodosin Control	BMI, kg/mm² (mean ± SD) Silodosin Control	Male, No. (%) Silodosin Control	Stone size, mm (mean ± SD) Silodosin Control	Location of ureteral calculi (upper/middle/ lower) Silodosin Control
Alaridy et al., 2020 (2)	Non-RCT	Placebo	1	7	34 34	33.29 ± 9.51 34.60 ± 12.01	NA	25 (73.52) 25 (73.52)	10.35 ± 2.38 10.41 ± 2.43	3/6/25 3/6/25
Aydin et al., 2017 (11)	RCT	No pre-treatment	1	3	47 5	43.00 ± 14.29* 37.50 ± 12.50*	NA	32 (68.08) 33 (66.00)	NA	12/9/26 8/12/30
Bhattar et al., 2017 (12)	RCT	Placebo	NA	14	23 21	35.52 ± 11.00 33.22 ± 10.07	23.34 34.10	15 (65.21) 15 (71.42)	9.14 ± 1.52 9.74 ± 1.98	5/4/14 6/3/12
Diab et al., 2023 (1)	RCT	Placebo	3	7	69 67	41.40 ± 14.26 42.40 ± 15.44	26.90 ± 3.79, 27.30 ± 3.97	38 (46.37) 41 (61.19)	12.50 ± 3.91 13.00 ± 3.71	70/0/0 70/0/0
Goyal et al., 2021 (13)	RCT	Placebo	0.5	10	84 141	39.28 ± 8.25 38.22 ± 8.34	27.75 ± 2.22 27.46 ± 2.29	53 (63.19) 86 (60.99)	8.77 ± 4.12 8.53 ± 0.49	0/0/84 0/0/93
Kim et al., 2021 (14)	RCT	No pre-treatment	3	3	43 44	48.50 ± 11.60 45.80 ± 13.80	26.80± 4.90, 25.20 ± 3.30	29 (67.44) 23 (52.27)	8.86 ± 3.60 8.68 ± 5.07	50/0/0 50/0/0
Köprü et al., 2020 (15)	RCT	No pre-treatment	3	10	38 38	45.41 ± 12.88* 46.52 ± 14.52*	NA	30 (78.94) 23 (60.52)	19.02 ± 5.90 17.94 ± 4.60	2/8/6 2/6/7
Mohey et al., 2018 (16)	RCT	Placebo	1	10	62 65	38.27 ± 9.37 39.67 ± 9.54	27.55 ± 2.28 27.80 ± 3.50	39 (62.90) 39 (60.00)	12.60 ± 1.25 12.90 ± 1.29	0/0/62 0/0/65
Shaher et al., 2023 (17)	RCT	Placebo	1	10	50 50	44.65 ± 10.13 45.37 ± 12.78	26.12 ± 2.63 26.34 ± 2.74	37 (74.00) 30 (60.00)	18.33 ± 5.17 17.61 ± 4.25	11/0/0 8/0/0

BMI = Body Mass Index; RCT = Randomised controlled trial; NA = Not available
* Mean and standard deviation (SD) estimated from median and interquartile range or median and range

Figure 2 - Forest plots for pooled risk ratio and mean difference of significant ureteral wall injury (A), operative time (B), SFR (C), and ureteral dilation required (D).





well as fewer cases of postoperative fever (RR 0.49; 95% CI 0.27 - 0.88; p = 0.02; I^2 = 0%; Figure-S3A) (see material supplementary) and haematuria (RR 0.52; CI 0.28 - 0.98; p = 0.04; I^2 = 0%; Figure-S3B) (see material supplementary) all continued to favour the silodosin group. The SFR remained statistically similar between the silodosin and control groups (RR 1.12; 95% CI 0.95 - 1.33; p = 0.17; I^2 = 92%; Figure-2C). This consistency across RCTs strengthens the robustness of the findings and supports silodosin's effectiveness as a preoperative option for patients undergoing URS.

Subgroup Analysis Stratified by Duration of Preoperative Therapy (≥10 days vs <10 days)

In the subgroup analyses stratified into studies that conducted pre-URS therapy for ten days or more and those with therapy lasting fewer than ten days, the previously observed outcomes remained consistent in both direction and statistical significance (Figures S4, S5, and S6) (see material supplementary), except for the SFR outcome. A significant improvement in SFR was observed compared to the control in the subgroup receiving Silodosin for ≥ 10 days (RR 1.17, 95% CI: 1.10 – 1.26, p < 0.00001; I^2 = 0; Figure-S7) (see material supplementary). In contrast, the subgroup with therapy duration < 10 days showed no significant difference (RR 1.11, 95% CI: 0.82 – 1.49, p = 0.48; I^2 = 93; Figure-S5) (see material supplementary). Despite these findings, the test for subgroup differences revealed no statistically significant effect modification by therapy duration (p = 0.70).

Subgroup Analysis of Different Calculi Location

We performed a subgroup analysis stratifying data by stone location (distal ureteric stones, proximal ureteric stones, and studies including mixed locations) (Figures S8-S11) (see material supplementary).

The use of preoperative silodosin was associated with improved outcomes, particularly for distal ureteral calculi, whereas proximal stones generally showed non-significant results for several endpoints. This pattern was consistently observed across operative time, need for analgesia, and SFR.

Distal calculi treated with silodosin demonstrated a significant reduction in operative time (MD -8.02; 95% CI: –13.45 to –2.59; p = 0.004; I^2 = 96%; Figure-S8) (see material supplementary), whereas proximal calculi showed a non-significant reduction (MD -21.92; 95% CI: –59.09 to 15.26; I^2 = 98%; p = 0.25; Figure-S8). Silodosin significantly reduced the requirement for postoperative analgesia in distal stones (RR 0.31; 95% CI: 0.12–0.79; p = 0.01; Figure-S9) (see material supplementary), while no significant difference was observed for proximal (RR 0.45; 95% CI: 0.12–1.77; p = 0.25; I^2 = 0%; Figure-S9). Distal calculi exhibited a significant improvement in SFR with silodosin (RR 1.21; 95% CI: 1.12–1.31; p < 0.00001; I^2

= 0%; Figure-S11) (see material supplementary), as did mixed-location stones (RR 1.17; 95% CI: 1.04–1.32; p = 0.008; I^2 = 0%; Figure-S11). Proximal stones showed no significant effect (RR 1.02; 95% CI 0.90–1.16; p = 0.73; I^2 = 46%; Figure-S11).

Interestingly, silodosin significantly reduced wall injury rates for proximal calculi (RR 0.26; 95% CI: 0.14–0.50; p < 0.0001; I^2 = 0%; Figure-S8) and mixed-location stones (RR 0.37; 95% CI 0.17–0.82; p = 0.01; I^2 = 0%; Figure-S8), while a non-significant reduction was observed for distal stones (RR 0.37; 95% CI: 0.13–1.09; 0.07; I^2 = 0%; Figure-S8).

Due to a lack of events, no pooled effect could be estimated for proximal calculi on the outcome of need for ureteral dilation. However, distal (RR 0.29; 95% CI: 0.19–0.44; p < 0.0001; I^2 = 21%; Figure-S9) and mixed-location stones (RR 0.46; 95% CI 0.32–0.68; p < 0.0001; I^2 = 0%; Figure-S9) showed consistent significant reductions.

When stratified by stone location, no significant differences were observed for either fever or haematuria (Figure-S10) (see material supplementary). However, pooled analysis across all locations revealed a significant reduction in postoperative fever (p = 0.02) and haematuria (p = 0.02) with preoperative silodosin.

Sensitivity Analysis

We conducted leave-one-out sensitivity analyses to assess the robustness of our findings for outcomes with elevated heterogeneity. For ureteral wall injury, operative time, and ureteral dilation, the exclusion of individual studies did not impact the statistical significance or the I^2 statistics. This confirms the consistency of the results and indicates they are not disproportionately influenced by any single study. However, the SFR, excluding the study by Diab et al. (13), resulted in a substantial change in effect size, favouring the silodosin group with a RR of 1.18 (95% CI 1.11 - 1.25; p < 0.00001). Moreover, the I^2 statistic decreased dramatically from 91% to 0% upon the exclusion of this study. These findings highlight its significant impact on the overall results and suggest it was a major source of variability.

DISCUSSION

This systematic review and meta-analysis demonstrated that preoperative silodosin improves both the safety and efficiency of ureteroscopy (URS) for ureterolithiasis. Specifically, silodosin significantly reduced ureteral wall injury, operative time, ureteral dilation, need for analgesia, fever, and haematuria.

Moreover, these findings align with those of Bhojani et al. (18), who showed that alpha-blockers benefit URS outcomes. However, their study evaluated the drug class as a whole, whereas ours focused specifically on silodosin. Notably, silodosin has shown superiority over tamsulosin, likely due to its higher α1A receptor selectivity (3).

Ureteral wall injury, a key endpoint in six studies, can cause serious complications such as avulsion (19). In this context, our analysis demonstrated consistent reductions in injury rates across subgroups and in sensitivity analyses. In addition, the reduced operative time observed in the silodosin group may reflect its ability to relax ureteral smooth muscle, thereby easing scope passage and decreasing the need for mechanical dilation (20).

Consequently, shorter surgeries may also explain the lower incidence of postoperative fever, as reduced tissue manipulation and trauma likely diminish the risk of infection. By facilitating smoother endoscope advancement, silodosin minimizes ureteral irritation, which may translate to fewer postoperative complications.

Regarding treatment duration, it ranged from 3 to 14 days across the included studies. Although all durations demonstrated some benefit, longer silodosin treatment was associated with significantly higher SFR, supported by low heterogeneity (I^2 = 0%) and narrower confidence intervals. In contrast, the subgroup with <10 days of treatment showed no significant benefit and exhibited high heterogeneity. Although the difference between subgroups was not statistically significant, longer silodosin exposure may enhance ureteral relaxation and stone clearance, thus warranting further investigation.

Regarding stone location, preoperative silodosin significantly improved outcomes in ureteroscopy, particularly for distal ureteral stones, where reductions in operative time, analgesic requirement, and higher stone-free rates were observed. This is consistent with the known distribution of α1-adrenergic receptors, which are more densely expressed in the distal ureter (21). Proximal calculi did not show consistent benefits in efficiency but demonstrated a marked reduction in wall injury.

Furthermore, variability in surgical techniques, such as the use of rigid versus flexible ureteroscopes, access sheaths, and different laser technologies, may have influenced the observed outcomes. Institutional resources and surgeon experience likely contributed to these variations. Additionally, patient-related factors, including comorbidities and stone characteristics (size and location), may have added to the heterogeneity. While some studies focused on distal ureteral stones, where alpha-blockers are particularly effective (22, 23), others included stones at various ureteral locations. Regarding BMI, all included studies reported a mean BMI within the overweight range in both the silodosin and control groups. The only exception was one study (12), in which the mean BMI was in the normal range for the silodosin group, whereas the control group had a mean BMI in the class I obesity range. These discrepancies likely explain the heterogeneity in certain outcomes, despite subgroup and sensitivity analyses.

A key strength of this meta-analysis is its individualized assessment of each complication, thereby avoiding potential bias from composite outcome reporting. Indeed, grouping complications could lead to double-counting patients and obscure drug-specific effects. Our findings, therefore, support silodosin's favourable safety profile, showing reductions in complications and operative time. Although adverse events were not uniformly reported, existing data suggest that silodosin may be safer than other alpha-blockers such as tamsulosin (3, 24).

In conclusion, silodosin appears to be an effective and safe preoperative adjunct in URS. It reduces complications and operative time, with potential advantages for extended preoperative use. Nevertheless, heterogeneity across studies and inconsistent adverse event reporting underscore the need for standardized protocols and further high-quality trials to define its optimal clinical application.

Limitations

This meta-analysis provides Level 1 evidence supporting preoperative silodosin use before URS for ureterolithiasis. However, several limitations must be acknowledged.

First, the stone location varied considerably among patients, potentially influencing procedural difficulty and outcomes. Second, significant heterogeneity was noted in the assessment of SFR, including inconsistent definitions (e.g., residual fragments < 2 mm vs. 0 mm), different imaging modalities (CT, X-ray, or ultrasound), and varied follow-up timing (1 week to 3 months). These inconsistencies limit the comparability of SFR results.

Third, none of the RCTs accounted for spontaneous stone expulsion rates, which may have reduced the true effect size in patients who might not have required surgery. Fourth, essential procedural variables, such as stone location, surgical technique, stent placement, and duration, were not uniformly reported across studies, potentially confounding analyses of postoperative outcomes like pain and hematuria, which may often be attributed to ureteric stent use and may not significantly impact patient management or outcomes after ureteroscopy.

Lastly, stricture formation, a relevant long-term complication, was not addressed in any of the included studies. This omission restricts the evaluation of silodosin's potential long-term protective effects.

These limitations underscore the challenge of synthesizing data from heterogeneous trials and highlight the need for future research employing standardized protocols, uniform definitions, and comprehensive outcome reporting to better define silodosin's role in URS optimization.

CONCLUSIONS

In this meta-analysis, utilizing silodosin as a preoperative treatment in the URS approach for ure-

terolithiasis improves both the safety and efficiency of the procedure compared to no preoperative therapy. Future research should prioritize RCTs that incorporate stratification based on stone location while also focusing on standardizing the definition of SFR, ensuring proper follow-up, and optimizing preoperative silodosin treatment duration.

ABBREVIATIONS

BMI = Body Mass Index
CI = Confidence intervals
MD = Mean difference
PICOT = Population, intervention, comparison, outcome, and type of studies
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO = Prospective Register of Systematic Reviews
RCT = Randomized controlled trial
RoB 2 = Risk of Bias 2
ROBINS-I = Risk of Bias in Non-Randomized Studies of Interventions
RR = Risk ratio
SD = Standard deviation
SFR = Stone-free rate
URS = Ureteroscopy

Ethical approval

Ethical approval was not required for a meta-analysis of previously published studies.

Research involving human participants and/or animals

The study did not involve human participants and/or animals.

CONFLICT OF INTEREST

None declared.

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APPENDIX

SUPPLEMENTARY MATERIALS

Impact of Preoperative Silodosin on Ureteroscopy Outcomes for Ureterolithiasis: A Systematic Review and Meta-Analysis

SUPPLEMENTARY FIGURES

Figure S1 - Diagram of Risk of Bias assessment in randomised trials using the RoB 2 tool (A) and non-randomised trials using the ROBINS-I tool (B).

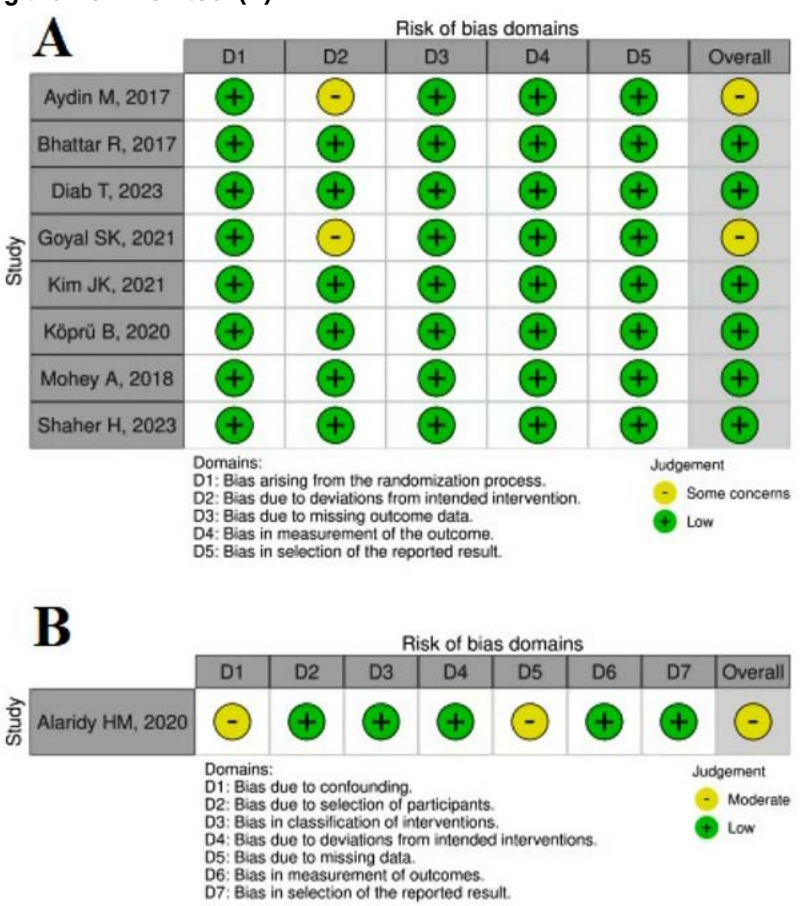


Figure S2 - Forrest plot: Need for analgesia.

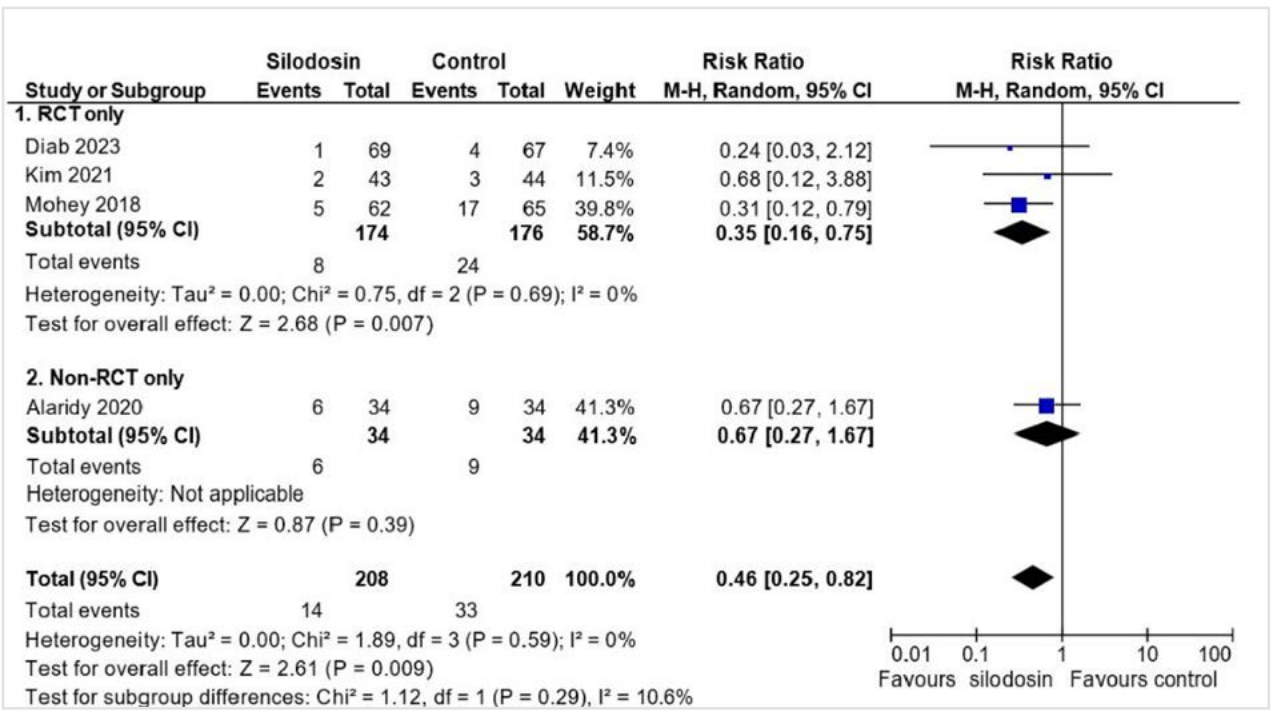
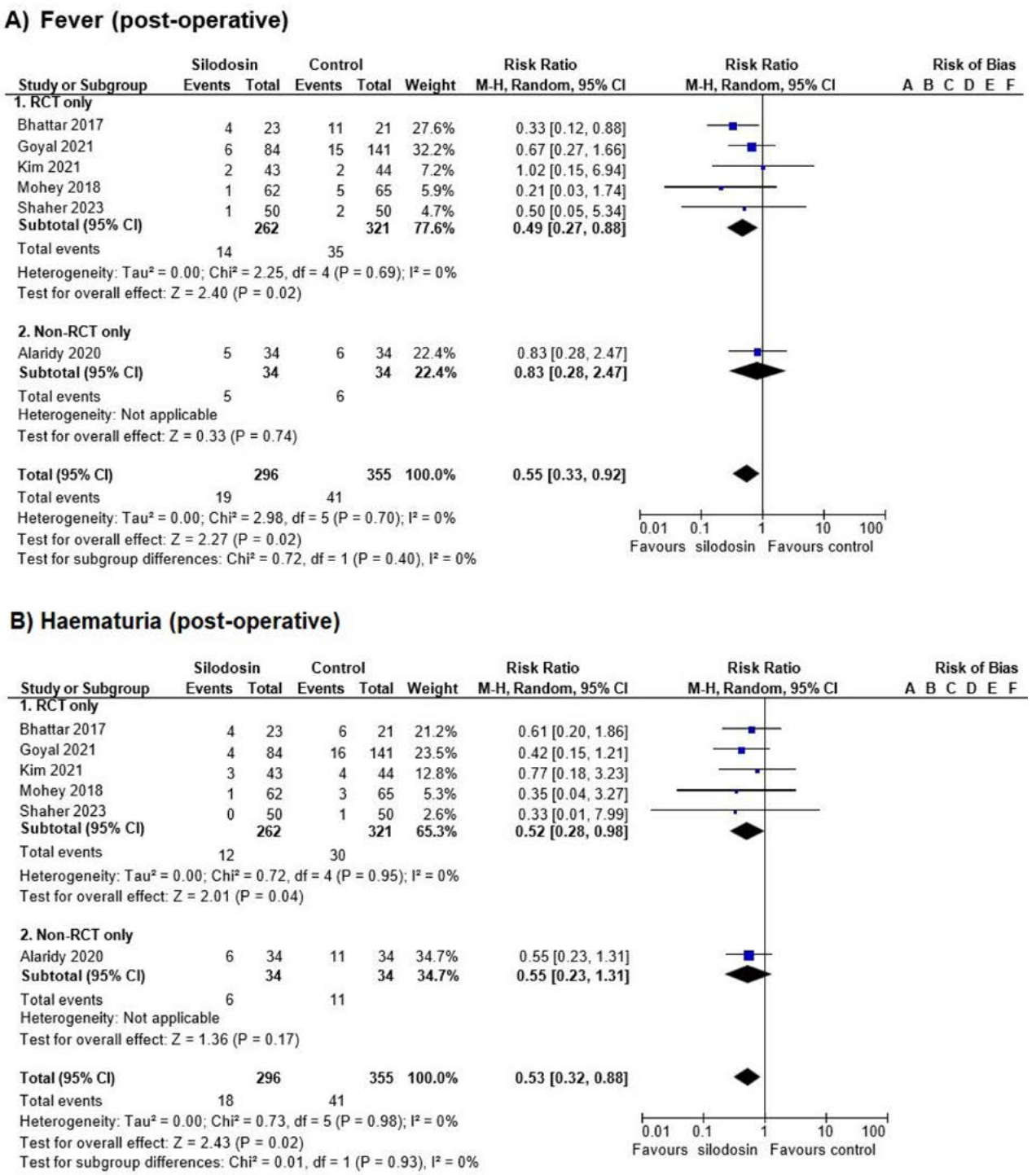
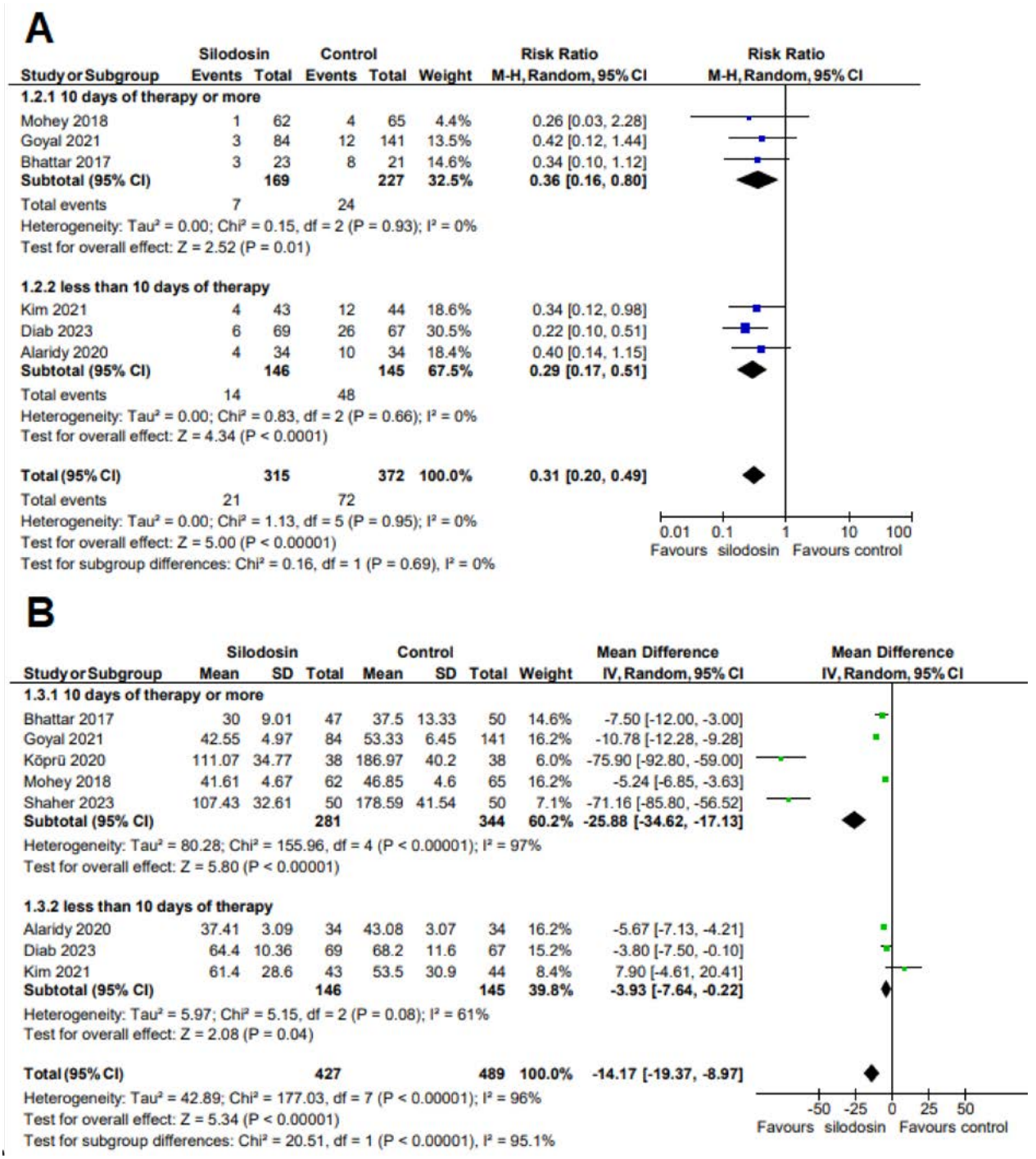


Figure S3 - Forrest plot: Post-operative fever (A) and hematuria (B).



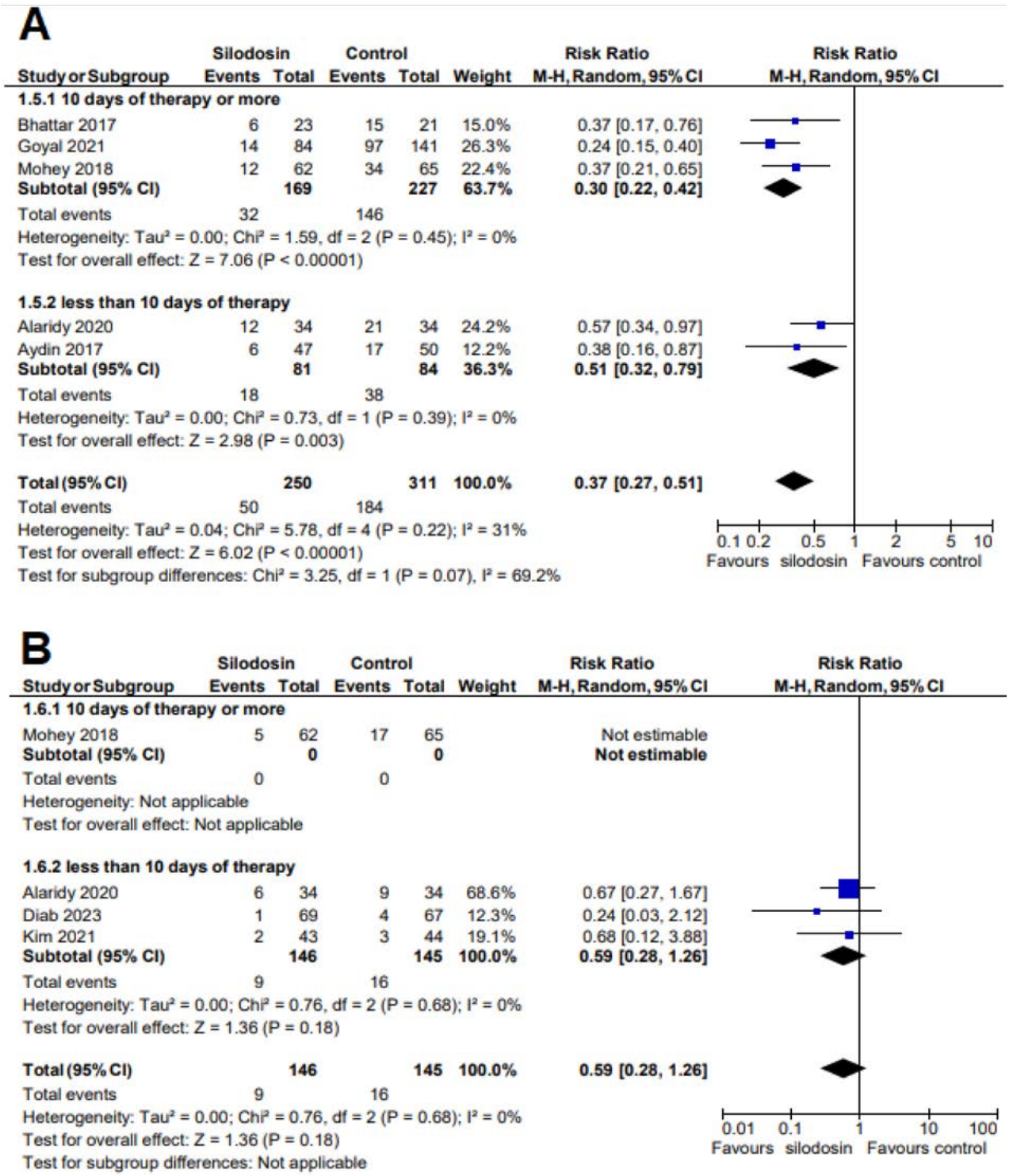
Subgroup Analyses - 10 days or more of silodosin preoperative therapy:

Figure S4 - Forrest plot: Ureteral wall injury (A) and Operative time (B).



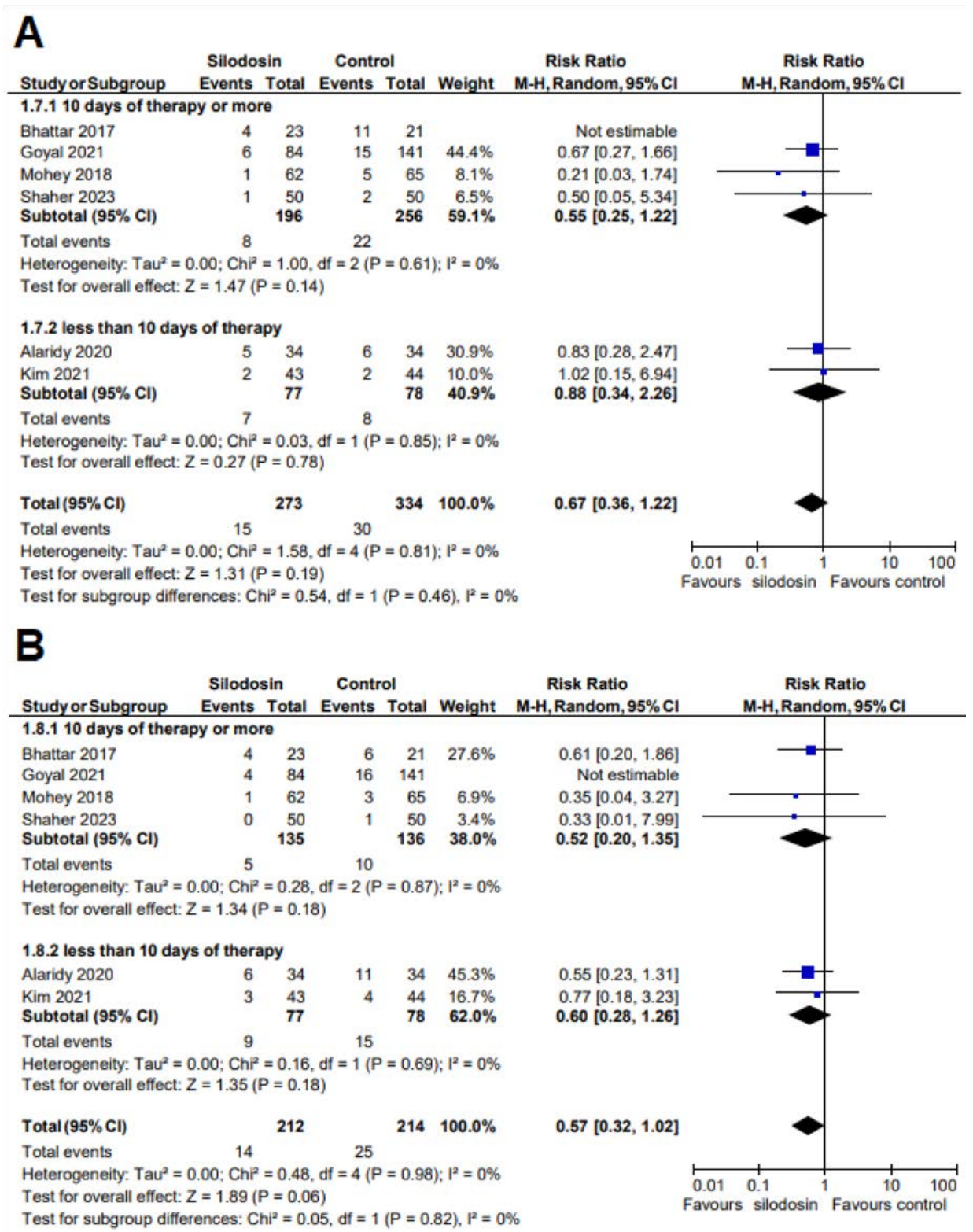
Subgroup Analyses - 10 days or more of silodosin preoperative therapy:

Figure S5 - Forrest plot: Need for ureteral dilation (A) and need for analgesia (B).



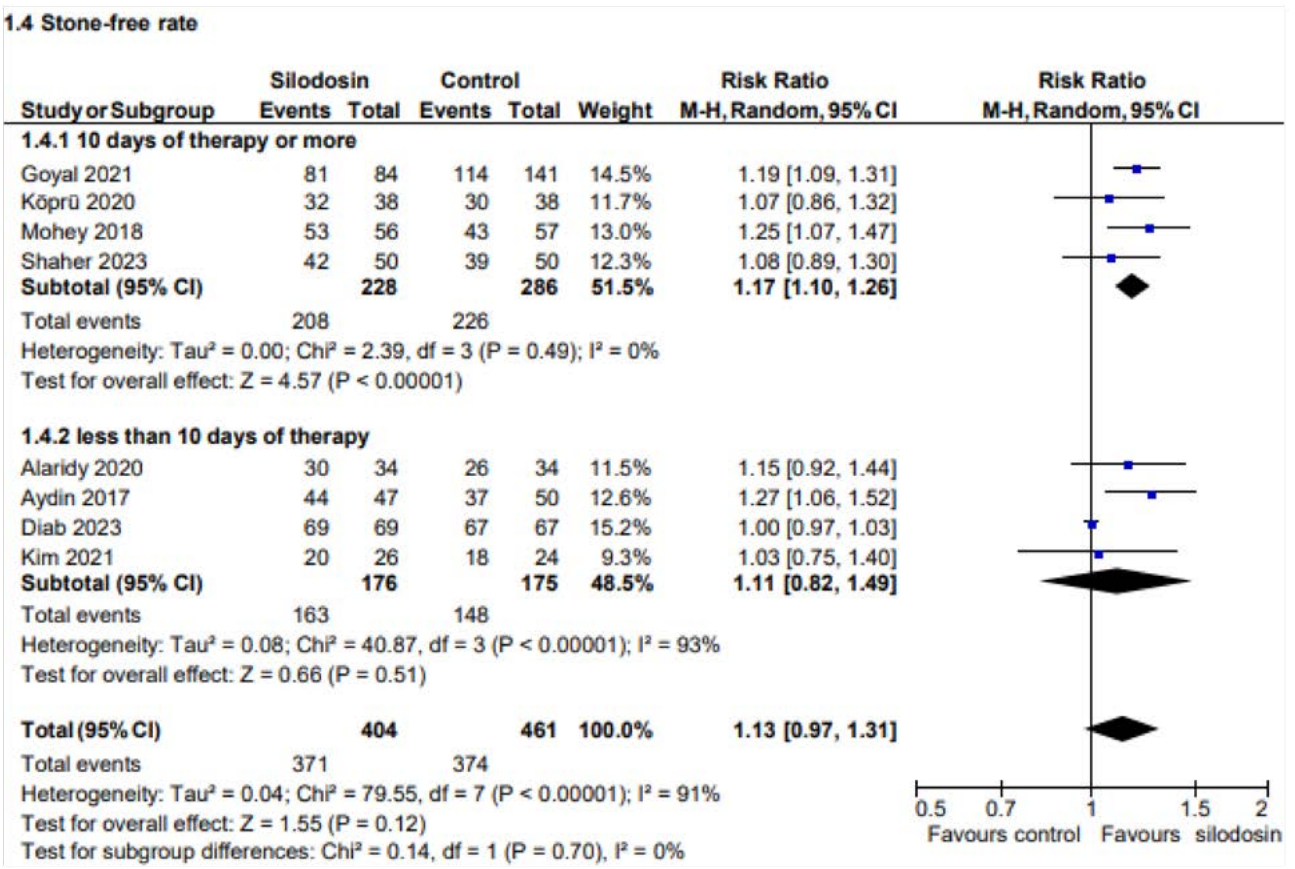
Subgroup Analyses - 10 days or more of silodosin preoperative therapy:

Figure S6 - Forrest plot: Post-operative fever (A) and haematuria (B).



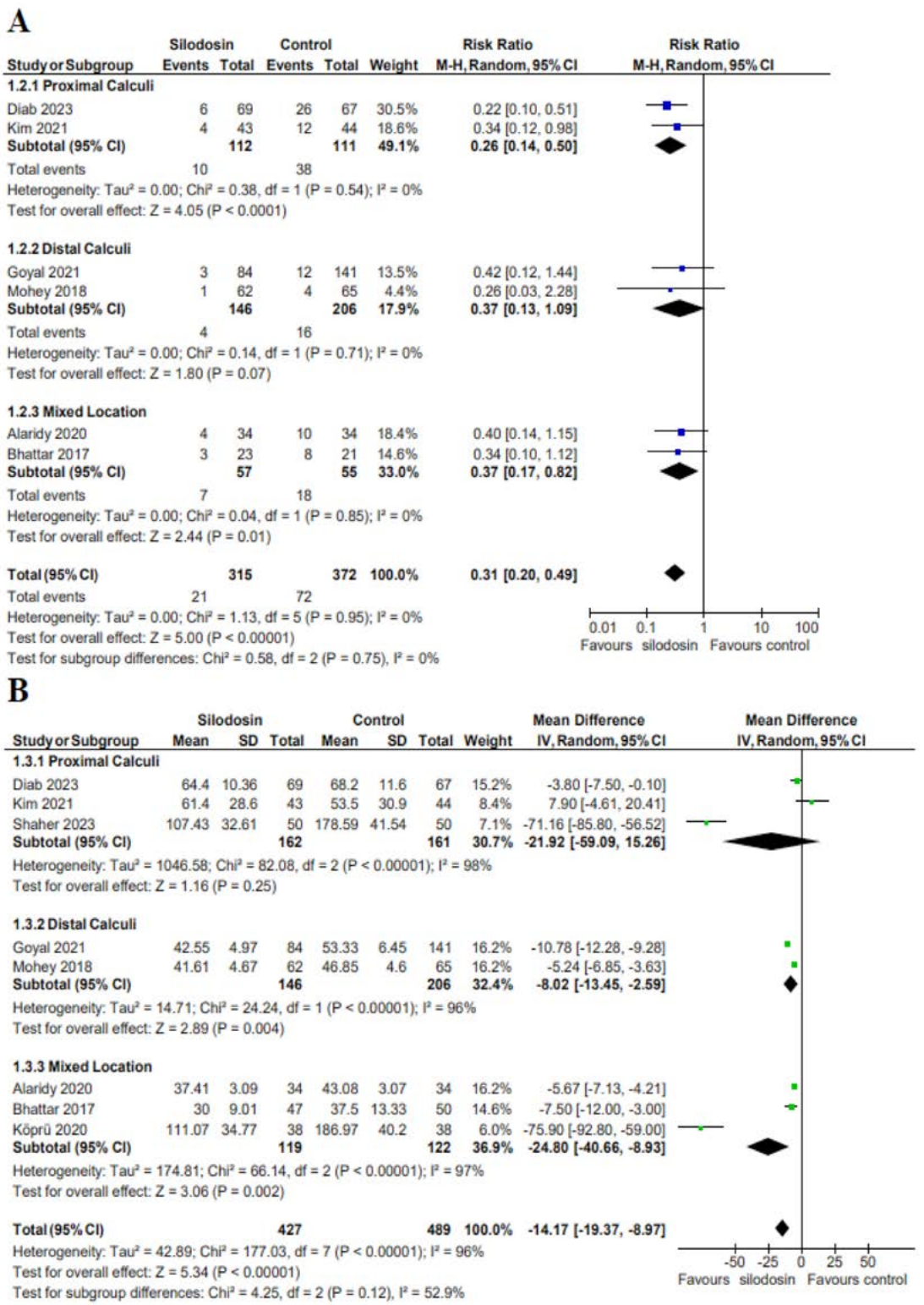
Subgroup Analyses - 10 days or more of silodosin preoperative therapy:

Figure S7 - Forrest plot: Stone-free rate.



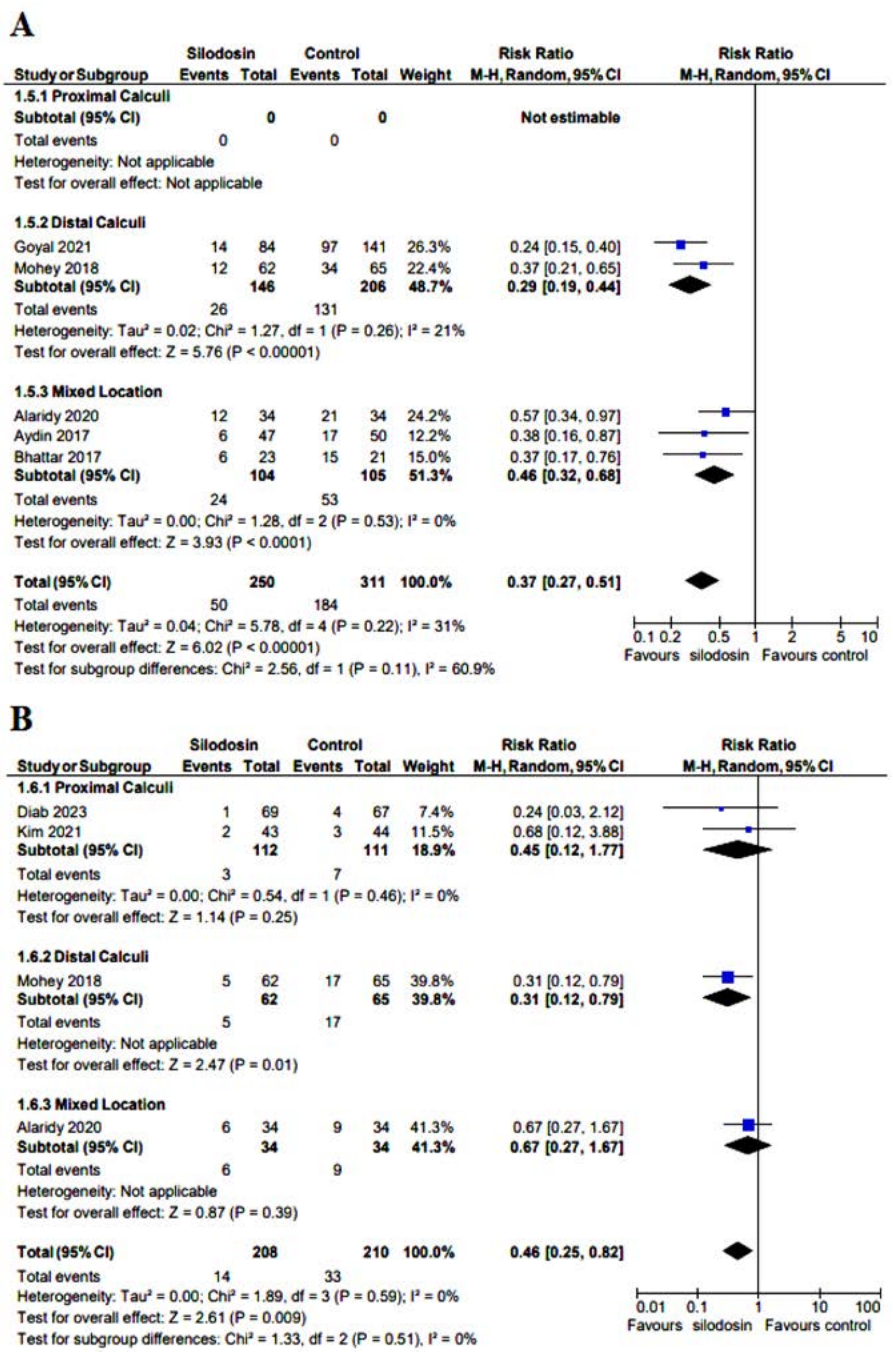
Subgroup Analyses - Different calculi location (proximal, distal, and mixed location):

Figure S8 - Forrest plot: Ureteral wall injury (A) and Operative time (B).



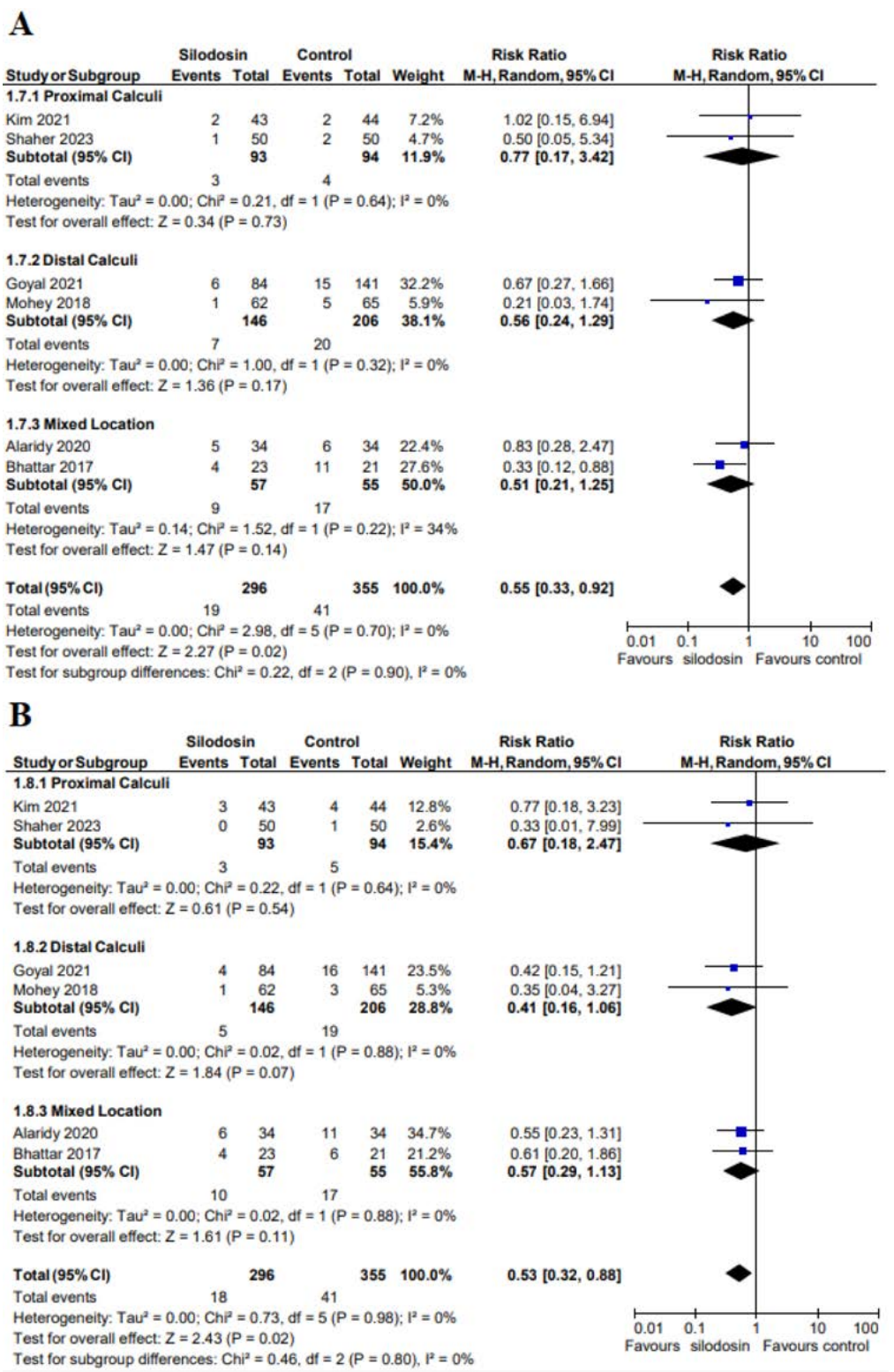
Subgroup Analyses - Different calculi location (proximal, distal, and mixed location):

Figure S9 - Forrest plot: Need for ureteral dilation (A) and need for analgesia (B).



Subgroup Analyses - Different calculi location (proximal, distal, and mixed location):

Figure S10 - Forrest plot: Post-operative fever (A) and haematuria (B).



Subgroup Analyses - Different calculi location (proximal, distal, and mixed location):

Figure S11 - Forrest plot: Stone-free rate.

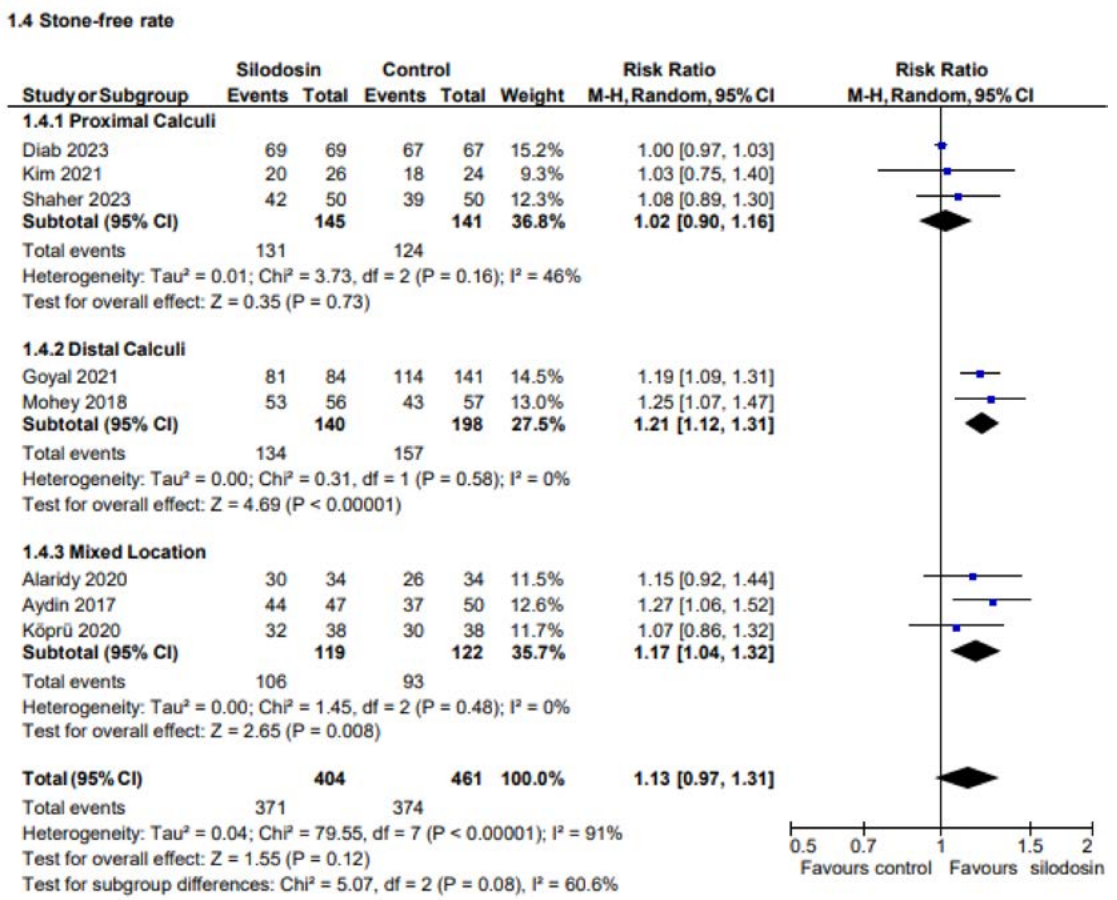


Figure S12 - PRISMA 2020 Checklist, Part 1.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, page 1.
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract, page 2.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction, paragraph 2.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, paragraph 3.
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods –Inclusion and Exclusion Criteria.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods - Search Strategy.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Material – Table S1.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods - Study Selection and Data Extraction.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods - Study Selection and Data Extraction.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods -Endpoints and Definitions
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Results – Table 1. Supplementary Material – Table S2, Table S3.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods - Quality Assessment.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods - Statistical Analysis.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods - Endpoints and Definitions.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods - Statistical Analysis; Results – Table 1.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods –

Figure S13 - PRISMA 2020 Checklist, Part 2.

Section and Topic	Item #	Checklist item	Location where item is reported
			Statistical Analysis.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods - Statistical Analysis.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods - Statistical Analysis.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods - Statistical Analysis.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods – Quality Assessment
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods - Statistical Analysis.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results – Figure 1.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results – Figure 1.
Study characteristics	17	Cite each included study and present its characteristics.	Results – Table 1.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Material – Figure S1.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results – Figure 2; Supplementary Material – Figure S2-S7.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results - Quality Assessment.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results – Figure 2; Supplementary Material – Figure S2-S7.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results -Endpoints Pooled analyses; Discussion, paragraph 6 and 7.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results - Sensitivity analyses.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results - Quality Assessment.
Certainty of	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results - Endpoints

Figure S14 - PRISMA 2020 Checklist, Part 3.

Section and Topic	Item #	Checklist item	Location where item is reported
evidence			Pooled analysis.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion, paragraph 2, 3, 4, 5, 7 and 8.
	23b	Discuss any limitations of the evidence included in the review.	Discussion – Limitation.
	23c	Discuss any limitations of the review processes used.	Discussion – Limitation.
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion, paragraph 1. Conclusion.
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods, paragraph 1.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods, paragraph 1.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Acknowledgements.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements.
Competing interests	26	Declare any competing interests of review authors.	Acknowledgements.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Table S1 - Detailed search strategy according to each database.

Database	Search strategy
PubMed/ MEDLINE	("ureteral stones" OR "ureteral calculi"[Mesh] OR "ureteral stone" OR "ureteral calculi" OR "ureterolithiasis" OR "ureteric stones" OR "ureteric calculi" OR "ureteric stone" OR "ureteric calculi" OR "ureteroscopy" OR "ureteroscopic" OR "ureterorenoscopy" OR "ureteral access") AND ("silodosin")
Embase	('ureteral stones' OR 'ureteral calculi' OR 'ureteral stone' OR 'ureteral calculi' OR 'ureterolithiasis' OR 'ureteric stones' OR 'ureteric calculi' OR 'ureteric stone' OR 'ureteric calculi' OR 'ureteroscopy' OR 'ureteroscopic' OR 'ureterorenoscopy' OR 'ureteral access') AND ('silodosin')
Cochrane	("ureteral stones" OR "ureteral calculi"[Mesh] OR "ureteral stone" OR "ureteral calculi" OR "ureterolithiasis" OR "ureteric stones" OR "ureteric calculi" OR "ureteric stone" OR "ureteric calculi" OR "ureteroscopy" OR "ureteroscopic" OR "ureterorenoscopy" OR "ureteral access") AND ("silodosin")

Table S2 - Extended baseline characteristics of the included studies.

Study, year	Study Design	Type of Control	Follow-up (months)	Time of therapy (days)	Baseline Population Size, No. Silodosin Control	Age, years (mean ± SD) Silodosin Control	Male, No. (%) Silodosin Control	BMI, kg/mm² (mean ± SD) Silodosin Control	Stone size, mm (mean ± SD) Silodosin Control	Location of ureteral calculi (upper/middle/lower) Silodosin Control	Stent Placement, No. (%) Silodosin Control	Type of procedure (both groups)	Ureteral access sheat (both groups)	Surgeon experience (both groups)	Anatomical abnormality (both groups)	History of ipsilateral ureteric surgery (both groups)	Infection (both groups)	Stone surface, mm² (median ± SD) Silodosin Control	Stone density, Hounsfeld unit (mean ± SD) Silodosin Control
Alaridy et al., 2020 (2)	Non-RCT	Placebo	1	7	34 34	33.29 ± 9.51 34.60 ± 12.01	25 (73.52) 25 73.52)	NA	10.35 ± 2.38 10.41 ± 2.43	3/6/25 3/6/25	NA	Semi-rigid	NA	Senior urologist	Excluded	Excluded	Excluded	NA	NA
Aydin et al., 2017 (11)	RCT	No pretreatment	1	3	47 5	43.00 ± 14.29* 37.50 ± 12.50*	32 (68.08) 33 (66.00)	NA	NA	12/9/26 8/12/30	NA	Semi-rigid	NA	NA	NA	Excluded	Excluded	38 (NA) 35.5 (NA)	NA
Bhattar et al., 2017 (12)	RCT	Placebo	NA	14	23 21	35.52 ± 11.00 33.22 ± 10.07	15 (65.21) 15 (71.42)	23.34 34.10	9.14 ± 1.52 9.74 ± 1.98	5/4/14 6/3/12	23 (100.00) 21 (100.00)	NA	NA	Senior urologist	Excluded	Excluded	Excluded	NA	NA
Diab et al., 2023 (1)	RCT	Placebo	3	7	69 67	41.40 ± 14.26 42.40 ± 15.44	38 (46.37) 41 (61.19)	26.90 ± 3.79, 27.30 ± 3.97	12.50 ± 3.91 13.00 ± 3.71	70/0/0 70/0/0	69 (100.00) 67 (100.00)	Flexible	Yes	Senior urologist	Excluded	Excluded	Excluded	NA	1022 ± 259.6 1008.7 ± 266.4
Goyal et al., 2021 (13)	RCT	Placebo	0.5	10	84 141	39.28 ± 8.25 38.22 ± 8.34	53 (63.19) 86 (60.99)	27.75 ± 2.22 27.46 ± 2.29	8.77 ± 4.12 8.53 ± 0.49	0/0/84 0/0/93	NA	Semi-rigid	NA	Senior urologist	Excluded	Excluded	NA	NA	NA
Kim et al., 2021 (14)	RCT	No pretreatment	3	3	43 44	48.50 ± 11.60, 45.80 ± 13.80	29 (67.44) 23 (52.27)	26.80± 4.90, 25.20 ± 3.30	8.86 ± 3.60 8.68 ± 5.07	50/0/0 50/0/0	43 (100.00) 44 (100.00)	Flexible	Yes	Senior urologist	Excluded	Excluded	NA	NA	589 ± 290 532 ± 325
Köprü et al., 2020 (15)	RCT	No pretreatment	3	10	38 38	45.41 ± 12.88*, 46.52 ± 14.52*	30 (78.94) 23 (60.52)	NA	19.02 ± 5.90 17.94 ± 4.60	2/8/6 2/6/7	21 (55.26) 23 (60.52)	Flexible	Yes	NA	NA	NA	NA	NA	NA
Mohey et al., 2018 (16)	RCT	Placebo	1	10	62 65	38.27 ± 9.37, 39.67 ± 9.54	39 (62.90) 39 (60.00)	27.55 ± 2.28 27.80 ± 3.50	12.60 ± 1.25 12.90 ± 1.29	0/0/62 0/0/65	62 (100.00) 65 (100.00)	Semi-rigid	NA	Senior urologist	Excluded	Excluded	NA	NA	907.66 ± 208.52 898.97 ± 212.04
Shaher et al., 2023 (17)	RCT	Placebo	1	10	50 50	44.65 ± 10.13 45.37 ± 12.78	37 (74.00) 30 (60.00)	26.12 ± 2.63 26.34 ± 2.74	18.33 ± 5.17 17.61 ± 4.25	11/0/0 8/0/0	26 (52.00) 30 (60.00)	Flexible	Yes	NA	Excluded	Excluded	NA	NA	837.64 ± 234.3 819.5 ± 240.1

BMI = Body Mass Index; RCT = Randomised controlled trial; NA = Not available

* Mean and standard deviation (SD) estimated from median and interquartile range or median and range

REVIEW ARTICLE

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Transperineal Laser Ablation for Treatment of Lower Urinary Tract Symptoms in Benign Prostate Enlargement: A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: This is a systematic review and meta-analysis of the outcomes of transperineal prostate laser ablation (TPLA) in men with benign prostatic enlargement.

Materials and Methods: Pubmed, Embase, Scopus, and Cochrane Library databases were searched from inception to July 2024. Random-effects model was employed to compute mean differences for continuous endpoints. Heterogeneity was evaluated by prediction interval and I-squared statistics. Results were reported following the PRISMA guidelines.

Results: Seventeen studies involving 777 patients with mean age of 62 to 80 years were included. Over 12-month follow-up, TPLA decreased the International Prostate Symptom Score (MD -12.62; 95% CI -14.87 to -10.37; p<0.001; I2 = 90%), post-void residual (MD –73.24 mL; 95% CI –96.91 to –49.57; p<0.001; I2 = 89%), and prostate volume (MD -21.23 mL; 95% CI -32.65 to -9.81; p<0.001; I2 = 84%). TPLA increased the maximum urinary flow rate (MD 6.32 mL/s; 95% CI 4.69 to 7.95; p<0.001; I2 = 81%). Ejaculatory and erectile functions were not impacted. Compared to TURP, TPLA was associated with ejaculatory function preservation, shorter operating time and length of stay. Risk of bias for the non-randomized studies was moderate, and low for the randomized studies.

Conclusions: TPLA demonstrated favorable outcomes for BPE without a negative impact on sexual function. This minimally invasive treatment was found to have advantages over TURP, such as, ejaculatory function preservation, reduced operative time, and shorter hospital stay. Evidence for this MIST is emerging but remains predominantly retrospective with short follow-up, highlighting the need for further comparative prospective studies.

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Data Availability
All data generated or analysed during this study are included in this published article

INTRODUCTION

Benign Prostatic Enlargement (BPE) frequently causes lower urinary tract symptoms (LUTS) in adult men, significantly affecting their quality of life (QoL) (1). If untreated, BPE can lead to serious complications such as acute urinary retention, hydronephrosis, and acute kidney injury (2).

International guidelines recommend lifestyle changes and pharmacological therapies as initial management for male LUTS (3). Surgical options may be indicated when pharmacotherapy fails or is not tolerated (4). However, these treatments often impact sexual function, particularly ejaculatory function, leading to poor adherence or discontinuation, mostly in young patients who want to preserve antegrade ejaculation (5). Therefore, improvements in minimally invasive and endoscopic methods for BPE have expanded therapeutic options, to minimize side effects and increase treatment efficacy (6).

Endoscopic laser treatments have made significant advances, proving to be effective, but still with significant adverse events and complications, such as retrograde ejaculation (7). Minimally invasive surgical therapies (MISTs) offer faster recovery and effective relief from LUTS with minimal side effects (8). Nevertheless, these newer methods generally have inferior functional results compared to traditional transurethral treatments (9).

In this context, transperineal laser ablation of the prostate (TPLA) has emerged as an alternative option that could maintain ejaculatory function in patients with BPE (10). Recent studies indicate promising perioperative and functional outcomes with TPLA in carefully selected patients with BPE/LUTS (11). This systematic review and meta-analysis aim to assess TPLA efficacy in treating BPE/LUTS and its influence on sexual function.

MATERIALS AND METHODS

Study Design

This systematic review and meta-analysis follow the Cochrane Collaboration recommendations and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guideline (Table-S1) (12). The study protocol was registered on June 21st, 2024, in the PROSPERO database, under the identification number CRD42024556034.

Eligibility Criteria

Inclusion in this meta-analysis was restricted to studies that met the following eligibility criteria: (1) randomized controlled trials (RCTs) or nonrandomized cohorts; (2) transperineal laser ablation of the prostate in treating LUTS decurrent from BPE; and (3) enrollment of male patients older than 18 years with BPE. Additionally, studies were only included if they reported any clinical outcomes of interest, including primary outcome measures related to LUTS relief and side effects. Exclusion criteria were applied to studies with (1) potential overlapping populations; (2) unavailable full text; and (3) publications in non-English languages.

Search Strategy and Data Extraction

Two authors (I.Z. and M.P.) independently conducted searches on PubMed, Embase, and Cochrane Central Register of Controlled Trials from inception to June 2024, using specific search terms: 'benign prostatic enlargement', 'BPE', 'lower urinary tract symptoms', 'LUTS', 'transperineal laser ablation', and 'TPLA'. The complete and detailed search strategy is available in supplementary materials. Reference lists from all included studies were also manually searched for additional studies. Titles and abstracts of all electronic records were screened for potential eligibility. Subsequently, the articles regarded as eligible were retrieved as full texts. Then, any studies that did not report the outcomes of interest or fulfilled inclusion criteria were excluded. Three authors (I.Z., M.P., and M.G) independently extracted data following predefined search criteria and quality assessment. Disagreements were resolved through discussion with a fourth author (R.S.) and, when necessary, by consultation with the senior author (M.A.A).

Endpoints

Primary endpoints consisted of the International Prostatic Symptoms Score (IPSS) and objective parameters, such as the maximum urinary flow rate (Qmax), prostate volume (PV), and post-void residual (PVR). Secondary endpoints included ejaculatory and erectile function, evaluated by the Male Sexual Health Questionnaire - Ejaculatory Dysfunction (MSHQ-EjD) and the International Index of Erectile Function (IIEF-5); surgical aspects, comprised by operating time and length of stay; and quality of life reported by the IPSS Q8.

Quality Assessment

Randomized and nonrandomized studies were evaluated using the Cochrane Collaboration's risk-of-bias tools: RoB-2 (13) and ROBINS-I (14), respectively. Two independent authors (T.M. and M.G.) adhered to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) handbook guidelines to assess the evidence's certainty level, utilizing categorizations ranging from high to very low (15). Publication bias was investigated by funnel-plot analysis of point estimates according to study weights (16).

Statistical Analysis

Data was synthesized using a random effects meta-analysis through a restricted maximum likelihood estimator. The random effects model was employed to account for potential clinical, methodological, and statistical heterogeneity since no assumption can be made that there would be no heterogeneity and that the intervention's true effect will be the same in the included studies (16, 17). Continuous endpoints were summarized using mean difference (MD). Additionally, a subgroup analysis was performed to compare outcomes between TPLA and TURP, the conventional standard therapy, from available randomized trials. Statistical significance was established by a 95% confidence interval (CI) and a p-value under 0.05. Evidence of heterogeneity was assessed with the Chi2 test, Tau and Tau2. To avoid misleading interpretation with a pre-determined threshold for I2 statistics, the extent of heterogeneity was evaluated by associating it with the prediction interval (PI) (18, 19). Additionally, a "leave-one-out" sensitivity analysis was performed to identify potential sources of heterogeneity. All statistical analyses were performed in R software version 4.4.1 (R Foundation for Statistical Computing) (20).

For outcome data presented in medians and interquartile ranges (IQRs), we used the most recent calculator to convert them into means and standard deviations (21). Additionally, for the study by Chen et al. (22), which reported outcomes using change scores rather than direct means and SDs, we employed an additional specialized calculator to facilitate the conversion, available at https://www.statstodo.com/CombineMeansSDs.php.

RESULTS

Study Selection and Baseline Characteristics

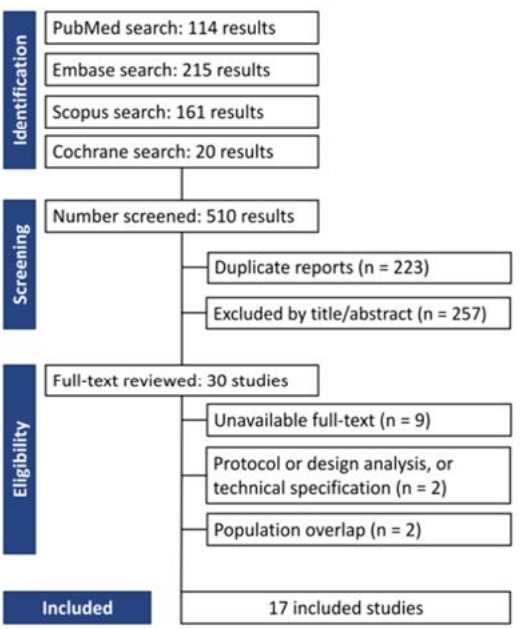
As reported in Figure-1, the initial search yielded 510 results. After excluding 223 duplicates, 257 articles were excluded based on title and abstract review. Subsequently, 30 articles were fully evaluated. In this comprehensive analysis, 9 articles were excluded due to full-text unavailability, 2 for protocol or design analysis and technical specification, and the last 2 excluded had overlapping populations. In this case, we selected the studies with the larger number of participants or the number of reported outcomes. Finally, 17 studies with 777 patients with BPE were included (22-38). These comprised 3 RCTs and 14 cohort studies, published from 2017 to 2024.

The baseline characteristics of the included studies are shown in Table-1.

Operative and Perioperative Aspects

All the patients were placed in lithotomy position. An 18Fr three-way vesical catheter was placed and continuous saline irrigation for urethral cooling was applied. The procedure was performed under transrectal ultrasound (TRUS) guidance. The use of a multi-channel needle applicator with a dedicated

Figure 1. PRISMA flow diagram of study screening and selection. Flow diagram illustrating the process of literature identification, screening, eligibility assessment, and inclusion. Of 510 records initially retrieved, 17 studies met the inclusion criteria and were analyzed in the meta-analysis.



Abbreviations: PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

software display grid overlapping the ultrasound images could also aid the procedure (23, 37). Local anesthesia was administered in 16 studies (22, 24-38), with concurrent conscious sedation or optimal sedation used in 13 studies (25-30, 32-38). One study performed standard spinal anesthesia (23).

TPLA was performed using EchoLaser (SoracteLite) and Asclepion. The diode laser generator with four independent channels, provided by Elesta, was employed for all procedures, except Chen et al. 2023 (22), where Asclepion Laser Technologies was provided. A 21G trocar needle was used to accommodate the 300-μm flat-tip optical fiber and a continuous mode with a wavelength of 1064 nm was employed. Lo Re, Sessa, De Rienzo, and Manenti (30, 31, 37, 38) initially set the power at a higher level (5 W, 4.5 W, and 5 W, respectively) and then reduced it after 1-2 minutes, while others used a fixed power setting of 3 W. The power deployed by Chen varied from 3 to 5 W (22).

The energy setting for the single fiber was 1800 J, except for Patelli and Sessa (34, 38), who reported settings ranging from 1200 to 1800 J. Up to three fibers per lobe were used with simultaneous laser emission, depending on prostate volume and surgeon preference. A second ablation cycle, called pull-back, was executed in larger prostates. This involved retracting the fiber 10 mm along its trajectory to deliver an additional 1200–1800J (22, 24, 26-29, 31-35, 37, 38).

Ten studies used antibiotic prophylaxis (26-29, 31, 33-35, 37, 38). At the end of the treatment, four studies utilized dexamethasone to reduce edema and inflammatory reactions, (6, 25, 27, 33) while two studies prescribed prednisone (31, 37). Chen et al. and Sessa et al. applied one dose of dexamethasone and methylprednisolone intravenously after treatment, respectively (22, 38). The mean procedural time ranged from 16 to 60.9 minutes (24, 25). Additionally, the mean length of stay ranged from 1.5 hours to 2.5

days (22, 24), while the catheterization period ranged from 4 to 22.8 days (23, 35).

Table-S2 summarizes the technical parameters of all selected studies.

Inclusion and Exclusion Criteria of the Included Studies

The inclusion and exclusion criteria differed between the studies. Eligible studies normally included patients over 18 years old with a PV ranging from 30 to 100 mL, measured by TRUS or magnetic resonance imaging (MRI), who were candidates for treatment with TPLA. The usual inclusion criteria also involved LUTS with an IPSS of 8 or more, a Qmax of 15 mL/s or less, or a PVR of 50 to 400 mL.

Ten studies reported the pharmacological treatments used for BPE (23, 26-31, 35, 37, 38). One study (31) focused exclusively on patients using combination therapy, while another did not describe the pharmacological treatment (35).

Common exclusion criteria included previous procedures on the urethra or prostate, prostate-specific agent levels higher than 4 ng/mL or suspected prostate cancer, a history of urethral stricture, neurological diseases, allergies to ultrasound contrast, underactive detrusor, bladder cancer, anterior prostatic abscess, acute or chronic prostatitis, active urinary tract infection, gland volume greater than 100 mL, bladder stones and active hematuria. Table-S3 provides a detailed list of these conditions. Some studies did not contraindicate the treatment for patients with a median lobe / intravesical prostatic protrusion (IPP) (27, 28, 33, 34, 37) or taking anticoagulants or antiplatelet agents (23, 25-27, 30, 33, 36-38). However, Minafra et al. (32) reported that a predictive factor for treatment failure in their cohort was the presence of the median lobe/IPP.

Functional Outcomes by Follow-up Time

In our pooled analysis, improvement in Qmax was observed after three months of treatment (MD 3.42 mL/s; 95% CI 2.44 to 4.40; p<0.001; I2 = 31%. Figure-2). Within six and twelve months, Qmax increased progressively (MD 5.02 mL/s; 95% CI: 3.80 to 6.24; p<0.001; I2 = 72%, and MD 6.32 mL/s; 95% CI 4.69 to 7.95; p<0.001; I2 = 81%. Figure-2). TPLA was associated with a significant decrease in IPSS as of one-month follow-up (1 month: MD –4.48; 95% CI –6.92 to –2.03; p<0.001; I2 = 41%. 3 months: MD –11.11; 95% CI –12.72 to –9.51; p<0.001; I2 = 66%. 6 months: MD –12.46; 95% CI –14.25 to –10.66; p<0.001; I2 = 82%; 12 months: MD –12.62; 95% CI –14.87 to –10.37; p<0.001; I2 = 90%. Figure-3; Figure S13 and S14). Reduction in prostate volume was observed within twelve months (MD –21.23 cm^3; 95% CI –32.65 to –9.81; p<0.001; I2 = 84%. Figure-S1). PVR also decreased over twelve months (3 months: MD –46.09 mL; 95% CI –65.66 to –26.51; p < 0.001; I2 = 62%. 6 months: MD –48.30 mL; 95% CI –60.53 to –36.07; p < 0.001; I2 = 57%. 12 months: MD –73.24 mL; 95% CI –96.91 to –49.57; p<0.001; I2 = 89%. Figure-S2). However, in the first month after the surgery, it had no statistically significant change (MD –28.78 mL; 95% CI –57.91 to 0.35; p = 0.053; I2 = 55%. Figure-S2). TPLA was associated with better quality of life by decreasing the IPSS Q8 score in six, twelve, and thirty-six months (MD –2.60; 95% CI –2.99 to –2.22; p < 0.001; I2 = 70%. MD –3.07; 95% CI –3.51 to –2.62; p < 0.001; I2 = 89%. MD -3.19; 95% CI -4.06 to -2.32; p < 0.001; I2 = 83%. Figure-S3).

Sexual Function by Follow-up Time

Eight studies analyzed ejaculatory dysfunction by MSHQ-EjD. At one-month follow-up, there was no statistically significant change (MD 1.91; 95% CI –0.29 to 4.10; p = 0.089; I2 = 62%. Figure-S4). After three and six months, there was a significant improvement in ejaculatory function (MD 2.01; 95% CI 0.71 to 3.31; p = 0.002; I2 = 32%, and MD 3.28; 95% CI 1.93 to 4.6; p < 0.001; I2 = 0%. Figure-S4). After twelve months, the ejaculatory function remained stable compared to baseline (MD 1.64; 95% CI –0.47 to 3.75; p = 0.127; I2 = 85%. Figure-S4). The IIEF-5 was performed in nine studies to evaluate erectile function. There was no significant statistical alteration in erectile function after the surgery during twelve months (MD 0.54; 95% CI –0.62 to 1.69; p = 0.363; I2 = 0%. Fugire-S5).

Comparative Analysis Studies (TPLA x TURP)

In our subgroup analysis of RCTs comparing TPLA against TURP, there was no significant difference in the treatment of LUTS, as assessed by the IPSS (MD 1.81; 95% CI –2.14 to 5.76; p = 0.369; I2 = 84%. Figure-4A). Additionally, TPLA was demonstrated to be more effective in preserving ejaculatory

Table 1. Baseline characteristics of the included studies. Summary of patient demographics, prostate volume, baseline functional parameters, and sexual function indices prior to intervention. Data are presented as mean ± standard deviation (SD) or median (interquartile range, IQR).

Study author/year	Time	N	Age [1] (years)	BMI [1] (kg/m²)	PV [1] (mL) (%)*	PSA [1] (ng/mL)	Qmax [1] (mL/min)	PVR [1] (mL)	IPSS [1]	IIEF-5 [1]	MSHQ-EjD3 [1]	IPSS-Q8 [1]
Bertolo, 2023	Baseline	51 (TPLA 26 / TURP 25)	63 (57–70.5)	NA	TPLA 49 (37–65) / TURP 55 (25–88)	TPLA 3.0 (1.1–4.0) / TURP 2.0 (1.2–2.2)	TPLA 10.2 (8.7–12.0) / TURP 10.0 (6.5–11.6)	TPLA 70 (20–100) / TURP 30 (20–70)	TPLA 24.0 (16.0–29.0) / TURP 20 (18.5–24.0)	TPLA 17.0 (15.0–21.0) / TURP 20.0 (16.0–20.5)	TPLA 29.0 (25.0–30.0) / TURP 29.0 (25.5–30.5)	TPLA 5 (3–5) / TURP 4 (3–5)
	1 month	NA	NA	NA	NA	NA	NA	NA	NA	18 (14–23) / 19 (18–23)	29.0 (25.0–30.0) / 20.0 (10.0–25.0)	NA
	6 months	NA	NA	NA	NA	NA	15.2 (13.5–18.3) / 26.0 (22.0–48.0)	0 (0–5) / 0 (0–20)	11 (8–15) / 8 (3–9)	NA	NA	2 (2–4) / 2 (1–2)
Cai, 2021	Baseline	20	73.9 ± 9.2	NA	70.8 ± 23.8	NA	8.5 ± 3.0	78.7 ± 58.8	22.7 ± 5.3	NA	NA	4.9 ± 1.7
	6 months	NA	NA	NA	54.7 ± 20.9	NA	15.2 ± 4.8	30.3 ± 34.2	9.1 ± 3.2	NA	NA	2.3 ± 1.3
Canat, 2023	Baseline	50 (TPLA 25 / TURP 25)	65.58 ± 6.59	TPLA 27.85 ± 2.12 / TURP 27.93 ± 2.27	TPLA 66.77 ± 25.28 / TURP 63.63 ± 21.10	TPLA 4.79 ± 4.63 / TURP 3.71 ± 3.26	TPLA 8.73 ± 3.77 / TURP 8.32 ± 3.54	TPLA 125 ± 68.50 / TURP 139.4 ± 58.73	TPLA 20.14 ± 6.02 / TURP 21.17 ± 4.33	TPLA 14.84 ± 3.93 / TURP 14.17 ± 4.09	TPLA 10.75 ± 2.42 / TURP 11.07 ± 1.87	TPLA 4.75 ± 0.75 / TURP 4.69 ± 0.75
	12 months	NA	NA	NA	TPLA 47.32 ± 13.59 / TURP NA	NA	TPLA 14.26 ± 3.73 / TURP 21.37 ± 6.04	TPLA 46.88 ± 32.40 / TURP 49.13 ± 31.54	TPLA 10.14 ± 3.21 / TURP 10.95 ± 4.33	TPLA 14.68 ± 3.92 / TURP 13.44 ± 4.53	TPLA 10.33 ± 2.31 / TURP 5.93±4.01	TPLA 1.50 ± 0.90 / TURP 1.31 ± 0.75
Chen, 2023	Baseline	51 (TPLA 25 / TURP 26)	69.27 ± 9.67	TPLA 24.38 ± 2.91 / TURP 23.18 ± 2.66	TPLA 60.48 ± 21.1 / TURP 65.19 ± 21.1	TPLA 3.63 ± 1.73 / TURP 3.32 ± 1.84	TPLA 77.14 ± 6.11 / TURP 75 ± 6.27	TPLA 92.5 ± 73,282.5 / TURP 104 ± 62,104	TPLA 23.14 ± 5.38 / TURP 21.40 ± 4.15	TPLA 9.86 ± 4.31 / TURP 10.12 ± 4.28	6.09 ± 3.84 / 6.41 ± 2.28	4.57 ± 0.65 / 4.25 ± 0.58
	3 months[2]				TPLA 73.27 ± 12.94* / TURP 68.59 ± 19.38*	TPLA 0.55 ± 2.02 / TURP -1.56 ± 0.63	TPLA 5.28 ± 4.24 / TURP 16.33 ± 9.82	TPLA -39 (-97,-35) / TURP -85 (-140,-25)	TPLA -14.17 ± 6.13 / TURP -13.19±5.86	TPLA -0.27 ± 1.56 / TURP 0.06 ± 0.93	TPLA 0.49 ± 1.08 / TURP -1.52 ± 0.67	TPLA -2.33 ± 0.89 / TURP -2.5 ± 0.97
Destefanis, 2023	Baseline	40	80 (72.5–84)	24 (22–27)	38 (30.5–73)	2.2 (0.8–3.8)	8 (5.5–10)	38 (30.5–73) cc	25 (19–30)	NA	NA	6 (5–6)
	3 months	NA	NA	NA	35 (26–49)	2.3 (1.7–2.7)	12.5 (9.5–14)	30 (0–60)	10.5 (7.5–13)	NA	NA	3 (0–4)
	6 months	NA	NA	NA	34 (28–49)	1.8 (0.9–8)	12 (10–13)	30 (0–60)	8 (6–11.5)	NA	NA	2 (0–4)
Frego, 2021	Baseline	22	61.9 (55–65.5)	27.16 (24.8–28.6)	65 (46.5–81)	2.24 (1.4–4.5)	9 (5–12.5)	60 (25–107.5)	22 (19.5–25.25)	NA	NA	4 (4–5)
	3 months	NA	NA	NA	46(28.4–69)	NA	12 (9–16.5)	39 (10–87.5)	8 (4.5–11)	22 (19.5–24)	NA	1 (0.5–2)
	6 months	NA	NA	NA	42.3 (39.5–59	NA	15 (11.5–20.5	40(16–63)	5(3–8.5)	23 (20.5–24)	NA	1(0–2)
	12 months	NA	NA	NA	41.5 (36.25–55)	NA	20.5 (14.25–23.75)	30 (5–50)	6(4.25–7)	21.5 (17.25–23.75)	NA	1 (1–2)
Kollenburg, 2024	Baseline	20	70.3 ± 7.3	NA	65.5 ± 23.0	5.0 ± 3.3	9.7 ± 3.5	61.8 ± 58.3	21.3 ± 5.2	35.4 ± 23.6	NA	4.9 ± 0.9
Frego, 2021	3 months	NA	NA	NA	NA	NA	12.8 ± 6.1	64.8 ± 70.4	12.8 ± 6.0	36.9 ± 24.8	NA	2.6 ± 1.7
Kollenburg, 2024	6 months	NA	NA	NA	NA	NA	12.1 ± 6.1	74.2 ± 87.4	11.7 ± 5.2	40.5 ± 23.3	NA	1.8 ± 1.0
Lagana, 2023	12 months	NA	NA	NA	63.2 ± 20.6	NA	14.9 ± 6.0	44.2 ± 55.8	10.9 ± 5.5	31.1 ± 24.4	NA	1.9 ± 1.1

Laganà 2023	Baseline	63	72.3 ± 10	30.2 ± 7.1	63.6 ± 29.7	4.82 ± 1.8	8.6 ± 3.5	124.8 ± 115.4	20.8 ± 7.4	NA	NA	4.7 ± 1.4
Manenti, 2021	3 months	NA	NA	NA	45.6 ± 21.8	NA	NA	43.6 ± 53.6	11.0 ± 6.6	NA	NA	1.5 ± 1.2
Pacella, 2019	12 months	NA	NA	NA	NA	2.89 ± 1.2	16.2 ± 4.3	40.6 ± 53.6	8.4 ± 5.9	NA	NA	1.2 ± 0.8
Lo Re, 2024	Baseline	100	66.5 (60–75)	25.9 (23.5–27.6)	50 (40–70)	NA	9.1 (6.9–12)	90 (50–150)	18 (15–23)	NA	6 (2–11)	4 (3–4)
Patelli, 2024	3 months	NA	NA	NA	NA	NA	11 (8.8–14.8)	45 (20–77,5)	10 (6–13)	NA	10 (5–13)	2 (1–3)
Polverino, 2023	6 months	NA	NA	NA	NA	NA	11 (8.5–16.0)	50 (20–90)	10 (5.7–14)	NA	11 (5–14)	2 (1–3)
Rienzo, 2021	12 months	NA	NA	NA	NA	NA	13 (8.5–16.9)	45 (1.2–87.5)	10 (5–16.5)	NA	9 (5–13)	2 (1–3)
Manenti, 2021	Baseline	44	72.1 ± 6.6	NA	102.42 ± 36.3	7.3 ± 1.8	7.6 ± 4.2	138.4 ± 40.8	18.5 ± 5.5	21 ± 4	4.9 ± 3.7	5.8 ± 1.4
	12 months	NA	NA	NA	48.12 ± 19.2	2.1 ± 0.8	16.2 ± 4.9	18.8 ± 8.5	6.2 ± 3.8	22 ± 3	7.7 ± 3.2	2.1 ± 1.1
Minafra, 2023	Baseline	21	63 (55–70)	NA	41.5 (40.0–54.3)	NA	8.8 (7.8–10.8)	70.0 (33–120)	18 (16–21)	17 (15–21)	4 (3–8)	4 (4–5)
	6 months	NA	NA	NA	NA	NA	13.9 (5.0–32.0)	14.0 (0–50)	6 (3–12)	18 (3–25)	9 (15–13)	2 (1–3)
	3 years	NA	NA	NA	35.0 (32.0–38.8)	NA	11.0 (9.0–12.8)	15.0 (0– 25)	12 (10–15)	17 (15–20)	11(7–21)	2 (1–2)
Pacella, 2019	Baseline	160	69.8 ± 9.6	NA	75.0 ± 32.4	NA	8.0 ± 3.8	89.5 ± 84.6	22.5 ± 5.1	NA	NA	4.5 ± 1.1
	6 months	NA	NA	NA	60.3 ± 24.5	NA	14.3 ± 3.9	27.2 ± 44.5	7.7 ± 3.3	NA	NA	1.8 ± 1.0
	12 months	83	NA	NA	58.8 ± 22.9	NA	15.0 ± 4.0	17.8 ± 51.0	7.0 ± 2.9	NA	NA	1.6 ± 0.9
Patelli, 2017	Baseline	18	71.7 ± 9.4	NA	69.8 ± 39.9	NA	7.6 ± 2.7	199.9 ± 147.3	21.9 ± 6.2	NA	NA	4.7 ± 0.6
	3 months	NA	NA	NA	54.8 ± 29.8	NA	13.3 ± 76.2	81.5 ± 97.8	10.7 ± 4.7	NA	NA	2.1 ± 1.2
Patelli, 2024	Baseline	40	65.1 ± 8.3	NA	66 (48.5–86.5)	NA	9.8 ± 6.2	108 (38–178)	23 (19–26)	NA	NA	5 (4–5)
	12 months	NA	NA	NA	46 (36–65)	NA	12.8 ± 7.4	13.5 (0–40.5)	5 (4–9)	NA	NA	1 (0–1)
	24 months	NA	NA	NA	48 (31–84)	NA	10.8 ± 6.9	23 (5–54)	5 (4–10)	NA	NA	1 (0–1)
	36 months	38	NA	NA	49.5 (31–79)	NA	10.4 ± 4.8	21 (5–49)	7 (3–10)	NA	NA	1 (0–2)
Polverino, 2023	Baseline	23	77 (68–84)	24.5 (22–27)	42 (39–70)	NA	NA	NA	NA	NA	NA	4 (3–5)
	12 months	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (1–3)
Rienzo, 2021	Baseline	21	62 (54–69)	27 (25–28)	40 (40–50)	2.0 ± 1.1	9.2 ± 3.4	81.8 ± 62.6	18.3 ± 3.9	17.8 ± 6.6	5.7 ± 4.5	4.1 ± 1.0
	1 months	NA	NA	NA	NA	3.0 ± 1.9	12.1 ± 6.4	37.4 ± 25.7	12.0 ± 5.6	17.4 ± 5.0	9.6 ± 4.1	2.4 ± 1,6
	3 months	NA	NA	NA	NA	1.7 ± 0.8	13.3 ± 6.7	18.7 ± 21.2	8.3 ± 3.8	17.7 ± 6.7	6.8 ± 3.5	1.4 ± 0.9
	6 months	NA	NA	NA	NA	1.7 ± 0.8	13.9 ± 6.2	14.0 ± 17.7	6.1 ± 2.6	18.3 ± 5.7	8.6 ± 3.1	1.7 ± 0.8
Sessa, 2022	Baseline	38	71.5 (63.5–79)	25 (22–29)	46 (38–71)	1.86 (0.56–2.76)	9.1 (8–11.5)	100 (70–150)	20 (16–25)	15 (7–24)	6 (2–10)	4 (3–5)
	1 month	NA	NA	NA	NA	NA	10.6 (9–13.6)	55 (32.5–97.5)	15 (12–20)	16 (8–21)	7 (6–10)	3 (2–4)
	3 months	NA	NA	NA	NA	NA	11 (9.4– 13.6)	50 (35–95)	11 (9–16)	18 (8–24)	8 (7–11)	1 (1–3)

NA, not available; BMI, body mass index; IIEF, International Index of Erectile Functions; IPSS, International Prostatic Symptoms Score; MSHQ-EJD, Male Sexual Health Questionnaire-Ejaculatory Dysfunction; PSA, prostate-specific antigen; PV, prostate volume; PVR, Post-Void Residual; Qmax, Maximum urinary flow; IPSS-Q8, International Prostatic Symptoms Score - question 8; TPLA, Transperineal Prostate laser ablation; TURP, transurethral resection of the prostate. [1] Mean (Standard Deviation) or median (IQR).
[2]Variation from the baseline to 3 months.

Figure 2. Forest plots of changes in Qmax at different follow-up intervals after TPLA. TPLA produced a consistent and statistically significant improvement in urinary flow over time, reflecting enhanced bladder emptying capacity.

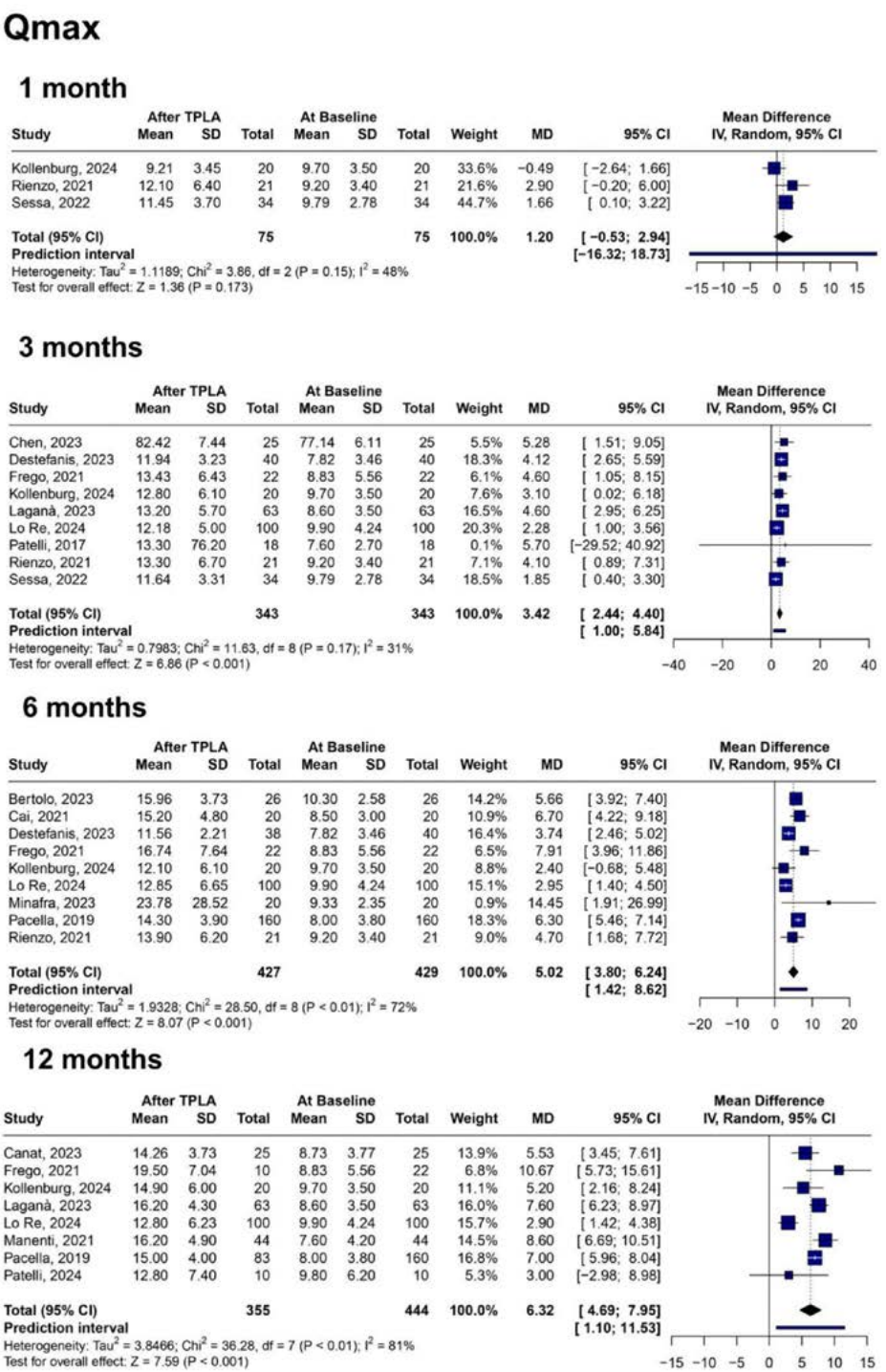
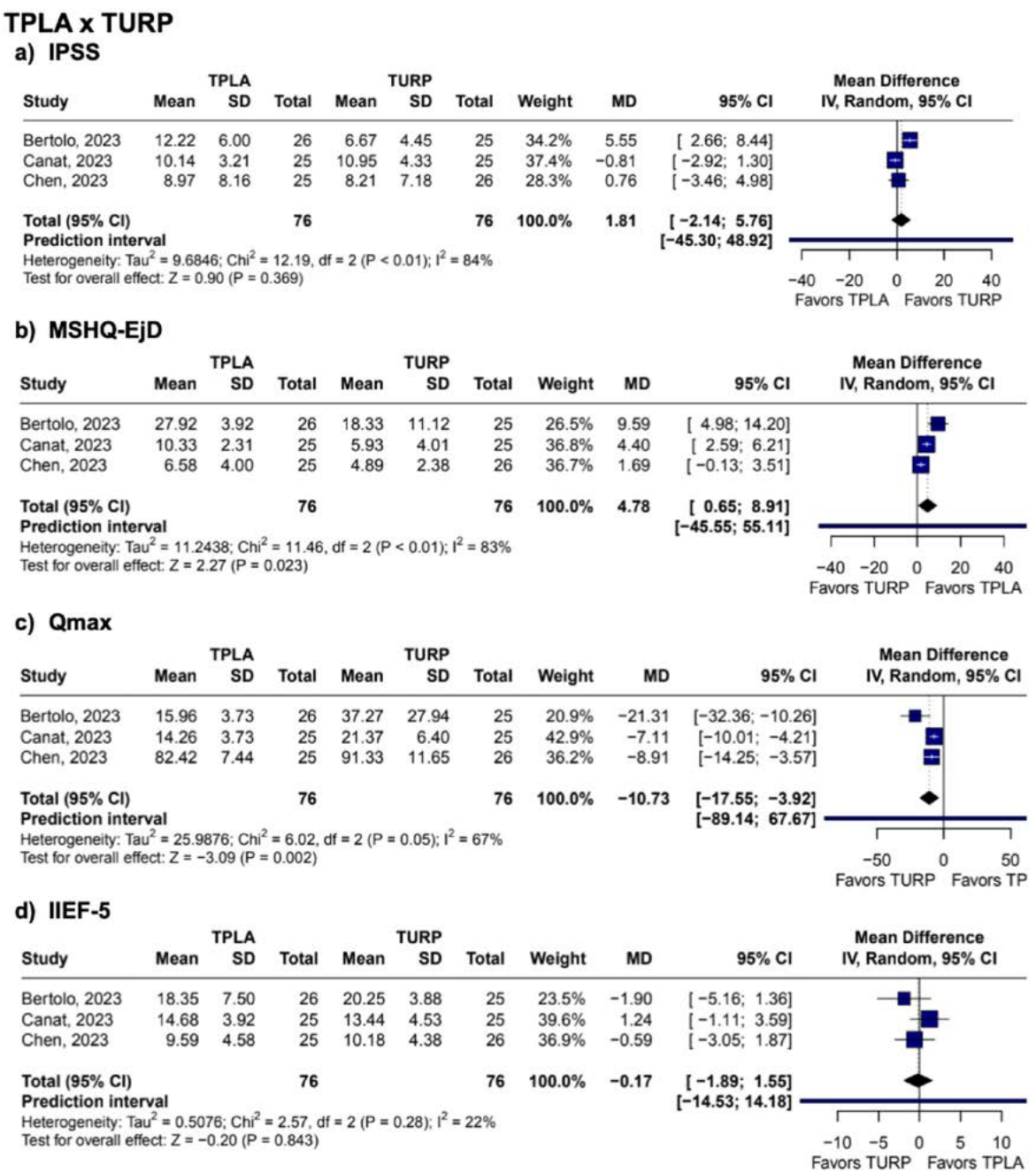
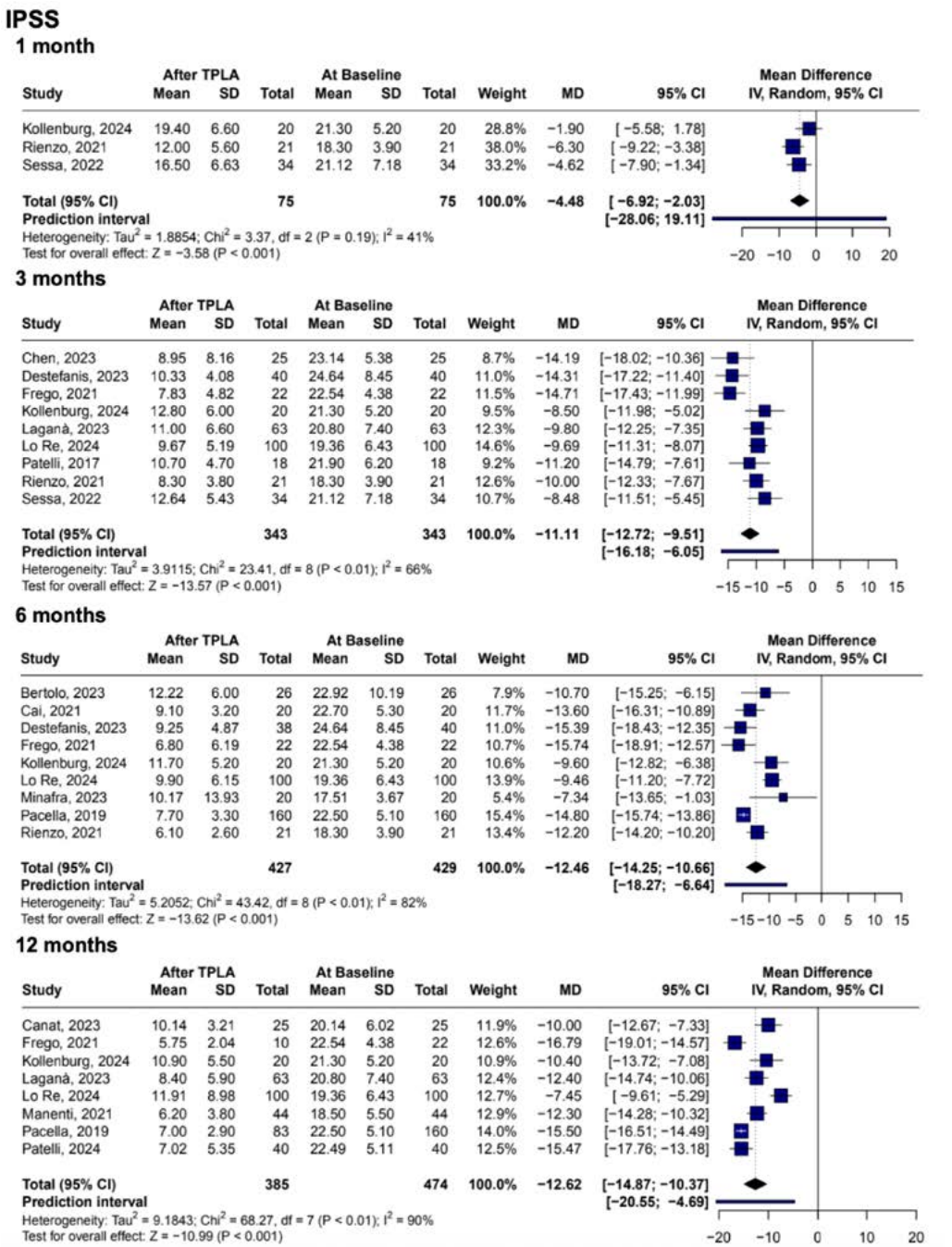


Figure 3. Forest plots of changes in IPSS at different follow-up intervals after TPLA. Pooled analysis demonstrates progressive and significant reduction in IPSS from baseline to 12 months, indicating sustained symptomatic relief in LUTS.



Abbreviations: IPSS – International Prostate Symptom Score; CI – Confidence Interval; MD – Mean Difference; LUTS – Lower Urinary Tract Symptoms; TPLA – Transperineal Prostate Laser Ablation.

Figure 4. Comparative forest plots between TPLA and transurethral resection of the prostate (TURP): (a) IPSS; (b) Ejaculatory function (MSHQ-EjD); (c) Maximum urinary flow rate (Qmax); (d) Erectile function (IIEF-5). There was no significant difference in LUTS relief (IPSS), and TPLA preserved ejaculatory function (MSHQ-EjD). TURP achieved greater improvement in urinary flow (Qmax), while erectile function (IIEF-5) remained comparable between techniques.



Abbreviations: TPLA – Transperineal Prostate Laser Ablation; TURP – Transurethral Resection of the Prostate; IPSS – International Prostate Symptom Score; MSHQ-EjD – Male Sexual Health Questionnaire for Ejaculatory Dysfunction; Qmax – Maximum Urinary Flow Rate; IIEF-5 – International Index of Erectile Function; CI – Confidence Interval; MD – Mean Difference.

function, as measured by the MSHQ-EjD (MD 4.78; 95% CI 0.65 to 8.91; p = 0.023; I2 = 83%. Figure-4B). Conversely, TURP was more effective in improving the Qmax (MD –10.73mL/s; 95% CI –17.55 to –3.92; p = 0.002; I2 = 67%. Figure-4C). IIEIF-5 did not differ and showed no statistically significant difference between the procedures (MD –0.17; 95% CI –1.89 to 1.55; p = 0.843; I2 = 22%. Figure-4D). TPLA presented lower operating time and length of stay compared to TURP (MD –43.46min; 95% CI –47.26 to –39.65; p < 0.001; I2 = 4%, and MD –0.54 days; 95% CI –0.73 to –0.35; p < 0.001; I2 = 0%. Figure-S6 A and B)

Leave-one-out analysis

To explore heterogeneity, a sensitivity analysis was performed to detect studies contributing to the I^2 value. In the Qmax and PVR outcomes at one month, after omitting the study by Kollenburg, a significant result was found, with heterogeneity reduced to zero. Additionally, omitting Kollenburg et from IPSS outcome at 1 month follow up, the heterogeneity reduced to zero. Still in the first month, regarding the IIEF outcome, after omitting Kollenburg, the heterogeneity resulted in zero, and regardless of the excluded study, no significance was observed. At 12 months of follow up, Canat et al. significantly contribute to the high heterogeneity in the MSHQ-EjD outcome. Excluding this study, TPLA demonstrated to significantly improve the ejaculatory function by 12 months (MD 2.75; CI 95% 1.63 to 3.86; I2 = 0%). The sensitivity analysis of the single arm outcomes by follow up is illustrated in Figures S7, S8, and S9. The leave-one-out sensitivity analysis of the RCTs did not identify a study for the possible source of heterogeneity for most of the outcomes. However, omitting Bertolo et al. of the Qmax analysis, the heterogeneity reduced to zero, and omitting Chen et al. from the PVR outcome, the heterogeneity, also, was zero, but the results in both outcomes were still the same. The sensitivity analysis of the RCTs is shown in Figure-S10.

Complications

Fourteen studies described the type and the number of complications (22-24, 26-34, 37, 38), and eight classified it according to the Clavien–Dindo system (26-30, 33, 36, 37). Sessa et al. (38) did not describe postoperative complications or sequelae in detail; nevertheless, they specified that no Clavien-Dindo grade ≥2 complications were experienced. Acute urinary retention, urinary tract infection, hematuria, and prostatic abscess were the most frequent complications. According to Chen et al. (22), TPLA had fewer complications than TURP (16% vs. 19.23%). Most of TPLA complications were Clavien-Dindo grade I and II. Table-S4 specifies all the reported complications.

Risk of Bias and Certainty of Evidence

The overall risk of bias for most of the non-randomized studies was moderate (Figure-S11), and low for the randomized studies (Figure-S12). The full GRADE assessment of the certainty of evidence is available in the supplementary materials (Table-S5).

DISCUSSION

The novel therapeutic options for BPE aim to treat non-neurogenic LUTS and avoid sexual side effects, which are a major source of dissatisfaction for men undergoing treatments for BPE. Therefore, the sexual side effects should be carefully considered, and the patient should be properly counseled before starting medical or surgical therapies. MISTs are becoming a new promise, especially with the concern of preserving sexual function and improving urodynamics parameters.

In this systematic review and meta-analysis of 17 studies and 777 patients, TPLA was assessed as a single-arm intervention and against the conventional TURP strategy. Our analysis demonstrated that TPLA was able to decrease IPSS and prostate volume from baseline while increasing the maximum urinary flow rate. Concerning the ejaculatory function, evaluated by the MSHQ-EjD, TPLA did not impose a negative effect. No changes were observed in the erectile function measured by the IIEF-5. In addition, TPLA was associated with a shorter operating time and length of stay than TURP. According to Chen et al.,

there was a minimum per-protocol hospitalization time in the TPLA group of up to 2.5 days. However, there was a benefit in terms of short hospital stays in the studies evaluating the new technology in general, as evidenced in the comparison of TPLA versus TURP in the RCTs (22).

A usual indication for the surgical treatment of BPE is moderate or severe voiding symptoms refractory to drug therapy. Although TURP has remained the gold standard due to its well-established technique and efficacy, it has been linked with numerous complications, (39) while MISTs are generally associated with fewer adverse events. (6) However, despite the American Urological Association (AUA) and European Association of Urology (EAU) guidelines on non-neurogenic male LUTS included MISTs as new therapeutic approaches for selected patients, the recommendations are still low to moderate in strength as they await more robust data (3).

Several trials have evaluated different MISTs interventions as alternatives to TURP, observing favorable outcomes (22, 23, 25). Recent data from a network meta-analysis of RCTs comparing new MISTs with standard surgical methods demonstrated similar symptom improvement profiles in the short and medium term, with less sexual dysfunction. However, the same data indicated that TURP provided greater benefits in increasing Qmax (40). Indeed, our comparative analysis revealed a 10-point difference in post-procedure Qmax favoring TURP. This could be explained by the extent of tissue removal and the immediate effect of TURP compared to the delayed prostatic volume response to TPLA (41). Nevertheless, TPLA has shown a 5-point reduction in Qmax in our analysis, consistent with what is expected from currently available therapies (42). It is worth noting that, while improvements in uroflowmetry parameters are important, patient-centered outcomes are as crucial since LUTS heavily impacts patients' QoL (43). As such, IPSS has been widely used as a symptom index for BPE and should be repeated after non-invasive and minimally invasive treatments (44). Our pooled analysis revealed an 11-point reduction in IPSS with TPLA treatment, along with no observable difference when compared to TURP, suggesting a similar patient-perceived treatment response.

In regard to sexual function, TPLA did not change erectile function from baseline, as evaluated with the IIEF-5 score (45), nor did it differ when compared to TURP. BPE procedures do not appear to impact erectile function, as stated in a comprehensive review of forty-five RCTs. However, there seems to be lesser risk of retrograde ejaculation with the new MISTs compared to TURP (46). In our pooled analysis, the ejaculatory function, assessed with the MSHQ-EjD form (47), did show a slight improvement from baseline, although we acknowledge that a 1.5-point change may not be clinically relevant. Nevertheless, when compared to TURP, the new treatment was able to preserve ejaculatory function, showing a clear benefit of the procedure. Although the advantages of TPLA over TURP, such as shorter operating time, and preservation of sexual function, are notable, TURP still is more effective in increasing Qmax and other parameters in terms of clinical significance.

Recent data demonstrated that prolonged surgical time may be a modifiable risk factor for complications due to an incidence likelihood of 14% for every additional 30 minutes of surgery, as reported by a meta-analysis of sixty-six studies (48). The impact of surgical time was further assessed by a 10-year analysis of patients undergoing TURP, which demonstrated a significant overall complication rate of 9%, and an increased complication risk as surgical time prolongs (49). In our pooled analysis, TPLA not only reduced operating time but also resulted in a slight decrease in hospitalization time compared to TURP, which could potentially improve safety outcomes and patient willingness to undergo the procedure (23). However, benefits are not limited to patient-related outcomes. Along with technological advancements, shortened operating time and faster recovery may allow these procedures to be performed in an office-based setting (50) and may represent a cost-effective alternative to current standard approaches (30).

This study has limitations. Nearly all included studies were single arm with no comparators, pos-

ing a significant limitation to the scope of our analysis. Only three RCTs were included in the analysis, which limited the robustness of the results and affected the certainty of evidence, since most of the included studies were non-randomized and had moderate risk of bias. Furthermore, current literature on TPLA is limited by the short follow-up period (≤ 12 months), unlike other procedures, which have long follow-up periods (51). This limits confidence in durability, retreatment rates, possible late complications, and long-term sexual/functional outcomes; consequently, we moderate the conclusiveness of our statements to reflect these limitations. Moreover, there was variability among procedure techniques. Significant variation in laser settings, procedural protocols, and follow-up durations across studies were noted. Differences in laser power settings, ablation time and a greater number of fibers potentially influence both the efficacy and safety of the procedure, with higher intensities yielding better results, but also increasing the risk of adverse effects. The minimum distance from bladder neck, urethral and between needles, also, had a few variations among studies. This technical and methodological heterogeneity contributes to variability between studies in terms of functional outcomes and complications. Future evidence syntheses should stratify results by key parameters (power/energy settings, fibers per lobe, total energy delivered, and energy density expressed in joules/mL of baseline prostate volume) and evaluate the device platform and perioperative protocols as additional moderators to identify technically optimized and patient-centered protocols, as well as clarify trade-offs between efficacy, ejaculation preservation, and complications. In addition, discrepancies in the duration of follow-up can lead to inconsistent assessments of long-term efficacy, as some benefits or complications may only emerge over time. To increase the clinical applicability of the results, future analyses should consider comparing studies with similar methodologies, grouping them based on key parameters to identify more consistent trends. This approach would provide clinicians with clearer, evidence-based insights to optimize laser treatments and minimize risks.

Although this new technology is being extensively researched, and many recent studies have been published, our study presents significant advances in terms of scope, methodological rigor, and analytical depth. First, among the reviews already published, ours included a larger number of patients (n=777) and studies (17), reflecting a broader and more up-to-date literature search. In addition, we conducted a complete quantitative meta-analysis with the application of random effects models, subgroup analysis (including direct comparisons between TPLA and TURP), assessment of the certainty of evidence via the GRADE approach, and leave-one-out sensitivity analysis to investigate sources of heterogeneity. Another relevant difference was the inclusion of functional data stratified by follow-up time (1, 3, 6, and 12 months), allowing a more detailed view of the clinical evolution of patients. Our work also stood out by presenting quality of life and sexual function data based on validated instruments (MSHQ-EjD and IIEF-5), which reinforces the clinical relevance of the findings. Finally, by strictly following the PRISMA guidelines and registering the protocol in PROSPERO, we ensured transparency and reproducibility. These characteristics consolidate our review as a more comprehensive, current, and methodologically robust contribution to the literature on TPLA in the treatment of LUTS secondary to BPE.

This review provides the most complete quantitative appraisal of TPLA for BPH, integrating symptoms, flow, perioperative, and sexual outcomes with consistent analytic standards (random-effects, sensitivity analyses, GRADE) and head-to-head context versus TURP when available. Beyond summarizing effects, it maps key technical drivers (power/energy, fibers-per-lobe, energy density) that may explain heterogeneity and offers a framework for future studies. These contributions enhance clinical interpretability—particularly around ejaculatory preservation and recovery—while highlighting evidence gaps (nonrandomized designs, short follow-up) that should shape the next generation of trials. Therefore, future randomized trials are advised to be performed in a multicentric fashion with a greater number of patients, comparing other treatment options to increase the generalizability of the findings. Never-

theless, observational studies often include a broader and more diverse population, and allow for a longer follow-up, thus, providing further insights into a real-world clinical setting.

CONCLUSION

TPLA demonstrated favorable outcomes for LUTS/BPE without a negative impact on sexual function. This minimally invasive treatment was found to have advantages over TURP, such as reduced operative time and shorter hospital stay. The evidence on this new MIST is emerging, but more comparative studies are required to understand the role of this technology, as this study consists mainly of retrospective studies. To date, this is the first meta-analysis to compare TURP and TPLA, and a substantial number of studies published in the literature have been included, although the available evidence is limited.

CONFLICT OF INTEREST

None declared.

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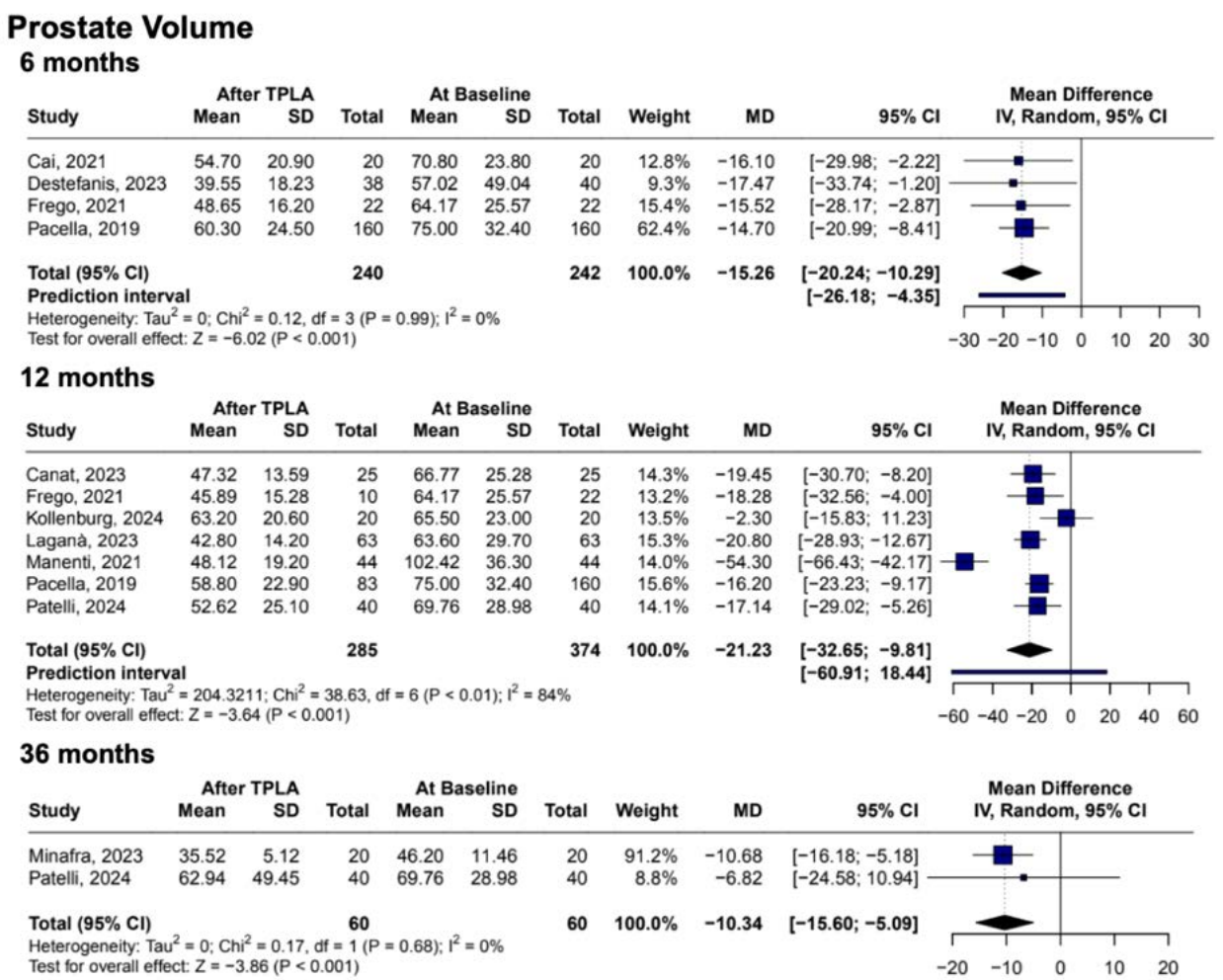
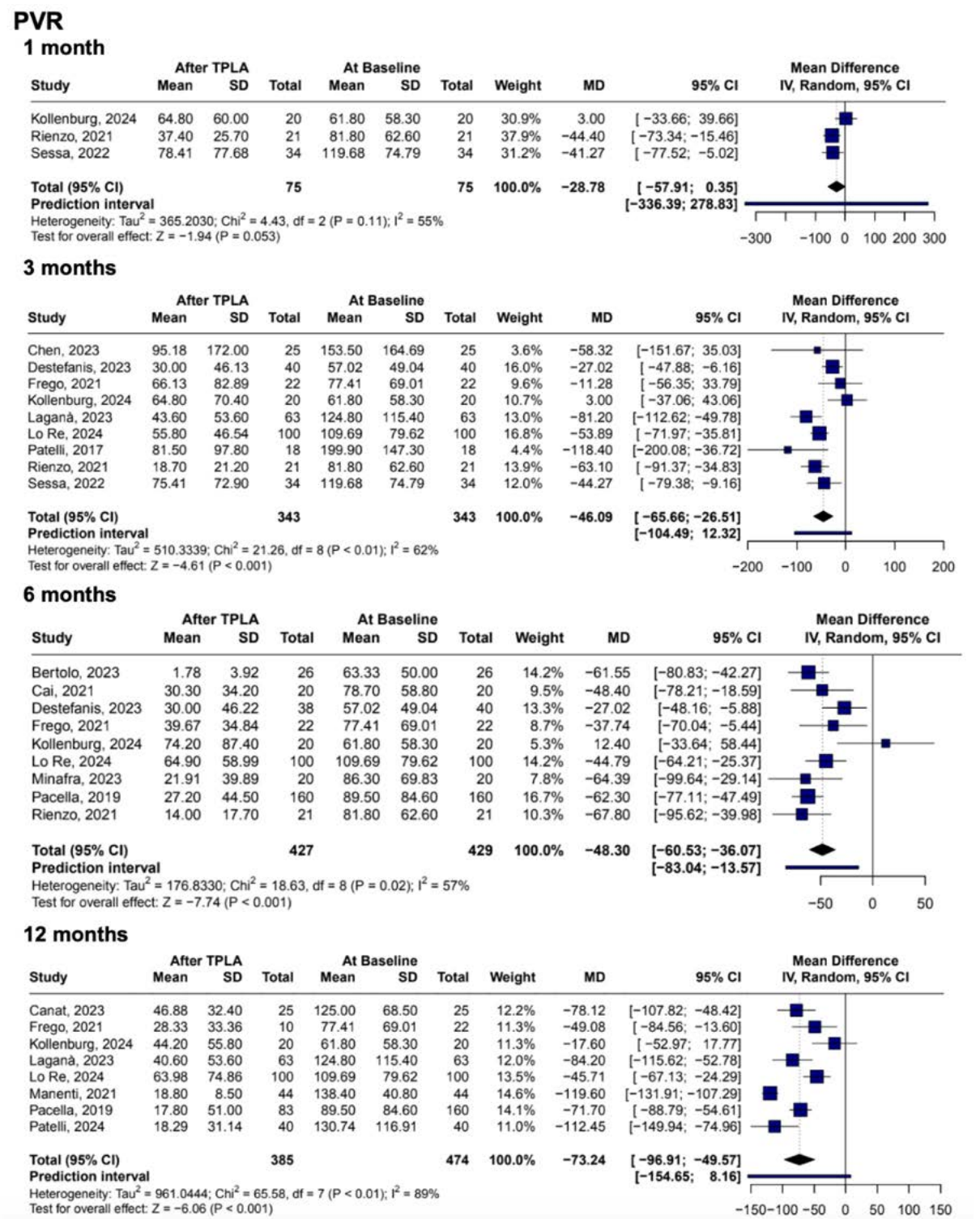
SUPPLEMENTARY MATERIAL

Figure S1. Changes in prostate volume at each follow-up period after TPLA. A progressive and statistically significant decrease in PV was observed up to 12 months, indicating sustained reduction in gland size.



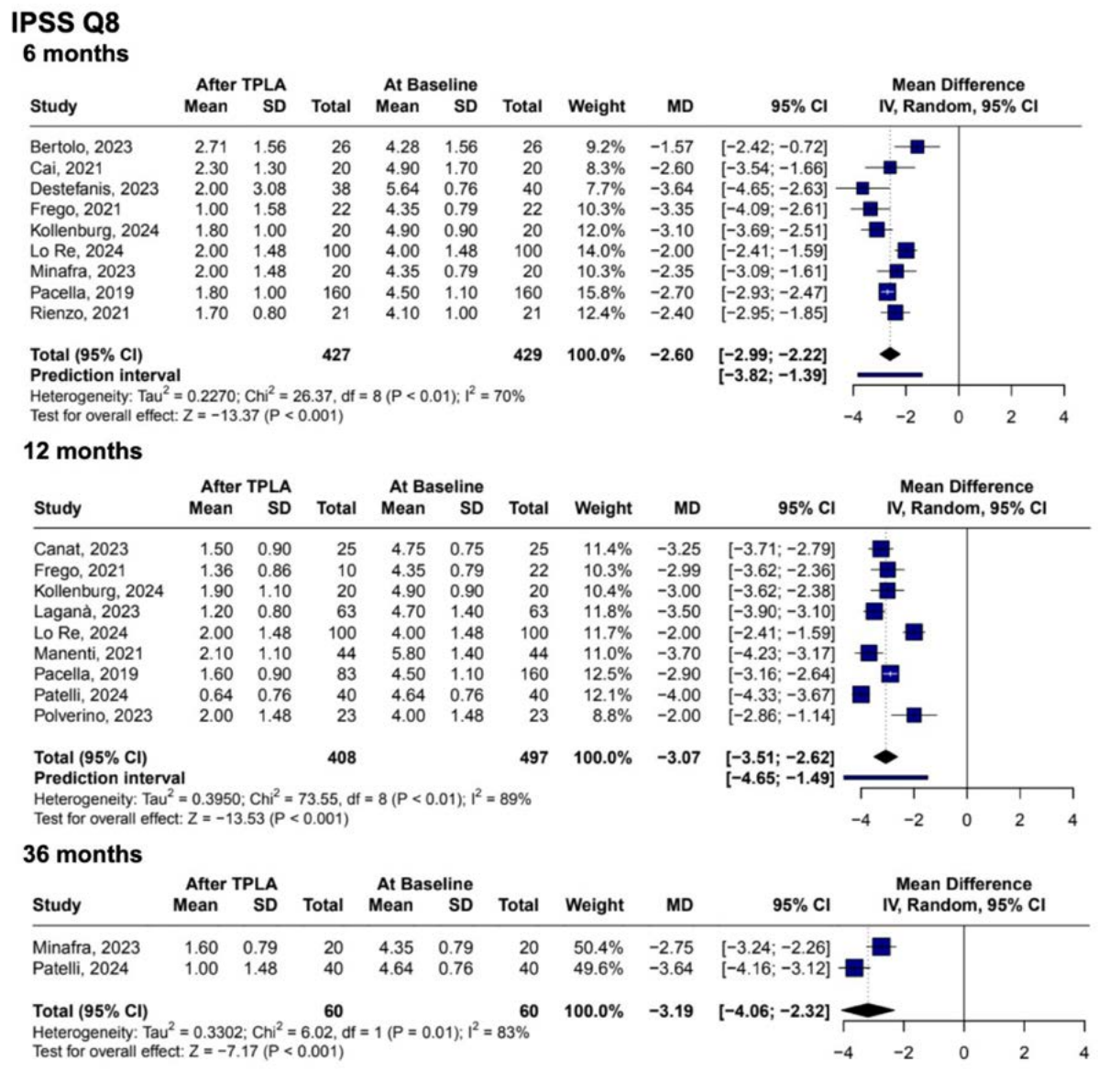
Abbreviations: PV – Prostate Volume; TPLA – Transperineal Prostate Laser Ablation; CI – Confidence Interval; MD – Mean Difference

Figure S2. Changes in post-void residual urine volume at each follow-up period. TPLA significantly reduced PVR from baseline at 3, 6, and 12 months, showing improved bladder emptying over time.



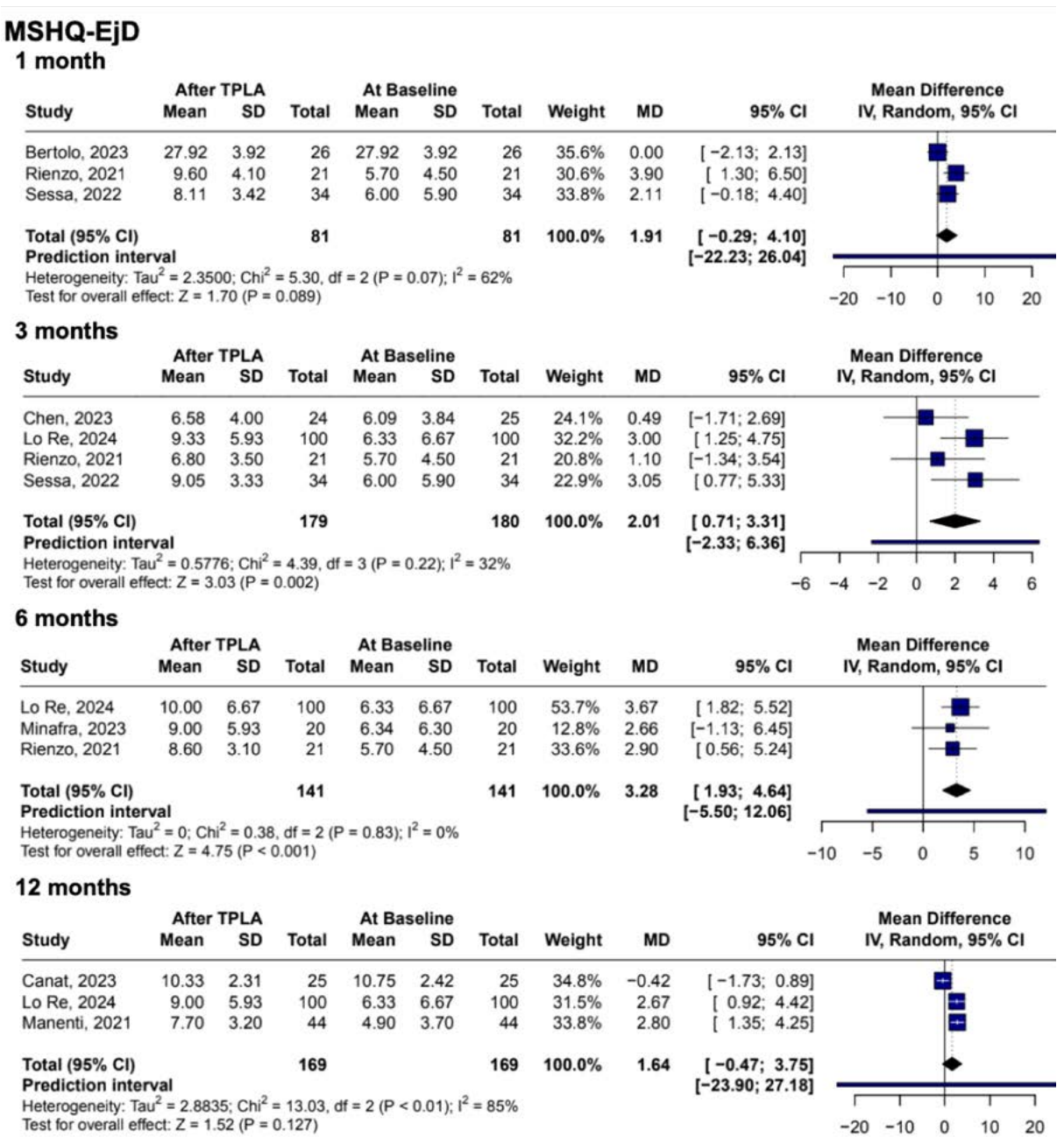
Abbreviations: PVR – Post-Void Residual; TPLA – Transperineal Prostate Laser Ablation; CI – Confidence Interval; MD – Mean Difference.

Figure S3. Changes in quality-of-life IPSS Question 8 following TPLA at each follow-up. The IPSS-Q8 domain, which assesses patients perceived quality of life, improved significantly across all follow-up intervals, reflecting symptom relief and better daily functioning.



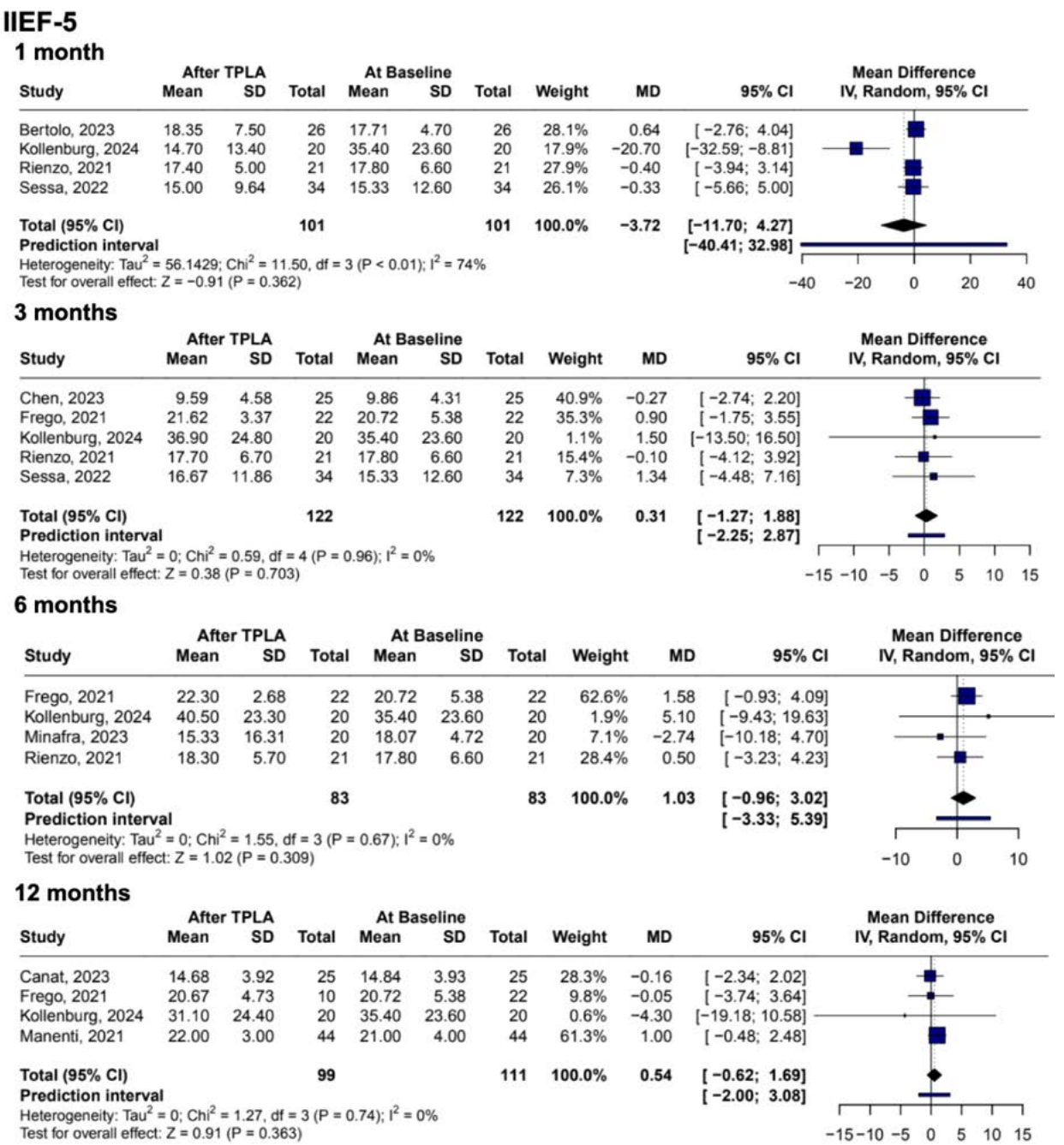
Abbreviations: IPSS – International Prostate Symptom Score; CI – Confidence Interval; MD – Mean Difference; TPLA – Transperineal Prostate Laser Ablation.

Figure S4. Changes in MSHQ-EjD after TPLA. Ejaculatory function showed mild improvement within 3–6 months after the procedure and remained stable thereafter, suggesting preservation of sexual function.



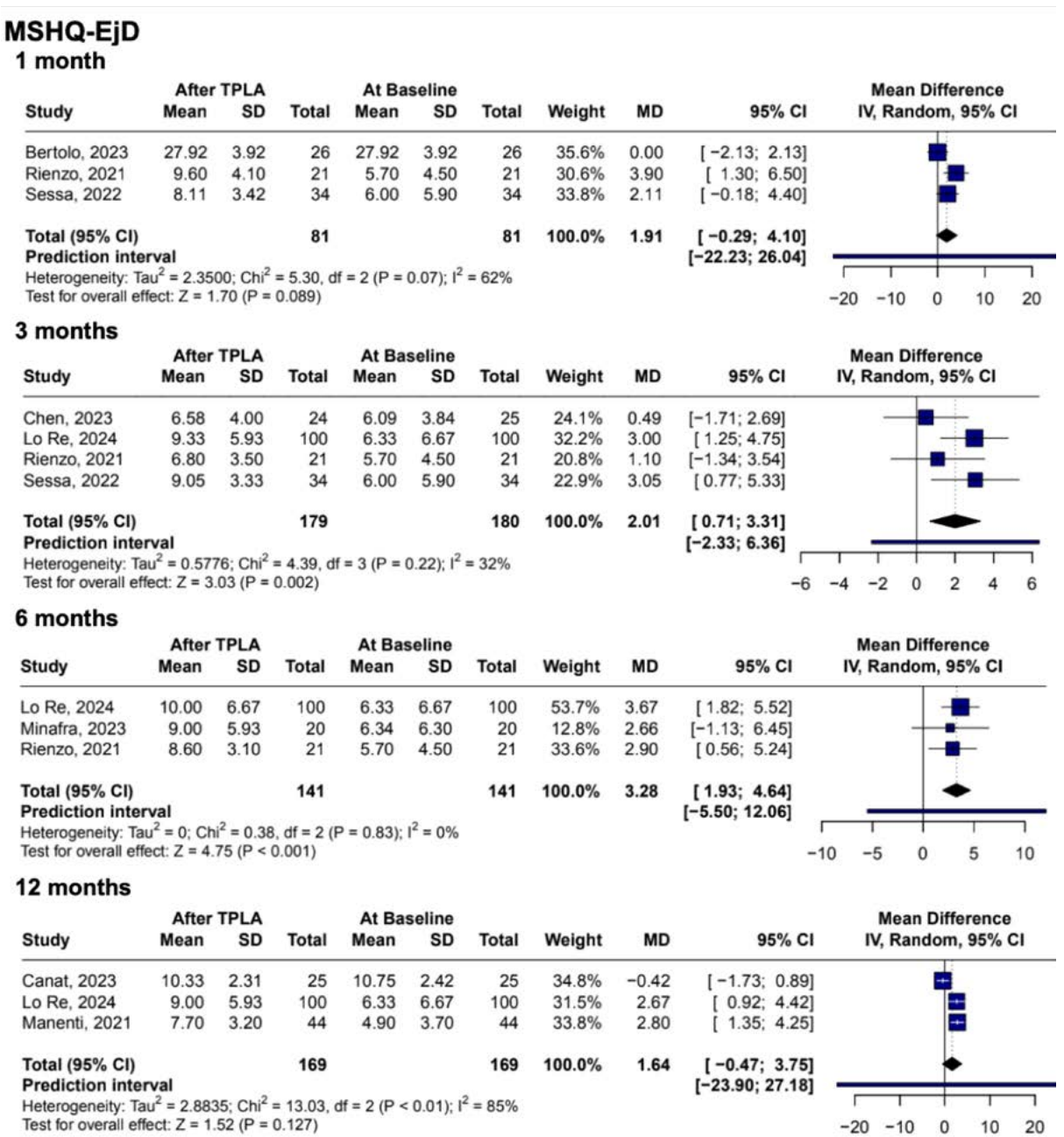
Abbreviations: MSHQ-EjD – Male Sexual Health Questionnaire for Ejaculatory Dysfunction; CI – Confidence Interval; MD – Mean Difference; TPLA – Transperineal Prostate Laser Ablation

Figure S5. Changes in IIEF-5 following TPLA. No significant differences were observed at any follow-up, indicating that TPLA does not adversely affect erectile function.



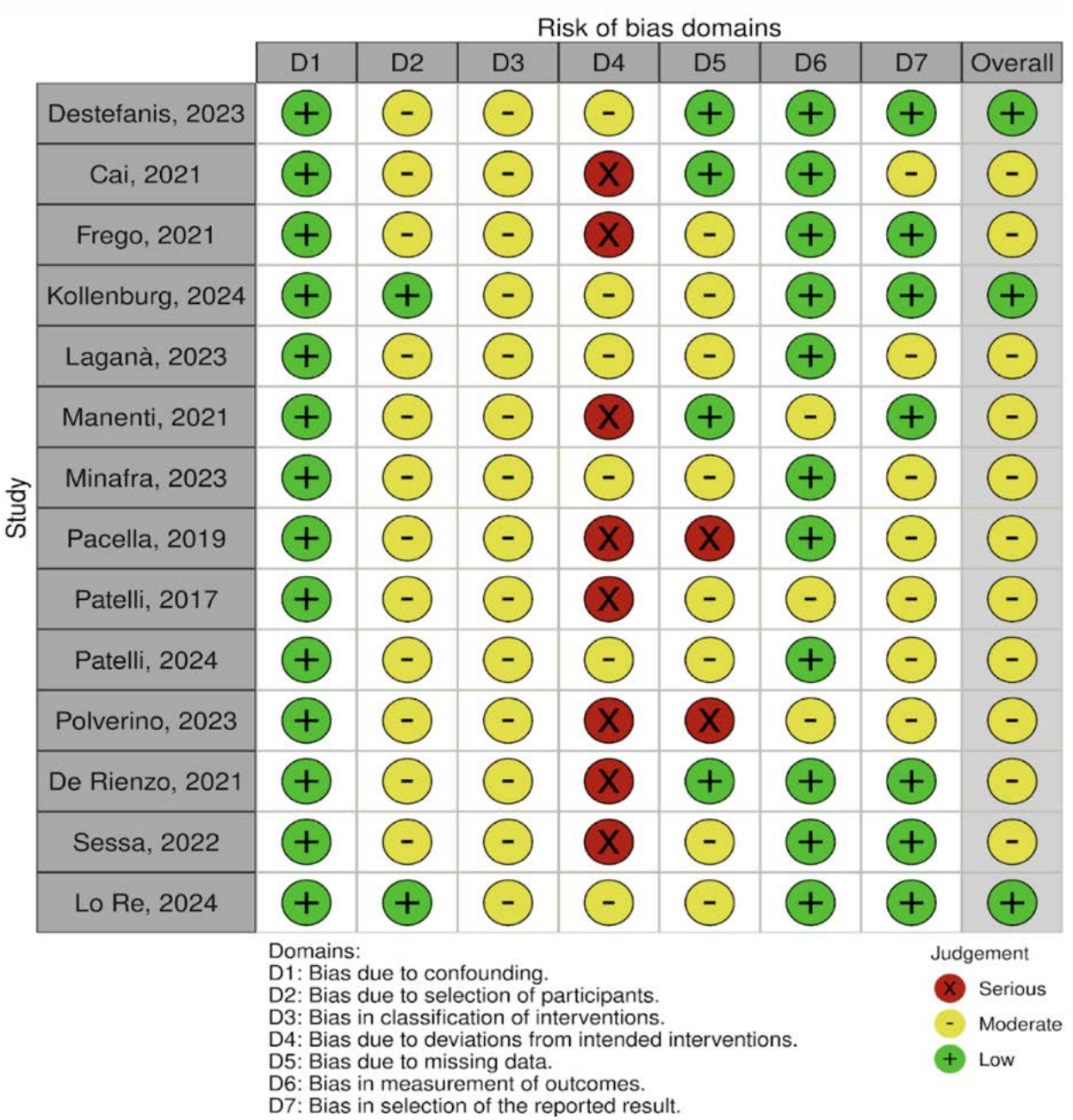
Abbreviations: IIEF-5 – International Index of Erectile Function; CI – Confidence Interval; MD – Mean Difference; TPLA – Transperineal Prostate Laser Ablation.

Figure S6. Comparative analysis between TPLA and TURP: (a) Operating time; (b) Length of hospital stay. Compared to TURP, TPLA demonstrated shorter operative times and reduced hospitalization periods, confirming the minimally invasive nature of the procedure.



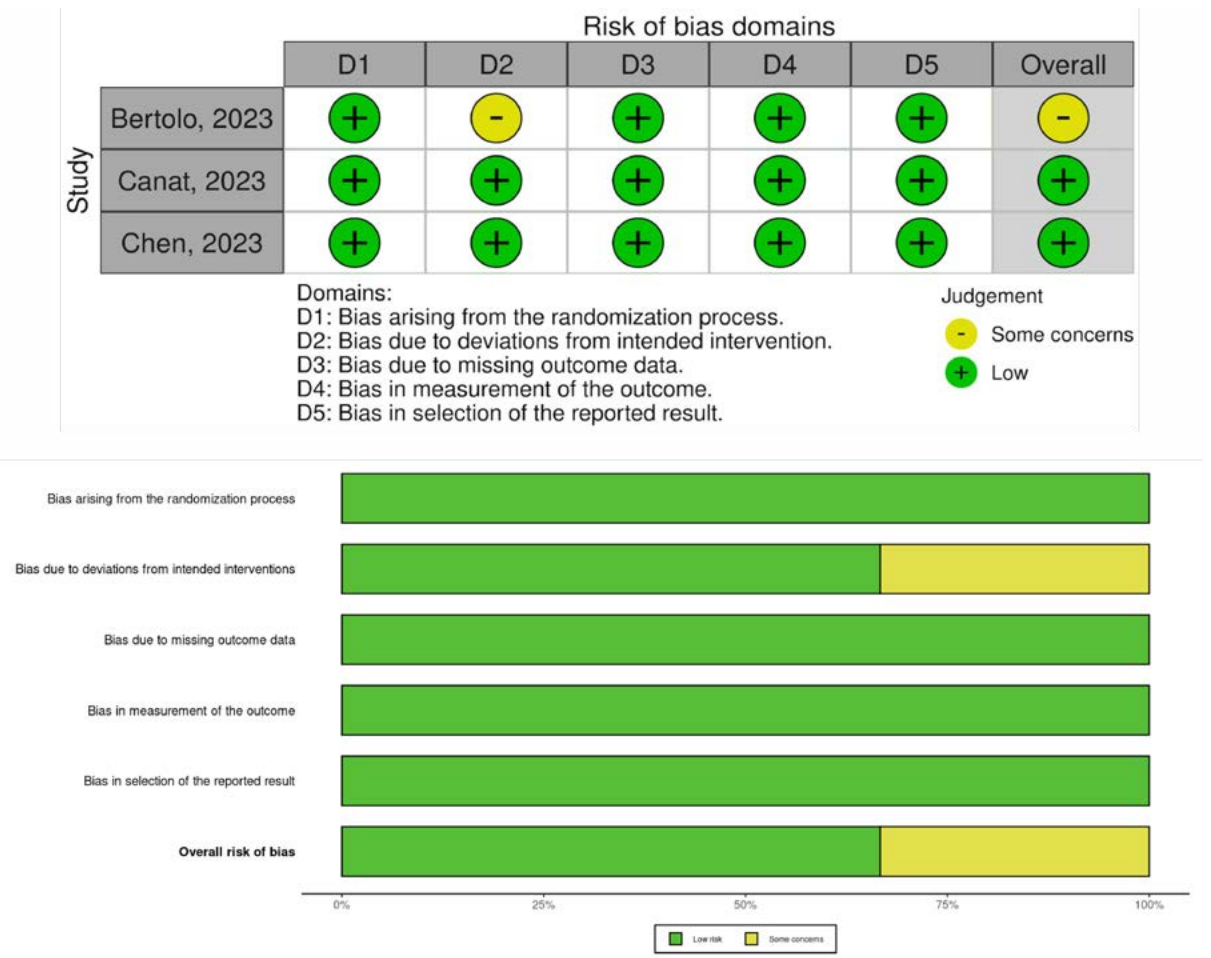
Abbreviations: TPLA – Transperineal Prostate Laser Ablation; TURP – Transurethral Resection of the Prostate; CI – Confidence Interval; MD – Mean Difference.

Figure S7. Risk of bias assessment for non-randomized studies using the ROBINS-I tool. Most studies were classified as having moderate risk of bias, primarily due to non-randomized design and potential confounding.



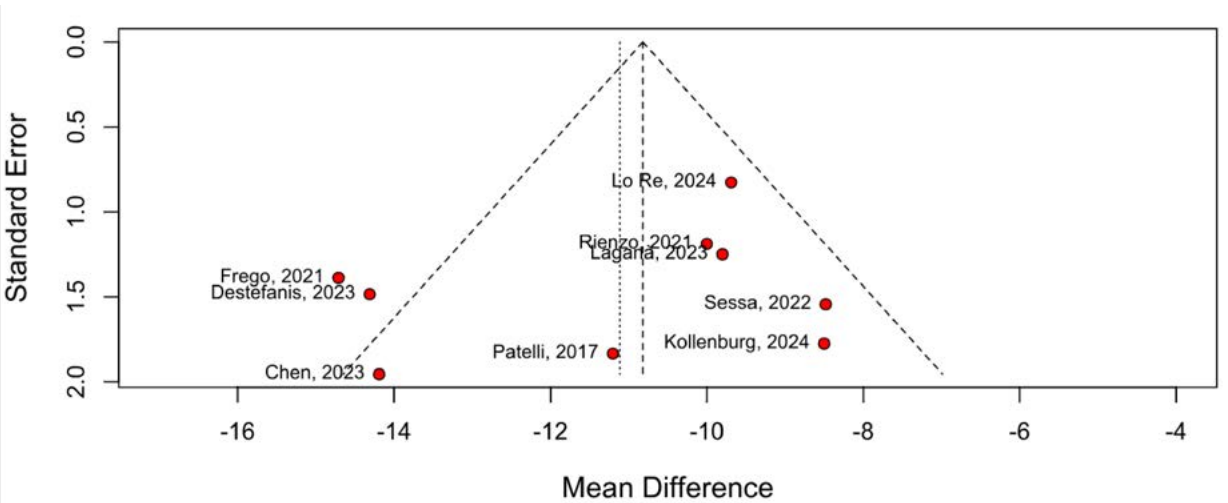
Abbreviations: ROBINS-I – Risk Of Bias In Non-randomized Studies of Interventions

Figure S8. Risk of bias assessment for randomized controlled trials using the RoB 2 tool. All included randomized trials demonstrated low risk of bias across major domains, supporting the robustness of comparative findings.



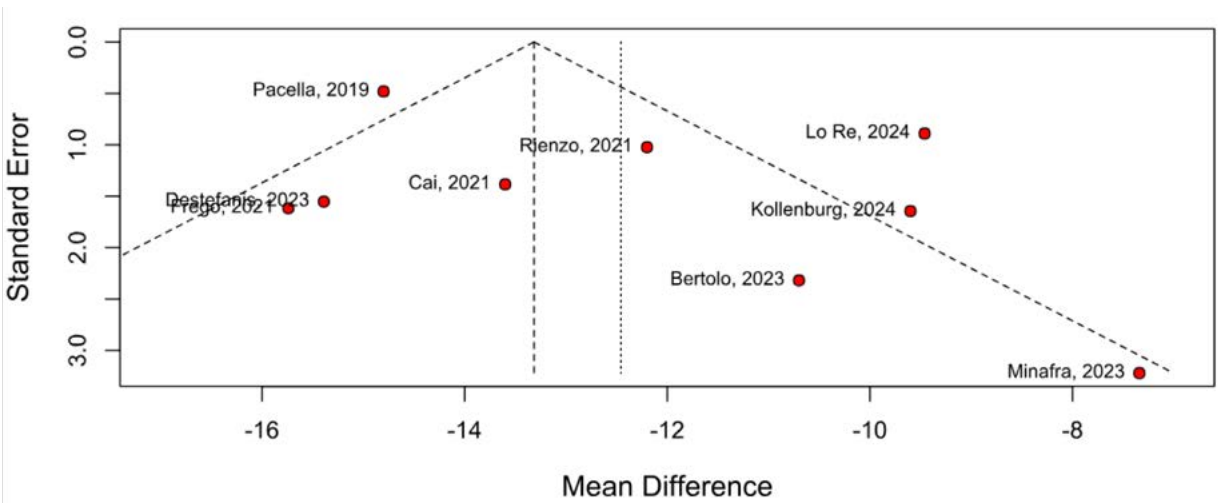
Abbreviations: RoB 2 – Revised Cochrane Risk of Bias tool for Randomized Trials.

Figure S9. Funnel plot for IPSS change at 3 months after TPLA. The scatter appears approximately symmetric around the pooled mean difference, with no prominent visual asymmetry. Given the limited number of studies at this time point, we cannot exclude small-study effects; observed dispersion is compatible with between-study heterogeneity in technique and follow-up.



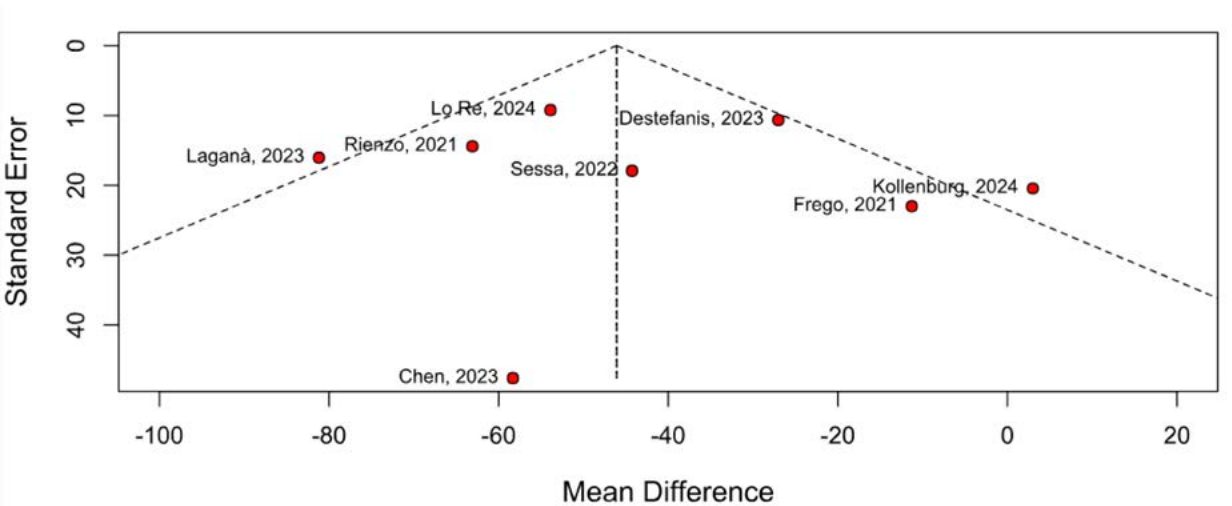
Abbreviations: TPLA – Transperineal Prostate Laser Ablation; IPSS – International Prostate Symptom Score; MD – Mean Difference; SE – Standard Error; CI – Confidence Interval.

Figure S10. Funnel plot for IPSS change at 6 months after TPLA. A broadly symmetric distribution is observed around the summary effect, without a clear directional pattern of small studies. The wider spread among less precise studies is expected and may reflect variability in power/energy settings and fibers-per-lobe across studies.



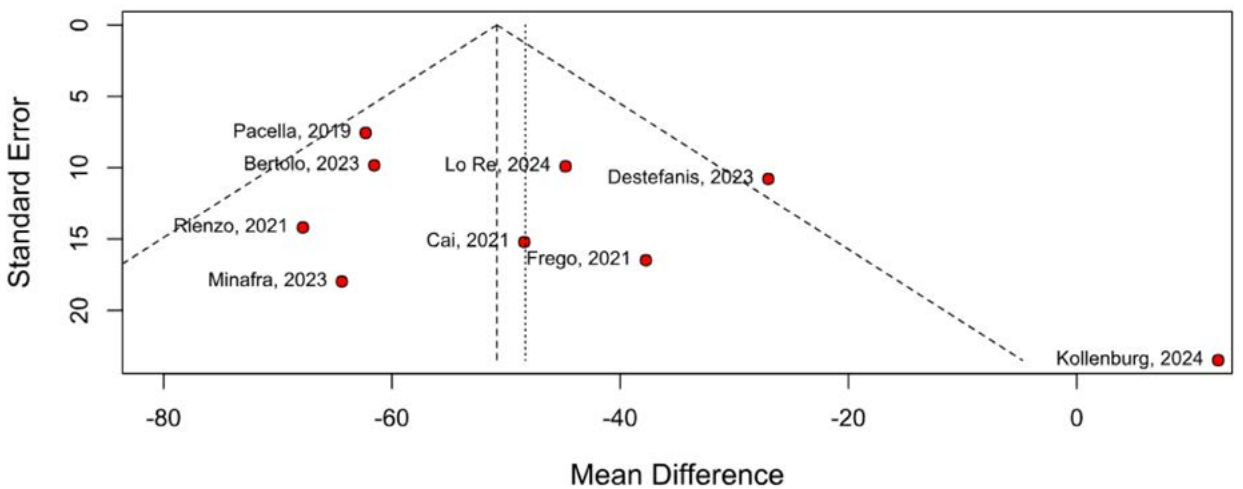
Abbreviations: TPLA – Transperineal Prostate Laser Ablation; IPSS – International Prostate Symptom Score; MD – Mean Difference; SE – Standard Error; CI – Confidence Interval.

Figure S11. Funnel plot for PVR change at 3 months after TPLA. No marked visual asymmetry is evident. The dispersion among smaller studies likely reflects clinical and technical heterogeneity (e.g., energy per fiber, inter-fiber spacing). Caution is warranted due to the limited number of contributing studies.



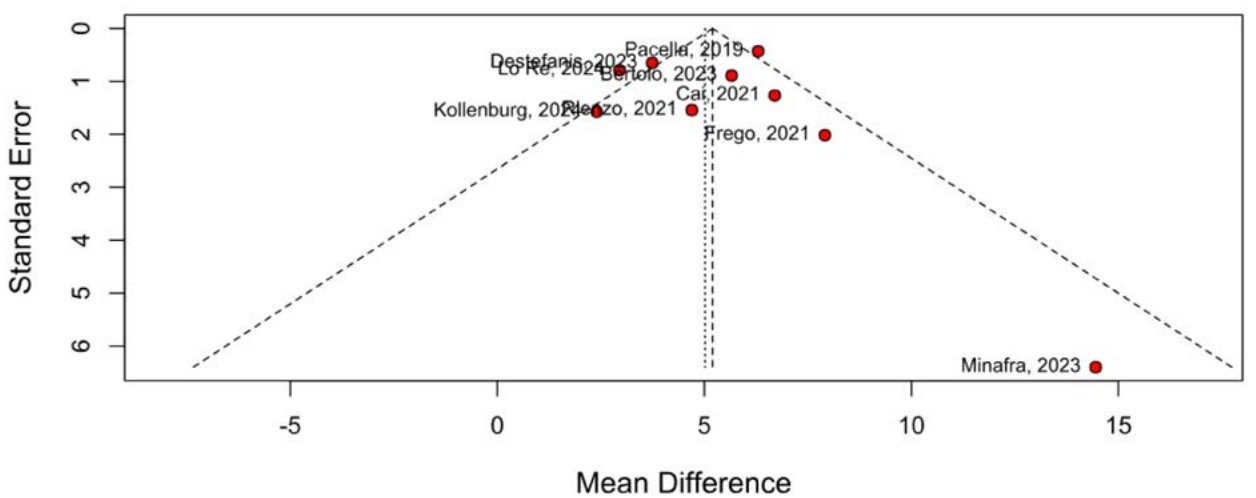
Abbreviations: PVR – Post-Void Residual; TPLA – Transperineal Prostate Laser Ablation; MD – Mean Difference; SE – Standard Error; CI – Confidence Interval.

Figure S12. Funnel plot for PVR change at 6 months after TPLA. The plot shows approximate symmetry around the pooled estimate with a typical funnel shape. Any subtle imbalance in the wings is insufficient to assert publication bias and may instead indicate heterogeneity of technique and perioperative protocols.



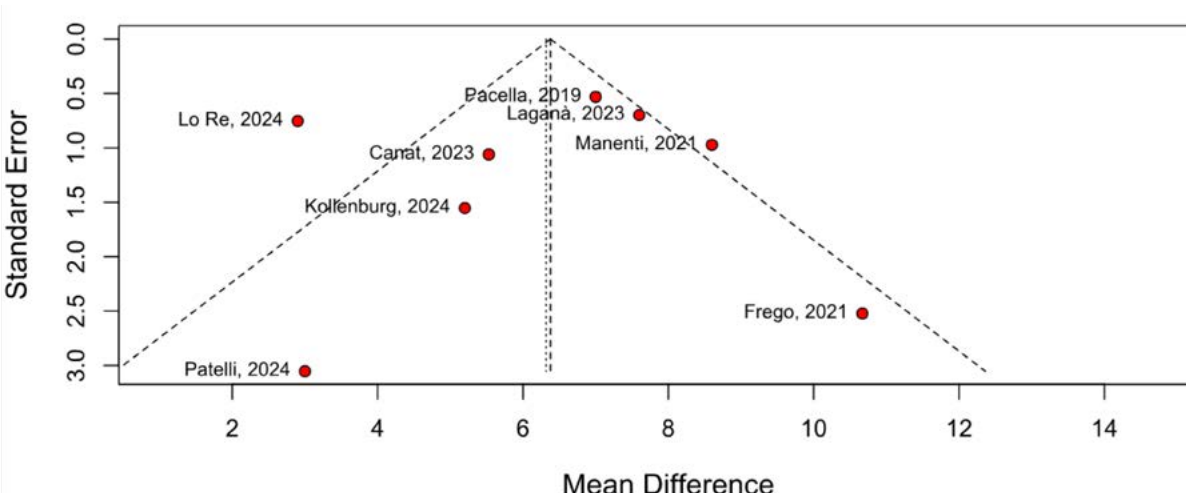
Abbreviations: PVR – Post-Void Residual; TPLA – Transperineal Prostate Laser Ablation; MD – Mean Difference; SE – Standard Error; CI – Confidence Interval.

Figure S13. Funnel plot for Qmax change at 6 months after TPLA. Visual inspection suggests near-symmetric scatter; however, a slightly broader spread among less precise studies is noted, consistent with methodological/technical variability. Small-study effects cannot be ruled out.



Abbreviations: Qmax – Maximum Urinary Flow Rate; TPLA – Transperineal Laser Ablation; MD – Mean Difference; SE – Standard Error; CI – Confidence Interval.

Figure S14. Funnel plot for Qmax changes 12 months after TPLA. The distribution is broadly symmetric with few studies near the base of the funnel, limiting the ability to detect asymmetry. Findings should be interpreted with caution given sample size and heterogeneity across techniques and follow-up schedules.



Abbreviations: Qmax – Maximum Urinary Flow Rate; TPLA – Transperineal Laser Ablation; MD – Mean Difference; SE – Standard Error; CI – Confidence Interval.

Table S1. PRISMA 2020 checklist of items for systematic reviews. Checklist of 27 items used to ensure transparency and completeness of reporting according to PRISMA 2020 guidelines.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 01
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 02
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 03
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 03
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 04
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 04
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 04
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 04
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 05
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 05
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 05
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 09
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 05
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 05
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 05
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 05
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 05
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 05
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 05

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 09
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 09
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 06
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 06
Study characteristics	17	Cite each included study and present its characteristics.	Page 06
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 09
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 07
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 06
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 06
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 06
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 07
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 09
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 09
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10
	23b	Discuss any limitations of the evidence included in the review.	Page 11
	23c	Discuss any limitations of the review processes used.	Page 11
	23d	Discuss implications of the results for practice, policy, and future research.	Page 11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 01
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 04
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 04
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 12
Competing interests	26	Declare any competing interests of review authors.	Page 12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 05

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/

Abbreviations: PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table S2 Technical parameters and perioperative data of the included studies. Overview of procedural characteristics, including anesthesia type, laser settings, number of fibers, and perioperative management strategies.

Study author/ year	Anesthesia	Laser system	Power setting (W)	Energy setting	Number and type of needles	Minimum distance from bladder neck (mm)	Minimum distance from the urethra (mm)	Minimum distance between Needles (mm)	No of fibres	Procedure time (min)	Ablation time (min)	Hospitalization	Catheterization time (days)	Antibiotic prophylaxis	Therapy at discharge	Pre-Op BPH Therapy N (%)	Antiaggregant/ Anticoagulant therapy N (%)
Bertolo et al. (23), 2023	Standard spinal anesthesia	SoracteLite EchoLaser, Elesta	4.5 reduced to 3.5 after 1-2 min	1800 J/ fiber/firing	1 or 2 needles per lobe 21 G	15	8	10	1 each needle	TPLA 35 (30-55) / TURP 68 (60-95)	NA	TPLA 2 (2-3) days / TURP 3 (3-4) days	TPLA 4 (2-7) / TURP 3 (3-4)	NA	NA	23 (88.5) / 22 (88)	10 (38.5%) / 0
Cai et al. (24), 2021	Local anesthesia (2% lidocaine)	SoracteLite EchoLaser, Elesta	3	1800 J/ fiber/firing	1 needle per lobe 21 G	15	8	15	1 each needle	60.9 (10.8)	42.6 (9.9)	1.5 (0.5) hours	16.5 (4.2)	NA	NA	NA	NA
Canat et al. (25), 2023	Sedation (Midazolam) + Local anesthesia (2% lidocaine)	SoracteLite EchoLaser, Elesta	NA	1800 J/ fiber/firing	1 needle per lobe 1 more needle if PV >60 mL 21 G	15	8	NA	2 (2-2.5)[1]	16 (2.35)	NA	TPLA 0.67 ±0.49 days / TURP 1.27 ±0.46 days	TPLA 6.5 (1.02) / TURP 2.27 (0.46)	NA	Dexamethasone and non-steroidal anti-inflammatory	NA	9 (36%) / 0
Chen et al. (21), 2023	Local anesthesia (2% lidocaine)	Asclepion Laser Technologies GmbH	3-5	1800 J/ fiber/firing	1 needle per lobe 21 G	20	8	10	1 each needle	TPLA 60.1 (19.67) / TURP 111 (49.09)	TPLA 36 (16) / TURP 100.63 (48.51)	TPLA 2.5 (0.52) days / TURP 2.94 (0.57) days	TPLA 11.38 (2.81) / TURP 8.88 (2.22)	NA	Antibiotic therapy for 7 days.	NA	NA
Destefanis et al. (26), 2023	Optional sedation + Local anesthesia (lidocaine/ bupivacaine)	SoracteLite EchoLaser, Elesta	NA	NA	Multiple 21 G Chiba needles	NA	NA	NA	2 (2-2.5)[1]	42.5 (35-50)	17.5 (8.5-18.5)	NA	NA	According to preop urine culture	NA	a-blockers 12 (30%) 5-ARIs 4 (10%) Combined therapy 15 (37.5%)	22 (55%)
Frego et al. (27), 2021	Sedation (Midazolam) + Local anesthesia (2% lidocaine)	SoracteLite EchoLaser, Elesta	3	1800 Joule/ fiber/firing in 600 s	1 needle per lobe 1 more needle if PV 60 mL 21 G Chiba	15	10	10	1 each needle	NA	17.21 (10-18.8)	1 day	7	Levofloxacin 500 mg (1 day before and for 5 days after procedure)	Antibiotic for 5 days; Dexamethasone 8 mg and Ketoprofen 100 mg for 7 days	a-blockers 22 (100%); Combined therapy 6 (27.3%)	NA
Kollenburg et al. (28), 2024	Optional sedation (Midazolam) + Local anesthesia (2% lidocaine)	SoracteLite EchoLaser, Elesta	3	1800 J/ fiber/firing	1 needle per lobe	15	8	NA	1 each needle	59 (14)	17.2 (6.3)	6.5 (5.0) hours	15.2 (3.5)	Ciprofloxacin 500 mg single dose	Dexamethasone 8 mg for 7 days	a-blockers 12 (60%); 5-ARIs 8 (40%) B3-agonist 1 (5)	NA
Laganà et al. (29), 2023	Sedation + Local anesthesia	SoracteLite EchoLaser, Elesta	3	1800 J/ fiber/firing	1-2 needles per lobe 21 G	15	8	10	NA	48.8 (14.3)	13 (1.95)	NA	14.9 (7.5)	2 g cephazolin IV (before the start of the procedure)	NA	a-blockers 27 (42.9%) 5-ARIs 6 (9.5%)	NA
Lo Re et al. (30), 2024	Sedation (Oral BZD*) + Local anesthesia (2% lidocaine)	SoracteLite EchoLaser, Elesta	5 reduced to 3.5 after 2 min	NA	1-2 needles 21 G	15	8	NA	2 (2-2)[1]	NA	NA	99% of patients were discharged within daily hospital stay.	7 (7-7)	NA	NA	a-blockers 60 (60%) 5-ARIs 4 (4%); Combined therapy 17 (17%)	24 (24%)
Manenti et al. (31), 2021	Local anesthesia with 2% lidocaine	SoracteLite EchoLase, Elesta	5 reduced to 3 after 2 min	1800 J/ fiber/firing	1 needle per lobe 1 more needle if PV >45 mL 21 G Chiba	15	10	8	1 each needle	28.2 (10.6)	NA	NA	NA	Levofloxacin 500 mg (1 h before and for 5 days after the procedure).	Antibiotic for 5 days; Acetaminophen 1000 mg if necessary; Prednisone 25 mg for 5 days with subsequent dose tapering; Alpha-blockers for 30 days	Combined therapy 44 (100%)	NA

Study author/ year	Anesthesia	Laser system	Power setting (W)	Energy setting	Number and type of needles	Minimum distance from bladder neck (mm)	Minimum distance from the urethra (mm)	Minimum distance between Needles (mm)	No of fibres	Procedure time (min)	Ablation time (min)	Hospitalization	Catheterization time (days)	Antibiotic prophylaxis	Therapy at discharge	Pre-Op BPH Therapy N (%)	Antiaggregant/ Anticoagulant therapy N (%)
Minafra et al. (32), 2023	Sedation + Local anesthesia (2% lidocaine)	SoracteLite EchoLase, Elesta	NA	NA	1-2 needles per lobe	15	8	NA	1 each needle	NA	NA	NA	NA	NA	NA	NA	NA
Pacella et al. (33), 2019	Sedation (Midazolam) + Local anesthesia (2% lidocaine)	SoracteLite EchoLase, Elesta	3	1800 J/ fiber/firing	1 needle per lobe 1 more needle if PV > 40 mL 21 G Chiba	15	8	8	1 each needle	44.1 (12.9)	23.4 (10.2)	1.8 (0.4) days	11.3 (11.5)	Ciprofloxacin 500 mg single dose	NA	NA	NA
Patelli et al. (34), 2017	Sedation (Midazolam) + Local anesthesia (2% lidocaine)	SoracteLite EchoLase, Elesta	3	1200-1800 J/fiber/ firing	1-2 needles per lobe 21 G Chiba	15	8	15	1 each needle	43.3 (8.7)	15.9 (3.9)	1.5 (0.4) days	17.3 (10.0)	Antibiotic therapy from the previous day and for a variable period	NA	NA	NA
Patelli et al. (35), 2024	Sedation (Midazolam) + Local anesthesia (2% lidocaine)	SoracteLite EchoLase, Elesta	3	NA	1 needle per lobe 21 G	NA	NA	NA	3.5[2]	43.4 (8.7)	17.3 (4.4)	NA	22.8 (10.9)	Levofloxacin (initiated the day before and 7 days after procedure)	NA	16 (100%)	NA
Polverino et al. (36), 2023	Sedation (Oral BZD[a]) + Local anesthesia (2% lidocaine)	SoracteLite EchoLase, Elesta	NA	NA	NA	NA	NA	NA	2 (2-2)[1]	NA	NA	1	7 (7-9)	NA	NA	NA	18 (78%)
Rienzo et al. (37), 2021	Sedation + Local anesthesia (2% lidocaine)	SoracteLite EchoLaser, Elesta	4.5 reduced to 3.5 after 1–2 min	1800 J/ fiber/firing	1 needle per lobe 1 more needle if PV > 55–60 mL 21 G Chiba	15	8	10	2.2 (0.5)[2]	36 (9.5)	NA	20.8 (3.6) hours	8.7 (2.5)	Oral cephalosporines or fluoroquinolones (1 h before and for 7 days after procedure)	Antibiotic for 5 days; prednisone 25 mg for 15 days with subsequent tapering of the dose; bromelain for 30 days; Alpha-blockers for 30 days	a-blockers 14 (66.7%) 10 5-ARI (47.6%) 8 combination therapy (38.1%)	NA
Sessa et al. (38), 2022	Sedation (Oral BZD solution) + Local anesthesia (2% lidocaine and lidocaine-prilocaine 5% cream)	SoracteLite EchoLase, Elesta	5 reduced to 3.5 after 2min	1400 J/ fiber/ firing [b]	1 needle per lobe 21 G Chiba	15	8	NA	2 (2-2)[1]	31.5 (28-37)	NA	6.4 (5.9-7.2) hours	7 (7-7)	2 g cephazolin IV (1h before the start of the procedure)	Antibiotic (cefixime 400 mg daily), for 7 days; Gastroprotective therapy (pantoprazole 20 mg daily) for 7 days; Ibuprofen 600 mg twice a day for 7 days	a-blockers 20 (52.6%) 6 5-ARI (15.8%) combination therapy 5 (10.5%).	11 (28.9%)

Values are presented in absolute numbers unless otherwise specified. 5-ARI, 5-alpha reductase inhibitor; BZD, benzodiazepine; G, Gauge; IV, intravenous; NA, Non available; PV, Prostate volume; TPLA, Transperineal laser ablation; TURP, transurethral resection of the prostate; W, Watt.

[1] median, fiber per patient.

[2] mean, fiber per patient.

[a] According to patients' preference.

[b] In the case of large prostates, additional laser energy was delivered up to 1800J per fiber.

Table S3. Inclusion and exclusion criteria of the included studies. Detailed eligibility criteria applied in each study, including design, recruitment period, patient characteristics, and follow-up duration.

Study author/year	Design	Recruitment period	Inclusion criteria	Exclusion criteria	Follow-up	N (TPLA/TURP)
Bertolo et al. (23), 2023	RCT (TPLA versus TURP); Open-label; Monocentric	Jan 2020-Sep 2021	Age 18-75 Normal ejaculatory function and presence of antegrade ejaculation before surgery IPSS ≥ 10 Qmax <15 mL/s PV <100mL Normal pre-operatory urine analysis	Previous prostate surgery, history of PCa or urethral stricture, Marion's disease, concomitant bladder stones, presence of median obstructive lobe, and neurological disorders*.	6 months	51 (26/25)
Cai et al. (24), 2021	Non comparative; Retrospective; Monocentric	June 2018-Jan 2020	Age >50 PV ≥ 30mL PVR 50-400 IPSS ≥12 Qmax <=15	Previous prostate, bladder neck, or urethral surgery, PSA >4 ng/mL, diagnosed PCa, severe urethral stricture, neurological disorders*, hypersensitivity to ultrasound contrast media.	6 months	20
Canat et al. (25), 2023	RCT (TPLA versus TURP); Monocentric	Nov 2021-Feb 2023	Age ≥ 50 IPSS >12 Qmax ≤ 15 mL/s TURP candidates	Urethral stricture, previous bladder or prostate surgery, bladder dysfunction, long-standing urethral catheters, PCa, neurological disorders*, and patients who had undergone rectal surgery.	15 months	50 (25/25)
Chen et al. (22), 2023	RCT (TPLA versus TURP); Open-label; Monocentric	Jun 2019-Dec 2021	Age >50 IPSS >8 PV 30-100mL Qmax ≤ 15 mL/s RUV ≥ 50 mL Failure with prior treatment or patients who were unsuitable for medical treatment as judged by the clinician	Urethral stenosis, previous prostate, bladder or urethral surgery, bladder calculi or tumor, PCa, PSA >4 ng/ml, neurological disorders*, post-rectal surgery or patients with anal atresia, severe coagulation disorders or infection	12 months	51 (25/26)
Destefanis et al. (26), 2023	Non comparative; Prospective; Monocentric	Oct 2020-June 2022	High hemorrhagic risk due to ongoing pharmacological therapy or due to pre-existent diseases ASA score > 3 Indwelling bladder catheter or intermittent catheterization IPSS > 8 Qmax < 15 ml/s	Clinical suspicion of hypo or non-contractile bladders, PVR >500mL, PCa, urethral stricture, PV <30mL, previous prostate, bladder or bladder neck surgery, neurological disorders* or cognitive impairment	6 months	40
Frego et al. (27), 2021	Non comparative; Prospective; Monocentric	July 2019-Jan 2020	Age ≥ 45 IPPS ≥ 8 PSA < 4 ng/mL, previous negative prostate biopsy, or negative DRE Qmax 15 mL/s PVR ≤ 150 mL PV 30–100 mL	Previous bladder neck, urethral or prostatic surgery, previous diagnosis of BCa or PCa, neurological disorders*, gross hematuria, active UTI	12 months	22
Kollenburg et al. (28), 2024	Non comparative; Prospective; Multicentric	NA	Age ≥ 45 IPSS ≥8 PSA < 4 ng/mL or PSA >4 ng/ml with previously negative prostate biopsy and negative DRE Qmax ≤ 15ml/s PVR ≤ 150mL PV 30-100mL	Prostate, bladder neck or urethral surgery, PCa or BCa, neurological disorders*, acute UTI or macroscopic hematuria	12 months	20
Lagana et al. (29), 2023	Non comparative; Prospective; Monocentric	Jan 2020-Jan 2022	Desire to spare antegrade ejaculation Intolerance of poorly compliant to medical therapy, with no indication for surgery.	Acute and chronic prostatitis, prior prostatic abscess, PV>85 mL, PSA>4.0 ng/mL without a negative MRI scan or negative biopsy for PCa	12 months	63
Lo Re et al. (30), 2024	Non comparative; Prospective; Monocentric	April 2021-July 2023	Age ≥ 45 IPPS ≥ 8 PV 30-100 mL Lack of efficacy, intolerance, or poor compliance to previous medical therapy or strong desire to preserve antegrade ejaculation or very high risk for standard surgery due to comorbidities	Clinical suspicion or previous PCa, neurologic disorders*, urethral strictures, bladder stones, large median lobe, previous prostatic surgery	Baseline, 3, 6, 12 months, last follow up	100
Manenti et al. (31), 2021	Non comparative; Prospective; Monocentric	May 2018-Feb 2020	Age > 50 IPPS ≥12 PV > 30 mL lack of efficacy, intolerance, or poor compliance to previous medical therapy	Urethral stricture, previous prostatic surgery, clinical or imaging findings suspicious for malignancy confirmed by biopsy, neurological disorders*, large median lobe, indwelling catheter, previous diagnosis of BCa or PCa	12 months	44

Study author/year	Design	Recruitment period	Inclusion criteria	Exclusion criteria	Follow-up	N (TPLA/TURP)
Minafra et al. (32), 2023	Non comparative; Retrospective; Monocentric	Sep 2018-Mar 2019	IPPS ≥ 12 Qmax ≤ 15 mL/s PV 30-100 mL (TRUS)	Previous treatment for BPO, history of bladder neck or urethral surgery, indwelling catheter or intermittent catheterization, bladder stones, detrusor acontractility or severely impaired contractility, urethral strictures, neurological disorders*, active UTI, macroscopic hematuria, history of clinical suspicion of PCa (elevated PSA without a negative prostate biopsy or negative DRE), history or clinical suspect of BCa.	3 years	21
Pacella et al. (33), 2019	Non comparative; Retrospective; Multicentric	NA	Age > 50 IPSS ≥ 12 PV > 30 mL (TRUS) Qmax < 15 mL/s PVR < 400 ml	Urethral stricture, previous prostatic surgery, neurological disorders*, previous diagnosis of PCa	12 months	160
Patelli et al. (34), 2017	Non comparative; Prospective; Monocentric	May 2014-May 2016	Age > 50 IPSS ≥ 13 PV > 30 mL (TRUS) Qmax ≥ 5 to ≤ 15 mL/s PVR ≥ 50 ml	Urethral stricture, previous prostate, bladder neck, or urethral surgery, PCa or PSA >4 ng/mL. neurological disorders*.	3 months	18
Patelli et al. (35), 2024	Non comparative; Prospective; Monocentric	May 2014-Sep 2018	Age > 50 IPSS ≥ 13 PV > 30 mL (TRUS) Qmax ≥ 5 to ≤ 5 mL/s PVR > 50 ml	Urethral stricture; PCa or suspected neoplastic disease; known neurological disorders*	36 months and last follow up	40
Polverino et al. (36), 2023	Non comparative; Prospective; Monocentric	April 2021-Feb 2023	ASA score ≥ 3 IPSS ≥ 8 PV 30-100 mL	NA	12 months	23
Rienzo et al. (37), 2021	Non comparative; Prospective; Monocentric	Sep 2018-Mar 2019	Age 40–90 IPSS ≥ 12 PV ≥ 100 mL lack of efficacy, intolerance, or poor compliance to previous medical therapy	Previous surgical treatment for BPH, indwelling catheter or intermittent catheterization, bladder stones, detrusor acontractility or hypocontractility (BCI < 50), urethral strictures, neurological disorders*, previous diagnosis of BCa of PCa	6 months	21
Sessa et al. (38), 2022	Non comparative; Prospective; Monocentric	April 2021-Feb 2022	Age ≥ 45 IPPS ≥ 12 PV 30-100 mL (TRUS) lack of efficacy,bintolerance, or poor compliance to previous medical therapy	Clinical suspicion or previous PCa, neurological disorders*, urethral strictures, bladder stones, indwelling catheter with severe detrusor hypo-contractility	1, 3 months and last follow up (4-12 months)	38

Values are presented in absolute numbers unless otherwise specified. ASA, American Society of Anesthesiologists; BCa, Bladder cancer; BCI, Bladder contractility index; BPH, Benign prostatic obstruction; BPO, Benign prostatic obstruction; Dec, December; DRE, Digital rectal examination; Feb: February; IPPS, International Prostatic Symptoms Score; Jan: January; Mar: March; Mo, Months; MRI, Magnetic resonance imaging; NA, Non available; Nov, November; Oct, October; PCa, Prostate cancer; PSA, Prostate-specific antigen; P, Prostate volume; PVR, Post-Void Residual; Qmax, Maximum urinary flow; RCT, Randomized controlled trials; RUV, Residual urine volume; Sep, September; TPLA, Transperineal laser ablation; TRUS, Transrectal ultrasonographic images; TURP, transurethral resection of the prostate; UTI, urinary tract infection.*neurological disorders: e.g., multiple sclerosis, Parkinson's disease, or known history of spinal cord injury.

Table S4. Reported postoperative complications and management strategies among included studies. Complication rates are stratified by Clavien-Dindo classification. Most complications were mild (Grade I–II) and included transient urinary retention, infection, and hematuria.

Study author/year	N	Type and number of complications	Management	Complication rate: N (%)	Clavien-Dindo: N (%)
Bertolo et al. (23), 2023	51	No complications	NA	0 (0)	NA
Cai et al. (24), 2021	20	Intraoperative urethral burn: 1 Transient urinary retention: 1	Bladder catheter for 25 days	2 (10)	NA
Canat et al. (25), 2023	50	TPLA No complications TURP Urethral stenosis: 1	NAP	NA	NA
Chen et al. (22), 2023	51	TPLA Urinary retention: 1 Prostate abscess: 1 Overactive bladder: 1 Urinary infection: 1 TURP Electrolyte disturbance: 1 Urge-incontinence: 1 Hematuria: 1 Urinary infection: 1	Oral medications and supportive treatment	TPLA 4 (16) TURP 5 (19.23)	NA
Destefanis et al. (26), 2023	40 (3 months) / 38 (6 months)	Catheter displacement or malfunction: 3 Urinary tract infection: 5 Hematuria: 1 Acute urinary retention: 13 Blood transfusion: 1 Acute heart failure: 3.		19 (47,5)	Grade I: 16 (40) Grade II: 9 (22.5) Grade III: 1 (2.5)
Frego et al. (27), 2021	22	Dysuria: 8 Acute urinary retention: 3 Urinary infection: 2	Antibiotics therapy	13 (59)	Grade I: 8 (36.3) Grade II: 5 (22.7)
Kollenburg et al. (28), 2024	20	Dysuria: 5 Urgency: 4 Haematuria: 3 Pain: 2 Frequency: 1 Urinary retention: 10 Urinary tract infection: 7	Conservative treatment and antibiotics		Grade I: Dysuria: 5 (25) Urgency: 4 (20) Haematuria: 3 (15) Pain: 2 (10) Frequency: 1 (5) Grade II: Urinary retention: 10 (50) Urinary tract infection: 7 (35)
Laganà et al. (29), 2023	63	Prostatic abscess: 2 Orchitis: 1	Abscess drainage Antibiotics	3 (4,8)	Grade II: 1 (1,6) Grade IIIa: 2 (3.2)
Lo Re et al. (30), 2024	100	Urinary infection: 2	Oral antibiotics	2 (2)	Grade II: 2 (2)
Manenti et al. (31), 2021	44	Urinary blockage and urinary clots: 5	Catheter reposition	5 (11,3)	NAP
Minafra et al. (32), 2023	21	No patient complained about the development of late-onset complications	NAP	NAP	NAP
Pacella et al. (33), 2019	160	Transient hematuria: 3 Acute urinary retention: 3 Orchitis: 1 Prostatic abscess: 1	None Bladder catheter for 15 days Antibiotic Antibiotic and percutaneous drainage	8 (5)	Grade I: 7 (4.3) Grade III: 1 (0.6)

Study author/year	N	Type and number of complications	Management	Complication rate: N (%)	Clavien-Dindo: N (%)
Patelli et al. (34), 2017	18	0	NAP	NAP	NAP
Patelli et al. (35), 2024	40	Prostatitis: 1 UTI: 1	NA	NA	NA
Polverino et al. (36), 2023	23	NA	NA	NA	Grade ≥2: 0 (0)
Rienzo et al. (37), 2021	21	Prostatic abscess: 1	Transperineal drainage and antibiotic	1 (4.7)	Grade III: 1 (4.7)
Sessa et al. (38), 2022	38	Acute urinary retention: 2	NA	NA	NA

NAP: not applicable; NA: not available

Table S5. GRADE assessment of the certainty of evidence across outcomes. Certainty of evidence graded according to GRADE domains (risk of bias, inconsistency, indirectness, imprecision, and publication bias). All main outcomes demonstrated high certainty.

Author(s): Iago Zang Pires, Marília Oberto da Silva Gobbo, Tanize Louize Milbradt, Renan Yuji Ura Sudo, Mable Pereira, Nilson Marquardt Filho, Márcio Augusto Averbeck.
Question: Transperineal Prostate Laser Ablation compared to Transurethral Resection of the Prostate for Benign Prostatic Enlargement

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transperineal Prostate Laser Ablation	Transurethral Resection of the Prostate	Relative (95% CI)	Absolute (95% CI)		
International Prostate Symptom Score changes (assessed with: points; Scale from: 0 to 35)												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	76	76	-	Mean 1.81 Pontos more (2.14 fewer to 5.76 more)	⊕⊕⊕⊕ High	CRITICAL
Maximum urinary flow rate changes (assessed with: ml/s)												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	76	76	-	Mean 10.73 ml/s lower (17.55 lower to 3.92 lower)	⊕⊕⊕⊕ High	CRITICAL
Male Sexual Health Questionnaire for Ejaculatory Dysfunction changes (assessed with: points)												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	76	76	-	Mean 4.78 pontos higher (0.65 higher to 8.91 higher)	⊕⊕⊕⊕ High	CRITICAL
Simplified International Index of Erectile Function changes (assessed with: points)												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	76	76	-	Mean 0.17 pontos lower (1.89 lower to 1.55 higher)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval

Abbreviations: GRADE – Grading of Recommendations, Assessment, Development and Evaluation.

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Robot-assisted Partial Nephrectomy with and without Mixed Reality - REALITATEM study

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ABSTRACT

Purpose: This randomized clinical trial (RCT) was developed to analyze the efficacy of using Mixed Reality (MIXREAL), the combination of virtual (VR) and augmented realities (AR), in robot-assisted partial nephrectomy (RAPN).

Materials and Methods: Forty-five patients with renal masses (RM) were allocated to RAPN with or without use of MIXREAL, Realitatem Group (RG) and Control Group (CG), respectively.

Results: Analyses indicated statistically significant difference in ischemia time favoring RG (p = 0.045), with a mean difference of 3.8 minutes. Classically, the limit widely accepted as suitable for ischemia time is 20-25 minutes, but every 1 minute saved may reduce renal injury. Analyses also indicated statistically significant difference in decision for selective clamping favoring RG (p = 0.013); main renal artery clamping globally exposes the renal parenchyma to ischemia. The percentage of residual parenchyma after surgery is also an important variable to renal function recovery, and this study presented a trend towards the enucleation technique being facilitated in the RG. No difference was detected regarding complication rate. Despite those results, no difference was detected in both short and long-term renal function outcomes. The small sample is an important drawback.

Conclusion: This RCT demonstrates the feasibility and safety of MIXREAL in RAPN, as well as its potential to support intraoperative decision-making. It represents the first RCT evaluating MIXREAL in RAPN. Larger studies with longer follow-up are needed to confirm potential functional benefits.

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INTRODUCTION

Kidney cancer has had a rising incidence (1) and PN is the standard of care for RM stage cT1/2 (2); PN may be supported by a variety of tools, such as three-dimensional (3D) models (3). VR is defined as an artificial 3D visual environment and AR, as virtual objects superimposed on the real world (4); MIXREAL is the association between VR and AR (5).

The first clinical experience using AR in a PN was in 2008 (6), and since then, clinical trials of 3D assisted minimally invasive PN have been developed, such as the first trial evaluating both AR and VR in videolaparoscopic PN (7), and the first RCT evaluating VR in RAPN (8); subsequently, Porpiglia et al. and Li et al. published trials of RAPN using exclusively AR (9, 10).

We aim to assess perioperative outcomes of RAPN with the use of MIXREAL. To our knowledge, this is not only the first study in Latin America to employ MIXREAL in minimally invasive PN, but also the first RCT worldwide to combine VR and AR in the context of RAPN. We hypothesize that as well as the pioneering studies mentioned, we will demonstrate primarily feasibility and safety of MIXREAL in RAPN and can expect improvements in perioperative outcomes.

MATERIALS AND METHODS

After approval by the ethics commission (IRB: 66791623.8.0000.5330) of Moinhos de Vento Hospital (Porto Alegre, Rio Grande do Sul), patients from hospital's clinic with solid or cystic RM requiring PN were prospectively randomized (protocol NCT06903260) to either RG or CG in a 1:1 ratio; the random sequence was generated using a computer-based random number generator. Patients were blinded to the group allocation. Exclusion criteria comprised patients with metastatic disease, RM staged ≥ cT3 or cN1, tumors with an infiltrative growth pattern, or lesions suspected of urothelial histology.

A computerized tomography (CT) angiography was performed within one month from the surgery. The images were exported in DICOM (Digital Imaging and Communications in Medicine) and applied in Brainlab Elements® software (Brainlab AG, Munich, Germany), where the images and 3D drawing were rendered to obtain the VR (Figures 1, 2 and 3). Planned cases were available via cloud services for immediate use in the operating room (www.brainlab.com).

All surgeries were robot-assisted, transperitoneal, and executed at Moinhos de Vento Hospital, from August 2022 to January 2024 by 8 urologists with experience in RAPN. AR was obtained through the Magic Leap 1 goggle (Magic Leap Inc., Plantation, FL, USA) (Figures 4 and 5).

Besides tumor and patient's baseline characteristics and intra-operative data, such as vessel clamping, ischemia time, estimated blood loss (EBL), use of hemostatic agents and excision technique, post-operative

Figure 1 - Images exemplifies the marking of anatomical structures on the image of angio-TC through Brainlab® software; note that each category has a different color and that the marking has to be done manually in many cuts of a single window (coronal, in this instance).

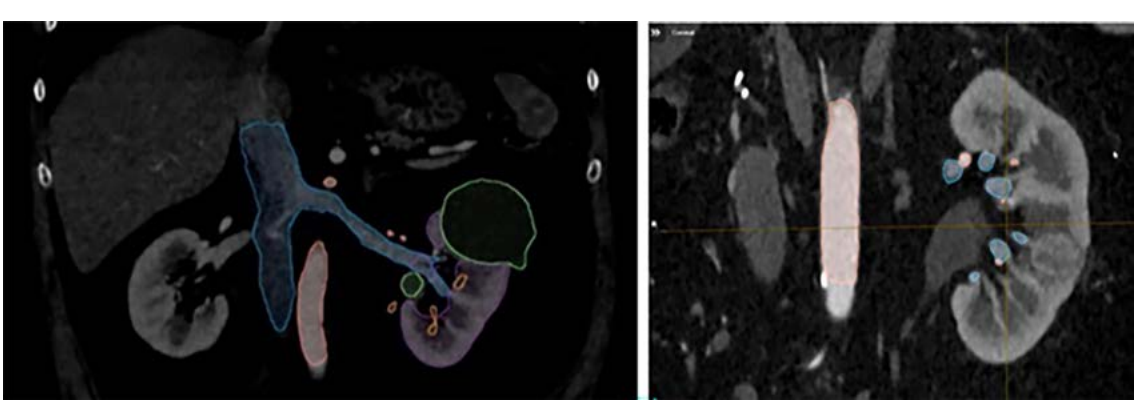
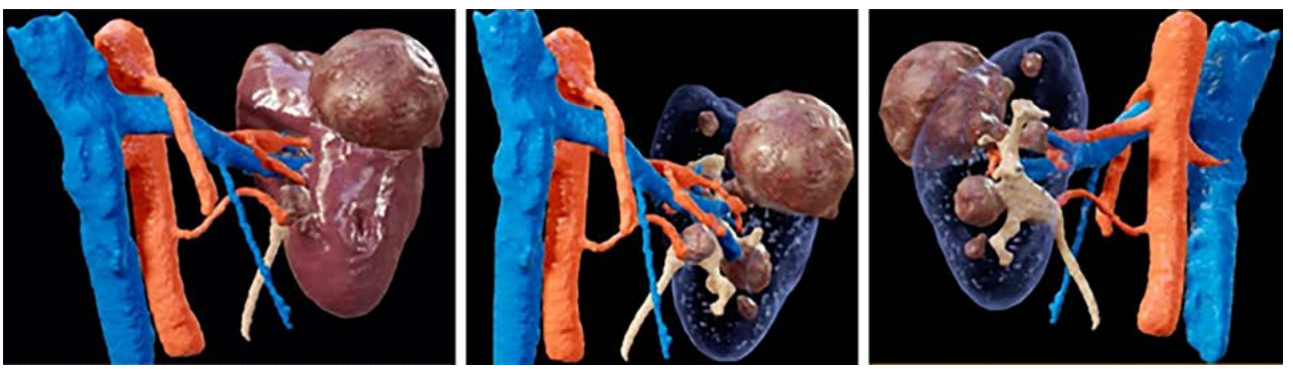


Figure 2 - Examples of virtual reality through the coronal axis, depicting venous, arterial and collecting systems, parenchyma and the tumors: 2a keeps the parenchyma, evidencing in an anterior view only the exophytic portions of the tumors; in 2b the parenchyma was removed, evidencing the endophytic portions and its relation to vessels and collecting system; 2c has the same purpose of 2b, but through a posterior view.



data, such as renal function, pathology results, complication rate and hospital staying, were also recorded. Our primary outcome was ischemia time.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and as frequencies for categorical variables; comparisons were made between GR and GC through non-parametric tests Mann-Whitney, Chi-

Figure 3 - QR code to access the video of the complete 3D reconstruction of the case presented in figure 2, from the anatomical marking to the final virtual reality result.

Figure 4 - The Magic Leap 1 is an Augmented Reality device made up of three main components. The Lightwear is the headset that projects 3D digital images into the real world, along with sensors and eye-tracking for environment and user interaction. The Lightpack is a small, wearable processing unit that handles all computing tasks, battery, and runs the device's operating system. The Control is a handheld controller with a touchpad, buttons, motion sensors, and haptic feedback, allowing precise interaction with virtual elements.

Figure 5 - QR code to access a video of the theatre room during the intraoperative of a case from our study, through the lenses of the Magic Leap Goggle, depicting how virtual objects can be superimposed on the real world.

square (CH2) and, when necessary, Fisher's exact test. A GEE (Generalized Estimating Equations) model was fitted to evaluate the effect of treatment over time on the delta of serum creatinine and glomerular filtration rate (GFR). For all analyzes performed, it was adopted the 95% confidence interval and the significance level of 5% ($p \leq 0.05$).

The sample was calculated using the Risk Calc software. Assuming a difference in mean ischemia rate between treatment groups to be 3.9 minutes (11), an expected population SD to be 3.23 (10) and a clinically relevant difference to be of 1 minute (12), to achieve 80% power (i.e., $1-\beta=0.8$) at the level of significance of 5% ($\alpha=0.05$) with equal allocation (i.e., k=1) and dropout rate of 5%, a total sample of at least 34 patients, divided into two groups, would be required.

RESULTS

Regarding sociodemographic data (Table-1), the groups were homogeneous, with a predominance of males, in their 60s, overweight and moderately comorbid, according to Charlson comorbidity index (CCI). Regarding tumor data (Table-1), most were solid, with mean size range of 3.1-3.4 cm, and of intermediary complexity, according to RENAL Nephrometry Score.

Perioperative data are shown in Table-2. Regarding ischemia, mean ischemia time was 14.6 and 18.4 minutes in RG and CG, respectively ($p = 0.045$), and in RG there were 5 selective clamping cases, while in the GC, none ($p = 0.013$). Off clamp procedure occurred in 40% and 28% of RG and CG surgeries, respectively ($p = 0.527$).

The EBL was 264.6 mL and 138.0 mL in RG and CG, respectively ($p = 0.085$). Regarding hemostatic agent, 95% of RG and 88% of CG used it ($p = 0.394$), and only 1 patient underwent transfusion of red blood cells, from CG ($p = 0.556$). As for the resection technique, enucleation occurred more frequently in the RG (40 vs 20%; $p = 0.288$). Conversion to radical nephrectomy (RN) occurred only in CG, in 2 cases, where the tumor was hilar and the main renal vein drained directly from the tumor. No case was converted to open surgery.

Regarding complication, there was no difference between groups, and most were Clavien-Dindo grade I. Two RG patients needed complementary clinical treatment (grade II), a pancreatitis case and an ARI (acute renal injury) case. Regarding grade III, 1 RG patient presented with a late urinary fistula, treated with ureteral catheter, while 1 CG patient had a spleen injury during surgery, being managed with thermal energy and hemostatic agent only. Hospitalization staying was similar (3.3 vs. 2.7 days; $p = 0.261$).

Pathology results were similar between the groups, with most staged T1a, of clear cells variant, and with no positive margin at all.

Regarding participants' functional variables, there were no statistically significant differences between groups in the changes from baseline in serum creatinine or GFR at 30, 90, and 180 days after surgery.

DISCUSSION

In this study, 3D images were generated using Brainlab Elements and visualized via the Magic Leap 1 device. Yoshida et al. used 3D HoloLens and printed models, while Edgecube et al. applied intracorporeal AR projection (Paris system) involving a projector, receptor, and laparoscopic ultrasound (13, 14). All approaches proved feasible and reproducible.

Significant differences were observed in ischemia time and selective clamping, with the RG showing

Table 1 - Sociodemographic and preoperative data, distributed across groups.

Variable		RG (n=20)	CG (n=25)	p
Gender, n (%)	Female	7 (35.0)	7 (28.0)	
	Male	13 (65.0)	18 (72.0)	
Age, *Mean (SD)*		60.2 (12.0)	60.4 (15.4)	
Ethnicity, n (%)	White	17 (85.0)	25 (100.0)	0.045
	Black	3 (15.0)	-	
BMI (kg/m^2), *Mean (SD)*		28.6 (4.1)	26.8 (5.1)	
Family history of kidney cancer, n (%)	Yes	2 (10.0)	1 (4.0)	
Previous abdominal surgery, n (%)	Yes	8 (40.0)	7 (28.0)	
	Nephrectomy	4	-	
Renal Lesion type, n (%)	Nodule	17 (85.0)	21 (84.0)	
	Cyst	3 (15.0)	4 (16.0)	
	Bosniak III	2	3	
	Bosniak IV	1	1	
Renal Lesion size (cm), *Mean (SD)*		3.1 (1.0)	3.4 (2.4)	
Renal Lesion Laterality, n (%)	Left	10 (50.0)	14 (56.0)	
	Right	8 (40.0)	10 (40.0)	
	Both	2 (10.0)	1 (4.0)	
Multiple lesions	Yes	6 (30.0)	2 (8.0)	
	Two	4	2	
	Three or more	2	-	
CCI, *Mean (SD)*		4.0 (1.9)	4.4 (2.7)	
R.E.N.A.L. Score, n (%)	Low (≤6)	5 (25.0)	11 (44.0)	
	Intermediary (7-9)	9 (45.0)	12 (48.0)	
	High (≥10)	6 (30.0)	2 (8.0)	
ASA Score, n (%)	I	1 (5.0)	-	
	II	17 (85.0)	20 (80.0)	
	III	2 (10.0)	5 (20.0)	

RG = Realitatem group; CG = Control group; n = number of patients; *p* = statistical significance; Me = mean; SD = standard deviation; BMI = body mass index; CCI = Charlson comorbidity index; ASA = American Society of Anesthesiologists.

Table 2 - Perioperative data, distributed across groups.

Variable		RG (n=20)	CG (n=25)	p
TST (min), *Mean (SD)*		181.0 (59.0)	153.0 (68.1)	
Off-Clamp, n (%)	Yes	8 (40.0)	7 (28.0)	
Ischemia Time (min), *Mean (SD)*		14.6 (12.6)	18.4 (8.9)	0.045
Selective Clamping, n (%)	Yes	5 (25.0)	-	0.013
EBL (mL), *Mean (SD)*		264.6 (223.6)	138.0 (147.5)	
Use of hemostatic agents, n (%)	Yes	19 (95.0)	22 (88.0)	
Red blood cell transfusion, n (%)	Yes	0 (0)	1 (4.0)	
Excision technique, n (%)	Wedge resection	5 (25.0)	5 (20.0)	
	Enucleoresection	7 (35.0)	15 (60.0)	
	Enucleation	8 (40.0)	5 (20.0)	
Conversion to RN, n (%)	Yes	0 (0)	2 (8.0)	
	Yes	3 (15.0)	1 (4.0)	
Perioperative complication, n (%)	I	2	-	
*Clavien-Dindo Classification	II	1	1	
HS (days), *Mean (SD)*		3.3 (2.5)	2.7 (1.6)	
	pT1a	13 (65.0)	16 (64.0)	
	pT1b	2 (10.0)	3 (12.0)	
Staging, n (%)	pT2	-	2 (8.0)	
	pT3	2 (10.0)	-	
	Benign	3 (15.0)	4 (16.0)	
	Clear cell	10 (50.0)	18 (72.0)	
Malignant variants, n (%)	Papillary	6 (30.0)	1 (4.0)	
	Chromophobe	1 (5.0)	2 (8.0)	
Baseline Cr, *Mean (SD)*		1.17 (0.47)	0.99 (0.30)	
30 days PO **Δ**Cr, *Mean (SD)*		0.123 (0.51)	0.37 (0.36)	
***missing (n)*		2	4	
90 days PO ΔCr, *Mean (SD)*		-0.04 (0.71)	0.2 (0.44)	
*missing (n)		7	15	
180 days PO ΔCr, *Mean (SD)*		-0.17 (0.76)	-0.02 (0.34)	
*missing (n)		8	17	
Baseline GFR, *Mean (SD)*		74.51 (34.09)	83.32 (27.76)	
30 days PO **Δ**GFR, *Mean (SD)*		-8.58 (24.9)	-17.64 (17.29)	
*missing (n)		2	4	
90 days PO ΔGFR, *Mean (SD)*		-2.18 (25.39)	-6.71 (20.1)	
*missing (n)		7	15	
180 days PO ΔGFR, *Mean (SD)*		-5.28 (22.97)	1.44 (15.54)	
*missing (n)		8	17	

RG = Realitatem group; CG = Control group; n = number of patients; p = statistical significance; Me = mean; SD = standard deviation; EBL = estimated blood loss; RN = radical nephrectomy; HS = hospital staying; Cr = creatinine in mg/dL; PO = postoperative; GFR = glomerular filtration rate in mL/min/1,73m2 ; Δ = difference from baseline.

a mean ischemia time 3.8 minutes shorter than the CG (14.6 vs. 18.4 min; p = 0.045), consistent with previous findings (mean difference of 3.96 min) from a systematic review (11). While the accepted ischemia time limit is 20–25 minutes, every

1 minute saved is worthy. A retrospective study of 362 solitary kidney patients undergoing PN showed an odds ratio of 1.05 for AKI per 1-minute increase in ischemia time (12). This benefit is clearly illustrated by the regression line in a study using renal scintigraphy to assess long-term function of the operated kidney (15).

Although in PN the clamping is traditionally done in the main renal artery, it globally exposes the renal parenchyma to ischemia; selective clamping can better preserve kidney function without compromising oncologic results (16). In our study, MIXREAL use was associated with a shift toward selective clamping: 25% of RG patients underwent selective clamping versus 0% in the CG (p = 0.013). While this finding may be limited by sample size, it aligns with Piramide et al., who found a lower global ischemia rate in the 3D group despite 25.9% of the 2D group also receiving selective clamping (OR 0.22; p = 0.02) (17). Although no significant difference was found regarding off-clamp use between groups, MIXREAL may facilitate its adoption in future studies, since MIXREAL eases the understanding of the relation between the tumor and segmental vessels; the possibility to avoid ischemia at all is potentially more beneficial than selective clamping.

Percentage of residual parenchyma after surgery is as critical as ischemia time and the percentage of parenchyma subjected to ischemia for renal function recovery (18). Enucleation maximizes nephron preservation and thus renal function (19). Porpiglia et al. showed significantly higher enucleation rates when minimally invasive PN was combined with MIXREAL (9, 20), a finding supported by a meta-analysis reporting enucleation rate of 31.3% in 3D versus 18.9% in 2D groups (17). Although not statistically significant in our study, enucleation was more frequent in RG (40% vs. 20%); we can hypothesize this lack of significance to small sample and to the fact that RG tumors presented a higher trend towards high-risk RENAL score (30% vs 8%) (p = 0.124) and presence of multiple lesions (30% vs 8%) (p = 0.055).

Despite the trend toward more complex lesions in RG, complication rates were similar between RG and CG. The use of advanced tools like MIXREAL is valuable not only for managing complex tumors but also for challenging surgical scenarios, such as the dense inflammation often seen in salvage PN after ablative therapies (21). Systematic reviews also show no difference in complication rates (22), and some evidence suggests that 3D technologies may reduce the risk of collecting system entry (9). Combining MIXREAL with other strategies, such as retroperitoneal access—now more common with the spread of single-port robotic platforms (23)—may further reduce complications. For example, the spleen injury observed in our cohort might have been avoided with retroperitoneal access. Notably, a systematic review of 160 RAPN cases using single-port systems reported a low complication rate (5%) and a mean EBL of 64.25 mL (24).

In this study there was no statistical difference for TST (total surgical time). On the other hand, most evidence, with statistical significance, points out that the use of MIXREAL adds shorter surgical time, with an average of 22 minutes less (11, 25) TST and may, in fact, contribute to reduce TST.

Possibly due to the greater complexity of RM from RG, mean EBL was higher (264.6 mL vs 138.0 mL), but as well as there was no statistical significance for this outcome, there was no difference in the use rate of haemostatics, nor in the rate of transfusion, and conversion to RN only occurred in the CG (0% vs. 8%); although absence of statistical significance (p=0.495), it is important to emphasize that conversion to radical nephrectomy represents the most unfavorable scenario with respect to functional outcome, and any harmless resource available should be used to potentially avoid RN. Also, we have to consider that a mean EBL difference of 126 mL is not clinically significant. Furthermore, lower EBL rate in the context of 3D use, with statistical significance, is evidenced since the first meta-analysis that compared PN with and without the use of MIXREAL (25), which is still reproduced in more recent studies (20).

Renal injury is determined by some variables, such as resection technique, ischemia time and EBL, being quantified through the GFR. In the present study,

even with RG having shorter average ischemia time and greater enucleation percentage, there was no statistical difference between groups regarding renal function variability over time. In systematic review by Jiaqi, renal function was also evaluated in 3 and 6 months, and there was no statistical difference (25). One hypothesis is that there may be a difference in the postoperative renal function in favor of MIXREAL, but that this difference is masked by compensatory effect of a healthy contralateral kidney. Some studies support this hypothesis, such as Li et al, which compared the use or not of AR in RAPN, but in single kidney patients, with those of the intervention group presenting a lower loss of renal function, with statistical significance (10). In the same line, Porpiglia et al. used DMSA scintigraphy to estimate the absolute renal function of each kidney and found a better outcome in the group submitted to AR, also with statistical significance (9).

Regarding oncologic outcomes, the use of MIXREAL had already proven to be safe, as seen in systematic reviews (26, 27); for instance, our study had no cases of positive margin. More than safe, MIXREAL possibly offers better oncologic outcomes, which can be hypothesized by the fact that there is already study showing that enucleation reduces the risk of positive surgical margin compared to nucleo-resection (28), and that the use of MIXREAL favors the chances of being able to make enucleation (9).

The high cost for the absorption of 3D systems compared to 2D systems is still one of the main reasons for the lack of broader diffusion of MIXREAL (29). In our institution, the cost for acquisition of the software, previously from the study, and of the goggle was 80,000 and 9,000 USD, respectively, while the cost of each rendering by an engineer is estimated to be 500 USD; in our study, the images were rendered by an engineer (AK) for free and by the first author, whose average time for 3D rendering after the learning curve was approximately 120 minutes.

Another disadvantage of MIXREAL technology available at the moment is that extreme renal rotations and posterior tumors still represent limitations to the superimposing of virtual images on the surgical field. It is expected that in the future, the application of artificial intelligence with "Deep Learning" algorithms may be a reliable option for renal visualization throughout the procedure (22). Nonetheless, 35% of RG lesions were located posteriorly and there was no heterogeneity with the CG in relation to the location of the tumor.

Finally, in relation to the limitations of the study it is noteworthy that the small sample size may be associated with the lack of statistical significance in several variables. Also, it is worth mentioning that the heterogeneity of the surgeons, even though all were experienced, can also impact several perioperative variables and that this was the first study using the Brainlab Elements® software for this purpose, so the 3D reconstructions are likely to improve their quality over time, which can influence statistical data.

CONCLUSIONS

In view of all the already proven and potential benefits for the use of MIXREAL, it is expected that its use can increase PN indications and improve the nephron sparing surgery success rate. Three-dimensional models can be accessed by the surgeon for a detailed study of the case before surgery or may be used intraoperatively as both consultation and overlay in real time.

Within the limitations of this RCT, our results primarily demonstrate the feasibility and safety of MIXREAL in the setting of RAPN, as well as its potential to support intraoperative decision-making. Importantly, this is the first RCT to evaluate MIXREAL in RAPN, and the first such experience in Latin America. Yet, further studies with larger samples and longer follow-up are required to establish the possible functional benefits MIXREAL in minimally invasive PN.

ABBREVIATIONS

RCT = Randomized clinical trial
MIXREAL = Mixed reality
VR = Virtual reality
AR = Augmented reality
RAPN = Robot-assisted partial nephrectomy
RM = Renal masses
RG = Realitatem Group

CG = Control Group
PN = Partial nephrectomy 3D = Three-dimensional
IRB = Institutional Review Board
CT =Computerized tomography
DICOM = Digital Imaging and Communications in Medicine
EBL = Estimated blood loss
SPSS = Statistical Package for the Social Sciences
SD = Standard deviation
IQR = Interquartile range
CH2 = Chi-square
BMI = Body mass index
CCI = Charlson comorbidity index
TST = Total surgical time
RN = Radical nephrectomy
ARI = Acute renal injury
GFR = Glomerular flow rate

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Posterior Bulboprostatic Excision and Primary Anastomosis for Pelvic Fracture Urethral Injury: Long-term Objective and Patient-reported Outcomes

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ABSTRACT

Purpose: Posterior bulboprostatic excision and primary anastomosis (EPA) is considered standard of care for obliterative or disruptive pelvic fracture urethral injuries (PFUIs), yet validated patient-reported outcomes (PROMs) in this setting remain limited. We aimed to evaluate long-term reintervention-free survival (RFS) and PROMs following EPA.

Patients and Methods: This retrospective study included male patients undergoing transperineal bulboprostatic EPA for PFUI between 2014 and 2024 at a tertiary reconstructive referral center. Data collected included trauma etiology, comorbidities, prior interventions, operative details, and follow-up duration. Co-primary endpoints were RFS estimated by Kaplan-Meier analysis, and PROMs assessed using validated instruments.

Results: Seventy patients (median age 48 years) underwent EPA. Initial management included suprapubic catheter (77%), endoscopic (21%), or open realignment (1.4%). Median operative time was 77 minutes; median follow-up was 53 months. RFS was 87% at 2 years and 84% at 5 years. PROMs—available in 53% of patients at median 71 months—included moderate voiding/incontinence symptoms (median LUTS score 6; ICIQ-UI SF 7), severe erectile dysfunction (IIEF-EF 7), preserved ejaculatory function (MSHQ-Ej 24), high satisfaction (ICIQ-S 21; global satisfaction 9), and negligible decision regret (median 0). Limitations include retrospective design and incomplete PROM data (53% response rate).

Conclusions: Bulboprostatic EPA offers durable anatomical success and high long-term patient satisfaction despite persistent functional impairments largely linked to initial trauma. Most patients expressed minimal regret and willingness to repeat the procedure. These outcomes reinforce EPA's role as the standard of care in PFUI management.

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INTRODUCTION

Bulboprostatic excision and primary anastomosis (EPA) is the gold standard for managing pelvic fracture urethral injuries (PFUIs) involving complete urethral disruption. These injuries typically result from road traffic accidents, motor vehicle collisions, or falls from height and most often affect otherwise healthy men in midlife who suddenly face profound functional and quality-of-life impairments. In cases of partial urethral rupture, primary realignment may be feasible and is associated with a reduced risk of stricture formation. In contrast, complete ruptures generally require urinary diversion followed by delayed urethroplasty (1).

Although bulboprostatic EPA for PFUI is widely performed and strongly endorsed by both American (2) and European guidelines (1)—with numerous surgical series available—there remains a notable lack of data on patient-reported outcome measures (PROMs). Most existing studies focus exclusively on anatomical or functional endpoints, often overlooking quality-of-life domains that are highly relevant to this patient population (3-19). This is particularly striking given that current urethral stricture disease guidelines explicitly recommend the use of PROMs to assess patient satisfaction and outcomes (20).

This gap is especially important because PFUIs predominantly affect young men in the prime of life. For these individuals, treatment goals extend well beyond technical success—they include the restoration of continence, sexual function, and overall well-being after a life-altering trauma. In this context, PROMs are essential for capturing outcomes that truly matter to patients.

We hypothesized that patients undergoing bulboprostatic EPA for PFUI would report high levels of treatment satisfaction but may experience long-term functional sequelae, particularly affecting urinary continence and sexual function. To address this knowledge gap, we analyzed long-term functional and patient-reported outcomes in a contemporary cohort of patients who underwent bulboprostatic EPA for PFUI at our high-volume reconstructive referral center over the past decade.

PATIENTS AND METHODS

Study Population and Data Extraction

This retrospective observational study was approved by the Ethics Committee of the Medical Council of Hamburg (No. PV4123) and conducted in accordance with the Hamburg Hospital Act (§12.1 HmbKHG). We identified all male patients who underwent bulboprostatic EPA, defined by the operation and procedure classification system (OPS) code 5-584.5, between June 2014 and May 2024. Eligible patients had a documented history of PFUI with partial or complete urethral disruption at the bulbomembranous junction. Patients with posterior urethral stenoses of other etiologies, such as vesicourethral anastomotic stenosis following radical prostatectomy, were excluded. Electronic medical records were reviewed to extract data on demographics, trauma characteristics, stricture extent, prior interventions, and surgical details. Follow-up was conducted via structured telephone interviews and an online questionnaire.

Study End Points

Endpoints included both objective and subjective outcomes. Objective outcomes comprised functional success, defined as reintervention-free survival, with recurrence indicated by any postoperative intervention for recurrent urethral stricture (21) and perioperative complications within 30 days, classified according to the Clavien–Dindo system (22).

Subjective outcomes were assessed using a comprehensive set of validated PROMs. All instruments use linear scoring systems and have been validated to assess patient-centered outcomes across key domains, including voiding symptoms, continence, erectile and ejaculatory functions, treatment satisfaction, and decision regret. Lower urinary tract symptoms (LUTS) were evaluated using the Urethral Stricture Surgery (USS) PROM six-item LUTS score ranging from 0 to 24 (23, 24); higher scores indicate more severe symptoms. Urinary incontinence was assessed using the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF), comprising three items and yielding a total score between 0 and

21 (25) with higher scores reflecting greater incontinence severity. Erectile function was measured using the erectile function domain of the International Index of Erectile Function (IIEF-EF), which includes six items and produces a score ranging from 1 to 30 (26); higher scores indicate better erectile function. To account for non-intercourse responses, scoring was adjusted according to the method proposed by Vickers et al. (27). Ejaculatory function was assessed using the ejaculatory function domain of the Male Sexual Health Questionnaire (MSHQ-Ej), which includes seven items and yields a score from 1 to 35 (28) with higher scores indicating better function. Satisfaction with surgical outcomes was measured using the ICIQ-Satisfaction module (ICIQ-S), consisting of six items forming an outcome score between 0 and 24, along with a separate item for overall satisfaction with surgery rated on a scale from 0 to 10; (29) higher scores reflect greater satisfaction. Decisional regret was evaluated using the five-item Decision Regret Scale (DRS), with a total score ranging from 0 to 100 (30); higher scores indicate greater regret regarding the decision to undergo surgery.

Perioperative Management and Surgical Procedure

Preoperative evaluation followed our institutional protocol and included medical history, physical examination, urinalysis, and combined retrograde urethrography with voiding cystourethrography to assess stenosis extent. All patients had a suprapubic catheter in place before surgery. Procedures were performed by two experienced reconstructive urologists (MF, RD) using a standardized perineal approach, as originally described by Webster (3, 31).

Briefly, the patient was positioned in lithotomy, and a midline perineal incision was made. The bulbospongiosus muscle was dissected from the corpus spongiosum, and the bulbar urethra was mobilized to the pelvic floor. A 22 F metal sound was introduced through the external meatus to identify the distal edge of the stenosis, which was then transected and spatulated just distal to the fibrotic cone. Proximal dissection continued until healthy urethra at the prostatic apex was reached and similarly spatulated. A tension-free end-to-end anastomosis was performed using eight interrupted 4-0 absorbable monofilament sutures. Ancillary maneuvers—such as extensive urethral mobilization, corporal body separation, or inferior pubectomy—were used when needed to bridge the urethral gap (3, 31, 32). A 16 F silicone catheter was placed transurethrally, and a drain was positioned between the bulbar urethra and bulbospongiosus muscle, typically removed after 24–48 hours. Patients were usually discharged on postoperative day 5. At three weeks postoperatively, a voiding cystourethrogram was performed. In the absence of contrast extravasation and with successful spontaneous voiding, the suprapubic catheter was removed. If extravasation was present, the catheter was maintained for one additional week, followed by repeat imaging. Both the surgical technique and postoperative management were standardized across the cohort.

Statistical Analyses

Baseline clinical characteristics were summarized descriptively. Continuous variables are presented as medians with interquartile ranges (IQRs) and as means with standard deviations (SDs); categorical variables are shown as absolute frequencies and percentages. Median follow-up among censored patients was estimated using the reverse Kaplan–Meier method. Reintervention-free survival was analyzed and visualized with Kaplan–Meier survival curves. To retrospectively assess recalled erectile function after the initial trauma but prior to bulboprostatic EPA, patients were asked: "Did you notice any deterioration in your erectile function after the traumatic urethral injury/pelvic trauma?" Response options were: 1 – Yes, significantly worse; 2 – Yes, somewhat worse; 3 – No, unchanged; 4 – No, somewhat improved; 5 – No, significantly improved. Validated PROMs were assessed according to their respective scoring guidelines. Scores are presented as medians with IQRs and were visualized using violin plots. All statistical analyses were performed using Stata, Release 18 (StataCorp LLC, College Station, TX, USA).

RESULTS

Clinical Baseline Characteristics

A total of 70 patients underwent bulboprostatic EPA between June 2014 and May 2024 at our institution. Baseline characteristics are summarized in Table-1. The median age at surgery was 48 years (IQR 31–56), and the median body mass index (BMI) was 26 kg/m² (IQR 24–28). Concomitant bladder neck injury was present in 7 patients (10%), and rectal injury occurred in 6 patients (8.8%) at the time of initial trauma. Initial urethral management consisted of suprapubic catheter placement in 54 patients (77%), endoscopic realignment in 15 patients (21%), and open realignment in 1 patient (1.4%). The median interval from trauma to reanastomosis was 11 months (IQR 6–20), and the median operative time of bulboprostatic EPA was 77 minutes (IQR 65–93). To achieve a tension-free anastomosis, corporal splitting was performed in 65 patients (93%), and inferior pubectomy was required in 2 cases (2.9%).

Reintervention-Free Survival and Postoperative Complications

At a median follow-up of 53 months (IQR 8–78), 8 patients (11%) required reintervention for recurrent urethral stricture. The estimated reintervention-free survival was 87% at 2 years and 84% at 5 years (Figure-1). Specifically, five patients underwent endoscopic interventions, including internal urethrotomy (n = 5); in one case, this was combined with transurethral scar tissue resection. Three patients required repeat bulboprostatic EPA due to recurrent stricture. Of these, one ultimately underwent permanent suprapubic catheter placement following failed revision surgery. Two patients (2.9%) experienced major postoperative complications classified as Clavien–Dindo grade ≥IIIa. Both presented with wound infections and localized abscess formation, which were managed with drainage under local anesthesia.

Patient-reported Outcome Measures

PROMs were collected at a median follow-up of 71 months (IQR 49–103), with complete data available for 37 patients (53%). Of all patients who responded to the retrospective question on erectile function after the initial trauma but prior to urethral reconstruction, 29 (78%) reported that their erectile function had become significantly or somewhat worse compared to their pre-trauma baseline. The distribution of the validated postoperative PROM scores is illustrated in Figure-2. The median postoperative LUTS score was 6 (IQR 3–12), indicating generally restored voiding function. The median ICIQ-UI SF score was 7 (IQR 0–12), corresponding to moderate urinary incontinence.(33) Erectile function, as measured by the IIEF-EF domain, had a median score of 8 (IQR 4.5–27), suggesting substantial variability in postoperative outcomes. Notably, the distribution was bimodal, with two distinct peaks indicating subgroups with preserved versus impaired erectile function. Median ejaculatory function, assessed via the MSHQ-Ej, was 24 (IQR 16–31), suggesting relatively better preservation of this domain. The median ICIQ-S outcome score was 21 (IQR 19–23), and the median overall satisfaction with surgery was 9 (IQR 6–10), reflecting a high level of patient satisfaction. Figure-3 illustrates the distribution of responses to the six individual ICIQ-S items, which collectively form the ICIQ-S outcome score (range: 0–24). Finally, the median DRS score was 0 (IQR 0–15), indicating negligible regret regarding the decision to undergo surgery.

DISCUSSION

Successful treatment of PFUIs through open reconstruction hinges on two central outcomes: long-term urethral patency without the need for reintervention and optimal functional recovery following severe trauma. This includes satisfactory voiding, continence, preservation of sexual function, high treatment satisfaction, and minimal decision regret. While multiple studies have reported on anatomical outcomes and surgical techniques for bulboprostatic EPA in the context of PFUI (3-19), this is the first study to incorporate a comprehensive battery of validated PROMs—offering a detailed view of patient-centered outcomes in this high-impact clinical scenario.

Table 1 – Clinical baseline and surgical characteristics in 70 men undergoing transperineal bulboprostatic excision and primary anastomosis between June 2014 and May 2024 at a tertiary reconstructive referral center.

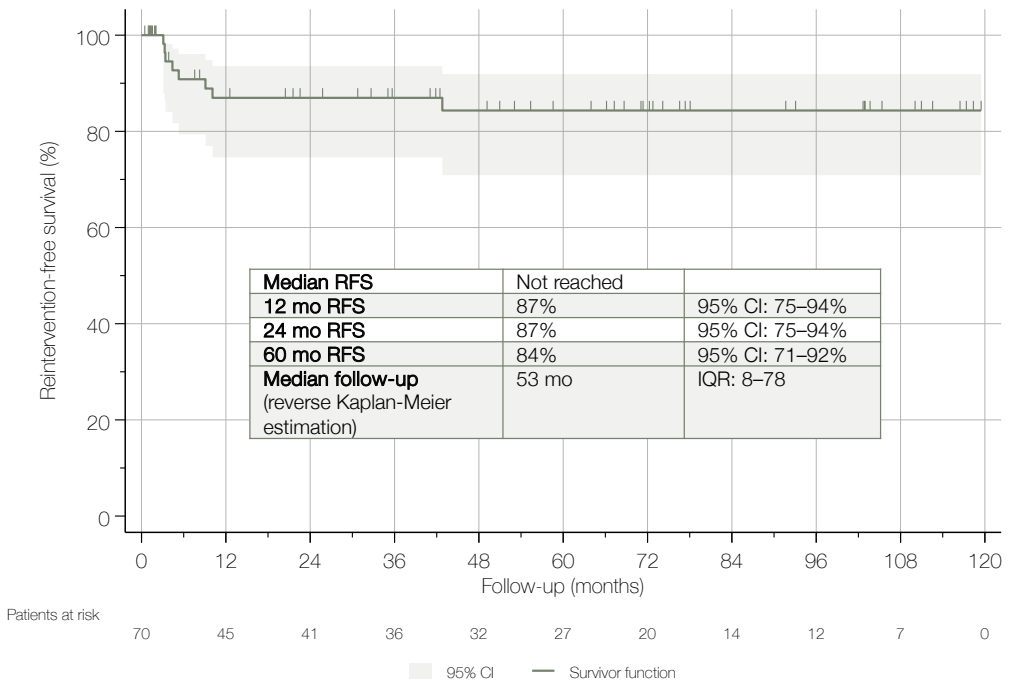
Baseline and surgical characteristics	
Patients, n (%)	70 (100)
Age at surgery (yr), median (IQR); mean (SD); range	48 (31–56); 44 (15); 16–72
BMI, median (IQR); mean (SD); range	26 (24–28); 26 (4.2); 18–36
Comorbidities, n (%)	
Diabetes	2 (2.9)
Hypertension	9 (13)
Smoking	26 (37)
ASA physical status, n (%)	
I	12 (17)
II	48 (69)
III	10 (14)
Concomitant primary trauma characteristics, n (%)	
Rectal injury	6 (8.8)
Bladder neck injury	7 (10)
Initial urethral management, n (%)	
Suprapubic catheter only	54 (77%)
Endoscopic realignment	15 (21)
Open realignment	1 (1.4)
Time from initial trauma to reanastomosis (months), median (IQR); mean (SD); range	11 (6-20); 36 (86); 1–550
Operative time (minutes), median (IQR); mean (SD); range	77 (65–93); 79 (47); 44–170
Ancillary maneuvers performed intraoperatively, n (%)	
Corporal splitting	65 (93%)
Inferior pubectomy	2 (2.9%)

ASA = American Society of Anesthesiologists; BMI = body mass index (kg/m^2); IQR = interquartile range; SD = standard deviation.

Our findings confirm that bulboprostatic EPA offers durable reintervention-free survival, with 2- and 5-year success rates of 87% and 84%, respectively. These results are consistent with previously reported outcomes and reinforce the status of bulboprostatic EPA as the gold standard for managing complete PFUI (3-19). Importantly, this study goes beyond technical success to examine functional outcomes from the patient's perspective, an aspect that has been underrepresented in literature to date.

Despite restored urethral patency in the majority of cases, our PROM data show that many patients continue to experience moderate voiding symptoms and urinary incontinence. These findings underscore the fact that anatomical success does not necessarily equate to complete functional recovery. While earlier studies have described incontinence following bulboprostatic surgery (3-19), definitions of continence and incontinence vary widely, and few have used validated tools to assess this domain. This

Figure 1 – Kaplan-Meier curve depicting reintervention-free survival in 70 patients undergoing transperineal bulboprostatic excision and primary anastomosis for pelvic fracture urethral injury.



CI = confidence interval; IQR = interquartile range; RFS = reintervention-free survival.

study provides the first PROM-based quantification of urinary function after bulboprostatic EPA for PFUI, revealing meaningful residual symptoms that may warrant further management in selected patients.

Sexual function emerged as another domain with notable impairment. Erectile function, as assessed by the IIEF-EF, was the most adversely affected PROM, with scores indicating relatively severe dysfunction in a substantial proportion of patients. Interestingly, the bimodal distribution of IIEF-EF scores suggests heterogeneity in postoperative outcomes—likely reflecting differences in the severity of initial trauma and preexisting erectile dysfunction. In fact, 78% of patients had documented erectile dysfunction prior to surgery, consistent with the understanding that sexual function is often compromised by the injury itself rather than the reconstructive procedure. This aligns with the limited number of studies that have applied validated PROMs in this setting. Two such studies demonstrated that erectile dysfunction was primarily attributable to the initial trauma, with reconstructive surgery having little further impact on sexual outcomes (14, 19). Our findings support this conclusion and emphasize the importance of preoperative counseling regarding realistic expectations for postoperative sexual function. In contrast to erectile dysfunction, ejaculatory function appeared to be relatively well preserved in our cohort. While few prior studies have addressed this specific domain, our results indicate that ejaculatory function may remain intact in many patients—even in the context of extensive urethral reconstruction. Further research is warranted to explore the mechanisms underlying this preservation and to confirm these findings in larger cohorts.

Patient satisfaction and decision-making confidence are critical—yet often overlooked—outcomes in reconstructive urology. To our knowledge, this is the first study to assess both treatment satisfaction and decisional regret using validated instruments in a PFUI population undergoing bulboprostatic EPA. The high satisfaction scores and low DRS values observed in our cohort suggest that, despite ongoing functional limitations, most patients viewed their surgical outcomes

Figure 2 – Violin plots illustrating the distribution of scores for validated patient-reported outcome measures in 37 of 70 patients undergoing bulboprostatic excision and primary anastomosis. ICIQ indicates International Consultation on Incontinence Questionnaire; ICIQ-UI SF, International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form; IIEF, International Index of Erectile Function; IQR, interquartile range; LUTS, lower urinary tract symptoms; MSHQ, Male Sexual Health Questionnaire; USS PROM, Urethral Stricture Surgery Patient-Reported Outcome Measure.

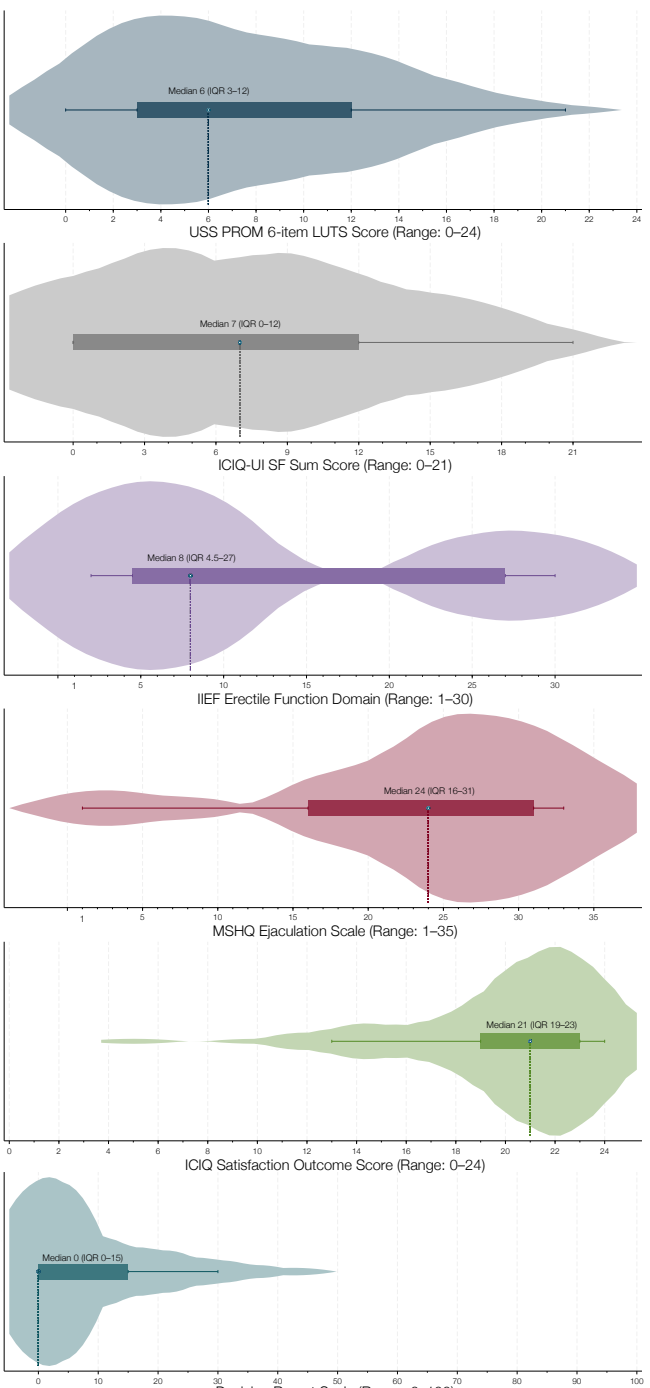
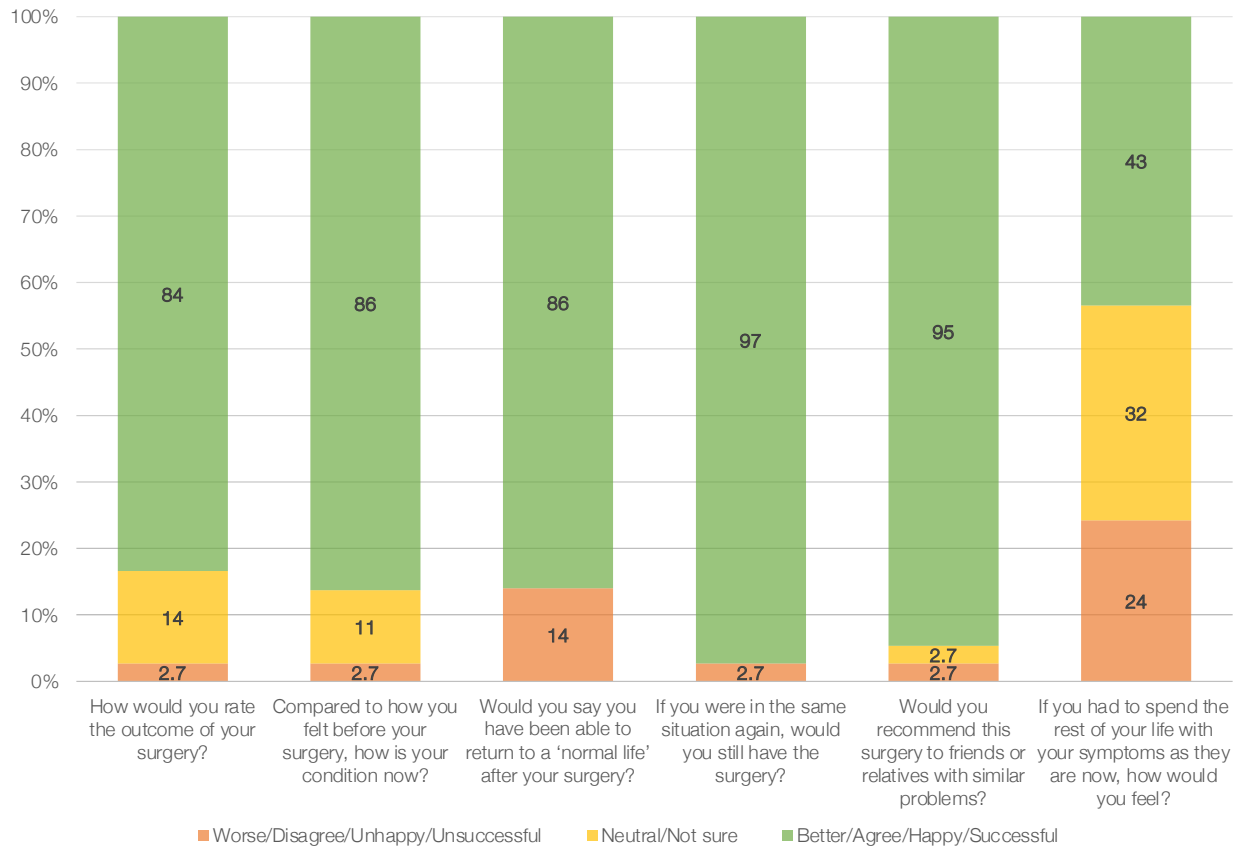


Figure 3 – ICIQ-Satisfaction (ICIQ-S) outcomes questions survey results (n = 37). Percentages may not add up to 100%, as they are rounded.



positively and would choose the intervention again. This highlights the overall value of bulboprostatic EPA not only as a technically effective procedure but also as a meaningful intervention from the patient's perspective.

Our findings should be interpreted considering several limitations. First, the retrospective design and relatively small sample size limited our ability to perform multivariable analyses to identify predictors of adverse outcomes. Second, the cross-sectional nature of PROM collection may not fully capture longitudinal changes in patient function and satisfaction. Third, the lack of preoperative PROM data restricts our ability to quantify change over time, particularly in functional domains such as continence and sexual health. However, our inclusion of treatment satisfaction and decisional regret offers important complementary insight into the overall patient experience. Fourth, recall and response bias cannot be excluded, particularly in retrospective assessments of preoperative function or satisfaction. Fifth, although the response rate of 53% for the PROMs is suboptimal, this limitation is common in retrospective and survey-based studies. Consequently, the available data may be subject to response bias, as patients who complete PROMs are often more motivated or satisfied than non-responders. Nonetheless, this study fills a literature gap by applying a validated, multi-dimensional PROM framework to a procedure that is both technically demanding and functionally consequential. By systematically evaluating the outcomes that matter most to patients—beyond anatomical success—we offer a more complete understanding of the benefits and limitations of bulboprostatic EPA for PFUI.

CONCLUSIONS

Bulboprostatic EPA offers durable reintervention-free survival and remains the gold standard for the

surgical management of PFUIs. While validated PROMs highlight ongoing functional challenges—particularly related to urinary incontinence and erectile dysfunction—these issues likely reflect the severity of the initial trauma rather than surgical shortcomings. Despite these limitations, patient-reported satisfaction was high, and decisional regret was minimal. Most patients indicated they would choose the procedure again, underscoring the meaningful clinical and quality-of-life benefits of bulboprostatic EPA. These findings emphasize the importance of incorporating PROMs into routine outcome assessment and support the role of bulboprostatic EPA as a patient-centered, effective treatment for PFUI.

CONFLICT OF INTEREST

None declared.

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Quality of Life in Patients with Ureteral Stones: Translation and Validation of the Brazilian Version of the Cambridge Ureteral Stone PROM (Br-CUSP)

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ABSTRACT

Purpose: There is currently no validated instrument in Brazil specifically designed to assess the quality of life (QoL) of patients with ureteral stones. The Cambridge Ureteral Stone Patient-Reported Outcome Measure (CUSP) is a self-administered questionnaire that evaluates the QoL impact of ureteral stones over the preceding seven days. This study aimed to translate, culturally adapt, and validate the CUSP for Brazilian Portuguese (Br-CUSP) for clinical and research applications.

Materials and Methods: The CUSP questionnaire was translated into Portuguese according to Guillemin's cross-cultural adaption guidelines. Patients with and without ureterolithiasis completed both the Br-CUSP and SF-12 questionnaires. Psychometric validation included assessment of internal consistency, test-retest reliability, convergent validity, and discriminant validity.

Results: A total of 156 participants completed both questionnaires. No inconsistencies emerged during univariate analysis. Confirmatory factor analysis supported the six-factor model with satisfactory fit indices. All factor loadings exceeded 0.50. Internal consistency was high across all domains (Cronbach's α = 0.72 - 0.98; McDonald's ω = 0.73 - 0.98). Test-retest reliability demonstrated strong temporal stability. Inter-domain correlations (Spearman's p = 0.45 - 0.82) supported structural coherence. Convergent validity was confirmed through inverse correlations with SF-12 scores. Discriminant validity was demonstrated by significant score differences between patients with and without ureteral stone, with large effect sizes.

Conclusions: The Brazilian Cambridge Ureteral Stone Patient-Reported Outcome Measure is a valid, reliable tool for assessing health-related quality of life in Brazilian patients with ureteral stones. Its implementation can enhance both clinical assessment and research into patient-centered outcomes in urolithiasis.

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INTRODUCTION

Urolithiasis is a highly prevalent condition that significantly impairs patients' quality of life (QoL) due to unexpected pain, discomfort, and temporary disability (1-5). Recurrence rates range from 30% to 50% within five years, imposing a substantial and often recurrent burden on patients' daily lives (6-10).

Despite its clinical impact, outcome measures primarily focus on stone-free rates (SFR), neglecting patient-centered outcomes such as QoL (11). Notably, neither the European Association of Urology nor the American Urological Association guidelines currently recommend the routine incorporation of QoL metrics in treatment planning for ureteral stones (12, 13).

Integrating health-related quality of life (HRQoL) assessment into clinical care offers a more holistic view of disease burden by capturing patient's physical, psychological, and social functioning. This approach aligns with patient-centered care principles by ensuring treatment strategies reflecting both clinical efficacy and individual patient experiences (14, 15).

Patient-reported outcome measures (PROMs) are validated instruments designed to objectively quantify the patient's perception of disease impact (16). The Cambridge Ureteral Stone PROM (CUSP) is a disease-specific, self-administered questionnaire comprising 26 items across six domains: pain, fatigue, daily activities, sleep disturbances, anxiety, and urinary symptoms. Each item is rated on a five-point Likert scale, with higher scores indicating worse HRQoL (17). Unlike other HRQoL tools, the CUSP is specifically designed for ureteral stone patients and uniquely evaluates symptom burden over the preceding seven days, enhancing its clinical relevance for monitoring short-term treatment outcomes (12).

No validated instruments currently exist in Brazilian Portuguese to assess QoL specifically in patients with ureteral stones. We hypothesize that the CUSP questionnaire can be effectively validated for use in Brazil. Therefore, the objective of this study was to conduct a cross-cultural adaptation and psychometric validation of the CUSP questionnaire for Brazilian Portuguese (Br-CUSP), ensuring linguistic and conceptual equivalence while maintaining its measurement properties.

MATERIALS AND METHODS

Study Design and Participants

This prospective study was conducted at a specialized public university hospital between December 2022 and May 2023. Eligible participants were adults over 18 years old, fluent in Portuguese, with or without tomography verified ureteral stones. All participants provided written informed consent prior to enrollment. The study adhered to the principles of the Declaration of Helsinki and received ethical approval from the institutional review board (IRB approval number 64388822.9.0000.0068).

Exclusion criteria included the presence of kidney stones, other urological conditions, pelvic pain syndrome, use of anticholinergics, alpha-blockers, calcium channel blockers, phosphodiesterase type 5 inhibitors, age under 18 years, illiteracy, or known psychiatric disorder.

Translation and Cultural Adaptation

The CUSP questionnaire was translated into Brazilian Portuguese by two independent native Portuguese-speaking translators with expertise in Urology. Next, a consensus meeting involving the authors was held. Subsequently, an independent bilingual professional back-translated the questionnaire into English. The original author compared both versions, resolving discrepancies through further consensus meetings. A pilot test was conducted with 20 patients to evaluate comprehension and clarity.

Data Collection

Patients completed the self-administered Br-CUSP questionnaire twice, with a two to three hours interval between administrations to assess test-retest reliability. Discriminant validity was assessed using SF-12 Health Survey (version 1.0), a generic measure of health-related quality of life already

translated and validated for Brazilian Portuguese (18). The SF-12 consists of two components: Physical Component Score (PCS-12) and Mental Component Score (MCS-12), with higher scores indicating better QoL. These scores are interpreted inversely relative to CUSP, in which higher scores denote worse HRQoL.

Statistical Analysis

Internal Structure Validity

Analyses were performed using JASP software (version 0.18.3). Confirmatory Factor Analysis (CFA) was conducted to assess the internal structure of the Br-CUSP, following the six-domain model originally proposed by Tran et al. (17). Given the categorical nature of the Likert-scale data, the mean- and variance-adjusted weighted least squares (WLSMV) estimator with robust standard errors based on polychoric correlations was used. A factor loading threshold of > 0.40 was applied.

Model fit was assessed using chi-square ($\chi 2$), degrees of freedom (df), $\chi 2$/df ratio (acceptable < 5; ideal < 3), Root Mean Square Error of Approximation (RMSEA; acceptable < 0.08), Comparative Fit Index (CFI; > 0.95), Tucker-Lewis Index (TLI; > 0.95), and Standard Root Mean Square Residual (SRMR; < 0.08).

Internal Consistency and Reliability

Internal consistency of the Br-CUSP domains was assessed using Cronbach's alpha and McDonald's omega, with values ≥ 0.70 considered acceptable. Additionally, the Average Variance Extracted (AVE) was calculated to evaluate the proportion of variance captured by each construct relative to error variance, with AVE ≥ .50 considered adequate.

Convergent Validity

Convergent validity was evaluated using Spearman's correlation (rho) between the Br-CUSP domains and SF12 scores. Negative correlations were expected, as higher Br-CUSP scores reflect worse HRQoL, while higher SF-12 scores reflect better HRQoL. Correlation values were interpreted as follows: ± 0.1 represents a small effect, ± 0.3 a medium effect, and ± 0.5 a large effect.

Discriminant Validity

Discriminant validity was assessed by comparing Br-CUSP scores between patients with and without ureteral stones. Independent sample t-tests were used for comparisons. Levene's test assessed variance homogeneity, and Welch's statistic was used when homogeneity was not met. Bootstrapping procedures (1,000 resamplings; 95% CI BCa) corrected distribution normality deviations and increased result reliability (19). Effect sizes was calculated using Hedges' g to adjust for unbalanced sample bias. Effect sizes were interpreted as follows: negligible effect (< 0.20); small effect (0.21- 0.39); medium effect (0.40 - 0.79); large effect (≥ 0.80).

RESULTS

Participants

Demographic and clinical characteristics are summarized in Table-1. A total of 156 patients completed both self-administered questionnaires. The sample was gender-balanced, comprising 78 males and 78 females (50.0%). The most common education level was high school (n = 72; 46.15%).

Among the study cohort, 129 participants (82.7%) had ureteral stones confirmed by computed tomography, while 27 (17.3%) had no urinary stones. Of those with ureteral stones, 48 (30.7%) had stones located in the proximal ureter, and 42 (26.9%) had an indwelling double-J stent. A history of previous stone events was reported by 90 patients (57.7%). Most participants had no comorbidities (n = 89, 57.1%).

Construct Validity

No univariate inconsistency was detected. Item means ranged from 1.92 to 3.25, with acceptable skewness and kurtosis values. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was 0.95, and Bartlett's test of sphericity was significant ($\chi 2 = 1675.1$, df = 325; $p < 0.001$).

Table 1 - Demographic and clinical features of the study population.

Feature	N	%
Sex		
Female	78	50.0
Education		
Incomplete	10	6.4
Elementary school	36	23.1
High school	72	46.2
University graduate	26	16.7
Postgraduate studies	12	7.7
Race		
White	74	47.4
Black / African American	19	12.2
Asian	6	3.9
More than one race	54	34.6
Missing	3	1.9
Occupation		
Student	7	4.5
Working	100	64.1
Unemployed	9	5.8
Retired	23	14.7
Housewife	17	10.9
Ureteral stone	129	82.7
Previous stone event	90	57.7
Indwelling ureteral stent	42	26.9
Comorbidity	67	43.0
ASA		
I	77	49.4
II	73	46.8
III	5	3.2

ASA = American Society of Anesthesiologists Physical Status

The results from the confirmatory factor analysis are presented in Supplementary material 1. All factor loadings were statistically significant and exceeded 0.50. The values indicate an adequate fit for the six-factor model ($\chi2 = 180.855$, df = 284, $p < 0.001$; $\chi2/df$ ratio = 0.64, CFI =0 .99, TLI = 0.99, RMSEA = 0.05 [90% CI: 0.04 - 0.06], SRMR = 0.04).

Internal Consistency

Internal consistency of the Br-CUSP domains was high across all six factors: Factor 1 - pain: $\alpha = 0.98$ (95% CI: 0.97-0.98), $\omega = 0.98$ (95% CI: 0.97-0.98); Factor 2 - fatigue: $\alpha = 0.95$ (95% CI: 0.94-0.97), $\omega = 0.96$ (95% CI: 0.94-0.97); Factor 3 - work, daily activities, and travel: $\alpha = 0.95$ (95%

CI: 0.93-0.96), ω = 0.95 (95% CI: 0.93-0.96); Factor 4 - sleep disturbances: α= 0.92 (95% CI: 0.89-0.94), ω= 0.92 (95% CI: 0.90-0.94); Factor 5 - anxiety: α = 0.89 (95% CI: 0.85-0.92), ω= 0.89 (95% CI: 0.84-0.93); Factor 6 - urinary symptoms: α = 0.72 (95% CI: 0.64-0.79), ω= 0.73 (95% CI: 0.63-.81). The Average Variance Extracted (AVE) was 0.90 for Factor 1, 0.88 for Factor 2, 0.90 for Factor 3, 0.76 for Factor 4, 0.79 for Factor 5, and 0.57 for Factor 6, all of which considered adequate.

Inter-Domain Correlations

Supplementary material 2 summarizes the Spearman's correlation coefficient between Br-CUSP domains ranged from 0.45 to 0.82, indicating that each evaluated domain captures a distinct but related dimension of the patient's experience.

Convergent Validity

Spearman's correlation coefficients between Br-CUSP domains and the two components of the SF-12 scale were significant and negative, as hypothesized. Correlations with the PCS-12 and MCS-12 scores ranged from -0.67 to -0.42, confirming that higher Br-CUSP scores were associated with lower SF-12 scores (Supplementary material 2).

Discriminant Validity - Known Groups Analysis

Welch's t-test detected significant differences in all Br-CUSP domains between patients with and without ureteral stones (Table-2). In all comparisons, scores were higher (worse QoL) for the ureteral stone group, with large effect sizes ([Total score: ΔM = -51.72, 95% CI Bca (-56.17; -47.35), g = 3.10; Pain: ΔM = -19.39, 95% CI Bca (-21.24; -17.56), g = 2.87; Fatigue: ΔM = -9.59, 95% CI Bca (-10.70; -8.44), g = 2.30; Work: ΔM = -6.19, 95% CI Bca (-6.97; -5.40), g = 2.32; Sleep: ΔM = -7.79, 95% CI Bca (-8.79; -6.73), g = 2.39; Anxiety: ΔM = -5.62, 95% CI Bca (-5.62; -3.80), g = 1.76; Urinary Symptoms: ΔM = -3.99, 95% CI Bca (-4.65; -3.37), g = 1.76]).

Test-Retest Reliability

Spearman's correlations for the CUSP-Br domains between time 1 (baseline) and time 2 were high (rho 0.96 – 0.99), indicating excellent temporal stability.

DISCUSSION

This study presents the first cross-cultural adaptation and validation of a disease-specific QoL questionnaire for patients with ureteral stones into Brazilian Portuguese (Br-CUSP), while preserving

Table 2 - Evidence of discriminant validity.

Domain	Patients without ureteral stone (n = 27)	Patients with ureteral stone (n = 129)	Welch	Df	Difference	CI 95% - Bca Bootsstrap (Lower; Upper)		Effect's size (Hedges'g)
Total Score	**30.93 (4.27)**	**82.64 (23.11)**	**-23.57***	**153.11**	**-51.72**	**-56.17**	**-47.35**	**3.10**
Pain	8.52 (1.34)	27.91 (9.42)	-22.33*	147.20	-19.39	-21.24	-17.56	2.87
Fatigue	5.78 (1.22)	15.37 (5.75)	-17.19*	153.93	-9.59	-10.70	-8.44	2.30
Work	3.74 (1.29)	9.93 (3.53)	-15.56*	114.58	-6.19	-6.97	-5.40	2.32
Sleep	5.56 (1.91)	13.34 (4.18)	-14.98*	86.65	-7.79	-8.79	-6.73	2.39
Anxiety	3.96 (1.85)	8.74 (3.35)	-10.33*	67.45	-4.77	-5.62	-3.80	1.76
Urinary Symptoms	3.37 (0.74)	7.36 (3.10)	-12.94*	151.72	-3.99	-4.65	-3.37	1.76

*p <0 .001

Df = degrees of freedom

Welch = Welch's t-value from independent-samples t-test allowing unequal variances. Negative values indicate higher symptom scores in patients with ureteral stones compared with healthy participants

its psychometric robustness. Understanding patient's subjective experiences and emotional burden is critical in ureteral stone disease, as it directly informs clinical management and enhances patient-centered care. By offering a comprehensive, symptom-focused assessment, Br-CUSP serves as a robust patient-reported outcome measure that captures the unique and acute burden of ureteral stone disease on patients' daily lives. Furthermore, the Br-CUSP enables standardized, culturally relevant assessment of QoL, facilitating comparative studies, epidemiological research, and clinical trials tailored to the Brazilian population. This tool supports the development of evidence-based interventions, improves understanding of disease burden across diverse socioeconomic and regional contexts, and fosters international collaboration by aligning Brazilian urological research with global standards.

Our findings confirm that Br-CUSP is a reliable and valid instrument for evaluating health-related quality of life in this patient population. Reliability of Br-CUSP was demonstrated by high internal consistency across all domains and test-retest strong correlation demonstrated temporal stability. The two to three hours retest interval is appropriate given the acute nature of ureteral colic symptoms and the questionnaire's seven-day symptom recall period, ensuring minimal recall bias while accurately reflecting recent symptom burden. Convergent validity of Br-CUSP was demonstrated by inverse correlation with SF-12. Discriminant validity scores were significantly higher in all Br-CUSP domains among patients with ureteral stones compared to controls, with large effect sizes.

Quality of life should be recognized as a core outcome metric in the management of urolithiasis, providing insights beyond traditional endpoints such as SFR and complications (1, 20-24). Although Short Form 36, a generic questionnaire, is commonly used for assessing health-related quality of life in many medical conditions, it is not accurate enough to monitor quality of life in urinary stone disease (25).

The Wisconsin Stone Quality of Life (WISQOL) questionnaire is well-established PROM for nephrolithiasis (26). While WISQOL assesses broader urinary stone disease burden, CUSP focuses uniquely on the acute symptomatology of ureteral stones, offering more specific insights. Unlike WISQOL, which evaluates long-term QoL impact, CUSP captures recent (previous seven days) symptom burden, making it particularly useful for monitoring acute treatment effects (17). Future studies using Br-CUSP and WIQOL may help define their respective roles and determine whether Br-CUSP can serve as a complementary or superior alternative in the acute setting.

A key strength of our study lies in its rigorous and comprehensive validation methodology, which includes CFA, McDonald's omega for internal consistency, and robust construct validity testing. These methodological enhancements provide a level of psychometric rigor that extends beyond the original CUSP validation study (17). Notably, the inclusion of McDonald's omega offers a more reliable estimate of internal consistency than Cronbach's alpha alone. Furthermore, our validation was conducted in a demographically diverse population, supporting the broader applicability and generalizability of the CUSP questionnaire in varied clinical settings.

Nonetheless, this study is not without limitations. It was conducted at a single center, and a longitudinal responsiveness to treatment interventions was not assessed. Future research should explore Br-CUSP sensitivity to clinical changes over time and its correlations with objective clinical outcomes, such as SFR and complication rates.

CONCLUSIONS

The Brazilian Cambridge Ureteral Stone Patient-Reported Outcome Measure is the first validated, disease-specific Patient Related Outcome Measure for ureteral stones in Brazilian Portuguese, addressing a crucial gap in patient-centered outcome assessment. Its strong psychometric properties make it a reliable tool for evaluating the acute impact of ureteral stones on quality of life. Future research should explore its application in clinical decision-making, particularly by correlating quality of life outcomes with stone-free rates and complication rates.

CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplementary material 1 - Latent Variable, Indicators, and Their Respective Estimated Loadings for the Br-CUSP Scale.

Latent variables	Indicator	Standardized Factor Loading	Standard Error	z	p	R^2
Factor 1						
	#1	0.949	0.013	80.71	<0.001	0.901
	#2	0.953	0.013	74.968	<0.001	0.908
	#3	0.963	0.013	78.464	<0.001	0.927
	#4	0.935	0.015	66.646	<0.001	0.875
	#5	0.954	0.015	68.488	<0.001	0.910
	#6	0.970	0.014	74.086	<0.001	0.941
	#7	0.946	0.015	66.385	<0.001	0.895
	#8	0.927	0.020	49.318	<0.001	0.860
Factor 2						
	#9	0.943	0.01	70.35	<0.001	0.889
	#10	0.927	0.021	47.155	<0.001	0.860
	#11	0.924	0.023	42.789	<0.001	0.854
	#12	0.949	0.018	55.435	<0.001	0.900
	#13	0.956	0.019	52.475	<0.001	0.913
Factor 3						
	#14	0.934	0.020	60.19	<0.001	0.872
	#15	0.952	0.021	47.630	<0.001	0.906
	#16	0.962	0.024	43.063	<0.001	0.925
Factor 4						
	#17	0.935	0.020	50.54	<0.001	0.874
	#18	0.756	0.044	18.298	<0.001	0.572
	#19	0.880	0.032	29.783	<0.001	0.774
	#20	0.918	0.029	34.425	<0.001	0.843
Factor 5						
	#21	0.859	0.03	25.18	<0.001	0.738
	#22	0.904	0.062	17.071	<0.001	0.818
	#23	0.903	0.051	20.473	<0.001	0.816
Factor 6						
	#24	0.838	0.07	12.67	<0.001	0.702
	#25	0.622	0.117	6.363	<0.001	0.387
	#26	0.787	0.097	9.674	<0.001	0.620

Br-CUSP = Brazilian version of the Cambridge Ureteral Stone Patient-reported Outcome Measure

Supplementary material 2 - Spearman's Correlation Coefficients between Patients' Mean Scores in Each Domain and between Patients' Scores in Each Domain of the Br-CUSP and SF-12 Scale Dimensions.

Domain		Domain	*Rho*	Br-CUSP	SF-12	rho
Pain	-	Fatigue	0.82*	Total score	PCS	-0.67*
Pain	-	Work	0.81*	Total score	MCS	-0.64*
Pain	-	Sleep	0.73*	Pain	PCS	-0.65*
Pain	-	Anxiety	0.60*	Pain	MCS	-0.52*
Pain	-	Urinary symptoms	0.55*	Fatigue	PCS	-0.57*
Fatigue	-	Work	0.76*	Fatigue	MCS	-0.58*
Fatigue	-	Sleep	0.72*	Work	PCS	-0.68*
Fatigue	-	Anxiety	0.63*	Work	MCS	-0.50*
Fatigue	-	Urinary symptoms	0.50*	Sleep	PCS	-0.53*
Work	-	Sleep	0.66*	Sleep	MCS	-0.55*
Work	-	Anxiety	0.62*	Anxiety	PCS	-0.47*
Work	-	Urinary symptoms	0.51*	Anxiety	MCS	-0.66*
Sleep	-	Anxiety	0.63*	Urinary symptoms	PCS	-0.42*
Sleep	-	Urinary symptoms	0.52*	Urinary symptoms	MCS	-0.44*
Anxiety	-	Urinary symptoms	0.45*			

*p<0.001

Rho = spearman correlation; Br-CUSP = Brazilian version of the Cambridge Ureteral Stone Patient-reported Outcome Measure; SF-12 = Short-Form 12; PCS = Physical Component Score; MCS = Mental Component Score

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Validation of the Brazilian Version of the Cambridge Renal Stone Patient-Reported Outcome Measure (Br-CReSP) versus a Generic Questionnaire for Assessing Health-Related Quality of Life in Nephrolithiasis

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ABSTRACT

Purpose: No validated tool specifically assesses health-related quality of life (HRQoL) in Brazilian patients with kidney stones. The Cambridge Renal Stone Patient-Reported Outcome Measure (CReSP) is a self-administered questionnaire that evaluates the impact of kidney stones on patients' QoL over the preceding seven days. This study aimed to translate the CReSP into Portuguese, validate it, and compare it with the validated generic SF-12 questionnaire.

Materials and Methods: The CReSP questionnaire was translated into Portuguese following Guillemin's guidelines. Patients with and without kidney stones completed the Brazilian version of the CReSP (Br-CReSP) and SF-12 questionnaires. Internal consistency, test-retest reliability, discriminant validity, and convergent validity with SF-12 components were evaluated. Logistic regression assessed the discriminant capacity of Br-CReSP and SF-12 components for nephrolithiasis.

Results: One hundred patients completed both questionnaires. Internal consistency was high across all domains and the total score (Cronbach's $\alpha = 0.92$). Test-retest reliability demonstrated strong correlations for all domains and the total score (ICC = 0.94). Discriminant validity was evidenced by significant differences between patients with and without kidney stones, with large effect sizes. Convergent validity was shown by significant inverse correlations between the Br-CReSP and SF-12 ($p < 0.001$). The Br-CReSP outperformed PCS-12 and MCS-12 in predicting nephrolithiasis (AUC = 0.91 vs. 0.84 and 0.73, respectively).

Conclusions: The validated Br-CReSP outperforms SF-12 in assessing HRQoL in Brazilian patients with kidney stones.

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INTRODUCTION

Nephrolithiasis, a prevalent urological condition, significantly impairs health-related quality of life (HRQoL) due to acute pain, transient disability, and, in severe cases, renal function loss (1-6). Its incidence varies globally, influenced by geographic, climatic, ethnic, dietary, and genetic factors (7). With recurrence rates reaching up to 50% within five years, nephrolithiasis imposes a substantial and recurrent burden on patients' daily functioning (8-10).

Current outcome measures for nephrolithiasis primarily emphasize stone-free rates (SFR) and complications, often overlooking patient-centered outcomes such as HRQoL (11). Evidence on HRQoL in nephrolithiasis treatment remains limited, and neither the European Association of Urology (EAU) nor the American Urological Association (AUA) guidelines currently integrate HRQoL assessments into treatment decision-making (12, 13). Incorporating HRQoL data through validated questionnaires can standardize and quantify patients' physical and psychological well-being, fostering shared decision-making and aligning with patient-centered care principles (14, 15).

Patient-reported outcome measures (PROMs) are validated instruments designed to capture patient's perspective on disease impact (16). The Cambridge Renal Stone Patient-Reported Outcome Measure (CReSP) is a disease-specific PROM comprising 14 questions across six domains — pain, urinary symptoms, work and daily activities, anxiety, and dietary changes, and overall quality of life — scored on a Likert scale, with higher scores indicating worse HRQoL (17). Unlike other HRQoL tools, the CReSP is tailored to kidney stone patients and focuses on symptom burden over the preceding seven days, making it uniquely suited for evaluating treatment outcomes in nephrolithiasis.

We hypothesized that a disease-specific questionnaire for assessing HRQoL in patients with kidney stones would provide greater accuracy than a generic questionnaire, enabling urologists to better understand patient needs and enhance clinical practice. This study aimed to translate and validate the CReSP into Brazilian Portuguese (Br-CReSP), ensuring linguistic and conceptual equivalence while preserving its psychometric robustness. Additionally, we compared the disease-specific Br-CReSP with the generic SF-12 questionnaire to assess their relative performance in evaluating HRQoL in Brazilian patients with nephrolithiasis.

MATERIALS AND METHODS

Study design and participants

This prospective study was conducted at a specialized public university hospital, enrolling native Portuguese-speaking patients aged 18 years or older, with or without kidney stones. All participants provided written informed consent. Exclusion criteria included ureteral stones, other urological conditions, pelvic pain syndrome, use of anticholinergics, alpha-blockers, calcium channel blockers, or phosphodiesterase type 5 inhibitors, illiteracy, psychiatric disorders, or age under 18 years. Data collection occurred between December 2022 and January 2024, adhering to the Declaration of Helsinki. The study was approved by the institutional review board (IRB approval number: 83672324.7.0000.0068).

Translation and adaptation of the CReSP questionnaire

The Cambridge Renal Stone Patient-Reported Outcome Measure (CReSP) was translated into Brazilian Portuguese (Br-CReSP) following established guidelines for cross-cultural adaptation. Two independent, native Portuguese-speaking urologists performed the initial translation. A consensus meeting with the study authors resolved discrepancies. An independent bilingual professional back-translated the questionnaire into English, and the original CReSP author reviewed both versions to ensure conceptual equivalence, with further consensus meetings addressing any discrepancies (Supplementary material 1).

Data Collection

Participants completed the self-administered Br-CReSP and the validated Brazilian Portuguese SF-12 questionnaire (version 1.0, public domain) (18). The SF-12, a shortened version of the short Form 36, comprises two components: the Physical Component Score (PCS-12) and the Mental Component Score (MCS-12), with higher scores indicating better quality of life, in contrast to the

Br-CReSP, where higher scores reflect worse HRQoL. To assess temporal stability, participants completed the Br-CReSP twice, with a seven-day interval.

Statistical Analysis

Statistical analyses were performed using JASP software (version 0.18.3). Confirmatory Factor Analysis was conducted to evaluate the Br-CReSP's internal structure based on the model by Ragab et al. (17). Internal consistency was assessed using Cronbach's alpha for the total score and individual domains of Br-CReSP, with $\alpha \geq 0.70$ considered acceptable. Temporal stability was evaluated using Spearman's correlation coefficient for test-retest reliability, with coefficient interpreted as low (± 0.1), moderate (± 0.3), or strong (± 0.5). The Blant-Altman method assessed agreement between test and retest measurements.

Discriminant validity was evaluated by comparing Br-CReSP mean scores between patients with kidney stones and controls using independent sample t-tests. Levene's test assessed variance homogeneity, and Welch's statistic was applied when necessary. Bootstrapping (1,000 resamplings; 95% Bias-Corrected and accelerated confidence intervals) was used to address non-normal distributions and enhance result reliability (19). Effect sizes were categorized as small (0.20 - 0.49), medium (0.50 - 0.79), or large (≥0.80).

Convergent validity was assessed by calculating Spearman's correlation coefficient between Br-CReSP total score and the PCS-12 and MCS-12 scores of the SF-12. To compare the predictive performance of the Br-CReSP, PCS-12, and MCS-12 for kidney stones, logistic regression models were fitted for each tool, adjusted using the Wald test. Performance metrics, including area under the curve (AUC), accuracy, sensitivity, specificity, and precision, were calculated. A p-value < 0.05 was considered statistically significant.

RESULTS

Participant Characteristics

Demographic and clinical features of study population are presented in Table-1. A total of 100 patients completed both the Br-CReSP and SF-12 self-administered questionnaires. Of these, 56% were female, 66% were Caucasians, and 67% were employed. Kidney stones were present in 70 (70%) participants, with 41 (58.6%) of these reporting a previous stone event.

Validation

Descriptive statistics for the 14 items of the Br-CReSP are provided in Table-2. No univariate inconsistencies were detected. Confirmatory factor analysis confirmed an adequate fit for the six-factor structure of the Br-CReSP. Items related to pain and anxiety about pain yielded the highest scores, indicating their significant impact on patient's health-related quality of life.

Internal Consistency

Internal consistency was robust across the Br-CReSP domains and total score: pain (α = 0.91, 95% CI [0.86-0.96]), work and daily activities (α = 0.94, 95% CI [0.91-0.97]), anxiety (α = 0.85, 95% CI [0.80-0.91]), dietary changes (α = 0.82, 95% CI [0.72-0.93]), and total score (α =0.92, 95% CI[0.90-0.94]). Average inter-item correlations were 0.84 for pain, 0.84 for work and daily activities, 0.60 for anxiety, 0.70 for dietary changes, and 0.55 for the total score, all deemed satisfactory. Cronbach's alpha could not be calculated for single-item domains (urinary symptoms and intestinal symptoms); however, these domains contribute to the overall validity of the instrument.

Convergent validity

Convergent validity was assessed using Spearman's correlation between the Br-CReSP total score and the SF-12 components. As expected, significant negative correlations were observed with the PCS-12 ($r = -0.61$, $p < 0.001$) and MCS-12 ($r = -0.44$, $p < 0.001$), confirming the Br-CReSP's alignment with established HRQoL measures.

Discriminant validity

Welch's statistic revealed significant differences in all Br-CReSP domains between patients with and without kidney stones (Supplementary material 2). Scores were consistently higher in the kidney stone

Table 1 - Demographic and clinical features of the study population.

Feature	Respondents without kidney stones (N=30)	Respondents with kidney stones (N=70)
Age, years, mean (SD)	50.30 (13.21)	54.21(10.14)
Female gender, N (%)	14 (46.67)	42 (60.00)
Marital status, N (%)		
Single	7 (23.33)	18 (25.71)
Married	19 (63.33)	40 (57.14)
Window	2 (6.67)	4 (5.71)
Divorced	1 (3.33)	6 (8.57)
Missing	1 (3.33)	1 (1.43)
Other	0 (0.00)	1 (1.43
Ethnicity, N (%)		
Caucasian	20 (66.67)	46 (65.71)
African American	3 (10.00)	13 (18.57)
More than one race	7 (23.33)	11 (15.71)
Educational level, N (%)		
Incomplete	0 (0.00)	11 (15.71)
Elementary school	8 (26.67)	17 (24.29)
High school	6 (20.00)	32 (45.71)
University graduate	6 (20.00)	7 (10.00)
Postgraduation	10 (33.33)	3 (4.29)
Ocupation, N (%)		
Working	26 (86.67)	41 (58.57)
Unemployed	0 (0.00)	6 (8.57)
Retired	1 (3.33)	15 (21.43)
Housewife	3 (10.00)	8 (11.43)
Stone event, N (%)		
No	30 (100.00)	29 (41.43)
Previous treatment, N (%)		
Medical expulsive therapy	1 (3.33)	24 (34.29)
Ureteroscopy	3 (10.00)	8 (11.43)
Shockwave lithotripsy	1 (3.33)	20 (28.57)
Percutaneous nephrolithotomy	2 (6.67)	13 (18.57)
No treatment	23 (76.67)	5 (7.14)

SD = Standard deviation

Table 2 - Descriptive statistics for the 14 items of Br-CReSP.

Descriptor	Mean	Standard Deviation	Variance	Skewness	Kurtosis
1. How much did pain interfere with your day-to-day activities?	2.12	1.37	1.86	0.85	-0.66
2. How much did pain interfere with your enjoyment of life?	2.06	1.43	2.06	0.98	-0.57
3. how much did you worry about pain?	4.70	3.77	14.21	0.35	-1.58
4. I have had blood in my urine	1.55	1.12	1.26	2.06	3.11
5. I have nausea	1.61	1.02	1.05	1.71	2.30
6. I have trouble doing all my usual work include work at home	2.07	1.35	1.82	0.82	-0.77
7. I have trouble doing all my regular leisure activities with others	1.95	1.31	1.72	1.13	-0.05
8. I have trouble doing all my family activities that I want to do	1.92	1.28	1.65	1.09	-0.20
9. I felt fearful	2.22	1.45	2.09	0.75	-0.84
10. I found it hard to focus on anything over than my anxiety	2.01	1.28	1.63	0.97	-0.28
11. My worries overwhelmed me	2.47	1.50	2.25	0.47	-1.23
12. I am bothered by side effects of treatment	1.78	1.24	1.53	1.45	0.98
13. How much have you been bothered by recommended alterations to your fluid intake?	1.63	1.06	1.12	1.73	1.93
14. How much have dietary of fluid changes affected your daily life?	1.62	1.07	1.15	1.72	1.83

group, with large effect sizes, demonstrating the Br-CReSP's ability to discriminate between groups based onHRQoL. Logistic regression models predicting nephrolithiasis demonstrated superior performance for the Br-CReSP compared to PCS-12 and MCS-12, with higher accuracy (0.86 vs. 0.74 vs. 0.68), ACU (0.91 vs. 0.84 vs. 0.73), sensitivity (0.86 vs. 0.79 vs. 0.86), specificity (0.87 vs. 0.63 vs. 0.27), and precision (0.94 vs. 0.83 vs. 0.73), respectively.

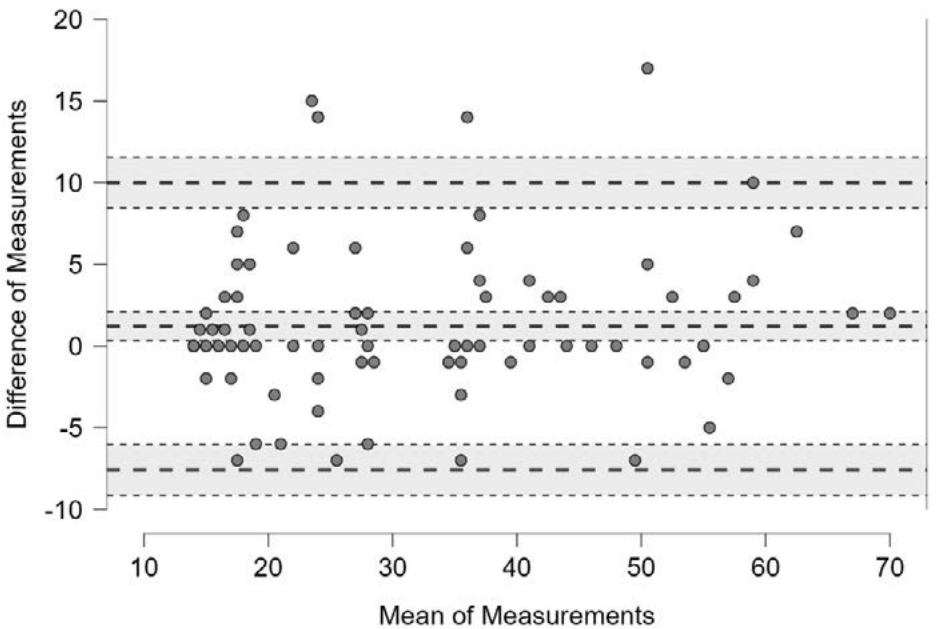
Temporal Stability

Test-retest reliability, assessed over seven-day interval, showed strong Spearman's correlations for all Br-CReSP domains and total score indicating temporal stability. The Bland-Altman analysis (Figure-1) revealed a low mean difference between test and retest scores (1.21, 95% CI [0.32 – 2.10]), with most data points within the limits of agreement, confirming the Br-CReSP's stability across varying patient scores.

DISCUSSION

This study presents the first translation and validation of the Cambridge Renal Stone Patient-Reported Outcome Measure into Brazilian Portuguese, establishing a disease-specific tool for assessing HRQoL in patients with kidney stones. The Br-CReSP demonstrated superior accuracy, AUC, sensitivity, specificity, and precision compared to the generic SF-12 questionnaire, highlighting its enhanced suitability for evaluating

Figure 1 - Bland-Altman scatter plot. The X-axis shows the mean of test and retest scores for each patient, while the Y-axis shows the difference between the two measurements. A horizontal dotted line close to 0 represents the mean difference (bias) between the test and retest measurements [1.21 (95% CI 0.32 – 2.10). The two horizontal dotted lines above and below the mean difference dotted line represent the 95% limits of agreement: -7.58 (95% CI -9.13 - -6.04) and 10.00 (95% CI 8.46 – 11.55).



HRQoL of patients with kidney stones. As a comprehensive, disease-specific instrument, the Br-CReSP effectively captures the patient's perspective on the impact of nephrolithiasis, offering a valuable tool for clinical and research applications.

Incorporating HRQoL assessment into the evaluation of nephrolithiasis outcomes is essential, as it provides insights beyond traditional metrics such as SFR and complications (1, 6, 20). While generic instruments like the Short Form 36 are widely used across medical conditions, they lack the specificity required to accurately monitor HRQoL in kidney stone patients (21). The Br-CReSP addresses this gap by offering a tailored approach to capture the unique burdens of nephrolithiasis.

The psychometric robustness of the Br-CReSP was confirmed through rigorous validation. High internal consistency across all domains (Cronbach's $^{b} \geq$ 0.82) and strong test-retest correlations demonstrated its reliability and temporal stability. Convergent validity was established though significant inverse correlations with the SF-12 components. Discriminant validity was evidenced by significant differences in Br-CReSP domain and total score between patients with and without kidney stones, with large effect sizes underscoring its construct validity. Notably, the Br-CReSP outperformed the SF-12 in discriminating nephrolithiasis, supporting its adoption in clinical practice for precise HRQoL assessment.

The Wisconsin Stone Quality of Life (WISQOL) questionnaire is another disease-specific PROM for nephrolithiasis (22). However, a retrospective multicenter study found no association between SFR post-surgical intervention and improved HRQoL using WISQOL (23). Both WISQOL and CReSP demonstrated improvement in scores for patients opting for surgery over observation (24). While WISQOL assesses the broader burden of urinary stone disease, the CReSP focuses specifically on kidney stones and their impact over the preceding seven days, making it particularly suited for evaluating acute treatment effects, such as post-ureteroscopy pain, which sig-

nificantly affects HRQoL in the first seven postoperative days (25).

A key strength of this study is its rigorous validation methodology, in a diverse population, including direct comparisons of discriminant capacity with a generic questionnaire, an original contribution to the literature. This approach extends beyond the original CReSP validation study (17), reinforcing the Br-CReSP's utility as a disease-specific HRQoL tool.

However, limitations include the single-center design and lack of longitudinal assessment. Future research should evaluate the Br-CReSP responsiveness to treatment interventions and compare it with other PROMs like WISQOL. Additionally, exploring correlations between Br-CReSP scores and objective clinical outcomes, such as SFR and complication rates, would further validate its role in guiding treatment decisions.

CONCLUSIONS

The Br-CReSP is the first validated, disease-specific PROM for assessing HRQoL in Brazilian patients with kidney stones. It addresses a critical gap in patient-centered outcome evaluation by providing a reliable and precise tool tailored to nephrolithiasis. The Br-CReSP's superior psychometric properties and discriminant capacity compared to generic instruments like the SF-12 underscore its potential to enhance clinical practice. Future studies should explore its utility in guiding treatment decisions and investigate correlations between Br-CReSP sores, SFR, and complication rates to further integrate HRQoL into evidence-based management of nephrolithiasis.

CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplementary material 1 - CReSP questionnaire.

Thank you for agreeing to complete this form.
This will help us to understand the impact that your kidney stone has on your life.

Please respond to each question or statement by marking one box per row.

Pain	**1**	**2**	**3**	**4**	**5**
During the past 7 days	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. How much did pain interfere with your day to day activities?					
2.How much did pain interfere with your enjoyment of life?					

Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
During the past 7 days	Not at all									Very much
3.How much did you worry about pain?										

Urinary Symptoms:	**1**	**2**	**3**	**4**	**5**
During the past 7 days	Not at all	A little bit	Somewhat	Quite a bit	Very much
4.I have had blood in my urine					

GIT Symptoms:	1	2	3	4	5
During the past 7 days	Not at all	A little bit	Somewhat	Quite a bit	Very much
5.I have nausea					

Work, daily activities and travel plans	**1**	**2**	**3**	**4**	**5**
During the past 7 days	Never	Rarely	Sometimes	Often	Always
6.I have trouble doing all of my usual work (include work at home)?					
7. I have trouble doing all of my regular leisure activities with others					
8.I have trouble doing all of the family activities that I want to do					

Anxiety	**1**	**2**	**3**	**4**	**5**
During the past 7 days	Never	Rarely	Sometimes	Often	Always
9.I felt fearful					
10. I found it hard to focus on anything other than my anxiety					
11. My worries overwhelmed me					
12. I am bothered by side effects of treatment					

Dietary changes:	**1**	**2**	**3**	**4**	**5**
During the past 7 days	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. How much have you been bothered by recommended alterations to your fluid intake?					
2.How much have dietary or fluid changes affected your daily life?					

Thank you for completing this for

Supplementary material 2 - Evidence of discriminant validity.

	Nephrolithiasis		Levene						95% CI for Cohen's d	
Domain	**No (n=30)**	**Yes (n=70)**	**F**	**t**	**df**	**Lower**	**Upper**	**Cohen's d**	**Lower**	**Upper**
Pain	2.20 0.76	5.03 ± 2.77	68.54*	-7.87	88.87*	-3,514	-2,082	-1.39	-1.86	-0.91
Urinary Symptoms	1.03 ± 0.18	1.77 ± 1.28	45.00*	-4.73	75.34*	-1,046	-0,445	-0.81	-1.25	-0.36
Work and Daily Activities	3.30 ± 1.29	7.07 ±3.87	48.81*	-7.27	94.35*	-4,706	-2,728	-1.31	-1.77	-0.84
Anxiety	4.97 ± 1.71	9.99 ± 4.59	26.50*	-7.95	96.80*	-6,305	-3,744	-1.45	-1.92	-0.97
Dietary changes	2.23 ± 1.10	3.69 ± 2.10	25.05*	-4.52	93.75*	-2,064	-0,766	-0.87	-1.31	-0.42
Total Score	16.43 ± 4.59	35.40 ± 15.40	38.35*	-9.38	91.26*	-22,957	-14,855	-1.67	-2.16	-1.17

*p < 0.001

F = the test statistic for Levene's test. Larger values indicate greater evidence against the null hypothesis of variances; t = t-statistic; df = degrees of freedom

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Robot-assisted Reduction Pyeloplasty with 3D Image Navigation for Adult Giant Hydronephrosis: Technique and Clinical Outcomes

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ABSTRACT

Purpose: To describe the surgical technique and evaluate the clinical outcomes of robot-assisted reduction pyeloplasty for adult giant hydronephrosis (GH) secondary to ureteropelvic junction obstruction (UPJO).

Materials and Methods: Between May 2019 and August 2024, 18 adult patients with GH caused by UPJO underwent robot-assisted laparoscopic reduction pyeloplasty. Patients' characteristics, perioperative variables, and clinical outcomes were prospectively recorded. Three-dimensional (3D) reconstructions generated from CTU were used for preoperative planning and intraoperative navigation. The surgical technique was described, and outcomes were assessed.

Results: All procedures were completed successfully with no conversions to open surgery. The median (range) operative time was 153 (77-241) minutes, with a median (range) estimated blood loss of 20 (10-100) mL. No intraoperative complications were observed. During a median (range) follow-up of 10 (6-40) months, all patients achieved complete symptomatic relief and significant reduction in hydronephrosis. Renal parenchymal thickness improved significantly after surgery (11.9 ± 3 mm vs 9.2 ± 4.4 mm, P=0.0207). Split renal function [38.7 (15.4-48.7) vs 25.7 (3.6-53.5), P=0.0131] showed significant improvement after surgery, which was consistent in patients in poorly functioning kidney subgroup [26.0 (19.2-24.6) vs 21.9 (11.6-24.6), P=0.0273].

Conclusion: Our results show that robot-assisted reduction pyeloplasty is a safe and effective option for managing GH, facilitating significant improvement in renal functional outcomes, even in patients with borderline renal function.

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INTRODUCTION

Giant hydronephrosis (GH) is an uncommon but clinically significant urological condition, predominantly reported in children and rarely observed in adults (1, 2). It is typically defined as the accumulation of more than 1000 mL of fluid within the renal collecting system. Radiographically, it is characterized by a hydronephrotic kidney that crosses the midline or extends more than the height of five vertebral bodies (2). The most common underlying cause is ureteropelvic junction obstruction (UPJO), followed by urolithiasis, distal ureteral stricture, and tumors (1).

Reconstructive surgery is considered the optimal treatment for GH, with the goals of relieving obstruction and preserving renal function. However, the severe anatomical distortion and mass effect of GH make the surgical reconstruction in these patients particularly challenging. In addition to the anatomical obstruction caused by UPJO, this condition also exhibits a functional obstruction arising from increased non-functional intrarenal space, which could cause urinary stasis and thereby increase the risk of urolithiasis and infection (3, 4). Reduction pyeloplasty, derived from traditional dismembered pyeloplasty, is designed to excise the redundant pelvis and restore a funnel-shaped configuration (5). This non-kidney-invasive approach could effectively reduce intrarenal dead space and optimize urinary drainage.

In the era of minimally invasive surgery, laparoscopic pyeloplasty has gradually supplanted open pyeloplasty because of its minimal invasiveness and shorter recovery (6). However, the limitations of laparoscopic surgery, including two-dimensional (2D) visualization and restricted instrument dexterity, are amplified in complex UPJO reconstructions, especially in GH (7, 8). Moreover, reduction pyeloplasty involving extensive excision of the redundant renal pelvis, requires more and precise intracorporeal suturing, which increases the risk of urine leakage (5, 9). Recently, robot-assisted surgery has been widely adopted for complex urinary tract reconstruction, owing to its unique advantages of magnified three-dimensional (3D) vision and better intracorporeal suturing (8,9). Nevertheless, its application in the management of GH secondary to UPJO remains scarcely reported, especially in adults (9–11). We hypothesize that robot-assisted reduction pyeloplasty, assisted by three-dimensional (3D) image navigation, may improve surgical precision and facilitate renal function preservation in these complex cases. This study describes the surgical technique and clinical outcomes of robot-assisted reduction pyeloplasty for adult GH, aiming to provide a safe, feasible, and minimally invasive alternative for this rare but challenging condition.

MATERIALS AND METHODS

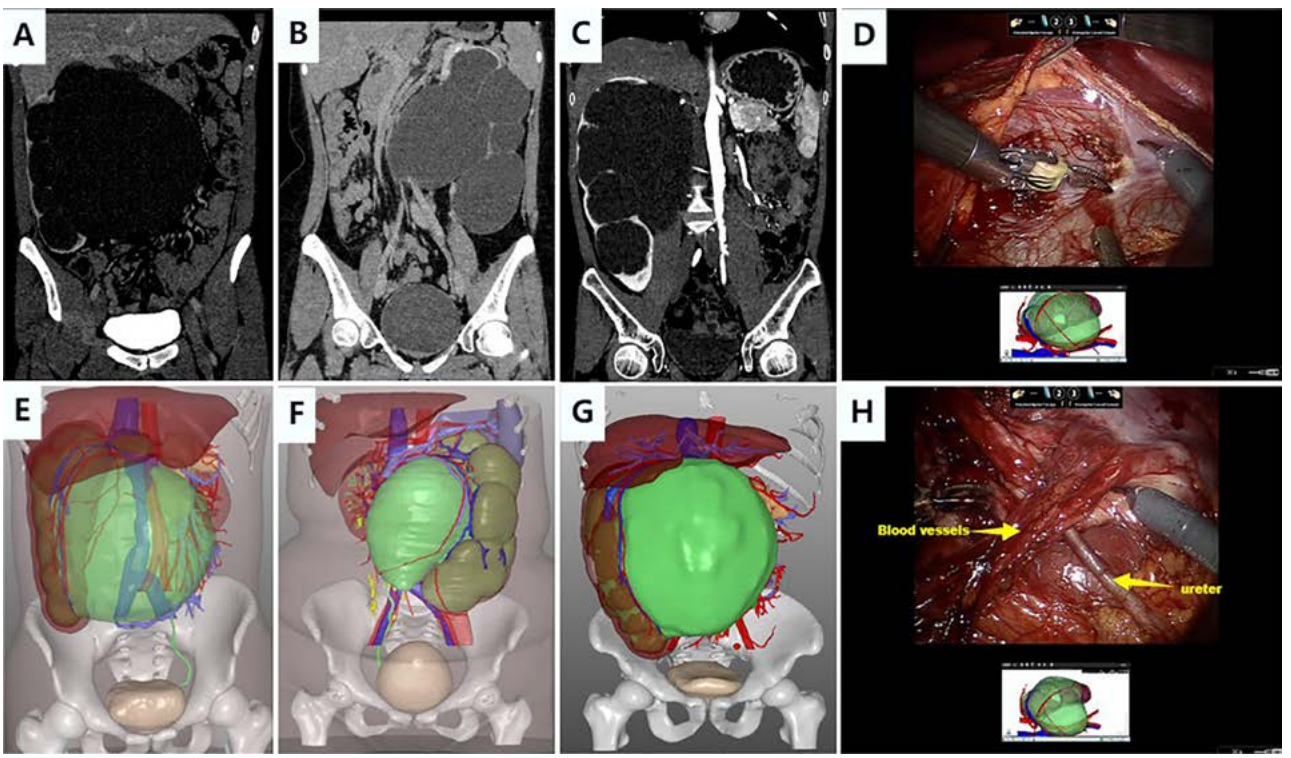
Study Population

Between May 2019 and August 2024, eighteen patients diagnosed with GH secondary to UPJO underwent robot-assisted reduction pyeloplasty, performed by an experienced surgeon. Patients' characteristics, perioperative data, and clinical outcomes were prospectively recorded in the Reconstruction of Urinary Tract: Technology, Epidemiology and Result (RECUTTER) database. All procedures were conducted following the standards of the Ethics Committee of Peking University First Hospital (No. 2023-602) and the Declaration of Helsinki (as revised in 2013).

Inclusion criteria were as follows: (1) adult patients diagnosed with GH secondary to UPJO who underwent robot-assisted reduction pyeloplasty; (2) patients with preoperative CTU available for 3D reconstruction. Exclusion criteria were as follows: (1) patients with incomplete data or follow-up; (2) patients with GH caused by other etiologies.

The diagnosis of GH was based on the computed tomography urography (CTU) with 3D reconstructions (Figure-1). Giant hydronephrosis was defined as a hydronephrotic volume exceeding 1000 mL. Radiologically, it was characterized by a dilated kidney that crossed the midline or extended beyond the height of five vertebral bodies (1, 2). Ultrasonography and CTU were routinely conducted in all patients. Diuretic renography was employed to evaluate affected renal function. Poorly functioning kidney (PFK) was defined as split renal function (SRF) ≤ 30% (12). Ureteral stent placement or percutaneous nephrostomy (PCN) was performed in

Figure 1 - Representative CTU images of GH and the application of 3D reconstruction images in preoperative planning and intraoperative navigation.



(A-C) CTU images in three representative patients with GH. A) Marked dilatation of the renal collecting system with absence of excretory-phase opacification, indicating severe urinary obstruction; B) Mass effect of GH with compression of major abdominal vessels and adjacent organs; C) Hydronephrotic kidney with markedly thinned parenchyma and preserved arterial-phase cortical enhancement, suggesting residual renal function.

(E-G) 3D reconstruction images for perioperative planning. E) Visualize GH (green) occupying most of the abdomen; F) Identify surrounding vessels (arteries in red and veins in blue); G) Clarify spatial relationships between GH and adjacent organs (liver in brown and pancreas in yellow). (D and H) The application of intraoperative 3D image navigation by the surgeon's cognitive fusion. D) Guide dissection to avoid iatrogenic injury; H) Identify critical structures in distorted anatomy.

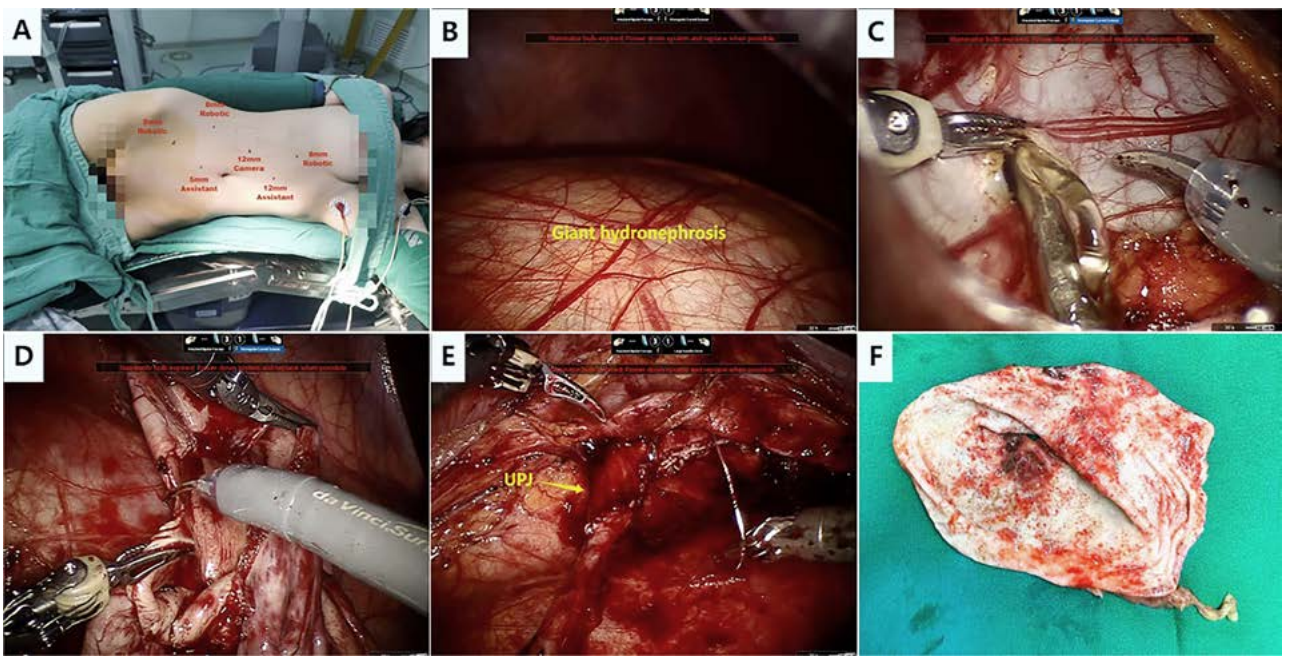
CTU = computed tomography urography; GH = giant hydronephrosis; 3D = three-dimensional

some patients to alleviate hydronephrosis and preserve renal function. In patients who underwent PCN, daily nephrostomy drainage was recorded to assess affected renal function. 3D image generated by CTU was utilized for preoperative planning and intraoperative navigation, enabling improved anatomical recognition and reducing the risk of iatrogenic injury (13).

SURGICAL TECHNIQUE

Patient positioning, port placement and surgical images are shown in Figure-2. Following induction of general anesthesia and tracheal intubation, transurethral retrograde double-J stent placement was performed in cases without preoperative drainage of hydronephrosis. The patient was then positioned laterally (45-60°) with the affected side facing upward. Four robotic ports (one 12 mm optical trocar and three 8 mm robotic trocars) and two assistant ports (one 5 mm trocar and one 12 mm trocar) were typically utilized. All procedures were performed using a transperitoneal approach. After incising the posterior peritoneum along the paracolic gutter, the colon was mobilized medially. Due to the severely enlarged kid-

Figure 2 - Intraoperative images of robot-assisted reduction pyeloplasty.



A) Patient position and port placement for robot-assisted laparoscopic reduction pyeloplasty; B) Marked mass effect of giant hydronephrosis; C) Decompression of the dilated collecting system to enlarge the operative workspace; D) Excision of the redundant pelvis; E) Funnel-shaped ureteropelvic junction configuration following reconstruction; F) Resected renal pelvis tissue and stenotic ureteric segment.

ney occupying most of the operative field, dissection and exposure of the ureteropelvic junction became extremely difficult. To alleviate the mass effect of GH, the markedly dilated renal pelvis was incised, and a large volume of intrarenal urine was aspirated. Meanwhile, adjacent organs and vessels were carefully protected to avoid iatrogenic injury. 3D images were utilized for intraoperative navigation by the surgeon's cognitive fusion during dissection (Figure-1).

Following adequate identification of the renal pelvis and ureter, an oblique incision was made in the renal pelvis. Redundant renal pelvic tissue was excised to reduce the pelvic size and improve drainage efficiency. The ureteral stricture was subsequently incised longitudinally until healthy ureteral tissue was encountered. Pyeloplasty was then performed, followed by continuous tension-free suturing. The first stitch was placed between the lowest corner of the renal pelvis and the ureter to prevent torsion and to serve as a landmark for the subsequent anastomosis. The posterior-wall anastomosis was completed first. In cases without a preexisting double-J stent, stent insertion was performed using a flexible guidewire before anastomosis of the anterior wall. Finally, the open renal pelvis was sutured. The ureteropelvic anastomosis was configured into a funnel shape following hydrodynamic principles to optimize renal pelvic drainage. In cases with concomitant renal calculi, stones were removed by forceps under direct vision.

Postoperative treatment and follow-up

The Foley catheter was removed on postoperative Day 7. The double-J stent was removed 2 months after surgery by cystoscopy. At 3 months postoperatively, the modified Whitaker test was performed in patients with a nephrostomy tube to evaluate the feasibility of tube removal (14). Postoperative follow-up was conducted at three-month intervals during the first year and at six-month intervals thereafter, up to the second year. Postoperative complications were defined and graded by the Clavien-Dindo (CD) classification (15). Hydronephrosis was assessed using

renal ultrasonography, CTU, and magnetic resonance urography. Changes in renal morphology were assessed using renal parenchymal thickness (RPT). All RPT measurements were performed by senior urological ultrasonography doctors with more than 5 years of experience, following standardized urological ultrasound protocols. For each patient, preoperative and postoperative measurements were performed by the same doctor to control inter-observer variability.

Renal function was evaluated by glomerular filtration rate (GFR) and SRF of diuretic renography. Renal function outcomes were categorized as improvement, stability and deterioration. Based on biological variation studies in both healthy and chronic kidney disease populations, the physiological fluctuation of estimated glomerular filtration rate is approximately 12.5%-16.5% (16, 17). To minimize the impact of inherent variability on our results, we therefore defined a relative change of 20% in renal functional parameters as the threshold for a meaningful change. Improvement was defined as an increase of ≥20% in SRF for non-solitary kidneys or in GFR for solitary kidneys at the last follow-up relative to baseline. Deterioration was defined as a ≥20% decline in SRF for non-solitary kidneys or in GFR for solitary kidneys at the last follow-up relative to baseline. Stability was defined as changes within ± 20% of baseline values.

Statistical analysis

Categorical variables were expressed as frequency (percentage). The distribution of continuous variables was first assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution were presented as mean ± standard deviation (SD), while those not following a normal distribution were reported as median (range). For paired comparisons of preoperative and postoperative parameters, the distribution of paired differences was assessed using the Shapiro-Wilk test. If the paired differences were normally distributed, data were compared using the paired t-test. If the paired differences were not normally distributed, data were compared using the Wilcoxon signed-rank test. All statistical analyses were performed using SPSS software (version 27.0), and a P-value < 0.05 was considered statistically significant.

RESULTS

As shown in Table-1, 18 patients diagnosed with GH were included, comprising 11 men and 7 women. The mean age was 26.8 ± 10.0 years. All cases of GH were attributed to UPJO. The left side was affected in 9 (50.0%) patients. In terms of clinical presentation, 12 (66.7%) patients experienced flank pain, 1 (5.6%) patient presented with an abdominal mass, and 5 (11.1%) patients were asymptomatic. 17 (94.4%) patients had primary UPJO, 1 (5.6%) patient had a history of failed endoscopic ureteral balloon dilatation, and no patient had a history of prior pyeloplasty. 9 (56.2%) patients were diagnosed with PFK. For preoperative drainage, 3 (16.6%) cases had double-J stent placement and 6 (33.3%) had PCN. For patients with PCN, nephrostomy output was recorded. The median (range) nephrostomy output was 2000 (700-3000) mL. All patients underwent robot-assisted reduction pyeloplasty. All procedures were completed successfully without conversion to open surgery. The median (range) operative time was 153 (77-241) minutes, and the median (range) estimated blood loss was 20 (10-100) mL. No perioperative complications were recorded.

The clinical outcomes are shown in Table-2 and Figure-3. The median (range) follow-up period was 10 (6-40) months. Postoperative imaging demonstrated a substantial reduction in hydronephrosis. We compared the RPT before surgery and at the last follow-up. It revealed a significant improvement in RPT (11.9 ± 3.0 mm vs 9.2 ± 4.4 mm, P = 0.0207) after surgery (Table-2 and Figure-3I). All patients experienced relief of clinical symptoms. During follow-up, a 4.7 mm renal calculus developed in 1 patient, who remained asymptomatic and was managed conservatively. No other major long-term complications, including urinary tract infection or recurrent obstruction, were observed.

For renal function outcomes, the last follow-up SRF [38.7 (15.4-48.7) vs 25.7 (3.6-53.5), P = 0.0131]

Table 1 - Patients' characteristics and perioperative data.

Variable	Results
Number of patients, n	18
Gender, n (%)	
Male	11 (61.1)
Female	7 (38.9)
Age (years), mean ± SD	26.8 ± 10.0
BMI (kg/m^2), mean ± SD	22.0 ± 3.2
Affected side, n (%)	
Left	9 (50.0)
Right	9 (50.0)
Clinical presentation, n (%)	
Flank pain	12 (66.7)
Abdominal mass	1 (5.6)
No symptom	5 (27.8)
Solitary kidney, n (%)	2 (11.1)
SRF group, n (%)	
> 30%	7 (43.8)
≤ 30%	9 (56.2)
History of endoscopic dilation, n (%)	1 (5.6)
History of ureteral reconstruction, n (%)	0 (0.0)
Concomitant urolithiasis (n%)	2 (11.1)
Preoperative DJ stent indwelling, n (%)	3 (16.6)
Preoperative PCN, n (%)	6 (33.3)
PCN output (mL), median (range)	2000 (700-3000)
Operative time (min), median (range)	153 (77-241)
Conversion to open surgery	0 (0/18)
Estimated blood loss (mL), median (range)	20 (10-100)
Postoperative hospitalization (day), median (range)	4 (4-6)

BMI = body mass index; SRF = split renal function; PCN = percutaneous nephrostomy; SD = standard deviation

Table 2 - The clinical outcomes of patients.

Variable	Results
Number of the total patients, n	18
Number of non-SK	16
Number of SK	2
Follow up time (months), median (range)	10 (6-40)
Preoperative Scr (μmol/L), mean ± SD	85.7 ± 17.6
Follow-up Scr (μmol/L), mean ± SD	82.9 ± 13.6
Preoperative SRF for non-SK (%), median (range)	25.7 (3.6-53.5)
Follow-up SRF for non-SK (%), median (range)	38.7 (15.4-48.7)
Preoperative GFR for SK (mL/min/1.73 m^2), mean ± SD	53.5 ± 2.1
Follow-up GFR for SK (mL/min/1.73 m^2), mean ± SD	79.3 ± 2.4
Preoperative RPT (mm), mean ± SD	9.2 ± 4.4
Follow-up RPT (mm), mean ± SD	11.9 ± 3.0
Symptom relief, n (%)	18 (100)
Renal function, n (%)	
Improvement	10 (55.6)
Stability	7 (38.9)
Deterioration	1 (5.6)
Hydronephrosis improvement, n (%)	18 (100%)
Long term complication, n (%)	1 (5.6)

Scr = serum creatinine; SRF = split renal function; GFR = glomerular filtration rate; SK = solitary kidney; RPT = renal parenchymal thickness; SD = standard deviation

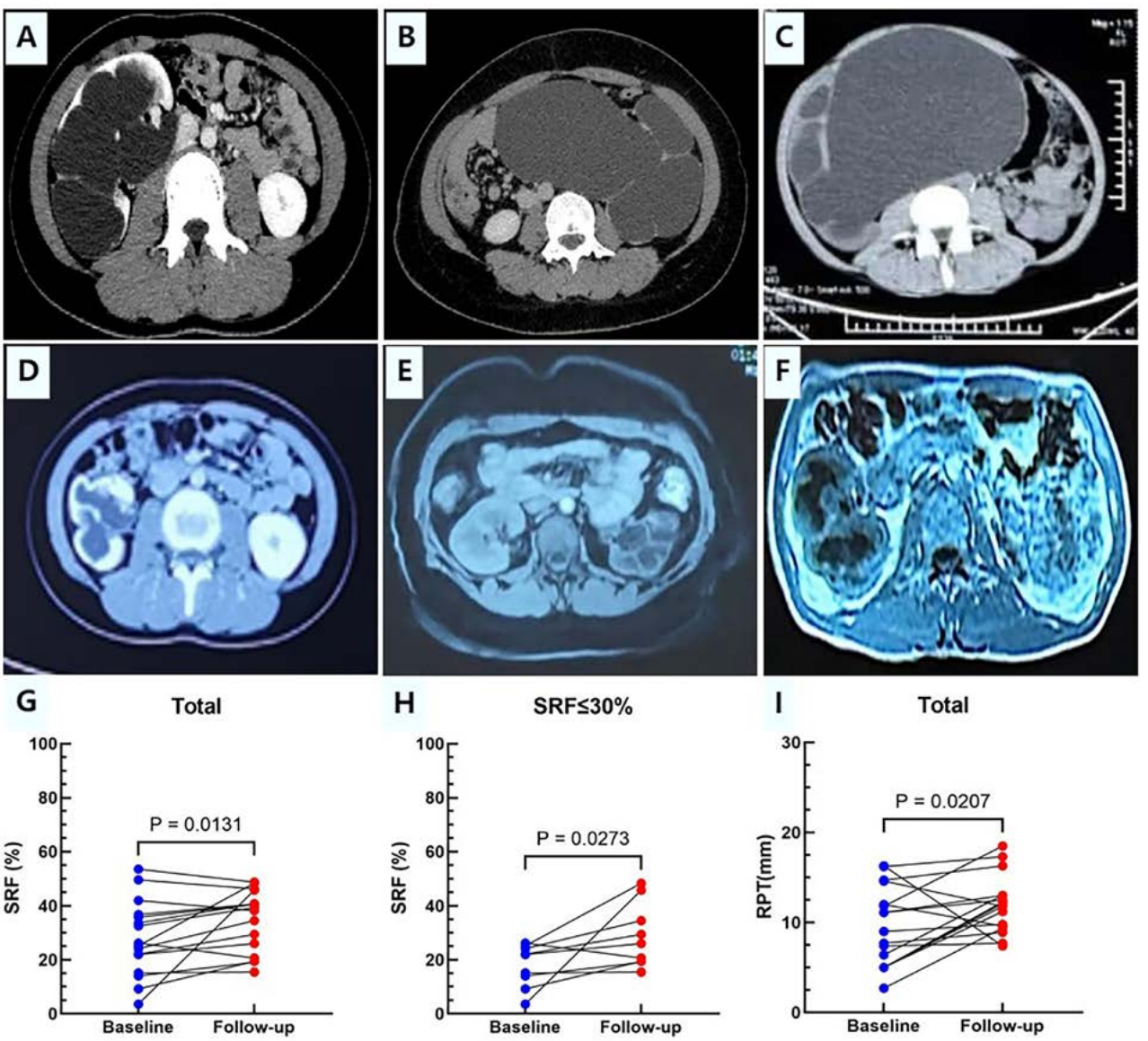
for 16 non-solitary kidneys showed significant improvements compared to preoperative values, which was consistent in patients with PFK [26.0 (19.2-24.6) vs 21.9 (11.6-24.6), P = 0.0273]. In two patients with a solitary kidney, the mean postoperative increase in GFR was 25.8 mL/min/m2. In the overall cohort, renal function improved in 10 (55.6%) patients, remained stable in 7 (38.9%), and deteriorated in 1 (5.6%). In the patient with worsening renal function, SRF declined from 26.2% to 20.6%, representing a 21% decrease relative to baseline, and remained stable at this reduced level during follow-up. Despite this decrease, there was no evidence of recurrent obstruction, urinary tract infection, or other major postoperative complications, and no additional intervention was required.

DISCUSSION

GH is a rare condition defined as hydronephrosis containing fluid more than 1000 mL (2). The etiology in approximately 80% of cases is UPJO (18). GH progresses slowly and insidiously, and flank or abdominal discomfort may be the only symptom. Such subtle signs are easily overlooked by patients, potentially resulting in the development of a non-functional kidney (19).

To date, there are no established consensus guidelines for the surgical management of GH. In clin-

Figure 3 - Renal function and morphological outcomes.



(A-C) Baseline images for GH. A) Cystic dilatation of the collecting system with parenchymal thinning; B) Mass effect of GH compressing adjacent organs; C: Severe hydronephrosis crossing the midline with thinning parenchyma.

(D-F) Significant radiographic improvement after surgery. D) Marked reduction in hydronephrosis with parenchymal thickening; E) Substantial resolution of mass effect. F) Marked reduction in dilatation of renal pelvis.

G) Marked reduction in dilatation of renal pelvis. G) The change of SRF in 16 non-solitary kidney patients after surgery. The SRF was compared with a paired-sample t-test; H) The change of SRF in patients with PFK (n=9) after surgery. The SRF was compared with a paired- sample t-test; I) The change of RPT in total patients (n=18). The RPT was compared with a paired-sample t-test.

GH = giant hydronephrosis; SRF = split renal function; PFK = poorly functioning kidney; RPT = renal parenchymal thickness

ical practice, the decision between nephrectomy and kidney-sparing surgery is primarily determined by the function of the affected kidney (19). Nephrectomy is generally recommended when SRF is poor (20). However, available methods of evaluating SRF in patients with GH have inherent limitations. Diuretic renography is the standard tool for SRF measurement, but increased intrarenal pressure in GH may impair radionuclide uptake, resulting in an underestimation of the true SRF, especially in young adults (21, 22). Renal parenchymal thickness (RPT) may reflect residual function, but severe distortion of renal anatomy caused by hydronephrosis and the operator-dependent ultrasound measurements may produce inconsistent results (23). Our results demonstrated that significant postoperative improvements in both SRF and RPT, providing preliminary evidence for the feasibility and benefits of kidney-sparing in GH, even among patients with borderline renal function. Although one patient experienced a postoperative functional decline, there was no evidence of restenosis or other complications. The preoperative symptoms resolved completely, and renal function remained stable at this reduced level throughout follow-up. Therefore, we considered that this patient still attained a clear clinical benefit from surgery.

Given the potential for renal preservation and its clinical benefits, the kidney-sparing surgery is recommended in patients with GH, especially in younger individuals. However, reconstruction in GH remains technically challenging, which demands meticulous dissection and intracorporeal suturing, and knotting within a confined, distorted operative field (9). The robotic technique offers several advantages, such as 3D visualization, greater dexterity, and precise suturing, thereby facilitating complex reconstruction such as GH (8, 9, 24). However, existing studies on robot-assisted pyeloplasty for GH have limited generalizability due to small sample sizes (9–11). In the present study, robot-assisted reduction pyeloplasty with 3D image navigation was performed in 18 patients with GH. Perioperative and follow-up outcomes demonstrated that favorable results, including minimal blood loss, shorter hospital stay, and fewer complications, were achieved.

Optimal outcomes in such complex cases depend not only on advanced surgical technique but also on meticulous preoperative planning and intraoperative navigation with the assistance of 3D reconstruction based on CTU. During preoperative planning, 3D image clearly delineated the anatomy of the hydronephrotic kidney and adjacent vasculature (13, 25). Furthermore, intraoperative 3D image navigation by the surgeon's cognitive fusion was used to achieve more precise identification and dissection within the distorted anatomy, thereby potentially reducing the risk of iatrogenic injury. However, the generation of patient-specific 3D models is time-consuming, costly, and highly dependent on advanced radiology platforms and experienced operators. As a result, this technique has not been wildly adopted for routine clinical use and is currently more suitable for complex cases.

The mass effect caused by GH markedly interferes with precise dissection and adequate exposure of the ureteric stricture. Based on our experience, several strategies can be employed to mitigate these constraints on intracorporeal manipulation. First, preoperative decompression of hydronephrosis is essential. In patients without prior drainage, retrograde transurethral placement of a double-J stent is performed at the outset of surgery to achieve preliminary decompression. Secondly, a transperitoneal approach is adopted to provide a broader operative field. Careful robotic port placement is essential to avoid iatrogenic injury to bowel loops, renal pedicle vessels, and other vital structures, with the initial port inserted under direct vision when necessary. Thirdly, the markedly dilated renal pelvis is incised to aspirate the intrarenal fluid, thereby enlarging the workspace and facilitating subsequent dissection and reconstruction.

In GH, the affected kidney exhibits an extremely dilated renal collecting system and a thinned renal cortex. Even after the anatomical obstruction has been surgically relieved, functional obstruction factors, including redundant intrarenal space and compromised peristaltic activity of the collecting system, may still persist, leading to urinary stasis and predisposing patients to urolithiasis and infection (3, 4). Various surgical techniques have been employed to address this type of functional obstruction, including nephroplication, ureterocalicostomy, and reduction pyeloplasty (2, 3, 9, 26).

Nephroplication is a complex, parenchyma-invasive procedure in which the upper and lower renal poles are sutured and folded toward the middle pole, thereby facilitating calyceal drainage (3). However, this technique carries potential risks, including renal hemorrhage and parenchymal volume loss, which are of particular concern in patients with PFK. In a recent report, a novel suture-free nephroplication was introduced using a four-dimensional printed biodegradable pouch to compress and fold the dilated kidney (10). Although initial outcomes appear promising, further studies are needed to validate this technique before it can be widely adopted in clinical practice. Ureterocalicostomy involves excision of the lower renal pole and direct anastomosis of the lower calyx to the ureter (26). It is a viable reconstruction alternative for patients with a severely compromised collecting system due to prior failed pyeloplasty, as well as for those with anatomical anomalies such as an intrarenal pelvis (27–29).

To maximize renal function preservation in patients with GH, we prefer to choose a non-kidney-invasive surgical approach. In our study, robot-assisted reduction pyeloplasty was undertaken, which involved routine excision of the UPJ stricture, supplemented by resection of the redundant dilated pelvis (5). This volume-reducing strategy can decrease non-functional intrapelvic space and restore a funnel-shaped configuration, thereby optimizing urinary drainage (5). However, owing to the extensive reduction and a lengthy suture line required, laparoscopic execution is technically demanding with a prolonged learning curve (9). Difficulty in intracorporeal suturing has been identified as a major cause of conversion from laparoscopic to open surgery (30). The robotic surgical technique, with its advantages of 3D magnified visualization and precise suture, appears to effectively overcome these challenges, resulting in a shorter anastomosis time and a lower complication rate (8, 9). In our study, these advantages translated into favorable outcomes. All robot-assisted procedures were completed successfully without intraoperative complications. The mean operative time was 153 minutes, with an acceptable estimated blood loss.

In summary, this study describes robot-assisted reduction pyeloplasty for managing GH. This non-parenchyma-invasive procedure could effectively address both anatomical and functional obstructions. In addition, we incorporated CTU-based 3D reconstruction into preoperative planning and intraoperative cognitive fusion navigation to minimize the risk of iatrogenic injury in this challenging condition. Beyond symptomatic relief, we report postoperative improvements in both renal functional and morphological parameters, providing important evidence for kidney-sparing strategies for GH. However, several limitations of this study should be acknowledged. Firstly, although it represents the largest published cohort of robotic reconstruction for adult GH, the sample size remains limited due to the rarity of this condition. Secondly, we could not perform a comparison of reduction pyeloplasty with other approaches. Thirdly, the relatively short follow-up duration may have limited the evaluation of long-term renal functional outcomes. Multicenter studies with larger cohorts and prolonged follow-up are required to further validate these findings. Despite these limitations, our study provides valuable insights into the management of this rare but technically challenging condition and further provides important evidence for kidney-sparing strategies for GH.

CONCLUSIONS

Nephrectomy should be performed with greater caution in patients with a poorly functioning kidney caused by giant hydronephrosis, especially in younger individuals. Robot-assisted laparoscopic reduction pyeloplasty with 3D image navigation is a safe and effective technique for managing giant hydronephrosis secondary to UPJO in adults and it promotes renal preservation even in patients with borderline renal function. However, large sample, multicenter, and long-term studies are essential in the future.

ABBREVIATIONS

3D = three dimensional
2D = two-dimensional
GH = giant hydronephrosis
UPJO = ureteropelvic junction obstruction
CTU = computed tomography urography

GFR = glomerular filtration rate
SRF = split renal function
PFK = poorly functional kidney
PCN = percutaneous nephrostomy
CD = Clavien-Dindo
RPT = renal parenchymal thickness

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Hao Dong, Pan Song and Zhihua Li contributed similarly as first author

CONFLICT OF INTEREST

None declared.

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Focal Cryotherapy in Prostate Cancer. Does Gleason Impact Results?

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ABSTRACT

Purpose: Focal cryotherapy is a minimally invasive treatment for localized prostate cancer (PCa), but its oncological outcomes, particularly in relation to baseline Gleason Grade Group (GG), remain understudied. This study evaluates its efficacy and the impact while radical of baseline Gleason score on recurrence-free survival.

Materials and Methods: A retrospective analysis included 111 patients with localized PCa treated with focal cryotherapy between 2014 and January 2024. Patients with prior treatments or follow-up <12 months were excluded. All patients underwent MRI and transperineal biopsy, and cryotherapy was performed using the Visual ICE Cryoablation System. Confirmatory biopsies were recommended at 12–24 months post-treatment. Recurrence was classified as either in-field (treated or adjacent areas) or out-field (non-adjacent areas). Any recurrence-free survival was defined as the absence of positive biopsy or additional treatment. Radical treatment-free survival was defined as the absence of whole-gland treatment (e.g., radical prostatectomy, radiotherapy), androgen deprivation therapy, metastasis, or death. Outcomes were compared between patients with baseline GG 1 and GG >1.

Results: Median follow-up was 35 months (IQR 24–49). Confirmatory biopsies were performed in 78% of patients (n=87), revealing in-field recurrence in 10% and out-field recurrence in 23%. There were no statistically significant differences between ISUP 1 and ISUP >1 groups in terms of protocol biopsy positivity for either in-field recurrence (HR 0.41; 95% CI 0.09–1.9) or out-field recurrence (HR 0.77; 95% CI 0.3–1.98). At three-years, the rates of any recurrence-free and radical treatment-free survival were 63% and 85%, respectively, with no significant variation by baseline GG.

Conclusion: Focal cryotherapy provides favorable short-term oncological outcomes in localized PCa, with no significant differences in recurrence-free survival based on baseline Gleason score.

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INTRODUCTION

Prostate cancer (PCa) is one of the most diagnosed malignancies in men worldwide. In Europe, it is the most frequently diagnosed cancer in men and ranks as the third leading cause of cancer-related mortality. The standard treatment options for patients with localized PCa are active surveillance (AS), radical prostatectomy (RP) or radiotherapy (RT). However, RP and RT are associated with significant morbidity, including urinary incontinence and erectile dysfunction, all of which can adversely impact quality of life (1). Additionally, active surveillance requires regular follow-up consisting of PSA testing, clinical examination, MRI imaging and repeated prostate biopsies (2, 3). More than one-third of patients are reclassified during follow-up, with the majority undergoing curative treatment due to disease progression (4). To enhance the benefit-to-risk ratio, alternative therapies have emerged that aim to minimize adverse effects while maintaining positive oncological outcomes (5, 6).

Focal cryotherapy, also known as cryoablation or cryosurgery, is a promising alternative for localized PCa. It enables targeted destruction of tumor tissue while preserving surrounding healthy structures. This technique induces apoptosis by the application of cryoneedles into the targeted area, leading to cell death via coagulative necrosis (7). The ideal candidate for focal cryotherapy remains uncertain. Patients with intermediate D'Amico risk with visible lesion in the MRI appear to be the primary candidates (8). Additionally, patients with low-risk disease but MRI-visible lesions have been reported to have worse oncological outcomes compared to those with non-visible lesions when initiating an active surveillance protocol (9). Furthermore, there is a lack of data comparing oncological outcomes based on patient's Grade Group (GG) Gleason score following focal therapy (FT). To our knowledge, there are no proven clinical factors, such as GG, to be used as indication for focal cryotherapy.

Several studies have highlighted the favorable functional outcomes of cryoablation, particularly, when compared to standard treatments (RP or RT) (10-12). However, oncological outcomes remain a critical area of investigation to determine the safety of this approach in managing localized PCa. Current guidelines from the NCCN (13) and EAU (14) recommend performing cryotherapy within prospective registries or clinical trials. To date, only a few centers have reported oncological outcomes following cryotherapy, and there is minimal evidence regarding GG and cryotherapy outcomes (15). Given the established prognostic value of Gleason score in PCa, we hypothesize that this variable impacts the likelihood of achieving disease control following focal cryotherapy.

In this study, we present our experience with short-term follow-up of patients treated with focal cryotherapy, focusing on the influence of baseline Gleason score.

MATERIALS AND METHODS

This retrospective study included consecutive patients with primary localized PCa who underwent focal cryotherapy between 2014 and January 2024 at our institution. Exclusion criteria included previous prostate cancer treatments, suspicion of extra-prostatic disease, or follow-up shorter than 12 months. Patients were considered eligible if they had a single, histologically confirmed lesion in contiguous areas, whether visible or not on MRI. Factors such as age, PSA, prostate volume, high Gleason score, or severe LUTS were not considered exclusion criteria. Data were collected from a PCa registry (CAPROSIVO), which was approved by the local ethics committee.

All patients underwent preoperative MRI, with or without regions of interest (ROI), followed by transperineal biopsy. Most MRIs were performed at the Valencian Institute of Oncology using the General Electric Signa Artist 1.5 Tesla model. The images were interpreted by three experienced radiologists using the PI-RADS 2.0 or 2.1 version. For each ROI, 3-5 targeted biopsy cores were obtained, and systematic sextant biopsies (20 to 30 cores) were performed following a modified version of the Dickinson scheme, as previously described (16). Biopsies were conducted using the Hitachi V70 ultrasound system, with Biopsee software® (Medcom) used for fusion when required.

Cryotherapy was performed by the same experienced urologist (J.C.R) using the Visual ICE Cryoablation System (Boston Scientific). Patients were treated under general anesthesia with 2-4 IceSeed needles and were discharged the following day with a bladder catheter. The first visit took place 7–10 days after surgery, when the bladder catheter was removed. Follow-up visits were scheduled at 3, 6, and 12-months post-treatment, during which only PSA levels were measured. At 12 months, a multiparametric MRI was performed prior to the protocol biopsy. Beyond 12 months, patients underwent PSA testing every six months and MRI scans every 1 to 2 years to detect potential recurrence. Additional diagnostic procedures were reserved for cases with clinical suspicion of recurrence. Digital rectal examination was limited to the diagnostic phase and was not routinely employed during follow-up. No adjuvant androgen deprivation therapy (ADT) was used. Patients were advised to undergo a single confirmatory biopsy at 12–24 months after cryotherapy, unless recurrence was suspected earlier.

Regarding oncological outcomes, in-field recurrence was defined as any cancer foci within the previously treated area or directly adjacent regions. Adjacency was determined based on the transverse or craniocaudal sextants, excluding oblique or other sextants. Out-field recurrence referred to the detection of any cancer in non-adjacent areas of the prostate. Any recurrence-free survival was defined as the absence of a positive biopsy or any additional treatment at any time during follow-up. Radical treatment-free survival was considered as the absence of whole-gland treatment (brachytherapy, RT, RP), ADT, metastasis or death. Comparisons were performed between patients with baseline GG 1 vs GG >1, as well as according to baseline PSA level (≤6 vs >6 ng/mL) and PIRADS score (<3 vs ≥3).

Statistical analysis

Differences in categorical variables were assessed using chi-square tests, while differences in continuous variables were evaluated with t-test or Mann-Whitney U tests, as appropriate. The Log-Rank test and Kaplan-Meier curves were used to compare any recurrence and radical treatment-free survival across groups. All statistical analyses were performed using Python 3.13.0 software, with a significance level set at $p < 0.05$.

RESULTS

A total of 111 patients with localized PCa treated with focal cryotherapy were included. The median follow-up was 35 months (IQR 24-49). The median age at the time of cryotherapy was 70 years (IQR 64-74), and the median PSA was 6.3 ng/mL (IQR 4.6-8.6). As shown in Table-1, the majority of patients had non-palpable disease (91%) but visible lesions on MRI (80%).

At the end of the analysis, among the 111 patients in the cohort, 87 patients (78%) agreed to undergo a confirmatory biopsy, with a median time to biopsy of 18 months (IQR 14-19). The confirmatory biopsies revealed no cancer in 57 cases (66%), while 18 (21%) had Grade Group 1 disease, 8 (9%) had Grade Group 2 disease, and 4 (4%) had Grade Group >3 disease. Thus, 30 of these 87 patients (34%) had positive confirmatory biopsies, Grade Group ≥1 disease. In the entire cohort (111 patients), 36 patients experienced recurrence, defined as positive biopsy, radiological recurrence, or additional treatment, including four, identified by off-protocol biopsies and two by PSMA PET imaging. In-field recurrence was found in 10% of patients, while out-field recurrence was found in 23% of patients. There were no statistically significant differences between ISUP 1 and ISUP >1 groups in terms of protocol biopsy positivity for either in-field recurrence (HR 0.41; 95% CI 0.09–1.9) or out-field recurrence (HR 0.77; 95% CI 0.3–1.98). Patients who declined confirmatory biopsy had no clinical suspicion of recurrence, with a median PSA of 2 ng/mL (0.9-4.9) and negative MRI findings during follow-up.

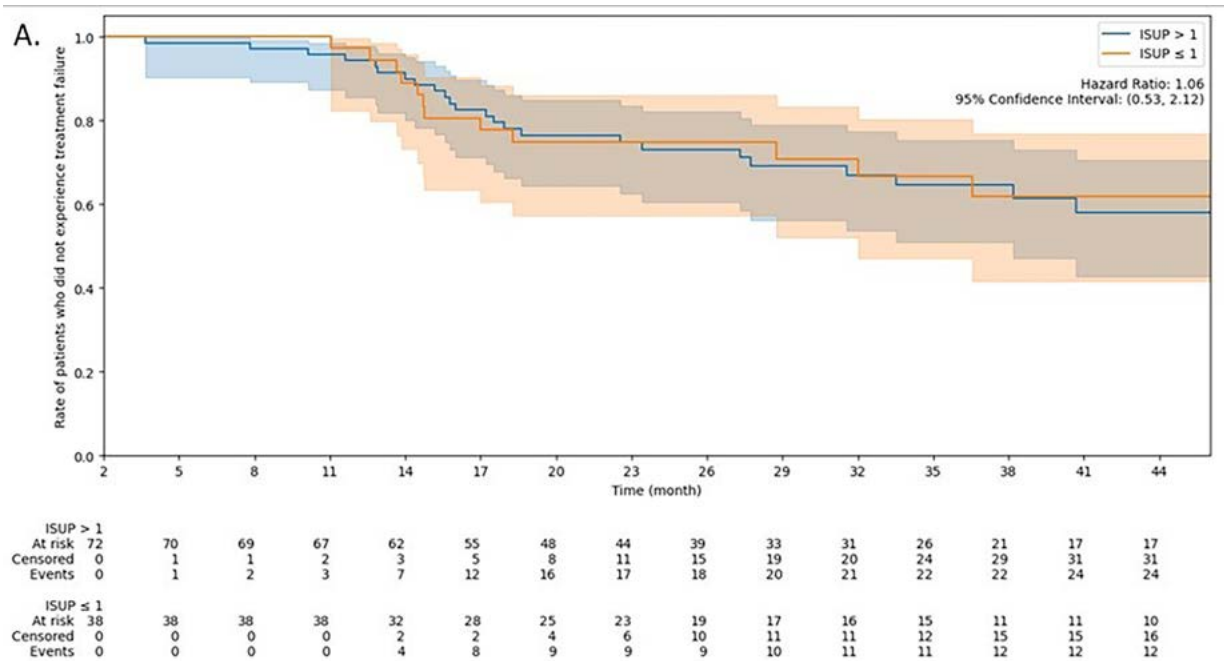
Twenty (18%) of the 111 patients required secondary treatments, including brachytherapy (5 patients), second cryotherapy (7 patients), RT (2 patients), PT (2 patients), lymphadenectomy (1 patient) and ADT (3 patients). Radical treatments, excluding repeat cryotherapy and lymphadenectomy, were performed in 12 patients. At 3 years, 65% of patients were free from any recurrence, and 88% were free from radical treatment. As shown in Figure-1, no significant differences were

Table 1 - Baseline patients characteristics.

	Total (N=111)	GG 1 (N=40)	GG >1 (N=71)	P value
Age, years				
Mean ± SD	68 ± 6.9	66 ± 7	70 ± 6.6	0.003
Range	50–79	51–77	50–80	
PSA, ng/mL				
Mean ± SD	7.2 ± 4.4	6.44 ± 3.18	7.5 ± 4.9	0.29
Range	2.6–29	1.2–17	2.6–29	
Clinical stage, n (%)				0.39
cT1c	101 (91)	39 (98)	63 (89)	
cT2	10 (9)	1 (2)	8 (11)	
Prostate volume, cc				
Mean ± SD	54 ± 26	57.4 ± 29	52 ± 24	0.39
Range	18–142	18–142	19–126	
MRI visible lesion, n (%)	88 (80)	26 (65)	62 (87)	<0.05
Grade Group, n (%)				
Grade Group 1	40 (36)	40 (100)	–	–
Grade Group 2	55 (50)	–	55 (77)	
Grade Group 3	13 (12)	–	13 (18)	
Grade Group 4–5	3 (2)	–	3 (5)	
Positive cores at initial biopsy				
Mean ± SD	3.3 ± 1.6	3.1 ± 1.7	3.3 ± 1.5	0.36
Range	1–8	1–8	1–7	
Positive millimeters at initial biopsy				
Mean ± SD	14 ± 11	13.6 ± 13.2	14.2 ± 9.3	0.27
Range	0.6–58	0.6–58	2–49	

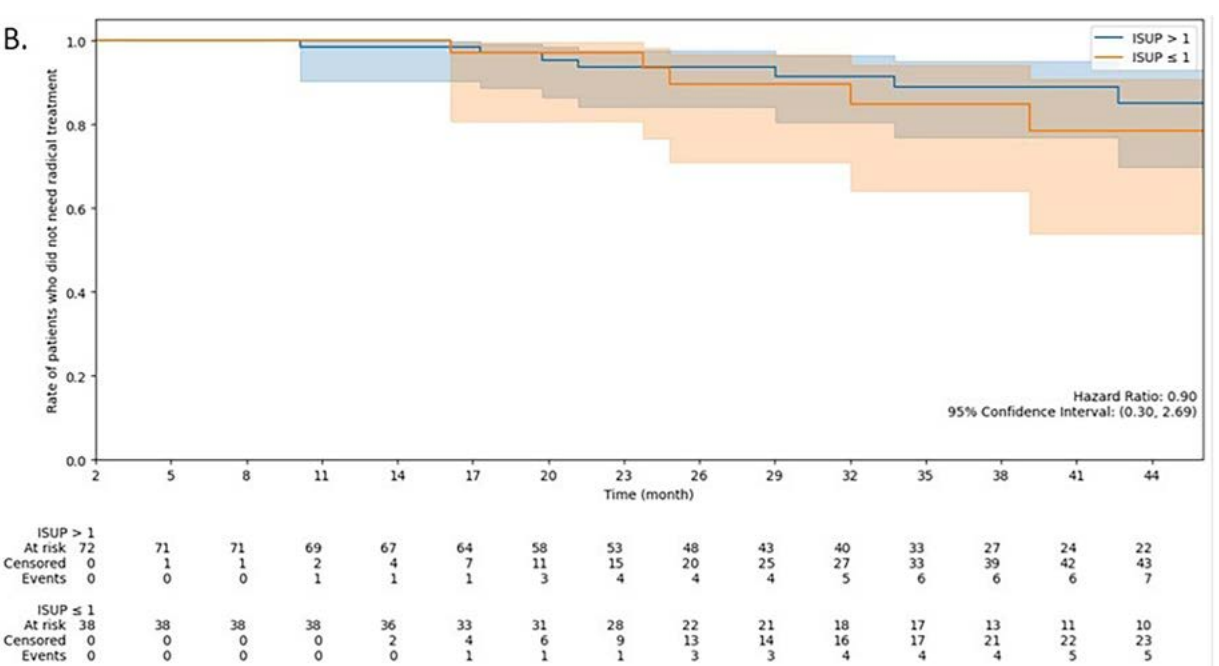
SD = Standard Deviation;PSA = prostate-specific antigen; MRI = magnetic resonance imaging; n = number of patients; GG = Grade Group; cc = cubic centimeters

Figure 1 - Kaplan-Meier curves by ISUP grade group (A) - Time to treatment failure (B) - Time to need for radical treatment.



ISUP > 1															
At risk	72	70	69	67	62	55	48	44	39	33	31	26	21	17	17
Censored	0	1	1	2	3	5	8	11	15	19	20	24	29	31	31
Events	0	1	2	3	7	12	16	17	18	20	21	22	22	24	24
ISUP ≤ 1															
At risk	38	38	38	38	32	28	25	23	19	17	16	15	11	11	10
Censored	0	0	0	0	2	2	4	6	10	11	11	12	15	15	16
Events	0	0	0	0	4	8	9	9	9	10	11	11	12	12	12

** ISUP – International Society of Urological Pathology grading system*



ISUP > 1															
At risk	72	71	71	69	67	64	58	53	48	43	40	33	27	24	22
Censored	0	1	1	2	4	7	11	15	20	25	27	33	39	42	43
Events	0	0	0	1	1	1	3	4	4	4	5	6	6	6	7
ISUP ≤ 1															
At risk	38	38	38	38	36	33	31	28	22	21	18	17	13	11	10
Censored	0	0	0	0	2	4	6	9	13	14	16	17	21	22	23
Events	0	0	0	0	0	1	1	1	3	3	4	4	4	5	5

observed between the initial GG 1 and GG > 1 groups regarding any recurrence-free survival (HR 1.2, 95% CI 0.6–2.5) or radical treatment-free survival (HR 1.1, 95% CI 0.35–3.2). Additionally, we compared recurrence-free survival according to baseline PSA levels (≤6 vs. >6 ng/mL) and PIRADS score (<3 vs. ≥3). No significant differences were observed in either analysis (HR 1.18, 95% CI 0.6–2.3 for PSA; HR 1.36, 95% CI 0.56–3.3 for PIRADS). The corresponding Kaplan–Meier curves are provided in the Supplementary Material (Figures S1 A and B).

DISCUSSION

Focal cryotherapy has demonstrated excellent functional outcomes; however, its oncological efficacy remains under investigation due to limited data on cancer control. In this study, we found that three years following cryoablation, seven out of eight patients remained free of radical treatment, and two out of three were free of any recurrence. Notably, we observed no significant difference in prognosis between patients with GG 1 disease and those with a higher GG at diagnosis.

The impact of FT on urinary and sexual function has been well-documented, with severe complications reported in less than 3% and 6% of patients, respectively. In contrast, RP and RT are associated with urinary incontinence rates of 13% and 4%, and erectile dysfunction rates of 76% and 72%, respectively (2, 17).

All patients with GG1 disease should be counseled to consider active surveillance as the recommended first-line strategy, given its favorable long-term oncological outcomes. However, for selected patients, focal therapy may provide a suitable, minimally invasive alternative.

Given that FT has already demonstrated superior functional outcomes compared to conventional treatments, our study focused on its primary challenge: oncological outcomes.

Follow-up protocols after focal therapy vary widely across studies, impacting the interpretation of oncological outcomes. There is a heterogeneity in biopsy approaches (e.g., number of cores, transrectal vs. transperineal, targeted vs. systematic) and triggers for biopsy (e.g., protocolized vs. based on clinical suspicion such as rising PSA or MRI findings). Recent expert consensus recommends performing an MRI and control biopsy within 6–12 months post-treatment (18, 19). In our protocol, an initial MRI was performed within six weeks to detect complications, followed by a second MRI at 12 months to evaluate potential recurrences before performing a confirmatory biopsy. The median time to biopsy in our study was 18 months, compared to 6, 12, and 24 months reported in other series (20-22).

In our cohort, 24 patients (22%) declined confirmatory biopsy, consistent with refusal rates of 16–23% reported in other studies (20, 23). The primary reason for refusal was low suspicion of recurrence, based on stable PSA levels and negative MRI findings. In the absence of suspicious clinical or imaging features, it is possible that a proportion of these patients would have had negative biopsy results; however, this remains hypothetical due the lack of histological confirmation. Our overall positive biopsy rate of 32% is slightly lower than the rates reported by Baskin, Esaú, and Marra, but significantly higher than the 7% reported by Wysock et al. (20) (21-23). These different cryotherapy cohorts in the literature show that confirmatory biopsy positivity rates in patients with baseline Grade Group 1 (GG 1) prostate cancer vary widely, ranging from 7% to 49%. This variation is influenced by factors such as biopsy technique and follow-up duration, with higher positivity rates observed in studies utilizing more extensive sampling (e.g., 24-core biopsies) and longer surveillance periods. Notably, outfield progression was more frequently observed than in-field recurrence, highlighting the multifocal nature of prostate cancer and the importance of comprehensive biopsy strategies to guide treatment planning.

We performed cryotherapy in 34% of patients with GG1 disease, 65% of whom had MRI-visible lesions. While active surveillance (AS) remains the standard of care for GG1 disease, patients with MRI-visible lesions have a higher risk of AS discontinuation at five years (63% vs. 48% for those with negative MRI) (9). Although intermediate-risk patients are often considered the primary candidates for FT, this recommendation is largely based on expert opinion (8). Our findings suggest that oncological outcomes are comparable between patients with baseline GG1 and GG >1 disease. These results are

in line with those of Khan et al. (15), who, in a cohort of 163 patients, also found no significant differences between Gleason 6 and higher-grade disease when using biochemical recurrence-free survival (Phoenix criteria) as the primary endpoint. While our study focused on histological recurrence and the need for additional treatments, the concordance between both studies supports the idea that baseline Gleason score may not substantially influence recurrence outcomes after focal cryotherapy, thereby challenging the notion that GG should limit FT eligibility.

Beyond biopsy findings, biochemical recurrence and the need for secondary treatments have been proposed as early oncological endpoints for FT. A recent systematic review identified Phoenix criteria for BCR, salvage focal re-treatment, and salvage radical treatment as the most commonly used endpoints (24). We did not analyze BCR due to its variable definitions and unproven correlation with more robust endpoints (e.g., biopsy results, clinical recurrence, metastasis) in the context of FT. At three years, 65% of our patients remained recurrence-free. Unlike previous studies that excluded biopsy findings from their recurrence definitions, we propose that any recurrence—including positive biopsies and secondary treatments—provides a more comprehensive measure of treatment failure.

Additionally, 88% of our patients avoided radical treatment at three years. This aligns with findings from Baskin, Shah, and Marra, who reported radical treatment-free survival rates of 96%, 91%, and 88% at two, three, and five years, respectively. Although small sample sizes and varying baseline characteristics (e.g., 76% GG1 in Marra's study vs. 5% in Baskin's) may influence these outcomes, the consistency across studies suggests that FT provides reliable oncological control across diverse patient populations. In our cohort, no significant differences were observed between GG1 and GG >1 groups in recurrence-free survival (HR 1.2, 95% CI 0.6–2.5) or radical treatment-free survival (HR 1.1, 95% CI 0.35–3.2).

In summary, we present short-term oncological outcomes from a cohort of primary PCa patients treated with focal cryotherapy at a single institution. Our findings demonstrate adequate cancer control with this technique at 3 years of follow-up, with no significant differences in outcomes based on baseline Gleason score. However, this study is limited by its retrospective design, which carries risks of selection and information bias, and by its relatively small sample size, which may reduce the statistical power to detect significant differences between Gleason score subgroups. The median time to confirmatory biopsy exceeded the recommended timeframe of 6 to 12 months, according to international consensus, potentially underestimating early recurrences. Additionally, the choice of salvage treatment was not protocolized. Further prospective studies with larger cohorts are warranted to validate these findings and to clarify whether Gleason score should play a role in the indication for focal cryotherapy.

CONCLUSION

Focal cryotherapy provides effective short-term cancer control for localized prostate cancer, with the majority of patients remaining free from recurrence and radical treatment at three years. Importantly, outcomes were similar regardless of baseline Gleason score, suggesting that cryotherapy is a viable option for a broad range of patients. However, the study's retrospective design and limited sample size highlight the need for larger, prospective studies to confirm these findings and further refine patient selection criteria.

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Kinga Mate and Pedro de Pablos-Rodríguez contributed similarly as first author

CONFLICT OF INTEREST

None declared.

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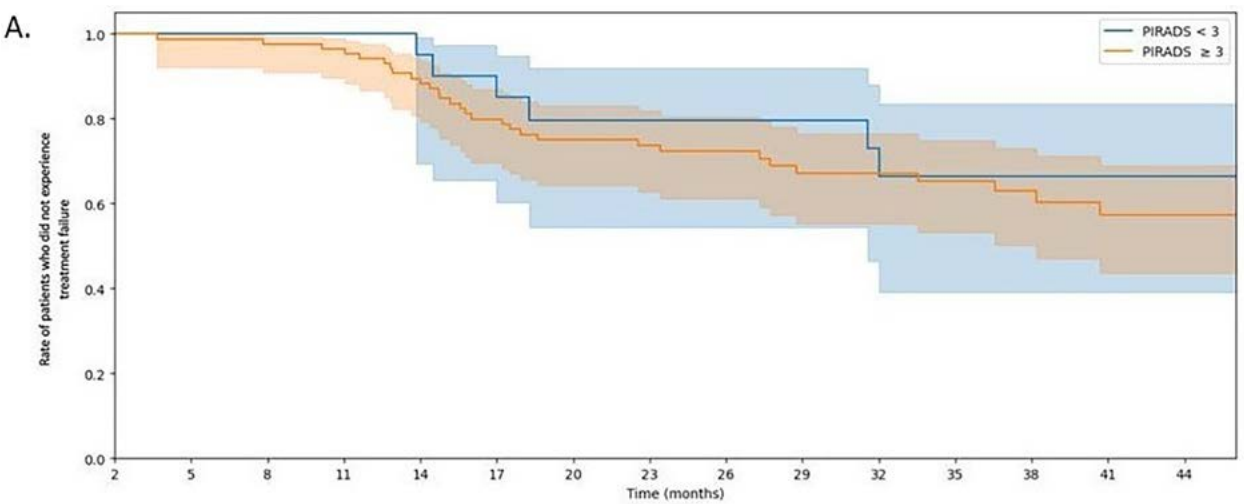
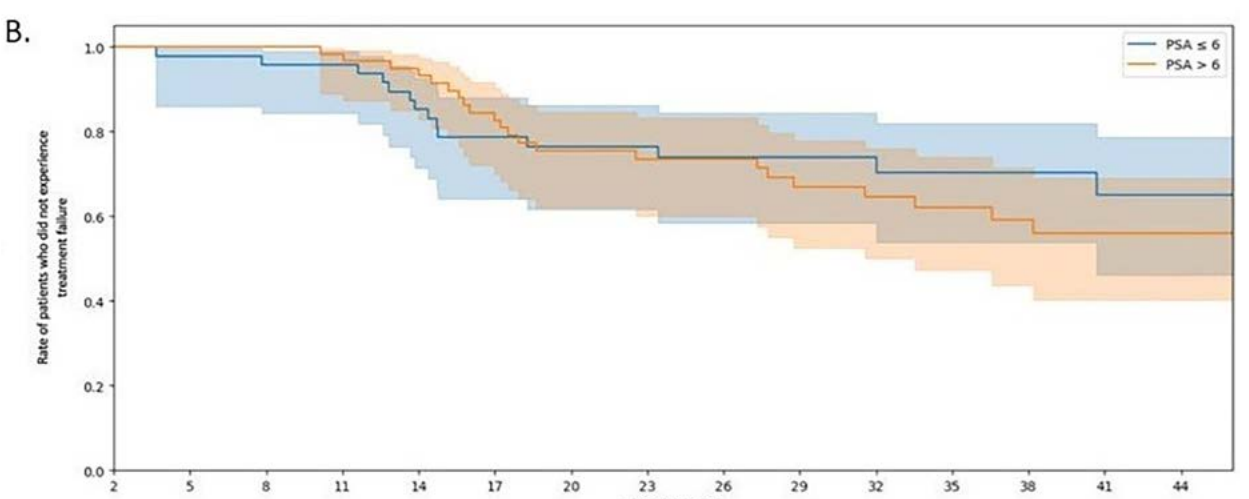
APPENDIX

Supplementary Figure 1 - Kaplan-Meier curves for recurrence=free survival according to (A) MRI findings and (B) baseline PSA level.



PIRADS < 3														
At risk	22	22	22	22	19	17	15	14	13	12	10	9	9	9	9
Censored	0	0	0	0	2	2	3	4	5	6	6	7	7	7	7
Events	0	0	0	0	1	3	4	4	4	4	6	6	6	6	6
PIRADS ≥ 3															
At risk	88	86	85	83	75	66	58	53	45	39	38	33	24	20	19
Censored	0	1	1	2	3	5	9	13	20	23	24	28	36	38	39
Events	0	1	2	3	10	17	21	22	23	26	26	27	28	30	30

* *PIRADS* - Prostate Imaging – Reporting and Data System



PSA ≤ 6														
At risk	49	47	46	46	40	36	33	30	24	21	20	18	14	12	12
Censored	0	1	1	1	2	3	5	8	13	16	16	18	22	23	23
Events	0	1	2	2	7	10	11	11	12	12	13	13	13	14	14
PSA > 6															
At risk	61	61	61	59	54	47	40	37	34	30	28	24	19	17	16
Censored	0	0	0	1	3	4	7	9	12	13	14	17	21	22	23
Events	0	0	0	1	4	10	14	15	15	18	19	20	21	22	22

* *PSA – Prostate-Specific Antigen*

ORIGINAL ARTICLE

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Penile Length can be Estimated by the Foot-Length? Study in Human Fetuses with Neural Tube Defects

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ABSTRACT

Background: There are no reports comparing penile length with foot-length between normal and anencephalic fetuses.

Aim: To compare the penile length with foot-length in fetuses with anencephaly and without anomalies.

Materiais and methods: We studied 32 fetuses without anomalies, aged 11-22 weeks post-conception (WPC) and 13 anencephalic fetuses, aged 13-19 WPC. We evaluated penile free portion length and width, penile root length and width and total penile length with a digital caliper and the aid of computer programs (Image Pro and Image J). The Shapiro-Wilk test was employed to ascertain the normality of the data and to compare quantitative data between normal vs. anencephalic fetuses. Simple linear correlations were calculated for penile measurements according to foot-length.

Outcomes: This is a morphometric study of human fetuses using a standardized technique to measure the penis in human fetuses.

Results: Total penile length varied from 4.69 to 29.77mm (mean =15.67) in normal fetuses and from 7.49 to 18.46mm (mean=11.48) in anencephalic fetuses without significant differences. The linear regression analysis indicated that the total penile length has a strong and significant correlation with the foot length in the control group (r2=0.8505, p<0.001) and a moderate correlation of total penile length and foot length in the anencephalic group (r2=0.6813; p=0.0032) and the penile body and root width increased significantly and positively with fetal foot length in normal and anencephalic fetuses.

Clinical Implications: This study may suggest a correlation between foot size and penis size in human fetuses during the 2nd gestational trimester of development.

Strengths & Limitations: Sample size was small; however, anencephalic fetuses are rare, so observations of a small sample are still relevant.

Conclusions: Penile length increased significantly and positively when correlated with foot length during the 2nd trimester of gestational development. We can suggest that foot size can be considered an indicator of penis size in human fetuses.

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INTRODUCTION

Penile size has been suggested to associate with sexual strength, virility, and vitality in men, as well as a man's self-esteem (1, 2). Medical consultations related to penis size are very common at pediatric, urology and endocrinology clinics, because the issue has significant medical, sexual, psychological and social relevance (3, 4). There is no indication that penis size differs between ethnicities (5).

Perceptions of penis size are culture specific. The males of ancient Greece believed that small penises were ideal. Large penises in Greek art are reserved exclusively for comically grotesque figures (6). Ancient Egyptian cultural and artistic conventions generally prevented large penises from being shown in art, as they were considered obscene (7).

Several studies measured the penile size and correlated with several body parameters like nose size, height and digit ratio (2D:4D) (8-10). Some studies analyzed the relationship between nose size and penile size (8). Height shows a weak-but-real relationship with penis length (9). A lower digit ratio (ring finger longer than index finger) has been linked to longer stretched penile length (10), but even these correlations are modest and insufficient for making accurate individual predictions.

Anencephaly is the worst form of neural tube defects and can work a model of impairment of the pelvic nerves and their development. The structure of the penis in anencephalic fetuses did not differ from that of fetuses without anomalies in previous studies (11).

There are no reports comparing penile length with foot-length between normal and anencephalic fetuses during human fetal development. Our hypothesis was that there are no differences between anencephaly and normal fetuses penile development during the human fetal period. The objective of the study was to compare the penile length and penile width with foot-length in fetuses with anencephaly and without anomalies.

MATERIALS AND METHODS

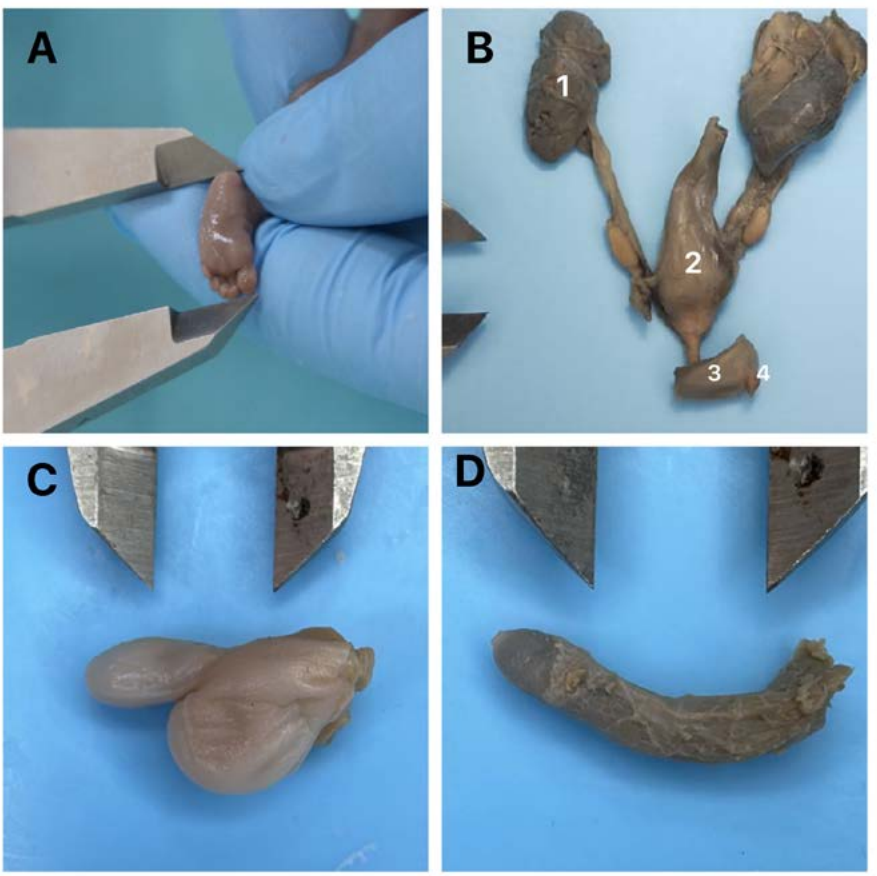
This study was carried out in accordance with the ethical standards of the hospital's institutional committee on human experimentation. (IRB: 2.475.334, CAAE: 91095525700005259).

We studied 45 human fetuses (32 without apparent anomalies and 13 anencephalic), aged 10-22 weeks post-conception (WPC) during the period from July 2023 to October 2025, which had been aborted due to hypoxia and therefore for causes unrelated to the urinary tract. The fetuses came to our laboratory as donations from the obstetric section of our hospital. The fetuses in the control group were macroscopically well preserved, with no signs of malformation, and the stillbirth was due to hypoxia. The gestational age was determined in WPC according to the foot-length criterion. This criterion is currently considered the most acceptable parameter to estimate gestational age (12-14). The fetuses were also evaluated regarding total length (TL), crown-rump length (CRL) and body weight immediately before dissection. For the evaluation of the Total length (TL) we used a metric tape and the measurement was performed from the most prominent point of the skull to the calcaneus. The same observer performed all measurements.

Using a standardized technique, the fetuses were dissected with extraction of the pelvis "en bloc" and then identified according to gestational age and date of dissection. The pelvis blocks were then reserved in a formalized container until the moment of microdissection performed in our laboratory. The fetuses were carefully dissected with the aid of a microscope (Zeiss Discovery V8 microscope with stereoscopic lens with 16/25X magnification). The pelvis was opened to expose and identify the urogenital organs and separate the genital and urinary tracts. All fetuses were dissected under identical conditions by the same researcher, who has practical experience in microsurgery.

After dissection the penile total length and width, penile root and penile body length and width were measured with a digital caliper and the aid of computer programs (Image Pro and Image J) photographs were taken by the camera attached to the microscope (Zeiss Axiocam 506 Color, 6 megapixels), and the images were stored in a TIFF file (Figure-1). The biometric parameters were recorded and measurements were performed by the same observer using the Image J software, version

Figure 1 - Foot length and penile measurements.



A) Measurement of foot length with a digital caliper; B) The figure shows the urogenital block after fetal dissection, 1 - Right kidney, 2 - Bladder, 3 - penile root and 4 - penle body; C) We can observe the penis of a fetus aged 16 weeks post-conception during the measurement of penile body and D) Dissection of penile root of the same fetus with 16 weeks post conception to measure penile root.

1.46r, because of the high intra-observer precision compared to inter-observer analysis (15, 16). The data were expressed in millimeters.

Statistical Analysis

All parameters were statistically processed and graphically described. The Shapiro-Wilk test was employed to ascertain the normality of the data and to compare quantitative data between normal vs. anencephalic fetuses. Simple linear correlations (r^2 values less than 0.4 reflect very weak correlation, while r^2 between 0.4 and 0.7 reflect moderate correlation and r^2 greater than 0.7 indicates strong correlation) were calculated for penile and fetal measurements. Statistical analysis was performed with the GraphPad Prism program (Version 6.01).

RESULTS

Findings regarding fetal age, weight, crown-rump length, total length and penile measurements in normal and anencephalic fetuses are shown in Table-1. Mean gestational age of the normal group was 15.8 WPC, while for the anencephalic group it was 15.4 WPC, with an overall variation between 12 and 22 WPC.

Total penile length varied from 4.69 to 29.77mm (mean=15.67) in normal fetuses and from 7.49 to 18.46mm (mean=11.48) in anencephalic fetuses without significant differences. The linear regression analysis indicated that

Table 1 – The table shows the analyzed parameters in normal and anencephalic human fetuses and penile measurements. WPC=weeks post-conception, SD=standard deviation.

Parameter	Normal Fetuses (13 to 19WPC)	Anencephalic Fetuses (11 to 22WPC)	p value
Weight	16 to 525 g (mean=208.91 /SD±139.3)	32 to 248g (mean=116.16 /SD±61.1)	p<0.05
Total Length	9.5 to 30 cm (mean=21.14/SD±5.71)	12 to 22cm (mean=16.96/SD±2.54)	p<0.05
Crown Rump Length	6.5 to 20.5 cm (mean=14.84 /SD±3.76)	7.5 to 14cm (mean=15.11 /SD±1.74)	p<0.05
Right Foot Length	9.9 to 40.1 mm (mean=24.99/SD±8.45)	15.17 to 35.81mm (mean=23.19 /SD±5.69)	**p<0.05**
Left Foot Length	10.41 to 40.36 mm (mean=25.41/SD±8.45)	16 to 36.28mm (mean=23.9/SD±5.96)	**p<0.05**
Total Penile length	4.69 to 29.77 mm (mean=15.87 /SD±6.53)	7.49 to 18.46mm (mean=11.48 /SD±3.4)	**p<0.05**
Penile Root Width	1.62 to 8.6 mm (mean=4.23 /SD±1.77)	2 to 5.56mm (mean=3.73 /SD±1)	p=0.337
Penile Root Length	2,22 to 16.75 mm (mean=9.02/SD±3.55)	4.14 to 12.23mm (mean=7.07/SD±2.59)	p<0.05
Penile Free Portion Length	1.37 to 18.16 mm (mean = 6.84/SD±3.66)	1.21 to 4.12mm (mean=2.79 /SD±1.37)	**p<0.05**
Penile Free Portion Width	0.85 to 7.73mm (mean = 3.66/SD+-3.66)	1.21 to 4.12mm (mean=2.79 /SD+-1.37)	p=0.097

total penile length increased significantly and positively with fetal foot length during the 2nd gestational trimester in normal (r^2= 0.8505; p<0.0001) and anencephalic fetuses (r^2=0.6813; p=0.0032), a strong correlation between the total penile length and foot length in normal fetuses and a moderate correlation of total penile length and foot length in anencephalic fetuses (Figure-2).

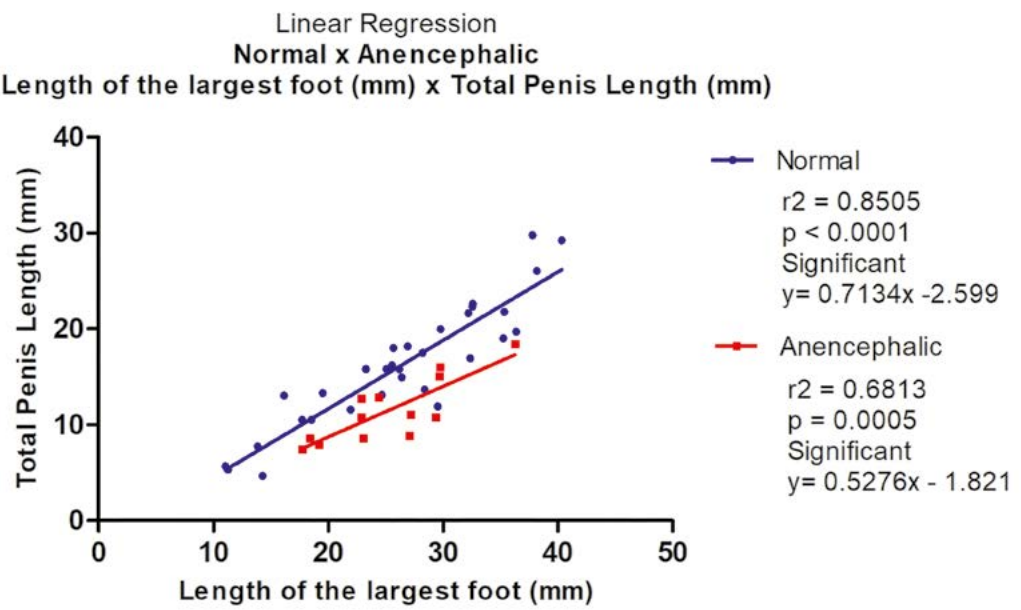
The linear regression analysis indicated that penile body and root width increased significantly and positively with fetal foot length in normal (Penile body: r^2=0.7076; p<0.0001; Penile root: r^2=0.7222; p<0.0001) and anencephalic fetuses during the 2nd gestational trimester (Penile body: r^2=0.4606; p=0.0108l; Penile root: r^2=0.3968; p=0.0210). The r^2 value higher than 0.7 indicates strong correlation between the penile width with foot length in normal fetuses, but the r^2 value below 0.4 and 0.7 reflected a moderate correlation between penile body width and foot length in anencephalic fetuses. Width of penile root in anencephalic was below 0.4 which reflected a weak correlation with foot length.

DISCUSSION

Masculinization and penile development occur due to the influence of testosterone released by Leydig cells in response to the release of luteinizing hormone by the pituitary gland during the 1st gestational trimester (17, 18). One of the first signs of masculinization is an increase in the distance between the anus and the genital structures, followed by elongation of the penis, formation of the penile urethra from the urethral groove, and development of the foreskin (18). The human penile growth after birth occurs in two stages: the first between infancy and the age of five; and then between about one year after the onset of puberty and, at the latest, approximately 17 years of age (3, 4, 17, 18). In the present paper we studied human fetuses without anomalies and anencephalic fetuses during the 2nd gestational trimester, a very important period to estimate the formation of genital organs and the influence of neural tube defects in penile development (11, 19).

Penile size mostly linked to endocrine and genetic factors. Conditions like congenital hypogonadism or isolated gonadotropin deficiency are well documented to result in significantly smaller penises, often corrected through endocrinology treatment (20). Besides the natural variability of human penises in general, there are factors that lead to minor variations in a particular male, such as the level of arousal, time of day, ambient temperature, anxiety level, physical activity, and frequency of sexual activity (21). Compared to other primates, includ-

Figure 2 - Correlation of Total penile length analyzed with fetal foot length, during the fetal period studied in normal (blue) and anencephalic fetuses (red). The points plotted represent the mean values obtained for each week studied. The linear regression analysis indicated that penile length increased significantly and positively with fetal age in normal (r2= 0.8505; p<0.0001) and anencephalic fetuses (r2=0.6813; p=0.0032).



ing large examples such as the gorilla, the human penis is thickest, both in absolute terms and relative to the rest of the body (22).

There may be a link between the malformation of the genitalia and the human limbs. The development of the penis in an embryo is controlled by some of the same Hox genes (in particular HOXA13 and HOXD13) as those that control the development of the limbs (23). Mutations of some Hox genes that control the growth of limbs cause malformed genitalia (hand-foot-genital syndrome) (24). While some minor correlations with height, nose size, or digit ratio exist, they are too weak to predict individual anatomy (3, 8, 10). Men with larger noses averaged about 5.3 in (13.5 cm) stretched vs. 4.1 in (10.4 cm) for smaller noses (8).

Stretch penile length should be interpreted in relation to anthropometric parameters in newborns, particularly body and foot length (25). Correlations between flaccid penis length, stretched out, penile circumference, height, weight, and length of the left foot were evaluated, finding low or no correlation between those mentioned, except for flaccid and stretched length (9). A previous study measured 104 men (average penile length was 3cm and the average shoe size was 9-European 43) and found no statistically significant correlation between the two parameters (21). In present paper the penile length had a significant correlation with fetal foot length during the 2nd gestational trimester.

There is currently no scientific evidence suggesting that men or boys with neurologic development disorders differ in penile size compared to neurotypical peers. Most studies on autism, ADHD, or intellectual disability focus on 2D:4D digit ratios as markers of prenatal androgen exposure, but they do not measure penile length (26) The majority of research links penile size to endocrine function and prenatal hormone exposure, not neurological development (20, 21, 24, 27).

Our study presents a comparative study about the normative parameters of penile development during the second gestational trimester in fetuses with neural tube defects. We observed some alterations in morphology of the penile development in the anencephalic group:

Total penile length, penile root length and penile free portion length were significantly greater in the normal group and penile root and penile free portion width were not significantly different between the groups.

The penile length measurements were significantly greater in the normal group, demonstrating the impact of neural tube disorder on the development of the cranial-caudal axis of the penis. Previous studies show similar findings in bladder and urethra development (28). We did not find statistical significance in the penile width measurements between groups. We can speculate that the neural tube defects impair penile development during this period, but more studies (especially structural and ultrastructural studies and penile innervation) are necessary to confirm these findings.

Some limitations of our study should be mentioned: (a) the WPC of the anencephalic and control fetuses was unequal; (b) we did not conduct pathological analysis of the penis in the samples; (c) the sample size was small (however, anencephalic fetuses are rare, so observations of a small sample are still relevant); and (d) the biometric parameters of the penis were measured by a single observer, which could potentially generate measurement bias.

CONCLUSIONS

This paper is the first to report on the correlation between penile length and fetal foot-length in human fetuses. We observe significant differences in penile length measurements in anencephalic fetuses, demonstrating the impact of neural tube defects on penile development. The penile length increased significantly and positively when correlated with foot length during the 2nd trimester of gestational development. We can suggest that foot size can be considered an indicator of penis size in human fetuses.

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CONFLICT OF INTEREST

None declared.

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Beyond the Basics: Best Practices in Scrotal Ultrasound for the Infertile Male

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INTRODUCTION

Infertility affects up to 12% of men (1-3). Despite scientific advances, especially in sperm biology and genetics, its etiology is still unknown in half of the cases (1, 2). To fill this gap, the imaging of the male genital tract (MGT) has progressively expanded to improve diagnosis, allowing for the complete evaluation of the infertile male when medical history, physical examination, semen analysis, and blood parameters do not provide sufficient information for adequate management (2). The use of MGT imaging to investigate infertility is recommended by the European Academy of Andrology (EAA) (3-7), the European Society of Urogenital Radiology (ESUR) (8), the European Association of Urology (EAU) (9), and the American Urological Association/American Society for Reproductive Medicine (AUA/ASRM) (10). In addition, MGT imaging is useful for assessing male general health, improving the characterization of scrotal and pelvic pain, inflammation, or masses of the MGT organs (1-3, 6, 11-14).

In the evaluation of the infertile male, color-Doppler ultrasound (CDUS) represents the gold-standard method to investigate the scrotal (2, 4, 6, 7) and prostate-vesicular (2, 13-17) regions. US is a simple, rapid, and harmless diagnostic tool and, among imaging techniques, is the least expensive (2, 7). Scrotal US can assess (i) features related to testicular damage, associated with non-obstructive oligo-/azoo-spermia, astheno- and/or terato-zoospermia, (ii) abnormalities of the epididymis and/or vas deferens, suggesting partial or complete obstruction of the proximal seminal tract, and (iii) varicocele (2,6-8). Prostate-vesicular US can investigate features related to obstructive oligo-/azoo-spermia and/or low seminal volume and pH (2, 5, 6, 8, 16, 17), as well as characteristics suggestive of prostate and seminal vesicles inflammation or malignancy (2, 5, 13-15, 17).

This Expert Opinion critically addresses the role of scrotal CDUS in the evaluation of the infertile male, with implications for both reproductive and general health, according to evidence-based studies. In addition, it reports on Standard Operating Procedures (SOPs) to perform scrotal CDUS properly.

Scrotal CDUS

Scrotal CDUS is useful to assess (i) reproductive health, (ii) scrotal pain, (iii) masses, and (iv) trauma (2, 7, 11, 18).

Concerning reproductive health, CDUS can detect abnormalities in the size, echotexture, and vascularization of the testes, which are associated with sperm abnormalities and low testosterone levels (2, 7, 8). Furthermore, it provides information on epididymis and vas deferens alterations associated with sperm abnormalities (2, 7, 8). Finally,

it allows the detection and staging of varicocele, which could negatively influence sperm parameters (2, 8, 19).

As for scrotal pain/soreness, CDUS can detect abnormalities in the size and echotexture of the testes or epididymis. These abnormalities are associated with hypervascularization, suggesting inflammation (orchitis or epididymitis), or absent testicular vascularization, suggestive of testicular torsion or infarction (2, 7, 11). Furthermore, scrotal CDUS can detect varicoceles or inguinal/scrotal hernias, which may be associated with discomfort, a sense of heaviness, or pain (2, 7, 13, 19).

CDUS also plays a key role in the study of testicular and extratesticular masses, characterizing them as benign or malignant with good accuracy, although without providing diagnostic certainty. It is also involved in the investigation of risk factors for testicular cancer (TC), such as cryptorchidism and diffuse microlithiasis (2, 7, 11). Finally, CDUS is useful to evaluate scrotal trauma (18).

The EAA recently developed SOPs for CDUS evaluation of the scrotal organs (Table-1) based on a multicenter consensus (4,6,7), and published evidence-based "normative" CDUS parameters derived from healthy, fertile men (3, 4, 6) (Table-2). More recently, the ESUR produced recommendations on the role of scrotal imaging in evaluating male infertility (8). Below and in Table 3, the main scrotal CDUS parameters are reported to investigate male reproductive and general health. Figure-1 shows some normal and pathological CDUS findings.

Testicular volume

Testicular volume (TV) evaluation is critical in investigating the infertile male because it generally mirrors the testicular function. TV correlates positively with all conventional sperm parameters and testosterone levels, and negatively with FSH and LH levels (2, 4, 6, 7), as well as with unconventional semen parameters (e.g., sperm DNA fragmentation, chromatin compactness, mitochondrial membrane potential, phosphatidylserine externalization, apoptotic M540 bodies) (2, 7). TV reflects not only seminal and hormonal status but also previous or current testicular or systemic disorders (2, 7).

TV is usually estimated in clinical practice with the Prader orchidometer, which offers a good surrogate of the real TV, and correlates positively with the US-TV in both fertile and infertile subjects (2, 4, 6, 7). However, the evaluation of TV by the US is more accurate. It is necessary when the physical examination is not informative, such as in the presence of a large hydrocele, inguinal cryptorchidism, small testis, or epididymis enlargement (2, 7).

US-TV can be calculated using different mathematical formulas (e.g., ellipsoid, Lambert's, and Hansen's), starting from the measurements of length (d1), width (d2), and height (d3) of the testis (2, 7, 8). The EAA (4, 6) and ESUR (8) support the ellipsoid formula ($TV=d1\times d2\times d3\times 0.52$), which correlates better with the Prader orchidometer-TV and is easier to use in clinical practice since US consoles automatically calculate it.

According to the EAA, the average TV in healthy, fertile men is 17±4 mL, and is significantly lower in infertile subjects (4, 6). The lower reference limit of US-TV for right and left testes in fertile males is 12 and 11 mL, respectively, evidence-based thresholds defining "testicular hypotrophy" (4,6). Very small (<4 mL) and hard testes, associated with elevated gonadotropin levels, suggest Klinefelter syndrome (2, 8). Small, soft testes associated with low gonadotropin levels suggest hypogonadotropic hypogonadism (2, 8). However, a normal TV does not exclude non-obstructive azoospermia (NOA), since patients with maturation arrest often have normal TV (2, 8).

Testicular echotexture

The normal adult testis is characterized by a homogeneous granular echotexture, consisting of uniformly distributed medium-level echoes (homogeneous and normoechoic testis) (2, 4, 6, 7). The alteration of the echotexture, and in particular testicular inhomogeneity (TI), is often related to testicular damage, abnormal sperm parameters, and low testosterone levels (2, 7, 8, 20, 21).

TI investigation is critical because, unlike TV, it cannot be assessed clinically and can only be evaluated with the US. TI is characterized by the presence of hypoechoic parenchymal striae (expression of a greater representation of the interlobular septa, usually not visible, and periseptal tubular atrophy), which give a "zebra-like appearance" to the testis, or, in more severe cases,

Table 1 - EAA Standard Operating Procedures (SOPs) to assess scrotal CDUS.

Testis
Testicular volume
Evaluate the three maximum diameters of each testis (anterior-posterior [height] and transverse [width] diameters in transverse scan; longitudinal diameter [length] in longitudinal scan)
Calculate testicular volume using the ellipsoid formula (length x height x width x 0.52)
Testicular homogeneity
Use a four point-Likert scale: 0.homogeneity 1.mild (grade 1) inhomogeneity [presence of small hypoechoic foci/thin hypoechoic striae] 2.moderate (grade 2) inhomogeneity [presence of thick hypoechoic striae – "zebra-like appearance"] 3.severe (grade 3) inhomogeneity [diffuse inhomogeneity with "reticulation"/"geographical map" appearance])
Testicular echogenicity
Use a three point-Likert scale: 0.normoechoic 1.mainly hypoechoic 2.mainly hyperechoic
Calcifications and microlithiasis
Macrocalcifications: calcifications with a size > 3 mm
Microcalcifications: small (1–3 mm) bright echogenic foci with no acoustic shadowing
Microlithiasis: presence of ≥ 5 microcalcifications in a single US scan, classified as 1.limited, 2.'clusters' or 3.diffuse ('starry sky' appearance). Report localization in the upper, middle and lower third of the testis
Testicular nodules
Evaluate the three diameters and characteristis (0.cystic; 1.mixed; 2.solid), shape (0.regular; 1.irregular), homogeneity (0.homogeneous; 1.inhomogeneous), echogenicity (0.normal echogenicity; 1.mainly hypoechoic; 2.mainly hyperechoic), calcifications and/or cysts (0.absent; 1.present) and vascularization (0.absent, 1.peripheral, 2.intranodular)
Testicular vascularization
Qualitative assessment: normal, reduced, enhanced (in the entire testis and/or focal areas); compare the two testes
Quantitative assessment*: evaluate arterial PSV (or acceleration, RI and PI) in the testicular artery -in the spermatic cord, 2 cm before the gonadal hilum- and the intratesticular arteries (recurrent rami of the centripetal arteries).
Other findings
Evaluate and measure **dilated rete testis**
Evaluate and measure **parenchimal cysts**
Evaluate and measure **testis appendices**
Evaluate and measure **extratesticular calcifications** (including scrotoliths).
Evaluate and measure **hydrocele** (three diametes and volume); use convex probe when bulky.
Epididymis and vas deferens
Evaluate the CDUS features of the three epididymal segments (head, body and tail) and vas deferens
Size (diameters)
Head: measure the longitudinal diameter from the top to the base of the triangle
Body and tail: measure the anterior-posterior diameters in a single longitudinal scan (if possible including the proximal vas deferens)
Vas deferens: evaluate presence or absence. Measure the anterior-posterior diameter (if possible in the same longitudinal scan with epididymal body and tail)

Homogeneity/inhomogeneity
Report it as a dummy variable (0. homogeneous; 1. inhomogeneous),
Echogenicity
Use a three-point Likert scale (0. normal echogenicity; 1. mainly hypoechoic; 2. mainly hyperechoic)
Vascularization
Qualitative assessment: normal, reduced, enhanced; compare the two epididymes
Quantitative assessment*: evaluate arterial PSV(or acceleration, RI and PI) at the level of the head (branch of the testicular artery) and of the tail (branch of the the deferential artery)
Other findings
Evaluate the presence of **nodules** (in the same way of "testicular nodules")
Evaluate the presence and number of **cysts**
Evaluate and measure epididymal **calcifications**
Evaluate and measure epididymal **appendices**
Pampiniform plexus/varicocele
1.Measure the largest vein, irrespective of location, with the patient standing, at rest, bilaterally. CDUS varicocele is defined in presence of venous vessels > 3 mm at rest, with retrograde venous flow detected at least during Valsalva manouvre.
2.Evaluate the extension of the largest vein to the funicular region, upper or lower pole of the testis.
3.Evaluate the presence of a retrograde venous flow in the patient standing, at rest, using CDUS, and classify it as a dummy variable (0.absent or intermittent/fluctuating during spontaneous breath; 1.continuous).
4. Then evaluate the variation of venous flow during Valsalva manouvre. -if basal retrograde venous flow in the patient standing, at rest, is absent, report if there is vascular enhancement during Valsalva manouvre (if yes: varicocele grade 1-3 according to extension of the largest vein to the funicular region, upper or lower pole of the testis, respectively – see below *EAA classification of varicocele*) -if basal retrograde venous flow in the patient standing, at rest, is present, perform Valsalva manouvre and report if there vascular enhancement (grade 4) or not (grade 5) – see below *EAA classification of varicocele*).
Use Sarteschi et al./Liguori et al. classifications for grading varicocele (7, 8).
"Severe" varicocele: venous vessels dilation (> 3 mm) characterized by a continuous venous reflux at rest, increasing or not during a Valsalva manoeuvre (consistent with grade 4 and 5 of Sarteschi et al./Liguori et al. classifications)
Subclinical varicocele: venous reflux detected by CDUS but not clinically evident
EAA classification of varicocele. -grade 1: venous vessels dilation (> 3 mm) at rest at the funicular region with retrograde venous flow absent/intermittent at rest and enhanced during Valsalva manouvre. -grade 2: venous vessels dilation (> 3 mm) at rest at the upper pole of the testis with retrograde venous flow absent/intermittent at rest and enhanced during Valsalva manouvre. -grade 3: venous vessels dilation (> 3 mm) at rest at the lower pole of the testis with retrograde venous flow absent/intermittent at rest and enhanced during Valsalva manouvre. -grade 4: venous vessels dilation (> 3 mm) at rest (irrespective of location, but usually extending to the peritesticular region) with retrograde venous flow *continuous* at rest and enhanced during Valsalva manouvre. Possible testicular hypotrophy. -grade 5: venous vessels dilation (> 3 mm) at rest (irrespective of location, but usually extending to the peritesticular region) with retrograde venous flow *continuous* at rest and not increasing during Valsalva manouvre. Possible intratesticular varices and/or testicular hypotrophy.

The EAA SOPs are derived and adapted from the EAA scrotal US study (4). PSV, peak systolic velocity; RI, resistive index; PI, pulsatility index. *So far, testis and epididymis vascular "quantitative" assessment is not routinely recommended.

Table 2 - EAA CDUS reference ranges and classifications for the scrotal organs and thresholds suggesting CDUS abnormalities.

	EAA CDUS reference ranges and classifications for the scrotal organs	Thresholds suggesting CDUS abnormalities of the scrotal organs
Testis		
Mean TV (ellipsoid)	17 ± 4 mL	Mean testis hypotrophy: < 12 mL
Right TV	Range: 12 – 26 mL	Right testis hypotrhophy: < 12 mL
Left TV	Range: 11 – 24 mL	Left testis hypotrhophy: < 11 mL
Testicular inhomogeneity (TI): classification	0.Homogeneity	Any testicular inhomogeneity: pathologic
	1.Mild inhomogeneity (presence of small hypoechoic foci/thin hypoechoic striae)	
	2.Moderate inhomogeneity (presence of thick hypoechoic striae-"zebra-like appearance")	
	3.Severe inhomogeneity (diffuse TI with "reticulation"/"geographical map" appearance)	
Testicular microlithiasis (TML)	Normal:<5 microcalcifications per field of view	TML: ≥ 5 microcalcifications per field of view
Testicular vascularization	Normal: ome color-Doppler spots with discrete distribution	Pathologic: -Diffuse testicular hyperemia: a)diffuse: suggestive of orchitis or, more rarely, diffuse testicular hematological neoplasms b)in a testicular nodule: suspected tumor -Absence of testicular vascularization: a) diffuse: suspected torsion; b) limited, in a cuneiform hypoechoic area: suspected lobular infarction
	Norma PSV of: -testicular artery: 3 – 11 cm/s -intratesticular artery: 3.7 – 7 cm/s	
Epididymis and vas deferens		
Epididymal head	Range: 7 - 11.5 mm (with no cysts) Range: 7 – 12 mm (with cysts)	Dilated >12 mm: likely inflammation or distal obtruction
Epididymal body	Range: 2.5 - 5 mm	Dilated > 5 mm: likely inflammation or distal obtruction
Epididymal tail	Range: 4 - 6 mm	Dilated > 6 mm: likely inflammation or distal obtruction
Vas deferens	Range: 2.3 - 4.5 mm	Dilated > 4.5 mm: likely distal obstruction
Vascularization	Normal: discrete color-Doppler spots following the deferential artery route	Pathologic: Diffuse hyperemia or one or more segments: current inflammation
Varicocele	Normal: absent (venous vessels < 3 mm with no basal or provoked reflux)	Pathologic: varicocele: Venous vessels > 3 mm at rest, irrespective of location, with retrograde venous flow detected at least during Valsalva manouvre, with grading according to Sarteschi et al. /Liguori et al. See EAA classification (7) and ESUR recommendations on varicocele (19).

TV = testicular volume; PSV = peak systolic velocity; EAA = European Academy of Andrology; ESUR = European Society of Urogenital Radiology; CDUS = color-Doppler ultrasound.

Table 3 - Scrotal color-Doppler ultrasound (CDUS) and reproductive and general health: what to investigate and why.

Main scrotal CDUS parameters to evaluate	Why to evaluate
Testis	
Volume	-Positive association with sperm parameters and testosterone; negative association with FSH and LH and unconventional sperm parameters (e.g., sperm DNA fragmentation) -Bilateral very small (<4 mL) [and hard, with elevated gonadotropins] testes suggestive of Klinefelter syndrome -Bilateral small [and soft, with low gonadotropin levels] testes suggestive of hypogonadotropic hypogonadism -A normal volume (with normal FSH) does not exclude NOA
Echotexture	-Testicular inhomogeneity: negative association with sperm parameters and testosterone levels -Rete testis dilation: suggestive of post-testicular obstruction -Multiple hypoechoic micronodules in Klinefelter syndrome: suggestive of Leydig cell hyperplasia islets
Nodular lesions/masses	Solid or mixed nodules, vascularized: suggestive of cancer
Microlithiasis	-Association with testicular cancer (especially in men with "additional risk factors" or with "starry sky microlithiasis"): perform annual follow-up up to 55 years of age. -Possible association with infertility (debated)
Localization	-Cryptorchidism or history of cryptorchidism/orchidopexy: negative association with sperm parameters and testosterone levels; increased risk of testicular cancer: annual follow-up up to 55 years of cryptorchid and contralateral testis.
Vascularization	-Absent: a) diffusely: testicular torsion (especially in men with pain); b) localized: possible lobular infarction -Diffuse hyperemia: sign of ongoing inflammation (orchitis) or, more rarely, of diffuse hematological neoplasms (leukemia in children, lymphoma in elderly men). -All cases: possible transient or permanent negative effect on sperm parameters (and possibly on testosterone levels)
Varicocele	-Negative association with sperm parameters (and, sometimes, with testosterone levels), especially for high grades (4 and 5) -Association with male infertility debated
Epididymis	
Dilatation	- Suggestive for post-testicular (sub)obstruction (at the level of the (i) epididymis [if vas deferens with regular size], (ii) vas deferens [including CBAVD or CUAVD] or (iii) prostate [evaluate the prostate-vesicular region with US]) with possible negative effect on sperm parameters -Suggestive of previous or ongoing inflammation, with possible negative effect on sperm parameters -Only overt bilateral epididymal dilation (suggested, but not proven, with US) is associated with OA

Hyperemia	- Sign of ongoing inflammation (epididymitis), with possible transient or permanent negative effect on sperm parameters
Absence	-Associated with CBAVD with OA -Associated with CUAVD with normal or altered sperm parameters (see "vas deferens")
Vas deferens	
Dilation	-Suggestive of downstream (sub)obstruction, including (i) obstruction of the retroperineal vas deferens [possibly evaluable with MRI] or (ii) vasectomy or (iii) surgical sequelae of repair of inguinal hernia or, (iv) rarely, absence of the distal portion of the deferens] or (v) at the level of the prostate [evaluate the prostate-vesicular region with US to investigate EDO -including MPC-]) with possible negative effect on sperm parameters
Absence	-CBAVD associated with OA -CUAVD: normal or altered sperm parameters -extend the investigation to the prostate-vesicular region to study the SV (bilateral absence in 50% of CBAVD subjects; ipsilateral absence in 90% of CUAVD subjects) and to the abdomen to study the kidneys (frequent ipsilateral absence in CUAVD men, rare unilateral absence in CBAVD men) and consider genetic counseling (especially for CBAVD, evaluate *CFTR* gene mutation).

NOA = non-obstructive azoospermia; OA = obstructive azoospermia; CBAVD = congenital bilateral absence of vas deferens; CUAVD = congenital bilateral absence of vas deferens; EDO = ejaculatory duct obstruction; MPC = midline prostatic cyst; SV = seminal vesicle; CFTR = Cystic Fibrosis Transmembrane Conductance Regulator. Adapted from (8).

by the presence of a hypoechoic "reticulation" or a "geographic map" appearance (2, 7, 8).

On histology, TI reflects parenchymal atrophy and fibrosis (2, 7). TI has been detected in numerous conditions associated with male infertility, including cryptorchidism and acquired testicular damage (2, 7, 8). Furthermore, TI is frequently observed in Klinefelter syndrome, often characterized by hypoechoic micronodules and the expression of islets of Leydig cell hyperplasia (2, 7, 8). TI has historically been classified on a 5-point scale (2, 7, 8) and, recently, by the EAA on a 4-point scale (4,6), where higher scores suggest more severe testicular damage. As a corollary, the testis echotexture alteration also includes rete testis dilation, which suggests post-testicular obstruction (2, 8).

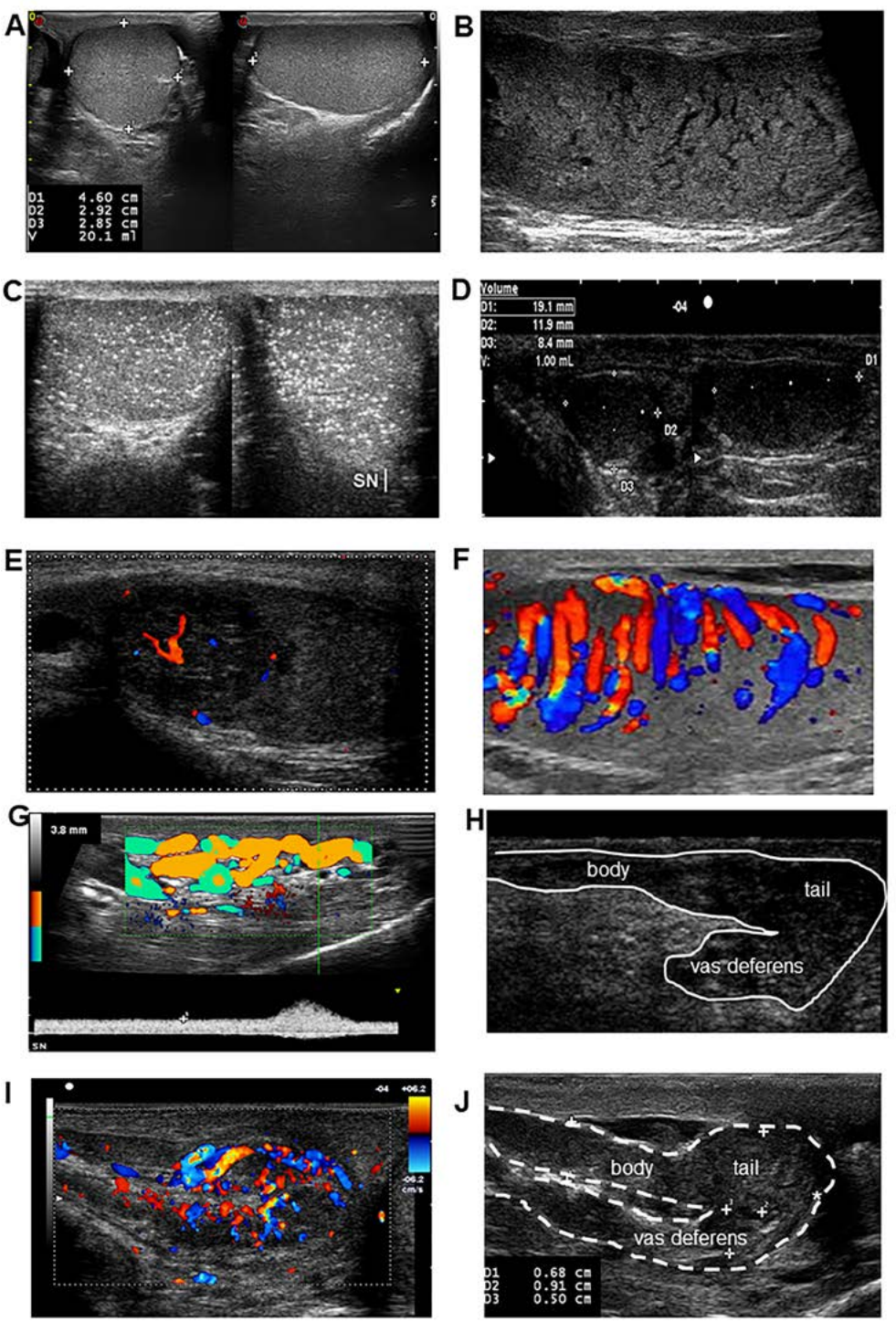
Testicular microlithiasis

Testicular microlithiasis (TML) is a US diagnosis, defined as ≥5 microcalcifications (bright hyperechoic spots <3 mm with no acoustic shadowing) per visual field (2, 7, 8). Its association with infertility and TC is widely debated. Regarding infertility, although some studies reported a higher prevalence of TML in infertile compared with fertile men, the TML-infertility association is not fully recognized (2, 7, 8). Regarding TC, recent meta-analyses supported a significant association with TML. However, literature reviews report that TML is not an independent risk factor but is associated with TC when "additional risk factors" are present (7, 8, 11). The ESUR guidelines recommend annual US follow-up up to age 55 in patients with TML and "additional risk factors" (personal/family history of TC, cryptorchidism, orchidopexy, testicular atrophy, infertility) and in men with diffuse TML ("starry sky") (8).

Cryptorchidism

Cryptorchidism is the absence of at least one testis in the scrotum (2,7,8,11,22). Its prevalence is 30% in premature newborns, 3% in full-term newborns, 1% in children at the third month of life (2, 7, 8, 11, 22), and, notably, almost 10% in males with severe oligozoospermia (23). The undescended testis is unilateral in 90% of cases. Approximately 80% of undescended testis are

Figure 1 – A) normal testis (normal volume, homogeneous, normoechoic); B) testicular inhomogeneity ("hypoechoic reticulation"); C) diffuse "starry sky" microlithiasis; D) cryptorchid testis (hypotrophic, inhomogeneous, hypoechoic); E) vascularized testicular nodule (seminoma), F) orchitis; G) grade 4 varicocele; H) agenesis of the vas deferens; I) acute epididymitis (body and tail); J) dilated epididymis (body and tail). Adapted from (2, 7).



located within the inguinal canal, 5-16% in the abdomen, and are rarely ectopic (2, 7, 8, 11, 22).

Cryptorchidism is associated with an increased risk of infertility and TC (2, 7, 8, 11, 22). Infertility has been reported in ~10% of men with unilateral and almost 40% of men with bilateral cryptorchidism (22). The risk of TC is 3-6-fold higher than in the general population (22). TC usually develops in the undescended testis; however, 20% of TC develop in the contralateral descended testis (2, 7, 8, 11, 22).

The ESUR recently recommended performing testicular US in men with a history of cryptorchidism due to the increased risk of infertility and TC (8). The US plays a key role in cancer detection and/or in the follow-up of the cryptorchid and contralateral testis, and an annual US follow-up is recommended up to age 55 (8). In addition, it is recommended to perform scrotal/inguinal US in adult men with a nonpalpable testis (8). If the US is equivocal, inguinal/abdominal MRI or surgical exploration is advocated (8). In the US, the cryptorchid testis is often hypotrophic, non-homogeneous, hypoechoic, and with calcifications. Nodular lesions may be present and should be managed according to available guidelines (2, 7-9, 11, 24).

Testicular lesions

Testicular lesions represent a clinical and US challenge. They can be detected incidentally during male infertility screening and/or when a subject complains of the detection of a scrotal lump, discomfort/sense of heaviness, or, rarely, scrotal pain (2, 7, 11). When dealing with large, hard, palpable nodules, management is primarily clinical and requires testis CDUS to confirm that they are solid, vascularized lesions suggestive of malignancy (2, 7, 11). However, when CDUS characteristics are uncertain, or when lesions are nonpalpable, "multiparametric US", which includes grey-scale and color-Doppler US combined with contrast-enhanced US (CEUS) and sonoelastography, improves their characterization to differentiate benign and malignant lesions (7, 11). This is very important, since testicular lesions are frequent, TC are the most common neoplasms in young adults (which are those of reproductive age and include most of infertile men), and the accurate evaluation of a testicular lesion is essential to define its correct management: testicular salvage and US follow-up or orchiectomy (2, 7, 11). The main clinical and multiparametric US characteristics of benign and malignant testicular lesions are reported in detail elsewhere (7, 11). Recently, ESUR published recommendations on the impact of US on the management of nonpalpable testicular lesions (24).

Testicular vascularization

Testicular vascularization plays a key role in the diagnosis of (i) orchitis, where it appears diffusely increased, (b) malignancy, generally hypervascularized, (c) testicular torsion or infarction, where the vascularization is absent in a diffuse or scattered manner, respectively, and (iv) scrotal trauma (2, 7, 8, 11, 18). All the above-mentioned conditions can be associated with sperm abnormalities (2, 7, 8). Recently, the EAA reported a standardization of the measurement of testicular vascular parameters and their reference ranges in healthy, fertile subjects (4, 6).

Varicocele

Varicocele is an abnormal dilatation of the pampiniform plexus characterized by retrograde venous flow (2, 8, 13, 19). The prevalence in men with primary infertility is ~35% (2, 8, 13, 19). Similar data have been found in healthy, fertile men (4, 6). Several studies report abnormal sperm parameters in infertile subjects with varicocele (2). However, 75% of subjects with varicocele have normal semen parameters (2). Therefore, the impact of varicocele on couple fertility is still debated, but it seems modest, and international scientific societies support varicocele correction only in highly selected cases (2, 6, 8). Physical examination has a lower accuracy in detecting varicocele compared to CDUS (2, 8, 19). CDUS is useful to assess varicocele, mainly (i) when physical examination is inconclusive or unreliable, (ii) to confirm and better classify a clinical varicocele, and (iii) to detect post-operative recurrence/persistence (2, 8, 19). Recently, ESUR reported recommendations for the standardization of CDUS in varicocele (19), and in agreement, EAA has produced a shared classification of varicocele (7). ESUR and EAA underline the importance

of a standardized examination and provide diagnostic criteria (6-8, 19) (Tables 1 and 2).

Epididymis and vas deferens

Scrotal US is the gold-standard imaging tool to investigate the epididymis and vas deferens (2, 7, 8). Their evaluation is critical, especially to distinguish OA and NOA in specific cases. In particular, the congenital bilateral absence of the vas deferens (CBAVD) and the bilateral complete obstruction of the epididymis are associated with OA (2, 7, 8). Furthermore, CDUS is useful to investigate epididymitis in subjects with scrotal pain (2, 7, 8). Recently, the EAA reported a standardization of measurements and identified reference ranges and normative thresholds for the size of the epididymal segments (head, body, tail < 12, 5, and 6 mm, respectively), proximal vas deferens (<4.5 mm) (4, 6) and deferential ampulla (<6 mm) (5,6) (Table-2) and related vascular parameters (4, 6).

Vas deferens

The US detection of CBAVD places a specific diagnosis of OA (2,7,8). CBAVD is present in 1-2% of infertile men and in 4-17% of azoospermic men (2,7,8,25). Since CBAVD is often associated with seminal vesicle (SV) agenesis, azoospermia is frequently linked to low seminal volume and pH. Therefore, US examination should be extended to the prostate-vesicular region (2, 7, 8, 25) (Table-3).

Since CBAVD is usually associated with the mutation of the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene, genetic counseling is recommended in affected individuals (2, 7, 8, 25) (Table-3). Men with CBAVD usually have normal TV and testicular function. Therefore, if they want to achieve a pregnancy, surgical sperm retrieval is indicated (2, 7).

Scrotal US can also detect congenital unilateral absence of a vas deferens (CUAVD). This condition is present in 1% of infertile men. However, men with CUAVD may show normal semen parameters and be fertile (2, 7, 8, 25). Since CUAVD is frequently associated with agenesis of the ipsilateral SV, affected subjects may present low seminal volume and pH, and the US examination should be extended to the prostate-vesicular region (2, 7, 8, 25) (Table-3). Since CUAVD is frequently associated with ipsilateral renal agenesis (rare in patients with CBAVD), the US examination should also be extended to the abdominal region (2, 7, 8) (Table-3). Finally, although CUAVD is not usually associated with mutations in the CFTR gene, genetic counseling is prudent (7, 8). In cases of CAVD, epididymis may be present and dilated, often with tubular ectasia, or it may be partially absent (2, 7, 25). In both cases, the head of the epididymis is always detectable and can be dilated or small (2).

Epididymis

Scrotal US plays a key role in investigating abnormalities in the size, echotexture, and vascularization of the epididymis, which, when considered alone or in combination, can suggest different diagnoses (2, 7, 8, 25). In subjects with scrotal pain or prostatitis-like symptoms, epididymal dilation associated with hypervascularization suggests inflammation (2, 7, 8, 11). A dilated epididymis associated with echotexture abnormalities may also represent the outcome of a previous infection/inflammation in pauci-/a-symptomatic patients (2, 7, 8). In subjects with obstructive oligo-/azoo-spermia, epididymal dilatation with tubular ectasia may suggest, as an indirect sign, post-testicular obstruction, at the level of the (i) epididymis, (ii) vas deferens, or (iii) prostate (2, 7, 8, 12, 16, 17), the latter to be investigated by extending the US examination to the prostate-vesicular region (5, 6, 8, 16, 17). Current or previous inflammation of the epididymis and/or its obstruction has been associated with sperm abnormalities (2,7,8,12). Only proven bilateral epididymal complete obstruction can diagnose proximal OA. However, so far, the US can only suggest, but not demonstrate, the presence of epididymal complete obstruction (8). Scrotal US also allows the evaluation of epididymal nodules, often represented by cysts, with no proven role in OA, or rarely by tumors (2, 11).

CONCLUSIONS

Scrotal CDUS is useful for investigating and managing the infertile male, addressing both reproductive and general health. The use of SOPs, report stan-

dardization, and knowledge of normative parameters to distinguish normal and pathologic CDUS features and attribute them with correct clinical meaning are decisive for performing a correct US and benefiting from it for diagnostic and management purposes.

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CONFLICT OF INTEREST

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Scrotal Ultrasound in the Infertile Male—A Practical Compass for the Urologist

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COMMENT

The scrotal ultrasound (US) examination is a valuable extension of the clinical evaluation of men presenting with infertility (1). Despite its widespread use, significant heterogeneity persists in how the examination is performed, interpreted, and reported. In this issue of the International Brazilian Journal of Urology, Professor Francesco Lotti provides an expert and meticulously crafted roadmap for urologists to perform scrotal ultrasound with precision and consistency (2).

From Routine Imaging to a Structured Diagnostic Tool

In his invited Expert Opinion, "Beyond the Basics: Best Practices in Scrotal Ultrasound for the Infertile Male (2)," Prof. Lotti synthesizes the latest evidence and consensus from leading societies, including the European Academy of Andrology (EAA), the European Society of Urogenital Radiology (ESUR), and the European Association of Urology (EAU). The article delivers an exemplary step-by-step description of the scrotal US examination, highlighting its diagnostic role in evaluating testicular volume, echotexture, vascularization, and the epididymis and vas deferens. Importantly, the paper integrates standard operating procedures (SOPs) and evidence-based reference values derived from healthy, fertile men—an invaluable contribution to the standardization of male infertility workups. It also discusses when the scrotal ultrasound should be combined with transrectal ultrasound examination, which is invaluable for the diagnosis and management of infertility due to ejaculatory duct obstruction (3).

Why the Formula Matters: Ellipsoid vs. Lambert

One of the practical pearls emphasized by the author—and deserving special attention—is the recommendation to adopt the ellipsoid formula (length × width × height × 0.52) for calculating testicular volume. This method, endorsed by both EAA and ESUR, correlates more closely with Prader orchidometer estimates and is automatically computed by most US consoles. Historically, the Lambert formula (×0.71) was recommended by radiological societies, but evidence now supports the ellipsoid correction factor of 0.52 for superior accuracy and clinical reproducibility. The shift to the ellipsoid formula thus represents more than a technical adjustment—it signifies the alignment of urologic practice with validated andrology-based standards.

Technical Precision: Getting the Basics Right

Although the article does not delve deeply into the technical setup of scrotal ultrasonography, it is worth emphasizing a few practical considerations that further enhance the quality and diagnostic yield of the scrotal ultrasound examination. For optimal image resolution, a high-frequency linear transducer (7 MHz or higher) should be used in most cases. In comparison, a lower frequency probe (3–4 MHz) or curved linear transducer (5–7 MHz) may be employed for larger scrotal contents such as hydroceles. The equipment must feature Color and Spectral Doppler, a wide dynamic range, and ideally a trapezoidal imaging mode to enable comprehensive assessment of testicular and epididymal anatomy and perfusion.

A frequency range between 7 and 15 MHz is generally recommended for normal-sized scrotums, ensuring optimal visualization of superficial structures, whereas lower frequencies provide greater tissue penetration when necessary. The trapezoidal imaging feature, available on many modern probes, expands the field of view, facilitating complete visualization of both testes and epididymides. Equipment with a wide dynamic range improves tissue contrast, while Color and Spectral Doppler modes are indispensable for assessing testicular and spermatic cord perfusion. They are also crucial for detecting slow blood flow in conditions such as varicocele or torsion, where Power Doppler often provides greater sensitivity.

Adjustable depth (typically 1–5 cm for scrotal contents) and Doppler frequency settings are essential to optimize image quality. Generous gel application ensures good acoustic coupling, and while elastography can aid in characterizing focal lesions, it remains an optional adjunct rather than a standard requirement.

Clinical Context Still Rules: The Case of Varicocele

A further highlight is the nuanced discussion of varicocele assessment. While Doppler ultrasound offers superior sensitivity in detecting venous reflux and grading disease severity, treatment decisions must remain anchored in clinical examination, not imaging alone (4, 5). This principle—reaffirmed by major international guidelines—safeguards against overdiagnosis and ensures that surgical correction is reserved for clinically significant cases (6, 7). Indeed, the surgical repair of clinical varicocele has been associated with improvement in semen parameters, increased rates of natural assisted pregnancies, and reduction in sperm DNA fragmentation rates (8-14). The intervention is indicated for infertile men with clinical varicocele (grades I to III) accompanied by semen abnormalities (concentration, motility, and/or morphology, or DNA fragmentation) or altered biochemical markers (e.g., creatine kinase, reactive oxygen species) (1,8,10). The preferred surgical technique is microsurgical subinguinal varicocelectomy due to its high success rate and lower complication rate (1, 10).

CONCLUSIONS

Prof. Lotti, from the University of Florence, Italy, has been instrumental in defining normative scrotal US parameters and advancing the standardization of male genital imaging. As he notes: "*Our goal is to provide a shared language and reproducible framework for scrotal ultrasonography in male infertility. By harmonizing technique and interpretation, we can bridge radiologic precision and clinical relevance, ensuring that every examination truly informs patient care.*"

This Expert Opinion by Prof. Lotti represents a must-read for all urologists and andrologists. It merges scientific rigor with clinical pragmatism and will undoubtedly serve as a reference for training, clinical practice, and research. By advocating standardized methodology and evidence-based interpretation, it sets a new benchmark for quality in male reproductive imaging and strengthens the bridge between diagnostic precision and therapeutic decision-making.

CONFLICT OF INTEREST

None declared.

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Artificial Intelligence and Peer Review: Preserving Integrity in the Pursuit of Efficiency

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INTRODUCTION

We aim to contribute to the ongoing discussion about the integration of artificial intelligence (AI) in the peer review process, a topic of increasing relevance in the scientific community.

Large language models (LLMs) are rapidly entering manuscript handling and peer review within scientific publishing. AI tools are most effective in the preliminary stages of review, such as manuscript triage, reviewer matching, and structured integrity checks, while the crucial evaluation of scientific quality remains the responsibility of human reviewers (1–3). Used judiciously and under human supervision, LLMs can help alleviate reviewer shortages and accelerate timelines, particularly in high-volume fields such as medical publishing (1, 2).

However, alongside these efficiency gains come important challenges. LLMs lack the capacity for critical judgment and contextual nuance required in complex scientific evaluation (3–5). Their use also raises concerns regarding transparency, accountability, and the integrity of academic publishing (6, 7). The rapid adoption of AI, progressing faster than regulatory guidance, requires the scientific community to critically assess both its benefits and inherent limitations. Clear policies and responsible disclosure are essential to preserve confidence and maintain rigorous standards in scientific communication (7).

Evidence and Limitations

Recent pilot studies demonstrate meaningful time savings in early editorial tasks. For instance, the 2024 Fast & Fair peer review pilot at Biology Open reported markedly faster reviewer identification and editorial throughput, with all manuscripts receiving a first decision within seven business days (1). Editors and reviewers noted no decline in review quality but emphasized that the benefits were concentrated in triage and reviewer assignment (2, 3). Similar initiatives confirm that LLMs can reduce manual workload, identifying overlapping as well as additional qualified reviewers (4). Still, their contributions remain confined to early phases and do not replace expert evaluation of methodological soundness, novelty, or validity (5, 6).

Limits of AI Reviews and Detectors

AI-generated reviews often lack the domain-specific judgment needed to assess unconventional methodologies, subtle flaws, or the broader implications of new findings (4–6). LLMs also struggle with ambiguous data

or ethical considerations in trial design—tasks requiring expert intuition beyond learned patterns (5). Detectors for AI-generated text are similarly unreliable, prone to false positives and frequent failures in identifying manipulated or AI-produced content (6, 7). The opacity of both generative AI and detection tools raises further ethical concerns, as their limitations are seldom visible to editors or authors (7).

Policy Landscape: Transparency and Accountability

Leading organizations have clarified core principles regarding AI in academic publishing. The International Committee of Medical Journal Editors (ICMJE) requires authors to disclose any AI use while remaining fully responsible for accuracy and integrity (8). The Committee on Publication Ethics (COPE) similarly states that AI cannot be credited as an author and stresses transparency and human accountability (8). Together, these positions reinforce a simple principle: AI may assist, but human judgment must prevail.

Practical Disclosure for Authors

Authors increasingly employ AI for language polishing, reference formatting, and drafting (2, 4). Disclosures should include the tool or model used, access date, and the specific tasks performed (e.g., grammar, figure legend editing). Authors must confirm that they have verified all AI-assisted content and have not uploaded confidential or identifiable information to public systems (8).

Good Practice for Reviewers

Undisclosed AI use in peer review is increasingly reported (4, 6), often resulting in generic or checklist-driven critiques (5, 7). Some AI-influenced reviews demand standards suited to high-impact generalist journals, disregarding the aims, scope, or audience of specialized publications (7). This mismatch occurs because LLMs optimize for comprehensive standards, not journal-specific context (9). Consequently, reviewers relying on AI without oversight risk producing evaluations misaligned with editorial mission and expectations (6, 7).

Reviewers should disclose whether AI was used and for which steps (8), refrain from uploading confidential manuscripts to public tools (9), and confirm that they evaluated quality in relation to the journal's aims and scope. Checklists such as STROBE and CONSORT remain valuable when applied with context-sensitive, critical oversight (7).

Key Points for Responsible AI Integration

We propose the following considerations for journals seeking to balance efficiency and integrity in adopting AI-assisted editorial processes:

- Dual disclosure: Authors and reviewers disclose how AI was used, specifying tool/model, access date, and tasks performed (7, 9).
- Allowable vs. prohibited uses: Permitted tasks include triage (scope/fit), language polishing, structured summarization, and checklist assistance (2, 4). Prohibited uses include end-to-end review generation, reliance on AI without human verification, and uploading confidential content to public models (6).
- Detector caution: AI detectors may serve as screening aids but should never be the sole basis for editorial decisions (6, 7).
- Confidentiality and security: Preference should be given to secure, organization-approved AI tools that protect confidentiality and enable audit logs (8, 9). Until institutional solutions are more widely available, policies should encourage best practices without creating inequities.
- Ongoing evaluation: Monitor effects on editorial speed, workload, satisfaction, and error rates, updating policies as evidence accumulates (9).

CONCLUSIONS

With clear rules, dual disclosure, and safeguards that preserve human oversight, AI can serve as a valuable assistant in peer review—enhancing efficiency without compromising impartiality, scientific rigor, or the trust that underpins scholarly communication (2, 7, 9).

DISCLOSURES

During the preparation of this manuscript, the authors used several AI-assisted technologies. The LLM ChatGPT-5 (Thinking model, last accessed September 12, 2025) was employed for language refinement, formatting, and structured summarization. Grammarly was used for grammatical review, and SciSpace for bibliographic verification. Following the use of these tools, all content was thoroughly reviewed, edited, and approved by the authors, who take full responsibility for the accuracy and integrity of the published work.

CONFLICT OF INTEREST

None declared.

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A Why Open Testicular Mapping (OTEM) Should Precede, and Often Replace, Micro-TESE in Nonobstructive Azoospermia

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COMMENT

Non-obstructive azoospermia (NOA) represents the most severe form of male infertility, poses significant challenges for clinical management. For men with NOA, the only opportunity for biological fatherhood depends on retrieving testicular spermatozoa to be used in intracytoplasmic sperm injection (ICSI). Currently, the gold-standard technique for this purpose is microdissection testicular sperm extraction (micro-TESE), a procedure first described by Schlegel in 1999 (1).

Micro-TESE, a microsurgical inspection of the testicular parenchyma under an operating microscope, allows identification of seminiferous tubules with focal spermatogenesis in approximately 40% to 60% of cases (1, 2).

However, micro-TESE has several drawbacks. The procedure is costly, as it requires both a surgical microscope and a highly trained microsurgical team. The cost and limited availability of operating microscopes, still lacking in many centers, have led many urologists to continue performing conventional TESE (2) or to adopt alternative methods such as loupe-assisted microdissection (l-TESE) (3), despite their inferior outcomes relative to micro-TESE. Moreover, hormonal alterations following micro-TESE have also been reported, with studies describing a transient decline in serum testosterone levels from 303 ng/dL to 248 ng/dL. Testosterone recovery to baseline may take up to 18 months in 95% of patients, and a small subset of patients may develop persistent hypogonadism (4).

In this context, open testicular mapping (OTEM), first described by Vieira et al. (5), has emerged as a less invasive and cost-effective alternative. The technique involves exposure of the testicle through a scrotal incision, followed by perforation of the tunica albuginea with a large-bore (19-gauge) needle. Manual compression of the testicle allows extrusion of testicular parenchyma through the puncture, which is then gently collected with microsurgical forceps. The number of biopsies, usually ranging from 12 to 16 depending on testicular volume, is distributed across the entire testis to ensure comprehensive sampling of the parenchyma. When immediate evaluation by an embryologist is available at the fertility laboratory, the procedure can be discontinued as soon as spermatozoa are identified in one of the earlier samples. The puncture sites in the albuginea do not require suturing. In their original study, Vieira et al. reported a sperm retrieval rate of 54% in 92 men with histologically confirmed NOA (5).

Keywords: *Non-obstructive azoospermia; testicular sperm extraction; micro-TESE; open testicular mapping; male infertility; sperm retrieval*

Subsequent studies have corroborated the effectiveness of OTEM. Lopes et al. evaluated 118 NOA patients who underwent this technique and reported a sperm retrieval rate of 55.8%. Among the 67 couples who proceeded to in vitro fertilization (IVF), fertilization, clinical pregnancy, and live birth rates were 62.1%, 46.3%, and 44.3%, respectively (6).

One of the pathophysiological explanations for OTEM's efficacy lies in the heterogeneous distribution of spermatogenesis within the testicular tissue of men with NOA. Jarvi et al. (7) performed fine-needle aspiration (FNA) mapping in 82 men with previously failed micro-TESE and found sperm in 29.3% of cases. Notably, the authors demonstrated that residual spermatogenesis was preferentially located in the peripheral rather than central regions of the testis. Because OTEM samples primarily the subcapsular region, this finding may help explain OTEM's success rate despite being a less invasive approach.

OTEM offers clear advantages: it is less expensive, does not require a surgical microscope, and, by avoiding a large albugineal incision, is less invasive and may reduced testicular morbidity. Importantly, a failed sperm retrieval with OTEM does not preclude proceeding with micro-TESE in the same operative session, offering a stepwise and cost-effective approach. In light of the above, we encourage and propose that urologists perform OTEM prior to micro-TESE in their next NOA case, as in approximately 55% of patients, micro-TESE may prove unnecessary.

Comparison between Micro-TESE and OTEM.

Characteristic	Micro-TESE	OTEM
Invasiveness	High (large albugineal incision)	Low (multiple punctures)
Microscope required	Yes	No
Cost	High	Low
Risk of hypogonadism	5% (4)	Theoretically lower
Sperm retrieval rate	40–60% (1, 2)	~55% (5, 6)
Allows sequential procedure	Not applicable	Yes (micro-TESE may follow)

CONFLICT OF INTEREST

None declared.

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Editorial Comment: Two-stage Fowler-Stephens orchidopexy in management of undescended testes: Is it time for a change? A UK multi-centre retrospective study

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COMMENT

Ikeda et al. (1) present an interesting perspective on the use of β3-adrenoceptor agonists in the treatment of nocturnal enuresis. These agents have emerged as a promising therapeutic option in the management of nocturnal enuresis (NE), particularly in patients with bladder overactivity (2, 3). β3-adrenoceptor agonists act by selectively stimulating β3-adrenergic receptors located in the detrusor muscle of the urinary bladder. Activation of these receptors promotes detrusor relaxation during the storage phase, thereby increasing functional bladder capacity. As a result, involuntary bladder contractions occurring during sleep may be reduced (4, 5).

In nocturnal enuresis—especially when associated with nocturnal polyuria or reduced bladder capacity—β3-adrenoceptor agonists may help stabilize bladder function overnight (3, 4). Unlike anticholinergic agents, they do not inhibit muscarinic receptors, which reduces the risk of common adverse effects such as dry mouth, constipation, and cognitive impairment. This favorable safety profile is particularly relevant in pediatric and adolescent populations.

In children and adolescents with enuresis, especially those with underlying bladder overactivity or reduced bladder capacity, mirabegron may help reduce involuntary detrusor contractions during sleep. By improving bladder storage and reducing nocturnal urgency, the drug may decrease the frequency of bedwetting episodes. Its use has

been reported mainly as an off-label treatment, often in patients refractory to standard therapies such as desmopressin or anticholinergic agents (3, 4).

The present study evaluated 387 children aged 5–18 years who received vibegron (50 mg once daily) for refractory nocturnal enuresis. The authors concluded that vibegron is a safe and effective option for pediatric patients with treatment-resistant NE. Add-on strategies—particularly triple therapy—were more effective than switching monotherapy, supporting the incorporation of vibegron as part of multimodal treatment approaches. Given the retrospective design of the study, prospective randomized trials are warranted to confirm these findings and to optimize treatment protocols.

CONFLICT OF INTEREST

None declared.

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Robot-assisted Repair of Rectovesical Fistula after Radical Prostatectomy using the Hugo™ RAS System

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ABSTRACT

Introduction: Rectovesical fistula (RVF) is a rare complication after robot-assisted radical prostatectomy (RARP) (1), often requiring complex surgery (2). Robotic systems provide dexterity and visualization for deep pelvic procedures (3, 4). We report the first RVF repair using the Hugo™ RAS System.

Materials and Methods: A 76-year-old male developed fecaluria one week after catheter removal following RARP. MRI revealed a 1.3 cm fistulous tract between the bladder and rectum. Initial management included transurethral and suprapubic catheters, plus a loop colostomy. Robotic repair was performed five months later. Trocar placement, adapted to the stoma, included four robotic and two assistant ports. Posterior bladder wall dissection allowed removal of two joined catheters. The posterior bladder wall, urethrovesical anastomosis dehiscence, and a 1 cm anterior rectal defect were repaired. Fibrotic tissue and residual clip were removed. A peritoneal flap was interposed between the bladder and rectum, and a new bladder neck and vesicourethral anastomosis were created using barbed sutures. Intraoperative testing confirmed integrity, and a bladder catheter was placed.

Results: The postoperative course was uneventful, with patient discharge on day 4. The bladder catheter was removed after 3 weeks. At the 2-month follow-up, urinary function was normal with good continence. Ultrasound confirmed good bladder filling and no post-void residual. Cystoscopy showed a well-healed urethrovesical anastomosis without fistula. Colostomy reversal is pending.

Conclusions: This case demonstrates the feasibility and effectiveness of the Hugo™ RAS System for RVF repair post-RARP. Robotic surgery can manage complex defects with favorable outcomes (5). Robotic platforms may expand telesurgery, allowing patients to undergo procedures locally with expert surgeons operating remotely (6).

CONFLICT OF INTEREST

None declared.

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Robotic-Assisted Retroperitoneal Lymph Node Dissection in a Challenging Post-Chemotherapy Case

Willy Baccaglini [1, 2, 3], Gabriel Chahade Sibanto Simões [2], Julio Calderón [2], Nicolle Christofe [2], Luis G. Medina [4], Paulo Priante Kayano [2], Gustavo Lemos [2], Arie Carneiro [2]

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ABSTRACT

Introduction: Robotic retroperitoneal lymph node dissection (RPLND) has emerged as a minimally invasive alternative for the management of testicular germ cell tumors, offering reduced morbidity and faster recovery when performed in experienced centers (1-3). However, post-chemotherapy cases remain technically demanding. We present a case of robotic RPLND performed for a bulky residual mass following systemic treatment.

Methods: A 23-year-old male with no comorbidities underwent right orchiectomy for clinical stage IIC non-seminomatous germ cell tumor (60% yolk sac, 20% embryonal carcinoma, 20% post-pubertal teratoma), followed by three cycles of BEP chemotherapy. Tumor markers normalized, but imaging revealed a persistent 5.4-cm interaortocaval mass. Robotic RPLND was carried out using four robotic ports and one 12-mm assistant port. The procedure included a complete bilateral template dissection (paraaortic, interaortocaval, and paracaval), en bloc tumor removal, and meticulous sharp and blunt dissection using advanced bipolar energy.

Results: Operative time was 300 minutes, with minimal blood loss (50 mL) and no intraoperative complications. The bulky lesion was successfully resected with excellent anatomical exposure, despite significant tumor adherence to the aorta. The patient was discharged on postoperative day one and resumed normal activities within two weeks. Pathology revealed teratoma in 1 of 34 resected lymph nodes. At 6-month follow-up, he remained disease-free, with normal tumor markers, preserved renal function, and no complications.

Conclusion: This case demonstrates the feasibility of robotic RPLND for large post-chemotherapy residual masses. The robotic platform enables precise dissection even in challenging settings, with favorable perioperative and oncologic outcomes. Centralized expertise and standardized technique are essential to achieve optimal results (1, 4-6).

CONFLICT OF INTEREST

None declared.

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Standardizing Suction Ureteral Access Sheath Technique in Retrograde Intrarenal Surgery (RIRS): Tips, Tricks & Troubleshooting

Giovanni Scala Marchini [1], Alexandre Danilovic [1], Fábio Cesar Miranda Torricelli [1], Fábio Carvalho Vicentini [1], Carlos Alfredo Batagello [1], Rodrigo Perrella [1], Pedro Antonio Araújo Simões [1], Alexandre Gilberto Silva [1], William Carlos Nahas [1], Eduardo Mazzucchi [1]

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ABSTRACT

Introduction: Suction ureteral access sheaths (FANS, S-UAS) are reshaping retrograde intrarenal surgery (RIRS) by improving stone-free rates and reducing complications compared to traditional UAS (1–5). Since their use requires significant technical adjustments with limited standardization, we present an instructional video detailing setup, operative choreography, and troubleshooting.

Methods: Single-center instructional case from a tertiary unit. Index patient: 67-year-old man with a 25-mm right pelvic stone (1560 HU; ~3500 mm^3). Preoperative considerations included selective prior stenting and off-label α-blockers. We typically use 10/12 or 11/13 Fr suction UAS with 7.5–8.5 Fr flexible ureteroscopes. Setup: pressurized irrigation to the ureteroscope; lateral suction port connected to a labeled collector cup via a vacuum regulator, creating a closed-loop, pressure-aware system. Under fluoroscopy, the sheath is positioned above the ureteropelvic junction (UPJ) with careful advancement into the target calyx. Laser strategy combines dusting and fragmentation with suction. Fragments are evacuated through coordinated suction bursts and slow scope withdrawal. Final inspection defines stent placement and dwell.

Results: Operative time was 115 min, with 25 min of laser use. POD-1 CT confirmed stone-free status. The patient was discharged after 24 h, and the double-J stent with string was removed on day 5. The high-definition video illustrates connections, target pressures, inflow/outflow rules, and provides concise troubleshooting algorithms for common issues: impassable UPJ (use as conventional UAS), friction/kinks, clogging, and system collapse (increase inflow, reduce suction, or reopen outflow).

Conclusion: A standardized suction-UAS technique is feasible and reproducible, optimizing visualization, fragment clearance, pressure control, and safety during RIRS for large stones (6–8). Standardization videos such as this may enhance training, support wider adoption, and improve consistency of outcomes.

CONFLICT OF INTEREST

None declared.

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Large Language Models and the "Centaur Model" in Urological Training in Latin America

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To the editor,

I read with great interest the letter by Reis "ChatGPT for medical applications and urological science" (1). The authors highlight the potential of large language models (LLMs) to support clinical reasoning, scientific writing, and knowledge synthesis. Here, I expand this discussion by examining their relevance for urological training in resource-variable environments, particularly in Latin America.

In Colombia and other countries of the region, urology residency programs face persistent structural constraints. Surgical exposure varies considerably across institutions; high- volume centers are geographically concentrated, and access to simulation labs, robotic surgery, and minimally invasive training remains uneven (2). Moreover, many programs operate with limited protected academic time and non-standardized mentorship structures, contributing to variability in operative autonomy and readiness for independent practice among graduating residents.

Within this context, LLM-based tools may offer a standardized cognitive scaffold to help reduce disparities in academic exposure. However, while generative models excel at producing fluent text, their internal reasoning processes are often opaque. This contrasts with explainable AI (XAI), which emphasizes interpretability and traceability of model outputs in clinical contexts (3). For educational purposes, the distinction is crucial: medical training must cultivate clinical judgment, not merely produce correct answers.

Recent studies published in this Journal illustrate both the promise and limitations of these tools. Braga et al. demonstrated that ChatGPT can provide helpful general frameworks for pediatric urology but that its clinical suggestions may sometimes be incomplete or misleading, requiring expert oversight (4). Pinto et al. similarly found that although ChatGPT aligned more closely with guideline-based recommendations in post-prostatectomy incontinence management, both LLMs still required specialist supervision for safe application (5). Together, these findings suggest that LLMs may support cognitive development in training but should not function as autonomous clinical guides.

This aligns with the "centaur model" of medical practice, wherein clinicians and AI systems collaborate, each compensating for the limitations of the other (6). In surgical training, the clinician contributes contextual interpretation, ethical reasoning, and adaptability, while the AI system provides structured analytical support and rapid access to medical evidence. When combined with XAI-based learning interfaces, this hybrid approach may help address academic inequities across training programs.

However, responsible integration remains essential. Challenges include hallucination risk, underrepresentation of Latin American populations in training data, language-adaptation barriers, and the potential to reinforce existing educational disparities. Therefore, LLMs should be incorporated as supervised, curriculum-embedded tools rather than independent instructional or evaluative agents.

Reis LO (1) initiated an important discussion. The next step is to evaluate supervised, context-sensitive LLM-based educational interventions across urology residency programs in low- and middle-income settings, where training variability remains a major structural barrier (2).

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CONFLICT OF INTEREST

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Tuberculous Chronic Prostatitis: a Neglected Disease

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To the editor,

An interesting and timely review on prostatitis was recently published in JAMA by Borget et al. (1). However, an important omission must be highlighted: tuberculous chronic prostatitis. In the review, tuberculosis is mentioned only once, under the "Epidemiology and Risk Factors" section of chronic bacterial prostatitis: "...Risk factors for chronic bacterial prostatitis include prior acute bacterial prostatitis, urethral surgery or catheterization, urinary stasis, unprotected anal intercourse, and genitourinary tuberculosis...." This limited reference has also been observed in other reviews and guidelines, underscoring that tuberculous chronic prostatitis remains a neglected condition (2).

Nearly 90% of new tuberculosis cases occur in 30 countries, including Brazil and 29 countries in Africa and Asia. Nevertheless, due to migration and globalization, tuberculosis must be regarded as a worldwide health concern. Urogenital tuberculosis, and specifically prostatic involvement, though uncommon in developed countries, has been documented globally (3). Importantly, *Mycobacterium tuberculosis* is a treatable cause of chronic prostatitis and is underdiagnosed rather than rare.

In Russia, Kulchavenya et al. followed a cohort of 73 patients with chronic prostatitis for at least two years, diagnosing tuberculous prostatitis in 17 patients (23.3%). This included 2 cases (11.8%) initially classified as nonbacterial chronic prostatitis and 15 cases (88.2%) classified as bacterial chronic prostatitis (4). More recently, our group in Brazil published in this journal a qualitative study analyzing 18 patients with prostatic tuberculosis (5). In 10 patients (55.6%), the presentation was chronic prostatitis, either recurrent (2 patients) or persistent with sterile pyuria (8 patients). All patients achieved pain resolution with pharmacological treatment. Notably, 6 patients were diagnosed within one year, coinciding with the implementation of systematic tuberculosis screening for all chronic prostatitis cases.

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) substantially impairs quality of life and remains therapeutically challenging. However, CP/CPPS is also a clinical manifestation of prostatic tuberculosis and may be effectively treated when recognized. Therefore, reviews and guidelines on prostatitis should emphasize that:

- Patients with CP/CPPS must be systematically screened for tuberculosis using culture and nucleic acid amplification testing of urine and semen.

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Books:

- Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

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