ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL

SOCIEDADE BRASILEIRA DE UROLOGIA

Confederación Americana de Urología

Associação Portuguesa de Urologia

VOLUME 52, NUMBER 3, MAY - JUNE, 2026

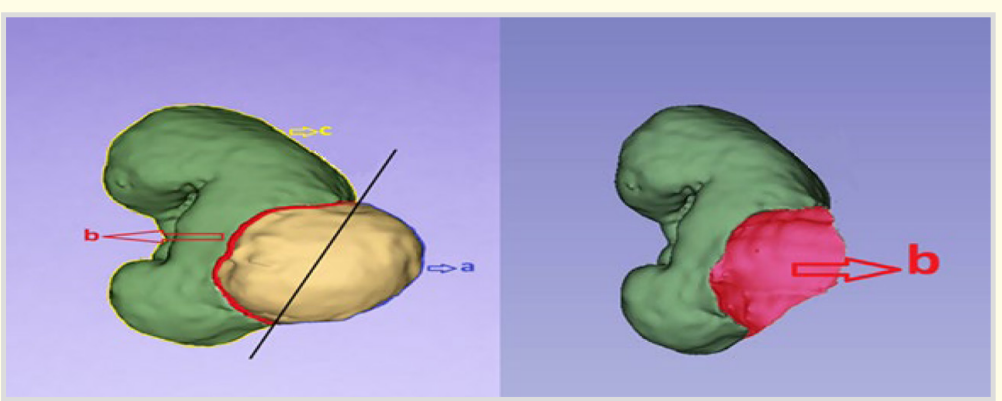


Figure 1 - Calculation of the Tumor-to-Kidney Contact Surface Area in Non-Endophytic Tumors. *e20250665*

Suppose we define the exophytic surface area of the tumour as "a", the endophytic surface area as "b", and the outer surface area of the healthy parenchyma as "c". In that case, the 3D Slicer software allows us to calculate the values of "a + c", "a + b", and "b + c". Using these known values, the unknown "b" value, which represents the tumour-to-kidney contact surface area, was calculated using the following formula:

$$b = \text{tumour-to-kidney contact surface area} = \frac{(b + c) - (a + c) + a + b}{2}$$

52 YEARS INTERNATIONAL BRAZ J UROL

XLI Brazilian Congress of Urology
November 20 - 23, 2027 - Rio de Janeiro - RJ - Brazil

Full Text Online Access Available www.intbrazjurol.com.br

INTERNATIONAL
BRAZ J UROL
OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY - SBU

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

CONSULTING EDITORS

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

Eletronic Version: Full text with fully searchable articles on-line:

https://www.intbrazjurol.com.br

Correspondence and Editorial Address:

Rua Real Grandeza, 108 - conj. 101 - 22281-034 — Rio de Janeiro — RJ — Brazil
Tel.: + 55 21 2246-4003; E-mail: brazjurol@brazjurol.com.br

The paper on which the International Braz J Urol is printed meets the requirements of ANSI/NISO Z39, 48-1992 (Permanence of Paper). Printed on acid-free paper.

The International Braz J Urol is partially supported by the Ministry of Science and Technology. National Council for Scientific and Technological Development.
Editorial and Graphic Composition

The International Braz J Urol, ISSN: 1677-5538 (printed version) and ISSN: 1677-6119 (electronic version) is the Official Journal of the Brazilian Society of Urology–SBU, is published 6 times a year (bimonthly, starting in January - February).

The International Braz J Urol is indexed by: EMBASE/Excerpta Medica; SciELO, Lilacs/Latin America Index; Free Medical Journals; MD-Linx; Catálogo Latindex; SCImago, Index Medicus - NLM, PubMed/MEDLINE, PubMed/Central, ISI - Current Contents / Clinical Medicine and Science Citation Index Expanded.

ONLINE manuscript submission: **www.intbrazjurol.com.br**

DISCLAIMER

CONTENTS

Volume 52 | number 3 | May . June, 2026 | INT BRAZ J UROL

EDITORIAL IN THIS ISSUE

REVIEW ARTICLE

ORIGINAL ARTICLE

INFORMATION FOR AUTHORS

EDITORIAL
IN THIS ISSUE

Vol. 52 (3): e20260301, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2026.03.01

Prostate Biopsy Once Again Is a Hot Topic in This Issue of the International Brazilian Journal of Urology

Luciano A. Favorito [1, 2]

[1] Unidade de Pesquisa Urogenital - Universidade do Estado do Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil; [2] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil

The May-June number of International Brazilian Journal of Urology presents original contributions with a lot of interesting papers in different fields: Prostate cancer, Prostate biopsy, Male hypogonadism, Uro-Radiology, Posterior Urethral Valves, Transplant, Robotic Surgery, Kidney cancer, Infertility, Prostate Cancer and Reconstructive Urology. The papers came from many different countries such as Brazil, Italy, China, Egypt, USA, Portugal and Turkey, and as usual the editor´s comment highlights some of them. The editor in chief would like to highlight the works about Prostate biopsy.

Dr. Chua and collegues from USA, presented in page e20250512 (1) a nice study about the Pain Perception During Transperineal and Transrectal Prostate Biopsy (PBx) Under Local Anesthesia (LA) and concluded that PBx under LA alone are generally well tolerated; however, there is a subset of patients who experience more pain, including Black and Latino, younger patients, and those with more MRI suspicious lesions. Discussion of these pain risk factors is important for pa- tients when choosing to have a biopsy performed under LA versus sedation.

Dr. Pina and collegues from Portugal, presented in page e20250653 (2) a interesting study about systematic biopsy (SB) after targeted biopsy for the detection of clinically significant prostate cancer in MRI and concluded that SB offers limited diagnostic value when combined with a mpMRI-targeted approach and support the latter as a stand-alone procedure in men with suspicious lesions.

Prostate biopsy has been showing great prominence in diagnosis of prostate cancer recently (3-6). These 2 studies are very interesting and will greatly assist the urologist in diagnosing this disease.

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

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Chua KJ, Ramacciotti LS, Kaneko M, Inoue Y, Navarro LM, Cai J, Aron M, Halteh P, Kau E, Schuckman A, Hemal S, Desai M, Djaladat H, Gill IS, Aron M, Abreu AL. Pain Perception During Transperineal and Transrectal Prostate Biopsy Under Local Anesthesia: a Prospective Analysis of a Multi-ethnic and Diverse Cohort. Int Braz J Urol. 2026 May-Jun;52(3):. doi: 10.1590/S1677-5538.IBJU.2025.0512.
2. Pina JM, Guerra J, Lança MB, Dias JL, Lucas RN, Pinheiro LC. Is there still a role for systematic biopsy after targeted biopsy for the detection of clini-cally significant prostate cancer in MRI suspicious lesions? Int Braz J Urol. 2026 May-Jun;52(3):e20250653. doi: 10.1590/S1677-5538.IBJU.2025.0653.
3. Ramacciotti LS, Strauss D, Cei F, Kaneko M, Mokhtar D, Cai J, Jadvar D, Cacciamani GE, Aron M, Halteh PB, Duddalwar V, Gill I, Abreu AL. Transperineal versus Transrectal MRI/TRUS fusion-guided prostate biopsy in a large, ethnically diverse, and multiracial cohort. Int Braz J Urol. 2024 Sep-Oct;50(5):616-628. doi: 10.1590/S1677-5538.IBJU.2024.0354.
4. Morote J, Paesano N, Picola N, Muñoz-Rodriguez J, Ruiz-Plazas X, Muñoz-Rivero MV, Celma A, García-de Manuel G, Miró B, Servian P, Abascal JM. Validation of the Barcelona-MRI predictive model when PI-RADS v2.1 is used with trans-perineal prostate biopsies. Int Braz J Urol. 2024 Sep-Oct;50(5):595-604. doi: 10.1590/S1677-5538.IBJU.2024.0204.
5. Paesano N, Catalá V, Tcholakian L, Alomar X, Barranco M, Trilla E, Morote J. The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies. Int Braz J Urol. 2024 May-Jun;50(3):296-308. doi: 10.1590/S1677-5538.IBJU.2023.0558.
6. Zhou Z, Li T, Zhang Y, Zhou X, Wang X, Cui D, Zhu Y, Jiang C, Guo W, Han B, Ruan YJ. Biplanar or Monoplanar Prostate Biopsy: Should Transrectal and Transperineal Ap-proaches be Combined for Prostate Cancer Detection? Int Braz J Urol. 2025 Mar-Apr;51(2):e20240630. doi: 10.1590/S1677-5538.IBJU.2024.0630.

Luciano A. Favorito, MD, PhD
Unidade de Pesquisa Urogenital
da Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

ARTICLE INFO

Luciano A. Favorito
https://orcid.org/0000-0003-1562-6068

REVIEW ARTICLE

Vol. 52 (3): e20260121, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2026.0121

The WHO 2025 Guideline for the Prevention, Diagnosis and Treatment of Infertility: A Comprehensive Review with Focus on Male Reproductive Health

Sandro C. Esteves [1,2,3]

[1] ANDROFERT, Clínica de Andrologia e Reprodução Humana, Campinas, SP, Brasil; [2] Departamento de Cirurgia (Disciplina de Urologia), Universidade Estadual de Campinas - UNICAMP, Campinas, SP, Brasil; [3] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

ABSTRACT

Infertility affects millions worldwide and is increasingly recognized as a major public-health concern. Despite advances in reproductive medicine, the lack of a unified global framework has contributed to substantial heterogeneity in clinical practice, particularly in the evaluation and management of male infertility. In 2025, the World Health Organization (WHO) issued its first comprehensive Guideline for the Prevention, Diagnosis, and Treatment of Infertility, establishing a global, evidence-based standard applicable across diverse resource settings. Notably, the guideline integrates male reproductive health throughout prevention, diagnosis, and treatment pathways, reinforcing the essential role of paternal factors in reproductive outcomes. This review summarizes the development, scope, and methodological foundations of the WHO guideline, including its use of systematic evidence synthesis, the GRADE framework, and structured consensus processes. Particular emphasis is placed on male-focused recommendations and good practice statements on lifestyle risk modification, sexually transmitted infections, standardized semen analysis, diagnostic algorithms, unexplained infertility, antioxidant supplementation, and varicocele repair. The review also clarifies the guideline's public-health scope and delineates areas that remain within the domain of specialty practice. Finally, we discuss dissemination, implementation challenges, and research priorities, highlighting persistent evidence gaps in male reproductive biology, sperm function, and clinically meaningful treatment outcomes. By aligning public-health principles with contemporary understanding of male physiology, the WHO guideline provides a global foundation for equitable and systematic infertility care.

ARTICLE INFO

Esteves, SC
https://orcid.org/0000-0002-1313-9680

Keywords:
Reproductive Health; Primary Prevention; Practice Guideline [Publication Type]; Review [Publication Type]

Submitted for publication:
February 12, 2026

Accepted:
February 19, 2026

Published as Ahead of Print:
March 04, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

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

INTRODUCTION

Infertility affects an estimated one in six individuals worldwide and represents a growing public-health challenge with profound social, psychological, and economic consequences (1). Although substantial progress has been achieved in assisted reproductive technologies, global infertility care remains highly variable, particularly in low- and middle-resource settings where access to diagnostic services and effective treatments is limited. Historically, policy frameworks and clinical pathways have disproportionately emphasized female evaluation, reflecting entrenched assumptions about causation and societal expectations. Male infertility, in contrast, has often been under-recognized, inconsistently investigated, and insufficiently integrated into national reproductive-health strategies (2-4).

The publication of the 2025 World Health Organization (WHO) Guideline for the Prevention, Diagnosis, and Treatment of Infertility marks a significant milestone in global reproductive care (5). It is the first comprehensive WHO document to address infertility across its full spectrum, explicitly encompassing both male and female contributors. The guideline was developed to provide a globally applicable, evidence-based, and equity-oriented framework suitable for implementation across health systems with differing resource levels. Its scope extends from population-level prevention to clinical diagnosis, management, and medically assisted reproduction, with an emphasis on feasibility, person-centered care, and minimizing unnecessary interventions.

A particularly transformative aspect of the guideline is its structured integration of male infertility into the care pathway. By embedding men within prevention strategies, diagnostic evaluation, and treatment recommendations, the guideline addresses longstanding gaps that have contributed to delayed or incomplete assessment of male reproductive health. This shift is timely. Increasing evidence demonstrates that paternal health—including lifestyle factors, environmental exposures, endocrine function, and sperm molecular characteristics—plays a critical role in fertility potential, embryo development, and long-term offspring outcomes (6-13). As a result, prioritizing male reproductive assessment is not only clinically justified but essential for achieving equitable and biologically coherent infertility care (14).

This review provides a detailed examination of the WHO guideline through the lens of male reproductive health. Following a description of the guideline's rationale, scope, methodological foundations, and evidence-grading process, we analyze the male-relevant recommendations on good practice statements, prevention, diagnosis, and treatment. Particular attention is paid to lifestyle and environmental risk modification, sexually transmitted infections, semen analysis, the structure and limitations of the diagnostic algorithm, unexplained infertility, antioxidant supplementation, and varicocele management. We conclude by discussing dissemination strategies, implementation considerations, and research priorities that emerge from the guideline, highlighting key areas where evidence is currently insufficient and where future studies could strengthen subsequent guideline iterations.

GUIDELINE OVERVIEW

Infertility has long been recognized as a significant global health concern (2, 3, 11, 15), yet until 2025, there was no unified World Health Organization guideline addressing its prevention, diagnosis, and treatment for males and females. The development of the WHO Guideline for the Prevention, Diagnosis, and Treatment of Infertility was driven by the need for a coherent, evidence-based framework to guide countries with widely differing resources, infrastructure, and clinical capacity (5). The initiative reflects WHO's broader mandate to support reproductive health as part of universal health coverage and acknowledges infertility as a condition with profound medical, psychological, and social implications for individuals, couples, and communities.

Rationale for Developing the Guideline

The rationale for creating this guideline emerged from persistent global inequities in access to infertility care (2-4, 11, 15-17). In many regions, diagnostic evaluation is fragmented or unavailable, medically assisted reproduction (MAR) is financially inaccessible, and cultural stigma restricts help-seeking behavior—particular-

ly for men (3, 4, 11). Prior guidance documents, explicitly focusing on male infertility, such as the American Urological Association/American Society for Reproductive Medicine (AUA/ASRM), European Association of Urology (EAU), and Brazilian Society for Human Reproduction (SBRH), provide detailed clinical recommendations but are primarily oriented toward high-resource settings (18-23). The WHO guideline was created to complement, rather than replace, such specialty resources by establishing a global baseline for essential services that can be adapted across diverse health systems. It also reflects an expanded understanding of infertility as a condition that warrants recognition and management within reproductive-rights frameworks.

Importantly, the guideline integrates male infertility throughout its structure. Historically, policy and clinical pathways have disproportionately focused on women, despite evidence that male factors contribute to infertility in up to half of all couples. The WHO document acknowledges this imbalance by embedding male evaluation within preventive strategies, diagnostic algorithms, and treatment recommendations, thereby reinforcing the principle of couple-based assessment.

Scope and Target Audience

The scope of the WHO guideline is broad and intentionally inclusive. It covers:

i. Prevention of infertility across the life course, with guidance applicable to the general population, individuals planning a pregnancy, and couples undergoing infertility evaluation.

ii. Diagnosis of infertility in both partners, emphasizing standardized assessment, structured history-taking, focused physical examination, and the judicious use of semen analysis.

iii. Treatment, including lifestyle modification, management of sexually transmitted infections (STIs), and interventions for clinical varicocele.

The guideline applies to individuals and couples attempting to conceive naturally and those who may require assisted reproduction. The document is designed to support implementation across low-, middle-, and high-resource settings, with recommendations that are feasible, equitable, and adaptable to local infrastructure and regulatory environments.

The guideline also clearly defines its boundaries. It does not attempt to provide detailed procedural guidance for ovarian stimulation, embryology laboratory techniques, endocrine management of spermatogenic dysfunction, or surgical reconstruction for obstructive azoospermia, nor does it offer guidance on genetic evaluation or advanced tests of sperm function. These omissions reflect the guideline's purpose as a public-health instrument rather than a specialty clinical manual. While it complements detailed professional-society guidelines, its primary aim is to establish a minimum global standard that can be expanded upon by national programs or specialty organizations where resources permit.

The target audience for this guideline encompasses clinicians directly involved in reproductive care—including urologists, reproductive endocrinologists, gynecologists, and primary-care providers—who must integrate its recommendations into daily practice. It also speaks to fertility nurses, midwives, counselors, and allied health professionals who deliver infertility services. Policymakers, program managers, and public health authorities are also central users, given the guideline's emphasis on systems-level implementation, resource allocation, and regulatory considerations. Researchers, educators, and trainees in reproductive medicine represent another key audience, as the guideline provides a conceptual foundation that aligns with contemporary evidence while identifying areas where data remain insufficient. By directing its content to such a diverse readership, the guideline underscores that infertility care is not confined to specialist clinics but forms an integral component of comprehensive reproductive-health systems.

METHODS USED IN DEVELOPING THE GUIDELINE

The guideline was developed through a structured process aligned with WHO's internal standards for guideline development (Table-1). A multidisciplinary Guideline Development Group (GDG) was convened, comprising clinicians in reproductive medicine, urolo-

Table 1 - Summary of Methods Used in Developing the WHO Infertility Guideline.

Component	Summary
Guideline Development Group	Multidisciplinary panel including urologists, andrologists, reproductive endocrinologists, embryologists, epidemiologists, public-health scientists, methodologists, program managers, and patient representatives.
Formulation of Questions	Structured using the PICO framework. Prioritized questions with global relevance, feasibility, and potential impact on health-system equity. Male-focused topics included semen analysis, repeat testing, antioxidants, varicocele, STIs, and unexplained infertility.
Evidence Retrieval and Synthesis	Systematic reviews commissioned or updated by WHO, complemented by targeted searches. Evidence profiles developed to summarize effectiveness, certainty, harms, acceptability, feasibility, and resource needs.
GRADE Methodology	Applied to assess certainty of evidence and determine strength of recommendations. Informed decisions on antioxidants (no recommendation) and varicocele repair (conditional recommendation).
Consensus Process	Recommendations finalized by group consensus; formal voting used when needed. Reflected balance of evidence, feasibility, values, and equity.
External Review	Draft guideline underwent peer review by external experts in infertility, public health, and methodology. Revisions incorporated before WHO final approval.
WHO Approval	Final guideline reviewed and approved by WHO's internal guideline review committee, ensuring adherence to methodological and ethical standards.

GRADE, Grading of Recommendations Assessment, Development and Evaluation; STIs, sexually transmitted infections; PICO, P stands for Patient or Problem, I is for Intervention, C is for Comparison, and O is for Outcome; WHO, World Health Organization

gists, andrologists, epidemiologists, embryologists, public health experts, methodologists, program managers, and patient representatives (5).

Clinical and public-health questions were formulated using the PICO (Population, Intervention, Comparison, Outcome) framework, prioritizing topics with high global relevance, implementation feasibility, and potential to reduce inequities in infertility care (24). Male-focused questions addressed semen analysis, indications for repeat testing, antioxidant supplementation, clinical varicocele repair, sexually transmitted infections, and criteria for unexplained infertility. Highly specialized investigations—such as advanced sperm function testing, endocrine management, and genetic evaluation—were purposely excluded because they fall outside the public health scope and are addressed in specialty guidelines.

Evidence was sourced through systematic reviews commissioned or updated by WHO, supplemented by targeted searches for randomized and observational data. Findings were synthesized into standardized evidence profiles that summarized effect size, certainty, harms, feasibility, and resource implications. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework was applied to assess the certainty of the evidence and determine the strength of the recommendations (25). This process was central to determining, for example, that evidence for antioxidant supplementation was too heterogeneous and indirect to support a recommendation. By contrast, evidence supporting clinical varicocele repair was sufficient to justify a conditional recommendation. Recommendations were finalized through structured GDG deliberation, with formal voting and consensus. Drafts underwent external expert review before final approval by WHO's internal guideline review committee.

SUMMARY OF GUIDELINE MALE-RELATED CONTENT

The guideline presents a framework that integrates preventive strategies, standardized diagnostic

evaluation, and evidence-informed treatment options. The recommendations are organized into Good Practice Statements (GPS)—reflecting interventions supported by strong ethical, clinical, or public health principles—and formal recommendations derived from systematic evidence appraisal. The structure emphasizes global applicability, feasibility, and equity, while also incorporating clinically meaningful guidance for male infertility.

This section provides an overview of the content most relevant to male reproductive health, including the rationale and intent behind the WHO recommendations.

Good Practice Statements

Several GPS pertain directly or indirectly to the male partner, thus reflecting interventions considered essential for quality infertility care regardless of setting (Table-2). GPS are not formal recommendations because they do not rely on GRADE-based evidence assessment; instead, they represent actions clearly supported by ethical considerations, consensus, and accumulated clinical experience.

Importantly, the guideline affirms that infertility care must be couple-based and that both partners should be evaluated systematically, regardless of which partner initially seeks care, a statement aligned with other relevant infertility guidelines (18-21, 26). Health-care providers are encouraged to deliver fertility information proactively, including education on modifiable risk factors, timing of intercourse relative to ovulation, and the impact of age, sexually transmitted infections, and lifestyle behaviors. The guideline also asserts that individuals and couples should

Table 2 - Good Practice Statements (GPS) on the General Approach and Management of Infertility in the WHO Guideline.

Good Practice Statement as written in the WHO guideline	Interpretation / Relevance to Clinical Practice
Select diagnostic tests based on the clinical findings from the medical history and physical examination to ensure that evaluation is systematic and cost-effective.	Emphasizes structured, stepwise evaluation. Diagnostic testing should follow clinical findings—not precede them—to avoid unnecessary investigations and support equitable access, especially in resource-constrained settings.
Listen to individuals and couples, respect their preferences, discuss if psychological and social or peer support is needed, and if needed, provide it or refer patients for it.	Positions infertility care within a person-centered framework. Psychological and social dimensions must be addressed alongside medical factors. Counseling and support services should be integrated or readily accessible.
Base treatment decisions on benefits and harms, patient values and preferences, feasibility, costs and availability of resources.	Reinforces shared decision-making and transparent counseling. Treatments should not be offered solely on theoretical benefit; they must be feasible, affordable, and aligned with patient priorities.
Consider the cost-effectiveness of treatment (e.g., least expensive but effective treatments should be provided initially).	Prioritizes rational, equitable sequencing of treatment. First-line options should be effective and affordable; high-cost interventions such as MAR should follow only when justified.
Discuss the plan for clinical follow-up and management of potential risks that may occur during infertility treatment.	Requires clinicians to communicate treatment expectations, safety considerations, monitoring plans, and contingency pathways. This applies to both male and female interventions.
Document the outcomes of pregnancies resulting from infertility treatment.	Supports surveillance, quality improvement, and public-health monitoring. Documentation enables outcome auditing, safety assessment, and future refinement of care pathways.

MAR = medically assisted reproduction.

have equitable access to timely, respectful, culturally appropriate infertility care. This includes counseling, psychosocial support, and linkage to specialized services when indicated. These GPSs serve as the conceptual foundation for the more detailed recommendations that follow.

Prevention

Prevention constitutes one of the most forward-looking and transformative elements of the WHO guideline. Rather than confining infertility care to individuals who are already attempting conception, the guideline adopts a life-course, population-level perspective in which fertility awareness becomes a core component of general health promotion for both women and men. This shift is particularly significant for male reproductive health, which has historically received less structured preconception attention despite clear evidence that paternal factors influence fertility, early embryo development, and long-term offspring well-being(7, 11, 15, 27-42).

For the prevention of infertility in men, the guideline highlights four major domains, as outlined in Table-3. The guideline frames prevention as a shared responsibility between individuals, couples, and health systems. Its preventive recommendations are couple-oriented but explicitly acknowledge the need to provide men with tailored guidance. Men often underutilize primary care, seek medical attention later than women, and rarely receive structured counseling about reproductive risks. The WHO document counters this by encouraging countries to integrate fertility information into existing health-promotion platforms, such as school curricula, adolescent sexual health programs, workplace initiatives, and community outreach activities.

The guideline underscores that preventive counseling must be culturally sensitive, accessible, and matched to local realities. Men should receive clear, actionable guidance regarding the timing and frequency of intercourse, fertility at different ages, the influence of acute and chronic illnesses, and the importance of addressing genital symptoms or potential exposures early. The message is universal: male reproductive health is modifiable, and early engagement can improve fertility outcomes. Indeed, spermatogenesis is acutely sensitive to metabolic variation, oxidative stress, heat, toxins, endocrine disruptors, and genital infection. Time-to-pregnancy studies and mechanistic data indicate that paternal behaviors—even before conception—can influence embryo quality, blastulation rates, and miscarriage risk (9, 10, 16, 28, 32, 33, 35, 43-46). Integrating male fertility awareness into broader health education ensures that men receive the information necessary to understand their role in establishing optimal conditions for conception (4, 14, 15).

Diagnosis

Diagnosis represents one of the most actionable components of the guideline. Diagnostic evaluation is organized around a structured, stepwise approach that integrates history, physical examination, and semen analysis, designed to ensure that every man in an infertile couple receives a basic, meaningful, and systematic assessment, regardless of geographic setting, clinician background, or health-system resources (Figure-1).

These elements are integrated through a diagnostic algorithm that functions primarily as a triage system rather than a full clinical decision tree, enabling non-specialists to address reversible causes while promoting timely referral to clinicians with expertise in male infertility—most commonly, urologists.

The first step identifies modifiable risk factors (e.g., tobacco use, heat exposure), reversible causes (e.g., infection), and clinical abnormalities (e.g., varicocele, testicular atrophy). Standardized semen analysis should be conducted according to the WHO manual (47, 48): normal result → no repeat; abnormal result → repeat at ≥11 weeks, following the duration of one spermatogenic cycle (49). If reversible or treatable causes such as lifestyle exposures, genital infection, or medication effects are identified, these should be addressed first, followed by reassessment. Additionally, if semen parameters remain below reference limits after repeat testing, or if history/exam reveals persistent abnormalities, referral to clinicians experienced in male infertility (typically urologists) is indicated. The most relevant findings in history/exam warranting referral include palpable varicocele, endocrine or sexual dysfunction, symptoms or signs of genital tract obstruction, suspected genetic ab-

Table 3 - Male-Relevant Recommendations from the 2025 WHO Infertility Guideline Relative to Prevention.

Category	Recommendation	Remarks
Information provision on fertility and infertility	For the general population of reproductive age, WHO suggests providing information about fertility and infertility using low-cost strategies or whenever there is opportunity (Conditional recommendation, very low certainty of evidence).	Low-cost strategies may include information in digital or paper format when opportunities occur in schools, at primary health care centers or at reproductive health (contraceptive, sexual health) clinics. Information adapted to local contexts and audiences, including how to reduce risk factors for infertility, lifestyle modification, age-related fertility decline/potential, and timely medical consultation, may increase the likelihood of information uptake and beneficial outcomes.
	For individuals and couples with infertility, WHO suggests providing low-cost lifestyle advice before and during infertility treatment. (Conditional recommendation, very low certainty of evidence).	Lifestyle advice may include advice to change diet, alcohol intake, smoking, physical activity and/or weight management.
Risk reduction from tobacco smoking	WHO recommends that brief advice be consistently provided by health care providers as a routine practice to all tobacco users accessing any health care settings (Strong recommendation, moderate certainty of evidence).	This is an existing WHO recommendation for the general population that also applies to individuals and couples who are planning a pregnancy, attempting to achieve a pregnancy or with infertility, given the association between infertility and current or previous history of smoking. Assessment of lifestyle, including the use of tobacco, is part of medical history when evaluating individuals and couples for infertility. Brief advice is advice to stop using tobacco – usually taking only a few minutes – given to all tobacco users, usually during a routine consultation or interaction. Brief advice should include informing individuals and couples that (i) use of tobacco, particularly smoking, is associated with a higher risk of infertility; (ii) the risk of infertility due to tobacco smoking is higher among women; and (iii) a range of interventions to assist in cessation of tobacco use exist. Brief advice should include the 5As: asking about tobacco use; advising to make a quit attempt; assessing readiness to quit; assisting in making a quit plan; and arranging a follow-up. Advice should be tailored or personalized based on individual circumstances. All adults interested in quitting smoking should be offered or referred to interventions to assist in tobacco cessation as recommended by existing WHO guidelines for preventing tobacco use uptake, promoting tobacco cessation or diagnosing and treating tobacco dependence (https://iris.who.int/handle/10665/377825).
Risk reduction from sexually transmitted infections (STIs)	Couples and individuals planning or attempting to achieve pregnancy who are accessing any health care settings should be routinely informed about sexually transmitted infections (STIs), including the risk of infertility when STIs are untreated (Good practice statement)	If symptoms of an STI are present, or if infection is confirmed, WHO guideline recommendations on the management of STIs are available (https://iris.who.int/handle/10665/342523; https://iris.who.int/handle/10665/378213)

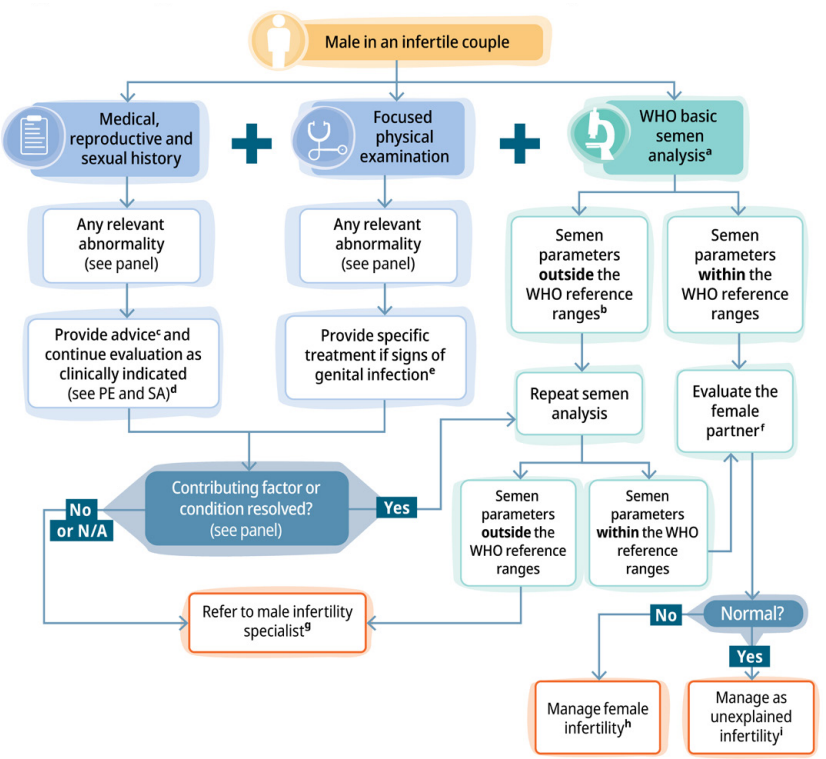
Certainty of evidence: high (we are very confident that the true effect lies close to that of the estimate of the effect); moderate (we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); low (we have limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect); very low (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect).

Good practice statements were made in topics where the Guideline Development Group (GDG) agreed that guidance was necessary, but a review of the evidence was not warranted because the benefits of the practice were unequivocal and other factors (such as equity) would not have an impact. Good practice statements were rooted in the fact that answers were deemed obvious by the GDG. The methodologist guided the development of good practice statements based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Strong recommendation: For patients (most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences); for clinicians (most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator; for policy-makers (the recommendation can be adopted as policy in most situations);

Conditional recommendation: For patients (the majority of individuals in this situation would want the suggested course of action, but many would not); for clinicians (Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences); for policy-makers (policy-making will require substantial debate and the involvement of various stakeholders)

Figure 1 - The WHO Male Diagnostic Algorithm.



The algorithm outlines a stepwise, resource-sensitive pathway that begins with a comprehensive medical history and physical examination, followed by semen analysis in accordance with the WHO 6th edition laboratory standards. Abnormal findings prompt targeted management—such as treatment of genital infections or referral for further diagnostic steps (e.g., hormonal, genetic, or imaging evaluation)—culminating in evidence-based intervention led by male infertility specialists, typically urologists. This pragmatic framework integrates prevention, diagnosis, and referral within the broader context of equitable reproductive care.

History	Components
1 Medical history	• Age • Systemic diseases (e.g. diabetes, cirrhosis, hypertension) • Sexually transmitted diseases, tuberculosis, viral infections, genital and systemic bacterial infections, history of fever, respiratory infection, anosmia • Cancers (e.g. testicular cancer, lymphoma, leukaemia) • Galactorrhoea, visual disturbances
2 Reproductive history	• Age of partner, length of time attempting to conceive • Contraceptive methods and duration • Previous pregnancy or miscarriage (current partner or another partner) • Previous treatments • Treatments or evaluations of female partner
3 Sexual history	• Potency, libido, lubricant use • Orgasm, ejaculation, timed intercourse, frequency of sex or masturbation
4 Childhood and development	• Cryptorchidism, hernia, testicular trauma, testicular torsion, infection (e.g. mumps) • Sexual development, puberty onset
5 Previous surgery or treatment	• Orchidopexy, herniorrhaphy, orchiectomy (e.g. testicular cancer, torsion) • Retroperitoneal and pelvic surgery (e.g. prostatectomy) • Other inguinal, scrotal or perineal surgery • Bariatric surgery, bladder neck surgery, transurethral resection of the prostate
6 Family history	• Cystic fibrosis, endocrine diseases • Infertility in the family
7 Gonadotoxin exposure	• Endocrine-disrupting chemicals (e.g. phthalates, bisphenol A, some pesticides, among others) • Some medication (e.g. chemotherapy agents) • Some organic solvents, heavy metals • High temperatures, ionizing radiation (e.g. high doses above recommended therapeutic or occupational levels)
8 Current health status/lifestyle	• Obesity/diet, metabolic syndrome • Anabolic steroids, tobacco smoking, alcohol

Physical exam	Components
1 Overall body characteristics	• Poor virilization, gynaecomastia • Obesity, BMI
2 Inguinal and genital areas	• Scar
3 Penis	• Hypospadias, epispadias, phimosis, curvature
4 Testes	• Location, size, consistency, pain/nodules/tenderness
5 Ductal structures (vas, epididymis)	• Present/absent • Normal/signs of obstruction or inflammation
6 Spermatic cord/ scrotum	• Varicocele, hydrocele, cysts

[a]See the WHO laboratory manual for the examination and processing of human semen (sixth (WHO, 2021) or latest edition); [b]Consider post-ejaculate urinalysis to rule out retrograde ejaculation if low (or no) semen ejaculate volume; see WHO laboratory manual for the examination and processing of human semen (sixth (WHO, 2021) or latest edition); [c]See Chapter 4 in the guideline (World Health Organization, 2025), for details on information provision; [d]Evaluation should include PE and SA regardless of history findings; [e]See Chapter 4 in the guideline (World Health Organization, 2025) and the WHO guideline for the management of sexually transmitted infections (World Health Organization, 2021); [f]Female evaluation is essential and should proceed regardless of semen analysis outcome; see Chapter 5 in the guideline (World Health Organization, 2025) for the assessment of the female partner; [g]Healthcare provider with appropriate qualifications; for example, urologist, clinical andrologist or reproductive medicine specialist with relevant qualifications; [h]See Chapters 6, 7 and 8 in the guideline (World Health Organization, 2025); [i]See Section 5.8 and Chapter 10 in the guideline (World Health Organization, 2025). Abbreviations: N/A, not applicable; PE, physical examination; SA, semen analysis; WHO, World Health Organization. Reprinted from: Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World Health Organization; 2025. License: CC BY-NC-SA 3.0 IGO: (https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

normalities, and complex medical conditions affecting reproduction. By contrast, the diagnosis of unexplained infertility is established only when the male partner has an unremarkable medical, reproductive, and sexual history, physical examination reveals no clinically significant abnormalities, and semen parameters fall within WHO reference ranges, and the female partner has normal ovulatory function and patent fallopian tubes.

The algorithm thus helps prevent the common situation in which male evaluation is reduced to a semen analysis alone (50, 51). By explicitly linking abnormal findings with specialist referral, the guideline reinforces the essential role of urologists in male reproductive care. Additionally, the WHO provides a detailed template for comprehensive male reproductive history-taking, covering developmental conditions, prior genital infections, systemic diseases, surgeries, medications, lifestyle exposures, occupational hazards, sexual function, previous fertility, and timing/frequency of intercourse (Figure-2-See Appendix). This structured approach helps ensure that clinically relevant risk factors are not overlooked, particularly by providers without specialized training.

Physical Examination

The guideline recommends a focused physical examination assessing testicular size and consistency, presence of varicocele, abnormalities of the epididymis or vas deferens, signs of hypogonadism or endocrine disorders, and evidence of genital infection. By incorporating physical examination into the diagnostic algorithm, WHO stresses that male evaluation cannot be laboratory-only and must include clinically relevant observations that remain the domain of trained clinicians, particularly urologists. This examination often yields findings that meaningfully alter diagnostic direction. For example, a palpable varicocele, absent vas deferens, and signs of hypogonadism each require different diagnostic and therapeutic strategies that cannot be inferred from semen analysis alone (6, 11, 12, 19, 20, 27, 34, 52-59).

Semen Analysis

Semen analysis remains the cornerstone laboratory test of male evaluation in the guideline. Two explicit recommendations govern its use: If semen parameters fall within WHO reference ranges, no repeat test is required. If one or more parameters fall outside the reference ranges, the test should be repeated after a minimum of 11 weeks (Table-4). The guideline stresses that semen analysis must be performed according to the latest WHO laboratory manual, which provides standardized procedures and updated reference limits (47, 48).

The WHO approach aligns with the 2024 EAU guideline, which likewise recommends repeat testing only when the first analysis is abnormal (21). This contrasts with the AUA/ASRM guideline, which recommends at least two semen analyses by default to account for biological variability (18). The difference reflects scope: WHO aims for a globally feasible minimum standard, while specialty societies aim for improving diagnostic precision in high-resource environments.

Nevertheless, it is crucial to underscore the limitations of a basic semen analysis, focusing on volume, count, motility, and morphology (17, 60, 61). It should not be interpreted as a measure of sperm function. Although conventional parameters capture broad features of spermatogenesis, they do not reliably reflect DNA fragmentation, chromatin packaging, epigenetic marks, mitochondrial performance, and sperm-borne RNA payloads. These molecular and functional attributes can be assessed by using specialized tests, and results may influence fertilization, embryo development, blastocyst progression, and miscarriage risk (6, 35, 50, 51, 62, 63). Therefore, clinicians must interpret semen parameters within clinical contexts, recognizing that patient history, physical findings, and reproductive outcomes may diverge from what basic parameters alone imply.

Treatment

The WHO treatment recommendations are deliberately conservative, reflecting limited evidence and the need to set minimum standards that are feasible, equitable, and implementable across health systems with vastly different resources. Only two areas yield specific male-directed recommendations: antioxidants and varicocele (Table-5). Other domains—such as hormonal therapy for idiopathic infertility, advanced sperm function testing, genetic evaluation, ejaculatory dysfunction, obstructive azoospermia, or surgical sperm retrieval—

Table 4 - Male-Relevant Recommendations from the 2025 WHO Infertility Guideline Relative to Diagnosis.

Category	Recommendation	Remarks
Semen analysis	For males (in couples with infertility) with one or more semen parameters outside the WHO reference ranges, WHO suggests repeating the semen analysis after a minimum of 11 weeks (Conditional recommendation, very low certainty of evidence). For males (in couples with infertility) with all semen parameters within the WHO reference ranges, WHO suggests not repeating the semen analysis (Conditional recommendation, very low certainty of evidence).	The latest edition of the WHO laboratory manual for the examination and processing of human semen provides WHO reference ranges for semen parameters and details about the standardized procedures for semen collection and analysis (https://iris.who.int/handle/10665/343208).
Diagnosis of unexplained infertility	WHO suggests making a diagnosis of unexplained infertility in a couple when all the following have occurred: (i) Failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse; (ii) Normal physical examination and medical history in both the male and female; (iii) Presumptive confirmation of ovulation and patent tubes in the female partner: and (iv) Semen parameters that are within the WHO reference ranges in the male partner (Conditional recommendation, very low certainty of evidence).	NA

Certainty of evidence and strength of recommendation: see Table 3 legend.
NA = not applicable; WHO = World Health Organization

are outside the scope of this WHO guideline and are covered in detail in specialty clinical practice guidelines (6, 18-21, 26, 56). This delineation is intentional, reflecting the WHO's mandate to focus on public-health–oriented, globally applicable guidance.

Antioxidant Supplementation

Oxidative stress is recognized as an important biological mechanism that can impair sperm function (64). Reactive oxygen species (ROS) influence sperm membrane integrity, motility, DNA fragmentation, chromatin compaction, and mitochondrial activity (65). Evidence from mechanistic studies strongly supports the hypothesis that excessive ROS disrupts sperm function and may impair fertilization and early embryo development (64, 65). These biological insights have motivated widespread clinical interest in oral antioxidant supplementation among infertile men.

The GDG examined evidence from a systematic review (66) and targeted search for randomized controlled trials up to April 2024 evaluating antioxidant supplementation in men with infertility and at least one semen parameter below WHO reference limits. The evidence base showed considerable heterogeneity in type of antioxidant (e.g., vitamin C, vitamin E, L-carnitine, coenzyme Q10, selenium, zinc, N-acetylcysteine, and multi-ingredient formulations), dosing and duration, study populations, and outcome measures, with most trials focusing on surrogate outcomes (semen parameters) rather than clinically meaningful endpoints (pregnancy, live birth).

The guideline therefore issues no recommendation for or against routine antioxidant supplementation in infertile men with semen abnormalities (Table-6). This is not equivalent to stating that "antioxidants do not work," nor is it a statement of insufficient evidence. Instead, it reflects an inability to formulate a global recommendation due to the heterogeneity of the evidence and the uncertainty around clinically meaningful outcomes.

Table 5 - Male-Relevant Recommendations from the 2025 WHO Infertility Guideline Relative to Treatment.

Category	Recommendation	Remarks
Use of antioxidants	For males with infertility and one or more semen parameters outside the WHO reference ranges who are attempting to achieve pregnancy with or without medically assisted reproduction, the WHO infertility Guideline Development Group (GDG) did not make a recommendation for or against the use of antioxidant supplements.	Optimal nutrition is important during the pre-pregnancy period for the couple; however, the effects of antioxidant supplements for males with specific male-factor pathologies in couples with infertility are currently not known.
Varicocele treatment – treatment vs expectant management	For males with infertility and clinical varicocele, WHO suggests surgical or radiological treatment over expectant management (Conditional recommendation, low certainty of evidence)*.	Males with clinical varicocele and semen parameters that are outside the WHO reference ranges are more likely to benefit from receiving treatment for varicocele, compared to men with semen parameters within the WHO reference ranges.
Varicocele treatment – type of treatment	For males with infertility undergoing treatment of varicocele, WHO suggests using either surgical or radiological treatment (Conditional recommendation, very low certainty of evidence)*.	When selecting whether to use surgical or radiological treatment, consider feasibility, the availability of trained health care providers and patient preferences regarding the type of treatment procedure.
Varicocele surgery – choice of surgical method	For males with infertility undergoing surgical treatment of varicocele, WHO suggests using microscopic surgery rather than other surgical procedures (Conditional recommendation, very low certainty of evidence)*.	Subinguinal microsurgery is a common surgical varicocelectomy procedure, while other surgical procedures include non-microscopic open approaches (such as inguinal and retroperitoneal) and laparoscopic methods. In settings where the expertise to perform microscopic surgery is not available, other surgical techniques may be used.
Varicocele surgery – open approaches	For males with infertility undergoing non-microscopic surgical treatment of varicocele, WHO suggests using either inguinal or retroperitoneal surgical procedures (Conditional recommendation, very low certainty of evidence)*.	When selecting whether to use an inguinal or retroperitoneal surgical procedure, consider feasibility and the availability of trained health care providers.

Certainty of evidence and strength of recommendation: see Table 3 legend.

* This recommendation applies to males with varicocele in couples with fertility who are not undergoing treatment with assisted reproductive technology (ART).

Table 6 - Male-Specific WHO Recommendations Mapped to Evidence-to-Decision (EtD) Considerations.

Male WHO Recommendation	EtD Consideration	Summary of How EtD Informed the Recommendation
Repeat semen analysis only when one or more parameters are below WHO reference ranges; do not repeat when all parameters are within reference limits	Balance of benefits and harms	Repeat testing provides confirmation when abnormal, but adds no clinical value when initial parameters are within reference limits. Avoids harm from unnecessary delay, anxiety, and cost.
	Certainty of evidence	Certainty moderate, grounded in long-standing WHO manual methodology and international laboratory experience.
	Values and preferences	Little variability—patients and clinicians generally prefer to avoid unnecessary tests.
	Acceptability	High global acceptability; aligns with the WHO manual and with EAU guidelines.
	Costs/resources	Reduces costs by minimizing unwarranted repeat testing.
	Feasibility	Highly feasible even in resource-limited settings.
	Equity	Increases equity by standardizing a low-cost approach worldwide.
	Strength (GRADE)	Conditional ("WHO suggests…") —because thresholds and feasibility vary across settings.
No recommendation for or against use of antioxidant supplements for infertile men with semen parameters below WHO reference ranges	Balance of benefits and harms	Benefits uncertain; heterogeneity in products and outcomes; potential harms (reductive stress) not well defined.
	Certainty of evidence	Low due to heterogeneity in formulations, dosing, populations, and reliance on surrogate outcomes (semen parameters rather than pregnancy/live birth).
	Values and preferences	High variability; some patients expect benefit, others are skeptical; clinicians differ widely in prescribing behavior.
	Acceptability	Varies significantly across regions; unregulated supplement markets contribute to inconsistency.
	Costs/resources	Supplements often costly and out-of-pocket; cost-effectiveness unknown.
	Feasibility	Feasible but unregulated; inconsistent product quality complicates implementation.
	Equity	Potential to worsen inequity if men spend significant resources on interventions without proven benefit.
	Strength (GRADE)	No recommendation —due to insufficient evidence for benefit or harm.

Repair of clinical varicocele in infertile men with abnormal semen parameters	Balance of benefits and harms	Benefits—improvement in semen parameters and pregnancy rates—outweigh harms when varicocele is clinical/palpable.
	Certainty of evidence	Moderate certainty (supported by trials and observational studies).
	Values and preferences	Majority of patients favor intervention in hopes of natural conception; variability low.
	Acceptability	Acceptable worldwide; microsurgical approach preferred, but alternative techniques acceptable where microsurgery not available.
	Costs/resources	Cost-effective relative to immediate use of MAR; resource needs vary by region.
	Feasibility	Globally feasible with flexibility in surgical approach; microsurgery availability influences choice.
	Equity	Improves equity by supporting a treatment that may reduce reliance on MAR.
	Strength (GRADE)	Conditional ("WHO suggests...") —because of variable surgical capacity and differences in feasibility across regions.

MAR = medically assisted reproduction; GRADE = Grading of Recommendations Assessment, Development and Evaluation

Nevertheless, the guideline emphasizes that optimal nutrition remains important during the pre-pregnancy period, even though the specific effects of antioxidant supplements on fertility outcomes remain uncertain. For clinicians, this means antioxidant therapy can be discussed on a case-by-case basis with appropriate counseling on benefits and uncertainties.

Varicocele Repair

Varicocele remains one of the most common correctable causes of male infertility worldwide (6, 34, 39, 45, 67-83). It was the only male condition for which the WHO issued a positive treatment recommendation (Table-5), reflecting both the quality of the available evidence and the guideline's public health scope.

Under a PICO framework, clinical varicocele was found to be the primary male infertility condition for which consistent, moderate-certainty evidence demonstrates improvements in semen parameters and a probable benefit in pregnancy rates when repair is performed in appropriately selected men. Repair is suggested for men with a clinical (palpable) varicocele, infertility, and abnormal semen parameters, thus aligned with the recommendations provided by most male infertility guidelines (6, 18, 19, 21, 26). The overall certainty of evidence was rated as moderate, sufficient to support a conditional recommendation but not a strong one (Table-6).

The guideline states that microsurgical repair is preferred when available, due to lower recurrence and complication rates. However, in settings without microsurgical expertise, inguinal, retroperitoneal, or radiological approaches remain acceptable alternatives. Therefore, lack of access to microsurgery should not prevent offering varicocele repair where clinically indicated.

In contrast, evidence for subclinical varicocele remains inconclusive, with trials showing inconsistent benefit and no reproducible improvement in natural or assisted reproduction outcomes (84). The GDG therefore determined that recommending repair of subclinical varicoceles would not meet the thresholds for certainty, feasibility, or cost-effectiveness required for global adoption. Similarly, the guideline refrained from

making recommendations on other male infertility interventions—such as hormonal therapy for idiopathic infertility or pre-sperm retrieval for males with non-obstructive azoospermia—because evidence quality was judged insufficient, heterogeneous, or primarily based on surrogate outcomes, which limited their suitability for global guidance.

By highlighting clinical varicocele, the WHO provides a clear, implementable, and evidence-aligned recommendation that can be applied across resource settings. This targeted approach reduces unnecessary testing and intervention, promotes appropriate use of surgical and radiological resources, and reinforces the importance of accurate physical examination as the cornerstone for identifying clinically meaningful varicoceles. For urologists, the WHO's focus on varicocele means that repair remains a key intervention for selected men with infertility and that decision-making should be individualized and aligned with patient values. Furthermore, proper diagnosis requires a clinical (not imaging-based) confirmation of varicocele, and counselling should address realistic expectations regarding semen improvement and timelines for attempting natural conception.

DISSEMINATION AND IMPLEMENTATION

Effective dissemination and implementation are essential for translating the WHO infertility guideline into meaningful improvements in care. Because infertility services are often fragmented and male evaluation is inconsistently performed, the WHO frames implementation as a health-system strengthening exercise rather than a simple distribution of recommendations.

The guideline is designed for global applicability, and WHO supports its uptake by providing implementation tools, educational materials, and integration

Table 7 - Key Components of WHO Guideline Implementation for Male and Couple-Based Infertility Care.

Implementation Component	Summary of Application to Male Infertility Care
Dissemination Strategy	WHO distributes the guideline through regional offices, workshops, and digital platforms, accompanied by implementation tools and educational materials.
National Adaptation	Countries contextualize recommendations based on local diagnostic capacity, surgical expertise, laboratory infrastructure, and financing models. Male evaluation is explicitly included.
Primary-Level Integration	Frontline clinicians conduct structured history, focused exam, and semen analysis; address reversible causes; and know when to refer. Ensures men enter the infertility pathway early.
Referral Pathways	Clear pathways established for referring men with persistent semen abnormalities, clinical varicocele, endocrine concerns, or suspected genetic/obstructive causes.
Linkage to Existing WHO Frameworks	Male infertility services integrated with STI guidelines, tobacco-cessation programs, sexual-health services, and the WHO semen analysis manual.
Training and Capacity Building	Urologists and reproductive specialists support education of primary-care providers and help establish minimal andrology laboratory standards.
Equity and Access	Implementation aims to reduce disparities by ensuring consistent male evaluation and availability of basic diagnostic and therapeutic services.
Monitoring and Evaluation	Countries encouraged to track semen-analysis availability, adherence to diagnostic algorithms, access to varicocele repair, and infertility-treatment outcomes, including pregnancies.

pathways linking infertility care to existing reproductive health platforms (Table-7). Countries are encouraged to adapt—rather than merely adopt—the recommendations, ensuring that diagnostic capacity, referral systems, and treatment options reflect local realities. For male infertility, this includes establishing reliable access to semen analysis performed according to the WHO manual; promoting structured history-taking and physical examination in primary care; and creating clear referral pathways for persistent abnormalities, varicocele, or suspected endocrine or genetic causes.

Implementation also requires reinforcing the connection between infertility care and other WHO frameworks, including STI management, tobacco cessation, and sexual-health services. Embedding male infertility within these broader systems improves feasibility and equity by leveraging established infrastructures. At the clinical level, the guideline encourages early engagement of men through prevention counseling, structured diagnostic assessment, and timely referral to specialists. For urologists, this represents an opportunity to lead national and local implementation efforts by training frontline providers, helping develop context-appropriate algorithms, and supporting the establishment of basic andrology laboratory capacity.

Ultimately, effective implementation depends on coordinated action among policymakers, clinicians, educators, and health-system planners. By positioning infertility—male and female—as a core component of reproductive health, the guideline aims to reduce longstanding disparities in access, ensure more consistent evaluation of men, and lay the foundation for equitable expansion of infertility services worldwide.

Gaps, Research Priorities, and Future Directions

The WHO guideline highlights significant gaps in the evidence supporting male infertility care, many of which limit the strength of recommendations and underscore the need for more rigorous research. While the guideline establishes a global minimum standard, several domains remain insufficiently characterized—scientifically, clinically, and from a public-health perspective.

A major gap concerns the limited evidence supporting therapeutic interventions for male infertility beyond clinical varicocele repair. Despite widespread use of hormonal therapies, including gonadotropins, selective estrogen receptor modulators, aromatase inhibitors, and other empiric medications, high-quality trials powered for pregnancy or live birth remain scarce (55, 85-93). Similarly, the evidence base for antioxidant supplementation is highly heterogeneous, with inconsistent formulations and reliance on surrogate endpoints rather than meaningful reproductive outcomes.

Diagnostic limitations also persist. Conventional semen analysis provides essential baseline information but does not capture molecular or functional sperm attributes such as DNA fragmentation, chromatin architecture, epigenetic signatures, mitochondrial function, or sperm-borne small RNAs. Validation and standardization of these biomarkers are prerequisites for future incorporation into guidelines.

From a public-health perspective, men remain underrepresented in reproductive programs. Better evidence is needed on how to engage men in preconception care, deliver counseling effectively, and integrate male services into primary care, STI programs, and community health settings. Data on access, acceptability, equity, and the psychosocial dimensions of male infertility are also lacking, especially in low- and middle-income countries.

The WHO Evidence-to-Decision framework further highlights priorities related to feasibility, cost-effectiveness, equity, and patient values—domains in which male reproductive health research is particularly thin. Addressing these gaps will be essential for future updates to the guideline and for strengthening global standards of care.

Looking ahead, key research priorities (Table-8) include validating molecular diagnostics, clarifying the paternal contribution to embryo development, expanding access to basic male infertility services, and improving the integration of male care within health systems. These efforts will require coordinated contributions from reproductive biologists, urologists, andrologists, embryologists, public-health experts, and policymakers.

Table 8 - Priority Research Areas to Strengthen the Evidence Base for Male Infertility Care.

Domain	Key Research Priorities
Diagnostic Advances	▪ Validate molecular biomarkers (DNA fragmentation, chromatin structure, epigenetic signatures, sperm RNA cargo). ▪ Standardize assays and laboratory methods across settings. ▪ Evaluate clinical utility and cost-effectiveness of expanded sperm testing.
Therapeutic Interventions	▪ Conduct randomized trials powered for pregnancy and live-birth outcomes for hormonal therapy, empiric medications, and antioxidants. ▪ Assess which patient subgroups may benefit from targeted treatments. ▪ Compare treatment pathways across resource settings.
Oxidative Stress & Antioxidants	▪ Standardize antioxidant formulations and dosing. ▪ Link oxidative-stress biomarkers to reproductive outcomes. ▪ Clarify potential harms (e.g., reductive stress).
Varicocele Management	▪ Evaluate long-term outcomes of different surgical and radiological techniques. ▪ Assess effectiveness in subgroups (e.g., borderline semen parameters, elevated sperm DNA fragmentation, various clinical varicocele grades).
Male Preconception Health	▪ Identify effective strategies for engaging men in lifestyle modification, tobacco cessation, and STI prevention. ▪ Assess effectiveness of interventions according in terms of quality of life and pregnancy outcomes ▪ Evaluate implementation models for preconception counseling in diverse settings.
Public Health & Health Systems	▪ Characterize barriers to male infertility care globally. ▪ Assess equity, acceptability, and feasibility of male-focused services. ▪ Develop scalable models for integrating male infertility into primary care and STI programs.
Psychosocial Dimensions	▪ Study the mental-health, relational, and social impacts of male infertility. ▪ Develop and validate support interventions tailored to men and couples.
Embryo Development & Paternal Biology	▪ Investigate associations between paternal health, sperm molecular signatures, early embryogenesis, and pregnancy outcomes. ▪ Clarify paternal contributions to miscarriage, implantation failure, and offspring health.

CONCLUSIONS

The 2025 WHO Guideline for the Prevention, Diagnosis, and Treatment of Infertility marks the first global framework to address both male and female infertility within a unified public-health strategy. By defining minimum standards for prevention, diagnosis, and treatment applicable across all resource settings, the guideline establishes a framework that underscores the importance of male reproductive health. For clinicians working in male infertility, the guideline provides a clear foundation: prevention through modifiable risk reduction, standardized semen analysis following WHO laboratory manual methods, structured history and physical examination, and timely referral to urologists when abnormalities persist. At the same time, the guideline acknowledges its scope limits. It is not a specialty practice document—and is not intended to replace the more detailed andrology-focused guidelines that address condition-specific evaluation and management. It also highlights major evidence gaps, particularly in molecular diagnostics, targeted treatments, oxidative stress, and the broader psychosocial and health-system dimensions of male

infertility. Importantly, the guideline reframes male infertility as both a reproductive and a public-health concern. The emphasis on early counseling, lifestyle modification, STI prevention, and couple-based care aligns with growing biological evidence linking paternal health to fertilization, embryo development, and pregnancy outcomes. This perspective encourages a shift from reactive to preventive male reproductive health. Lastly, by integrating feasibility, equity, and scientific rigor, the guideline provides a foundation for clinicians, researchers, and policymakers to build on. Its implementation has the potential to advance reproductive equity, improve diagnostic consistency, and ensure that men worldwide receive timely, structured, and evidence-aligned care. Strengthening the male infertility evidence base will be essential for future updates and for advancing reproductive equity worldwide.

ACKNOWLEDGMENTS

The author thanks the members of the WHO Guideline Development Group on Infertility and the WHO leadership involved in developing the Guideline for the Prevention, Diagnosis, and Treatment of Infertility (2025). The author also acknowledges Dr. Gitau Mburu and Dr. James Kiarie of the Contraception and Fertility Care Unit, Department of Sexual and Reproductive Health and Research (SRH/HRP), WHO, for their coordination of the guideline process, as well as the WHO technical team and external reviewers whose input informed the final document.

CONFLICT OF INTEREST

The author served on the WHO Infertility Guideline Development Group. He reports no financial compensation or conflicts of interest related to this work.

REFERENCES

1. World Health Organization. Infertility prevalence estimates: 1990–2021. Geneva: World Health Organization; 2023. [Internet]. Available at: https://iris.who.int/server/api/core/bitstreams/a22ced65-46b1-4482-bf85-058719fec649/
2. Rimmer MP, Howie RA, Anderson RA, Barratt CLR, Barnhart KT, Beebeejaun Y, et al. A core outcome set for future male infertility research: development of an international consensus. Fertil Steril. 2025;123(6):1017-1028. doi: 10.1016/j.fertnstert.2025.03.009
3. De Jonge CJ, Barratt CLR, Aitken RJ, Anderson RA, Baker P, Chan DYL, et al. Current global status of male reproductive health. Hum Reprod Open. 2024;2024(2):hoae017. doi: 10.1093/hropen/hoae017
4. Esteves SC, Humaidan P. Towards infertility care on equal terms: a prime time for male infertility. Reprod Biomed Online. 2023;47(1):11-14. doi: 10.1016/j.rbmo.2023.04.003
5. World Health Organization. Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World Health Organization; 2025. [Internet]. Available at: https://iris.who.int/server/api/core/bitstreams/ad3b700d-2c90-44fc-bd6f-fd93227b6a5a/content
6. Esteves SC, Zini A, Coward RM, Evenson DP, Gosálvez J, Lewis SEM, et al. Sperm DNA fragmentation testing: Summary evidence and clinical practice recommendations. Andrologia. 2021;53(2):e13874. doi: 10.1111/and.13874
7. Haddock L, Gordon S, Lewis SEM, Larsen P, Shehata A, Shehata H. Sperm DNA fragmentation is a novel biomarker for early pregnancy loss. Reprod Biomed Online. 2021;42(1):175-184.
8. Minhas S, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, et al. European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2021 Update on Male Infertility. Eur Urol. 2021;80(5):603-620. doi: 10.1016/j.eururo.2021.08.014
9. Aitken RJ, Koopman P, Lewis SE. Seeds of concern. Nature. 2004;432(7013):48-52. doi: 10.1038/432048a

10. Bertoncelli Tanaka M, Agarwal A, Esteves SC. Paternal age and assisted reproductive technology: problem solver or trouble maker? Panminerva Med. 2019;61(2):138-151. doi: 10.23736/S0031-0808.18.03512-7
11. Eisenberg ML, Esteves SC, Lamb DJ, Hotaling JM, Giwercman A, Hwang K, et al. Male infertility. Nat Rev Dis Primers. 2023;9(1):49. doi: 10.1038/s41572-023-00459-8
12. Esteves SC. Who cares about oligozoospermia when we have ICSI? Reprod Biomed Online. 2022;44(5):769-775. doi: 10.1016/j.rbmo.2022.04.012
13. Esteves SC, Roque M, Bedoschi G, Haahr T, Humaidan P. Intracytoplasmic sperm injection for male infertility and consequences for offspring. Nat Rev Urol. 2018;15(9):535-562. doi: 10.1038/s41585-018-0052-9
14. Bento FC, Figueira RCS, Esteves SC. Integrating Quality Management and Male Reproductive Health in Assisted Reproduction. Int Braz J Urol. 2025 Jul-Aug;51(4):e20250180. doi: 10.1590/S1677-5538.IBJU.2025.0180.
15. Augustyniak M, Coticchio G, Esteves SC, Kupka MS, Hong C, Fincham A, et al. A multi-faceted exploration of unmet needs in the continuing improvement and development of fertility care amidst a pandemic. Int Braz J Urol. 2024;50(5):631-650.
16. Esteves SC. Time has come to provide infertile men with an optimal fertility pathway. Int Braz J Urol. 2021 May-Jun;47(3):627-630. doi: 10.1590/S1677-5538.IBJU.2019.0362.1.
17. Esteves SC. Evolution of the World Health Organization semen analysis manual: where are we? Nat Rev Urol. 2022;19(7):439-446. doi: 10.1038/s41585-022-00624-8
18. Brannigan RE, Hermanson L, Kaczmarek J, Kim SK, Kirkby E, Tanrikut C. Updates to Male Infertility: AUA/ASRM Guideline (2024). J Urol. 2024:101097ju0000000000004180. doi: 10.1097/JU.0000000000004180
19. Esteves SC, Viana MC, Reis AB, Lira FT Neto, Teixeira TA, Camarço JP, et al. Male Infertility: Treatment Approach - A Committee Opinion. Int Braz J Urol. 2025 Nov-Dec;51(6):e20250224. doi: 10.1590/S1677-5538.IBJU.2025.0224.
20. Esteves SC, Viana MC, Reis AB, Lira FT Neto, Teixeira TA, Camarço JP, et al. Male Infertility: Diagnostic Approach - A Committee Opinion. Int Braz J Urol. 2025 Sep-Oct;51(5):e20250223. doi: 10.1590/S1677-5538.IBJU.2025.0223.
21. Minhas S, Boeri L, Capogrosso P, Cocci A, Corona G, Dinkelman-Smit M, et al. European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2025 Update on Male Infertility. Eur Urol. 2025;87(5):601-616. doi: 10.1016/j.eururo.2025.02.026
22. Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I. Fertil Steril. 2021;115(1):54-61. doi: 10.1016/j.fertnstert.2020.11.015
23. Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part II. Fertil Steril. 2021;115(1):62-69. doi: 10.1016/j.fertnstert.2020.11.016
24. National Library of Medicine (NLM). Using PICO to Frame Clinical Questions [Internet]. Bethesda (MD): NLM; [cited 2025 Jan 7]. Available from: https://www.nlm.nih.gov/oet/ed/pubmed/pubmed_in_ebp/02-100.html
25. Colunga-Lozano LE, Wang Y, Agoritsas T, Hultcrantz M, Iorio A, Montori VM, et al. Core GRADE unpacked: A summary of recent innovations in complementary GRADE Methodology. J Clin Epidemiol. 2025:112047.
26. Katz DJ, O'Donnell L, McLachlan RI, Moss TJ, Boothroyd CV, Jayadev V, et al. The first Australian evidence-based guidelines on male infertility. Med J Aust. 2025;223(11):653-663. doi: 10.5694/mja2.70080
27. Achermann APP, Esteves SC. Diagnosis and management of infertility due to ejaculatory duct obstruction: summary evidence. Int Braz J Urol. 2021;47(4):868-881. doi: 10.1590/S1677-5538.IBJU.2020.0536
28. Aitken RJ. Role of sperm DNA damage in creating de-novo mutations in human offspring: the "post-meiotic oocyte collusion" hypothesis. Reprod Biomed Online. 2022;45(1):109-124. doi: 10.1016/j.rbmo.2022.03.012
29. Aitken RJ, De Iuliis GN. On the possible origins of DNA damage in human spermatozoa. Mol Hum Reprod. 2010;16(1):3-13. doi: 10.1093/molehr/gap059
30. Barratt CL, Aitken RJ, Björndahl L, Carrell DT, de Boer P, Kvist U, et al. Sperm DNA: organization, protection and vulnerability: from basic science to clinical applications—A position report. Hum Reprod. 2010;25(4):824-838. doi: 10.1093/humrep/dep465
31. Carrell DT. Epigenetics of the male gamete. Fertil Steril. 2012;97(2):267-274. doi: 10.1016/j.fertnstert.2011.11.039

32. Chen T, Belladelli F, Del Giudice F, Eisenberg ML. Male fertility as a marker for health. Reprod Biomed Online. 2022;44(1):131-144. doi: 10.1016/j.rbmo.2021.09.023
33. Esteves SC. Who cares about oligozoospermia when we have ICSI. Reprod Biomed Online. 2022;44(5):769-775. doi: 10.1016/j.rbmo.2021.12.011
34. Esteves SC. What is varicocele? Int Braz J Urol. 2023;49(4):525-526. doi: 10.1590/S1677-5538.IBJU.2023.9904
35. Esteves SC. From Double Helix to Double Trouble: Sperm DNA Fragmentation Unveiled - A Reproductive Urologist Perspective (AUA Bruce Stewart Memorial Lecture - ASRM 2024). Int Braz J Urol. 2025;51(1):e20249924. doi: 10.1590/S1677-5538.IBJU.2024.9924
36. Esteves SC, Zini A, Coward RM. Best urological practices on testing and management of infertile men with abnormal sperm DNA fragmentation levels: the SFRAG guidelines. Int Braz J Urol. 2021;47(6):1250-1258. doi: 10.1590/S1677-5538.IBJU.2021.0377
37. Evenson DP, Djira G, Kasperson K, Christianson J. Relationships between the age of 25,445 men attending infertility clinics and sperm chromatin structure assay (SCSA®) defined sperm DNA and chromatin integrity. Fertil Steril. 2020;114(2):311-320. doi: 10.1016/j.fertnstert.2020.04.043
38. Gonzalez DC, Ory J, Blachman-Braun R, Nackeeran S, Best JC, Ramasamy R. Advanced paternal age and sperm DNA fragmentation: a systematic review. World J Mens Health. 2022;40(1):104-115. doi: 10.3346/wjmh.210085
39. Lira FTN, Campos LR, Roque M, Esteves SC. From pathophysiology to practice: addressing oxidative stress and sperm DNA fragmentation in varicocele-affected subfertile men. Int Braz J Urol. 2024;50(5):530-560. doi: 10.1590/S1677-5538.IBJU.2024.9917
40. Mikkelsen AT, Madsen SA, Humaidan P. Psychological aspects of male fertility treatment. J Adv Nurs. 2013;69(9):1977-1986. doi: 10.1111/jan.12084
41. Pozzi E, Boeri L, Candela L, Capogrosso P, Cazzaniga W, Fallara G, et al. Infertile couples still undergo assisted reproductive treatments without initial andrological evaluation in the real-life setting: a failure to adhere to guidelines? Andrology. 2021;9(6):1843-1852. doi: 10.1111/andr.13071
42. Teixeira TA, Oliveira YC, Bernardes FS, Kallas EG, Duarte-Neto AN, Esteves SC, et al. Viral infections and implications for male reproductive health. Asian J Androl. 2021;23(4):335-347. doi: 10.4103/aja.aja_82_20
43. Pereira TA, Thaker N, Rubez AC, Lima VFN, Bernie HL, Esteves SC, et al. Managing obesity-related male infertility: insights from weight loss intervention. Hum Reprod. 2025;40(11):2027-2037. doi: 10.1093/humrep/deaf180
44. Drevet JR, Hallak J, Nasr-Esfahani MH, Aitken RJ. Reactive oxygen species and their consequences on the structure and function of mammalian spermatozoa. Antioxid Redox Signal. 2022;37(7-9):481-500. doi: 10.1089/ars.2021.0235
45. Esteves SC, Santi D, Simoni M. An update on clinical and surgical interventions to reduce sperm DNA fragmentation in infertile men. Andrology. 2020;8(1):53-81. doi: 10.1111/andr.12724
46. Stenqvist A, Bungum M, Pinborg AB, Bogstad J, Englund AL, Grøndahl ML, et al. High sperm deoxyribonucleic acid fragmentation index is associated with an increased risk of preeclampsia following assisted reproduction treatment. Fertil Steril. 2025;123(1):97-104. doi: 10.1016/j.fertnstert.2024.08.316
47. Esteves SC. Evolution of the World Health Organization semen analysis manual: where are we? Nat Rev Urol. 2022;19(7):439-446. doi: 10.1038/s41585-022-00592-y
48. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 6th ed. Geneva: World Health Organization; 2021. [Internet]. Available at. https://www.who.int/publications/i/item/9789240030787
49. Esteves SC, Miyaoka R. Chapter 34 - Sperm physiology and assessment of spermatogenesis kinetics in vivo. In: Watson RR, editor. Handbook of fertility. San Diego: Academic Press; 2015. p. 383-396.
50. Esteves SC. Intracytoplasmic sperm injection versus conventional IVF. Lancet. 2021;397(10284):1521-1523. doi: 10.1016/S0140-6736(21)00843-6
51. Esteves SC, Humaidan P. Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for male infertility. Lancet. 2024;403(10430):880-881. doi: 10.1016/S0140-6736(24)00390-5
52. Esteves SC, Humaidan P. Approaching treatment of male infertility: the APHRODITE criteria. Int Braz J Urol. 2024;50(3):359-365. doi: 10.1590/S1677-5538.IBJU.2024.03.02

53. Esteves SC, Miyaoka R, Agarwal A. Sperm retrieval techniques for assisted reproduction. Int Braz J Urol. 2011;37(5):570-583. doi: 10.1590/S1677-55382011000500003
54. Esteves SC, Miyaoka R, Agarwal A. An update on the clinical assessment of the infertile male. Clinics (Sao Paulo). 2011;66(4):691-700. doi: 10.1590/S1807-59322011000400026
55. Esteves SC, Viana MC, Achermann APP, Santi D. Human chorionic gonadotropin-based clinical treatments for infertile men with non-obstructive azoospermia. Andrology. 2025. doi: 10.1111/andr.13578
56. Esteves SC, Humaidan P, Ubaldi FM, Alviggi C, Antonio L, Barratt CLR, et al. APHRODITE criteria: addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function. Reprod Biomed Online. 2024;48(4):103647. doi: 10.1016/j.rbmo.2024.103647
57. Esteves SC. From classification to clinical impact: the APHRODITE criteria and hormonal therapy for idiopathic male infertility. Andrology. 2025. doi: 10.1111/andr.13592
58. Andrade DL, Viana MC, Esteves SC. Differential diagnosis of azoospermia in men with infertility. J Clin Med. 2021;10(14):3157. doi: 10.3390/jcm10143157
59. Azevedo RA, Gualano B, Teixeira TA, Nascimento BCG, Hallak J. Abusive use of anabolic androgenic steroids, male sexual dysfunction and infertility: an updated review. Front Toxicol. 2024;6:1379272. doi: 10.3389/ftox.2024.1379272
60. Esteves SC. Clinical relevance of routine semen analysis and controversies surrounding the 2010 World Health Organization criteria for semen examination. Int Braz J Urol. 2014;40(4):443-453. doi: 10.1590/S1677-5538.IBJU.2014.04.02
61. Björndahl L, Esteves SC, Ferlin A, Jørgensen N, O'Flaherty C. Improving standard practices in studies using results from basic human semen examination. Andrology. 2023;11(7):1225-1231. doi: 10.1111/andr.13408
62. Gunes S, Esteves SC. Role of genetics and epigenetics in male infertility. Andrologia. 2021;53(1):e13586. doi: 10.1111/and.13586
63. Hamada A, Esteves SC, Nizza M, Agarwal A. Unexplained male infertility: diagnosis and management. Int Braz J Urol. 2012;38(5):576-594. doi: 10.1590/S1677-55382012000500002
64. Aitken RJ, Bromfield EG, Gibb Z. Oxidative stress and reproductive function: the impact of oxidative stress on reproduction: a focus on gametogenesis and fertilization. Reproduction. 2022;164(6):F79-F94. doi: 10.1530/REP-22-0202
65. Agarwal A. Oxidative stress in human reproduction: shedding light on a complicated phenomenon. Cham: Springer; 2017. doi: 10.1007/978-3-319-48490-0
66. de Ligny W, Smits RM, Mackenzie-Proctor R, Jordan V, Fleischer K, de Bruin JP, et al. Antioxidants for male subfertility. Cochrane Database Syst Rev. 2022;5(5):CD007411. doi: 10.1002/14651858.CD007411.pub5
67. Agarwal A, Hamada A, Esteves SC. Insight into oxidative stress in varicocele-associated male infertility: part 1. Nat Rev Urol. 2012;9(12):678-690. doi: 10.1038/nrurol.2012.197
68. Agarwal A, Sharma R, Harlev A, Esteves SC. Effect of varicocele on semen characteristics according to the new 2010 World Health Organization criteria: a systematic review and meta-analysis. Asian J Androl. 2016;18(2):163-170. doi: 10.4103/1008-682X.172638
69. Cho CL, Esteves SC, Agarwal A. Indications and outcomes of varicocele repair. Panminerva Med. 2019;61(2):152-163. doi: 10.23736/S0031-0808.18.03548-0
70. Esteves SC, Gosálvez J, López-Fernández C, Núñez-Calonge R, Caballero P, Agarwal A, et al. Diagnostic accuracy of sperm DNA degradation index (DDSi) as a potential noninvasive biomarker to identify men with varicocele-associated infertility. Int Urol Nephrol. 2015;47(9):1471-1477. doi: 10.1007/s11255-015-1073-7
71. Esteves SC, Miyaoka R, Agarwal A. Surgical treatment of male infertility in the era of intracytoplasmic sperm injection - new insights. Clinics (Sao Paulo). 2011;66(8):1463-1478. doi: 10.1590/S1807-59322011000800027
72. Esteves SC, Miyaoka R, Roque M, Agarwal A. Outcome of varicocele repair in men with nonobstructive azoospermia: systematic review and meta-analysis. Asian J Androl. 2016;18(2):246-253. doi: 10.4103/1008-682X.169570
73. Esteves SC, Oliveira FV, Bertolla RP. Clinical outcome of intracytoplasmic sperm injection in infertile men with treated and untreated clinical varicocele. J Urol. 2010;184(4):1442-1446. doi: 10.1016/j.juro.2010.06.024
74. Esteves SC, Roque M, Agarwal A. Outcome of assisted reproductive technology in men with treated and untreated varicocele: systematic review and meta-analysis. Asian J Androl. 2016;18(2):254-258. doi: 10.4103/1008-682X.169571

75. Hamada A, Esteves SC, Agarwal A. Insight into oxidative stress in varicocele-associated male infertility: part 2. Nat Rev Urol. 2013;10(1):26-37. doi: 10.1038/nrurol.2012.199
76. Lewis SEM, Esteves SC. What does a varicocele do to a man's fertility? There is much more than meets the eye. Int Braz J Urol. 2021;47(2):284-286. doi: 10.1590/S1677-5538.IBJU.2021.02.02
77. Lira Neto FT, Roque M, Esteves SC. Effect of varicocelectomy on sperm deoxyribonucleic acid fragmentation rates in infertile men with clinical varicocele: a systematic review and meta-analysis. Fertil Steril. 2021;116(3):696-712. doi: 10.1016/j.fertnstert.2021.04.030
78. Lira Neto FT, Roque M, Esteves SC. Effect of varicocele and varicocelectomy on sperm deoxyribonucleic acid fragmentation rates in infertile men with clinical varicocele. Minerva Obstet Gynecol. 2024;76(1):49-69. doi: 10.23736/S2724-606X.23.05058-5
79. Miyaoka R, Esteves SC. A critical appraisal on the role of varicocele in male infertility. Adv Urol. 2012;2012:597495. doi: 10.1155/2012/597495
80. Roque M, Esteves SC. Effect of varicocele repair on sperm DNA fragmentation: a review. Int Urol Nephrol. 2018;50(4):583-603. doi: 10.1007/s11255-017-1765-4
81. Samanta L, Agarwal A, Swain N, Sharma R, Gopalan B, Esteves SC, et al. Proteomic signatures of sperm mitochondria in varicocele: clinical use as biomarkers of varicocele-associated infertility. J Urol. 2018;200(2):414-422. doi: 10.1016/j.juro.2018.02.3181
82. Santana VP, James ER, Miranda-Furtado CL, Souza MF, Pompeu CP, Esteves SC, et al. Differential DNA methylation pattern and sperm quality in men with varicocele. Fertil Steril. 2020;114(4):770-778. doi: 10.1016/j.fertnstert.2020.06.013
83. Tiseo BC, Esteves SC, Cocuzza MS. Summary evidence on the effects of varicocele treatment to improve natural fertility in subfertile men. Asian J Androl. 2016;18(2):239-245. doi: 10.4103/1008-682X.169569
84. Kohn TP, Ohlander SJ, Jacob JS, Griffin TM, Lipshultz LI, Pastuszak AW. The effect of subclinical varicocele on pregnancy rates and semen parameters: a systematic review and meta-analysis. Curr Urol Rep. 2018;19(7):53. doi: 10.1007/s11934-018-0806-9
85. Al Wattar BH, Rimmer MP, Teh JJ, Mackenzie SC, Ammar OF, Croucher C, et al. Pharmacological non-hormonal treatment options for male infertility: a systematic review and network meta-analysis. BMC Urol. 2024;24(1):158. doi: 10.1186/s12894-024-01490-4
86. Tharakan T, Corona G, Foran D, Salonia A, Sofikitis N, Giwercman A, et al. Does hormonal therapy improve sperm retrieval rates in men with non-obstructive azoospermia: a systematic review and meta-analysis. Hum Reprod Update. 2022;28(5):609-628. doi: 10.1093/humupd/dmac015
87. Guo B, Li JJ, Ma YL, Zhao YT, Liu JG. Efficacy and safety of letrozole or anastrozole in the treatment of male infertility with low testosterone-estradiol ratio: a meta-analysis and systematic review. Andrology. 022;10(5):894-909. doi: 10.1111/andr.13189
88. Yang C, Li P, Li Z. Clinical application of aromatase inhibitors to treat male infertility. Hum Reprod Update. 2021;28(1):30-50. doi: 10.1093/humupd/dmab031
89. Khashaba S, Khashaba S, Krishan A, Bruce A, Almaghlouth A, Huang J, et al. Efficacy of clomiphene citrate and tamoxifen on pregnancy rates in idiopathic male subfertility: a systematic review and meta-analysis. Asian J Urol. 2025;12(1):15-22. doi: 10.1016/j.ajur.2024.09.002
90. Esteves SC, Achermann APP, Simoni M, Santi D, Casarini L. Male infertility and gonadotropin treatment: what can we learn from real-world data? Best Pract Res Clin Obstet Gynaecol. 2023;86:102310. doi: 10.1016/j.bpobgyn.2022.102310
91. Esteves SC, Achermann APP, Riccetto CLZ. To the editor: understanding presperm retrieval hormonal treatment effectiveness in nonobstructive azoospermia through real-world evidence. Fertil Steril. 2025;123(1):190-192. doi: 10.1016/j.fertnstert.2024.10.012
92. Esteves SC, Achermann APP, Miyaoka R, Verza S Jr, Fregonesi A, Riccetto CLZ. Clinical factors impacting microdissection testicular sperm extraction success in hypogonadal men with nonobstructive azoospermia. Fertil Steril. 2024;122(4):636-647. doi: 10.1016/j.fertnstert.2024.06.018
93. Laursen RJ, Alsbjerg B, Elbaek HO, Povlsen BB, Jensen KBS, Lykkegaard J, et al. Recombinant gonadotropin therapy to improve spermatogenesis in nonobstructive azoospermic patients – a proof-of-concept study. Int Braz J Urol. 2022;48(3):471-481. doi: 10.1590/S1677-5538.IBJU.2021.0304

Correspondence address:
Sandro C. Esteves, MD, PhD
ANDROFERT, Clínica de Andrologia e Reprodução Humana
Av. Dr. Heitor Penteado, 1464
13075-460, Campinas, SP, Brasil
E-mail: s.esteves@androfert.com.br

APPENDIX

Figure 2 - WHO template for the standardized male reproductive history and physical examination.

Components of male medical history and physical examination[1]

Personal information

Full name			
Date of birth		**Age**	
Address			
Contact information (phone, email)			
Occupation			
Marital or relationship status			

Relevant dates for evaluation

	Date		Month		Year	
Date of history taking						
Date of birth of male partner						

	Date		Month		Year	
Date of birth of female partner						

Infertility history

Infertility	☐ Primary ☐ Secondary
Duration of infertility/attempting to achieve pregnancy	_____ years
If secondary, months since last impregnation	_____ months
Previous investigation (s) and/or treatments for infertility	☐ No ☐ Yes *If yes, please specify:* _____
Contraceptive methods used	*Please specify:* _____ *Duration of contraception use:* _____
Previous pregnancy	☐ Current partner ☐ Another partner
Previous miscarriage	☐ Current partner ☐ Another partner
Treatments/evaluations of the *female* partner	*Please specify:* _____

1. Sexual history

Sexual activity and practices

Frequency of sexual activity	☐ Regular ☐ Irregular ☐ Rarely
Timing of intercourse	☐ Spontaneous ☐ Around ovulation
Erectile dysfunction	☐ Yes ☐ No ☐ Normal ☐ Inadequate
Ejaculatory dysfunction	☐ Yes ☐ No
Pain during intercourse	☐ Yes ☐ No
Presence of sexual anxiety	☐ Yes ☐ No
Stress	☐ Yes ☐ No
Psychological barriers to sexual function	☐ Yes ☐ No
Use of sexual performance enhancers or lubricants	☐ Yes ☐ No
Prolonged abstinence	☐ Yes ☐ No *If yes, please specify duration:* _____ days _____ months
Perceived quality of sexual activity	☐ Normal ☐ Inadequate
Previous or current sexual dysfunction	☐ Yes ☐ No

2. Childhood and development history

Pubertal development	Age at onset of puberty: _____

Sexual development	☐ Normal	☐ Delayed
History of undescended testicle	☐ Yes ☐ Left	☐ No ☐ Right
Treatment of undescended testicle	☐ Yes ☐ Medical	☐ No ☐ Surgical
Epispadia	☐ Yes	☐ No
Hypospadia	☐ Yes	☐ No
Pathology possibly causing testicular damage	☐ Yes **Injury** **Torsion** **Orchitis:** mumps **Orchitis:** other	☐ No ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right

3. Medical history

a. History of disease	☐ None
	☐ Diabetes ☐ Hypertension ☐ Thyroid disorders ☐ Autoimmune diseases ☐ Neurologic disease ☐ Fibrocystic of the pancreas ☐ Chronic respiratory tract disease ☐ Tuberculosis (or exposure) ☐ Other, *please specify:* _____
b. History of infection	☐ None
High fever in past 6 months	☐ Yes ☐ No
Urinary infection	☐ Yes ☐ No
Epididymitis	☐ Yes ☐ No *If yes, specify:* _____ ☐ Left ☐ Right
Orchitis	☐ Yes ☐ No *If yes, specify:* _____ ☐ Left ☐ Right
Sexually transmitted disease (STI)	☐ Yes ☐ No ☐ Syphilis ☐ Gonorrhoea ☐ Chlamydia ☐ Other, *specify:* _____
Treatment for STIs	☐ Yes ☐ No *If yes, specify treatment:* _____
Symptoms of current infection	☐ Yes ☐ No ☐ Discharge ☐ Testicular pain ☐ Fever ☐ Other, *specify:* _____

c. History of surgery	☐ None	
Retroperitoneal and/or pelvic surgery	☐ Prostrate	☐ Bladder neck
Inguinal, scrotal or perineal surgery	☐ Herniorraphy ☐ Inguinal hernia repair ☐ Hydrocele ☐ Vasectomy ☐ Epididymal cyst removal	☐ Orchiectomy ☐ Varicocele repair ☐ Testicular surgery ☐ Vasectomy reversal
Sperm retrieval	☐ PESA ☐ MESA ☐ Electroejaculation	☐ TESE ☐ Penile vibratory stimulation
Bariatric, bladder, or prostate surgery	☐ Bariatric surgery	☐ Transurethral resection of the prostate (TURP)
Cranial surgery	☐ Pituitary surgery	
Spinal surgery	☐ Spinal cord surgery	
Urethral and genital reconstruction	☐ Hypospadias repair	☐ Urethral structures surgery
Hernia treatment	☐ Yes ☐ No	
Sympathetic nervous system surgery	☐ Sympathectomy ☐ Other, *please specify:* _____	
d. Occupational history		
Current occupation	*Specify:* _____	
Duration	_____ years _____ months	
Work environment	☐ Indoors ☐ Outdoors	
Exposure to	☐ Extreme temperatures ☐ Noise ☐ Poor ventilation	
Exposure to chemicals	☐ Solvents ☐ Heavy metals ☐ Toxic substances at work *If yes, specify the substances:* _____	
Exposure to radiation	☐ Yes ☐ No *If yes, specify the source/type:* _____ *If yes, specify if doses were above recommended occupational levels* ☐ Yes ☐ No	

e. History of gonadotoxic medication	☐ ß-blockers ☐ Finasteride ☐ Opioids ☐ Chemotherapy	☐ Calcium blockers ☐ Serotonin reuptake inhibitors ☐ Anabolic steroids
Prescription medications	☐ Immunosuppressants (e.g. glucocorticoids, calcineurin inhibitors) ☐ Anti-epileptic drugs (AEDs) ☐ Selective serotonin reuptake inhibitors (SSRIs) ☐ Thiazide ☐ Other, *specify:* _____	☐ Cimetidine ☐ Allopurinol ☐ Sulfasalazine ☐ Colchicine ☐ Nitrofurantoin
f. Lifestyle History		
Physical activity	☐ Regular ☐ Irregular ☐ Rarely	
Diet	☐ Balanced ☐ High-protein ☐ Vegetarian ☐ Vegan ☐ Keto ☐ Mediterranean ☐ Processed ☐ *Please specify:* _____	
Smoking or use of tobacco products including electronic cigarette?	☐ Yes ☐ No	
Number of cigarettes	Per day: _____	Number of years smoking: _____
Consumption of alcohol	☐ Yes ☐ No *If yes, how often:* ☐ Regular ☐ Irregular ☐ Rarely How much? ____(units/week)	
Use recreational drugs?	☐ Yes ☐ No *If yes, which ones (specify):* _____ Frequency: ☐ Regular ☐ Irregular ☐ Rarely	
Recent stressors or changes in life	☐ Yes ☐ No *If yes, specify:* _____	
g. Family history		
Infertility in the family	☐ Yes ☐ No	
Genetic or hereditary conditions	☐ Cystic fibrosis ☐ Kartagener syndrome ☐ Varicocele ☐ Other, *specify:* _____	
Endocrine diseases	☐ Yes ☐ No *If yes, specify:* _____	

4. General physical examination

Height (cm) ☐☐☐ BMI ☐☐☐☐

Weight (kg) ☐☐☐ Blood pressure (mmHg) ☐☐☐ ☐☐☐

General physical examination	☐ Normal	Abnormal	☐ Hypoandrogenism ☐ Hyperandrogenism
Signs of virilization	☐ Normal	Abnormal	☐ Testicular enlargement ☐ Other, *specify:* _____

5. Uro-genital examination

Penis	☐ Normal ☐ Plaques ☐ Other, *specify:* _____	☐ Scars ☐ Epispadias	☐ Hypospadias ☐ Curvature	
Testes			Side:	Left - Right
Palpable in the scrotum	☐ Both palpable	☐ Abnormal	L ☐	R ☐
Palpable in inguinal region	☐ Both palpable	☐ Abnormal	L ☐	R ☐
	☐ Both palpable	☐ Thickened	L ☐	R ☐
		☐ Cystic/Nodule	L ☐	R ☐
		☐ Tender	L ☐	R ☐
Volume (ml)	Left: _____	Right: _____		
Device used for measurement	☐ Prader orchidometer ☐ Pachymeter ☐ Other			
Epididymis	☐ Both normal	☐ Thickened	L ☐	R ☐
		☐ Cystic	L ☐	R ☐
		☐ Tender	L ☐	R ☐
Vas deferens	☐ Both normal	☐ Non palpable	L ☐	R ☐
		☐ Thickened	L ☐	R ☐
Spermatic cord/Scrotum	☐ Normal	☐ Hydrocele	L ☐	R ☐
		☐ Hernia	L ☐	R ☐
Varicocele	☐ Normal	☐ Grade III	L ☐	R ☐
		☐ Grade II	L ☐	R ☐
		☐ Grade I	L ☐	R ☐
		☐ Subclinical	L ☐	R ☐
Inguinal examination	☐ Normal	☐ Lymphadenopaty	L ☐	R ☐

Scrotal skin	☐ Normal	☐ Infectious scars	L ☐ R ☐
		☐ Surgical scars	L ☐ R ☐
Rectal examination			
Prostate	☐ Normal	☐ Soft swelling	☐ Tender
		☐ Hard swelling	☐ Other
		☐ Palpable	☐ Abnormal
Seminal vesicles	☐ Normal	☐ Soft swelling	☐ Tender
		☐ Hard swelling	☐ Other
		☐ Palpable	☐ Abnormal

6. Additional information

_____

_____

_____

The figure provides a structured format for clinical assessment of the male partner, encompassing (i) Medical, developmental, and surgical history (including puberty, cryptorchidism, infection, systemic diseases), (ii) Lifestyle and occupational exposures (tobacco, alcohol, toxins, medications), (iii) Family and reproductive history, (iv) Physical examination, including virilization status, testicular volume (e.g., Prader orchidometer), palpation of epididymides and vasa deferentia, and varicocele diagnosis and grading. This standardized template promotes uniform documentation, improves diagnostic reproducibility, and supports clinician training and data harmonization across diverse health-care systems. Reprinted from: Guideline for the prevention, diagnosis and treatment of infertility. Geneva: World Health Organization; 2025.

ORIGINAL ARTICLE

Vol. 52 (3): e20250413, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0413

Safe to Spare? Predictors of Oncological Safety for Nerve-Sparing Technique during Robot-Assisted Radical Prostatectomy in High-Risk Prostate Cancer. Insight from a High-Volume Center with Centralized mpMRI Review

Luca Lambertini [1], Fabrizio Di Maida [1], Giulia Carli [1], Antonio Andrea Grosso [1], Sofia Giudici [1], Anna Cadenar [1], Simone Sforza [1], Daniele Paganelli [1], Filippo Lipparini [1], Neliana Kucuku [1], Rossella Catanzaro [1], Francesca Conte [1], Francesco Lupo Conte [1], Matteo Salvi [1], Simone Agostini [2], Fausto De Nisco [2], Gabriella Nesi [3], Rino Oriti [1], Gianni Vittori [1], Andrea Minervini [1], Andrea Mari [1]

[1] Department of Experimental and Clinical Medicine, University of Florence - Unit of Urology and Andrology, Careggi Hospital, Florence, Italy; [2] Department of Radiology, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy; [3] Department of Health Sciences, Division of Pathological Anatomy, University of Florence, Florence, Italy

ABSTRACT

Objective: To evaluate patterns and imaging-based predictors of positive surgical margins (PSMs) in patients with high-risk prostate cancer (PCa) undergoing nerve-sparing (NS) robot-assisted radical prostatectomy (RARP).

Materials and Methods: We retrospectively analyzed 1,235 consecutive patients with high-risk PCa treated with RARP between 2022 and 2024 at a high-volume tertiary referral center. Among them, 533 patients underwent preoperative multiparametric MRI (mpMRI) reviewed by two expert uro-radiologists and MRI–ultrasound fusion biopsy. A per-side analysis was performed to identify predictors of ipsilateral PSMs in cases where neurovascular bundle (NVB) preservation was attempted. Biochemical recurrence (BCR) was assessed, and multivariable logistic regression was used to determine independent predictors of PSMs.

Results: Overall, 36.1% of patients underwent non–nerve-sparing surgery, 49.5% unilateral NS, and 14.4% bilateral NS. Nerve sparing was performed on 418 surgical sides, with ipsilateral PSMs detected in 90 (21.5%). Sides with and without PSMs showed comparable nerve-sparing techniques (intra- vs interfascial) and similar 3-year BCR-free survival rates (68% vs. 69%) at a median follow-up of 36 months, although earlier biochemical failure at lower PSA thresholds was more frequent in PSM-positive sides. On multivariable analysis, larger prostate volume, apical tumor location, peripheral zone involvement, greater lesion diameter, and extracapsular extension on mpMRI were independently associated with an increased risk of ipsilateral PSMs.

Conclusions: Nerve-sparing RARP may be feasible in carefully selected high-risk PCa patients. The integration of mpMRI-based predictors can enhance patient selection, optimizing the balance between oncologic safety and functional preservation. Prospective studies are warranted to validate these findings and minimize selection bias.

ARTICLE INFO

Andrea Mari
https://orcid.org/0000-0001-9070-5706

Keywords:
Methods; Robotic Surgical Procedures; Prostatic Neoplasms

Submitted for publication:
July 30, 2025

Accepted after revision:
December 30, 2025

Published as Ahead of Print:
February 20, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Marcio C. Moschovas

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

INTRODUCTION

During the constant evolution of urologic surgery, the primary objective of radical prostatectomy (RP) has always been to eradicate prostate cancer (PCa) while striving to maintain the functionality of the pelvic organs whenever feasible (1). In this scenario, a nerve-sparing (NS) technique plays a key role in erectile function and might positively affect postoperative urinary continence (2), also potentially leading to positive surgical margins (PSM) and, therefore, biochemical recurrence (BCR) (3). Currently, the European Association of Urology (EAU) guidelines do not define strong recommendations over neurovascular bundle (NVB) preservation, only suggesting avoiding NS surgery when there is a clinical risk of ipsilateral extra-capsular extension (ECE) based on clinical staging, biopsy Gleason score or multiparametric magnetic resonance imaging (mpMRI) (4). To date, few large retrospective studies failed to confirm significant correlations between NVB preservation and BCR, risk of metastasis or mortality (5), even in high-risk patients with a baseline PSA over 20 ng/mL (6). These findings are possibly driven by several specific advancements in the urological surgery panorama. Particularly, Robot-assisted RP (RARP) enables us to perform a meticulous nerve-sparing also minimizing positive surgical margins (PSM), with a short learning curve supporting its global adoption (7). Indeed, the surgeon experience remains critical to minimizing PSM, particularly during nerve-sparing procedures where oncologic control and functional preservation must be carefully balanced (8). Moreover, a careful assessment of the MRI images also allows surgeons to better forecast and avoid potential areas of ECE, thereby reducing the likelihood of PSM (9). Three-dimensional models offer enhanced tumor and gland visualization, yet their application remains largely confined to research and has not been widely adopted in routine clinical practice (10).

The feasibility of nerve-sparing approaches in borderline cases, such as those involving high-risk (HR) patients, remains underexplored with limited studies addressing this critical aspect of surgical decision-making. An incremental NS technique, tailored according to the risk group, has been proposed for RARP (11). However, the direct impact of this approach on PSM and BCR remains unclear.

The aim of this study was to identify predictors of ipsilateral positive surgical margins in patients undergoing NS-RARP for high-risk PCa in a novel per-side fashion, based on side-specific mpMRI features in selected patients treated with RARP for HR-PCa in a tertiary referral institution, where the diagnostic process, including mpMRI and fusion biopsy, was centralized.

MATERIALS AND METHODS

Study Design

After Institutional Review Board approval, we retrospectively analyzed a consecutive cohort of patients treated with robot-assisted radical prostatectomy (RARP) for high-risk prostate cancer (PCa) between January 2020 and April 2023 at our tertiary referral center. Among this overall surgical population, a predefined subset of patients underwent preoperative multiparametric magnetic resonance imaging (mpMRI) performed and centrally reviewed at our institution by two expert uro-radiologists, as well as MRI–ultrasound fusion biopsy. The present study and all subsequent per-side analyses were restricted to this mpMRI-reviewed subgroup, which constituted the analytical cohort for side-specific evaluation of nerve-sparing decisions and ipsilateral positive surgical margins.

Main inclusion criteria were as follows: 1) high-risk PCa according to the EAU risk groups for biochemical recurrence (4); 2) mpMRI performed and evaluated or re-evaluated by two expert uro-radiologists (S.A., F.D.N.) at our Center; 3) MRI-ultrasound fusion biopsy performed by expert urologists or uro-radiologists at our center or ; 4) having completed a minimum of 24 months follow-up.

Main exclusion criteria were as follows: 1) Previous therapy for PCa, including RT, focal therapy or androgen deprivation therapy (ADT); 2) Evidence of distant metastasis, including non-regional lymph nodes, at preoperative conventional staging, consisting in bone scintigraphy (BS) and computed tomography (CT), or PET-PSMA. These exams were performed in all included patients; 3) mpMRI or ultrasound fusion biopsy performed in another

center or performed at our center by other operators with limited expertise.

Included patients were stratified according to the preservation of bundle: radical (Group A), monolateral nerve-sparing (NS) (Group B), bilateral NS (Group C).

Surgical technique

All procedures were performed by four experienced surgeons (≥100 RARP), with a standard six ports transperitoneal configuration. The Da Vinci surgical system Si, X or Xi (Intuitive Surgical, Sunnyvale, CA, USA) were used throughout the cases. In case of anticoagulant/antiplatelet (AC/AP) therapy, its suspension, replacement or maintenance was agreed with the anesthesiologist and the patient. An anterograde approach was chosen in all cases. Concomitant standard pelvic lymph node dissection (PLND) was performed in all cases according to standard anatomical landmarks, including the removal of lymphatic tissue along the external iliac vessels, within the obturator fossa, and around the internal iliac vessels. NS was performed with an intrafascial dissection between the peri-prostatic veins and the pseudocapsule of the prostate, or interfascial dissection along the peri-venous plane; or extrafascial dissection.

According to demographic, clinical and pathological features, NS side and technique were performed according to surgeon preference, also discussed and agreed with the patient prior to the surgery. The decision to perform NS or radical dissection was based on surgeon discretion and intraoperative judgement, which inevitably introduces selection bias. This limitation was acknowledged and considered in statistical interpretation. Change of strategy of NS technique during treatment was also reported. Pelvic drainage was placed at the end of the procedure at surgeon's discretion. A 18Ch Foley catheter was inserted during the procedure in all cases. Catheter removal was scheduled according to the surgeon's judgment.

Covariates and outcomes

The following clinical, imaging, and pathological variables were prospectively collected: patient age, body mass index (BMI), Charlson Comorbidity Index (CCI), presence of hypertension or diabetes mellitus, smoking status (categorized as current, former, or never smoker), history of previous transurethral resection of the prostate (TURP), and previous major abdominal surgery. Preoperative evaluation included serum prostate-specific antigen (PSA) levels and findings on digital rectal examination (DRE) performed by the attending urologist. Multiparametric MRI (mpMRI) parameters included prostate volume, Prostate Imaging Reporting and Data System (PI-RADS) score of the dominant lesion, maximum diameter of the index lesion, anatomical location (apex, mid-gland, base), and zonal distribution (anterior, peripheral, transitional zones). Radiological features suggestive of ECE and SVI were systematically assessed, with ECE defined by the presence of neurovascular bundle asymmetry, capsular bulge or irregularity, measurable extracapsular disease, or obliteration of the recto-prostatic angle on high-resolution T2-weighted images, and SVI based on direct tumor extension into seminal vesicles, low signal intensity, or abnormal contrast enhancement. In the absence of these features, organ-confined disease was assumed. Biopsy variables included ISUP grade group assignment according to the modified Gleason scoring system endorsed by the 2005 and 2014 ISUP consensus conferences, and clinical staging (cT and cN) were determined based on DRE and imaging findings. PSA persistence was defined as a prostate-specific antigen level ≥0.1 ng/mL measured at the first postoperative assessment, 4–6 weeks after surgery. Biochemical failure (BCF) was defined as the first occurrence of PSA ≥0.1 ng/mL at any time during follow-up, thereby capturing early biochemical progression and necessarily including patients with PSA persistence. Biochemical recurrence (BCR) was defined as a PSA ≥0.2 ng/mL confirmed on two consecutive measurements, in accordance with European Association of Urology guidelines, and was used to estimate biochemical recurrence–free survival. BCF and BCR represent distinct, non–mutually exclusive oncologic endpoints evaluated at different PSA thresholds and with different confirmation requirements; therefore, their proportions are not expected to sum to 100%. UI was de-

fined as the use of >1 pad per day. ED was defined as an IIEF-5 score <12 (moderate or severe).

Follow-up

First postoperative assessment included catheter removal, Kegel exercises were routinely illustrated concomitantly. Therefore, a postoperative assessment was scheduled approximately 30 days after surgery, and included clinical, histopathological and laboratory evaluation. Patients interested in erectile function recovery who underwent NS-RARP were provided with PDE5i treatment, which was offered free of charge by the National Health System (12)The International Index of Erectile Function-5 (IIEF-5) was self-administered to assess sexual function. Therefore, patients were followed up at 3, 6 and 12 months postoperatively, and then twice a year. Total PSA, urinary incontinence (UI) and erectile disfunction (ED) were evaluated.

Statistical analysis

Continuous variables are presented as median (IQR: interquartile range) and differences between groups were tested by Student's independent t-test or Mann-Whitney U-test according to their normal or non-normal distribution, respectively (normality of variables' distribution was tested by Kolmogorov-Smirnov test). Proportional data were assessed using Pearson's Chi-square test. Per-patient and per-side analyses were performed to evaluate PSM rate. Oncologic outcomes were evaluated on a per-patient analysis. Univariate and multivariate logistic regression analyses (MVA) were performed to identify independent predictors for clinically meaningful outcomes. Candidate variables included PSA, DRE findings, clinical T stage, and all mpMRI-derived features. Collinearity diagnostics were assessed using Variance Inflation Factors (VIF > 5) and Spearman's correlation. PSA and DRE were found to be highly correlated with MRI-derived markers (ECE and lesion diameter) and clinical T stage (VIFs = 4.8–5.1), leading to their exclusion from the final model to prevent multicollinearity. A sensitivity multivariable model including PSA and DRE is presented in Supplementary Table-1. Statistical significance was set as $p < 0.05$. Of note, all subsequent per-side analyses were conducted exclusively within the subgroup of patients who underwent centralized mpMRI review and fusion biopsy at our institution, as detailed in the Methods section. Statistical analysis was performed using SPSS v. 27 (IBM SPSS Statistics for Mac, Armonk, NY, IBM Corp).

RESULTS

Overall, 533 patients were included in the study. Median patient age was 69 years (IQR: 64–73), and median Charlson Comorbidity Index (CCI) was 3 (IQR: 2–4). Median body mass index (BMI) was 25.7 kg/m^2 (IQR: 23.9–27.8). Most patients had hypertension (72%) or diabetes mellitus (63%), with fewer having undergone previous major abdominal surgery (18%) or previous endoscopic treatment for benign prostatic obstruction (6.6%). Median baseline PSA was 7.4 ng/mL (IQR: 5.4–11), and DRE was positive in 82% of cases. RARP for HR PCa was performed either radically in 192 (36.1%), or with monolateral or bilateral NS in 264 (49.5%) and 77 (14.4%) patients, respectively (Supplementay Table-2). By dividing patients for the type of NS approach, a higher median age recorded in the radical group (p=0.01) was found compared to the Monolateral and Bilateral NS groups. Moreover, the radical group showed a significative higher rate of positive DRE and of clinical ECE at mpMRI (p=0.01 and p=0.02, respectively) compared to the counterparts. Baseline comorbidity burden, assessed by the Charlson Comorbidity Index and the prevalence of hypertension and diabetes mellitus, was comparable across nerve-sparing groups and is detailed in Table-1. For interpretability, CCI was also categorized as 0–2, 3–4, and ≥5. Functional outcomes (continence and erectile recovery) were stratified according to NS status, showing superior recovery in NS patients, although baseline functional status may have influenced surgical choice. These differences underscore the presence of selection bias, as patients with more adverse clinical features were more often managed with a radical approach. At per-side analysis, nerve-sparing was applied to 418 sides during RARP, with PSM identified in 90 (21.5%) of these sides. Sides with PSM exhibited larger median lesion diameters on mpMRI compared to those

Table 1 - Baseline, clinical and pathological preoperative features of patients with High risk PCa treated with Robot Assisted Radical Prostatectomy (RARP).

Characteristics	Overall N = 533[1]	Bilateral Radical N = 1921	Monolateral NS N = 264[1]	Bilateral NS N = 77[1]	p-value[2]
Age years, median (IQR)	73 (66-77)	75 (69-79)	73 (64-76)	67 (62-71)	**0.04**
BMI (kg/m2), median (IQR)	25.7 (23.9-27.8)	26.3 (22.1-29.9)	23.8 (21.6-27.6)	28.1 (24.2-31.2)	0.3
CCI, median (IQR)					0.8
0-2	229 (43)	89 (46)	109 (42)	31(41)	
3-4	298 (56)	101 (52)	152 (57)	45 (58)	
≥5	6 (1)	2 (2)	3 (1)	1 (1)	
Hypertension, n (%)	384 (72%)	142 (74%)	187 (71%)	55 (71%)	0.6
Diabetes mellitus, n (%)	336 (63%)	120 (63%)	171 (64%)	45 (61%)	0.7
Previous endoscopic surgery for BPO, n (%)	35 (6.6%)	13 (6.7%)	18(6.8%)	4 (5.1)	0.2
Previous major abdominal surgery, n (%)	95 (18%)	35 (18%)	44 (16%)	16 (20%)	0.12
Preoperative PSA, median (IQR)	7.4 (5.4-11)	9.1 (6.7-13.2)	7.2 (6.1-10)	5.9 (4.6-9)	0.08
Positive DRE, n (%)	437 (82%)	184 (95%)	213 (81%)	40 (52%)	**0.01**
Prostate Volume (cc), median (IQR)	52 (38-67)	54 (34-63)	49 (33-72)	42 (28-58)	0.18
Main lesion dimension at MRI, median (IQR)	19 (12-18)	21 (16-29)	18 (10-22)	9 (7-14)	**0.01**
Extracapsular estension, n (%)	202 (38%)	95 (49%)	88 (33%)	19 (24%)	**0.01**
Seminal Vescicles Invasion, n (%)	64 (12%)	26 (13.5%)	32 (12%)	6 (7.7)	0.06

BMI = Body Mass Index; BPO = Benign Prostatic Obstruction; CCI = Charlson Comorbidity Index, PSA = Prostate Specific Antigen; DRE = Digito-Rectal Examination

[1] Values are reported as median (interquartile range) or number (percentage), as appropriate.

[2] P-values were calculated using Mann–Whitney U test, Student's t-test, or Chi-square test, as appropriate.

free of PSM (18 mm [IQR: 10–22] vs. 12 mm [IQR: 10–16], p=0.01) and a greater frequency of lesions >15 mm (44% vs. 27%, p=0.02). Additionally, PIRADS 5 lesions were more prevalent on sides with PSM compared to sides without (44% vs. 24%, p=0.02). Apical lesion location was markedly more frequent in sides with PSM (58% vs. 26%, p=0.01), while mid (19% vs. 31.7%) and basal locations (23% vs. 42.3%) were less common (p=0.01). The presence of extracapsular extension (ECE) (44% vs. 27%, p=0.001) and seminal vesicle invasion (SVI) (21% vs. 12%, p=0.01) at mpMRI were higher in sides harboring PSM. Histological assessment confirmed pathological ECE was more frequent among sides with PSM (75% vs. 53%, p=0.01). Other relevant MRI and biopsy characteristics are detailed in Table-2.

Regarding perioperative outcomes, median operative time was 165 minutes (IQR: 124–193), with slightly longer operative durations observed for sides with PSM compared to those without (183 vs. 161 minutes, p=0.08). An intraoperative switch of nerve-sparing technique was recorded in 9.1% of cases, occurring more frequently in sides subsequently harboring positive surgical margins (21.0% vs. 6.1%, p=0.015), with the most common modification being from an intrafascial to an interfascial dissection.

Pathological staging demonstrated that pT3a

Table 2 - Magnetic Resonance Imaging (MRI) and pathological preoperative features of patients with High risk PCa treated with Nerve Sparing Robot Assisted Radical Prostatectomy (RARP).

Characteristic	Overall N = 418[1]	NO PSM same side N = 328[1]	PSM same side N = 90[1]	p-value[2]
Prostate Volume (cc), median (IQR)	45 (33-59)	48 (34-63)	45 (33-72)	0.13
Prostate Volume >80cc, n(%)	54 (13%)	34 (10.4%)	20 (22.2%)	**0.01**
PIRADS 5 (same side of bundle preservation), n (%)				**0.02**
Yes	118 (28%)	78 (24%)	40 (44%)	
PIRADS >15mm (same side of bundle preservation), n (%)				**0.02**
Yes	127 (30%)	88 (27%)	39 (44%)	
Main lesion dimension at MRI, median (IQR)	14 (12-18)	12 (10-16)	18 (10-22)	**0.01**
PIRADS location, n (%)				**0.01**
Apex	137 (33%)	85 (26%)	52 (58%)	
Mid	121 (29%)	104 (31.7%)	17 (19%)	
Base	160 (38%)	139 (42.3%)	21 (23%)	
PIRADS zone lesion, n (%)				**0.001**
Anterior	21 (5%)	14 (4.3%)	7 (8%)	
Periferic	322 (77%)	267 (76%)	55 (61%)	
Transitional	75 (18%)	47 (19%)	28 (31%)	
Extracapsular estension, n (%)	129 (31%)	89 (27%)	40 (44%)	**0.001**
Seminal Vescicles Invasion, n(%)	18 (9%)	7 (21%)	11 (12%)	**0.01**
ISUP grade, at biopsy, n (%)				0.06
4	374 (89%)	296 (90%)	78 (86%)	
5	44 (11%)	32 (10%)	12 (14%)	
Clinical T stage, n(%)				0.2
cT1c	79 (19%)	62 (19%)	17 (18%)	
cT2a	80 (19%)	65 (20%)	15 (16%)	
cT2b	9 (2%)	7 (2%)	2 (2%)	
cT2c	183(44%)	134 (41%)	49 (51%)	
cT3a	58 (14%)	46 (14%)	12 (13%)	
cT3b	9 (2.1%)	8 (2.2%)	1 (2%)	
cN, n(%)				0.6
cN0	391 (93%)	307 (94%)	82 (91%)	
cN1	27 (7%)	21 (6%)	8 (9%)	

[1] Values are reported as median (interquartile range) or number (percentage), as appropriate.

[2] P-values were calculated using Mann–Whitney U test, Student's t-test, or Chi-square test, as appropriate.

Table 3 - Perioperative, pathological and follow-up features of patients with high risk PCa treated with RARP with neurovascular bundle preservation.

Characteristic	Overall N = 418[1]	NO PSM same side N = 328[1]	PSM same side N = 90[1]	p-value[2]
Operative Time (min), median (IQR)	165 (124-193)	161 (111-181)	183 (158-203)	0.08
Estimated blood loss (mL), median (IQR)	200 (100- 350)	200 (80-300)	220 (120-400)	0.2
Intraoperative Complications, n. (%)	6 (1.3%)	4 (1.2%)	2 (2.2)	0.12
Intraoperative switch of NS technique, n %				0.014
from intrafascial to interfascial NS	32 (7.7%)	15 (4.6%)	17 (18.8%)	
from intrafascial to extrafascial NS	5 (1.2%)	4 (1.2%)	1 (1.1%)	
from interfascial to extrafascial NS	1 (0.2%)	1 (0.3%)	0 (0%)	
Nerve sparing technique performed, n. (%)				0.08
Intrafascial	84 (20.1%)	46 (14%)	17 (18.8%)	
Interfascial	328 (78.5%)	266 (81.1%)	62 (68.9%)	
Extrafascial	6 (1.4%)	5 (1.5%)	1 (1.1%)	
Time to drainage removal (days), median (IQR)	1(1-2)	1(1-2)	1(1-2)	0.9
Length of stay (days), median IQ**R**	3 (2-4)	3 (2-4)	3 (2-4)	0.9
Pathological T stage, n (%)				0.01
pT2	64 (15%)	54 (17%)	10 (11%)	
pT3a	235 (57%)	174 (53%)	61 (75%)	
pT3b	111 (27%)	92 (29%)	19 (21%)	
Pathological N stage, n. (%)				0.2
pN0	384 (92%)	302 (92%)	77 (86%)	
pN1	34 (8%)	26 (8%)	13 (14%)	
PSA persistence, n. (%)	17 (4.1%)	12 (3.7%)	5 (5.5%)	0.11
Biochemical failure, n. (%)	211 (50.4%)	165 (50.3%)	46 (51.1%)	0.09
3 Years Biochemical Recurrence Free Survival, n (%)	284 (68%)	222 (68%)	62 (69%)	0.8
Time to BCF (months)	6 (1-12)	6 (3-12)	4 (1-9)	0.07
Follow up (months), median (IQR)	36 (24-40)	36 (24-40)	32 (20-40)	0.08

Min = minutes; IQR = Inter Quartile Range; BCF = Biochemical failure

[1] Values are reported as median (interquartile range) or number (percentage), as appropriate.

[2] P-values were calculated using Mann–Whitney U test, Student's t-test, or Chi-square test, as appropriate.

tumors occurred more frequently in sides with PSM compared to those without (75% vs. 53%, p=0.01), while the rates of pT2 and pT3b stages were lower or comparable (Table-3). Among nerve-sparing techniques, interfascial dissection was the most adopted approach (85%), whereas intrafascial dissection was used in 15% of cases, with no significant difference according to PSM occurrence (p=0.08). Biochemical failure (PSA ≥0.1 ng/mL during follow-up) occurred in 211/418 sides (50.4%), with a slightly shorter median time to biochemical failure in sides with PSM (4 months [IQR: 1–9]) compared with those without PSM (6 months [IQR: 3–12], p=0.07), consistent with Table-3. In terms of 3-year biochemical-recurrence-free survival, no significant differences were observed between sides without and with PSM (68% vs 69%, p=0.8). At multivariable analysis, larger prostate volume (OR: 1.02; 95% CI: 1.01–1.03; p=0.01) and PIRADS lesion diameter (OR: 1.01; 95% CI: 1.006–1.32; p=0.02), apical lesion location (OR: 2.03; 95% CI: 1.23–3.37; p=0.01), peripheral vs transitional zone lesion (OR: 3.22; 95% CI: 1.18–4.76; p=0.001) and ECE (OR: 4.19; 95% CI: 2.89–6.86; p=0.001) detected at MRI were independently associated with the presence of PSM. In a sensitivity model including PSA and DRE, neither variable was independently associated with ipsilateral PSM (PSA p = 0.27; DRE p = 0.18), and model discrimination (AUC = 0.80) was comparable to the primary mpMRI-based model (AUC = 0.79), confirming the robustness of our findings. Other factors, including ISUP grade 5 on target biopsy and intraoperative switch of nerve-sparing technique, were not significantly associated with positive surgical margins (Table-4).

Table 4 - Multivariable analysis assessing the clinical predictors of positive surgical margin on the same side of neurovascular bundle preservation after Robot-Assisted Radical Prostatectomy for High-Risk Prostate Cancer.

Covariates	OR	95%CI	p value
Prostate Volume (100cc)	1.02	1.01-1.03	0.01
PIRADS location			
Base	Ref		
Mid	1.34	0.72 – 2.45	0.2
Apex	2.03	1.23 – 3.37	**0.01**
PIRADS zone lesion			
Anterior	Ref		
Peripheral	3.22	1.18 – 4.76	**0.001**
Transitional	1.8	0.85 – 2.73	0.4
PIRADS dimension (mm)	1.01	1.006 - 1.32	**0.02**
ISUP >4 on target samples			
No	Ref		
Yes	1.38	0.94-1.88	0.06
Extracapsular estension at MRI			
No	Ref		
Yes	4.19	2.89-6.86	**0.001**
Intraoperative switch of NS technique (yes/no)	1.26	0.94-1.67	0.11

OR = Odds Ratio; CI = Confidence Interval; MRI = Magnetic Resonance Imaging

DISCUSSION

Preoperative mpMRI has been shown to impact surgical planning by identifying laterality and extent of disease, allowing refinement of the NS approach (13). The NS surgery in HR-PCa remains a debated strategy due to the increased risk of ECE and PSM (14). However, advances in preoperative imaging and the precision of RARP have broadened the indications for NS in selected patients (15, 16). The EAU guidelines do not contraindicate NS in HR-PCa but recommend avoiding it when clinical or radiological predictors of ECE are present (4). The novelty of our work lies in the per-side analytical approach with centralized mpMRI review, allowing for refined correlation between imaging predictors and ipsilateral PSM.

High-quality evidence supporting the safety of NS in HR-PCa remains limited, particularly in standardized cohorts with centralized imaging and pathology review (17, 18). As a result, most available data on NS originates from low- or intermediate-risk populations, where the oncologic risk is lower and functional preservation is more routinely prioritized (19). In contrast, the application of NS in HR-PCa is yet to be determined, despite growing interest in surgical de-escalation strategies. Evidence specific to HR-PCa, and particularly to side-specific nerve preservation, is scarce. However, HR-PCa is a heterogeneous entity, and in selected patients with unilaterally localized lesions, wide bilateral excision may be unnecessarily aggressive (20, 21). When imaging confirms unilateral disease without features suggesting ECE, unilateral or incremental NS may be a feasible compromise. An mpMRI-based nomogram has been developed to guide NS grade selection based on the probability of ECE, offering a side-specific, risk-adapted approach to optimize the balance between functional recovery and oncologic control (22).

In this study, we evaluated the postoperative and oncological outcomes of NS-RARP in a highly selected cohort of patients with HR-PCa, treated in a tertiary referral center with centralized preoperative staging using mpMRI and fusion-targeted biopsy. All patients fulfilled high-risk criteria according to EAU classification, including ISUP grade group ≥4 (63.8%) or PSA >20 ng/mL (23.8%), while 48.5% had clinical stage ≥T3a. Nerve preservation was planned based on side-specific radiological and pathological findings, allowing risk-adapted surgical planning. Bilateral nerve-sparing was initially intended in 18.8% of cases, unilateral in 57.9%, and no nerve-sparing in 23.2%, with final decisions refined intraoperatively according to local findings.

From an oncologic standpoint, approximately half of the cohort experienced biochemical failure at the 0.1 ng/mL threshold during follow-up, and about one-third developed BCR within 3 years, highlighting that in carefully selected patients, nerve-sparing did not worsen short-term oncologic outcomes compared with non-nerve-sparing approaches, whereas long-term oncologic equivalence remains uncertain given the limited follow-up. This apparent discrepancy reflects the different biological and temporal meaning of the two endpoints, as BCF captures early PSA progression at a lower threshold, whereas BCR represents a more stringent and confirmed definition of biochemical relapse.

We also evaluated the role of different NS techniques—classified as intrafascial, interfascial, and extrafascial—performed on each side in relation to mpMRI features and pathological outcomes. The planned dissection plane was defined preoperatively but frequently modified intraoperatively based on direct assessment. These changes were systematically recorded, allowing us to analyze how surgical adaptability influenced ipsilateral PSM rates in relation to preoperative imaging and tumor localization. In our series, interfascial dissection was the most frequently performed nerve-sparing technique, representing 56.2% of all sides. Intrafascial dissection was used in 25.2% of cases, while a radical approach (i.e., complete excision of the bundle) was chosen in 18.6%, particularly when intraoperative findings raised concern for extracapsular extension. Notably, in 21.7% of cases, the initial nerve-sparing strategy was modified intraoperatively, most often by downgrading the dissection plane based on intraoperative judgment. No significant difference in PSM was observed between interfascial and intrafascial approaches, supporting the effectiveness of preoperative planning and intraoperative adaptability. This approach mirrors the logic of graded nerve-sparing, where the dissection plane is

tailored according to side-specific oncologic risk and is consistent with EAU recommendations to avoid nerve preservation only in the presence of clear predictors of extracapsular disease.

To better evaluate the relationship between nerve-sparing and surgical margins, we moved from a per-patient to a per-side analytical framework, allowing for a more granular assessment of how side-specific tumor features and surgical decisions influence ipsilateral PSM.

In this setting, our first key finding was that several mpMRI features were independently associated with the occurrence of PSM on the same side of NS, thus jeopardizing the oncological safety of surgery. Particularly, the presence of larger prostate volume (p=0.04), higher PIRADS lesion diameter (p=0.02), apical lesion location (p=0.01) as well as peripheral vs transitional zone lesion (p=0.001) predicted the occurrence of positive margins, also when the procedure was carried out by a highly experienced robotic surgeon. These findings potentially represent a strong argument in favor of the widening of surgical indications for the NS adoption, thus highlighting the importance of tailored surgical planning when balancing functional and oncologic outcomes(23-26). To date, no clinical features were included in the preoperative PSM prediction. In contrast, several series proposed a validated nomogram-based model incorporating mpMRI findings—including PI-RADS score, lesion location, and capsular contact—alongside clinical parameters. Particularly, Soeterik et al. (24) developed a preoperative risk model that combines mpMRI and clinical variables to predict side-specific ECE, with posterior and lateral lesion location identified as important contributors to risk stratification. Similarly, Nyarangi-Dix et al. proposed a nomogram that integrates imaging features such as PI-RADS score and lesion localization to improve prediction accuracy for ECE in high-risk patients (25, 27-30). Ostau et al. externally validated a bicenter risk model emphasizing the role of mpMRI markers—including lesion location and extent of capsular contact—for anticipating ECE, demonstrating improved performance over clinical-only tools (26). Although these models are primarily designed to predict ECE rather than PSMs directly, the anatomical predictors they incorporate—particularly posterior and apical involvement—are consistent with our findings. These regions are known to pose technical challenges during prostatectomy, and their accurate delineation on mpMRI is critical for margin control.

Our study further emphasizes the utility of centralized imaging review, which likely enhanced the consistency and reliability of lesion localization and feature interpretation. On the other hand, the centralization of the radiologic assessment enhanced the statistical predictive value of MRI predictors over the clinical one, particularly when only a high-risk patient's subset is analyzed. Indeed, while we did not use nomograms, our results underscore the pivotal role of high-quality, anatomically detailed mpMRI in predicting adverse pathological outcomes and guiding intraoperative strategy, particularly in clinical settings where predictive models are not routinely applied. An additional consideration concerns the generalizability of our findings. The predictive value of the identified variables relies heavily on high-quality mpMRI acquisition and expert interpretation, which were ensured in this study through centralized imaging review by dedicated uro-radiologists. Consequently, the applicability of our results may be limited in settings with heterogeneous imaging protocols or limited radiologic expertise. External validation in multicenter cohorts with varying levels of mpMRI standardization is therefore warranted before broader clinical implementation.

The present manuscript is not devoid from limitations. Firstly, the retrospective study design and the single center fashion might have induced several non-negligible biases in the analysis. Nevertheless, the centralization of the imaging assessment represented a key factor to properly evaluate the overall burden of preoperative imaging-based surgical planning on patient's outcomes. Secondly, the relatively small sample size might lower the replicability of the reported results. Moreover, the lack of randomization might have overestimated the NS feasibility in more complex cases. The absence of a statistically significant association between ISUP 5 and positive surgical margins in the multivariable model might reflect collin-

earity between histologic grade and MRI-detected extracapsular extension, both representing closely interrelated indicators of tumor aggressiveness. When both variables were included, ECE emerged as the stronger anatomical predictor, attenuating the apparent effect of ISUP grade. Similarly, although PSA and DRE are established clinical parameters in most preoperative risk models, in our cohort both were strongly correlated with MRI-derived markers of tumor extent, resulting in multicollinearity and their subsequent exclusion from the final model. Sensitivity analyses confirmed that their inclusion did not enhance model discrimination, reinforcing the predominance of imaging-derived predictors in this high-risk, imaging-centralized population. Nevertheless, it should be noted that the limited number of events per variable (90 sides with PSM) may have reduced the statistical power to detect weaker independent effects of clinical variables. With larger cohorts and a higher event count, modest associations for PSA, DRE, or ISUP grade could potentially emerge as significant. Key limitation is the potential for selection bias in NS choice. Importantly, our findings should be interpreted in the context of radiotherapy plus ADT being a well-established standard of care in HR-PCa, and surgery with NS may be considered only in individualized cases. Furthermore, the follow-up period of 36 months is too short to draw definitive oncologic conclusions in HR-PCa. The omission of key predictors such as PSA and DRE from final models further limits clinical generalizability.

CONCLUSIONS

The adoption of a nerve-sparing approach during RARP represents a feasible option only in carefully selected high-risk prostate cancer patients. Accordingly, the identification of imaging-based predictors such as prostate volume, apical location, peripheral zone involvement, lesion size, and ECE might enhance the patient selection process, thus optimizing the balance between functional and oncologic outcomes. These aspects warrant further evaluation in randomized settings and may help guide clinical decision-making.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wang J, Hu K, Wang Y, Wu Y, Bao E, Wang J, et al. Robot-assisted versus open radical prostatectomy: a systematic review and meta-analysis of prospective studies. J Robot Surg. 2023;17(6):2617–2631.
2. Michl U, Tennstedt P, Feldmeier L, Mandel P, Oh SJ, Ahyai S, et al. Nerve-sparing surgery technique, not the preservation of the neurovascular bundles, leads to improved long-term continence rates after radical prostatectomy. Eur Urol. 2016;69(4):584–589.
3. Wang X, Wu Y, Guo J, Chen H, Weng X, Liu X. Oncological safety of intrafascial nerve-sparing radical prostatectomy compared with conventional process: a pooled review and meta-regression analysis. BMC Urol. 2019;19(1):48.
4. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer 2024 update. Part I: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2024;86(2):148–163.
5. Preisser F, Gandaglia G, Arad F, Karakiewicz PI, Bandini M, Pompe RS, et al. Association of neurovascular bundle preservation with oncological outcomes in patients with high-risk prostate cancer. Prostate Cancer Prostatic Dis. 2021;24(1):193–201.
6. Spirito L, Chessa F, Hagman A, Lantz A, Celentano G, Sanchez-Salas R, et al. Long-term oncological outcomes after nerve-sparing robot-assisted radical prostatectomy for high-risk localized prostate cancer. Diagnostics (Basel). 2024;14(8):803.
7. Bonet X, Moschovas MC, Onol FF, Bhat KR, Rogers T, Ogaya-Pinies G, et al. The surgical learning curve for salvage robot-assisted radical prostatectomy: a prospective single-surgeon study. Minerva Urol Nephrol. 2021;73(5):600–609.
8. Da Cruz JAS, Porto BC, Terada BD, Gonçalves FGA, Orra SH, Martinez JVN, et al. Does the surgeon's learning curve impact pentafecta outcomes in radical prostatectomy? a systematic review and meta-analysis. BMC Urol. 2025 May 7;25(1):116. doi: 10.1186/s12894-025-01810-x.

9. Schiavina R, Bianchi L, Borghesi M, Dababneh H, Chessa F, Pultrone CV, et al. MRI displays the prostatic cancer anatomy and improves bundle management before robot-assisted radical prostatectomy. J Endourol. 2018;32(4):315–321. doi: 10.1089/end.2017.0701
10. Checcucci E, Pecoraro A, Amparore D, De Cillis S, Granato S, Volpi G, et al. The impact of 3D models on positive surgical margins after robot-assisted radical prostatectomy. World J Urol. 2022;40(9):2221–2229.
11. Martini A, Cumarasamy S, Haines KG, Tewari AK. An updated approach to incremental nerve sparing for robot-assisted radical prostatectomy. BJU Int. 2019;124(1):103–108.
12. Siena G, Mari A, Canale A, Mondaini N, Chindemi A, Greco I, et al. Sexual rehabilitation after nerve-sparing radical prostatectomy: free-of-charge phosphodiesterase type 5 inhibitor administration improves compliance. J Sex Med. 2018;15(2):120–123.
13. Panebianco V, Salciccia S, Cattarino S, Minisola F, Gentilucci A, Alfarone A, et al. Use of multiparametric MR with neurovascular bundle evaluation to optimize oncological and functional management in nerve-sparing radical prostatectomy. J Sex Med. 2012;9(8):2157–2166.
14. Bejrananda T, Takahara K, Sowanthip D, Motonaga T, Yagi K, Nakamura W, et al. Comparing pentafecta outcomes between nerve sparing and non nerve sparing robot-assisted radical prostatectomy in a propensity score-matched study. Sci Rep. 2023 Sep 22;13(1):15835. doi: 10.1038/s41598-023-43092-z.
15. Day E, Tzelves L, Dickinson L, Shaw G, Tandogdu Z. Impact of preoperative surgical planning in robotic-assisted radical prostatectomy on trifecta outcomes: systematic review and meta-analysis. Minerva Urol Nephrol. 2025;77(1):25–32.
16. Hu A, Lin Y, Zhu X, Li J, Luo F, Yu X. Does transurethral resection of the prostate before robot-assisted radical prostatectomy have adverse effects on patients diagnosed with prostate cancer: a comparative evidence-based analysis? J Robot Surg. 2025 Feb 20;19(1):74. doi: 10.1007/s11701-025-02234-3.
17. Morozov A, Barret E, Veneziano D, Grigoryan V, Salomon G, Fokin I, et al. Nerve-sparing surgery for high-risk prostate cancer: a systematic review. Minerva Urol Nephrol. 2021;73(3):283–291.
18. Ditonno F, Bologna E, Licari LC, Franco A, Cannoletta D, Checcucci E, et al. Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) during robot-assisted radical prostatectomy: a systematic review and meta-analysis of comparative studies. Prostate Cancer Prostatic Dis. 2025 Sep;28(3):623-631. doi: 10.1038/s41391-024-00891-3.
19. Liu Y, Deng XZ, Qin J, Wen Z, Jiang Y, Huang J, et al. Erectile function, urinary continence and oncologic outcomes of neurovascular bundle sparing robot-assisted radical prostatectomy for high-risk prostate cancer: A systematic review and meta-analysis. Front Oncol. 2023 Apr 5;13:1161544. doi: 10.3389/fonc.2023.1161544.
20. Kumar A, Samavedi S, Bates AS, Mouraviev V, Coelho RF, Rocco B, et al. Safety of selective nerve sparing in high-risk prostate cancer during robot-assisted radical prostatectomy. J Robot Surg. 2017;11(2):129–138.
21. Humke C, Hoeh B, Preisser F, Wenzel M, Welte MN, Theissen L, et al. Concordance between mpMRI and pathological stage and its influence on nerve-sparing surgery. Curr Oncol. 2022;29(4):2385–2394.
22. Martini A, Soeterik TFW, Haverdings H, Rahota RG, Checcucci E, De Cillis S, et al. Algorithm to personalize nerve sparing in unilateral high-risk prostate cancer. J Urol. 2022;207(2):350–357.
23. Mod M, Güngör HS, Karaca H, Tahra A, Sobay R, İnkaya A, et al. Factors determining early continence after robotic radical prostatectomy. J Clin Med. 2025;14(13):4405.
24. Soeterik TFW, van Melick HHE, Dijksman LM, Küsters-Vandevelde H, Stomps S, Schoots IG, et al. Nomogram to predict side-specific extraprostatic extension. Eur Urol Oncol. 2022;5(3):328–337.
25. Nyarangi-Dix J, Wiesenfarth M, Bonekamp D, Hitthaler B, Schütz V, Dieffenbacher S, et al. Combined clinical parameters and mpMRI for prediction of extraprostatic disease. Eur Urol Focus. 2020;6(6):1205–1212.
26. Ostau NEV, Handke AE, Wiesenfarth M, Albers P, Antoch G, Noldus J, et al. Bicenter validation of a risk model for the preoperative prediction of extraprostatic extension of localized prostate cancer combining clinical and multiparametric MRI parameters. World J Urol. 2024 Sep 20;42(1):530. doi: 10.1007/s00345-024-05232-6.

27. Martini A, Falagario UG, Villers A, Dell'Oglio P, Mazzone E, Autorino R, et al. Contemporary techniques of prostate dissection for robot-assisted prostatectomy. Eur Urol. 2020;78(4):583–591. doi: 10.1016/j.eururo.2020.07.017
28. Gamal A, Moschovas MC, Saikali S, et al. Comparing technological and intraoperative performances of da Vinci Xi and da Vinci 5 robotic platforms. Int Braz J Urol. 2025;51(1):e20240569. doi: 10.1590/S1677-5538.IBJU.2024.0569
29. Moschovas MC, Patel V. Nerve-sparing robotic-assisted radical prostatectomy: how I do it after 15,000 cases. Int Braz J Urol. 2022;48(2):369–370. doi: 10.1590/S1677-5538.IBJU.2022.99.03
30. Moschovas MC, Jaber A, Saikali S, et al. Long-term functional and oncologic outcomes after RARP following USPSTF PSA recommendations. Int Braz J Urol. 2024;50(1):65–79. doi: 10.1590/S1677-5538.IBJU.2023.0530

Correspondence address:
Andrea Mari, MD
Department of Experimental and
Clinical Medicine, University of Florence
Unit of Oncologic, Minimally Invasive
Robotic Urology and Andrology,
Azienda Ospedaliera Universitaria Careggi
Florence, 50134, Italy
Telephone + 39 055 275 8011
E-mail: andrea.mari@unifi.it

APPENDIX

Supplementary Table 1 - Sensitivity multivariable model accounting for both clinical and mp MRI features.

Variable	OR	95% CI	p value
PSA (ng/mL)	1.01	0.99–1.03	0.27
Positive DRE	1.34	0.86–1.94	0.18
Prostate volume	1.02	1.01–1.03	0.01
Apical lesion	2.11	1.24–3.43	0.01
Peripheral zone lesion	3.12	1.14–4.71	0.001
ECE at mpMRI	3.98	2.74–6.65	<0.001
Model AUC	0.80 (vs 0.79 in main model)		

Supplementary Table 2. Sensitivity multivariable model accounting for both2 - clinical and mp MRI features

Variable	OR	95% CI	p value
PSA (ng/mL)	1.01	0.99–1.03	0.27
Positive DRE	1.34	0.86–1.94	0.18
Prostate volume	1.02	1.01–1.03	0.01
Apical lesion	2.11	1.24–3.43	0.01
Peripheral zone lesion	3.12	1.14–4.71	0.001
ECE at mpMRI	3.98	2.74–6.65	<0.001
Model AUC	0.80 (vs 0.79 in main model)		

ORIGINAL ARTICLE

Vol. 52 (3): e20250500, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0500

Minimally Invasive Partial versus Radical Nephrectomy for Non-metastatic pT3a Renal Cell Carcinoma: a Multicenter Matched Cohort Study

Xiangpeng Zou [1, 2], Zhenhua Liu [1, 2], Yunhan Luo [1, 2], Peimin Zhou [3, 4, 5], Longbin Xiong [1, 2], Zhoujie Sun [3, 4, 5], Xuesong Li [3, 4, 5], Peng Hong [6], Kangbo Huang [1, 2], Chunsen Yang [7], Zhaohui Zhou [1, 2], Yulu Peng [1, 2], Xin Luo [1, 2], Junhang Luo [8], Xin Yao [7], Shengjie Guo [1, 2], Pei Dong [1, 2], Hui Han [1, 2], Fangjian Zhou [1, 2], Shudong Zhang [6], Wei Yu [3, 4, 5], Zhiling Zhang [1, 2]

[1] Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, P. R. China; [2] State Key Laboratory of Oncology in Southern China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China; State Key Laboratory of Oncology in Southern China, Guangzhou, P. R. China; [3] Department of Urology, Peking University First Hospital, Beijing, China; [4] Institute of Urology, Peking University, Beijing, China; [5] The National Urological Cancer Center of China, Beijing, China; [6] Department of Urology, Peking University Third Hospital, Peking, China; [7] Department of Urologic Oncology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China; [8]Department of Urology, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

ABSTRACT

Purpose: To evaluate oncological and functional outcomes of minimally invasive partial and radical nephrectomy (MIS-PN vs. MIS-RN) in patients with pT3aN0M0 renal cell carcinoma (RCC).

Materials and Methods: We performed a multicenter retrospective study of patients with pT3aN0M0 RCC treated with MIS-PN or MIS-RN. The primary outcome was recurrence-free survival (RFS). Secondary outcomes included de novo eGFR <60 mL/min/ 1.73 m^2 (CKD-S) and <45 mL/min/ 1.73 m^2 (CKD-S3b) at the new baseline (1-12 month postoperatively), as well as CKD-S at the latest follow-up (>1 year postoperatively). A 1:2 ratio propensity score matching (PSM) was applied to balance covariates, and inverse probability weighting (IPW) served as sensitivity analysis. Survival curves were estimated using the Kaplan-Meier method, and multivariable analyses (MVA) were performed to identify predictors of oncological and functional outcomes.

Results: A total of 303 patients were enrolled (113 MIS-PN/190 MIS-RN) with a median follow-up of 39.0 months (IQR 26.8-52.9). After PSM (66 MIS-PN/54 MIS-RN), no significant difference in RFS was observed between two groups (p=0.23). MVA revealed that surgical approach was not an independent predictor of RFS (HR: 1.00, p=1.00). Among patients with available new baseline eGFR after PSM (41 MIS-PN/37 MIS-RN), MIS-RN was independently associated with a higher risk of CKD-S (OR: 7.96, p=0.03). Among patients with available the latest follow-up eGFR after PSM (41 MIS-PN/37 MIS-RN), MIS-RN remained an independent

ARTICLE INFO

Zhang Zhiling
https://orcid.org/0000-0003-1821-4587

Keywords:
Carcinoma, Renal Cell; Nephrectomy; Minimally Invasive Surgical Procedures

Submitted for publication: September 09, 2025

Accepted after revision: December 16, 2025

Published as Ahead of Print: January 26, 2026

predictor of CKD-S at the latest follow-up (OR: 7.98, p=0.03). IPW analysis yielded consistent results. Additionally, IPW identified MIS-RN as an independent risk factor for CKD-S3b at the new baseline (OR: 18.29, p<0.01).

Conclusion: MIS-PN provided comparable mild term oncologic outcomes to MIS-RN while offering superior renal function preservation. MIS-PN may be a viable option for selected T3a RCC patients when nephron preservation is indicated.

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

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

INTRODUCTION

Partial nephrectomy (PN) is recommended as the preferred treatment for localized renal cell carcinoma (RCC), as it offers similar tumor control to radical nephrectomy (RN), while preserving more renal parenchyma and function(1, 2). This nephron-sparing effect has been associated with reduced cardiovascular morbidity and improved overall survival (OS) (3, 4). According to the 8th AJCC/TNM criteria (5), T3a RCC is defined as tumor extension into the renal vein or its segmental branches, invasion of the perirenal or renal sinus fat, or involvement of the pelvicalyceal system but not beyond Gerota's fascia, irrespective of tumor size. T3a RCC exhibited a higher recurrence risk compared to organ-confined T1-T2 lesions after surgery (6). Contemporary studies regarding the oncological outcomes of PN compared to RN for non-metastatic pT3a RCC remain inconsistent (7-11), and most of these studies are limited by a lack of adjustment for invasion patterns, as well as insufficiency of functional outcomes. While emerging evidence suggested that robot-assisted PN (RAPN) was feasible and safe for selected cT3a masses, considerable debate persisted regarding the expansion of PN indications to patients with cT3a RCC across all invasion patterns, particularly in the absence of a compelling indication for nephron preservation (12).

With the growing experience in the minimally invasive (MIS) surgery(13, 14), robust comparative data evidence specifically evaluating MIS-PN versus MIS-RN in pT3a RCC remains scarce. Thus, we conducted a multicenter, matched-cohort study to compare mild-term oncological and functional outcomes between MIS-PN and MIS-RN in patients with non-metastatic pT3a RCC.

MATERIALS AND METHODS

Patient population

With approval from the Institutional Review Board (approval number: B2025-341), a retrospective review was conducted on patients who underwent MIS (robot-assisted or laparoscopic) surgery for pT3a RCC between June 2016 and November 2023 at five tertiary centers in China. All patients received a comprehensive preoperative evaluation, including physical examination, laboratory testing, abdominal cross-sectional imaging (CT or MRI), and chest imaging (X-ray or CT). All procedures were performed by urological oncologists, and the choice of surgical approach (MIS-PN or MIS-RN) was determined based on patient characteristics and surgeon preference. Exclusion criteria included: reoperation for recurrent RCC; radiologic evidence of distant metastasis (cM1), lymph node metastasis (cN1), or pathologically confirmed metastasis (pN1/pM1); receipt of neoadjuvant therapy.

Patients underwent their first follow-up assessment at 3 months postoperatively, followed by surveillance every 6 to 12 months. Each follow-up included physical examination, laboratory testing, abdominal cross-sectional imaging (CT or MRI), and chest imaging (X-ray or CT). The detection of a new lesion on imaging was considered a recurrence, and the diagnosis was confirmed histologically. Lesions occurring adjacent to the resection site were classified as local recurrence, while metachronous lesions in the ipsilateral kidney (away from the resection bed) or in the contralateral kidney were not regarded as recurrences. Lesions identified in distant organs were classified as metastases.

Data collection

Recorded preoperative features included demographic variables (age, sex, body mass index [BMI]), comorbidities (hypertension [HTN], diabetes mellitus [DM] and chronic kidney disease [CKD]), radiologic tumor characteristics (clinical tumor size and the R.E.N.A.L. score (15)). Perioperative details recorded included operative time (OT), surgical approach, intraoperative transfusion, estimated blood loss (EBL), length of stay (LOS), postoperative complications and the status and regimen of adjuvant therapy. Histopathological features included pathological tumor size, histological subtype (clear cell RCC [ccRCC] or non-ccRCC), grade (according to WHO/ISUP (16), including G1–G4 and Gx), invasion pattern (as defined by 8th AJCC/TNM criteria (5), including perinephric fat invasion[PFI], sinus fat invasion[SFI], pelvicalyceal system invasion[PSI], and renal vein invasion[RVI]), surgical margin(SM) status, and the presence of sarcomatoid differentiation (SMD), necrosis, and lymphovascular invasion(LVI). Positive SM was defined as tumor extension to the inked surface of the resected specimen. Aggressive pathological features included positive SM, grade ≥ 3, necrosis, LVI and SMD.

Renal function was assessed using serum creatinine-based estimated glomerular filtration rate (eGFR), calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2021) equation (17). eGFR was recorded at three time points: pre-operation (pre-GFR, within 1 month before surgery), new baseline (NB-GFR, 1–12 months postoperatively (18)), and latest follow-up (latest-GFR, >12 months postoperatively). Survival status was recorded at last follow-up.

Statistical Analysis

Patients were stratified by the surgical approach (MIS-PN vs. MIS-RN). To minimize selection bias, two statistical adjustment methods were applied: 1) 1:2 nearest-neighbor propensity score matching (PSM) with a caliper of 0.1 (19), and 2) stabilized inverse probability of weighting (IPW) with weight truncation at the 1st and 99th percentiles (20), which was performed as a sensitivity analysis. Propensity scores were generated based on age, comorbidities (HTN/DM/CKD), clinical tumor size, R.E.N.A.L. score, and pre-GFR.

The primary outcome was recurrence-free survival (RFS). Secondary outcomes included CKD-S (pre-GFR>60 mL/min/ 1.73 m^2 but NB-GFR <60 mL/min/ 1.73 m^2), CKD-S3b (pre-GFR>60 mL/min/ 1.73 m^2 but NB-GFR <45 mL/min/ 1.73 m^2) and CKD-S at the latest follow-up (pre-GFR > 60mL/min/1.73m2 but latest-GFR < 60mL/min/1.73 m^2). Additional renal functional endpoints included ΔGFR (NB-GFR–pre-GFR), eGFR preservation rate% (NB-GFR/pre-GFR×100%). Multivariable analyses (MVA) were performed to identify predictors of oncological and functional outcomes:1) Cox regression model was used to assess association between surgical approach (MIS-RN vs MIS-PN) and RFS, with candidate variables selected a priori (21). All results were summarized as hazard ratios (HRs) with 95% confidence intervals (CIs), and 2) Logistic regression models were applied for CKD-S, CKD-S3b, and CKD-S at the latest follow-up, estimating odds ratios (OR) with 95% CIs for variables of interest, including age, sex, BMI, tumor complexity, comorbidities, surgical approach, pathological tumor size, and pre-GFR.

Descriptive statistics were performed for patient characteristics as frequencies for categorical variables, means with standard deviations (SDs) or medians with interquartile ranges (IQRs) for continuous variables. Group comparisons between MIS-PN and MIS-RN were made using chi-square or Fisher's exact tests for categorical variables, and Mann–Whitney U tests or independent t-tests for continuous variables. Kaplan–Meier survival analyses were performed, and comparisons were assessed using the log-rank test. All p values were two tailed, with p less than 0.05 considered statistically significant. All statistical analyses were performed using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad-Prism version-8.3.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

Patient characteristics

According to the inclusion and exclusion criteria, a total of 303 patients with pT3a RCC were enrolled,

comprising 113 (37.3%) patients who underwent MIS-PN and 190 (62.7%) who received MIS-RN. Clinicopathological characteristics are detailed in Table-S1. The median age of the overall cohort was 58.0 years, and 73.8% of the patients were male. Compared to the MIS-PN group, patients in the MIS-RN group were slightly older (58.5 vs. 56.0 years, p=0.02), and presented with larger (6.3 vs. 3.9 cm, p <0.01), higher R.E.N.A.L. score (10.0 vs. 7.0, p <0.01) tumors, as well as a significantly higher proportion of cT3a lesions (83.2% vs. 38.9%, p<0.01). Additionally, the MIS-RN group exhibited a higher incidence of LVI compared to the MIS-PN group (21.2% vs. 9.7%, p=0.01). After PSM (66 MIS-PN/54 MIS-RN), no significant differences were observed between two groups in terms of age, comorbidities, R.E.N.A.L. score, clinical tumor size and pre-GFR. Patients undergoing MIS-PN were more likely to present with PFI, whereas those in the MIS-RN group more commonly exhibited SFI, RVI and multifocal invasion. Table-1 demonstrates clinicopathological features after PSM.

Survival analysis

The median follow-up was 39.0 (IQR: 26.8-52.9) months, with 34.9 (IQR: 21.6-52.9) months in MIS-PN group and 40.3 (IQR: 31.1-52.3) months in MIS-RN group. During this mild term oncologic follow up period, recurrence was observed in 42 patients (13.9%), including 9 in the MIS-PN group and 33 in the MIS-RN group. Among these, 40 cases were classified as distant metastases (7 MIS-PN/33 MIS-RN), while 2 cases were identified as local recurrence, both in the MIS-PN group. After PSM and IPW, no significant difference in RFS was observed between MIS-PN and MIS-RN group (Figures 1A and B). However, the 3-year RFS rate was significantly lower in the MIS-RN group compared to the MIS-PN group before matching (83.7% vs. 92.7%, p = 0.047) (Figure-S1).

MVA Cox regression analyses are depicted in Table-2. MVA analyses revealed that surgical approach (MIS-RN vs. MIS-PN) was not significantly associated with RFS in PSM cohort (HR: 1.00, p = 1.00). Larger pathological tumor size (HR: 1.42, p= 0.02) and the presence of ≥2 aggressive pathological features (HR: 4.25, p= 0.01) were independently associated with worse RFS, and the IPW analysis yielded similar results. Considering the residual heterogeneity in invasion patterns, a sensitivity analysis was conducted in the subgroup of patients with fat invasion (99 MIS -PN/105 MIS-RN). In this subgroup, surgical approach remained non-significant as a prognostic factor for RFS after both PSM and IPW.

Functional analysis

Renal functional outcomes are detailed in Table-S2. Among patients with available NB-GFR (83 MIS-PN/139 MIS-RN). no significant difference was observed in pre-GFR between MIS-PN and MIS-RN group (95.98 vs. 92.06 mL/min/1.73 m^2, p =0.21). However, MIS-RN was associated with a significantly greater decline in renal function, reflected by a larger ΔGFR (25.85 vs 2.59 mL/min/1.73 m^2, p < 0.01) , a lower NB-GFR (66.42 vs.95.92 mL/min/1.73 m^2, p<0.01), and a reduced eGFR preservation rate (71.47% vs. 97.53%, p < 0.01). The incidences of CKD-S and CKD-S3b were both significantly higher in the MIS-RN group (both p<0.01). Among patients with available latest-GFR (83 MIS-PN/139 MIS-RN), those who underwent MIS-RN demonstrated significantly lower latest-GFR compared with MIS-PN (65.91 vs. 85.97 mL/min/1.73 m^2, p < 0.01) and a higher proportion of CKD-S at the latest follow-up (33.3% vs. 14.3%, p = 0.01).

Among patients with available NB-GFR after PSM (37 MIS-RN/ 41 MIS-PN), the MIS-PN group demonstrated significantly better postoperative renal functional outcomes. Specifically, MIS-PN was associated with a higher NB-GFR (93.92 vs. 66.42 mL/min/1.73 m^2, p < 0.01) (Figure 2A), a smaller ΔGFR (4.74 vs. 27.59 mL/min/1.73 m^2, p < 0.01), a lower incidence of CKD-S (7.3% vs. 29.7%, p = 0.02) (Figure 2B), and a greater eGFR preservation rate (94.92% vs. 69.42%, p < 0.01). Among patients with available latest-GFR after PSM (24 MIS-RN/27 MIS-PN), the MIS-PN group had a significantly higher NB-GFR (93.92 vs. 64.91 mL/min/1.73 m^2, p<0.01), latest-GFR (86.15 vs. 64.71 mL/min/1.73 m^2, p < 0.01), and a lower incidence of CKD-S (3.7% vs. 29.2%, p= 0.02) at the latest follow-up (Figures 2C and D) compared to the MIS-RN group.

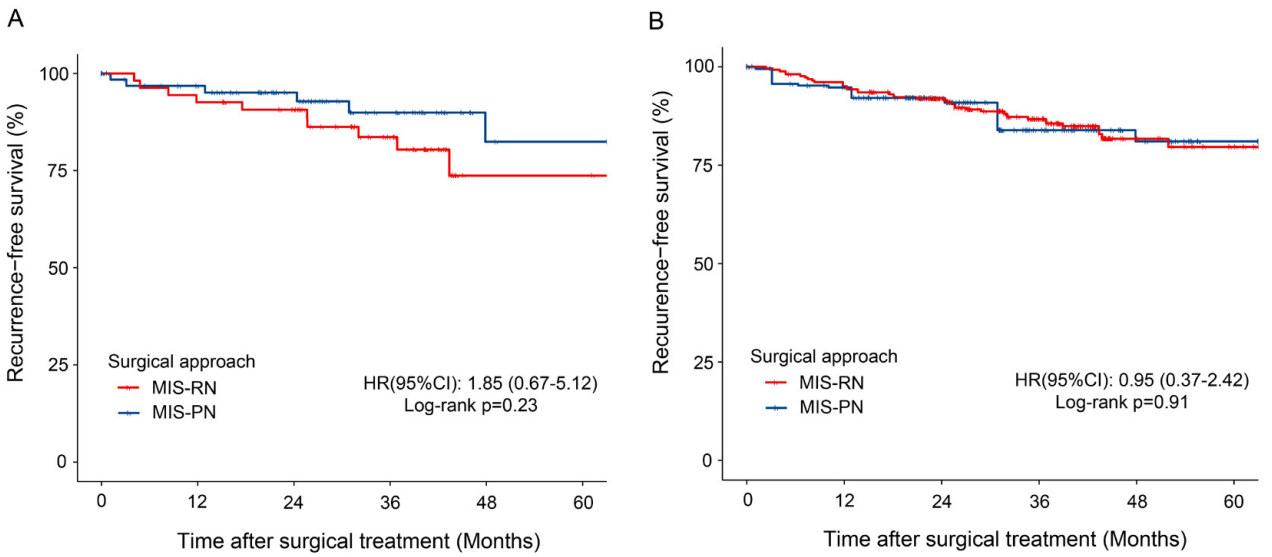
MVA logistic regression analyses were performed to identify independent predictors of CKD-S and CKD-S3b at new baseline, as well as CKD-S at the latest follow-up (Table-3). In the PSM cohort, MIS-RN re-

Table 1 - Patients clinicopathological features stratified by surgical type after PSM.

Variable	PSM		
	MIS-PN(n=66)	MIS-RN(n=54)	p-value
Median age, years (IQR)	57.0 (48.3, 63.0)	58.5 (49.0, 66.0)	0.29
Male, n (%)	50 (75.8)	41 (75.9)	1.00
Median BMI, kg/m^2, (IQR)	25.3 (23.3, 26.8)	24.28 (23.1, 26.1)	0.29
Comorbidity, n (%)	31 (47.0)	30 (55.6)	0.45
Median clinical tumor size, cm (IQR)	4.7 (4.0, 5.7)	5.1 (4.0, 6.0)	0.23
Clinical T stage, n (%)			**0.09**
cT1-2	28 (42.4)	14 (25.9)	
cT3a	38 (57.6)	40 (74.1)	
Median R.E.N.A.L. score (IQR)	8.0 (7.0, 9.0)	9.0 (7.0, 10.0)	0.49
Tumor complexity, n (%)			**0.49**
Low	6 (9.1)	7 (13.0)	
Moderate	46 (69.7)	32 (59.3)	
High	14 (21.2)	15 (27.8)	
Preoperative eGFR, mL/min/1.73m^2(IQR)	96.0(83.9, 103.9)	96.4(79.2, 105.0)	0.93
Median pathological tumor size, cm (IQR)	4.3 (3.3, 5.5)	5.0 (3.5, 5.7)	0.26
Histology, n (%)			**0.43**
ccRCC	50 (75.8)	45 (83.3)	
Non-ccRCC	16 (24.2)	9 (16.7)	
SMD, n (%)	3 (4.5)	3 (5.6)	1.00
Necrosis, n (%)	17 (25.8)	10 (18.5)	0.47
LVI, n (%)	7 (10.6)	11 (20.4)	0.22
Grade, n (%)			**0.73**
G1-2	34 (51.5)	27 (50.0)	
G3-4	22 (33.3)	21 (38.9)	
Gx*	10 (15.2)	6 (11.1)	
Invasion pattern for pT3a, n (%)			**<0.01**
PFI	49 (74.2)	5 (9.3)	
SFI	7 (10.6)	28 (51.9)	
PSI	3(4.5)	3(5.6)	
RVI	4(6.1)	4(7.4)	
Multifocal invasion	3 (4.5)	14 (25.9)	
Adjuvant therapy, n (%)	13(19.7)	6(11.1)	0.30

PSM= propensity score matching; MIS-RN= minimally invasive radical nephrectomy; MIS-PN= minimally invasive partial nephrectomy; BMI=body mass index; eGFR=estimated glomerular filtration rate; RCC=renal cell carcinoma; OT=operation time, EBL=estimated blood loss, LOS= length of stay, ccRCC=clear cell RCC; SMD=sarcomatoid differentiation; LVI= lymphovascular invasion; SM=surgical margin; PFI=perinephric fat invasion; SFI =sinus fat invasion; PSI=pelvicalyceal system invasion; RVI=renal vein invasion; R.E.N.A.L.=[R]adius, tumor size as maximal diameter; [E] xophytic/endophytic properties of tumor; [N]earness of tumor deepest portion to collecting system or sinus; [A]nterior/Posterior [p] descriptor; and [L]ocation relative to polar line. *Gx indicates missing or unclassified data on nuclear grade

Figure 1 - Kaplan-Meier survival analyses comparing recurrence-free survival between MIS-RN and MIS-PN.



(A) recurrence-free survival after PSM; (B) recurrence-free survival after IPW.
MIS-RN = minimally invasive radical nephrectomy; MIS-PN = minimally invasive partial nephrectomy; PSM = propensity score matching; IPW = inverse probability of weighting

mained an independent predictor of CKD-S both at new baseline and the latest follow-up, and the IPW analysis yielded similar results. In addition, the IPW analysis showed that MIS-RN (OR: 18.29, p< 0.01), high tumor complexity (OR: 6.91, p< 0.01), smaller pathological tumor size (OR: 0.69, p= 0.01), lower pre-GFR (OR: 0.92, p< 0.01) were significant predictors of CKD-S3b at new baseline (OR: 18.29, p< 0.01) (Table-3). Clinicopathological characteristics of patients with renal function follow-up after PSM are summarized in Table-S3.

DISCUSSION

The selection of treatment strategies for non-metastatic RCC is dependent on disease staging, with options ranging from RN, PN, ablation, and active surveillance(1, 2, 22, 23). With increasing experience and advancements in surgical techniques, treatment paradigms have gradually shifted. MIS-PN has been increasingly applied to larger, more complex, and even more aggressive renal tumors, with their feasibility in such cases well demonstrated (7, 24-26). However, given the morphological and biological heterogeneity of T3a RCC, MIS-PN remains challenging and controversial. We employed a robust matching design to compare oncological and renal functional outcomes of pT3aN0M0 RCC patients treated with MIS-PN versus MIS-RN. Our findings demonstrated that MIS-PN achieved non-inferior mild term oncological efficacy compared to MIS-RN in selected patients, with superior renal function preservation. Furthermore, our subgroup analysis for fat invasion also demonstrated equivalent oncological outcomes of MIS-PN vs. MIS-RN.

Existing evidence shows inconsistent results across comparative studies when all T3a invasion patterns are analyzed in aggregate. Capitanio et al. (11) compared 309 cT1aN0M0 patients pathologically upstaged to pT3a (71 PN / 238 RN) and found a significantly higher rate of PFI in the PN group (82.1% vs. 43.6%, p<0.001). After matching, MVA indicated that PN was not associated with an increased risk of metastatic progression (HR: 0.5, p=0.3) or cancer-specific mortality (CSM) (HR 0.6, p=0.4). Similarly, in a retrospective matched analysis of 140 pT3aN0M0 RCC patients (70 RAPN/70

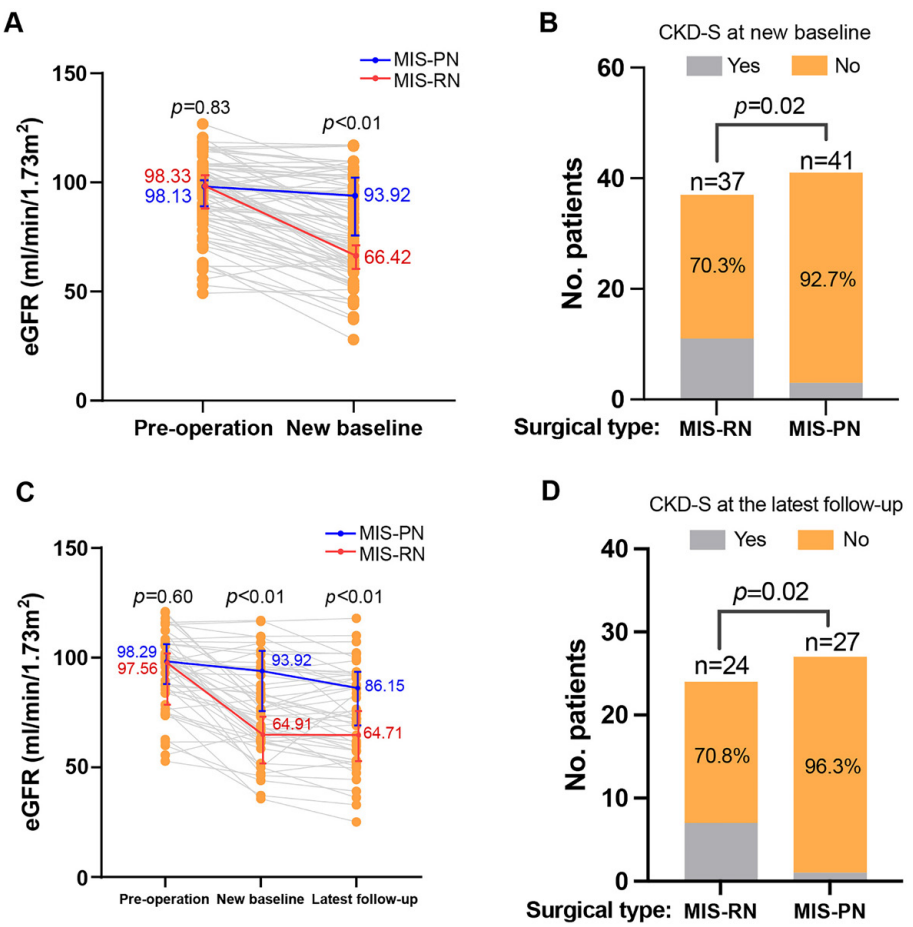
Table 2 - Multivariable cox regression of variables associated to recurrence-free survival in whole and fat invasion cohort after PSM and IPW.

Variable	Ref	PSM		IPW	
		HR (95%CI)	p-value	HR (95%CI)	p-value
The whole cohort					
Age		1.01(0.95-1.07)	0.84	1.01(0.98-1.05)	0.45
Comorbidities	No	1.93(0.45-8.24)	0.37	2.31(0.97-5.53))	0.06
High tumor complexity	Low/moderate	0.98(0.26-3.76)	0.98	0.96(0.46-1.98)	0.91
MIS-RN	MIS-PN	1.00(0.24-4.15)	1.00	0.49(0.12-2.01)	0.32
ccRCC	Non-ccRCC	0.42(0.11-1.63)	0.21	0.72(0.31-1.65)	0.44
Pathological tumor size		1.42(1.05-1.91)	0.02	1.18(0.99-1.40)	0.07
≥2 aggressive pathological features*	Negative	4.25(1.35-13.42)	0.01	2.94(1.41-6.10)	<0.01
Invasion pattern for pT3a					
SFI/PSI/RVI	PFI	2.87(0.61-13.47)	0.18	2.21(0.59-8.33)	0.24
Multifocal invasion		0.29(0.03-2.68)	0.28	1.46(0.42-5.08)	0.56
Adjuvant therapy	No	2.97(0.64-13.78)	0.16	1.40(0.47-4.16)	0.55
Fat invasion subgroup		HR (95%CI)	p-value	HR (95%CI)	p-value
Age		0.99(0.92-1.07)	0.86	0.99(0.95-1.03)	0.66
Comorbidities	No	1.87(0.41-8.54)	0.42	4.07(1.24-13.4)	0.02
High tumor complexity	Low/moderate	1.09(0.20-5.89)	0.92	0.97(0.40-2.34)	0.95
MIS-RN	MIS-PN	1.11(0.16-7.42)	0.92	0.17(0.03-1.01)	0.05
ccRCC	Non-ccRCC	0.83(0.15-4.61)	0.84	0.79(0.27-2.26)	0.66
Pathological tumor size		0.84(0.54-1.29)	0.42	1.30(0.95-1.79)	0.10
≥ 2 aggressive pathological features*	Negative	1.03(0.16-6.53)	0.97	4.11(1.60-10.56)	<0.01
Invasion pattern for pT3a					
SFI	PFI	1.75(0.29-10.39)	0.54	5.32(1.14-24.89)	0.03
Adjuvant therapy	No	6.05(0.92-39.9)	0.06	1.52(0.36-6.49)	0.57

MIS-RN= minimally invasive radical nephrectomy; MIS-PN= minimally invasive partial nephrectomy; ccRCC= clear cell renal cell carcinoma; SFI= sinus fat invasion; PSI= pelvicalyceal system invasion; RVI= renal venous invasion

*Aggressive pathological features: positive surgical margin, nuclear grade ≥ 3, necrosis, lymphovascular invasion or sarcomatoid differentiation

Figure 2 - Comparison of renal functional outcomes between MIS-PN and MIS-RN groups after PSM.



(A) Changes in eGFR from preoperative values to the new baseline. Data are presented as the individuals and the median with interquartile range. (B) Proportion of patients with CKD-S in each group. CKD-S is defined as CKD primarily due to surgical removal of nephrons (preoperative eGFR>60 mL/min/1.73 m² but new baseline eGFR <60 mL/min/ 1.73 m²). (C) Changes in eGFR from preoperative values to the new baseline and the latest follow-up. Data are presented as the individuals and the median with interquartile range. (D) Proportion of patients with CKD-S at the latest follow-up in each group. CKD-S at the latest follow-up is defined as preoperative GFR>60 mL/min/1.73 m² but the latest follow-up GFR <60 mL/min/ 1.73 m².
MIS-RN= minimally invasive radical nephrectomy; MIS-PN= minimally invasive partial nephrectomy; PSM=propensity score matching; eGFR= estimated glomerular filtration rate

RN), Andrade et al.(21) reported comparable 3-year cancer-specific survival (94% vs. 95%, p=0.78), OS (90% vs. 84%, p=0.42), and RFS (95% vs. 100%, p=0.06), with PFI as the predominant invasion pattern in the RAPN group (50% vs. 22.9%, p < 0.001). Pecoraro et al. (11) compared PN and RN in non-metastatic pT3a RCC using the Surveillance, Epidemiology, and End Results database and found that RN was associated with increased CSM (HR 2.10, p<0.001) in the propensity score-adjusted multivariable competing-risks regression model. Notably, PFI was more frequent in the PN group (70.3% vs. 36.4%) among patients with clearly defined pT3a invasion patterns (734 PN/ 3442 RN) before matching. However, a study by Shah et al. (8) reported contrasting findings, where patients undergoing PN for upstaged pT3a RCC from cT1 had significantly worse RFS compared to those receiving RN (HR = 5.39, p = 0.001). This discrepancy may reflect that more than 20% of cases in the PN group exhibited more aggressive T3a phenotypes (SFI or/and RVI). T3a RCC is highly heterogeneous, and evidence

Table 3 - Multivariable logistic regression of variables associated with CKD-S3b,CKD-S at new baseline, and CKD-S at latest follow-up after PSM and IPW.

Subgroup and variable	Ref	PSM		IPW	
		OR (95%CI)	p-value	OR (95%CI)	p-value
CKD-S3b at new baseline					
Age		n/a *	-	1.05(0.99-1.12)	0.12
Male	Female	n/a *	-	1.45(0.42-4.96)	0.56
BMI		n/a *	-	1.10(0.91-1.33)	0.34
High tumor complexity	Low/moderate	n/a *	-	6.91(2.10-22.79)	<0.01
Comorbidity	No	n/a *	-	2.68(0.82-8.75)	0.11
Pathological tumor size		n/a *	-	0.69(0.51-0.92)	0.01
Preoperative eGFR		n/a *	-	0.92(0.89-0.96)	<0.01
MIS-RN	MIS-PN	n/a *	-	18.29(2.53-132.01)	<0.01
CKD-S at new baseline					
Age		1.14(1.00-1.30)	0.04	1.05(1.01-1.09)	0.02
Male	Female	0.53(0.05-6.02)	0.61	1.27(0.54-2.97)	0.58
BMI		1.30(0.96-1.77)	0.09	1.06(0.95-1.20)	0.30
High tumor complexity	Low/moderate	2.43(0.24-24.36)	0.45	1.17(0.51-2.67)	0.71
Comorbidity	No	1.31(0.19-9.23)	0.79	1.10(0.50-2.39)	0.81
Pathological tumor size		0.63(0.34-1.14)	0.13	0.90(0.75-1.09)	0.29
Preoperative eGFR		0.94(0.90-0.99)	0.03	0.96(0.94-0.98)	<0.01
MIS-RN	MIS-PN	7.96(1.29-49.06)	0.03	5.67(2.07-15.48)	<0.01
CKD-S at the latest follow-up					
Age		1.08(0.96-1.21)	0.19	1.02(0.98-1.07)	0.35
Male	Female	4.80(0.59-39.13)	0.14	2.09(0.69-6.35)	0.20
BMI		1.08(0.75-1.57)	0.67	0.97(0.84-1.11)	0.64
High tumor complexity	Low/moderate	2.00(0.21-19.15)	0.55	0.51(0.18-1.42)	0.20
Comorbidity	No	0.63(0.11-3.70)	0.61	1.13(0.45-2.86)	0.80
Pathological tumor size		0.39(0.18-0.87)	0.02	1.06(0.86-1.32)	0.57
Preoperative eGFR		0.98(0.92-1.05)	0.57	0.95(0.92-0.97)	<0.01
MIS-RN	MIS-PN	7.98(1.29-51.07)	0.03	6.89(2.06-23.05)	<0.01

MIS-RN= minimally invasive radical nephrectomy; MIS-PN= minimally invasive partial nephrectomy; BMI=body mass index; eGFR=estimated glomerular filtration rate

n/a: not calculated due to low event numbers.

indicates that fat invasion carries a better prognosis than cases with RVI or multifocal invasion (27-30). Meta-analysis has shown that SFI is linked to higher CSM than PFI (31), likely due to the dense vascular and lymphatic networks in the renal sinus which increase the risk of tumor dissemination (32). In the present study, the invasion pattern in the MIS-PN cohort was predominantly characterized by PFI, which may partly explain why MIS-PN demonstrated favorable oncologic performance.

Our findings, showing that ≥2 aggressive pathological features independently predicted poorer RFS in both the PSM and IPW cohorts, closely align with prior studies(10,21). Notably, adjuvant therapy failed to improve RFS, contrasting with the KEYNOTE-564 trial (33). This discrepancy may reflect selection bias and the limitations of sample size and follow-up. Although Garofano et al. (34) suggested a potential benefit of adjuvant therapy in patients with positive SM, low positive SM rate in our study may also have reduced the ability to detect such an effect.

Compared with studies focusing on survival outcomes, research on renal functional outcomes following PN vs. RN in pT3a RCC patients remains limited. Andrade et al. (21) reported that renal function preservation rate was higher in the RAPN group than in the RN group at 3-6 months postoperatively (86.0% vs. 70.0%, $p < 0.001$). Similarly, Patel et al. (9) found that PN was associated with a smaller ΔGFR (6.1 vs. 19.4 mL/min/1.73 m^2, $p < 0.001$) and a lower incidence of new-onset CKD stage 3 at last follow-up (9.5% vs. 21%, $p = 0.008$) in upstaged T3a RCC patients who underwent PN. Our study also confirmed the advantages of MIS-PN in the renal function preservation, consistent with prior findings comparing PN and RN for T1/T2 tumors (35). Moreover, we identified RN as an independent risk factor for both CKD-S and CKD-S3b. The RENSAFE score developed by Saitta et al. (36) identified RN (HR 2.2, $p <0.01$) as an independent risk factor for developing de novo CKD ≥ 3b. In a subsequent analysis, Saitta et al. (10) further demonstrated that RN (HR 1.67, $p = 0.025$) was independently associated with a higher risk of CKD-S3b in pT3aN0M0 RCC patients. A key distinction lies in our primary reliance on the NB-GFR for assessing renal functional outcomes. Previous studies have shown that all-cause mortality is slightly higher in patients with CKD-S compared to those without CKD (HR 1.19, $p = 0.030$) and established that patients with NB-GFR < 45 mL/min/1.73 m^2 exhibit higher rates of progressive renal function decline and all-cause mortality (37, 38). Collectively, these findings encourage the consideration of PN for pT3aN0M0 patients when effective tumor control can be achieved.

While our findings corroborate the feasibility of MIS-PN for patients with pT3aN0M0 RCC, the surgical management of cT3a RCC requires careful consideration of tumor characteristics (size, location, and invasion patterns) and renal function. In our study, pathological upstaging occurred more frequently in the MIS-PN group versus the MIS-RN group (61.1% vs. 16.8, $p<0.001$). This discrepancy can be attributed to the substantially high proportion of PFI in the MIS-PN group, given that PFI is typically undetectable via preoperative imaging, with a reported diagnostic sensitivity of only 32% (39). Conversely, tumors in the MIS-RN cohort tended to be larger, more complex and biologically more aggressive. These characteristics accounted for the inferior RFS observed in the MIS-RN group before matching. Although Saitta et al. (10) revealed comparable survival outcomes among patients with upstaged and non-upstaged pT3aN0M0 RCC (HR 0.86, $p=0.69$), their study lacked detailed data regarding specific T3a invasion patterns, precluding stratified efficacy analysis. Yim et al. (40) reported that RAPN for cT3a tumors achieved a 5-year RFS of 82%, with 66.2% of patients considered to have fat invasion. However, their study did not include a comparison with RN. Our study confirmed the therapeutic equivalence of MIS-PN and MIS-RN (HR: 1.11, $p=0.92$) in the fat invasion subgroup. That said, given the limited sample size, further investigations in aggressive subgroups are warranted in future studies. For more aggressive T3a subtypes, although Morgan et al. (41) reported favorable outcomes for 45 pT3N0M0 RCC patients with venous tumor thrombus treated with RAPN, with 2-year local recurrence-free and metastasis-free survival rates of 95.4% and 95.3%, respectively, the follow-up period was relatively short and no comparison with RN was conducted. The limitations of existing evidence further underscore the necessity of implementing tailored treatment strategies. In the absence of high-quality evidence-based data,

RN may be preferred for cT3a RCC with suspected RVI or multifocal invasion if the contralateral kidney functions normally and the NB-GFR is expected to exceed 45 mL/min/1.73m^2. PN should only be considered in carefully selected patients with suspected fat invasion, particularly those with PFI. In addition, surgeon expertise should be fully considered in clinical decision-making.

This study has several limitations due to its retrospective nature. The choice of surgical approach was influenced by tumor characteristics, introducing inherent selection bias. Although robust matching methods were applied to mitigate this bias, the MIS-PN group was still predominantly composed of cT1–T2 RCC, whereas the MIS-RN group mainly included cT3a RCC with higher aggressiveness. While we confirmed that PN provides equivalent oncologic outcomes to RN in patients with fat invasion, the limited sample size prevents verification of such equivalence in subgroups with RVI or multifocal invasion, warranting further investigation. In addition, surgical approach selection was influenced by surgeon preference and institutional experience, and the study cohort was drawn from high-volume specialized centers, which may limit the generalizability of these findings to lower-volume centers. Furthermore, the follow-up period was relatively short, and long-term follow-up is needed to fully validate these results. Taken together, in the era of widespread adoption of minimally invasive surgery, our multicenter analysis with robust matching demonstrates that, in high-volume centers with experienced surgeons, MIS-PN for selected pT3aN0M0 RCC patients provides mild term oncologic outcomes comparable to MIS-RN, while offering superior renal function preservation.

CONCLUSIONS

Patients with pT3aN0M0 RCC treated with MIS-PN had comparable mild term oncological outcomes compared to MIS-RN, while providing superior renal functional preservation. As such, for carefully selected cT3a RCC cases, MIS-PN may be regarded as a viable option when technically feasible and nephron preservation is indicated. Continued follow-up is warranted to further elucidate the long-term oncological safety and refine selection criteria for MIS-PN in this subset of patients.

ACKNOWLEDGEMENTS

Xiangpeng Zou, Zhenhua Liu, Yunhan Luo, Peimin Zhou contributed similarly as first author

FUNDING

This study was supported by the National Natural Science Foundation of China (No. 82273031, 82273311, 82303922, 82373225, and 82472655), the China Postdoctoral Science Foundation (NO. 2023M734038 and 2024M763768), the Guangdong Natural Science Foundation (No. 2024A1515010303), the Guangzhou Science and Technology Project (No. 2024A04J4319), and the Chih Kuang Scholarship for Outstanding Young Physician-Scientists of Sun Yat-sen University Cancer Center (CKS-SYSUCC-2024006 and CKS-SYSUCC-2025008)

ETHICAL APPROVAL

The study protocol was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (approval number: B2025-341). The requirement for written informed consent was waived.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 update. Eur Urol. 2022;82(4):399-410. doi: 10.1016/j.eururo.2022.03.006
2. Campbell SC, Clark PE, Chang SS, Karam JA, Souter L, Uzzo RG. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: Part I. J Urol. 2021;206(2):199-208. doi: 10.1097/JU.0000000000001911

3. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol. 2006;7(9):735-40. doi: 10.1016/S1470-2045(06)70803-8
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305. doi: 10.1056/NEJMoa041031
5. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the eighth edition of the tumor-node-metastasis staging classification for urologic cancers. Eur Urol. 2018;73(4):560-9. doi: 10.1016/j.eururo.2017.12.018
6. Chevinsky M, Imnadze M, Sankin A, Winer A, Mano R, Jakubowski C, et al. Pathological stage T3a significantly increases disease recurrence across all tumor sizes in renal cell carcinoma. J Urol. 2015;194(2):310-5. doi: 10.1016/j.juro.2015.02.013
7. Shah PH, Moreira DM, Patel VR, Gaunay G, George AK, Alom M, et al. Partial nephrectomy is associated with higher risk of relapse compared with radical nephrectomy for clinical stage T1 renal cell carcinoma pathologically upstaged to T3a. J Urol. 2017;198(2):289-96. doi: 10.1016/j.juro.2017.03.012
8. Patel SH, Uzzo RG, Larcher A, Peyronnet B, Lane BR, Pruthi D, et al. Oncologic and functional outcomes of radical and partial nephrectomy in pT3a pathologically upstaged renal cell carcinoma: a multi-institutional analysis. Clin Genitourin Cancer. 2020;18(6):e723-9. doi: 10.1016/j.clgc.2020.05.002
9. Saitta C, Autorino R, Capitanio U, Lughezzani G, Meagher MF, Yim K, et al. Propensity score-matched analysis of radical and partial nephrectomy in pT3aN0M0 renal cell carcinoma. Clin Genitourin Cancer. 2025;23(3):102343. doi: 10.1016/j.clgc.2025.102343
10. Pecoraro A, Amparore D, Manfredi M, Piramide F, Checcucci E, Tian Z, et al. Partial vs radical nephrectomy in non-metastatic pT3a kidney cancer patients: a population-based study. Minerva Urol Nephrol. 2022;74(4):445-51. doi: 10.23736/S2724-6051.22.04680-8
11. Capitanio U, Stewart GD, Klatte T, Akdogan B, Roscigno M, Marszalek M, et al. Does the unexpected presence of non-organ-confined disease at final pathology undermine cancer control in patients with clinical T1N0M0 renal cell carcinoma who underwent partial nephrectomy? Eur Urol Focus. 2018;4(6):972-7. doi: 10.1016/j.euf.2017.02.020
12. Stout TE, Gellhaus PT, Tracy CR, Steinberg RL. Robotic partial vs radical nephrectomy for clinical T3a tumors: a narrative review. J Endourol. 2023;37(9):978-85. doi: 10.1089/end.2023.0173
13. Xia L, Talwar R, Taylor BL, Shin MH, Berger IB, Sperling CD, et al. National trends and disparities of minimally invasive surgery for localized renal cancer, 2010 to 2015. Urol Oncol. 2019;37(3):182.e17-27. doi: 10.1016/j.urolonc.2018.10.028
14. Patel HD, Mullins JK, Pierorazio PM, Jayram G, Cohen JE, Matlaga BR, et al. Trends in renal surgery: robotic technology is associated with increased use of partial nephrectomy. J Urol. 2013;189(4):1229-35. doi: 10.1016/j.juro.2012.10.024
15. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182(3):844-53. doi: 10.1016/j.juro.2009.05.035
16. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs-Part A: renal, penile, and testicular tumours. Eur Urol. 2016;70(1):93-105. doi: 10.1016/j.eururo.2016.02.029
17. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-49. doi: 10.1056/NEJMoa2102953
18. Campbell SC, Campbell JA, Munoz-Lopez C, Rathi N, Yasuda Y, Attawettayanon W. Every decade counts: a narrative review of functional recovery after partial nephrectomy. BJU Int. 2023;131(2):165-72. doi: 10.1111/bju.15848
19. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17(19):2265-81. doi: 10.1002/(SICI)1097-0258(19981015)17:19<2265::AID-SIM918>3.0.CO;2-B
20. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health. 2010;13(2):273-7. doi: 10.1111/j.1524-4733.2009.00671.x
21. Andrade HS, Zargar H, Akca O, Kara O, Caputo PA, Ramirez D, et al. Is robotic partial nephrectomy safe for T3a renal cell carcinoma? Experience of a high-volume center. J Endourol. 2017;31(2):153-7. doi: 10.1089/end.2016.0622

22. Li D, Yang J, Wang X, Liu Y, Shan G, Zhang Z, et al. Risk-adjusted trifecta outcomes in ultrasound-guided RFA of T1a renal masses: experience from a large tertiary cancer center. Int Braz J Urol. 2025;51(4). doi: 10.1590/S1677-5538.IBJU.2025.0034
23. Silvestri A, Gavi F, Sighinolfi MC, Assumma S, Panio E, Fettucciari D, et al. Management of small renal masses: literature and guidelines review. Int Braz J Urol. 2025;51(5). doi: 10.1590/S1677-5538.IBJU.2025.0203
24. Bradshaw AW, Autorino R, Simone G, Yang B, Uzzo RG, Porpiglia F, et al. Robotic partial nephrectomy vs minimally invasive radical nephrectomy for clinical T2a renal mass: a propensity score-matched comparison from the ROSULA collaborative group. BJU Int. 2020;126(1):114-23. doi: 10.1111/bju.15064
25. Tsivian M, Tsivian E, Stanevsky Y, Bass R, Sidi AA, Tsivian A. Laparoscopic partial nephrectomy for tumors 7 cm and above: perioperative outcomes. Int Braz J Urol. 2017;43(5):857-62. doi: 10.1590/S1677-5538.IBJU.2016.0642
26. Feng CL, Franco A, Ditonno F, Manfredi C, Chow AK, Autorino R. Robotic salvage partial nephrectomy following surgical and ablative therapies. Int Braz J Urol. 2024;50(3):373-4. doi: 10.1590/S1677-5538.IBJU.2024.0117
27. Park M, Shim M, Kim M, Song C, Kim CS, Ahn H. Prognostic heterogeneity in T3aN0M0 renal cell carcinoma according to the site of invasion. Urol Oncol. 2017;35(7):458.e17-22. doi: 10.1016/j.urolonc.2016.05.019
28. Shah PH, Lyon TD, Lohse CM, Cheville JC, Leibovich BC, Boorjian SA, et al. Prognostic evaluation of perinephric fat, renal sinus fat, and renal vein invasion for patients with pathological stage T3a clear-cell renal cell carcinoma. BJU Int. 2019;123(2):270-6. doi: 10.1111/bju.14523
29. Guo S, Liu Z, Li X, Yao K, Dong P, Chen D, et al. The prognostic value of the site of invasion in T3aN0M0 clear cell renal cell carcinoma. Urol Oncol. 2019;37(5):301.e11-17. doi: 10.1016/j.urolonc.2019.01.019
30. Stühler V, Rausch S, Kroll K, Scharpf M, Stenzl A, Bedke J. The prognostic value of fat invasion and tumor expansion in the hilar veins in pT3a renal cell carcinoma. World J Urol. 2021;39(9):3367-76. doi: 10.1007/s00345-021-03638-0
31. Zhang Z, Yu C, Velet L, Li Y, Jiang L, Zhou F. The difference in prognosis between renal sinus fat and perinephric fat invasion for pT3a renal cell carcinoma: a meta-analysis. PLoS One. 2016;11(2):e0149420. doi: 10.1371/journal.pone.0149420
32. Bonsib SM, Gibson D, Mhoon M, Greene GF. Renal sinus involvement in renal cell carcinomas. Am J Surg Pathol. 2000;24(3):451-8. doi: 10.1097/00000478-200003000-00015
33. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med. 2021;385(8):683-94. doi: 10.1056/NEJMoa2106391
34. Garofano G, Saitta C, Musso G, Meagher MF, Capitanio U, Dabbas M, et al. Positive surgical margins in clear cell renal cell carcinoma: prognostic impact and implications for risk stratification and adjuvant therapy. J Clin Med. 2025;14(11):3908. doi: 10.3390/jcm14113908
35. Mir MC, Derweesh I, Porpiglia F, Zargar H, Mottrie A, Autorino R. Partial nephrectomy versus radical nephrectomy for clinical T1b and T2 renal tumors: a systematic review and meta-analysis of comparative studies. Eur Urol. 2017;71(4):606-17. doi: 10.1016/j.eururo.2016.08.060
36. Saitta C, Afari JA, Autorino R, Capitanio U, Porpiglia F, Amparore D, et al. Development of a novel score (RENSAFE) to determine probability of acute kidney injury and renal functional decline post surgery: a multicenter analysis. Urol Oncol. 2023;41(12):487.e15-23. doi: 10.1016/j.urolonc.2023.09.015
37. Lane BR, Demirjian S, Derweesh IH, Takagi T, Zhang Z, Velet L, et al. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: importance of the new baseline glomerular filtration rate. Eur Urol. 2015;68(6):996-1003. doi: 10.1016/j.eururo.2015.04.043
38. Wu J, Suk-Ouichai C, Dong W, Antonio EC, Derweesh IH, Lane BR, et al. Analysis of survival for patients with chronic kidney disease primarily related to renal cancer surgery. BJU Int. 2018;121(1):93-100. doi: 10.1111/bju.13994
39. Liu Y, Song T, Huang Z, Zhang S, Li Y. The accuracy of multidetector computed tomography for preoperative staging of renal cell carcinoma. Int Braz J Urol. 2012;38(5):627-36. doi: 10.1590/S1677-55382012000500007

40. Yim K, Aron M, Rha KH, Simone G, Minervini A, Challacombe B, et al. Outcomes of robot-assisted partial nephrectomy for clinical T3a renal masses: a multicenter analysis. Eur Urol Focus. 2021;7(5):1107-14. doi: 10.1016/j.euf.2020.10.011

41. Morgan TN, Dai JC, Kusin S, Kommidi V, Garbens A, Gahan J, et al. Clinical outcomes of robotic assisted partial nephrectomy for pathologic T3a renal masses with venous tumor thrombus. Urology. 2022;159:120-6. doi: 10.1016/j.urology.2021.06.054

Correspondence address:
Zhiling Zhang, MD, PhD
Department of Urology
Sun Yat-Sen University Cancer Center
Dongfengdonglu 651, Guangzhou, P. R. China
E-mail: zhangzhl@sysucc.org.cn

APPENDIX

Table S1 - Clinicopathological characteristics of the overall cohort and stratified by surgical type.

Variable	Overall(n=303)	MIS-PN(n=113)	MIS-RN(n=190)	p-value
Median age, years (IQR)	58.0(49.0~65.0)	56.0 (48.0~ 63.0)	58.5 (51.3~ 66.0)	0.02
Male, n (%)	223(73.6)	88(77.9)	135(71.1)	0.24
Median BMI, kg/m2, (IQR)	24.6 (22.8~26.6)	25.2 (23.0~ 26.8)	24.5 (22.6~ 26.3)	0.16
Comorbidities, n (%)	141 (46.5)	55 (48.7)	86 (45.3)	0.65
Median clinical tumor size, cm (IQR)	5.5 (4.0~ 7.2)	3.9 (3.0~ 4.8)	6.3 (5.2~ 8.1)	<0.01
Clinical T stage, n (%)				<0.01
T1-2	101(33.3)	69(61.1)	32(16.8)	
T3a	202(67.7)	44(38.9)	158(83.2)	
Median R.E.N.A.L. score (IQR)	9.0(7.0~ 10.0)	7.0 (6.0~ 9.0)	10.0 (8.0~ 10.0)	<0.01
Tumor complexity, n (%)				<0.01
Low	51 (16.8)	43 (38.1)	8 (4.2)	
Moderate	142 (46.9)	56 (49.6)	85 (45.3)	
High	110 (36.3)	14 (12.4)	96 (50.5)	
Laterality, n (%)				0.94
Left	164 (54.1)	62 (54.9)	102 (53.7)	
Right	139 (45.9)	51 (45.1)	88 (46.3)	
Surgical technique, n (%)				<0.01
Laparoscopic	189 (62.4)	45 (39.8)	144 (75.8)	
Robot-assisted	114 (37.6)	68 (60.2)	46 (24.2)	
Mean OT, min (SD)	142.1(59.8)	149.8(70.9)	137.6(51.7)	0.09
Median EBL, mL (IQR)	50.0(20.0-100.0)	50.0(20.0-150.0)	50.0(20.0-100.0)	0.51
Mean LOS, days (SD)	5.0(1.9)	5.1(2.0)	5.0 (1.8)	0.60
Intraoperative transfusion, n (%)	19(6.3)	8(7.1)	11(5.8)	0.84
Postoperative complications, n (%)	12(4.0)	8(7.1)	4(2.1)	0.07
Median pathological tumor size, cm (IQR)	5.0 (3.5~ 6.5)	3.5 (2.8~ 4.5)	6.0 (4.6~ 7.5)	<0.01
Preoperative eGFR, mL/min/1.73m^2 (IQR)	93.1 (79.7~102.9)	96.0 (84.0~ 102.8)	91.8 (77.0~ 103.0)	0.16
Histology, n (%)				0.04
ccRCC	235 (77.6)	80 (70.8)	155 (81.6)	
Non-ccRCC	68 (22.4)	33 (29.2)	35 (18.4)	
SMD, n (%)	11 (3.6)	3 (2.7)	8 (4.2)	0.70
Necrosis, n (%)	79 (26.2)	22 (19.5)	57 (30.0)	0.06
LVI, n (%)	52 (17.2)	11 (9.7)	41 (21.2)	0.01
Grade, n (%)				0.09
G1-2	146 (48.2)	62 (54.9)	84 (44.2)	
G3-4	121 (39.9)	36 (31.9)	85 (44.7)	
Gx*	36 (11.9)	15 (13.3)	21 (11.1)	
Positive SM, n (%)	2 (0.7)	2(1.8)	-	-
Invasion pattern for pT3a, n (%)				<0.01
PFI	115 (38.0)	87 (77.0)	28 (14.7)	
SFI	89 (29.4)	12 (10.6)	77 (40.5)	
PSI	19(6.3)	3 (2.7)	16 (8.4)	
RVI	21(6.9)	5(4.4)	16(8.4)	
Multifocal invasion	59(19.5)	6 (5.3)	53 (27.9)	
Adjuvant therapy, n (%)	51 (16.8)	24 (21.2)	27 (14.2)	0.16
TKI, n (%)	10(3.3)	3(2.7)	7(3.7)	
PD-1 inhibitor, n (%)	36(11.9)	19(16.8))	17(8.9)	
TKI plus PD-1 inhibitor, n (%)	5(1.7)	2(1.8)	3(1.6)	

BMI=body mass index; eGFR=estimated glomerular filtration rate; RCC=renal cell carcinoma; OT=operation time, EBL=estimated blood loss, LOS= length of stay, ccRCC=clear cell RCC; SMD=sarcomatoid differentiation; LVI= lymphovascular invasion; SM=surgical margin; PFI=perinephric fat invasion; SFI =sinus fat invasion; PSI=pelvicalyceal system invasion; RVI=renal vein invasion; TKI= tyrosine kinase inhibitor; PD-1= programmed death protein 1; R.E.N.A.L.=[R]adius, tumor size as maximal diameter; [E]xophytic/endophytic properties of tumor; [N]earness of tumor deepest portion to collecting system or sinus; [A]nterior/Posterior [p] descriptor; and [L]ocation relative to polar line.
*Gx indicates missing or unclassified data on nuclear grade

Table S2 - Renal function outcomes within and beyond 1 year after surgery in patients undergoing MIS-PN and MIS-RN.

Subgroup and variable	MIS-PN(n=83)	MIS-RN(n=139)	p-value
1-12 month postoperatively			
Preoperative eGFR, mL/min/1.73m^2(IQR)	95.98(85.63,102.61)	92.06(77.34,103.28)	0.21
New baseline eGFR, mL/min/1.73m^2(IQR)	95.92(75.47,106.21)	66.42 (53.27, 77.07)	<0.01
Median △GFR, mL/min/1.73m^2(IQR)	2.59(-1.50,10.87)	25.85(17.25,33.96)	<0.01
Median eGFR preservation, %(IQR)	97.53(86.87,101.40)	71.47(63.55,81.41)	<0.01
CKD-S, n (%)	8(9.6)	48(34.5)	<0.01
CKD-S3b, n (%)	1(1.2)	18(12.9)	<0.01
Subgroup and variable	MIS-PN(n=63)	MIS-RN(n=99)	p-value
> 1 year postoperatively			
Latest follow-up eGFR, mL/min/1.73m^2(IQR)	85.97(71.18-98.19)	65.91(56.08,80.06)	<0.01
CKD-S, n (%)	9(14.3)	33(33.3)	0.01

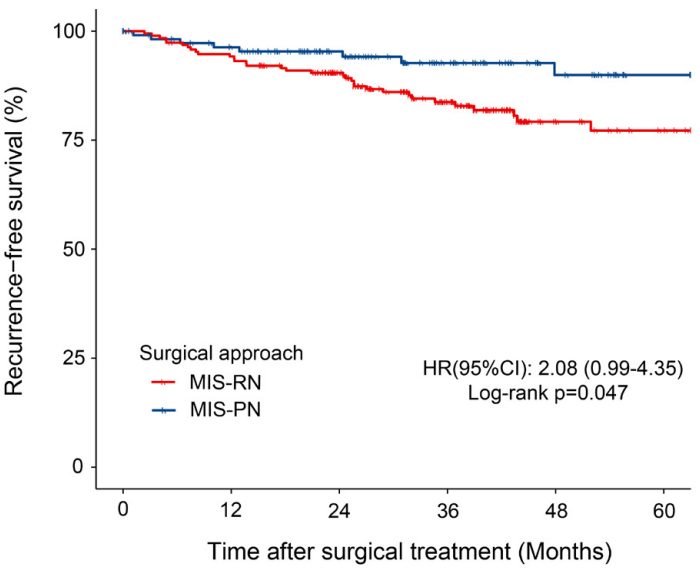
eGFR: estimated glomerular filtration rate

Table S3 - Clinicopathological characteristics of patients with renal function follow-up within and beyond 1 year postoperatively, stratified by surgical type after PSM

Subgroup and variable	PSM		
1-12 month postoperatively	MIS-PN(n=41)	MIS-RN(n=37)	p-value
Median age, years (IQR)	57.0(49.0-63.00)	56.0(49.0-65.0)	0.92
Male, n (%)	29(70.7)	27(73.0)	1.00
Median BMI, kg/m^2, (IQR)	25.0(23.7-26.6)	24.5(22.9-26.8)	0.60
Comorbidities, n (%)	17(41.5)	16(43.2)	1.00
Median clinical tumor size, cm (IQR)	5.0(4.1-6.1)	5.6(4.0-6.3)	0.45
Median R.E.N.A.L. score (IQR)	8.0(7.0-9.0)	9.0(7.0-10.0)	0.47
Tumor complexity, n (%)			0.57
Low	4(9.8)	5(13.5)	
Moderate	27(65.9)	20(54.1)	
High	10(24.4)	12(32.4)	
Preoperative eGFR, mL/min/1.73m^2(IQR)	98.1(86.0-106.3)	98.3(81.0-105.4)	0.83
Median pathological tumor size, cm (IQR)	4.5(3.8-6.0)	5.0(4.0-5.7)	0.68
>1 year postoperatively	MIS-PN(n=27)	MIS-RN(n=24)	p-value
Median age, years (IQR)	58.0(50.5-63.0)	58.0(42.8-64.3)	0.96
Male, n (%)	18(66.7)	18(75.0)	0.73
Median BMI, kg/m^2, (IQR)	25.1(24.1-26.6)	23.9(23.0-25.9)	0.14
Comorbidities, n (%)	11(40.7)	11(45.8)	0.93
Median clinical tumor size, cm (IQR)	5.3(4.2-6.6)	5.6(4.9-6.5)	0.44
Median R.E.N.A.L. score (IQR)	8.0(7.0-9.0)	8.0(7.0-10.0)	0.71
Tumor complexity, n (%)			0.83
Low	3(11.1)	2(8.3)	
Moderate	18(66.7)	15(62.5)	
High	6(22.2)	7(29.2)	
Preoperative eGFR, mL/min/1.73m^2(IQR)	98.3(87.6-106.2)	97.6(77.9-102.9)	0.60
Median pathological tumor size, cm (IQR)	5.0(4.0-6.0)	5.0(4.0-6.0)	0.64

MIS-RN= minimally invasive radical nephrectomy; MIS-PN= minimally invasive partial nephrectomy; BMI: body mass index; eGFR: estimated glomerular filtration rate; R.E.N.A.L.=[R]adius, tumor size as maximal diameter; [E]xophytic/endophytic properties of tumor; [N]earness of tumor deepest portion to collecting system or sinus; [A]nterior/Posterior [p] descriptor; and [L]ocation relative to polar line.

Figure S1 - Kaplan-Meier survival analyses comparing recurrence-free survival between MIS-RN and MIS-PN before matching.



MIS-RN = minimally invasive radical nephrectomy; MIS-PN = minimally invasive partial nephrectomy

ORIGINAL ARTICLE

Vol. 52 (3): e20250512, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0512

Pain Perception During Transperineal and Transrectal Prostate Biopsy Under Local Anesthesia: a Prospective Analysis of a Multi-ethnic and Diverse Cohort

Kevin Joseph Chua [1], Lorenzo Storino Ramacciotti [1, 2], Masatomo Kaneko [1, 2], Yuta Inoue [1, 2], Luis Medina Navarro [1], Jie Cai [1], Manju Aron [3], Pierre Halteh [4], Eric Kau [1], Anne Schuckman [1], Sij Hemal [1], Mihir Desai [1], Hooman Djaladat [1], Inderbir S. Gill [1, 2], Monish Aron [1], Andre Luis Abreu [1, 2, 4]

[1] USC Institute of Urology and Catherine & Joseph Aresty Department of Urology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA; [2] USC Institute of Urology, Center for Image-Guided Surgery, Focal Therapy and Artificial Intelligence for Prostate Cancer; [3] Departments of Pathology Keck School of Medicine, University of Southern California, Los Angeles, California, USA; [4] Departments of Radiology Keck School of Medicine, University of Southern California, Los Angeles, California, USA

ABSTRACT

Purpose: To assess factors associated with patients' self-assessed pain scores during prostate biopsy (PBx) performed exclusively under local anesthesia (LA).

Materials and Methods: Consecutive patients who underwent MRI followed by a transperineal (TP) or transrectal (TR) PBx under LA were prospectively assessed. Race and ethnicity were self-reported according to NIH standards. Socioeconomic status was assessed using the Distressed Community Index (DCI). Pain was evaluated with a visual analog scale (0-10) after the procedure. Univariable and multivariable linear regression analyses were performed to correlate clinical parameters related to pain.

Results: A total of 419 patients underwent TP (77%) or TR (23%) PBx. Overall, 14% of patients were Asian, 5% Black, 17% Latino, 12% Others, and 53% White. Of the cohort, 20% of Black and 27% of Latino patients were most distressed (DCI 80-100) compared with 4% of Asian, 9% of Other, and 5% of White patients ($p<0.001$). The median (IQR) self-assessed pain levels were higher for Black 5 (2-5) and Latino 4 (3-5) compared to Asian 3 (2-4), Other 3 (2-5), and White 3 (2-4) patients ($p=0.01$). On multivariable analysis, younger patients, Black or Latino patients, and the number of lesions on MRI were independent predictors for pain levels.

Conclusions: PBx under LA alone are generally well tolerated; however, there is a subset of patients who experience more pain, including Black and Latino, younger patients, and those with more MRI suspicious lesions. Discussion of these pain risk factors is important for patients when choosing to have a biopsy performed under LA versus sedation.

ARTICLE INFO

Andre Abreu
https://orcid.org/0000-0002-9167-2587

Keywords:
Prostatic Neoplasms; Race Factors; Socioeconomic Factors

Submitted for publication:
September 12, 2025

Accepted after revision:
January 05, 2026

Published as Ahead of Print:
January 28, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

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

INTRODUCTION

The diagnosis of prostate cancer is usually made by a prostate biopsy (PBx), making this one of the most common procedures in Urology with more than 1 million PBx being performed in the US and Europe combined (1-4). While performing PBx in the operating room under sedation may decrease a patient's pain, it may increase the costs, risk of complications, and is subject to operating room availability. Although PBx under local anesthesia may be more practical, time-efficient and cost-effective, a proportion of patients may experience severe pain. Therefore, identifying predictors for pain during prostate biopsy may allow for improved prebiopsy counseling.

Several potential factors may influence pain perception during medical procedures including race/ethnicity and socioeconomic status (SES) (5, 6). Within an experimental setting, as demonstrated by Rahim Williams et al., lower pain tolerances were seen in African American and Hispanic populations (7). Additionally, Thurston et al had identified that lower SES was associated with increased postoperative pain (8). To the best of our knowledge, there is no study evaluating the impact of race/ethnicity and socioeconomic status on perception of pain during a prostate biopsy. The aim of this study is to identify different factors associated with pain during an in-office PBx exclusively under local anesthesia with the hypothesis that race/ethnicity, SES, age and other clinical and demographic parameters would affect pain levels and tolerance to PBx.

MATERIALS AND METHODS

Study Population

Consecutive patients who underwent multiparametric MRI (mpMRI) followed by transperineal (TP) or transrectal (TR) PBx between June 2020 and May 2023 were prospectively assessed (IRB #HS-13-00663). Exclusion criteria were I) mpMRI acquired more than 6 months prior to the PBx; II) mpMRI that did not meet Prostate Imaging Reporting & Data System (PIRADS) standards. III) prior treatment for prostate cancer IV) prior surgery for benign prostatic hyperplasia; V) Saturation PBx.

MRI Acquisition and Interpretation

All mpMRIs, whether performed at an outside institution or our institution, were interpreted at our institution in accordance with the Prostate Imaging Reporting & Data System (PIRADS) v2.0 or v2.1 by radiologists with expertise in prostate mpMRI reading.(9) The index lesion location was assigned as base, mid or apex, and anterior or posterior according to PIRADS definition (9). If a PIRADS ≥ 3 lesion was traversing more than one of these areas, it was counted for both.

Prostate Biopsy Protocol

All PBx were carried out transperineally or transrectally by a single urologist (ALA) using a three dimensional organ tracking elastic image fusion system (Trinity, Koelis®, Grenoble, France) and 18G needle biopsy as previously described (10-15). All patients underwent MRI followed by TP or TR 12-14 core systematic PBx, with a minimum of two additional target-PBx cores per PIRADS ≥ 3 lesion. The PBx specimens were evaluated by a uropathologist according to International Society of Urological Pathology (ISUP) guidelines (16). Clinically significant prostate cancer (CSPCa) was defined as Grade Group ≥2.

During the study period, the operator (ALA) was transitioning from TR to TP PBx. Once this transition was complete, TP biopsies became the preferred approach, while TR biopsies were performed solely based on patient preference. The operator had extensive experience with both biopsy techniques, having surpassed their respective learning curves. Patient characteristics, lesion location, imaging findings, or other individual factors did not influence the biopsy approach for each patient.

Local Anesthesia Administration

All procedures were performed exclusively under local anesthesia, using techniques widely accepted as part of the current standard of care (17, 18). No additional analgesics, anxiolytics, or sedatives were used. Prior to the biopsies the patients were appropriately counseled about the procedure protocols and watched an educational and informative video

acess: LINK

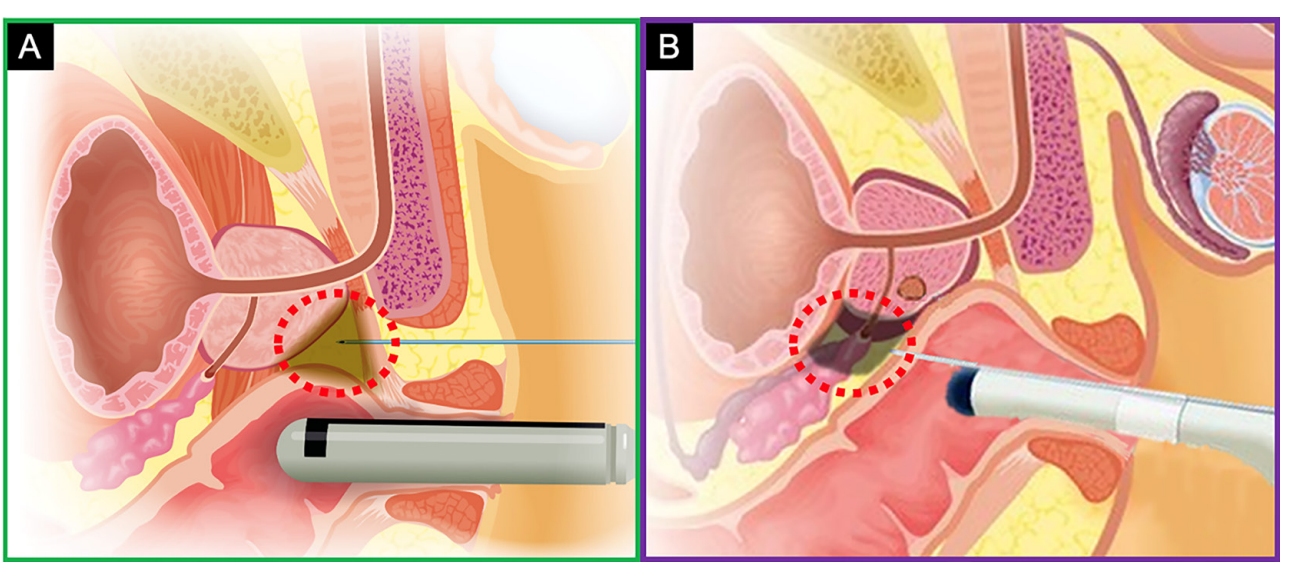
For a TP biopsy, the patient is placed into dorsal lithotomy position. A total of 10 mL of 2% lidocaine gel is instilled into the rectum and a digital rectal exam is performed. The perineum is prepped with chlorhexidine and the patient is draped. A side-fire endocavity 3D-TRUS probe is then inserted into the rectum. The local anesthesia mixture consists of 40mL of 0.5% lidocaine, as follows: 20 mL of Lidocaine 1%, 18mL of NaCl 0.9% (normal saline) and 2mL of sodium bicarbonate 18%. Sodium bicarbonate is added to the mixture to increase the pH of the acidic anesthetic solution which help reduce a burning sensation. Overall, 5mL of the solution is injected into the perineal skin of each side about 1-2cm anterior to the rectum and 1-2cm lateral to the midline (Figure-1) (14). Under real-time TRUS guidance, a periapical triangle (bounded by levator ani, rhabdosphincter and external anal sphincter muscles) block is then performed using an 18-G spinal needle inserted through a 17-G coaxial introducer needle with 15mL of 0.5% lidocaine used on each side. The local anesthesia is injected into the perineum and periprostatic tissue as the needle is advanced towards the prostatic apex. The 18-G spinal needle is carefully removed, and the co-axial needle sheath is left in place.

For a TR biopsy, the patient is placed into left lateral decubitus position. A total of 10 mL of 2% lidocaine gel is instilled into the rectum and a digital rectal exam is performed. An end-fire endocavity 3D-TRUS probe is then inserted into the rectum. Local anesthesia was administered via a periprostatic nerve block, under real-time TRUS guidance, injecting 10mL of 1% lidocaine solution, 5mL in each side, at the bilateral neurovascular bundles at the junction of the prostate with the seminal vesicles.

Race, Ethnicity and Socioeconomic Status

Race and ethnicity were self-reported according to NIH standards and categorized as follows: Hispanic/Latino (Latino), non-Hispanic Asian (Asian), non-Hispanic Black or African American (Black), non-Hispanic White (White), and Others, which included individuals who did not report or identify with any specific race or ethnicity (19). Socioeconomic status (SES) was assessed using the Distressed Community Index (DCI) (database available at https://eig.org/distressed-communities), a metric developed by the Economic Innovation Group to evaluate the economic well-being of U.S. communities. The DCI is derived from the Census Bureau's Business

Figure 1 - A) Periapical triangle nerve block – performed during transperineal prostate biopsy. B) Periprostatic nerve block at the junction of the prostate base, seminal vesicles, and bilateral neurovascular bundles – performed during transrectal biopsy



Patterns and the American Community Survey 5-Year Estimates (2016–2020) and provides a zip code-based composite score. This score incorporates community education levels, poverty rate, unemployment rate, housing vacancy rate, median household income, as well as changes in employment and business establishments. The DCI score ranges from 0 to 100, where 0 represents the most prosperous communities and 100 indicates the most economically distressed. Higher DCI scores correspond to lower SES (20). Each patient's 5-digit zip code was matched to the DCI database, and their respective DCI scores were analyzed.

Endpoints

The primary endpoint was pain. The patients' self-assessed pain during PBx, using a visual analog scale ranging from 0 to 10, was assessed immediately after the procedure. Patients were asked to rate the overall pain experienced during the biopsy with the Wong-Baker FACES Pain Scale (Supplemental Figure). The FACES scale is recommended for people ages three and older and is a self-assessment tool for physical pain. The tool comes with instructions which include explaining to the patient the amount of pain each face depicts.

Secondary endpoints included PCa and CSPCa detection rates and procedure time (recorded from the moment the TRUS was inserted into the patient's rectum to the moment it was removed).

Statistical Analysis

The Wilcoxon rank sum test was used for continuous variables, and Pearson's chi-square or Fisher exact test was used for categorical variables. Univariable and multivariable linear regression analyses were performed to correlate clinical parameters related to pain. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

A total of 419 patients underwent TP (n= 322, 77%) or TR (n= 97, 23%) PBx. Overall, 14% of patients were Asian, 5% Black, 17% Latino, 12% Others, and 53% White (Table-1). The median age, PSA, PSA density, prostate volume, PIRADS distribution, PBx approach (TP or TR), and the number of cores sampled were similar between ethnical/racial groups. Clinically significant prostate cancer was detected in 60.1% (196/326) of patients with PIRADS 3-5 lesions and 11.8% (11/93) of patients with PIRADS 1-2 lesions. There was no significant difference for detection of CSPCa based on PIRADS scores between ethnic groups (Table-2A).

Of the cohort, 20% of Black and 27% of Latino patients were most distressed (DCI 80-100), in contrast to 4% of Asian, 9% of Other, and 5% of White patients (p<0.001) (Table-1). The median (IQR) self-assessed pain level for all patients was 3 (2-5). Pain levels were higher for Black 5 (2-5) and Latino 4 (3-5) compared to Asian 3 (2-4), Other 3 (2-5), and White 3 (2-4) patients (p=0.01) (Table-2B, Figures 2 and 3). Median operative time was 15 minutes (IQR 15 – 21 minutes), and it was not significantly different between ethnic groups (Tables 1 and 3, Figures 2 and 3). Pain levels were not statistically significantly associated with increased procedure time (β 0.003, 95% CI -0.03, 0.04; p = 0.87) or the detection of prostate cancer (β -0.11, 95% CI -0.51, 0.28; p = 0.57). On multivariable analysis, younger age (β -0.04, 95% CI -0.06, 0.01), Black (β 1.11, 95% CI 0.25, 1.98) or Latino (β 0.72, 95% CI 0.19, 1.26) race, and the number of lesions on MRI (β 0.30, 95% CI 0.07, 0.53) were independent predictors for pain levels, but the biopsy approach (TP or TR) and the DCI were not (Table-3, Figure 2 and 3).

DISCUSSION

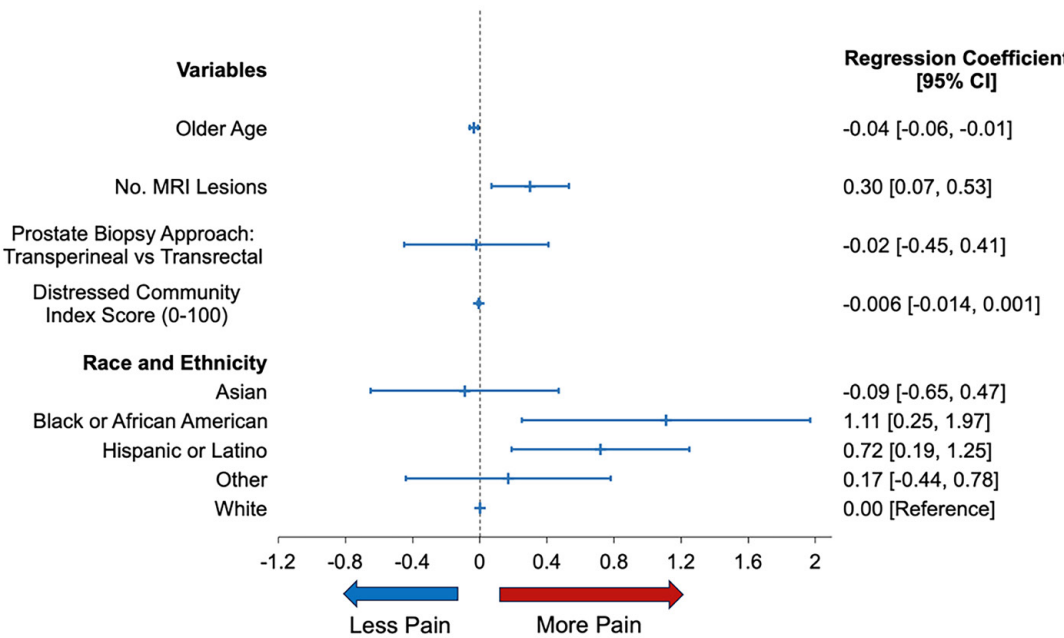
There were 419 patients in our cohort who underwent prostate biopsy with a transperineal or transrectal approach. There was no significant difference in pain based on approach. The median pain level for all patients was 3 / 10, and it was significantly higher for Black patients and Latino patients. Other predictors of pain included younger age and increased number of lesions on MRI. There was no association of pain with prostate size, biopsy history, operative time or PIRADS score on univariable analysis or DCI on multivariable analysis.

Table 1 - Baseline characteristics subdivided by patient race / ethnicity.

	All	Asian	Black	Latino	Other	White	p
No. of Patients, n (%)	419	58 (13.8)	21 (5)	72 (17.2)	48 (11.5)	220 (52.5)	
Age, year, mean (SD)	66.3 (8.0)	67.6 (9.6)	66.8 (7.4)	65 (8.6)	67.2 (6.6)	66.1 (7.7)	0.21
BMI, mean (SD)	28.4 (9.7)	25.1 (3.5)	27.5 (6.7)	30.2 (4.1)	28.4 (4.3)	27.9 (4.0)	**<.0001**
Family History PCa, n (%)	108	11 (19.6)	6 (30)	12 (18.8)	9 (20.5)	70 (33.8)	0.05
Biopsy History, n (%)							0.11
Naïve	272	38 (65.5)	17 (81)	38 (53.5)	26 (56.5)	153 (69.9)	
Negative	73	11 (19)	1 (4.8)	16 (22.5)	13 (28.3)	32 (14.6)	
In active surveillance	70	9 (15.5)	3 (14.3)	17 (23.9)	7 (15.2)	34 (15.5)	
PSA, ng/mL, mean (SD)	9.8 (18.8)	7.4 (3.6)	8.5 (7.5)	12.4 (27.8)	10.0 (13.1)	9.7 (19.3)	0.97
PSA density, ng/mL^2, mean (SD)	0.2 (0.4)	0.2 (0.1)	0.2 (0.2)	0.2 (0.5)	0.2 (0.4)	0.2 (0.4)	0.69
Suspicion for PCa on DRE, n (%)	98	11 (19)	3 (14.3)	18 (25)	11 (22.9)	55 (25)	0.73
PIRADS score, n (%)							0.36
PIRADS 1-2	93 (22.2)	17 (29.3)	7 (33.3)	15 (20.8)	8 (16.7)	46 (20.9)	
PIRADS 3-5	326 (77.8)	41 (70.7)	14 (66.7)	57 (79.2)	40 (83.3)	174 (79.1)	
Prostate volume, mean (SD)	59.1 (15.3)	52.3 (24.2)	62.4 (51.6)	67.6 (38.7)	59.6 (35.2)	57.6 (29.3)	0.16
No. of MRI lesions mean (SD)	1.1 (0.8)	1.1 (0.8)	0.8 (0.7)	1.2 (0.9)	1.2 (0.7)	1.1 (0.8)	0.53
MRI index lesion location, n (%)							
Anterior	136	16 (27.6)	5 (23.8)	22 (30.6)	26 (54.2)	67 (30.5)	**0.01**
Posterior	247	28 (48.3)	12 (57.1)	42 (58.3)	24 (50)	141 (64.1)	0.15
MRI index lesion location, n (%)							
Base	98	11 (19)	3 (14.3)	20 (27.8)	9 (19)	55 (25)	0.51
Mid	222	33 (56.9)	10 (47.6)	37 (51.4)	28 (58.3)	114 (51.8)	0.85
Apex	117	16 (27.6)	3 (14.3)	18 (25)	19 (39.6)	61 (27.7)	0.24
MRI index lesion size, mm, mean (SD)	15.3 (7.5)	13.4 (5.9)	13.9 (5.0)	17.0 (8.8)	15.2 (8.1)	15.3 (7.4)	0.37
No. of (SB + TB) cores taken mean (SD)	15.0 (2.2)	15.1 (2.6)	14.2 (2.5)	15.4 (1.6)	14.7 (2.6)	15 (2.1)	0.22
No. of TB cores taken mean (SD)	3.9 (2.9)	3.7 (2.8)	3.0 (2.5)	3.8 (2.8)	4.0 (2.4)	4.1 (3.0)	0.5
Biopsy approach, n (%)							0.63
Transperineal	322 (77)	47 (81)	15 (71.4)	51 (70.8)	37 (77.1)	172 (78.2)	
Transrectal	97 (23)	11 (19)	6 (28.6)	21 (29.2)	11 (22.9)	48 (21.8)	
Distress Community Index Quintiles, n (%)							**<.0001**
Prosperous (0-20)	133	17 (29.8)	7 (35.0)	9 (12.9)	16 (34.0)	84 (39.1)	
Comfortable (20-40)	94	14 (24.6)	3 (15)	10 (14.3)	11 (23.4)	56 (26.1)	
Mid-tier (40-60)	83	18 (31.6)	4 (20.0)	6 (8.6)	11 (23.4)	44 (20.5)	
At risk (60-80)	60	6 (10.5)	2 (10.0)	26 (37.1)	5 (10.6)	21 (9.8)	
Distressed (80-100)	39	2 (3.5)	4 (20.0)	19 (27.1)	4 (8.5)	10 (4.7)	

BMI = body mass index; DRE = digital rectal examination; IQR = interquartile range; MRI = magnetic resonance imaging; No. = number; PCa = prostate cancer; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate specific antigen; SB = standard biopsy; SD = standard deviation; TB = target biopsy

Figure 2 - Patients' self-assessed pain level during transperineal or transrectal prostate biopsy under local anesthesia

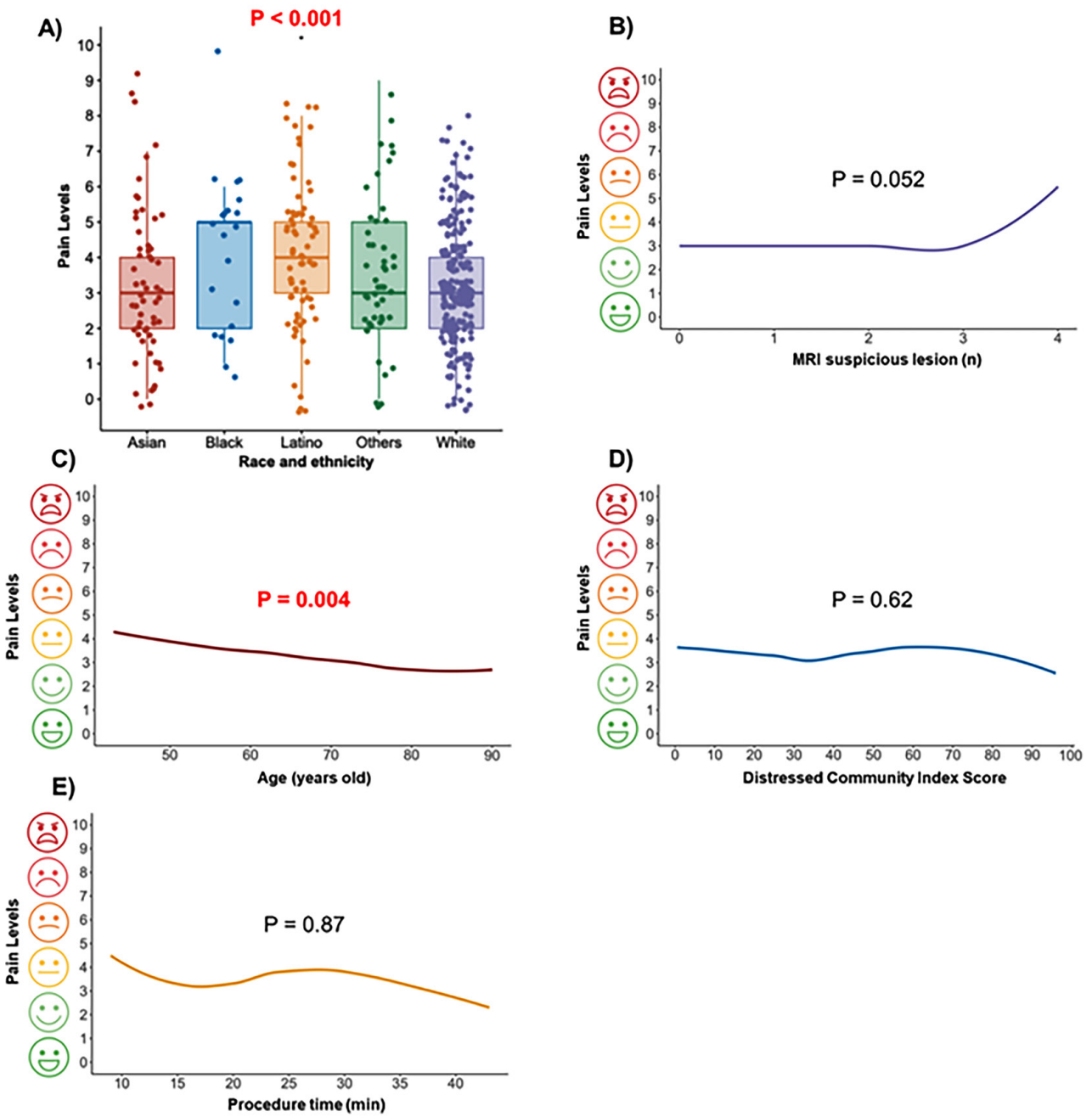


Our study is the first to demonstrate an ethnic difference in pain during prostate biopsy. While this has not been shown before in the setting of prostate biopsy, there have been other studies which have exhibited that Latino and Black patients have increased pain perception. Perry et al. performed a systematic review of a variety of procedures including tonsillectomy, hip and knee arthroplasty demonstrating that there were significantly higher preoperative and postoperative pain intensity scores reported by African American and Hispanic individuals compared with non-Hispanic whites (21). Meanwhile, in the laboratory setting, Hastie et al. experimented on thermal, pressure, and ischemic pain perception between non-Hispanic whites, non-white Hispanics and African Americans, and demonstrated that African Americans and Hispanics had decreased pain tolerance (22).

The reason for difference in pain perception in ethnicity is unclear, but it is likely multifactorial. One possible reason for increased pain in certain ethnicities is the presence of different genetic predispositions. In the review by Perry et al., they reported on studies showing that polymorphisms in the genes Catechol-O-methyltransferase (COMT) and mu opioid receptor 1 (OPRM1) were associated with pain. Specifically, there is a single nucleotide polymorphism (SNP) in codon 158 (val158met) which affects COMT protein stability and has been associated with pain (23). Lee et al. demonstrated that COMT polymorphisms associated with high pain sensitivity were more prevalent in African Americans than Caucasian patients (24). Meanwhile Hastie et al. demonstrated that a specific polymorphism for OPRM1 was present in about 28% of Hispanic patients and it was associated with increased pain sensitivity for Hispanic patients but not for Caucasian patients (22). While no study has looked specifically at genetic predispositions to prostate biopsy pain, there is evidence that genetic polymorphisms exist associated with pain.

Socioeconomic status has also been reported to be associated with increased postoperative pain. Additionally, it has been reported that there are inequalities in SES strongly patterned by race including African Americans persistently having higher levels of poverty than Caucasian people (25). Furthermore, lower SES has been shown to be associated with poorer mental health and increased psychologic stress which may impact pain per-

Figure 3 - Distribution of Pain Levels (A). Reported pain levels by Number of MRI Suspicious Lesions (B), Age (C), DCI (D), Procedure Time (E)



Each graph represents the smoothed median pain scale across age, DCI, procedure time, or number of MRI-suspicious lesions, fitted using LOESS regression to highlight the general trend in pain scale variation with each category. P value of MRI suspicious lesion was not statistically significant (p=0.052) on univariable analysis but significant (p=0.008) on multivariable analysis.

Table 2A - Pathologic Outcomes of MRI/TRUS fusion prostate biopsy.

	PIRADS 1-2						PIRADS 3-5					
	Asian	Black	Latino	Other	White	p	Asian	Black	Latino	Other	White	p
No. of Patients, n (%)	17	7	15	8	46		41	14	57	40	174	
PCa detection SB + TB, N (%)	4 (23.5)	4 (57.1)	7 (46.7)	2 (25)	19 (41.3)	0.43	32 (78.1)	11 (78.6)	35 (61.4)	32 (80)	130 (74.7)	0.20
PCa detection SB, N (%)	4 (23.5)	4 (57.1)	7 (46.7)	2 (25)	19 (41.3)	0.43	24 (58.5)	10 (71.4)	30 (52.6)	22 (55)	102 (58.6)	0.76
PCa detection TB, N (%)	-	-	-	-	-	-	28 (68.3)	11 (78.6)	31 (54.4)	28 (70)	117 (67.2)	0.30
CSPCa SB + TB, N (%)	2 (11.8)	1 (14.3)	4 (26.7)	1 (12.5)	3 (6.5)	0.35	28 (68.3)	10 (71.4)	32 (56.1)	23 (57.5)	103 (59.2)	0.65
CSPCa SB, N (%)	2 (11.8)	1 (14.3)	4 (26.7)	1 (12.5)	3 (6.5)	0.35	15 (36.6)	8 (57.1)	22 (38.6)	16 (40)	68 (39.1)	0.73
CSPCa TB, N (%)	-	-	-	-	-	-	25 (61)	9 (64.3)	28 (49.1)	21 (52.5)	97 (55.8)	0.73

CSPCa = clinically significant prostate cancer; No. = number; PCa = prostate cancer; PIRADS = Prostate Imaging Reporting and Data System; SB = systematic biopsy; TB = target biopsy

Table 2B - Perioperative outcomes after MRI/TRUS fusion prostate biopsy.

	Race/Ethnic Groups						
	All	White	Black	Latino	Asian	Other	p
Number of patients, n (%)	419	220 (52.5)	21 (5)	72 (17.2)	58 (13.8)	48 (11.5)	
Pain during biopsy, median (IQR)	3 (2-5)	3 (2-4)	5 (2-5)	4 (3-5)	3 (2-4)	3 (2-5)	0.01
Procedure time for PBx, minutes, median (IQR)	18 (15-21)	18 (16-20)	17 (15-21)	18 (15-20)	18 (14-22)	20 (17-25)	0.06

IQR = interquartile range; PBx = prostate biopsy

Table 3 - Univariable and Multivariable analyses for pain level during prostate biopsy under local anesthesia.

	Univariate			Multivariate		
Variables	β	CI (95%)	p	β	CI (95%)	**p**
Age, year	-0.03	-0.06 to -0.01	**0.004**	-0.03	-0.06 to -0.01	**0.006**
Family History PCa	-0.49	-0.92 to -0.07	**0.02**			
BMI	-0.01	-0.03 to 0.01	0.40			
Biopsy history						
Previous Negative biopsy vs Naïve	-0.14	-0.65 to 0.37	0.58			
Previous Positive biopsy vs Naïve	0.17	-0.34 to 0.69	0.50			
PSA, ng/mL	-0.003	-0.013 to 0.006	0.52			
PSA density*, ng/mL²	-0.11	-0.57 to 0.36	0.65			
Race						
Asian vs NH-White	-0.05	-0.61 to 0.51	0.85	-0.11	-0.68 to 0.45	0.69
Hispanic vs HN-White	0.77	0.26 to 1.29	**0.003**	0.87	0.30 to 1.45	**0.003**
Black vs NH-White	0.94	0.07 to 1.81	**0.03**	1.16	0.29 to 2.03	**0.009**
Others vs NH-White	0.27	-0.34 to 0.87	0.39	0.17	-0.45 to 0.79	0.59
DRE, suspicious vs non-suspicious	0.12	-0.32 to 0.56	0.59			
Prostate Volume, cc	-0.005	-0.010 to 0.001	0.11			
No. MRI lesions	0.23	-0.002 to 0.462	0.052	0.32	0.08 to 0.55	**0.008**
MRI lesion size, mm	0.006	-0.023 to 0.034	0.69			
PIRADS 3-5 vs PIRADS 1-2	0.31	-0.14 to 0.76	0.18			
No. TB cores taken	-0.04	-0.12 to 0.05	0.40			
Prostate biopsy approach TP vs TR	0.03	-0.04 to 0.10	0.37	0.01	-0.43 to 0.45	0.95
No. Bx (SB + TB) cores taken	-0.16	-0.60 to 0.29	0.49			
Procedure Time (min)	0.003	-0.033 to 0.039	0.16			
Presence of Prostate Cancer	-0.11	-0.51 to 0.28	0.57			
Distress Community Index Score (0-100)	-0.001	-0.009 to 0.005	0.62	-0.006	-0.014 to 0.001	0.10

PIRADS = Prostate Imaging Reporting and Data System; MRI = magnetic resonance imaging; OR = odds ratio; CI = confidence interval; PCa = prostate cancer; CSPCa = Clinically significant PCa (Grade Group > 1); DRE = digital rectal examination; DRE = digital rectal examination; NH = non-Hispanic
*PSA density was calculated per 0.01 unit.

ception (26). Thurston et al. found in a systematic review that lower SES was associated with worse pain perception after various procedures (8). Pain was not associated with DCI in our study, which could be related to its limited ability to accurately assess an individual patient's SES given that it is based on location (zip code).

Our study also demonstrated that pain was associated with younger age Younger age was also associated with prostate biopsy pain in studies by Marra et al. and Gomez-Gomez et al. (27, 28). As younger patients have had less exposure to health care and different medical interventions, increased pain perception may be attributed to a decreased familiarity with pain from such procedures (27, 28). We additionally demonstrated increased pain scores with a higher number of MRI lesions, despite number of biopsy cores, prostate size, operative time and lesion size not being significant. Upon examining Figure-3 the increased pain was seen in those with four different target lesions. It is possible that excessive manipulation of the needle and probe could lead to more discomfort and increase patient anxiety.

We have identified several patient characteristics associated with increased pain during biopsy: younger age, Latino ethnicity, Black race and multiple MRI lesions. Recognizing populations who are at more risk of severe pain is important as such patients can be counseled to undergo a biopsy under sedation. Cricco-Lizza et al. demonstrated that transperineal prostate biopsies under local anesthesia is safe and has comparable outcomes compared to those done under sedation, but median pain scores were 3/10 versus 0/10, respectively (29). Escobar et al. also demonstrated significant decrease in pain scores during transrectal prostate biopsy performed with the use of nitrous oxide in a randomized trial (30). Pre-procedure counseling regarding higher pain levels and discussion of additional strategies to mitigate pain can be performed in these populations with increased pain risk.

There are some limitations of our study. First, race and ethnicity can be broken down further to specific countries where patients' families are from which can further impact genetic and cultural factors. Second, DCI uses zip codes to determine SES at a community-level and is therefore limited in its ability to accurately identify SES at an individual level for each patient. Meanwhile, strengths include the diversity of the patient population and that the data is reliable given that it was collected prospectively through a well-managed protocol in a center of extensive experience in both transperineal and transrectal prostate biopsy (13-15).

CONCLUSIONS

We demonstrate that the risk factors for higher pain levels during prostate biopsy under local anesthesia are Black and Latino race, younger age and increased number of MRI lesions. Meanwhile, socioeconomic status did not have an impact on pain levels. Upon counseling patients for prostate biopsy, risk factors of higher pain levels may be discussed to ensure they are well-informed when making the decision to have a biopsy performed under local anesthesia versus sedation. Further validation studies are warranted.

ABBREVIATIONS

PBx = Prostate Biopsy
LA = Local Anesthesia
TP = Transperineal
TR = Transrectal
DCI = Distressed Community Index
SES = Socioeconomic Status
mpMRI = Multiparametric MRI
PIRADS = Prostate Imaging Reporting & Data System
CSPCa = Clinically Significant Prostate Cancer

ACKNOWLEDGEMENTS

Kevin Joseph Chua and Lorenzo Storino Ramacciotti contributed similarly as first author

We sincerely appreciate Tracy Campanelli Palmer, Clinical Research Regulatory Administrator, for her invaluable support and expertise in managing the prostate biopsy database. We also extend our gratitude to Daianna Lovos, Ultrasound Technologist, for her unwavering daily assistance in coordinating logistics.

ETHIC STATEMENT

Principles of Helsinki Declaration were followed in lieu of formal ethics committee approval

CONFLICT OF INTEREST

Inderbir Gill has equity interest in OneLine Health and Karkinos.
Andre Abreu is a proctor and speaker for Sonablate and EDAP, proctor and has research grant with Koelis; clinical trial with Francis; consultant for Procept BioRobotics. Other authors do not have any competing interests.

REFERENCES

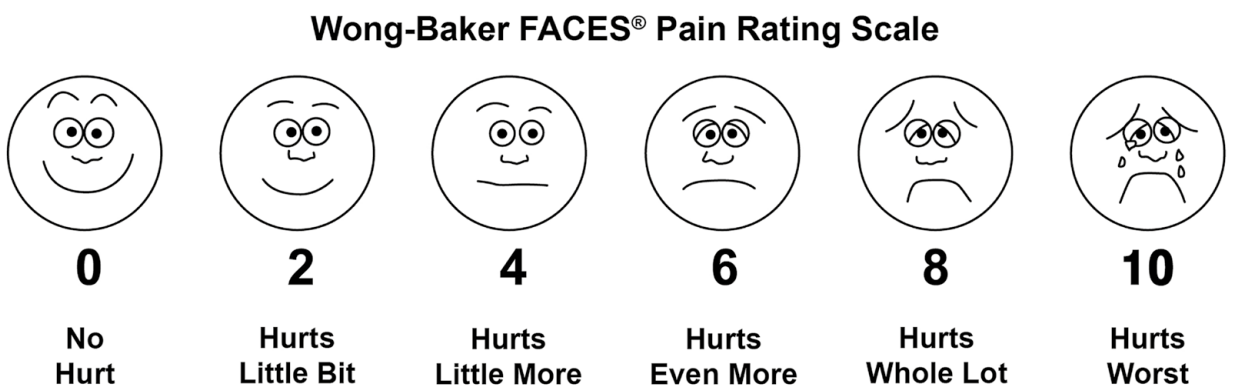
1. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, et al. Systematic review of complications of prostate biopsy. Eur Urol. 2013;64(6):876-92. doi: 10.1016/j.eururo.2013.05.049
2. Morote J, Paesano N, Picola N, Muñoz-Rodriguez J, Ruiz-Plazas X, Muñoz-Rivero MV, et al. Validation of the Barcelona-MRI predictive model when PI-RADS v2.1 is used with transperineal prostate biopsies. Int Braz J Urol. 2024;50(5):595-604. doi: 10.1590/S1677-5538.IBJU.2024.0204
3. Paesano N, Catalá V, Tcholakian L, Alomar X, Barranco M, Trilla E, et al. The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies. Int Braz J Urol. 2024;50(3):296-308. doi: 10.1590/S1677-5538.IBJU.2024.0061
4. Zhou Z, Li T, Zhang Y, Zhou X, Wang X, Cui D, et al. Biplanar or Monoplanar Prostate Biopsy: Should Transrectal and Transperineal Ap-proaches be Combined for Prostate Cancer Detection? Int Braz J Urol. 2025 Mar-Apr;51(2):e20240630. doi: 10.1590/S1677-5538.IBJU.2024.0630.
5. Vega J, Emara AK, Orr M, Klika AK, Piuzzi NS, Cleveland Clinic Arthroplasty Outcomes Research Group. Demographic and socioeconomic determinants are associated with poor preoperative patient-reported pain and function in primary TKA: a cohort study of 14,079 patients. J Bone Joint Surg Am. 2023;105(4):286-92. doi: 10.2106/JBJS.22.00565
6. Feldman CH, Dong Y, Katz JN, Donnell-Fink LA, Losina E. Association between socioeconomic status and pain, function and pain catastrophizing at presentation for total knee arthroplasty. BMC Musculoskelet Disord. 2015;16(1):18. doi: 10.1186/s12891-015-0475-8
7. Rahim-Williams FB, Riley JL 3rd, Herrera D, Campbell CM, Hastie BA, Fillingim RB. Ethnic identity predicts experimental pain sensitivity in African Americans and Hispanics. Pain. 2007;129(1-2):177-84. doi: 10.1016/j.pain.2006.12.016
8. Thurston KL, Zhang SJ, Wilbanks BA, Billings R, Aroke EN. A systematic review of race, sex, and socioeconomic status differences in postoperative pain and pain management. J Perianesth Nurs. 2023;38(3):504-15. doi: 10.1016/j.jopan.2022.10.007
9. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. Eur Urol. 2019;76(3):340-51. doi: 10.1016/j.eururo.2019.02.033
10. Tafuri A, Ashrafi AN, Palmer S, Shakir A, Cacciamani GE, Iwata A, et al. One-stop MRI and MRI/transrectal ultrasound fusion-guided biopsy: an expedited pathway for prostate cancer diagnosis. World J Urol. 2020;38(4):949-56. doi: 10.1007/s00345-019-02867-x
11. Kaneko M, Medina LG, Lenon MSL, Hemal S, Sayegh AS, Jadvar DS, et al. Transperineal vs transrectal magnetic resonance and ultrasound image fusion prostate biopsy: a pair-matched comparison. Sci Rep. 2023;13(1):13457. doi: 10.1038/s41598-023-40605-5
12. Tafuri A, Iwata A, Shakir A, Iwata T, Gupta C, Sali A, et al. Systematic biopsy of the prostate can be omitted in men with PI-RADS™ 5 and prostate specific antigen density greater than 15. J Urol. 2021;206(2):289-97. doi: 10.1097/JU.0000000000001735
13. Ramacciotti LS, Strauss D, Cei F, Kaneko M, Mokhtar D, Cai J, et al. Transperineal versus transrectal MRI/TRUS fusion-guided prostate biopsy in a large, ethnically diverse, and multiracial cohort. Int Braz J Urol. 2024;50(5):616-28. doi: 10.1590/S1677-5538.IBJU.2024.0354
14. Kaneko M, Medina LG, Lenon MSL, Sayegh AS, Lebastchi AH, Cacciamani GE, et al. Transperineal magnetic resonance imaging/transrectal ultrasonography fusion prostate biopsy under local anaesthesia: the "double-freehand" technique. BJU Int. 2023;131(6):770-4. doi: 10.1111/bju.15985

15. Nassiri N, Beeder L, Nazemi A, Asanad K, Um J, Gill I, et al. Step-by-step: fusion-guided prostate biopsy in the diagnosis and surveillance of prostate cancer. Int Braz J Urol. 2019;45(6):1277-8. doi: 10.1590/S1677-5538.IBJU.2019.06.24
16. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016;40(2):244-52. doi: 10.1097/PAS.0000000000000530
17. Cheng E, Davuluri M, Lewicki PJ, Hu JC, Basourakos SP. Developments in optimizing transperineal prostate biopsy. Curr Opin Urol. 2022;32(1):85-90. doi: 10.1097/MOU.0000000000000947
18. Li M, Wang Z, Li H, Yang J, Rao K, Wang T, et al. Local anesthesia for transrectal ultrasound-guided biopsy of the prostate: a meta-analysis. Sci Rep. 2017;7:40421. doi: 10.1038/srep40421
19. Office of Policy for Extramural Research Administration. NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research 2025 Available from: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-25-131.html>.
20. Storino Ramacciotti L, Kaneko M, Rodler S, Mohideen M, Cai J, Liang G, et al. A sustainable and expedited "One-Stop" prostate cancer diagnostic pathway to reduce environmental impact and enhance accessibility. BJUI Compass. 2024;5(12):1278-87. doi: 10.1002/bco2.447
21. Perry M, Baumbauer K, Young EE, Dorsey SG, Taylor JY, Starkweather AR. The influence of race, ethnicity and genetic variants on postoperative pain intensity: an integrative literature review. Pain Manag Nurs. 2019;20(3):198-206. doi: 10.1016/j.pmn.2018.09.005
22. Hastie BA, Riley JL 3rd, Kaplan L, Herrera DG, Campbell CM, Virtusio K, et al. Ethnicity interacts with the OPRM1 gene in experimental pain sensitivity. Pain. 2012;153(8):1610-9. doi: 10.1016/j.pain.2012.03.022
23. Diatchenko L, Nackley AG, Slade GD, Bhalang K, Belfer I, Max MB, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain. 2006;125(3):216-24. doi: 10.1016/j.pain.2006.05.027
24. Lee C, Liptan G, Kantorovich S, Sharma M, Brenton A. Association of catechol-O-methyltransferase single nucleotide polymorphisms, ethnicity, and sex in a large cohort of fibromyalgia patients. BMC Rheumatol. 2018;2:38. doi: 10.1186/s41927-018-0045-4
25. Williams DR, Mohammed SA, Leavell J, Collins C. Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. Ann N Y Acad Sci. 2010;1186:69-101. doi: 10.1111/j.1749-6632.2009.05339.x
26. Khalatbari-Soltani S, Blyth FM. Socioeconomic position and pain: a topical review. Pain. 2022;163(10):1855-61. doi: 10.1097/j.pain.0000000000002634
27. Marra G, Zhuang J, Marquis A, Zhao X, Calleris G, Kan Y, et al. Pain in men undergoing transperineal free-hand multiparametric magnetic resonance imaging fusion targeted biopsies under local anesthesia: outcomes and predictors from a multicenter study of 1,008 patients. J Urol. 2020;204(6):1209-15. doi: 10.1097/JU.0000000000001234
28. Gómez-Gómez E, Ramírez M, Gómez-Ferrer A, Rubio-Briones J, Iborra I, Carrasco-Valiente J, et al. Assessment and clinical factors associated with pain in patients undergoing transrectal prostate biopsy. Actas Urol Esp. 2015;39(7):414-9. doi: 10.1016/j.acuro.2015.01.007
29. Cricco-Lizza E, Wilcox Vanden Berg RN, Laviana A, Pantuck M, Basourakos SP, Salami SS, et al. Comparative effectiveness and tolerability of transperineal MRI-targeted prostate biopsy under local versus sedation. Urology. 2021;155:33-8. doi: 10.1016/j.urology.2021.06.023
30. Escobar AJ, Krishna S, Flowers KM, Abello A, Gershman B, Wagner AA, et al. Practical use of self-adjusted nitrous oxide during transrectal prostate biopsy: a double-blind randomized controlled trial. J Urol. 2024;211(2):214-22. doi: 10.1097/JU.0000000000003789

Correspondence address:
Andre Luis Abreu, MD
USC Institute of Urology
University of Southern California
1441 Eastlake Ave, Suite 7416,
Los Angeles, California 90089
Telephone: +1-323-865-3700
E-mail: andre.abreu@med.usc.edu

APPENDIX

Supplemental Figure - Wong-Baker FACES Pain Rating Scale.



ORIGINAL ARTICLE

Vol. 52 (3): e20250539, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0539

Concomitant Bladder Neck Incision in Patients with Posterior Urethral Valve and Bladder Neck Hypertrophy: Short-term Outcomes of a Randomized Controlled Trial

Ahmed ELghareeb [1], Mohamed Dawaba [1], Mona Eldeeb [2], Abdelwahab Hashem [3], El-husseiny I. Ibrahim [1], Ahmed Abdelhalim [1, 4]

[1] Department of Urology, Mansoura Urology and Nephrology Center, Mansoura University, Mansoura, Egypt; [2] Department of Radiology, Mansoura Urology and Nephrology Center, Mansoura University, Mansoura, Egypt; [3] Faculty of Medicine, Delta University for Science and Technology, Dakahlia, Egypt; [4] Department of Urology, West Virginia University, Morgantown, WV, USA.

ABSTRACT

Introduction: Concomitant bladder neck incision (BNI) with posterior urethral valve ablation (VA) was proposed to mitigate the long-term sequela of posterior urethral valve (PUV) and reduce the reoperation rates. This study aimed to investigate the short-term outcomes of concomitant BNI and VA, particularly short-term reoperation rates.

Patients and Methods: Patients with PUV and bladder neck hypertrophy on preoperative imaging were randomized to undergo VA only or VA with concomitant BNI. Surgical reoperation within one year was the primary endpoint. Renal function, UTI, hydronephrosis and VUR improvement at one year were secondary endpoints.

Results: Sixty-three patients were included in the final analysis, 33 in VA group (group A) and 30 in concomitant BNI and VA group (group B). After one year of follow-up, the reoperation rate was similar [5(15.2%) in group A and 3(10%) in group B, p=0.18]. The median (IQR) nadir serum creatinine was lower in group B [0.2 (0.1-0.3) vs. 0.2 (0.2-0.4) mg/dL in group A, p=0.049]. The last follow-up serum creatinine, eGFR [107 (96-163) in group A vs. 139(103-165) mL/min/1.73 m2 in groups B, p=0.37], and febrile UTI rates were not different between the two groups. Hydronephrosis improved/ resolved in 27 (40.9%) renal units in group A vs. 33 (55%) renal units in group B (p=0.286). Vesicoureteral reflux improved/ resolved in 23(34.8%) and 12 (20%) renal units in group A and B, respectively (p=0.074).

Conclusion: Concomitant BNI with VA does not confer a lower short-term reoperation rate or better upper urinary tract outcomes compared to VA only.

ARTICLE INFO

Ahmed Abdelhalim
https://orcid.org/0000-0002-4451-0032

Keywords:
Urinary Bladder Neck Obstruction; Reoperation; Ablation Techniques

Submitted for publication: September 17, 2025

Accepted after revision: January 10, 2026

Published as Ahead of Print: January 28, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

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

INTRODUCTION

Despite our improved understanding and the proactive management of bladder dysfunction in patients with posterior urethral valves (PUV), the long-term morbidity remains substantially high with 20-30% of patients progressing to end-stage renal disease in adolescence or early adulthood (1, 2). Bladder neck obstruction was hypothesized as one of the factors contributing to the bladder dysfunction seen in most patients after valve ablation (VA). Alpha-blocker treatment, clean intermittent catheterization (CIC), overnight bladder drainage, and bladder neck incision (BNI) were proposed as treatment options (2-4). BNI is viewed as the most definitive treatment of bladder neck obstruction with controversial benefits in PUV population. Kajbafzadeh et al. reported decreased long-term need for anticholinergics and CIC when BNI was concomitantly performed with VA. Further, BNI was associated with reduced short-term reoperation rates in their cohort. No short-term reinterventions were required in their cohort when BNI was concurrently done with VA compared to 24% reintervention rate in patients treated with VA only (5). The short-term benefits of BNI in PUV population is as debatable as its long-term gains. In a retrospective study by Abdelhalim et al., the short-term reoperation rate was not different among patients treated with VA or concomitant BNI and VA (6). To solve this controversy, this randomized controlled study was conducted to assess the effect of concomitant BNI on the short-term reoperation rates in patients with PUV. We hypothesize that concomitant BNI and VA are associated with less short-term reoperation rates than VA only.

PATIENTS AND METHODS

Patients

The study was approved by the Institutional Review Board (MS.21.09.1655) and was registered on ClinicalTrials.gov (NCT05087537). Patients younger than 12 years diagnosed with PUV at a single tertiary center between January 2020 and January 2022, were screened for eligibility. Patients were considered eligible if they had evidence of bladder neck hypertrophy, defined as bladder neck shouldering on preoperative VCUG. Bladder neck hypertrophy was confirmed by visualizing elevated posterior lip of the bladder neck on cystoscopic examination (7). Patients were excluded if they had prior surgical treatment for PUV. Parents/ legal guardians of eligible patients were approached by the study team, and the study methodology was thoroughly explained. The pros and cons of each treatment approach were discussed. Parents who agreed to enroll their children in the study provided informed consents. Patients were randomly assigned to one of the treatment groups using the closed envelop method in a 1:1 ratio. Patients in group A were managed with endoscopic VA only, whereas group B patients were treated with concomitant VA and BNI. Surgeries were conducted by one of three fellowship-trained pediatric urologists.

Baseline evaluation

Baseline evaluation included history, physical exam, and serum chemistry with calculation of the estimated glomerular filtration rate (eGFR) using the modified Schwartz formula (8), renal bladder ultrasound, and VCUG.

Surgical technique

Endoscopic valve ablation:

Transurethral VA was done under direct vision using the pediatric cold knife urethrotome. The valve leaflets were incised at 5, 7, and 12 o'clock positions.

Bladder neck incision:

In children assigned to concomitant BNI, an additional single incision through the bladder neck was made at 6 o'clock until the bladder lumen was visible with the tip of the scope at the verumontanum (6). In both groups, a Foley catheter was left for 24-48 hours.

Follow-up

Patients were followed up every 3 months for at least one year. Follow-up entailed history with emphasis on febrile UTI. Laboratory evaluation included serum creatinine with calculation of eGFR. Follow-

up imaging included renal bladder ultrasound every 3 months. Hydronephrosis severity was graded according to the Society of Fetal Urology (SFU) Hydronephrosis grading system (9) and measuring the antero-posterior diameter of the renal pelvis. VCUG was repeated at 3 and 12 months postoperatively. Patients with high-grade vesicoureteral reflux (VUR) or high-grade hydronephrosis were maintained on continuous antibiotic prophylaxis. Oxybutynin treatment was selectively considered for patients with non-improving hydronephrosis in the absence of anatomic obstruction (10). Alpha-blocker treatment was not given to any of the study participants to avoid its confounding effects.

Study outcomes

Primary study outcome:

Surgical reoperation rates within one year of the primary surgery, including check cystoscopy with or without the need for ablation of valve remnants, BNI, or urinary diversion. The clinical indications for reoperation were recurrent febrile UTI, weak urine stream or repeated urinary retention. The laboratory indications for reoperation were renal functional deterioration in the absence of radiological improvement manifested by non-improved hydronephrosis or VUR, or persistent dilation of the posterior urethra on follow-up VCUG.

Secondary study outcomes:

- Renal function outcomes: nadir serum creatinine (lowest serum creatinine within one year of surgery), serum creatinine, eGFR at 12 months of follow-up, progression to chronic kidney disease defined as eGFR ≤ 60 mL/min/1.73 m2.
- Febrile UTIs defined as fever ≥ 38˚ C in with a positive urinalysis and a positive urine culture of an appropriately collected urine specimen.
- Hydronephrosis improvement, defined as complete hydronephrosis resolution or improvement by one or more grades according to the SFU grading system.
- VUR improvement, defined as complete VUR resolution or downgrading by one or more grades on VCUG according to the International Reflux Study Grading System.

Sample size

The study sample size was calculated based on a previous study (11) in which reoperation was needed in 24% of PUV patients treated with VA only compared to 0% in those treated with concomitant VA and BNI. The G-power statistical software (Universität Düsseldorf) was used with an effect size of 24%, alpha error 0.05, study power 0.80, and an expected dropout rate of 10%. The total sample size was 56 patients, 28 patients in each study group.

Statistical Analysis

Statistical analysis was done by the Statistical Package for Social Sciences "IBM SPSS Statistics (Version 27)". Numbers and percentages were used to describe categorical data. Quantitative data was presented as medians and interquartile ranges. Mann–Whitney test was used to compare continuous variables and Chi-squared or Fisher's exact tests for the categorical variables. P value ≤ 0.05 was used to indicate statistical significance. Outcomes were analyzed based on the intention to treat.

RESULTS

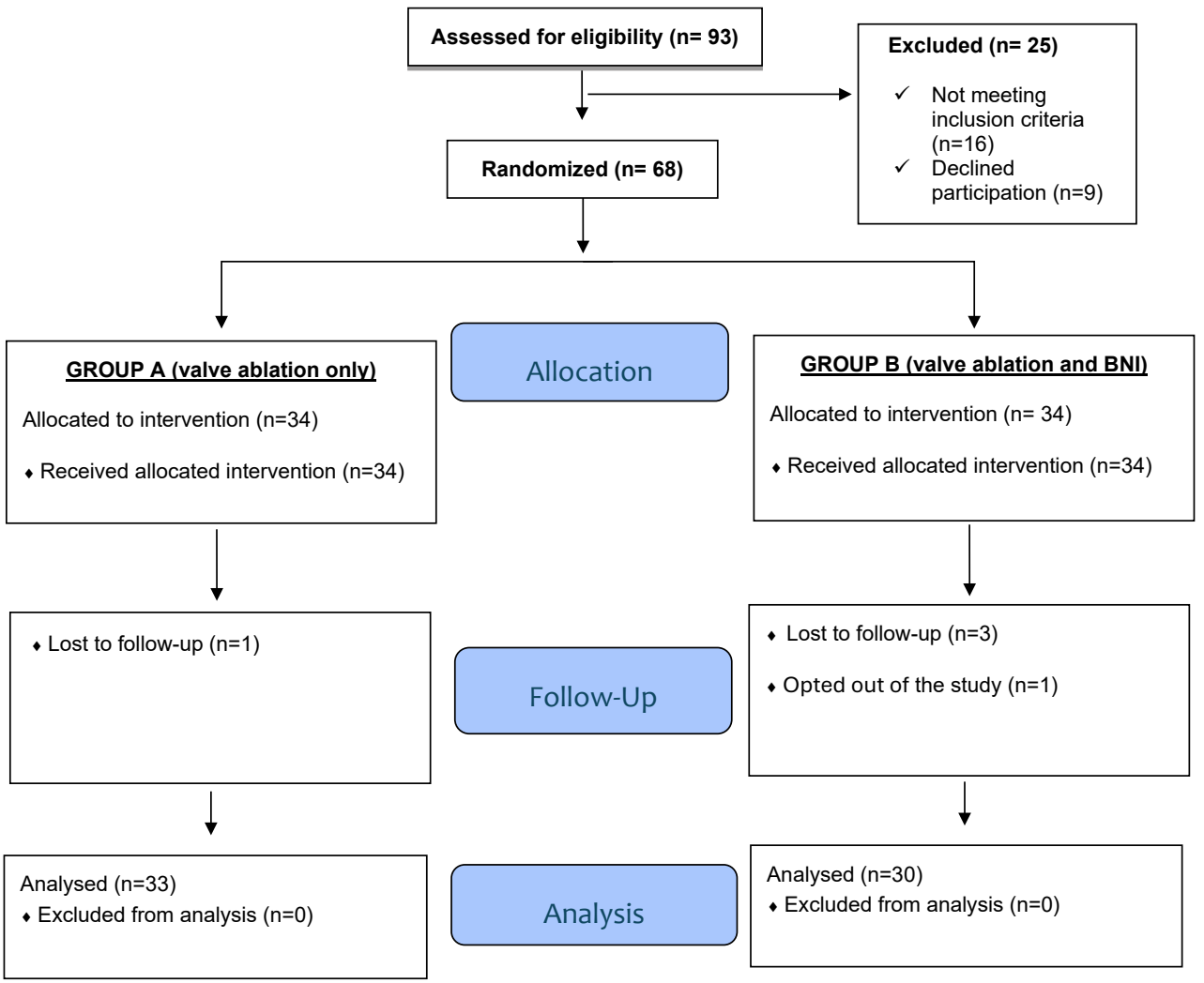
Study enrollment

Patients were recruited for participation in the study from January 2020 to January 2022. Out of 93 screened PUV patients, 16 patients did not meet the inclusion criteria (10 had prior surgical treatment of PUV, and 6 did not have high bladder neck on VCUG) and were excluded. Nine other patients refused to participate in the study.

Of the 68 patients enrolled in the study, 34 patients were assigned to group A (primary VA only) and 34 to group B (concomitant VA and BNI). After surgical intervention, one patient in group (A) and three patients in group (B) lost follow-up and were excluded from the analysis. Another group B patient opted out of the study during follow-up.

A total of 63 patients were included in the final analysis: 33 patients in VA (group A) and 30 patients in combined VA and BNI group (group B). The enrollment process is summarized in Figure-1.

Figure 1 - The study CONSORT flowchart.



Baseline demographics

Patients in group B were relatively younger. The median age at surgery was 4 and 1.75 months in groups A and B, respectively (p = 0.045). Otherwise, baseline demographics were similar between the study groups (Table-1). Overall, 37/63 (58.7%) of patients were suspected on prenatal imaging, 11 (17.5%) presented with febrile UTI, and 8 (12.7%) with urinary retention or urine stream abnormalities. Bilateral hydronephrosis was observed in 72.7% and 80% of group A and B, respectively (p =0.379). Oxybutynin treatment was administered in 3 (10%) patients in group A and 4 (12.1%) patients in group B for non-improving hydronephrosis after excluding bladder outlet obstruction at least 3 months following primary intervention. Baseline demographics are summarized in Table-1.

Study outcomes

The study outcomes are summarized in Table-2.

- **Reoperation rate within one year of follow-up:** Five patients (15.2%) in group A and 3 (10%) in group B required reoperation within one year of follow-up (p= 0.18). All patients who required reintervention were symptomatic.

Table 1 - Baseline demographics.

Baseline demographics	Group A: Valve ablation only (n =33)	Group B: Combined valve ablation and BNI (n = 30)	P value
Median age at surgery (IQR), months	4 (1.5-21.5)	1.75 (1-8.6)	0.045
Presentation (%)			
Antenatal hydronephrosis	18 (54.5)	19 (63.3)	
Febrile UTI	7 (21.2)	4 (13.3)	
Urine retention/ abnormal urine stream	6 (18.2)	2 (6.7)	0.452
Postnatal hydronephrosis	2 (6.1)	5 (16.7)	
Valve type (%)			
Type I	31 (93.9)	29 (96.7)	
Type III	2 (6.1)	1 (3.3)	0.612
Median baseline serum creatinine (IQR), mg/dl (mg/dl)	0.4 (0.3-0.8)	0.5 (0.3-0.73)	0.825
Median baseline eGFR (IQR), (mL/min/1.73 m^2)	66 (35.5-119)	59 (30.5-85.8)	0.401
Renal units with baseline hydronephrosis (%)	55/66 (83.3)	54/60 (90)	0.274
Baseline hydronephrosis laterality (%)			0.379
No	2 (6.1)	0	
Unilateral	7 (21.2)	6 (20)	
Bilateral	24 (72.7)	24 (80)	
Baseline highest grade of hydronephrosis (%)			0.073
No	2 (6.1)	0	
Grade I	5 (15.2)	2 (6.7)	
Grade II	11 (33.3)	7 (23.3)	
Grade III	14 (42.4)	14 (46.7)	
Grade IV	1 (3)	7 (23.3)	
Renal units with baseline vesicoureteral reflux (%)	31/66 (47)	21/60 (35)	0.137
Baseline vesicoureteral reflux laterality (%)			0.309
No	13 (39.4)	14 (46.7)	
Unilateral	9 (27.3)	11 (36.7)	
Bilateral	11 (33.3)	5 (16.7)	
Baseline highest grade of vesicoureteral (%)			0.440
No	13 (39.4)	14 (46.7)	
Grade I	0	0	
Grade II	1 (3)	0	
Grade III	0	0	
Grade IV	4 (12.1)	1 (3.3)	
Grade V	15 (45.5)	15 (50)	

p-value is in bold when differences were significant

Table 2 - Study outcomes at 12 months.

Study outcomes	Group A: Valve ablation only (n =33)	Group B: Combined valve ablation and BNI (n = 30)	P value
Overall reintervention (%)	5 (15.2)	3 (10)	
Check cystoscopy only	1 (3)	3(10)	
Ablation of valve remnants	0 (0)	0(0)	0.18
BNI	3 (9)	0(0)	
Ablation of valve remnants and BNI	1 (3)	0(0)	
Median nadir serum creatinine (IQR), mg/dl	0.2 (0.2 - 0.4)	0.2 (0.1 - 0.3)	0.049
Median serum creatinine at 12 months (IQR), mg/dl	0.3 (0.2 - 0.45)	0.2 (0.2 - 0.4)	0.09
Median eGFR (IQR) at 12 months, mL/min/1.73 m^2	107 (89.5-163)	139 (102-165)	0.374
Febrile UTI during follow up, patients (%)	9 (27.3)	7 (23.3)	0.778
Renal units with improved/ resolved hydronephrosis (%)	27/66 (40.9%)	33/60 (55%)	0.286
Renal units with improved/ resolved VUR (%)	23/66 (34.8%)	12/60 (20%)	0.074

p-value is in bold when differences were significant

In group A, the indications for reintervention were breakthrough UTI in 3 patients, difficulty and a weak urinary stream in one patient, and UTI with a weak urine stream in one patient. One patient had diagnostic cystoscopy with no evidence of bladder outlet obstruction, 3 had BNI, and one had ablation of valve remnants and BNI as salvage treatment for symptomatic patients. The indications for intervention in group B patients were recurrent breakthrough UTI in two patients and repeated urinary retention in one patient. All 3 patients in group B who required reoperation had check cystoscopies that ruled out anatomic bladder outlet obstruction, and no further intervention was deemed necessary.

- **Renal function outcomes**
  The median (IQR) nadir serum creatinine was lower in group B [0.2 (0.1-0.3) mg/dL vs 0.2 (0.2-0.4) mg/dL in group A, p=0.049]. The median serum creatinine and eGFR at 12 months of follow-up were not significantly different between the study groups. Five (15.2%) group A and 3 (10%) group B patients had eGFR < 60 mL/min/1.73 m2 at 12 months (Fisher's exact p = 0.710).
- **Febrile UTI**
  Nine patients (27.3%) in group A and 7 (23.3%) in group B had febrile UTIs during follow up (p = 0.778).
- **Follow-up imaging**
  Twenty-seven (40.9%) renal units in group A and 33 (55%) renal units in group B had improved/resolved hydronephrosis (p= 0.286). Vesicoureteral reflux improved/ resolved in 23 (34.8%) and 12 (20%) renal units in groups A and B, respectively (p = 0.074).

DISCUSSION

Following endoscopic ablation of PUV, vigilant monitoring and proactive management of the underlying bladder dysfunction are the pillars of modern urologic management of PUV. Left untreated, bladder dysfunction contributes to hydronephrosis and VUR persistence, increased risk of UTI and incontinence, and accelerates renal damage and progression to end-stage renal dis-

ease. In 1982, Dr. Mitchell coined the term valve bladder syndrome to describe the bladder dysfunction seen in 75-80% of patients following PUV ablation (12). Some of the theorized mechanisms for valve bladder syndrome are detrusor hypertrophy, increased extracellular matrix deposition, bladder wall ischemia, diminished bladder sensations, incomplete bladder emptying, and high urine output resulting from poor renal tubular concentration capacity. In addition to these possible causes, bladder neck obstruction caused by blader neck hypertrophy or dyskinesis can interfere with bladder emptying and contribute to elevated bladder pressures, detrusor decompensation and eventually myogenic failure (2, 7).

The diagnosis of bladder neck obstruction in children with PUV is challenging. To date, there is no consensus on how to define bladder outlet obstruction in children (13). As in this study, the radiologic and endoscopic appearance of the bladder neck was used by some investigators to diagnose bladder neck hypertrophy (7, 14). Glassberg and Combs believed that diagnosing bladder neck obstruction requires videourodynamic documentation of elevated voiding pressure, and obstructed uroflow with a silent electromyogram (3).

Alpha blockers, CIC, overnight bladder drainage, bladder neck botulinum toxin injection, and BNI were proposed as therapeutic options for bladder neck obstruction in PUV with varying results and limitations (2, 5, 6, 15, 16). For instance, some studies reported subjective improvement of the voiding pattern with decreased maximum voiding detrusor pressure, increased Qmax, and reduced postvoid residual (PVR) with alpha blocker treatment (4, 17, 18). Bajpai reported improved radiological appearance of BN hypertrophy, reduced PVR, and increased bladder capacity following prazosin treatment in PUV patients (19). Mendez-Serrano reported improved hydronephrosis and decreased risk of progression of chronic kidney disease when comparing patients treated with and without alpha blockers (20). Conversely, botulinum toxin injection into the bladder neck of patients with blader neck dysfunction following VA failed to improve urodynamic parameters, hydronephrosis or VUR resolution in a study by Mokhless et al. (15). Likewise, Sarin et al. failed to demonstrate any urodynamic benefit when BNI was combined with VA (14). Singh et al. reported improved Qmax and PVR with concomitant BNI, but similar compliance, detrusor overactivity, end-filling detrusor pressure, maximum Pdet at Qmax and VUR resolution rates in a prospective randomized study (21).

BNI is considered the most definitive treatment of bladder neck obstruction and was widely practiced in patients with PUV in the 1950s. This practice was later abandoned for fear of incontinence and risk of retrograde ejaculation (22). Concomitant VA and BNI was proposed as one-stop treatment to relieve bladder outlet obstruction, dramatically decrease voiding pressures, and decompress the dilated upper tracts. Recent data showing no ill effects of BNI on continence and antegrade ejaculation provided assurance to advocates of this approach. In a comparative study, 22 patients treated with VA and BNI had a significantly lower maximal voiding pressure (53±15cm H2O) and no detrusor overactivity, whereas 24 patients treated with VA only had Pdet maximal voiding pressure of 87±45cm H2O and 25% had detrusor overactivity. These favorable urodynamic effects were associated with less long-term need for anticholinergic treatment and CIC in patients treated with concomitant VA and BNI (5). Long-term follow-up of 301 patients treated with concurrent BNI and PUV ablation by the same group showed improved hydronephrosis from 88.3% at baseline to 24.3% and improved VUR from 62.5% to 6.6% after a mean follow-up of 5.1± 2.8 years. None of those patients had myogenic failure (23).

In addition to these potential long-term benefits of concomitant BNI, Kajbafzadeh et al. reported additional short-term advantage with lower rates of readmission and short-term reoperation. Patients treated with VA only had a reoperation rate of 24% compared to 0% in patients treated with concomitant BNI and VA (5). In our analysis, the reoperation rate within one year was similar with both approaches. 15% of patients treated with VA only and 10% of patients treated with concomitant VA and BNI failed to demonstrate clinical, laboratory, or radiological improvement and eventually required at least check cystoscopy to rule out residual bladder outlet obstruction. After one year of follow-up, hydronephrosis and VUR resolution or improvement were not sig-

nificantly different between the two study arms. Except for a marginally lower median nadir serum creatinine in the group treated with VA and BNI, other measures of renal function outcome were not significantly different between both groups. In a similar context, reoperation rates and renal function measures were not significantly different between VA only and concomitant VA and BNI in a retrospective comparative study after a median follow-up was 58 (18-230) months (6). It is noteworthy that 4 patients in group A underwent BNI after suffering repeated retention and/or febrile UTI in the absence of other evidence of mechanical bladder outlet obstruction. The results were analyzed based on the intention to treat. The 3 patients who had reoperation in group B had check cystoscopy only. These factors could have skewed the results in favor of VA only resulting in a statistically similar reintervention rate.

Recent long-term follow-up of patients who had BNI during childhood for a variety of conditions showed no effect of BNI on continence, antegrade ejaculation or semen quality (24, 25). Hennus reported antegrade ejaculation in 40 men who had superficial BNI at a mean age of 4.5 years, 10.8% had reduced ejaculate volume and 5.8% had moderate incontinence (26). However, lack of evidence of adverse effects of BNI does not justify its routine use in the absence of compelling evidence of its beneficial effects.

Several study limitations should be acknowledged. First, the study included a small number of patients. Second, the diagnosis of bladder neck hypertrophy was based on radiological and not urodynamic evaluation. However, urodynamic testing is not commonly practiced before VA and there is no consensus on the definition of bladder outlet obstruction in infants. Should there be evidence of bladder outlet obstruction on urodynamic testing, it would be impossible to tell if it is caused by the valve leaflet or bladder neck hypertrophy before VA. Salvage BNI was performed in four patients in the VA arm who suffered repeated urine retention and/or febrile UTI. The use of the intention-to-treat analysis could have resulted in the absence of significant outcome differences. Further, the study follow-up duration is not long enough to monitor renal function outcomes in chronic diseases like PUV, but the primary study question was whether BNI reduces the need for short term reoperation. A recent meta-analysis demonstrated potential long-term effects of BNI on PUV outcomes but similar reintervention rates (27). Finally, the study lacked urodynamic evaluation at follow-up. Despite its value, urodynamics have several limitations in the PUV population including sensate urethras, difficult catheter insertion in patients with bladder neck hypertrophy, the high prevalence of high-grade VUR, and rater variability. These factors do not only increase the technical difficulty of urodynamics, but also limit the accuracy of bladder volume, pressure and compliance measurements.

CONCLUSION

In patients with PUV, concomitant BNI and VA does not confer additional short-term benefits compared to VA only. Patients treated with concomitant BNI and VA had similar rates of short-term reoperation, UTI, hydronephrosis and VUR resolution. With short-term follow-up, renal function outcomes were similar among patients treated with VA only or with concomitant BNI.

ABBREVIATIONS

BNI = bladder neck incision
CIC = clean intermittent catheterization
eGFR = estimated glomerular filtration rate
PUV = posterior urethral valve
PVR = postvoid residual
VA = valve ablation
VUR = vesicoureteral reflux

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Hennus PM, van der Heijden GJ, Bosch JL, de Jong TP, de Kort LM. A systematic review on renal and bladder dysfunction after endoscopic treatment of infravesical obstruction in boys. PLoS One. 2012;7(9):e44663. doi: 10.1371/journal.pone.0044663

2. Abdelhalim A, Hafez AT. Antenatal and postnatal management of posterior urethral valves: where do we stand? Afr J Urol. 2021;27(1):140. doi: 10.1186/s12301-021-00238-7
3. Glassberg KI, Combs A. The valve bladder syndrome: 35+ years later. J Urol. 2016;196(1):16-17. doi: 10.1016/j.juro.2016.04.049
4. Combs AJ, Horowitz M, Glassberg KI. Secondary bladder neck obstruction in boys with a history of posterior urethral valve: revisited. J Urol. 2009;181(Suppl):171. doi: 10.1016/S0022-5347(09)60490-0
5. Kajbafzadeh AM, Payabvash S, Karimian G. The effects of bladder neck incision on urodynamic abnormalities of children with posterior urethral valves. J Urol. 2007;178(5):2142-2149.
6. Abdelhalim A, Hashem A, Abouelenein EE, Atwa AM, Soltan M, Hafez AT, et al. Can Concomitant Bladder Neck Incision and Primary Valve Ablation Reduce Early Re-admission Rate and Secondary Intervention? Int Braz J Urol. 2022 May-Jun;48(3):485-492. doi: 10.1590/S1677-5538.IBJU.2021.0383.
7. Androulakakis PA, Karamanolakis DK, Tsahouridis G, Stefanidis AA, Palaeodimos I. Myogenic bladder decompensation in boys with a history of posterior urethral valves is caused by secondary bladder neck obstruction? BJU Int. 2005;96(1):140-143.
8. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20(3):629-637. doi: 10.1681/ASN.2008030287
9. Fernbach SK, Maizels M, Conway JJ. Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol. 1993;23(6):478-480. doi: 10.1007/BF02012459
10. Abdelhalim A, El-Hefnawy AS, Dawaba ME, Bazeed MA, Hafez AT. Effect of early oxybutynin treatment on posterior urethral valve outcomes in infants: a randomized controlled trial. J Urol. 2020;203(4):826-831.
11. Kajbafzadeh AM, Payabvash S, Karimian G. The effects of bladder neck incision on urodynamic abnormalities of children with posterior urethral valves. J Urol. 2007;178(5):2142-2149.
12. Mitchell ME. Persistent ureteral dilatation following valve ablation. Dialogues Pediatr Urol. 1982;5(4).
13. Guha Vaze P, Saha S, Sinha R, Banerjee S. Urodynamics in Posterior Urethral Valve: Pursuit of prognostication or optimisation. J Pediatr Urol. 2021 Feb;17(1):111.e1-111.e8. doi: 10.1016/j.jpurol.2020.11.008.
14. Sarin YK, Sinha S. Efficacy of bladder neck incision on urodynamic abnormalities in patients with posterior urethral valves. Pediatr Surg Int. 2013;29(4):387-392.
15. Mokhless I, Zahran AR, Saad A, Yehia M, Youssif ME. Effect of Botox injection at the bladder neck in boys with bladder dysfunction after valve ablation. J Pediatr Urol. 2014;10:899-904.
16. Elkashef A, Abdelhalim A, Dawaba MS, Hafez AT. Effect of overnight bladder drainage on posterior urethral valve sequelae: a randomized controlled trial. J Pediatr Urol. 2025;21(2):528-531. doi: 10.1016/j.jpurol.2024.11.006
17. Abraham MK, Nasir AR, Sudarsanan B, Puzhankara R, Kedari PM, Unnithan GR, et al. Role of alpha adrenergic blocker in the management of posterior urethral valves. Pediatr Surg Int. 2009;25(12):1113-1115.
18. Aboulela WN, Eladawy MS, Latif AA. The effect of use of alpha-blockers in posterior urethral valve pediatric patients postvalve ablation in the absence of further outlet obstruction. Urol Ann. 2024;16(3):218-220.
19. Bajpai M, Baba A, Singh AK. Postablation and α-1 blocker therapy in children with congenital obstructing posterior urethral membrane. Formos J Surg. 2021;54(1):7-10.
20. Mendez-Serrano CG, Fang A, Fine R, Lee J, Brenseke W, Franco I. Effects of alpha blockers on hydronephrosis and renal function in patients with posterior urethral valves. J Urol. 2024;211(Suppl 5):e82.
21. Singh SK, Sharma V, Singh A. Urodynamic changes after valve fulguration alone and valve fulguration with bladder neck incision. J Indian Assoc Pediatr Surg. 2019;24(1):31-35.
22. Glassberg KI. The valve bladder syndrome: 20 years later. J Urol. 2001;166(4):1406-1414. doi: 10.1016/S0022-5347(05)65796-5
23. Sobhani S, Foroushani AR, Arshadi H, Hekmati P, Kajbafzadeh AM. Simultaneous primary posterior urethral valves ablation and bladder neck incision may decrease kidney and bladder failure in long-term follow-up in patients with bladder neck hypertrophy and poor bladder function at presentation: report of 301 cases. BMC Urol. 2024;24(1):154. doi: 10.1186/s12894-024-01546-0

24. Keihani S, Kajbafzadeh AM, Kameli SM, Abbasioun R. Long-term impacts of concurrent posterior urethral valve ablation and bladder neck incision on urinary continence and ejaculation. Urology. 2017;99:278-280.
25. Taskinen S, Heikkila J, Rintala R. Effects of posterior urethral valves on long-term bladder and sexual function. Nat Rev Urol. 2012;9(12):699-706. doi: 10.1038/nrurol.2012.196
26. Hennus PML, Hoenjet E, Kieft JH, de Jong T, de Kort LMO. The long-term effect of superficial bladder neck incision on ejaculation and incontinence in boys with primary and secondary bladder neck obstruction. Front Pediatr. 2017;5:152. doi: 10.3389/fped.2017.00152
27. Tharwat M, Ramadan R, Hashem A, Taha DE, Hussiny M, Elkashef A, et al. Bladder neck incision in posterior urethral valve management: a meta-analysis with insights into adjunctive bladder interventions. Curr Urol Rep. 2025;27(1):1. doi: 10.1007/s11934-025-01309-w

Correspondence address:
Ahmed Abdelhalim, MD, M.Sc
Department of Urology, Mansoura Urology and Nephrology Center, Mansoura University
One Medical Center Drive, Ste # 1310,
Morgantown, WV, 26506, USA.
Telephone: +1 304 293-2706
E-mail: a_halim_2010@yahoo.com

ORIGINAL ARTICLE

Vol. 52 (3): e20250601, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0601

Single-dose Tamsulosin Induces Reversible Azoospermia and Ejaculatory Dysfunction Suggesting Potential for on-demand Male Contraception

Leonardo Seligra Lopes [1], Julia Domingues Candelaria [1], Felipe Placco Araujo Glina [1], Thais Ventura Feitosa [2], Bruna Bizio Parra de Oliveira [2], Willy Roberto Camargo Baccaglini [1], Erik Montagna [1], Caio Parente Barbosa [2], Jose de Bessa Junior [3], Sidney Glina [1]

[1] Disciplina de Urologia do Centro Universitário FMABC, Santo André, SP, Brasil; [2] Instituto Ideia Fertil, Santo André, SP, Brasil; [3] Departamento de Cirurgia da Universidade Estadual de Feira de Santana, Feira de Santana, BA, Brasil

ABSTRACT

Purpose: Ejaculatory alterations are among the most frequent sexual side effects of α_1-adrenergic antagonists. Although often attributed to retrograde ejaculation, recent evidence indicates that tamsulosin primarily disrupts seminal emission, occasionally leading to transient azoospermia. This study evaluated the frequency, timing, and reversibility of ejaculatory and seminal changes following a single oral dose of 0.8 mg tamsulosin in healthy men.

Materials and Methods: Thirty-one healthy male volunteers (aged 18–45 years) underwent a baseline semen analysis, followed by six additional collections at 1–3 week intervals. Each collection was performed at a different post-dose time point, spaced every 4 hours, to construct a 24-hour post-administration profile. Semen parameters were assessed according to WHO criteria, and post-ejaculatory urine was examined to detect retrograde ejaculation. Temporal variations were analyzed using repeated-measures ANOVA, with effect sizes estimated by Cohen's d.

Results: Seminal volume decreased significantly in 93.6% of participants, with aspermia in 80.7%, peaking 12 h after ingestion ($p<0.001$, $d=2.05$). Sperm concentration declined markedly, with azoospermia in 80.7% ($p<0.001$, $d=1.59$) and normalized after wash-out in 2 days. No retrograde ejaculation was observed. Adverse effects were mild and self-limited. A single 0.8 mg dose of tamsulosin caused a consistent, time-dependent disruption of seminal emission, producing transient azoospermia rather than retrograde ejaculation.

Conclusions: A single 0.8 mg dose of tamsulosin transiently suppressed seminal emission, leading to reversible azoospermia within 12 hours most recovered by 24h, and all recovered within 48h. Its predictable, reversible effect supports caution in men seeking conception and further exploration as an on-demand male contraceptive model.

ARTICLE INFO

Leonardo Seligra Lopes
https://orcid.org/0000-0001-8253-3836

Keywords:
Ejaculatory Dysfunction; Azoospermia; Receptors, Adrenergic, alpha

Submitted for publication: October 16, 2025

Accepted after revision: December 29, 2025

Published as Ahead of Print: February 20, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Sandro C. Esteves

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

INTRODUCTION

Tamsulosin is a type of alpha-blocker that selectively targets α_1A-adrenergic receptors. It helps relieve lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH) and can also be used alongside other treatments to aid in passing ureteral stones (1, 2). Beyond its therapeutic role, alpha-blockers are known to cause ejaculatory disorders (1, 3), that vary among various drugs and are more significant depending on the dose used, which was classically interpreted as retrograde ejaculation. (1, 3-7). However, accumulating experimental and clinical evidence suggests that these events result instead from failure of seminal emission, leading to aspermia or even transient azoospermia (5, 8, 9).

Experimental models demonstrate that α_1A-receptors mediate contractility of the vas deferens, seminal vesicles, and epididymal tail (8, 10-14). Pharmacological blockades therefore disrupt coordinated emissions and prevent seminal fluid and sperm expulsion (9, 12, 15). Clinically, this results in anejaculation, markedly reduced volume, and sometimes complete absence of sperm in the ejaculate (9, 16).

The present study aimed to characterize the time course and reversibility of ejaculatory emission failure and azoospermia following a single 0.8 mg oral dose of tamsulosin in healthy volunteers, and to confirm whether these alterations are due to true emission failure rather than retrograde ejaculation.

MATERIALS AND METHODS

Male volunteers were recruited based on the following inclusion criteria: age between 18 and 45 years, lack of continuous alpha-blocker medication, and the ability to collect sperm by masturbation. The exclusion criteria were history of neurological disorders, liver disease, nephropathy, use of exogenous testosterone, anabolic or androgenic steroids, diabetes mellitus, pelvic or genital surgery, concomitant use of specific medications (ketoconazole, erythromycin, other alpha-blockers, warfarin, and diclofenac), altered sperm analysis according to WHO standards (17), and refusal to provide an informed consent form (ICF).

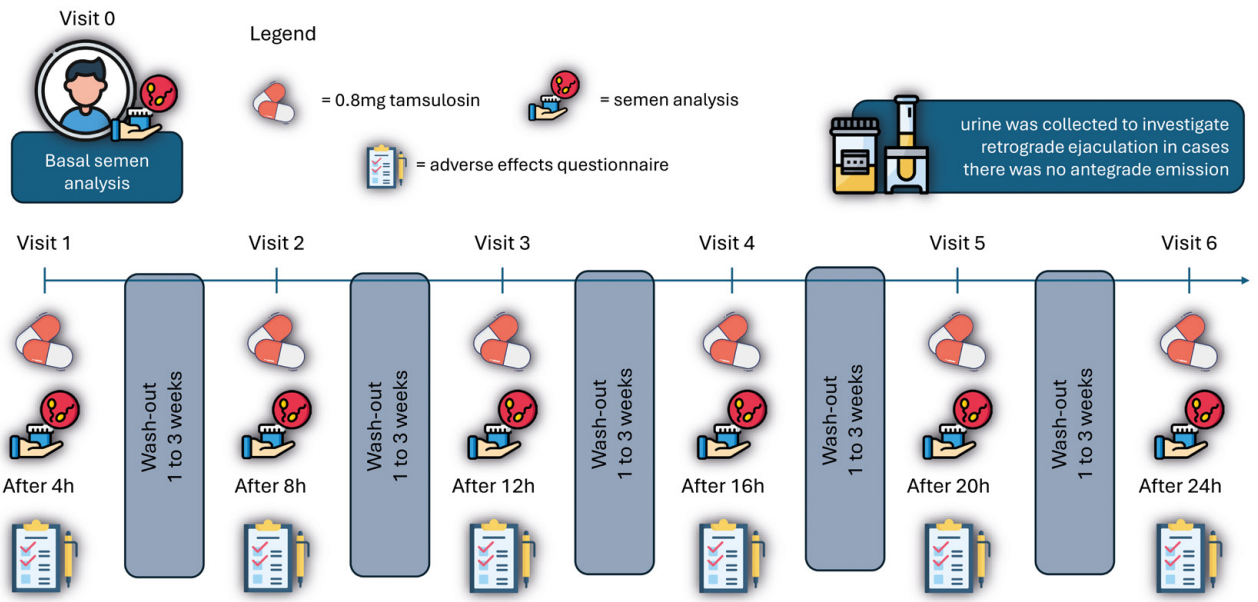
Individuals were clinically assessed for anatomical alterations in the genitourinary tract or neurological alterations associated with ejaculatory dysfunction risk within specific physical exam. An initial semen sample was collected to establish the baseline parameters for study inclusion and to serve as a control without the use of medication.

The medications should be taken using a commercial presentation of tamsulosin hydrochloride (OmnicOcas ® Astellas Pharma Europe B.V., Hogemaat 2, 7942 JG Meppel, The Netherlands, registered and imported by *Astellas Farma Brasil Importação e Distribuição de Medicamentos Ltda*, São Paulo, SP, Brazil) of 0.4 mg, and orally administered two tablets in a single dose totaling 0.8 mg under controlled ingestion, guided by a single evaluator, and reinforced by telephone. The administration time of medication was standardized to align with morning semen analysis. A 0.8 mg dose was chosen in accordance with previous studies reporting a more pronounced influence on ejaculatory dynamics and semen analysis findings compared with lower doses (10, 18).

Each collection was performed at a different post-dose time point, spaced every 4 hours (h), to construct a 24-h post-administration profile. All samples were collected by masturbation in a sterile collection bottle. The analyses were performed by experienced professionals from an assisted reproduction clinic under WHO recommendations (17), including a 2–3-day abstinence period and regulated quality standards, including centrifugation of the sample when no sperm was found in the initial evaluation. However, for statistical analysis, seminal volume and sperm concentration were considered. The individuals had their semen samples collected by masturbation, and immediately afterwards, their urine was collected to investigate retrograde ejaculation in cases where there was no antegrade emission or low volume. Urine was collected in a sterile vial containing 1 mL buffered culture medium (Figure-1, study design protocol).

The participants were questioned on their return visits about the potential adverse effects of single-dose alpha-blocker use.

Figure 1 - Study flow and medication schedule with subsequent semen analysis



The sample size was determined based on previously reported semen volumes and sperm concentration values after alpha-blockers oral intake (10, 16). The highest calculated values were obtained. Accordingly, to ensure statistical significance with a 95% confidence interval, a minimum of 14 participants was required. When limiting Type II errors with a statistical power of 0.8, the total number of participants required increased to 28.

We assumed that a reduction of > 95% would be considered clinically significant for changes in either volume or concentration. The variability in semen volume and sperm concentration is well recognized because of the intrinsic biological nature of spermatogenesis, which may exhibit high variation in response to different stimuli and conditions (17). Therefore, a sample size of 28 participants was selected to accommodate natural fluctuations and biological effects.

Categorical variables are expressed as relative and absolute frequencies. To compare the variation in the measurements, we used the repeated measures ANOVA test and post-hoc analysis with paired comparisons to identify the specific and significant moments of difference between the intervals, as well as the Benjamini-Hochberg correction to adjust the p-values and balance the risk of false positives. To assess the magnitude of the effect on ejaculatory volume and seminal concentration, we used the calculation proposed by Cohen, which is the difference between the means of the two groups divided by their joint standard deviation. The interpretation of Cohen's d depends on the values obtained: values less than or equal to 0.2 have a small effect, between 0.3 and 0.7, a medium effect and from 0.8 onwards, the effect is considered large. Phyton ® version 3.9, and Jupyter Notebook version 7.0.8 software were used.

This study was approved by the local ethics committee under protocol CAEE26124719.2.0000.0082 of May 2021 and was registered in the Brazilian Registry of Clinical Trials under number RBR-3hsj6g6.

RESULTS

Thirty-four individuals (mean age 24.45 years, SD 4.71) who met the inclusion criteria were recruited between December 2021 and January 2023. Two individuals were requested to leave the study because they were unable to complete the collection period adequately. One patient requested to leave owing to mild

adverse effects, as described later. Thirty-one patients completed the study. Tables 1 and 2 show the characteristics of the recruited individuals and baseline seminal volume and concentration values.

After all seminal analyses during the determined periods, a decrease in seminal volume was identified in 29/31 (93.6%) individuals, of which 25/31 (80.7%) had aspermia (Table-3A). In relation to sperm concentration, values below the 5th percentile of the WHO standard (17), considered oligozoospermia and/or azoospermia, were observed in 27/31 (87.1%) individuals. Of these, 25/31 (80.7%) presented azoospermia in at least one sample (Table-3B). Urine analyses confirmed the absence of spermatozoa, excluding retrograde ejaculation. Figure-2 demonstrates variation in seminal volume and sperm concentration over 24h. The decrease and subsequent recovery in seminal volume occurred concomitantly with changes in sperm concentration, indicating an effect throughout the entire ejaculatory pathway, from the vas deferens to the seminal vesicles. (Figure-3, scatter plot with smoothed regression lines).

Repeated-measures analysis of variance (repeated-measures ANOVA) was performed to assess differences in seminal parameters over different collection times. To identify pairs of moments with significant differences, we performed paired multiple comparison analysis (post-hoc analysis) (Table-4).

A sharp decline in seminal volume was observed as early as 4h post-dose and also there was a marked reduction in seminal volume during the first 12h, with the lowest average volume recorded during this period (0.55 mL). Sperm concentration also decreased

Table 1 - Characteristics of the study population.

Characteristics	n	%
Participants	31	100
Smoking		
Yes	3	09.68
No	28	90.32
Alcohol consumption		
Yes	15	48.39
No	16	51.61
Use of medication*		
Yes	7	22.58
No	24	77.42

*not described as related to seminal alteration or interaction with tamsulosin.

Table 2 - Seminal analysis baseline values.

Variables	Median	IQR	p*
Basal volume (mL)	3	2.25-4.0	0.024
Basal concentration (million/mL)	134.2	85.85-199.55	0.002

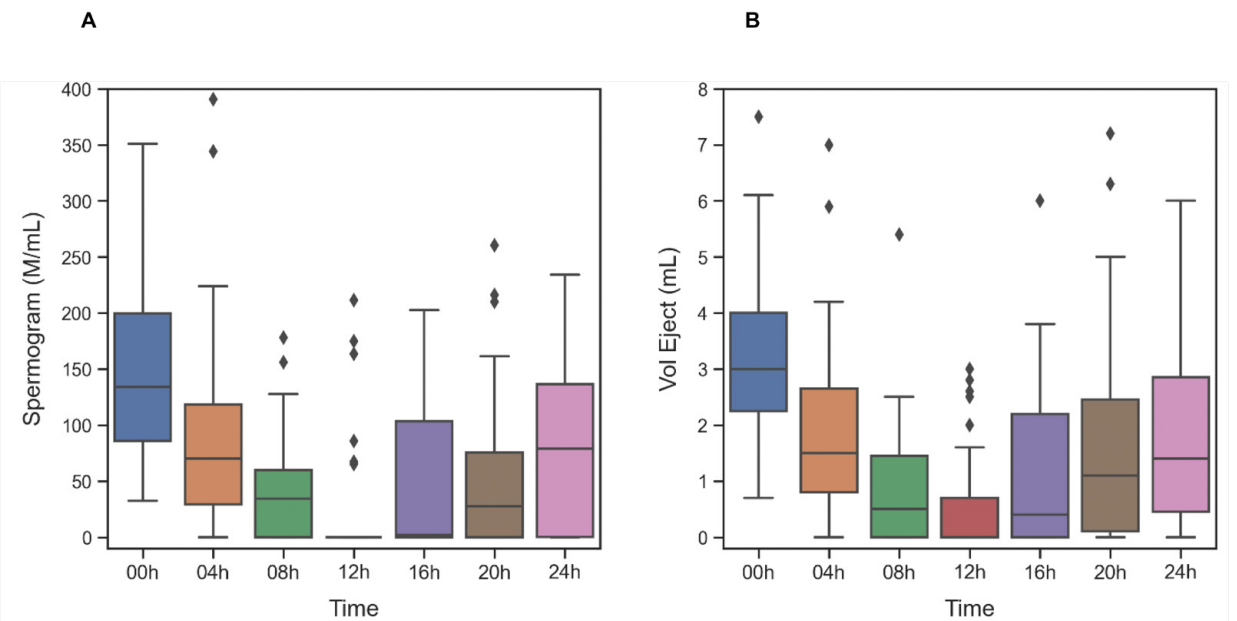
* Shapiro-Wilk test

Table 3 - Evaluation of seminal volume(3A) and sperm concentration (3B) in relation to the interval in hours after ingestion of tamsulosin 0.8mg.

3A	Collection interval (h)	Median [IQR]	hypospermia n (%)*	aspermia n (%)*
Seminal volume (mL)	Baseline	3.0 [2.25-4.0]	0 (0)	0 (0)
	4	1.5 [0.8-2.65]	12 (38.7)	2 (6.4)
	8	0.5 [0.0-1.45]	10 (32.2)	11 (35.4)
	12	0.0 [0.0-0.7]	4 (12.9)	21 (67.7)
	16	0.4 [0.0-2.2]	8 (25.8)	10 (32.2)
	20	1.1 [0.1-2.45]	9 (29.0)	8 (25.8)
	24	1.4 [0.45-2.85]	4 (12.9)	3 (9.6)
Number of individuals affected			29/31 (93.6)	25/31 (80.65)
3B	Collection interval (h)	Median [IQR]	Sperm concentration lower than WHO p5 n (%)*	azoospermia n (%)*
Sperm concentration (M/mL)	Baseline	134.2 [85.85-199.55]	0 (0)	0 (0)
	4	70.0 [29.3-118.25]	6 (19.35)	5 (16.1)
	8	34.3 [0.0-59.85]	14 (45.16)	13 (41.9)
	12	0.0 [0.0-0.0]	25 (80.65)	25 (80.65)
	16	2.0 [0.0-103.4]	17 (54.83)	15 (48.4)
	20	27.5 [0.0-75.55]	13 (41.93)	11 (35.48)
	24	79.0 [0.24-136.45]	13 (41.93)	7 (22.58)
Number of individuals affected			27/31 (87.1)	25/31 (80.7)

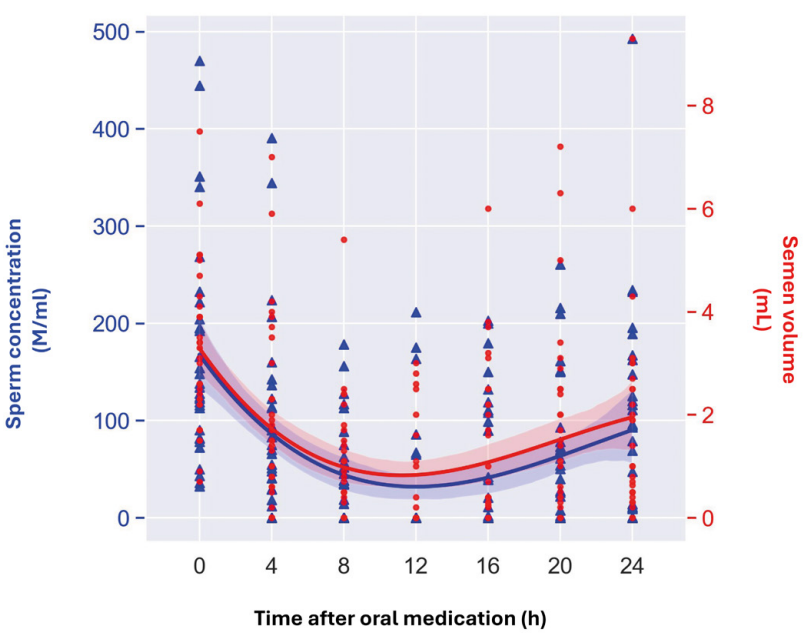
* Number of individuals in the period (there may be repetitions in the intervals)

Figure 2 - Variation in seminal volume and sperm concentration over 24 hours at intervals of every 4 hours after taking a single dose of tamsulosin 0.8mg.



A – Box plot of the median variation and 95% confidence interval of sperm concentration at each collection time; M/mL = Million/mL; B = Box plot of the median variation and 95% confidence interval of seminal volume at each collection time; mL = mililiter.

Figure 3 - Temporal variation in sperm concentration and seminal volume following a single 0.8 mg dose of tamsulosin.



M = Million; mL = milliliter; h = hours. Blue triangles represent individual sperm concentration values (left y-axis) and red circles represent seminal volume measurements (right y-axis) obtained at sequential post-dose time points. Smoothed regression lines illustrate the parallel decline and subsequent recovery of both parameters.

Table 4 - Analysis of the time of change in seminal parameters in relation to the tamsulosin 0.8mg intake interval.

Variable	Collection interval (h)	Mean	SD	p*	p cor**	d***
Seminal volume (mL)	Baseline	3.20	1.53			
	4	1.96	1.71	0.003	0.007	0.760
	8	0.95	1.17	< 0.001	< 0.001	1.647
	12	0.55	0.99	< 0.001	< 0.001	2.049
	16	1.23	1.54	< 0.001	< 0.001	1.282
	20	1.60	1.87	< 0.001	< 0.001	0.936
	24	1.89	1.99	0.001	0.003	0.734
Sperm concentration (M/mL)	Baseline	165.84	111.27			
	4	91.88	94.53	0,005	0,012	0.716
	8	41.50	50.96	< 0.001	< 0.001	1.437
	12	24.77	57.47	< 0.001	< 0.001	1.593
	16	51.41	68.02	< 0.001	< 0.001	1.241
	20	58.77	74.22	0.001	0.003	1.132
	24	90,91	106.79	0.012	0.023	0.687

* ANOVA of repeated measures; **post-hoc analysis with paired comparisons; ***Cohen's d effect size. mL = mililiter; M/mL = million/mL

significantly after the initial collection and then began to increase gradually, as with seminal volume. The reduction in concentration was substantial at 8h and 12h (d = 1.437 and 1.593, respectively), representing large effects.

At 24h post-dose 7 individuals (22.6%) remained with azoospermia, however all of them returned to antegrade ejaculation with spermatozoa confirmed with a sperm analysis 2 days after last oral medication (Figure-4, heat map showing individuals sperm concentration).

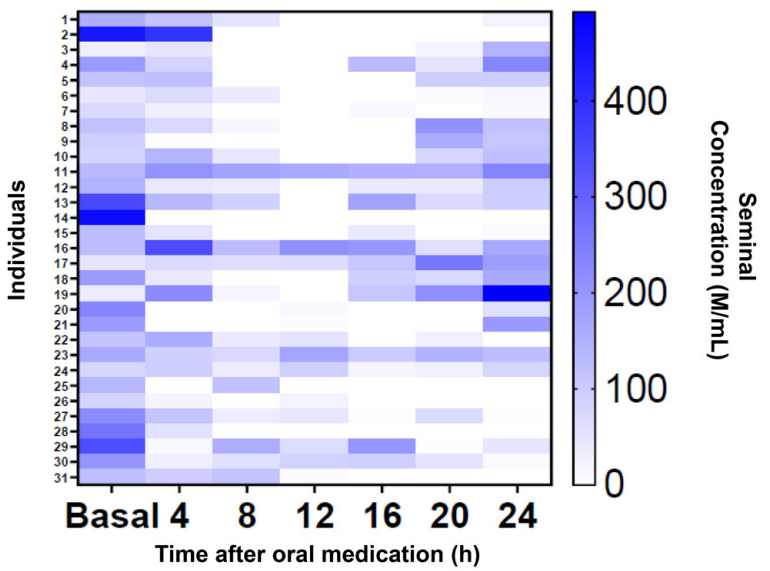
Adverse effects were mild (headache, dizziness, rhinitis), and no systemic intolerance occurred. No participant experienced nausea, syncope, or clinically significant hemodynamic changes (Table-5). One participant requested to leave the study because of diarrhea (one episode of liquid stool) within 48 hours of taking the medication.

DISCUSSION

A single 0.8 mg dose of tamsulosin produced a consistent, time-dependent interruption of seminal emission leading to azoospermia in over 80% of healthy men. The magnitude and reversibility of these findings reinforce the concept that selective α_1A-adrenergic blockade impairs emission rather than ejaculation per se.

Animal studies indicate that alpha1A-adrenergic receptors mediate contraction of the cauda epididymis (11), vas deferens (12, 19), and seminal vesicles (12) in rats and pigs, whereas alpha1D-adrenergic receptors affects (9) the contraction of both the epididymis and vas deferens when induced by noradrenaline, contributing to ejaculation disorder by altering the sperm emission phase. (19) A comparative study of four different types of alpha-blockers in rats revealed increased seminal

Figure 4 - Heat map showing individuals sperm concentration.



M/mL = Million/miliLiter; h = hours.

Table 5 - Occurrence of adverse effects potentially related to the use of oral tamsulosin 0.8mg single dose.

Symptoms	4h n (%)	8h n (%)	12h n (%)	16h n (%)	20h n (%)	24h n (%)
Dizziness	0 (0)	4 (12.9)	3 (9.6)	1 (3.2)	2 (6.4)	1 (3.2)
Headache	4 (12.9)	4 (12.9)	8 (25.8)	5 (16.1)	4 (12.9)	3 (9.6)
Palpitation	1 (3.2)	0 (0)	2 (6.4)	1 (3.2)	2 (6.4)	1 (3.2)
Postural hypotension	0 (0)	0 (0)	2 (6.4)	0 (0)	6 (19.4)	0 (0)
Rhinitis	0 (0)	5 (16.1)	7 (22.6)	5 (16.1)	0 (0)	6 (19.4)
Constipation	0 (0)	1 (3.2)	2 (6.4)	0 (0)	0 (0)	2 (6.4)
Diarrhoea	0 (0)	0 (0)	0 (0)	1 (3.2)	0 (0)	0 (0)
Skin rash	0 (0)	0 (0)	1 (3.2)	0 (0)	0 (0)	0 (0)
Itching	0 (0)	0 (0)	1 (3.2)	0 (0)	0 (0)	0 (0)
Weakness	0 (0)	0 (0)	1 (3.2)	1 (3.2)	0 (0)	0 (0)

vesicle dimensions and reduced ejaculatory function, with the effects depending on the type of medication and dose. (5) Studies in pigs have evaluated the role of both alpha- and beta-adrenergic receptors in response to noradrenaline stimulation in electrical impulses and the antagonistic effect of the use of beta- and alpha-blockers. (13, 14)

In clinical trials ejaculatory disorders were more prevalent with alpha-blockers than placebo (OR 5.88; p<0.0001), particularly selective alpha1A blockers

such as tamsulosin (OR 8.58; p=0.006) and silodosin (OR 32.5; p<0.0001). (6) Ejaculation effects can be reduced by adjusting the dosage and administration of tamsulosin (20, 21). In a study involving 1,740 men taking 0.4 mg of tamsulosin continuously for LUTS(21), 6.7% reported ejaculatory disorders and were randomized to reduce the dose to 0.2 mg, take 0.4 mg every other day or maintain the dosage for 3 months. The response rates for symptom maintenance were 9.6, 25.8, and 100%, respectively.

Differentiating between anejaculation and retrograde ejaculation is clinically relevant because anejaculation results in azoospermia. This differentiation, based solely on an individual's clinical complaint, can lead to under-diagnosis; therefore, it should ideally involve sperm testing in the urine after ejaculation (22). Grasso et al. (23) found sperm in the urine post-ejaculation in 6 of 10 individuals taking tamsulosin 0.4 mg for BPH who complained of decreased seminal volume. In another study of 42 individuals taking either 0.4 mg tamsulosin or 0.8 mg silodosin for 12 weeks for BPH, all reported changes in ejaculation after starting the medication, and 66.7% had no sperm in their urine (22).

A previous study on the effects of alpha-blockers on seminal parameters in healthy adult men showed a reduction in seminal volume and sperm concentration in a group that used tamsulosin, with five individual presenting with azoospermia; none had sperm in the urine after ejaculation. (8) In one individual with marked hypospermia, transrectal ultrasound revealed reduced sperm emission and turbulence in ejaculatory ducts.

However, in a double-blinded, randomized, placebo-controlled pilot study, 57 individuals using medication for a period of 5 days were randomized into 3 groups (placebo, tamsulosin and alfuzosin) with 90% of the individuals using tamsulosin showing a decrease in seminal volume, and a significantly greater change in volume was found in the tamsulosin group (-2.4±0.17 mL) compared to placebo (+0.4±0.18, p<0.0001) or alfuzosin (+0.3±0.18, p<0.001) (25). A total of 35.4% of individuals with anejaculation were identified in the tamsulosin group, with no change in the presence of sperm in the urine after orgasm compared to baseline and no difference with placebo (18). In the present study, of 29/31 (93.6%) patients showed a change in volume, identifying 80.7% of individuals with anejaculation. In addition, 25 (80.7%) patients had no spermatozoa detected in post-ejaculatory urine. The higher incidence of aspermia observed in this study compared to previous reports is related to the use of doses higher than those typically prescribed in clinical practice. Moreover, ejaculation was documented during masturbation, whereas in real-life settings patients may not notice seminal emission if they engage exclusively in penetrative sexual activity.

The presence of beta-adrenergic receptors 1, 2, or 3 in the prostate has been described in a few studies, and, the main action is related to Beta-2 adrenergic receptors, and their blockade results in tissue contraction, particularly in individuals without BPH (24). This could explain the inconsistency in the effect of reducing sperm volume and concentration with the use of alpha-blockers in the two individuals in this study, who were taking beta-blockers continuously because of systemic arterial hypertension.

The theory of possible male contraception which involves blocking alpha1A-adrenergic action is also based on animal studies. Administration of tamsulosin to rats reduced the number of spermatozoa in the ejaculate as well as the number of embryos per pregnancy (25). In humans, Wang et al. (10) evaluated 40 young men aged 22 to 31 in a randomized, crossover, placebo-controlled study with a single dose of 0.4 mg and 0.8 mg tamsulosin and analyzed the seminal profile and urine after orgasm 4-6 hours after taking the medication. Anejaculation and azoospermia were found in 100% of the individuals who used the 0.8 mg dose, with a decrease in seminal volume and total mobile sperm count when the 0.4 mg dose was used (10). In the present study, we observed anejaculation in 80.7% of the patients, all of whom were diagnosed with azoospermia using the 0.8 mg single dose. Using silodosin, a selective alpha-blocker, Kobayashi et al. (26) evaluated 15 volunteer urologists in a double-blind study using a dose of 4 mg twice daily for 6 days, which was compared to a placebo. The authors observed anejaculation in all individuals, with absolute azoospermia confirmed using post-orgasm urine analysis. More recently, Bhat and Shastry (27) prospectively evaluated a cohort of 63 men with normal sperm counts and partners of reproduc-

tive age for one year. Silodosin 8 mg was administered approximately 3 hours before sexual intercourse. No unintended pregnancies have been reported. In all cases, azoospermia was reversible after discontinuation of the alpha-blocker treatment.

Although this study was not designed to assess contraception, the consistent and reversible induction of azoospermia supports the theoretical feasibility of α_1A blockade as a non-hormonal approach to transient sperm suppression. The notion that selective α-blockers might act as reversible male contraceptives remains relevant, given accumulating evidence that men increasingly wish to share contraceptive responsibility with their partners (28). This has been a challenge for years, with most strategies using hormonal alternatives having undesirable side effects and/or long-term or irreversible effects on fertility (29). Because we did not evaluate repeated dosing, long-term use, pregnancy outcomes, or delayed doses, no contraceptive schedule or "safe window" can be proposed based on our findings. Because this was a mechanistic experiment, we selected the supratherapeutic dose to maximize detection of reversible ejaculatory blockade within a 24h window. The need for semen monitoring and contraceptive reliability requires dedicated larger and longer prospective studies.

An additional factor that may influence the magnitude and consistency of ejaculatory effects is the pharmaceutical formulation of tamsulosin. The oral controlled absorption system (OCAS) provides a slower and more uniform release profile, resulting in lower peak plasma concentrations and reduced fluctuations in systemic exposure compared with the immediate-release formulation (30). This pharmacokinetic behavior may attenuate the intensity of α_1A-adrenergic blockade at critical time points for seminal emission, potentially explaining the lower frequency or milder expression of ejaculatory dysfunction reported in some clinical series using OCAS formulations. Therefore, future studies aiming to precisely characterize the timing, reversibility, and magnitude of ejaculatory suppression should preferentially employ the immediate-release formulation of tamsulosin, allowing a clearer assessment of peak-related effects on seminal emission and facilitating comparison across pharmacodynamic endpoints.

The strengths of this study are represented by the standardized semen analysis, controlled timing of collections, objective urine analysis to rule out retrograde ejaculation, and paired intra-individual comparisons, guaranteeing the reversibility of the effect. The limitations include the small number of individuals in the sample despite the sample calculation and lack of hormonal assessment.

CONCLUSION

In conclusion, a 0.8 mg dose of tamsulosin significantly reduced seminal volume and sperm concentration within the first 12h, often leading to azoospermia in numerous individuals. All individuals recovered from ejaculatory dysfunction with normal sperm concentration more than 24h post-medication, confirming the reversibility of the effect in a safe manner, with minimal adverse effects. Given its marked and reversible impact on seminal emission, tamsulosin should not be prescribed to men actively attempting conception, as many patients may not perceive the reduction in ejaculate volume during penetrative intercourse, potentially leading to unrecognized iatrogenic infertility. These findings also warrant further investigation of tamsulosin and related agents as potential pharmacologic models for on-demand male contraception.

ACKNOWLEDGMENTS

Instituto Ideia Fertil for financial support for semen and urine samples analysis.

DISCLOSURE STATEMENT

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

INSTITUTIONAL REVIEW BOARD

CAEE 26124719.2.0000.0082

TRIAL REGISTRATION

Brazilian Registry of Clinical Trials ReBEC RBR-3hsj6g6 - https://ensaiosclinicos.gov.br/rg/RBR-3hsj6g6

Date of registration 09/20/2021 and date of enrollment of the first subject 12/20/2021

CONFLICT OF INTEREST

None declared.

REFERENCES

1. La Torre A, Giupponi G, Duffy D, Conca A, Cai T, Scardigli A. Sexual dysfunction related to drugs: a critical review. Part V: alpha-blocker and 5-ARI drugs. Pharmacopsychiatry. 2016;49(1):3–13. doi:10.1055/s-0035-1565100
2. Raison N, Ahmed K, Brunckhorst O, Dasgupta P. Alpha blockers in the management of ureteric lithiasis: a meta-analysis. Int J Clin Pract. 2017;71(1):e12917. doi:10.1111/ijcp.12917
3. Bearelly P, Avellino GJ. The role of benign prostatic hyperplasia treatments in ejaculatory dysfunction. Fertil Steril. 2021;116(3):611–617. doi:10.1016/j.fertnstert.2021.07.1199
4. Yokoyama T, Hara R, Fukumoto K, Fujii T, Jo Y, Miyaji Y, et al. Effects of three types of alpha1-adrenoceptor blocker on lower urinary tract symptoms and sexual function in males with benign prostatic hyperplasia. Int J Urol. 2011;18(3):225–230. doi:10.1111/j.1442-2042.2010.02708.x
5. Tatemichi S, Kobayashi K, Yokoi R, Kobayashi K, Maruyama K, Hoyano Y, et al. Comparison of the effects of four alpha1-adrenoceptor antagonists on ejaculatory function in rats. Urology. 2012;80(2):486.e9–486.e16. doi:10.1016/j.urology.2012.01.039
6. Gacci M, Ficarra V, Sebastianelli A, Corona G, Serni S, Shariat SF, et al. Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. J Sex Med. 2014;11(6):1554–1566. doi:10.1111/jsm.12525
7. Capogrosso P, Serino A, Ventimiglia E, Boeri L, Deho F, Damiano R, et al. Effects of silodosin on sexual function: realistic picture from everyday clinical practice. Andrology. 2015;3(6):1076–1081. doi:10.1111/andr.12095
8. Hisasue S, Furuya R, Itoh N, Kobayashi K, Furuya S, Tsukamoto T. Ejaculatory disorder caused by alpha1-adrenoceptor antagonists is not retrograde ejaculation but a loss of seminal emission. Int J Urol. 2006;13(10):1311–1316. doi:10.1111/j.1442-2042.2006.01535.x
9. Hayashi T, Takeya M, Nakamura K, Matsuoka K. Effects of silodosin and tamsulosin on the seminal vesicle contractile response. Low Urin Tract Symptoms. 2016;8(1):55–61. doi:10.1111/luts.12072
10. Wang J, Zhao Y, Jiang SB, Xia QH, Wei CX, Wang MW, et al. Assessment of tamsulosin as a potential male contraceptive in healthy volunteers. Urology. 2012;80(3):614–617. doi:10.1016/j.urology.2012.06.003
11. Pacini ESA, Castilho ACS, Hebeler-Barbosa F, Pupo AS, Kiguti LRA. Contraction of rat cauda epididymis smooth muscle to alpha1-adrenoceptor activation is mediated by alpha1A-adrenoceptors. J Pharmacol Exp Ther. 2018;366(1):21–28. doi:10.1124/jpet.117.246710
12. de Almeida Kiguti LR, Pupo AS. Investigation of the effects of alpha1-adrenoceptor antagonism and L-type calcium channel blockade on ejaculation and vas deferens and seminal vesicle contractility in vitro. J Sex Med. 2012;9(1):159–168. doi:10.1111/j.1743-6109.2011.02410.x
13. Hedqvist P, von Euler US. Inhibition by alpha- and beta-adrenoceptors of the twitch response to transmural stimulation in the guinea-pig vas deferens. Eur J Pharmacol. 1976;40(1):153–162. doi:10.1016/0014-2999(76)90365-4
14. Haynes JM, Hill SJ. Beta-adrenoceptor-mediated inhibition of alpha1-adrenoceptor-mediated and field stimulation-induced contractile responses in the prostate of the guinea pig. Br J Pharmacol. 1997;122(6):1067–1074. doi:10.1038/sj.bjp.0701466
15. White CW, Choong YT, Short JL, Exintaris B, Malone DT, Allen AM, et al. Male contraception via simultaneous knockout of alpha1A-adrenoceptors and P2X1-purinoceptors in mice. Proc Natl Acad Sci U S A. 2013;110(51):20825–20830. doi:10.1073/pnas.1318624110
16. Hellstrom WJ, Sikka SC. Effects of alfuzosin and tamsulosin on sperm parameters in healthy men: results of a short-term, randomized, double-blind, placebo-controlled, crossover study. J Androl. 2009;30(4):469–474. doi:10.2164/jandrol.108.006874

17. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 6th ed. Geneva: World Health Organization; 2021. doi:10.4067/S0717-95022022000100001
18. Hellstrom WJ, Sikka SC. Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. J Urol. 2006;176(4 Pt 1):1529–1533. doi:10.1016/j.juro.2006.06.004
19. Tambaro S, Ruiu S, Dessi C, Mongeau R, Marchese G, Pani L. Evaluation of tamsulosin and alfuzosin activity in the rat vas deferens: relevance to ejaculation delays. J Pharmacol Exp Ther. 2005;312(2):710–717. doi:10.1124/jpet.104.074740
20. Goktas S, Kibar Y, Kilic S, Topac H, Coban H, Seckin B. Recovery of abnormal ejaculation by intermittent tamsulosin treatment. J Urol. 2006;175(2):650–652. doi:10.1016/S0022-5347(05)00157-6
21. Soliman MG, Abou-Ramadan AR, El-Abd AS, El-Tatawy HH, El-Abd SA, El-Sakka AA. Outcome of modification of dose and time of administration of tamsulosin in men with abnormal ejaculation. Urol Int. 2019;102(4):482–486. doi:10.1159/000497295
22. Pavone C, Abrate A, Li Muli P, Guzzardo C, Guarneri AG, Dioguardi S, et al. Can we clinically distinguish anejaculation from retrograde ejaculation in patients on alpha1A-blockers therapy for lower urinary tract symptoms? Urology. 2020;139:129–133. doi:10.1016/j.urology.2020.01.027
23. Grasso M, Fortuna F, Lania C, Blanco S. Ejaculatory disorders and alpha1-adrenoceptor antagonists therapy: clinical and experimental researches. J Transl Med. 2006;4:31. doi:10.1186/1479-5876-4-31
24. Michel MC, Vrydag W. Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol. 2006;147(Suppl 2):S88–S119. doi:10.1038/sj.bjp.0706619
25. Ratnasooriya WD, Wadsworth RM. Tamsulosin, a selective alpha1-adrenoceptor antagonist, inhibits fertility of male rats. Andrologia. 1994;26(2):107–110. doi:10.1111/j.1439-0272.1994.tb00766.x
26. Kobayashi K, Masumori N, Hisasue S, Kato R, Hashimoto K, Itoh N, et al. Inhibition of seminal emission is the main cause of anejaculation induced by a new highly selective alpha1A-blocker in normal volunteers. J Sex Med. 2008;5(9):2185–2190. doi:10.1111/j.1743-6109.2008.00779.x
27. Bhat GS, Shastry A. A prospective double-blind, randomized, placebo-controlled study to evaluate the efficacy of silodosin 8 mg as an on-demand, reversible, nonhormonal oral contraceptive for males: a pilot study. World J Urol. 2020;38(3):747–751. doi:10.1007/s00345-019-02863-y
28. Wang C, Sitruk-Ware R, Serfaty D. It is time for new male contraceptives! Andrology. 2016;4(5):773–775. doi:10.1111/andr.12209
29. Wang C, Swerdloff RS. Hormonal approaches to male contraception. Curr Opin Urol. 2010;20(6):520–524. doi:10.1097/MOU.0b013e32833f11f8
30. Michel MC, Chapple CR. Comparison of the cardiovascular effects of tamsulosin oral controlled absorption system (OCAS) and alfuzosin prolonged release (XL). Eur Urol. 2006;49(3):501–508. doi:10.1016/j.eururo.2005.12.019

Correspondence address:
Leonardo Seligra Lopes, MD, PhD
Disciplina de Urologia do Centro Universitário FMABC
Av. Lauro Gomes, 2000
Santo André, SP, Brasil
Telephone: +55 11 9 9111-6667
E-mail: dr.leonardoseligralopes@yahoo.com.br

ORIGINAL ARTICLE

Vol. 52 (3): e20250610, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0610

Care of Patients with Male Hypogonadism: A Joint Position Statement from the Brazilian Society of Endocrinology and Metabolism (SBEM), the Brazilian Society of Urology (SBU), and the Brazilian Association for Sexual Medicine and Health (ABEMSS)

Alexandre Hohl [1], Leonardo Lopes [2], Marcelo Fernando Ronsoni [3], Eduardo P. Miranda [4], Tayane Muniz Fighera [5], Fernando Nestor Facio [6], Lucas Bandeira Marchesan [7], Luiz Otavio Torres [8]

[1] Serviço de Endocrinologia e Metabologia, Universidade Federal de Santa Catarina – UFSC, Florianópolis, SC, Brasil; [2] Disciplina de Urologia Faculdade de Medicina do ABC, Santo André, SP, Brasil; [3] Departamento Clínica Médica, Universidade Federal de Santa Catarina – UFSC, Florianópolis, SC, Brasil; [4] Centro Universitario Christus, Fortaleza, CE, Brasil; [5] Departamento de Medicina Interna, Universidade Federal do Rio Grande do Sul – UFRS, Porto Alegre, RS, Brasil; [6] Disciplina de Urologia, Faculdade de Medicina de São José do Rio Preto - FAMERP, São José do Rio Preto, SP, Brasil; [7] Serviço de Endocrinologia e Metabologia, Hospital Nossa Senhora da Conceição, Porto Alegre, RS, Brasil; [8] Serviço de Urologia, Centro Universitário de Belo Horizonte Campus Antonio Carlos Belo Horizonte, MG, Brasil

ABSTRACT

Male hypogonadism is a prevalent and clinically relevant condition with substantial effects on reproductive, metabolic, skeletal, and psychosocial health. Rising obesity rates, metabolic syndrome, and anabolic-androgenic steroid use have increased the frequency of functional hypogonadism in Brazil. Despite advances in diagnosis and treatment, clinical practice remains heterogeneous and access to standardized recommendations is limited.

This joint position statement from the Department of Female Endocrinology, Andrology and Transgenderism (DEFAT) of the Brazilian Society of Endocrinology and Metabolism (SBEM), the Brazilian Society of Urology (SBU), and the Brazilian Association for Sexual Medicine and Health (ABEMSS) provides practical, evidence-based guidance for the evaluation and management of male hypogonadism in Brazil. The document outlines diagnostic criteria, including morning total testosterone confirmation and assessment of gonadotropins, and emphasizes recognition of functional etiologies such as obesity-related hypogonadism. Therapeutic recommendations include testosterone replacement therapy for confirmed organic hypogonadism, preferential use of long-acting intramuscular or transdermal formulations, and fertility-preserving strategies (SERMs, hCG, aromatase inhibitors) when indicated. The statement also addresses monitoring protocols, safety considerations, and the management of adverse effects.

This is the first multidisciplinary Brazilian guideline harmonizing endocrine, urological, and sexual medicine perspectives to support national clinical practice. This consensus aims to promote consistent clinical decision-making, reduce underdiagnosis and overtreatment, and ensure safe, individualized care aligned with international principles and adapted to the national context.

ARTICLE INFO

Alexandre Hohl
https://orcid.org/0000-0002-8073-5837

Keywords:
Hypogonadism; Testosterone; Infertility, Male

Submitted for publication: October 19, 2025

Accepted after revision: December 04, 2025

Published as Ahead of Print: February 05, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

Data Availability
uninformed

INTRODUCTION

Male hypogonadism is a common endocrine disorder with significant clinical, metabolic, and psychosocial consequences. Its recognition and management have become increasingly complex due to the rising prevalence of obesity, metabolic syndrome, and the recreational or therapeutic use of anabolic-androgenic steroids (AAS). These factors not only affect circulating testosterone levels but also exert far-reaching effects on fertility, bone health, and overall quality of life.

Advances in understanding the pathophysiology of hypogonadism have emphasized the need for individualized, evidence-based therapeutic strategies. Testosterone replacement therapy remains the primary treatment for most patients with male hypogonadism. Selective estrogen receptor modulators are effective alternatives, particularly for men with functional hypogonadism who wish to preserve fertility. Current consensus guidelines advocate a multidisciplinary approach integrating endocrinology, urology, sexual medicine, and primary care to achieve optimal patient-centered outcomes.

This position statement introduces the first multidisciplinary Brazilian consensus developed jointly by the Brazilian Society of Endocrinology and Metabolism (SBEM), the Brazilian Society of Urology (SBU), and the Brazilian Association for Sexual Medicine and Health (ABEMSS) to guide the diagnosis and management of male hypogonadism; assist in the standardization of diagnostic thresholds and therapeutic targets for testosterone replacement in the Brazilian context and offers the adaptation of international evidence to local clinical practice and regulatory availability.

This position statement applies evidence-graded recommendations based on the strength and quality of available data, adapted from internationally recognized endocrine and urological guideline frameworks. Levels of evidence reflect methodological rigor and consistency of supporting studies, and recommendations are categorized according to clinical benefit and risk. When high-quality evidence is limited, expert consensus from specialists in endocrinology, urology, and sexual medicine was applied to guide best practice in the Brazilian setting. This approach ensures scientific rigor while maintaining practical applicability in routine clinical care.

DIAGNOSIS OF HYPOGONADISM IN MEN

Definition and Classification

Male hypogonadism is defined as a clinical syndrome characterized by a combination of specific signs and symptoms and confirmed biochemical evidence of testosterone deficiency. It reflects impaired testicular function resulting in decreased production of androgens and/or impaired spermatogenesis, with potential adverse effects on multiple organ systems and quality of life (1-5).

Hypogonadism is broadly classified into primary (hypergonadotropic) and secondary (hypogonadotropic) forms. Primary hypogonadism arises from intrinsic testicular failure, typically accompanied by elevated gonadotropin levels (2, 3). Secondary hypogonadism results from impaired hypothalamic or pituitary stimulation of the testes, characterized by low or inappropriately normal levels of gonadotropins (2-4). A compensated form is also recognized, characterized by normal testosterone levels with elevated luteinizing hormone (LH) (3). A third category, androgen resistance, refers to rare conditions where tissue insensitivity to testosterone is present, despite normal or elevated circulating testosterone levels. This includes partial or complete androgen insensitivity syndrome and enzymatic defects affecting androgen metabolism (3).

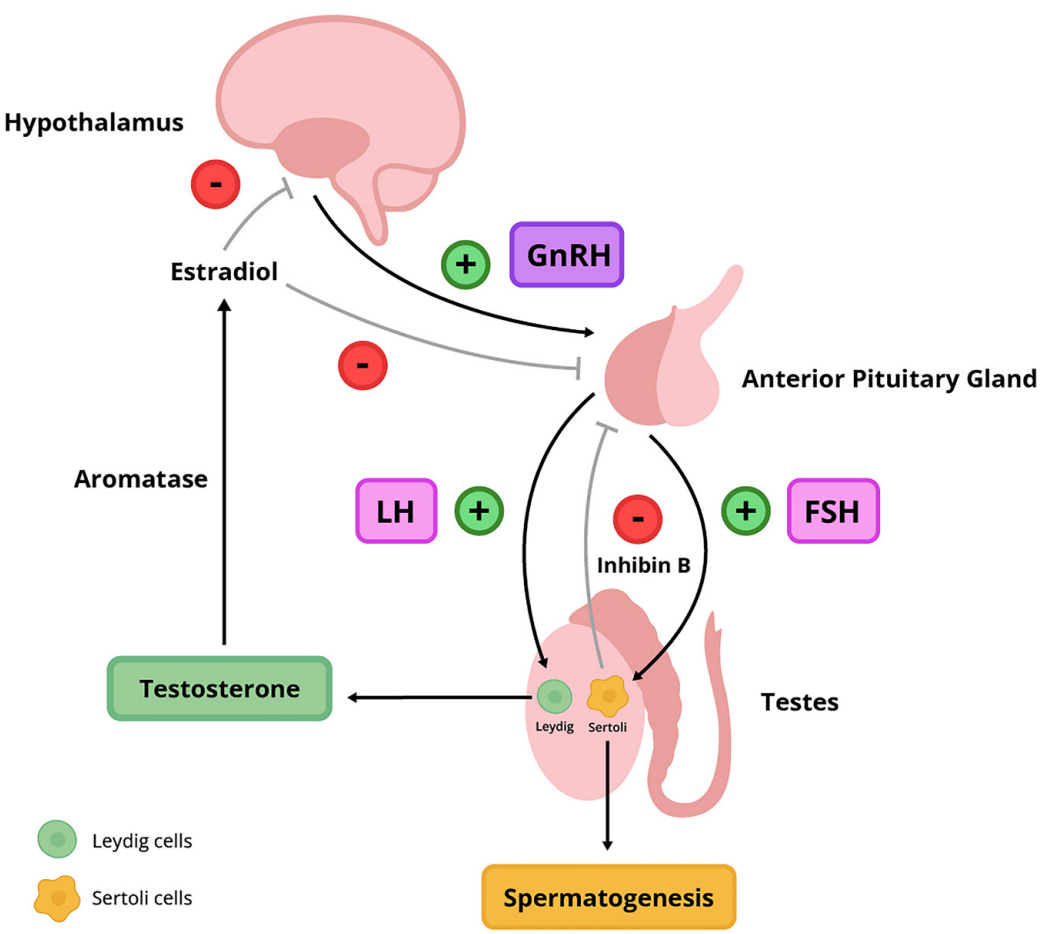
An important emerging concept is functional hypogonadism, which affects both young, middle-aged and older men. Functional hypogonadism is diagnosed when no identifiable organic pathology of the hypothalamic-pituitary-gonadal (HPG) axis is present. It is frequently associated with chronic systemic diseases, obesity, diabetes mellitus, and inflammatory conditions, all of which can impair the HPG axis and testosterone production (2, 3). Functional hypogonadism is often reversible with resolution or optimization of the underlying condition.

Physiology of the Hypothalamic-Pituitary-Gonadal (HPG) Axis

Clinicians must recognize that the HPG axis is fundamental for the regulation of male reproductive function and testosterone homeostasis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile fashion, which stimulates the anterior pituitary to release LH and follicle-stimulating hormone (FSH) (4, 6). LH primarily stimulates Leydig cells in the testes to produce testosterone, whereas FSH acts on Sertoli cells to promote spermatogenesis and inhibin B production. It is essential to maintain the physiological pulsatility of GnRH, as continuous stimulation can lead to receptor desensitization and impaired gonadotropin secretion (7). Figure-1 schematically describes the physiology of the HPG (Figure-1).

Healthcare providers should be aware that testosterone exerts widespread effects across multiple

Figure 1 - Schematic representation of the hypothalamic-pituitary-gonadal (HPG) axis and its regulatory feedback mechanisms.



The figure illustrates the hypothalamic–pituitary–gonadal (HPG) axis and the endocrine feedback loops that regulate male reproductive function. Gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus and stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts on Leydig cells to promote testosterone synthesis, whereas FSH acts on Sertoli cells to support spermatogenesis and stimulate the production of inhibin B. Testosterone and estradiol (via aromatization) exert negative feedback at both the hypothalamic and pituitary levels, while inhibin B selectively suppresses pituitary FSH secretion. The coordinated action of these hormones maintains testicular function and regulates male reproductive homeostasis.
GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone; HPG = hypothalamic–pituitary–gonadal.

organ systems, mediated through androgen receptors. Approximately 60% of circulating testosterone is bound to sex hormone-binding globulin (SHBG), 38% to albumin, and about 2% remains free and biologically active (1, 4). Peripheral conversion of testosterone to dihydrotestosterone (DHT) via 5α-reductase and to estradiol via aromatase must be considered, given their critical roles in androgenic activity and bone health, respectively. Both testosterone and estradiol exert negative feedback at the hypothalamic and pituitary levels, regulating GnRH, LH, and FSH secretion to maintain hormonal equilibrium (8).

When evaluating patients, clinicians must assess for potential disruptions at all levels of the HPG axis (9). A clear understanding of HPG axis physiology is indispensable for the precise diagnosis and individualized treatment of male hypogonadism.

Recommendation 01: Clinicians should perform a structured evaluation of the HPG axis, considering primary, secondary, and functional causes of hypogonadism (Class: I, Level of Evidence: B).

Epidemiology and Prevalence in Brazil

Hypogonadism often remains underdiagnosed, underreported, and paradoxically, sometimes overtreated. Prevalence estimates vary from 2% to over 30%, depending on the population studied (10).

Understanding the epidemiology of male hypogonadism allows for the determination of the merits of androgen deficiency screening, the predictive value of diagnostic tests, and the socio-economic impact associated with the disorder (10). In the United States, approximately 481,000 new cases of hypogonadism occur annually among men aged 40 to 69 years (11).

In Brazil, the epidemiological characterization of male hypogonadism remains limited, mainly due to the lack of large-scale population studies. Nevertheless, factors such as population aging, and the high prevalence of obesity and diabetes indicate that hypogonadism represents a significant public health issue (12). The association between obesity and functional male hypogonadism (MOSH: Male Obesity Secondary Hypogonadism) is widely recognized and corroborated by international guidelines, such as those from the medical societies of Endocrinology and Metabolism and Urology (3, 12, 13).

Demographic projections indicate that the proportion of individuals aged 65 and older will increase significantly in the coming decades. The literature shows that with aging, total serum testosterone decreases by 1.6% per year, and sex hormone-binding globulin (SHBG) levels increase by 1.3% annually (2-4). These physiological changes are related to overall health status. In Brazil, essential challenges persist, including the need for representative population studies, laboratory standardization, and awareness campaigns to reduce underdiagnosis of the condition.

Clinical Signs and Symptoms

The clinical manifestations of testosterone deficiency are predominantly nonspecific. The presentation varies according to the age at onset, severity of deficiency, presence of comorbidities, individual differences in androgen sensitivity, and prior exposure to testosterone therapy (3-5, 14). There are no population-based studies comprehensively evaluating the spectrum of symptoms and signs across the full severity range of male hypogonadism (4). Table-1 comprises specific and non-specific signs and symptoms suggestive of testosterone deficiency.

While screening questionnaires may offer clinical utility, they lack sufficient specificity to support their use in systematic screening for hypogonadism (3, 20).

In cases of suspected or confirmed hypogonadotropic hypogonadism, all individuals should be systematically queried regarding their sense of smell to evaluate for hyposmia or anosmia, which may indicate underlying genetic syndromes such as Kallmann syndrome (2-4).

Recommendation 02: All men should be asked during medical consultations about possible signs and clinical symptoms associated with low testosterone levels (Class: I, Level of Evidence: A).

Recommendation 03: We recommend against routine screening of men in the general population for hypogonadism. (Class: III, Level of Evidence: A).

Table 1 - Symptoms and signs suggestive of testosterone deficiency in Men (1-5, 14-19).

Specific testosterone deficiency
Incomplete or delayed sexual development
Loss of body (facial, axillary and pubic) hair
Very small testes (<6 mL)
Suggest testosterone deficiency
Decreased libido, diminished sexual thoughts
Erectile dysfunction, fewer spontaneous (morning and nocturnal) erections
Delayed ejaculation, reduced ejaculate volume, diminished orgasmic intensity
Gynecomastia
Eunuchoid body proportions
Infertility
Vasomotor symptoms (e.g., hot flushes, sweating),
Fine wrinkling of the skin (especially peri orally)
Height loss, low-trauma fractures, and reduced bone mineral density.
Nonspecific but associated with testosterone deficiency
Decreased energy levels, low or depressed mood, irritability, reduced motivation,
Fatigue
Cognitive changes (including impaired concentration and memory)
Sleep disturbances, excessive daytime sleepiness
Diminished muscle strength, reduced physical performance or activity
Increased adiposity (particularly visceral fat)
Unexplained mild normochromic, normocytic anemia

Recommendation 04: Individuals with hypogonadism, physical examination is an essential component of clinical assessment. It should include evaluation of secondary sexual characteristics (such as facial and body hair, and pubertal development), breast tissue (gynecomastia), body composition (weight and fat distribution), muscle mass, and skeletal structure/function. Examination of the testes should assess size, consistency, and location, while penile evaluation should include length and the position of the urethral meatus. Attention should also be given to the identification of syndromic features suggestive of underlying genetic or developmental disorders (Class: I, Level of Evidence: A).

Laboratory evaluation

The diagnosis of male hypogonadism depends on both clinical and biochemical findings. However, since clinical decisions can be made based on laboratory results at both the time of diagnosis and during follow-up, ensuring the reliability of these data is crucial. Total testosterone (TT) concentration is the recommended test for the initial evaluation of male hypogonadism. Its levels fluctuate throughout the day, peaking in the morning, and can be influenced by food and glucose intake. Therefore, blood samples should be collected in the morning, between 7 and 10 a.m., following an overnight fast. Any reduced levels should be confirmed by a second sample under the same conditions, ideally with a 4-week interval. Blood collections should not be performed during acute illness or during an exacerbation of chronic condition (4, 14, 21-24).

Conditions that affect SHBG levels can influence testosterone results. Obesity, diabetes mellitus, glucocorticoid use, androgenic and progestogenic steroids, nephrotic syndrome, acromegaly, and hypothyroidism are among the conditions that can reduce SHBG levels, thereby increasing free testosterone (FT) concentrations. Elevated SHBG levels may be associated with aging, liver disease, hyperthyroidism, HIV infection, estrogens and anticonvulsants (3, 4, 25).

In Brazil, most laboratories use automated immunoassays (chemiluminescence-based) for measur-

ing total testosterone. Immunoassays are considered acceptable for clinical evaluation in adult men. The gold standard method for total testosterone measurement is liquid chromatography-tandem mass spectrometry (LC-MS/MS), which is not routinely available in clinical practice in Brazil. This method offers superior accuracy and specificity, particularly at low testosterone concentrations (such as in children or men with severe hypogonadism). The Endocrine Society, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and the CDC Hormone Standardization Program (HoSt) recommend the use of LC-MS/MS or immunoassays calibrated with traceable reference standards (4, 14).

Laboratory values for the diagnosis of hypogonadism vary across different guidelines, based on studies conducted with populations of young men without comorbidities, using LC-MS/MS as a methodology for measuring total testosterone.

Several international societies provide reference thresholds for the biochemical diagnosis of male hypogonadism based on morning total testosterone (TT) measured with a validated assay. Most guidelines converge on lower TT limits between 264 and 350 ng/dL, depending on the methodology and population reference standards. The Endocrine Society recommends 264 ng/dL as the cutoff for low TT, whereas the American Urological Association adopts 300 ng/dL, and European and sexual medicine societies (EAU, EAA, ISSM) generally use values around 350 ng/dL (1-5, 15, 16).

In this consensus, TT values <264 ng/dL support the diagnosis of hypogonadism, values >350 ng/dL typically exclude the condition, and men with TT between 264–350 ng/dL require additional biochemical assessment — particularly when SHBG abnormalities are present. In cases of TT between 264 and 350 ng/dL, or conditions that alter SHBG levels, additional laboratory evaluation is required, including measurement of SHBG and albumin to estimate FT using the Vermeulen equation (http://www.issam.ch/freetesto.htm), as the gold-standard method (equilibrium dialysis) for direct FT measurement is expensive and not widely available. In these cases, a cutoff value of 6.5 ng/dL for calculated free testosterone (cFT) is recommended (4, 14, 23, 26).

Once the diagnosis of hypogonadism is confirmed, the next step is to investigate its etiology by distinguishing between primary and secondary causes, which can be done by measuring gonadotropins (LH and FSH) (2-4). Patients with low or inappropriately normal gonadotropin levels should undergo further investigation, including the measurement of prolactin, thyroid function, and transferrin saturation index, to rule out iron overload syndromes (28, 29).

Semen analysis represents a fundamental tool in the evaluation of men with hypogonadism, particularly when fertility preservation is a concern. Beyond its role as the gold standard for assessing male fertility potential, semen analysis provides indirect but clinically relevant information on testicular function, since spermatogenesis is a sensitive marker of the integrity of the HPG axis. Basic parameters, including semen volume, sperm concentration, motility, and morphology, allow characterization of both quantitative and qualitative aspects of spermatogenesis.

In patients with testosterone deficiency, abnormalities such as oligozoospermia, asthenozoospermia, or even azoospermia may reflect impaired Leydig and Sertoli cell function, with consequent reductions in both androgen production and germ cell support (1, 3). Current guidelines emphasize the importance of performing a baseline semen analysis prior to initiating testosterone therapy in men with hypogonadism who desire fertility, as exogenous testosterone suppresses gonadotropin secretion and profoundly impairs spermatogenesis (3, 30). Thus, knowledge of the patient's reproductive potential before therapy is critical for counseling, clinical decision-making, and, when necessary, the institution of fertility-preserving strategies such as cryopreservation or gonadotropin-based treatment (2).

According to the World Health Organization (WHO, 2021), the lower reference limits (5th percentile, p5) and median values (50th percentile, p50) for semen parameters were established based on fertile men whose partners achieved pregnancy within one year of unprotected intercourse. The ejaculate volume presents a lower reference limit of 1.4 mL, with a median of 3.0 mL, when collected after a period of 2–7 days of sexual abstinence. The sperm concentration should be at least

16 million spermatozoa per milliliter, with a median of 66 million/mL, while the total sperm count per ejaculate has a lower reference limit of 39 million and a median value of 210 million spermatozoa. In terms of motility, the total motility (progressive + non-progressive) should reach at least 42%, with a median of 64%, and the progressive motility (PR) alone should be ≥30% (median 55%), which is considered a strong predictor of fertilization capacity. Regarding vitality, at least 54% of spermatozoa must be alive (median 78%), as assessed preferably by eosin-nigrosin staining. For morphology, normal forms should represent ≥4% of the total spermatozoa, with a median of 14%, according to the strict Kruger criteria. The Ph of the semen should be ≥7.2, reflecting adequate function of the accessory glands. Other seminal characteristics include the presence of leukocytes <1 × 10^6/mL, since higher counts may suggest genital tract inflammation, and liquefaction within 60 minutes, which is considered normal. The viscosity should also be normal, as excessive viscosity can impair sperm motility and hinder fertilization (31).

Recommendation 05: The diagnosis of hypogonadism should be confirmed by measurement of TT with a validated assay on fasting morning blood samples obtained on two different days (Class: I, Level of Evidence: C).

Recommendation 06: Under conditions that alter SHBG or borderline values of TT, measuring or calculating FT is recommended if clinical suspicion of hypogonadism is strong (Class: I, Level of Evidence: C).

Recommendation 07: FSH and LH concentrations should be obtained for distinguishing between primary and secondary causes, with further evaluation to identify the etiology of hypothalamic, pituitary, e/or testicular disfunction (Class: I, Level of Evidence: C).

Differential diagnosis

Organic hypogonadism results from congenital, structural, or destructive abnormalities that cause permanent impairment of the gonadotropic axis. (4) On the other hand, functional causes lead to the reduction or suppression of gonadotropins and testosterone in a potentially reversible manner, since the underlying condition can be effectively treated (3-5, 32). Table-2 lists some of the common causes of organic and functional hypogonadism.

Increased prolactin levels, which may result from primary disorders of the hypothalamic-pituitary axis or as a secondary effect of chronic diseases and medications, can lead to suppression of GnRH and gonadotropin synthesis and release (33). Treating the underlying condition associated with hyperprolactinemia does not always resolve hypogonadism. In some cases, hypogonadism linked to pituitary adenomas may not respond to pharmacological treatments and may require more targeted therapy (34).

MOSH is the most common condition associated with functional hypogonadism. (32, 35, 36). Increased estrogen production by adipose tissue, leptin resistance, and chronic inflammation are some of the proposed mechanisms that explain the link between adiposity and male gonadal dysfunction. (35-37) Weight loss, regardless of the method used, can help restore testosterone levels. Failure to recover gonadal function with weight loss may suggest the presence of an underlying organic cause (2, 9, 35, 38-42). In addition, diabetes mellitus represents an important determinant of functional hypogonadism (36). High glucose levels, insulin resistance, and consequent hyperinsulinemia are key contributors to impaired GnRH secretion, ultimately resulting in decreased LH and testosterone levels (9, 36, 43-45).

Anabolic use of androgenic steroids should be considered in the evaluation of functional hypogonadism, as they block hypothalamic GnRH pulsatility and the release of pituitary gonadotropins. The dose and duration of gonadotropic axis blockade affect the likelihood of recovery of gonadal function after cessation. Prolonged use may result in incomplete recovery, even years after discontinuation (46-49).

Relative energy deficiency in sport (RED-S) has recently been used to refer to exercise-associated reproductive health disorders. It results from low-energy diets (intentional or unintentional) and/or excessive exercise, reducing the pulsatile hypothalamic release of GnRH and the release of gonadotropins from the anterior pituitary gland. These changes

Table 2 - Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism.

ORGANIC	FUNCTIONAL
Primary Hypogonadism	
Klinefelter syndrome Cryptorchidism, anorchia, myotonic dystrophy Some types of cancer, chemotherapy, testicular irradiation/damage, orchidectomy Orchitis Testicular trauma, torsion Advanced age	Medications (androgen synthesis inhibitors) End-stage renal disease*
Secondary Hypogonadism	
Hypothalamic/pituitary tumor Iron overload syndromes Infiltrative/destructive disease of hypothalamus/pituitary Idiopathic hypogonadotropic hypogonadism	Hyperprolactinemia Anabolic steroid use, glucocorticoids, opioids Alcohol and marijuana abuse* Systemic illness* Nutritional deficiency/excessive Exercise Severe obesity, some sleep Disorders Organ failure (liver, heart, and lung) * Comorbid illness associated with aging*

*Combined primary and secondary hypogonadism but classified to usual predominant hormonal pattern.

can promote acute or chronic relative hypogonadism with negative impacts on testosterone levels, fertility, and male bone health (50).

Several other conditions and substances can interfere with the functioning of the gonadotropic axis, leading to male hypogonadism (9). Depression is often associated with sexual dysfunction, and although treatment can alleviate sexual complaints, the use of antidepressants may induce sexual dysfunction. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are drugs associated with a high risk of adverse effects on sex drive and sexual function (51). Opioids, such as morphine, codeine, tramadol, heroin, and oxycodone, can reduce the pulsatility of hypothalamic GnRH and increase prolactin levels by inhibiting dopamine (52, 53). In the absence of other underlying causes of hypogonadism, opioid withdrawal is typically followed by a recovery in serum testosterone levels in a few weeks (52). Long-term use of glucocorticoids can result in androgen deficiency and sperm alterations by suppression of GnRH secretion. Prednisone-equivalent doses as low as 5mg daily can cause hypogonadism in older men (54, 55). It had been demonstrated that men receiving statin therapy present a higher prevalence of biochemical testosterone deficiency compared to non-users (56). However, despite the mild reduction in circulating testosterone levels observed in this population, the use of statins has not been associated with clinically significant hypogonadal symptoms or relevant impairment in sexual function. Therefore, while statins may slightly decrease serum testosterone concentrations, this effect is not considered to have meaningful clinical repercussions on androgen-related manifestations (56).

Recommendation 08: Men with overweight or obesity and Male Obesity Secondary Hypogonadism, lifestyle modifications and weight reduction should be recommended (Class: I, Level of Evidence: A).

Recommendation 09: Medications with the potential to suppress testosterone levels—including glucocorticoids, opioids, and anabolic steroids—should be carefully reviewed, and withdrawal or modification should be considered based on the clinical context (Class: II, Level of Evidence: B).

Role of imaging and complementary exams

Following a thorough clinical and biochemical assessment confirming hypogonadism, identifying the underlying cause is essential.

Klinefelter syndrome is the most common chromosomal cause of primary hypogonadism and is frequently underdiagnosed. Therefore, karyotype analysis in peripheral blood is recommended in men with primary hypogonadism, particularly when testicular volume is reduced (3-5).

Scrotal ultrasound should not be performed routinely, but it can be useful in cases where testicular complaints are present, such as palpable masses, pain, or tenderness (57). It is also valuable for accurately measuring testicular volume in cases of very small testes or when anatomical factors hinder the use of Prader orchidometry, such as in the presence of a large hydrocele or an inguinal testis. Moreover, scrotal ultrasound may play a role in the evaluation of male infertility, particularly for distinguish between obstructive and non-obstructive causes (3, 58) and it is also accepted in situations where physical examination is limited by patient discomfort.

Magnetic resonance imaging (MRI) of the sella turcica, may be indicated in the evaluation of secondary hypogonadism (4, 36, 59). MRI is specifically recommended in cases of suspected organic secondary hypogonadism, as in younger men, when serum testosterone is ≤150 ng/dL (4), in the presence of other pituitary hormone deficiencies, hyperprolactinemia, or symptoms suggestive of a pituitary mass (e.g., new-onset headaches or visual field defects) (3, 4).

Hypogonadism is a recognized risk factor for reduced bone mass and osteoporosis in men. Accordingly, several medical societies recommend dual-energy X-ray absorptiometry (DXA) scanning in men with risk factors such as hypogonadism. Repeat DXA may be considered 1-2 years after initiating testosterone replacement therapy and prior to the use of antiresorptive drug. (3, 4)

Additional evaluations, such as polysomnography, may be warranted based on clinical suspicion of OSA, a condition associated with hypogonadism (3, 4, 60).

Recommendation 10: Karyotype should be considered in primary hypogonadism, especially in men with low testicular volume (Class: I, Level of Evidence: B).

Recommendation 11: MRI of the sella turcica should be considered in men with suspected organic secondary hypogonadism, particularly in younger individuals with testosterone levels ≤150 ng/dL, coexisting pituitary hormone deficiencies, hyperprolactinemia, or symptoms of pituitary mass effect (Class: I, Level of Evidence: B).

Recommendation 12: DXA scanning is recommended for men at increased fracture risk, especially those over 50 years of age with hypogonadism (Class: I, Level of Evidence: B).

TREATMENT OF MALE HYPOGONADISM

Formal Indications for Initiating Therapy

It recommends testosterone therapy in men with hypogonadism to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.

Before initiating TRT, contraindications must be systematically assessed, including the presence of prostate or breast cancer, severe untreated obstructive sleep apnea, erythrocytosis (hematocrit >54%), severe heart failure (New York Heart Association class III or IV), and desire for future fertility, as exogenous testosterone suppresses spermatogenesis (3-5). Individualized risk–benefit evaluation and shared decision-making are mandatory. Therapy must aim to restore testosterone levels to the mid-normal physiological range and should be accompanied by regular monitoring of clinical and laboratory parameters.

Recommendation 13: Testosterone replacement therapy should be initiated only in men with persistent clini-

cal symptoms of testosterone deficiency and unequivocally low serum testosterone levels, after exclusion of contraindications (Class: I, Level of Evidence: A).

Therapeutic options available in Brazil

Several testosterone formulations are approved for the treatment of male hypogonadism in Brazil, offering clinicians flexibility to tailor therapy to individual patient preferences, comorbidities, and risk profiles. Available options include injectable testosterone (such as testosterone cypionate, testosterone esters and testosterone undecanoate), and transdermal testosterone (gel). (3-5, 36, 61) Each formulation has distinct pharmacokinetic properties, influencing serum testosterone fluctuations, ease of administration, cost, and side effect profiles.

Treatment of Male Hypogonadism: Focus on IM Formulations

Intramuscular (IM) testosterone preparations constitute a cornerstone of TRT in Brazil and globally, owing to their efficacy, relatively low cost, and wide availability. (3, 4)

The long-acting testosterone undecanoate (TU) 1000 mg formulation is currently the preferred IM preparation for sustained TRT. It is administered as a deep intramuscular gluteal injection with an initial loading phase (at weeks 0 and 6), followed by maintenance injections every 10–14 weeks (3, 36). TU provides relatively stable serum testosterone concentrations within the physiological range, with minimal fluctuations between doses, thereby reducing mood and sexual function variability (3-5).

Shorter-acting esters, such as a propionate plus a pool of testosterone esters (250 mg) and cypionate (200 mg), are also widely used in Brazil, particularly in public health settings and in clinical scenarios requiring flexible or temporary TRT (36). These formulations are typically administered every 2 to 3 weeks. However, they produce significant peaks and troughs in serum testosterone levels, which can lead to oscillations in energy, mood, and libido (3). These fluctuations must be discussed with patients prior to initiating therapy. The route of administration requires deep gluteal injection, which may necessitate trained healthcare personnel or adequate patient education for home administration. Pain or local site reactions may occur but are generally mild and transient (36).

Recommendation 14: Intramuscular testosterone formulations should be considered an option for TRT in men with hypogonadism. (Class: I, Level of Evidence: A)

Recommendation 15: Long-acting preparations are preferred rather than shorter-acting due to more stable serum levels, reduced fluctuations and lower injection frequency (Class: I, Level of Evidence: A).

Treatment of Male Hypogonadism: Focus on Transdermal Testosterone (Gel)

Testosterone gel is a widely used transdermal option in Brazil for treating male hypogonadism, providing a physiological mode of testosterone delivery through skin absorption. It offers advantages of stable serum testosterone concentrations, mimicking normal circadian rhythms without large peaks and troughs typical of injectable formulations (4, 5). Gels (1% or 1,62%) are usually applied once daily on clean, dry, intact skin areas (such as shoulders and upper arms), with absorption occurring over several hours. Steady-state testosterone levels are typically achieved within 2–3 days of consistent use (62).

Transdermal therapy is particularly beneficial for patients desiring a non-invasive, easily adjustable regimen or those at risk of erythrocytosis associated with injectable formulations (2). Nonetheless, clinicians must counsel patients regarding the risk of secondary exposure to others through skin contact, emphasizing the importance of covering the application site and washing hands after ap-

plication. Dose titration is often necessary, guided by serum testosterone levels obtained 2–4 hours after application and clinical symptom improvement (3). Skin irritation at the application site is a possible side effect but occurs in a minority of patients. The patient should be advised not to shower for up to 2 hours after applying or performing physical activities with excessive sweating, swimming pools or saunas.

Overall, testosterone gel represents an effective and safe alternative for long-term therapy in appropriately selected men with hypogonadism, if patients adhere to application instructions and appropriate monitoring is conducted. That short-acting formulation, particularly transdermal gels, may be preferred at treatment initiation, especially in cases where reversibility or rapid discontinuation may be needed due to adverse effects or diagnostic uncertainty.

Recommendation 16: Transdermal testosterone gel is recommended as an effective and safe option for the treatment of male hypogonadism, particularly in patients preferring non-invasive therapy and requiring steady testosterone levels (Class: I, Level of Evidence: A).

Other Formulations Available in Brazil

No oral or subcutaneous implants (pellets) testosterone formulations with validated and consistent pharmacokinetics are approved in Brazil for the treatment of male hypogonadism, and they are only available in the compounded market. Subcutaneous testosterone pellets are not recommended by medical specialty societies for the treatment of male hypogonadism in Brazil because compounded formulations do not have robust safety and efficacy studies (1, 63, 64) with high incidence of secondary polycythemia (65).

Recommendation 17: Oral testosterone formulations, subcutaneous testosterone pellets (compounded implants and manipulated gel formulations are not recommended for the treatment of male hypogonadism in Brazil, given the absence of approved formulations with validated and consistent pharmacokinetics. (Class: III, Level of Evidence: B)

Absolute and relative contraindications of testosterone

TRT requires close monitoring due to possible adverse effects, contraindications, and limited long-term safety data. For men who wish to avoid exogenous hormones, are not candidates for TRT, or do not tolerate its effects, non-hormonal pharmacological alternatives are available. (2, 3, 5).

TRT is contraindicated in men with hormone-sensitive tumors such as prostate or breast cancer. Men with prostate abnormalities on physical examination or elevated prostate-specific antigen (PSA) levels should be adequately evaluated before initiating TRT (3). The contraindications and the degrees of recommendation are outlined below.

Identifying and properly managing contraindications is a key step in ensuring the safety of testosterone therapy. While absolute contraindications preclude treatment, relative contraindications require an individualized approach, carefully balancing the potential benefits of TRT against the risks associated with the coexisting condition. Optimal comorbidity management and a rigorous, ongoing monitoring plan are essential when considering TRT in patients with relative contraindications.

Absolute Contraindications:

Male Breast Cancer: Although rare, these tumors may express hormone receptors, making TRT potentially harmful. Therefore, TRT is contraindicated in patients with a current or past diagnosis of breast cancer (1, 3-5) (Class: I; Level of Evidence: C).

Active Prostate Cancer: TRT is contraindicated in the presence of known or suspected prostate cancer without appropriate urologi-

cal evaluation and treatment. The risk stems from the potential stimulation of androgen-dependent tumors. Guidelines recommend a digital rectal exam and PSA testing before initiating TRT in men aged 55–69 or 40–69 with increased risk (1, 3-5) (Class: I; Level of Evidence: B).

Desire for Fertility: Exogenous testosterone suppresses the HPG axis, reducing spermatogenesis and potentially causing infertility. TRT is contraindicated in men who desire short-term fertility. Alternatives such as clomiphene citrate, aromatase inhibitors, or gonadotropins should be considered (1, 3-5) (Class: I; Level of Evidence: B).

Relative Contraindications and Precautions:

Elevated Hematocrit: Baseline hematocrit > 48% is a relative contraindication to TRT therapy because these men are more likely to develop a hematocrit > 54% when treated with testosterone. The risk of erythrocytosis is somewhat higher with IM formulations, particularly short-acting esters. Men with elevated hematocrit should undergo further evaluation before considering TRT (3, 66) (Class: IIa; Level of Evidence: B).

Obstructive Sleep Apnea: The impact of testosterone on OSA remains controversial (3, 60, 67, 68) and routine screening with polysomnography in asymptomatic men under TRT is not recommended. The therapy may worsen sleep apnea, particularly in severe and untreated cases. In patients with mild to moderate, or treated, OSA, TRT may be considered with close monitoring (3, 4, 60) (Class: IIa; Level of Evidence: B).

Lower Urinary Tract Symptoms (LUTS): TRT should be used cautiously in patients with severe LUTS (International Prostate Symptom Score (IPSS > 19). Evidence suggests minimal impact on mild to moderate symptoms. Urological evaluation is recommended before initiation, along with ongoing symptom monitoring (1, 3-5) (Class: IIb; Level of Evidence: C).

Heart Failure: Testosterone may worsen fluid retention and volume overload, especially in patients with decompensated heart failure. TRT should be avoided or used with extreme caution in patients with decompensation or severe heart failure (NYHA Class III or IV). Although some studies suggest that TRT benefits men with stable heart failure, its safety in decompensated cases has not been established (3, 4, 17) (Class: IIa; Level of Evidence: C).

Recent Cardiovascular Events: In men who have experienced acute myocardial infarction (MI) or stroke, TRT should be delayed for at least 6 months to allow clinical stabilization. Although the TRAVERSE trial showed no significant increase in major cardiovascular events with TRT in high-risk men, safety in the immediate post-acute phase was not specifically assessed (3-5, 69) (Class: IIa; Level of Evidence: C).

Venous Thromboembolism and Thrombophilia: Despite recent studies not showing a significantly increased risk, caution is advised in patients with a history of venous thromboembolism or known thrombophilic disorders, with individualized assessment (1, 3, 69) (Class: IIb; Level of Evidence: C).

Previously Treated Prostate Cancer: TRT may be considered with extreme caution in men previously treated with curative intent and no evidence of recurrence. The decision should be multidisciplinary, with informed consent and rigorous PSA monitoring. (1, 3, 5) (Class: IIb; Level of Evidence: C).

In men with a history of prostate cancer, the decision to initiate testosterone therapy requires individualized, multidisciplinary evaluation. Current evidence suggests that testosterone therapy may be considered in selected men previously treated with curative intent for low-risk disease and with no evidence of recurrence, provided that close urological monitoring is maintained. Clinicians should follow national recommendations from the Brazilian Society of Urology (SBU) and international urological guidelines when evaluating such patients.

Recommendation 18: TRT should NOT be initiated in men with:

- Male breast cancer (Class: I, Level of Evidence: C);
- Known or suspected prostate cancer (untreated nodule/induration, PSA > 4 ng/mL or > 3 ng/mL in high-risk individuals without urological evaluation) (Class: I, Level of Evidence: B);
- Active short-term fertility planning (Class: I, Level of Evidence: B).

Recommendation 19: Careful evaluation and individualized management are recommended before initiating TRT in men with the following conditions (relative contraindications):

- Baseline hematocrit > 48% or hematocrit at follow-up > 54% (Class: IIa, Level of Evidence: B);
- Untreated severe obstructive sleep apnea (Class: IIa, Level of Evidence: B);
- Decompensated heart failure (NYHA Class III or IV) (Class: IIa, Level of Evidence: C);
- Myocardial infarction or stroke within the past 6 months (Class: IIa, Level of Evidence: C).

Recommendation 20: TRT may be considered with caution and close monitoring in men with:

- Severe lower urinary tract symptoms (IPSS > 19), following urological evaluation and treatment optimization (Class: IIb, Level of Evidence: C);
- History of venous thromboembolism or known thrombophilia (Class: IIb, Level of Evidence: C);
- Low-risk prostate cancer treated with curative intent and no evidence of active disease after multidisciplinary discussion and informed consent (Class: IIb, Level of Evidence: C).

Treatment in men who want to preserve fertility

Testosterone replacement therapy is a well-established treatment for hypogonadism; however, it has been associated with several adverse effects and contraindications reported in the literature, including testicular atrophy and infertility. In this context, gonadotrofins, SERMS and aromatase inhibitors may be used (3, 5, 70).

Selective Estrogen Receptor Modulators (SERMs):

Clomiphene citrate (CC), a selective estrogen receptor modulator (SERM), acts by inhibiting estradiol's negative feedback on the HPG axis. This results in increased LH and FSH secretion and subsequent stimulation of Leydig cells, thereby enhancing endogenous testosterone production (71, 72). Even though it is an off-label indication, SERMs has been used to increase sperm count by restoring the physiological function of the HPG axis (3). Studies demonstrate that clomiphene citrate increases testosterone levels in 70–90% of men with secondary hypogonadism with an important role in the treatment of cases of functional hypogonadism and those associated with MOSH and secondary to the use of anabolic steroids. It significantly improves hypogonadal symptoms including sexual function, mood, and energy. It increases sperm count and improves semen parameters in men with infertility related to hormonal abnormalities, and maintains spermatogenesis during treatment, unlike conventional TRT.(3, 5) However, CC is less as effective in the treatment of primary testicular failure (73). Adverse effects include visual disturbances, headache, mood changes, hot flashes, nausea, thrombotic events (rare), and gynecomastia (rare). Contraindications include hypersensitivity to components, severe liver disease, history of thromboembolic events, and primary hypogonadism (73, 74).

Therapeutic Regimens: the starting dose is 25 to 50 mg daily, adjusted according to clinical response and testosterone levels. However, in Brazil, only the 50 mg presentation is commercially available. Therefore, the recommendation from this group is to use 50 on alternate days. Titration: Gradually increase the dose up to 50 mg daily based on response. Duration: continuous treatment as long as necessary and well tolerated. There are follow-up studies on CC use for up to 7 years (1, 71, 74).

Gonadotropins:

The most used agents are Human Chorionic Gonadotropin (hCG) and LH analog that stimulates Leydig cells to produce testosterone, recombinant FSH that stimulates Sertoli cells and spermatogenesis, and GnRH which is used in pulsatile regimens and stimulates the release of LH and FSH by the pituitary.(5) The main indications for gonadotropin treatment in patients with hypogonadism include promoting normal physical development and maintaining the physical well-being of patients who have experienced tumors, trauma, or malformations (75). Induction of mini puberty in individuals born with congenital hypogonadism is also an indication (76). In addition, since TRT significantly reduces spermatogenesis, gonadotropin treatment is indicated for hypogonadotropic individuals who wish to preserve their fertility (3). Both urinary and recombinant hCG preparations are effective, though recombinant forms offer more consistent dosing and lower immunogenic potential (77, 78). However, it is also important to highlight that HCG or LH analog monotherapies may suppress HPG axis, leading to a decrease in FSH levels and a consequent worsening of semen parameters (3). Adverse effects include injection site reactions, increased risk of fractures, peripheral arterial disease, water retention, cardiac complications, gynecomastia (due to aromatization of testosterone to estradiol), headache, and fatigue. Contraindications include hypersensitivity to components, androgen-dependent tumors, and primary hypogonadism (limited response), thereby emphasizing the need for specialized patient monitoring following treatment (3, 5, 17, 77, 78).

Therapeutic Regimens: hCG Monotherapy: Initial dose: 1,500 to 2,000 IU, 2-3 times per week, subcutaneously; dose adjustment based on serum testosterone levels (target: 400–700 ng/dL); duration: at least 3–6 months to assess response (3, 78). Combined Therapy (hCG + FSH): hCG and FSH: 75–150 IU, 2–3 times per week; recommended when there is no adequate response to hCG monotherapy after 6 months or in severe cases of hypogonadotropic hypogonadism (3, 5, 17, 78). Due to the lack of widespread availability of some doses in Brazil, weekly application of 5000 IU hCG is reasonable.

Aromatase Inhibitors:

Act by blocking the peripheral conversion of testosterone to estradiol, thereby reducing circulating estradiol levels. Like SERMs, this reduction in estradiol attenuates the negative feedback on the HPG axis, leading to increased LH and FSH and potentially stimulating endogenous testosterone production by the testes. The use of AIs in the treatment of male hypogonadism is off label (3, 5, 71, 79). Indications for use include patients with prolactinomas, obesity, and those who wish to preserve their fertility (3, 80). To assess the toxicity of an aromatase inhibitor, a clinical screening study involving patients with hypogonadism who sought to preserve fertility through treatment with letrozole showed an actual increase in testosterone levels and sperm concentration. Adverse effects include hypertension, increased PSA levels, head-

aches, reduced bone mineral density, joint and muscle pain, fatigue, mood changes, elevated liver enzymes, increased hematocrit, and elevated LDL cholesterol. Contraindications include hypersensitivity to components, presence of osteoporosis or significant osteopenia, and severe liver disease (81, 82). In this context, follow-up should be conducted to monitor their long-term effects (3).

Therapeutic Regimens: Anastrozole: Dose: 0.5–1 mg daily or on alternate days; Duration: continuous treatment as long as necessary and well tolerated (3, 5, 74). Letrozole: Dose: 0.5–2.5 mg daily or weekly; Duration: like anastrozole (74, 81, 82).

Gonadotropin releasing hormone agonist (GnRHa) therapy:

Abnormal germ cell development in cryptorchidism results from an endocrinopathy associated with impaired mini puberty, characterized by hormonal imbalance and altered gene expression, rather than a congenital dysgenesis. Low-dose GnRHa therapy in high-risk patients induces a broad transcriptional response within the HPG axis, leading to normal spermatogenesis in 86% of cases and absence of azoospermia. Therefore, post-orchidopexy hormonal treatment is strongly recommended for high-risk cryptorchid boys and may also serve as primary pre-surgical therapy to promote testicular descent and reduce postoperative testicular atrophy (83).

Recommendation 21: Men with testosterone deficiency who are interested in fertility should have a reproductive health evaluation performed prior to treatment (Class: I, Level of Evidence: B).

Recommendation 22: Use of selective estrogen receptor modulators, human chorionic gonadotropin, aromatase inhibitors, alone or in combination may be offered to selected men with testosterone deficiency desiring to maintain fertility (Class: I, Level of Evidence: C).

Adjunct and Alternative Therapies: Lifestyle Modifications and Weight Loss

Lifestyle changes, including weight loss and regular physical activity, represent the first-line therapeutic approach for many men with hypogonadism, especially those with MOSH (3-5, 35).

Regular physical exercise, both aerobic and resistance training, can increase testosterone levels, improve body composition, insulin sensitivity, and overall well-being. However, exhaustive and prolonged exercise may lead to a transient decrease in testosterone due to increased cortisol levels. Therefore, moderation and appropriate exercise programming are crucial (84, 85).

Given the lack of evidence, the TRT solely for glycemic control, weight loss, and cardiovascular risk reduction is not recommended (36, 86).

Despite positive preliminary studies, the evidence supporting the use of nutraceuticals and antioxidants in the treatment of male hypogonadism is still considered low, highlighting the need for further clinical trials (1, 3). Therefore, their routine use is not recommended (3, 84).

Recommendation 23: Lifestyle changes (weight loss, exercise) should be strongly recommended as first-line therapy for men with overweight and obesity and functional hypogonadism (Class: I, Level of Evidence: A)

Recommendation 24: TRT for the sole purposes of glycemic control, weight loss and cardiovascular risk reduction is not recommended (Class: III, Level of Evidence: C).

Recommendation 25: Routine supplementation with nutraceuticals or antioxidants is not recommended for the treatment of male hypogonadism (Class: III, Level of Evidence: C)

Recommendation 26: Patients considering or using adjuvant and alternative therapies should be informed about the limited evidence base, product variability, and potential risks, and should be appropriately monitored (Class: I, Level of Evidence: C)

Ethical Conditions for Testosterone Replacement Therapy

In terms of ethical conditions for TRT, it is important to ensure that therapy is administered appropriately, based on clear medical indications, and with full informed consent. Patients must be fully informed about potential benefits, risks (e.g., cardiovascular effects, fertility issues), and the long-term nature of therapy. It is essential to discuss the possibility of side effects like sleep apnea, erythrocytosis (increased red blood cells), and impacts on fertility (3-5, 26). Ethical management involves constant evaluation to decide whether therapy should continue, be adjusted, or stopped based on patient progress.

TRT should not be prescribed for off label uses like general age-related decline in testosterone or for performance enhancement without clear medical justification as it is linked to increased cardiovascular risk and serious complications (87, 88). The use of testosterone in sports for performance enhancement, without medical necessity, is considered doping (89).

MONITORING OF MALE HYPOGONADISM TREATMENT

Clinical Monitoring

Clinical monitoring is a fundamental aspect of TRT to ensure therapeutic efficacy, assess symptom resolution, detect adverse effects early, and guide dose adjustments (68, 90). Improvements in symptoms should be evaluated systematically, focusing on domains most affected by testosterone deficiency, such as sexual function (libido, erectile function), mood, vitality, muscle mass, body composition, and quality of life (1-5).

The most consistent and earliest improvements typically occur in sexual desire and libido, often within 3 to 6 weeks of initiating therapy, followed by gradual improvements in erectile function, energy levels, and mood over several months (90). Increases in lean body mass and reductions in fat mass generally become apparent after 12 to 16 weeks of continuous therapy (90). Monitoring should include structured clinical interviews, validated questionnaires when available (such as the International Index of Erectile Function – IIEF), and physical examination focused on body composition and potential adverse effects.

A lack of symptomatic improvement despite normalization of serum testosterone levels after an adequate treatment period (typically 6 months) should prompt a reassessment of diagnosis, adherence, comorbidities, and realistic patient expectations (3-5). It is important to counsel patients that improvements vary individually, and that testosterone therapy is not a panacea for all symptoms of aging. A holistic management approach addressing lifestyle, psychological factors, and comorbid illnesses enhances the likelihood of successful outcomes. We emphasize the need to continue treatment even if there is no improvement in symptoms in the initial phase, as there are different timeframes for symptom improvement. Figure-2 summarizes the expected times for symptom improvement after starting TRT.

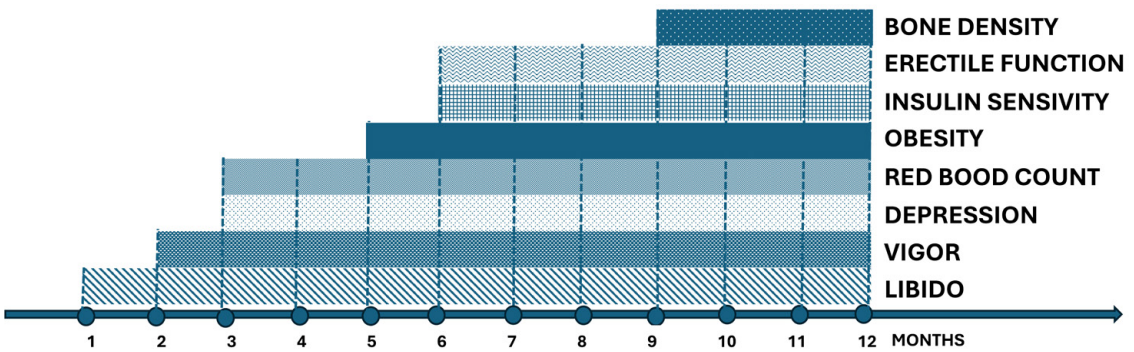
While the goal of therapy is clinical improvement and normalization of testosterone within the mid-normal range, a target value between 450–600 ng/dL is considered appropriate, aligning with the European Association of Urology (EAU) and Endocrine Society recommendation (3, 4).

Recommendation 27: During testosterone replacement therapy, clinicians should perform regular clinical evaluations to assess symptomatic improvement in libido, sexual function, vitality, mood, and body composition, using structured interviews and validated tools where appropriate (Class: I, Level of Evidence: A)

Dose Adjustments and Changes in Therapy Strategies

The need to change the therapeutic strategy may arise due to various factors, including inadequate symptomatic or laboratory response at the maximum tolerated dose of the current formulation, intolerable or persistent adverse effects, patient preference for a different route or dosing frequency, or cost and availability issues (5, 17). Management includes dose reduction, increased interval between injections, switching to a transdermal formulation, or performing therapeutic phlebotomy (68). If it persists, discontinuation should be considered (Table-3).

Figure 2 - Onset of effects of testosterone replacement therapy as a function of time. Adapted from (16).



Timeline of the expected onset of clinical effects after initiating testosterone replacement therapy, including sexual, metabolic, psychological, and musculoskeletal domains.

Table 3 - Dose adjustments and changes in therapeutic strategies. Adapted from (1, 3).

Clinical Situation	Recommended Action	Reevaluation Time
Start of TRT	Start with the standard dose of the chosen formulation	-
Testosterone levels within target range (400–700 ng/dL)	Maintain current dose	Monitor annually
Testosterone levels below target range and symptoms persist	Gradually increase dose	Reevaluate in 6–12 weeks
T levels above target	Gradually reduce dose	Reevaluate in 6–12 weeks
Dose-related adverse effects (e.g., mild erythrocytosis)	Gradually reduce dose	Reevaluate in 6–12 weeks
Symptoms persist despite testosterone levels within target range	Reassess diagnosis, consider other causes, discuss discontinuation	Individualized decision

Monitoring testosterone levels may vary depending on the pharmacokinetics of each formulation. When using short-acting options, it should be considered that the maximum plasma peak occurs rapidly around the first 2-5 days, with a median nadir around 15-20 days. This allows doses to be administered at intervals ranging from 2 to 4 weeks, depending on the patient's clinical response. The long-acting formulation tends not to peak, maintaining testosterone levels close to physiological levels for a period of 10 to 14 weeks. Testosterone measurement is recommended at the end of the ampoule administration interval. In the transdermal gel option, serum testosterone should be evaluated 2 to 8 hours after gel application, after the patient has been in treatment for at least 1 week. It is recommended to evaluate serum testosterone levels 2 to 3 months after the start of treatment (3, 4).

Transitioning to other formulations should be done in a way that minimizes fluctuations in testosterone levels and symptoms. Temporary or permanent discontinuation is indicated in the absence of clinical benefit after 3–6 months of adequate testosterone levels, development of contraindications (e.g., prostate cancer), severe unmanageable adverse effects, or patient desire (3).

Reassessment of symptoms, hormonal levels, and comorbidities should be performed after discon-

tinuation, as the HPG axis may take weeks to months to recover. In selected cases, alternative therapies may be implemented. (4, 91). The algorithm for dose adjustments and changes in therapeutic strategies is shown in Table-1.

Recommendation 28: Serum testosterone levels should be monitored at 3, 6, and 12 months after starting TRT, and every 6–12 months thereafter, with dose adjustments to achieve levels within the mid-tertile reference range (Class: I, Level of Evidence: A)

Recommendation 29: Transitioning between different testosterone formulations is a valid strategy in cases of inadequate response, adverse effects, or patient preference (Class: I, Level of Evidence: C)

Monitoring and management of side effects

Testosterone dosage should be adjusted to achieve serum levels within the mid-tertile reference range. If no clinical benefit is observed or significant changes in hematocrit or PSA levels occur after 6–12 months of therapy, TRT should be adjusted or discontinued. In such cases, the hormonal axis and comorbidities must be reassessed, and alternative therapeutic options considered (90).

TRT is associated with several potential adverse effects, including gynecomastia, acne, increased skin oiliness, baldness, erythrocytosis, reduced sperm production (potentially leading to infertility), decreased testicular volume, fluid retention and/or edema, symptoms related to obstructive sleep apnea and hypoventilation syndrome and growth of androgen-dependent neoplasms (68). Local irritation is common, and rotating application sites and moisturizing the skin may help. If persistent, consider changing the formulation (1, 3-5).

Gynecomastia has been observed in men receiving TRT when elevated estrogen levels occur. Routine monitoring of estradiol is not recommended. Tamoxifen may also be used to reduce breast tissue enlargement. In symptomatic cases that persist for at least 12 months despite medical management, elective plastic surgery may be considered (92-94).

Acne is a common side effect of TRT due to increased sebaceous gland activity. Topical therapies such as retinoids, benzoyl peroxide, azelaic acid, and/or combinations of topical agents are first-line treatments in managing mild to moderate acne. In more severe cases, oral antibiotics or isotretinoin may be indicated. Educating patients on proper skin care is also essential to help minimize acne outbreaks. Referral to a dermatologist should be considered for patients with persistent or severe acne (68, 95).

Patients should be assessed for testosterone and hematocrit levels at 3, 6 and 12 months after starting TRT, with subsequent annual evaluations (3-5, 15, 26). Elevation of hematocrit above the limit of normal is the most common adverse effect of TRT and has been associated with cardiovascular events and/or venous thromboembolism (VTE) due to blood hyperviscosity (3, 66, 68, 96). If the hematocrit level exceeds 54% during treatment, it is advisable to temporarily suspend therapy until the levels return to a safe range(68). Once normalized, TRT can be resumed at lower doses, potentially with a different formulation. The testosterone gel, for example, tends to have a lesser impact on hematocrit levels. The decision to perform phlebotomy should be made on a case-by-case basis. Additionally, addressing factors such as obesity, sleep apnea, and smoking may help reduce the risk of erythrocytosis (3, 4, 26). If a VTE episode occurs while in TRT and hematocrit values are within normal range, an underlying undiagnosed thrombophilia can be the cause (3, 5, 97). Lipid and glycemic profile should be evaluated at baseline and annually during testosterone therapy (3).

TRT is not recommended for men seeking fertility, as exogenous testosterone suppresses the HPT axis and subsequently impairs spermatogenesis (1-5, 26). The extent of the negative impact of TRT on fertility is variable. Evidence from studies in healthy men suggests that baseline fertility is typically restored in most patients within 24 months following cessation of TRT. However, data regarding this recovery in infertile males remain limited (1). Depending on the underlying cause of hypogonadism, and after evaluating the individual's fertility, it may be advisable to consider alternative medications to TRT (1-5). Every patient should be inquired about their future fertility plans regardless of age and should be counseled about fer-

tility preservation options. For those with fertility concerns, an assessment should be conducted through semen analysis and partner's fertility status (3). Referral to fertility specialists should be considered.

There is an increased risk of fluid retention and edema, which may exacerbate pre-existing edematous conditions, such as heart failure (4, 98). TRT does not appear to worsen LUTS in men who do not have severe LUTS prior to treatment. The effects of testosterone on men with severe LUTS remain unclear, as this group was excluded from clinical studies (3, 99-101). TRT in men with obstructive sleep apnea may exacerbate symptoms, so caution is advised when initiating TRT in these patients (60, 102).

The risk of prostate cancer should be evaluated before starting TRT using PSA measurements and digital rectal examination in men after 45 years and especially those at higher risk for prostate cancer (men of African descent and those with a first-degree relative with diagnosed prostate cancer or previously positive prostate biopsy, and in those with baseline PSA concentrations >1ng/mL at age 40 years or > 2ng/mL at age 60 years) (103). Recommendation to reassess PSA measurements again 3, 6 and 12 months after initiation (3, 5). After the first 12 months, local guidelines for prostate cancer screening for the general population should be followed which emphasize shared decision-making and risk stratification rather than universal testing (5). A urological evaluation should be requested prior or during TRT if any abnormalities are detected during the digital rectal examination, if there is a new onset or worsening of LUTS (5, 30). It is important to emphasize that a modest initial rise in PSA may occur within the first 3 to 6 months of TRT (up to 1.0 ng/dL), reflecting increased prostatic androgenic stimulation; however, PSA levels generally stabilize thereafter (104, 105). Persistent increases beyond the first year, a velocity of rise exceeding 0.75 ng/mL/year, or a rise >1.4 ng/mL within the first 12 months should prompt referral to a urologist (1, 3-5). PSA thresholds should be interpreted in an age-specific manner: values >2.5 ng/mL in men aged 40–49 years, >3.5 ng/mL in men aged 50–59 years, and >4.0 ng/mL in men aged ≥60 years are considered abnormal and warrant further evaluation (103).

Although not a common side effect of TRT, men with hypogonadism should be screened for osteoporosis (3, 4). Recently, the TRAVERSE study reported a higher incidence of fractures in men receiving TRT (106). However, this increase was observed mainly during the initial months of treatment and included all types of fractures. When considering only low-impact fractures, the risk was similar between the TRT and placebo groups (106). Although previous studies have shown improvements in BMD with TRT, it should not be used as a standalone treatment for patients at high risk of fracture, as evidence supporting its anti-fracture efficacy remains limited (4, 5, 26, 106).

Recommendation 30: Testosterone and hematocrit levels should be measured at 3, 6, and 12 months after the initiation of TRT, and then annually. If hematocrit exceeds 54%, TRT should be discontinued until levels decrease to a safe range. Treatment can then be resumed with a lower dose and a transdermal formulation (Class: I, Level of Evidence: B).

Recommendation 31: A digital rectal examination and PSA test should be performed at 3 and 12 months after starting TRT, and subsequently according to local guidelines for prostate cancer screening in the general population (Class: II, Level of Evidence: C).

Recommendation 32: Further evaluation should be considered if there is an increase in serum PSA levels > 1.4 ng/mL within 12 months of TRT, a confirmed PSA > 4 ng/mL at any time, a detection of a prostatic abnormality on digital rectal examination, or a significant worsening of LUTS (Class: II, Level of Evidence: C)

Discontinuation and Reassessment of Therapeutic Need

Organic male hypogonadism is generally considered a lifelong condition. However, spontaneous reversal may occur in select cases. Studies on congenital secondary hypogonadism have reported reversal in approximately 10-15% of patients undergoing TRT (107, 108). Clinicians should remain alert to this possibility, particularly in the presence of unexpected testicular enlarge-

ment during treatment (109, 110). A recent study involving men with congenital hypogonadotropic hypogonadism identified several predictors of reversibility, including larger testicular volume, absence of micropenis, and higher serum FSH levels. These features are consistent with Pasqualini syndrome (fertile eunuch phenotype). In contrast, the presence of pathogenic ANOS1 mutations was associated with irreversible hypogonadism (111).

While reversal is rare in cases of organic hypogonadism, functional hypogonadism may be resolved with the treatment of underlying conditions (2). Potentially reversible causes include hyperprolactinemia, end-stage renal disease, opioid use, previous anabolic steroid use, glucocorticoid therapy, excessive alcohol or cannabis use, systemic illness, nutritional deficiencies or excessive exercise, obesity, metabolic syndrome, certain sleep disorders, and other chronic diseases (4, 5, 36). When a reversible cause is identified, a trial discontinuation of TRT should be considered to reassess HPG axis function. The timing of this reassessment should account for the pharmacokinetics of the testosterone preparation used and the clinical scenario, including symptom resolution and biochemical normalization of testosterone levels. If endogenous testosterone levels remain normal and symptoms resolve, tapering or discontinuation of TRT may be appropriate, with close monitoring for recurrence of hypogonadal symptoms or hormonal decline (2-5).

CONCLUSIONS

Male hypogonadism is a multifaceted condition that requires timely recognition, careful diagnostic evaluation, and individualized management strategies. Incorporating evidence-based therapies, such as testosterone replacement therapy and selective estrogen receptor modulators, in the context of multidisciplinary care, is essential to optimize clinical outcomes and address patient-specific goals, including potential fertility preservation.

This position paper underscores the importance of continuous education, adherence to updated guidelines, and collaborative care across specialties. By providing practical recommendations and highlighting emerging therapeutic options, it seeks to enhance clinician awareness, reduce underdiagnosis, and improve the quality of care for men affected by hypogonadism.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Mulhall JP, Trost LW, Brannigan RE, Kurtz EG, Redmon JB, Chiles KA, et al. Evaluation and Management of Testosterone Deficiency: AUA Guideline. J Urol. 2018 Aug;200(2):423-432. DOI: 10.1016/j.juro.2018.03.115
2. Corona G, Goulis DG, Huhtaniemi I, Zitzmann M, Toppari J, Forti G, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: Endorsing organization: European Society of Endocrinology. Andrology. 2020 Sep;8(5):970-987. DOI: 10.1111/andr.12770
3. Salonia A, Capogrosso P, Boeri L, Cocci A, Corona G, Dinkelman-Smit M, et al. European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2025 Update on Male Hypogonadism, Erectile Dysfunction, Premature Ejaculation, and Peyronie's Disease. Eur Urol. 2025 Jul;88(1):76-102. DOI: 10.1016/j.eururo.2025.04.010
4. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018 May 1;103(5):1715-1744. DOI: 10.1210/jc.2018-00229
5. Khera M, Torres LO, Grober ED, Morgentaler A, Miner M, Jones TH, et al. Male hypogonadism: recommendations from the Fifth International Consultation on Sexual Medicine (ICSM 2024). Sex Med Rev. 2025 Oct 4;13(4):548-573. DOI: 10.1093/sxmrev/qeaf036
6. Rastrelli G, Corona G, Mannucci E, Maggi M. Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. Andrology. 2014 Nov;2(6):794-808. DOI: 10.1111/andr.262
7. Oduwole OO, Huhtaniemi IT, Misrahi M. The Roles of Luteinizing Hormone, Follicle-Stimulating Hormone and Testosterone in Spermatogenesis and Folliculogenesis Revisited. Int J Mol Sci. 2021 Nov 29;22(23):12735. DOI: 10.3390/ijms222312735

8. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002 Feb;87(2):589-598. DOI: 10.1210/jcem.87.2.8201
9. Spaziani M, Carlomagno F, Tarantino C, Angelini F, Vincenzi L, Gianfrilli D. New perspectives in functional hypogonadotropic hypogonadism: beyond late onset hypogonadism. Front Endocrinol (Lausanne). 2023;14:1184530. DOI: 10.3389/fendo.2023.1184530
10. Thirumalai A, Anawalt BD. Epidemiology of Male Hypogonadism. Endocrinol Metab Clin North Am. 2022 Mar;51(1):1-27. DOI: 10.1016/j.ecl.2021.11.016
11. Zarotsky V, Huang MY, Carman W, Morgentaler A, Singhal PK, Coffin D, et al. Systematic literature review of the epidemiology of nongenetic forms of hypogonadism in adult males. Hormones (Athens). 2014;13(3):356-369. DOI: 10.14310/horm.2002.1481
12. Oliveira VHM, Duarte ABA, Lima-Filho DAP, Oliveira FT, Castro GRS, Vasconcelos GB, et al. Relevance of obesity as an etiology of secondary hypogonadism: an integrative review. Res Soc Dev. 2022;11(14):e456111436689.
13. Negretto LAF, Rassi N, Soares LR, Saraiva ABC, Teixeira MEF, Santos LDR, et al. Testosterone deficiency in hypertensive men: prevalence and associated factors. Arq Bras Cardiol. 2024;121(3):e20230138. DOI: 10.36660/abc.20230138
14. Giagulli VA, Castellana M, Lisco G, Triggiani V. Critical evaluation of different available guidelines for late-onset hypogonadism. Andrology. 2020 Nov;8(6):1628-1641. DOI: 10.1111/andr.12839
15. Hackett G, Kirby M, Edwards D, Jones TH, Wylie K, Ossei-Gerning N, et al. British Society for Sexual Medicine guidelines on adult testosterone deficiency, with statements for UK practice. J Sex Med. 2017 Dec;14(12):1504-1523. DOI: 10.1016/j.jsxm.2017.10.067
16. Lunenfeld B, Mskhalaya G, Zitzmann M, Arver S, Kalinchenko S, Tishova Y, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male. 2015;18(1):5-15. DOI: 10.3109/13685538.2015.1004049
17. Grober ED, Krakowsky Y, Khera M, Holmes DT, Lee JC, Grantmyre JE, et al. Canadian Urological Association guideline on testosterone deficiency in men: evidence-based Q&A. Can Urol Assoc J. 2021 May;15(5):E234-E243. DOI: 10.5489/cuaj.7057
18. Majumdar S, Mukherjee JJ, Ray S, Goswami S, Jude E, Biswas A, et al. Testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism: an Integrated Diabetes and Endocrine Academy (IDEA) consensus guideline. Diabetes Metab Syndr. 2021;15(4):102191. DOI: 10.1016/j.dsx.2021.102191
19. Lee DS, Park HJ. Efficacy and safety of testosterone therapy based on guideline recommendations; re: clinical practice guideline by the American College of Physicians. World J Mens Health. 2020 Nov;38(4):397-401. DOI: 10.5534/wjmh.200116
20. Millar AC, Lau ANC, Tomlinson G, Kraguljac A, Simel DL, Detsky AS, et al. Predicting low testosterone in aging men: a systematic review. CMAJ. 2016 Jul 12;188(13):E321-E330. DOI: 10.1503/cmaj.150262
21. Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol (Oxf). 2007 Dec;67(6):853-862. DOI: 10.1111/j.1365-2265.2007.02976.x
22. Lehtihet M, Arver S, Bartuseviciene I, Pousette A. S-testosterone decrease after a mixed meal in healthy men independent of SHBG and gonadotrophin levels. Andrologia. 2012 Dec;44(6):405-410. DOI: 10.1111/j.1439-0272.2012.01296.x
23. Wu FCW, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010 Jul 8;363(2):123-135. DOI: 10.1056/NEJMoa0911101
24. Caronia LM, Dwyer AA, Hayden D, Amati F, Pitteloud N, Hayes FJ. Abrupt decrease in serum testosterone levels after an oral glucose load in men: implications for screening for hypogonadism. Clin Endocrinol (Oxf). 2013 Feb;78(2):291-296. DOI: 10.1111/j.1365-2265.2012.04486.x
25. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone's binding in circulation: physiological and clinical implications. Endocr Rev. 2017 Aug 1;38(4):302-324. DOI: 10.1210/er.2017-00025
26. Kanakis GA, Pofi R, Goulis DG, Isidori AM, Armeni E, Erel CT, et al. EMAS position statement: testosterone replacement therapy in older men. Maturitas. 2023 Dec;178:107854. DOI: 10.1016/j.maturitas.2023.107854

27. de Ronde W, van der Schouw YT, Pols HAP, Gooren LJG, Muller M, Grobbee DE, et al. Calculation of bioavailable and free testosterone in men: a comparison of 5 published algorithms. Clin Chem. 2006 Sep;52(9):1777-1784. DOI: 10.1373/clinchem.2005.063354
28. Corona G, Mannucci E, Fisher AD, Lotti F, Ricca V, Balercia G, et al. Effect of hyperprolactinemia in male patients consulting for sexual dysfunction. J Sex Med. 2007 Sep;4(5):1485-1493. DOI: 10.1111/j.1743-6109.2007.00569.x
29. Gabrielsen JS, Lamb DJ, Lipshultz LI. Iron and a man's reproductive health: the good, the bad, and the ugly. Curr Urol Rep. 2018 Jun 1;19(8):60. DOI: 10.1007/s11934-018-0808-x
30. Salter CA, Mulhall JP. Guideline of guidelines: testosterone therapy for testosterone deficiency. BJU Int. 2019 Nov;124(5):722-729. DOI: 10.1111/bju.14899
31. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 6th ed. Geneva: World Health Organization; 2021.
32. Tajar A, Forti G, O'Neill TW, Lee DM, Silman AJ, Finn JD, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. J Clin Endocrinol Metab. 2010 Apr;95(4):1810–1818. DOI: 10.1210/jc.2009-1796
33. Barber TM, Kyrou I, Kaltsas G, Grossman AB, Randeva HS, Weickert MO. Mechanisms of central hypogonadism. Int J Mol Sci. 2021 Jul;22(15):8217. DOI: 10.3390/ijms22158217
34. Ribeiro RS, Abucham J. Recovery of persistent hypogonadism by clomiphene in males with prolactinomas under dopamine agonist treatment. Eur J Endocrinol. 2009 Jul;161(1):163–169. DOI: 10.1530/EJE-09-0252
35. Fernandez CJ, Chacko EC, Pappachan JM. Male obesity-related secondary hypogonadism: pathophysiology, clinical implications and management. Eur Endocrinol. 2019;15(2):83–90. DOI: 10.17925/EE.2019.15.2.83
36. Hohl A, Spivakoski CS, Rigon FA, Sande-Lee S, Ronsoni MF. Hipogonadismo masculino na síndrome metabólica e DM2. Diretriz oficial da Sociedade Brasileira de Diabetes. Diabetol Metab Syndr (Suppl). [Internet]. 2023. Available at. <https://diretriz.diabetes.org.br/hipogonadismo-masculino-na-sindrome-metabolica-e-dm2/>
37. Carrageta DF, Oliveira PF, Alves MG, Monteiro MP. Obesity and male hypogonadism: tales of a vicious cycle. Obes Rev. 2019 Aug;20(8):1148–1158. DOI: 10.1111/obr.12866
38. Corona G, Rastrelli G, Monami M, Saad F, Luconi M, Lucchese M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol. 2013 Jun;168(6):829–843. DOI: 10.1530/EJE-12-0955
39. Rastrelli G, Carter EL, Ahern T, Finn JD, Antonio L, O'Neill TW, et al. Development of and recovery from secondary hypogonadism in aging men: prospective results from the EMAS. J Clin Endocrinol Metab. 2015 Aug;100(8):3172–3182. DOI: 10.1210/jc.2015-1571
40. Corona G, Rastrelli G, Morelli A, Sarchielli E, Cipriani S, Vignozzi L, et al. Treatment of functional hypogonadism besides pharmacological substitution. World J Mens Health. 2020 Apr;38(3):256–270. DOI: 10.5534/wjmh.190061
41. Escobar-Morreale HF, Santacruz E, Luque-Ramírez M, Botella Carretero JI. Prevalence of 'obesity-associated gonadal dysfunction' in severely obese men and women and its resolution after bariatric surgery: a systematic review and meta-analysis. Hum Reprod Update. 2017;23(4):390-408. DOI: 10.1093/humupd/dmx012
42. Salvio G, Ciarloni A, Ambo N, Bordoni M, Perrone M, Rossi S, et al. Effects of glucagon-like peptide 1 receptor agonists on testicular dysfunction: a systematic review and meta-analysis. Andrology. 2025;13(8):2022-2034. DOI: 10.1111/andr.70022
43. Ricci G, Catizone A, Esposito R, Pisanti FA, Vietri MT, Galdieri M. Diabetic rat testes: morphological and functional alterations. Andrologia. 2009;41(6):361-368. DOI: 10.1111/j.1439-0272.2009.00937.x
44. Brüning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, et al. Role of brain insulin receptor in control of body weight and reproduction. Science. 2000;289(5487):2122-2125. DOI: 10.1126/science.289.5487.2122
45. Pal L, Chu H-P, Shu J, Topalli I, Santoro N, Karkanias G. In vitro evidence of glucose-induced toxicity in GnRH secreting neurons: high glucose concentrations influence GnRH secretion, impair cell viability, and induce apoptosis in the GT1-1 neuronal cell line. Fertil Steril. 2007;88(4 Suppl):1143-1149. DOI: 10.1016/j.fertnstert.2007.01.007
46. Wu FCW, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab. 2008;93(7):2737-2745. DOI: 10.1210/jc.2007-1972

47. Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. J Clin Endocrinol Metab. 2007;92(2):549-555. DOI: 10.1210/jc.2006-1859
48. Christou MA, Christou PA, Markozannes G, Tsatsoulis A, Mastorakos G, Tigas S. Effects of anabolic androgenic steroids on the reproductive system of athletes and recreational users: a systematic review and meta-analysis. Sports Med. 2017;47(9):1869-1883. DOI: 10.1007/s40279-017-0709-z
49. Rasmussen JJ, Selmer C, Østergren PB, Pedersen KB, Schou M, et al. Former Abusers of Anabolic Androgenic Steroids Exhibit Decreased Testosterone Levels and Hypogonadal Symptoms Years after Cessation: A Case-Control Study. PLoS One. 2016;11(8):e0161208. DOI: 10.1371/journal.pone.0161208
50. Hackney AC. Hypogonadism in Exercising Males: Dysfunction or Adaptive-Regulatory Adjustment? Front Endocrinol (Lausanne). 2020;11:11. DOI: 10.3389/fendo.2020.00011
51. Rothmore J. Antidepressant-induced sexual dysfunction. Med J Aust. 2020;212(7):329–334. DOI: 10.5694/mja2.50476
52. Coluzzi F, Billeci D, Maggi M, Corona G. Testosterone deficiency in non-cancer opioid-treated patients. J Endocrinol Invest. 2018;41(12):1377–1388. DOI: 10.1007/s40618-018-0930-6
53. Vuong C, Van Uum SHM, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. Endocr Rev. 2010;31(1):98–132. DOI: 10.1210/er.2009-0009
54. Reid IR, Ibbertson HK, France JT, Pybus J. Plasma testosterone concentrations in asthmatic men treated with glucocorticoids. Br Med J (Clin Res Ed). 1985;291(6495):574.
55. MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med. 1986;104(5):648–651. DOI: 10.7326/0003-4819-104-5-648
56. Glina FPA, Lopes L, Esteves RS, Barros EAC, Biselli B, Glina S. Do statins decrease testosterone in men? Systematic review and meta-analysis. Int Braz J Urol. 2024;50(2):119–135.
57. Lotti F, Maggi M. Ultrasound of the male genital tract in relation to male reproductive health. Hum Reprod Update. 2015;21(1):56–83. DOI: 10.1093/humupd/dmu042
58. Spaggiari G, Maffei AR, Santi D. Testicular ultrasound inhomogeneity is an informative parameter for fertility evaluation. Asian J Androl. 2020;22(3):302–308. DOI: 10.4103/aja.aja_42_19
59. De Silva NL, Papanikolaou N, Grossmann M, Antonio L, Quinton R, Anawalt BD, et al. Male hypogonadism: pathogenesis, diagnosis, and management. Lancet Diabetes Endocrinol. 2024;12(10):761–774. DOI: 10.1016/S2213-8587(24)00179-5
60. Trost L. Update to the testosterone guideline. J Urol. 2024;211(4):608–610. DOI: 10.1097/JU.0000000000003846
61. Carter IV, Callegari MJ, Jella TK, Mahran A, Cwalina TB, Muncey W, et al. Trends in testosterone prescription amongst medical specialties: a 5-year CMS data analysis. Int J Impot Res. 2023;35(4):1–5. DOI: 10.1038/s41443-023-00662-8
62. Lakshman KM, Basaria S. Safety and efficacy of testosterone gel in the treatment of male hypogonadism. Clin Interv Aging. 2009;4:397–412.
63. McCullough A. A review of testosterone pellets in the treatment of hypogonadism. Curr Sex Health Rep. 2014;6(4):265–269. DOI: 10.1007/s11930-014-0033-1
64. Grober ED, Garbens A, Bozovic A, Kulasingam V, Fanipour M, Diamandis EP. Accuracy of testosterone concentrations in compounded testosterone products. J Sex Med. 2015;12(6):1381–1388. DOI: 10.1111/jsm.12894
65. Rotker KL, Alavian M, Nelson B, Baird GL, Miner MM, Sigman M, et al. Association of subcutaneous testosterone pellet therapy with developing secondary polycythemia. Asian J Androl. 2018;20(2):195–199. DOI: 10.4103/aja.aja_68_17
66. Ory J, Nackeeran S, Balaji NC, Hare JM, Ramasamy AR. Secondary polycythemia in men receiving testosterone therapy increases risk of major adverse cardiovascular events and venous thromboembolism in the first year of therapy. J Urol. 2022;207(6):1295–1301. DOI: 10.1097/JU.0000000000002518
67. Graziani A, Grande G, Ferlin A. The complex relation between obstructive sleep apnoea syndrome, hypogonadism and testosterone replacement therapy. Front Reprod Health. 2023;5:1219239. DOI: 10.3389/frph.2023.1219239

68. Basheer B, Ila V, Barros R, Mesquita F, Lopes LS, Lima VFN, et al. Management of adverse effects in testosterone replacement therapy. Int Braz J Urol. 2025;51(3).
69. Lincoff AM, Bhasin S, Flevaris P, Mitchell LM, Basaria S, Boden WE, et al. Cardiovascular safety of testosterone-replacement therapy. N Engl J Med. 2023;389(2):107–117. DOI: 10.1056/NEJMoa2301761
70. Zitzmann M, Cremers JF, Krallmann C, Soave A, Kliesch S. TRACK_9: testosterone replacement assessment: classical vs functional hypogonadism—knowledge from a 9-year study. Andrology. 2024;12(8):1675–1696. DOI: 10.1111/andr.13570
71. Krzastek SC, Sharma D, Abdullah N, Sultan M, Machen GL, Wenzel JL, et al. Long-term safety and efficacy of clomiphene citrate for the treatment of hypogonadism. J Urol. 2019;202(5):1029–1035. DOI: 10.1097/JU.0000000000000360
72. Hohl A, Chavez MP, Pasqualotto EB, Ferreira ROM, Sande-Lee SV, Ronsoni MF. Clomiphene or enclomiphene citrate for the treatment of male hypogonadism: a systematic review and meta-analysis of randomized controlled trials. Arch Endocrinol Metab. 2025;69(5):1–35.
73. Kim ED, Crosnoe L, Bar-Chama N, Khera M, Lipshultz LI. The treatment of hypogonadism in men of reproductive age. Fertil Steril. 2013;99(3):718–724. DOI: 10.1016/j.fertnstert.2012.11.028
74. Raheem OA, Chen T, Akula KP, Greenberg J, Le TV, Chernobylsky D, et al. Efficacy of non-testosterone-based treatment in hypogonadal men: a review. Sex Med Rev. 2021;9(3):381–392. DOI: 10.1016/j.sxmr.2020.09.004
75. Kliesch S, Behre HM, Nieschlag E. High efficacy of gonadotropin or pulsatile gonadotropin-releasing hormone treatment in hypogonadotropic hypogonadal men. Eur J Endocrinol. 1994;131(4):347–354. DOI: 10.1530/eje.0.1310347
76. Rhys-Evans S, d'Aniello F, Alexander EC, Dinah IF, Heger S, Nordenström A, et al. Gonadotropin therapy for mini-puberty induction in male infants with hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2025;110(4):e921–e931. DOI: 10.1210/clinem/dgae024
77. Isidori AM, Balercia G, Calogero AE, Corona G, Ferlin A, Francavilla S, et al. Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian Society of Endocrinology. J Endocrinol Invest. 2015;38(1):103–112. DOI: 10.1007/s40618-014-0153-2
78. Boeri L, Capogrosso P, Salonia A. Gonadotropin treatment for the male hypogonadotropic hypogonadism. Curr Pharm Des. 2021;27(24):2775–2783. DOI: 10.2174/1381612827666210419123204
79. Ide V, Vanderschueren D, Antonio L. Treatment of men with central hypogonadism: alternatives for testosterone replacement therapy. Int J Mol Sci. 2020;22(1):21. DOI: 10.3390/ijms22010021
80. Akirov A, Rudman Y. The role of aromatase inhibitors in male prolactinoma. J Clin Med. 2023;12(4):1267. DOI: 10.3390/jcm12041267
81. Tenti S, Correale P, Cheleschi S, Fioravanti A, Pirtoli L. Aromatase inhibitor–induced musculoskeletal disorders: current knowledge on clinical and molecular aspects. Int J Mol Sci. 2020;21(16):5625. DOI: 10.3390/ijms21165625
82. Jones TH, Dobs AS, Randeva H, Moore W, Parkin JM. Leflutrozole in male obesity-associated hypogonadotropic hypogonadism: a phase 2b double-blind randomized controlled trial. Eur J Endocrinol. 2023;189(3):297–308. DOI: 10.1093/ejendo/lvad090
83. Hadziselimovic F. Advocating hormonal treatment to prevent adult infertility in patients diagnosed with congenital undescended testes. Int Braz J Urol. 2024;50(1):20–27.
84. Santos HO, Cadegiani FA, Forbes SC. Nonpharmacological interventions for the management of testosterone and sperm parameters: a scoping review. Clin Ther. 2022;44(8):1129–1149. DOI: 10.1016/j.clinthera.2022.06.010
85. Gregori G, Celli A, Barnouin Y, Paudyal A, Armamento-Villareal R, Napoli N, et al. Cognitive response to testosterone replacement added to intensive lifestyle intervention in older men with obesity and hypogonadism. Am J Clin Nutr. 2021;114(5):1590–1599. DOI: 10.1093/ajcn/nqab201
86. Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Testosterone and cardiovascular risk: meta-analysis of interventional studies. J Sex Med. 2018;15(6):820–838. DOI: 10.1016/j.jsxm.2018.03.072

87. Windfeld-Mathiasen J, Heerfordt IM, Dalhoff KP, Andersen JT, Andersen MA, Johansson KS, et al. Cardiovascular disease in anabolic androgenic steroid users. Circulation. 2025;151(12):828–834. DOI: 10.1161/CIRCULATIONAHA.124.068135
88. Bhasin S. Testosterone replacement in aging men: an evidence-based patient-centric perspective. J Clin Invest. 2021;131(4):e146607. DOI: 10.1172/JCI146607
89. Breenfeldt Andersen A, Nordsborg NB, Bonne TC, Bejder J. Contemporary blood doping: performance, mechanism, and detection. Scand J Med Sci Sports. 2024;34(1):e14243. DOI: 10.1111/sms.14243
90. Lunenfeld B, Mskhalaya G, Zitzmann M, Corona G, Arver S, Kalinchenko S, et al. Recommendations on the diagnosis, treatment and monitoring of testosterone deficiency in men. Aging Male. 2021;24(1):119–138. DOI: 10.1080/13685538.2020.1867094
91. Smit DL, Buijs MM, de Hon O, den Heijer M, de Ronde W. Disruption and recovery of testicular function during and after androgen abuse: the HAARLEM study. Hum Reprod. 2021;36(4):880–890. DOI: 10.1093/humrep/deab013
92. Mannu GS, Sudul M, Bettencourt-Silva JH, Tsoti SM, Cunnick G, Ahmed SF. Role of tamoxifen in idiopathic gynecomastia: a 10-year prospective cohort study. Breast J. 2018;24(6):1043–1045. DOI: 10.1111/tbj.13119
93. Kanakis GA, Nordkap L, Bang AK, Calogero AE, Bartfai G, Corona G, et al. EAA clinical practice guidelines—gynecomastia evaluation and management. Andrology. 2019;7(6):778–793. DOI: 10.1111/andr.12636
94. Kacker R, Traish AM, Morgentaler A. Estrogens in men: clinical implications for sexual function and the treatment of testosterone deficiency. J Sex Med. 2012;9(6):1681–1696. DOI: 10.1111/j.1743-6109.2012.02727.x
95. Eichenfield DZ, Sprague J, Eichenfield LF. Management of acne vulgaris: a review. JAMA. 2021;326(20):2055–2067. DOI: 10.1001/jama.2021.17633
96. Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis following testosterone therapy. Sex Med Rev. 2018;6(1):77–85. DOI: 10.1016/j.sxmr.2017.04.001
97. Glueck CJ, Wang P. Testosterone therapy, thrombosis, thrombophilia, cardiovascular events. Metabolism. 2014;63(8):989–994. DOI: 10.1016/j.metabol.2014.05.005
98. Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo-controlled trial. Eur Heart J. 2006;27(1):57–64. DOI: 10.1093/eurheartj/ehi443
99. Rastrelli G, Vignozzi L, Corona G, Maggi M. Testosterone and benign prostatic hyperplasia. Sex Med Rev. 2019;7(2):259–271. DOI: 10.1016/j.sxmr.2018.10.006
100. Kathrins M, Doersch K, Nimeh T, Canto A, Niederberger C, Seftel A. The relationship between testosterone-replacement therapy and lower urinary tract symptoms: a systematic review. Urology. 2016;88:22–32. DOI: 10.1016/j.urology.2015.11.017
101. Kohn TP, Mata DA, Ramasamy R, Lipshultz LI. Effects of testosterone replacement therapy on lower urinary tract symptoms: a systematic review and meta-analysis. Eur Urol. 2016;69(6):1083–1090. DOI: 10.1016/j.eururo.2015.11.009
102. Hoyos CM, Yee BJ, Phillips CL, Machan EA, Grunstein RR, Liu PY. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnea. Eur J Endocrinol. 2015;173(5):625–637. DOI: 10.1530/EJE-15-0452
103. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer-2024 Update. Part I: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2024 Aug;86(2):148-163. doi: 10.1016/j.eururo.2024.03.027.
104. Kang DY, Li HJ. The effect of testosterone replacement therapy on prostate-specific antigen levels in men treated for hypogonadism: a systematic review and meta-analysis. Medicine (Baltimore). 2015;94(3):e410. DOI: 10.1097/MD.0000000000000410
105. Bhasin S, Thompson IM. Prostate risk and monitoring during testosterone replacement therapy. J Clin Endocrinol Metab. 2024;109(8):1975–1983. DOI: 10.1210/clinem/dgae239
106. Snyder PJ, Bauer DC, Ellenberg SS, Cauley JA, Buhr KA, Bhasin S, et al. Testosterone treatment and fractures in men with hypogonadism. N Engl J Med. 2024;390(3):203–211. DOI: 10.1056/NEJMoa2307873
107. Raivio T, Falardeau J, Dwyer A, Quinton R, Hayes FJ, Hughes VA, et al. Reversal of idiopathic hypogonadotropic hypogonadism. N Engl J Med. 2007;357(9):863–873. DOI: 10.1056/NEJMoa066494

108. Sidhoum VF, Chan YM, Lippincott MF, Balasubramanian R, Quinton R, Plummer L, et al. Reversal and relapse of hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2014;99(3):861–870. DOI: 10.1210/jc.2013-2802
109. Young J, Xu C, Papadakis GE, Acierno JS, Maione L, Hietamaki J, et al. Clinical management of congenital hypogonadotropic hypogonadism. Endocr Rev. 2019;40(2):669–710. DOI: 10.1210/er.2018-00116
110. Dwyer AA, Raivio T, Pitteloud N. Management of endocrine disease: reversible hypogonadotropic hypogonadism. Eur J Endocrinol. 2016;174(6):R267–R274. DOI: 10.1530/EJE-15-1207
111. Dwyer AA, McDonald IR, Cangiano B, Giovanelli L, Maione L, Silveira LFG, et al. Classes and predictors of reversal in male patients with congenital hypogonadotropic hypogonadism. Lancet Diabetes Endocrinol. 2024;12(4):257–266. DOI: 10.1016/S2213-8587(24)00039-4

Correspondence address:
Alexandre Hohl, MD
Departamento Clínica Médica, Serviço de Endocrinologia e Metabologia, Universidade Federal de Santa Catarina
Av. Prefeito Osmar Cunha, 416 sala 605 Centro
Florianópolis, SC, 88015-100, Brasil
E-mail: alexandrehohl@endocrino.org.br

ORIGINAL ARTICLE

Vol. 52 (3): e20250653, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0653

Is there still a role for systematic biopsy after targeted biopsy for the detection of clinically significant prostate cancer in MRI suspicious lesions?

João M. Pina [1], João Guerra [2], Miguel B. Lança [1], João L. Dias [3], Rita N. Lucas [3], Luis C. Pinheiro [1]

[1] Departamento de Urologia, ULS São José, Lisboa, Portugal; [2] Departamento de Urologia, Hospital Cruz Vermelha, Lisboa, Portugal; [3] Departamento de Radiologia, Hospital Lusíadas Lisboa, Lisboa, Portugal

ABSTRACT

Purpose: The combination of systematic biopsy (SB) and MRI-targeted biopsy (TB) is the current approach for prostate cancer (PCa) diagnosis; however, the clinical benefit of including SB remains controversial. This study aimed to determine whether SB adds value beyond TB in detecting clinically significant prostate cancer (csPCa) in men with suspicious lesions.
Materials and Methods: Retrospective, single-center study conducted between January 2019 and September 2023. It enrolled men with suspicious lesions identified on multiparametric MRI (PI-RADS≥3) who had undergone combined biopsy (TB+SB). Sociodemographic and clinical data were secondarily collected. csPCa was defined when ISUP≥2.
Results: This study included 997 men with a median age of 68 years, of whom 497 had a negative prior biopsy. The TB+SB approach identified 53.0% of PCa and 36.8% of csPCa cases. TB alone significantly outperformed SB in identifying csPCa, with detection rates of 34.8% vs. 10.3%, respectively, missing only 4.8% of PCa diagnosis—most of which were low-grade tumors. SB contributed marginally, identifying additional csPCa cases in 1.4% of patients. In patients with a prior negative biopsy, the addition of SB to TB only accounted for 12.5% of PCa diagnosis. Limitations include the study single-center design, restricting generalizability, and the lack of whole-mount prostatectomy for histological confirmation.
Conclusions: In conclusion, SB adds limited diagnostic value, with TB alone being sufficient for detecting csPCa cases in patients with MRI-visible lesions. The results suggest that SB may be safely omitted in selected patients to reduce biopsy burden and lead to better clinical outcomes.

ARTICLE INFO

João Magalhães Pina
https://orcid.org/0000-0002-6253-3211

Keywords:
Prostatic Neoplasms; Biopsy; Magnetic Resonance Imaging

Submitted for publication: November 07, 2025

Accepted after revision: February 19, 2026

Published as Ahead of Print: February 28, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

Data Availability
Data will be available upon request

INTRODUCTION

Prostate cancer (PCa) is a prevalent malignancy, ranking second as the most common cancer in men (1). One to three million cases of prostate cancer are diagnosed every year (2). Incidence varies greatly from 6.3 to 83.4 per 100,000 men worldwide, with Europe and North America presenting some of the highest rates (3). In Portugal, there were 62.6 PCa new cases and 11.1 related deaths per 100,000 individuals in 2022. These numbers are expected to rise up to 22% and 54%, respectively, by 2045 in the Portuguese population (3).

Blood tests for prostate-specific antigen (PSA) and digital rectal examination continue to be the main methods for initial screening and evaluation of PCa (4). Transrectal ultrasound (TRUS)-guided systematic biopsy (SB) has been the preferred diagnostic approach for PCa since a pivotal 1989 study demonstrated its superiority over digitally directed biopsy sampling (5). Currently, the gold standard diagnostic tool is the 12-core extended sextant TRUS. However, its essentially random needle placement leads to a high false-negative rate and can underestimate tumor grade in up to 38% of cases due to undersampling (6). On the other hand, random TRUS biopsy frequently detects low-grade, indolent cancers, potentially leading to overtreatment. Consequently, there is a growing need to improve patient selection and enhance biopsy techniques to better identify and target potentially aggressive lesions.

Multiparametric magnetic resonance imaging (mpMRI) has revolutionized the diagnosis and local staging of PCa. Suspicious lesions identified using Prostate Imaging-Reporting and Data System (PI-RADS) v2.1 criteria (7), can be targeted and fused with real-time ultrasound for biopsy (8). MRI/TRUS fusion, also known as targeted biopsy (TB), has improved the detection of clinically significant prostate cancer (csPCa) by enabling a more effective sampling of prostate lesions (9). Despite its effectiveness, the 2024 European Association of Urology Guidelines advise that biopsy-naive men should still undergo both SB of 12 prostate regions and TB to minimize the risk of missing csPCa. For men with a prior biopsy, SB may be omitted, although weakly recommended (10).

Notwithstanding, the added diagnostic value of combining SB with TB remains a matter of ongoing debate. We hypothesize that SB does not provide added value in the context of the diagnosis of clinically significant PCa. In this context, this study aimed to evaluate whether a random systematic approach still provides additional value beyond fusion-guided biopsies in detecting csPCa in men with suspicious lesions identified on mpMRI.

MATERIALS AND METHODS

Study Participants and Design

This is a retrospective study conducted in a tertiary care center between January 2019 and September 2023, including men with clinical suspicion of PCa, who were biopsy-naïve or had a previous negative SB, who underwent a mpMRI with at least one suspicious lesion (PI-RADS≥3) identified and had both TB and SB. Patients were excluded based on the following criteria: previous treatment for prostate cancer, absence of MRI-visible prostate lesions, or an inability to undergo MRI. All the patients provided written informed consent.

Data collection

Data were secondarily collected from the hospital medical records. It included sociodemographic characteristics (age) and clinical information (PSA levels, prostatic volume, lesions characteristics, PI-RADS and ISUP scores).

Image Acquisition and Analysis

mpMRI images were obtained using 1.5 and 3-Tesla systems without using an endorectal coil following PIRADS v2.1 guidelines (11). Examination included T2-weighted (T2WI) images in three planes and functional sequences (DWI, ADC map and DCE) (12). Images were interpreted by experienced uroradiologists, who segmented and marked up to two suspicious lesions using dedicated software (MiM-Symphony®), prioritizing those with the highest scores. Scans with inadequate image quality were repeated before biopsy.

Combined biopsy procedure and evaluation

All biopsies were done under general anesthesia by the same experienced urologist. Patients initially underwent TB followed by SB using the transperineal approach (13). The perineum was sterilized and mpMRI-TRUS software (MiM-Symphony®) was used to guide transperineal TB using a template grid, with a median of five cores taken per lesion. This was followed by systematic biopsy of the entire prostate, with denser sampling of the peripheral zone (Supplementary Figure-1). Core locations were precisely tracked and documented using a 3D prostate model with automatic motion compensation, and biopsy sites were visualized on MRI through image fusion. Samples were labeled by location and analyzed by experienced uropathologists according to ISUP grading. Clinically significant prostate cancer was defined as ISUP grade group ≥2, as ISUP 1 is not considered to be clinically significant, and patients do not require treatment. Cancer detection rates were compared between targeted biopsy, systematic biopsy alone, and their combination.

Statistical Analysis

All variables were summarized using descriptive statistics. Numerical variables were reported as medians with first and third quartiles (P25; P75), while categorical variables were described using absolute and relative frequencies. Demographic and clinical characteristics were analyzed for the overall sample and by prior biopsy history. PI-RADS score distributions were summarized, and prostate cancer detection rates were compared between systematic and targeted biopsies using McNemar's tests. Associations between biopsy methods and cancer detection were also assessed with McNemar's tests. Relationships between prior biopsy history and categorical variables were evaluated using Chi-squared or Fisher's exact tests, as appropriate. PI-RADS and ISUP scores were summarized by biopsy type, and ISUP score agreement between systematic and targeted biopsies was assessed with Cohen's kappa. All inferential tests were two-tailed, with a significance threshold of 5%.

The number needed for diagnosis (NND) was calculated as the inverse of the Youden index. Confidence intervals and comparisons between diagnostic methods were obtained using non-parametric bootstrap resampling (2,000 iterations), with statistical significance defined by a 95% confidence interval excluding zero.

A multinomial logistic regression analysis was performed to assess factors associated with patterns of prostate cancer detection. SB only was used as the reference category. Predictors included age, PSA, prostate volume and PSA density. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each predictor. Categories with small sample sizes were interpreted qualitatively if estimates were unstable. Patients without prostate cancer were excluded from this analysis.

The statistical analysis was carried out using the RStudio software v4.4.3. The multinomial model was implemented in R using the nnet::multinom() function.

Ethics

This work has been approved by the Ethics Committee of the institution where the study was conducted (12/2022/CEFCM).

RESULTS

Characterization of the study sample

Patients' demographic and clinical characteristics, overall and by previous biopsy status, are presented in Table-1. This study included 997 men, with a median age [P25; P75] of 68 [62; 72] years, from which 497 had undergone a previous biopsy that turned out negative. The median initial PSA and prostatic volume were 7.20 [5.04; 10.08] ng/mL and 57 [40; 79] mL, respectively. Both values were significantly higher in patients with previous biopsy (initial PSA: 8.26 [5.76; 11.24] ng/mL; prostatic volume: 64 [46; 87] mL) than in those biopsy-naïve ($p<0.0001$). Overall median PSA density was 0.12 [0.08; 0.19] ng/mL^2 and more than half of the patients (62.5%) would be classified as being on low PCa risk group based on this parameter only.

Global and biopsy-specific PCa detection rate

A total of 282 (28.3%) patients were classified as PI-RADS 3, 534 (53.6%,) as PI-RADS 4 and 181 (18.1%) as PI-RADS 5 (Supplementary Figure-2). The description of

Table 1 - Demographic and clinical characterization of the study sample.

	Total (*n*=997)	No previous biopsy (*n*=496)*	Previous biopsy (*n*=497)*	P-value
Age (years)				
Mean (SD)	66.90 (0.23)	66.30 (0.34)	67.45 (0.32)	0.0508
Median [P25; P75]	68 [62; 72]	67 [61; 72]	68 [63; 72]	
Min/Max	42/85	42/85	44/85	
Initial PSA (ng/mL),				
Mean (SD)	8.81 (0.33)	7.84 (0.54)	9.79 (0.39)	**<0.0001**
Median [P25; P75]	7.20 [5.04; 10.08]	6.19 [4.60; 8.41]	8.26 [5.76; 11.24]	
Min/Max	0.50/253.00	0.50/253.00	0.53/150.00	
Prostatic volume (mL)				
Mean (SD)	63.83 (1.06)	57.50 (1.39)	70.17 (1.57)	**<0.0001**
Median [P25; P75]	57 [40; 79]	50 [38; 69]	64 [46; 87]	
Min/Max	8/300	8/300	13/300	
PSA density (ng/mL^2)				
Mean (SD)	0.16 (0.00)	0.15 (0.01)	0.16 (0.01)	0.2279
Median [P25; P75]	0.12 [0.08; 0.19]	0.12 [0.08; 0.18]	0.12 [0.08; 0.20]	
Min/Max	0.01/2.14	0.01/2.14	0.01/1.56	
PCa risk group based on PSA density, *n* (%)				
Low risk (≤0.15 ng/mL^2)	618 (62.5%)	310 (62.9%)	305 (61.9%)	0.8099
High risk (>0.15 ng/mL^2)	371 (37.5%)	183 (37.1%)	188 (38.1%)	
Missing	8	3	4	

*4 patients had no information on previous biopsy status.

the lesions' location, size and histopathological features is presented in Supplementary Table-1 and Supplementary Table-2.

The overall rate of PCa positive cases detected by the combination approach (TB+SB) was 53.0% - 16.1% ciPCa and 36.8% csPCa (Table-2).

TB alone detected significantly more PCa cases than SB alone (48.1% vs. 19.5%, p<0.001).

The total csPCa cases diagnosed was three-fold higher with TB than with SB (34.8% vs. 10.3%; Table-2). Within each PI-RADS category, a similar result was observed, with TB detecting significantly higher csPCa rates (PI-RADS 3: p=0.021; PI-RADS 4: p<0.001; PI-RADS 5: p<0.001; Supplementary Table-3).

The comparison of PI-RADS and ISUP gradings by biopsy type are presented in Supplementary Tables 4 and 5, respectively. Analyzing PCa detection among patients with and without previous biopsy, the overall number of positive cases was higher for the biopsy-naïve group (59.3% vs. 46.9%, p<0.001; data not shown). This difference was observed particularly in the TB results (Supplementary Table-6), with this technique detecting significantly more positive cases in patients without previous biopsy than in those with a previous one (55.4%

Table 2 - PCa diagnosis by biopsy type.

	Total (n=997)			
	TB+SB	TB	SB	P-value
PCa diagnosis				
Positive	528 (53.0%)	480 (48.1%)	194 (19.5%)	**<0.0010**
Negative	469 (47.0%)	517 (51.9%)	803 (80.5%)	
ISUP grade				
ciPCa (ISUP=1)	161 (16.1%)	133 (13.3%)	91 (9.1%)	
csPCa (ISUP ≥2)	367 (36.8%)	347 (34.8%)	103 (10.3%)	
No PCa	469 (47.0%)	517 (51.9%)	803 (80.5%)	
		Previous negative biopsy (n=497)		
ISUP score				
ISUP 1	82 (16.5%)	65 (13.1%)	43 (8.7%)	
ISUP 2	64 (12.9%)	57 (11.5%)	27 (5.4%)	
ISUP 3	46 (9.3%)	43 (8.7%)	14 (2.8%)	**<0.0001**
ISUP 4	31 (6.2%)	29 (5.8%)	5 (1.0%)	
ISUP 5	9 (1.8%)	9 (1.8%)	1 (0.2%)	
No PCa	265 (53.3%)	294 (59.1%)	407 (81.9%)	
PCa				
ciPCa	82 (16.5%)	65 (13.1%)	43 (8.7%)	**<0.0001**
csPCa	150 (30.2%)	138 (27.8%)	47 (9.5%)	
No PCa	265 (53.3%)	294 (59.1%)	407 (81.9%)	

vs. 40.9%, p<0.001), namely csPCa, which was identified in nearly twice of the biopsy-naïve patients (41.7% vs. 27.8%, p<0.0001). On the contrary, in SB, a considerable smaller proportion of patients were diagnosed with PCa – 20.8% of biopsy-naïve patients and 18.2% of those who had already underwent a prostate biopsy (p=0.677).

Concerning patients with a previous negative biopsy (n=497), SB detected fewer PCa cases than TB (18.2% vs. 40.9%, p<0.0001), including csPCa (9.5% vs. 27.8%, p<0.0001), from 46.7% of total diagnosis (Table-2 and Supplementary Table-7). Still, adding SB to TB detected more 17 ciPCa and 12 csPCa cases, mainly ISUP 2 (Table-2, underlined) representing 12.5% of all PCa diagnosis in patients with a prior negative biopsy.

Comparison between diagnosis and ISUP scoring following TB and SB

Overall, TB alone diagnosed more PCa cases and detected higher ISUP grades than SB. In fact, SB missed or underscored 369 (37.0%) cases of PCa, whereas TB missed or underscored only 53 (5.3%) PCa (Supplementary Table-8).

When considering ISUP grading (Table-3), TB underestimated 12 (1.2%) PCa cases and missed 48 (4.8%)- 34 (70.8%; 3.4% in the overall sample) ciPCa and 14 (29.2%; 1.4% in the overall sample) csPCA by SB. On the opposite, SB underscored 53 (5.3%) PCa cases and missed 334 (33.5%)—106 (31.7%; 10.6% in the overall sample) ciPCa and 228 (68.3%; 22.9% in the overall sample) csPCA by SB. Still, 576 (57.9%) cases were equally classified by both techniques (kappa coefficient=0.19; gray highlight).

A detailed summary of differences in PCa diagnosis between TB and SB in positive patients is presented in Supplementary Table-9.

Overall, the SB method yielded a sensitivity of 36.7% and a specificity of 100.0%, corresponding to a number needed for diagnosis (NND) of 2.72 (95% CI,

Table 3 - Comparison of ISUP grading between targeted and systematic biopsies. Relative frequencies relate to the total number of patients. Values in bold represent csPCa cases. Values below the gray shading indicate upgrading by TB, and values above gray shading indicate upgrading by SB.

		SB					
		No PCa (n=803)	ISUP 1 (n=91)	ISUP 2 (n=60)	ISUP 3 (n=26)	ISUP 4 (n=14)	ISUP 5 (n=3)
TB	No PCa (n=517)	469 (46.9%)	34 (3.4%)	**10 (1.0%)**	**3 (0.3%)**	**1 (0.1%)**	**0 (0.0%)**
	ISUP 1 (n=33)	106 (10.6%)	22 (2.2%)	**5 (0.5%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
	ISUP 2 (n=168)	**112 (11.2%)**	**20 (2.0%)**	**32 (3.2%)**	**2 (0.2%)**	**1 (0.1%)**	**1 (0.1%)**
	ISUP 3 (n=93)	**58 (5.8%)**	**7 (0.7%)**	**9 (0.9%)**	**16 (1.6%)**	**2 (0.2%)**	**1 (0.1%)**
	ISUP 4 (n=66)	**41 (4.1%)**	**7 (0.7%)**	**3 (0.3%)**	**5 (0.5%)**	**10 (1.0%)**	**0 (0.0%)**
	ISUP 5 (n=20)	**17 (1.7%)**	**1 (0.1%)**	**1 (0.1%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.1%)**

kappa=0.19 (Slight agreement)

2.46–3.06). In contrast, the TB method demonstrated a sensitivity of 90.9% with the same specificity of 100.0%, resulting in a significantly lower NND of 1.10 (95% CI, 1.07–1.13).

In a multinomial logistic regression using PCa cases detected by SB only (48 patients) as the reference, higher PSA (p=0.037) and larger prostate volume (p=0.036) were modestly associated with exclusive detection by TB (OR 1.05 per ng/mL PSA, 95% CI 1.00–1.09; OR 1.05 per mL prostate volume, 95% CI 1.00–1.10). Age and PSA density were not significantly associated with detection patterns.

DISCUSSION

This retrospective single-center study provides new data on the diagnostic value of combining SB with TB.

The overall detection rate of PCa cases for combined biopsy (TB+SB) was 53.0%, of these 48.1% were diagnosed in TB and 19.6% in SB. These findings align with other studies (14, 15), where the detection of PCa following TB was 66% while for SB was 22% (15), as anticipated, as mpMRI enhances the detection of clinically significant disease (16). However, the diagnostic value of both techniques in scoring patients is still controversial. While one study showed lower ISUP grading with TB compared to SB – with 14% of the cases being upgraded in TB vs. 23% in SB, although non-significant (17), – other reported higher detection rates for ISUP scores ranging from 3 to 5. For instance, ISUP 4 was detected in 6.5% of SB cases vs. 10.2% for TB, and TB identified an additional 8.3% of cases above ISUP 3, compared to only 1.9% with SB (14). Accordingly, our results demonstrated the superiority of TB over SB in detecting ciPCa (13.3% vs. 9.1%) and csPCa cases (34.8% vs. 10.3%). CsPCa was defined as ISUP≥2. If ISUP 3 or higher were used, patients with intermediate-risk disease (considered clinically significant and therefore requiring treatment) would be excluded. Moreover, TB rarely underestimated the ISUP grading (12 cases, 1.2%) and missed only 4.8% of total PCa cases. This false negative rate can be explained by some small and less aggressive lesions being underestimated during imaging or by technical errors during imaging and biopsy (18). In fact, most cases (3.4%) were ciPCa and only 1.4% were csPCA by SB. A marginal addition of csPCa by SB may not justify the added cost of additional biopsies, patient discomfort and complications. Along with a global negative rate of 80.5% by SB – a higher value than that of other studies, which report from 14 to 37.6% of negative PCa (14, 19)– and the 33.5% false negative rate of the technique, these results support the limited value of the systematic approach in aiding to diagnosing PCa. Missed diag-

noses in SB are often due to small tumors, anterior or apical lesions, and under sampling of heterogeneous cancers – limitations that are better addressed with TB (20, 21). Moreover, a general advantage of reducing the number of cores is a reduced number of complications like minor bleeding and urinary symptoms (22). Kalahati et al. have also found that undergoing SB is associated with a higher number of urinary infections (2.7% after SB and 1.7% after TB) (23). The difference in NND between the two approaches also indicated that fewer examinations are required with the TB method to achieve a correct diagnosis.

SB can miss csPCa, particularly in patients with ongoing suspicion after a negative result (20, 24). In fact, approximately half of this study sample had previously undergone a negative biopsy, with significantly increased PSA and prostatic volume. This suggests a population that likely already presented risk factors prompting this first biopsy. More importantly, the rate of PCa detection was higher with TB, compared to SB in these patients (40.9% vs. 18.1%, from 46.7% total cases), especially csPCa, which supports the notion that there is no added value in performing a SB combined with TB after a negative SB result. PCa detection by TB also differed significantly between patients with and without a previous biopsy (40.9% vs. 55.2%). The high predictive value of TB for accurately determining a patient's true pathological grade group reduces the risk of misdiagnosis and may decrease diagnostic uncertainty, supporting a TB-only strategy in men with previous negative biopsies, alike reported before (21, 25). Additionally, our results support the clinical utility of TB particularly in patients with higher PSA levels or larger prostate volumes, likely reflecting sampling dilution effects inherent to biopsy procedures in larger glands. On the other hand, omitting SB could result in missed ciPCa, which are typically slow-growing and less aggressive tumors but may still pose long-term risks. However, high-risk patients can benefit from active surveillance, enabling timely detection of disease progression and early intervention. Collectively, our findings contribute by showing that undergoing TB alone is sufficient for many patients.

This study has several strengths, namely, including a high number of participants and biopsy samples, enrolled both biopsy-naïve patients and those with previous biopsy, and used a mapping grid with predetermined holes, to minimize of oversampling risk and targeting bias. All biopsies were performed by the same experienced urologist, thus minimizing operator-dependent variability and ensuring consistent, standardized assessments. Limitations of this study include the single-center design, which may restrict the generalizability of the findings, and the absence of whole mount prostatectomy for histopathological verification. Future studies are needed to develop risk-adapted models incorporating mpMRI findings, PSA and clinical parameters to determine when SB can be safely omitted. Long-term follow-up is also needed to evaluate the clinical impact of missed csPCa cases in patients undergoing TB alone.

CONCLUSIONS

Overall, these results suggest that SB offers limited diagnostic value when combined with a mpMRI-targeted approach and support the latter as a stand-alone procedure in men with suspicious lesions (Figure-1). Omitting SB would miss few PCa cases and result in marginal underdiagnosis of csPCa, particularly in previously biopsied patients. This less invasive approach could enhance patient comfort, streamline clinical decision-making, and enhance clinical outcomes.

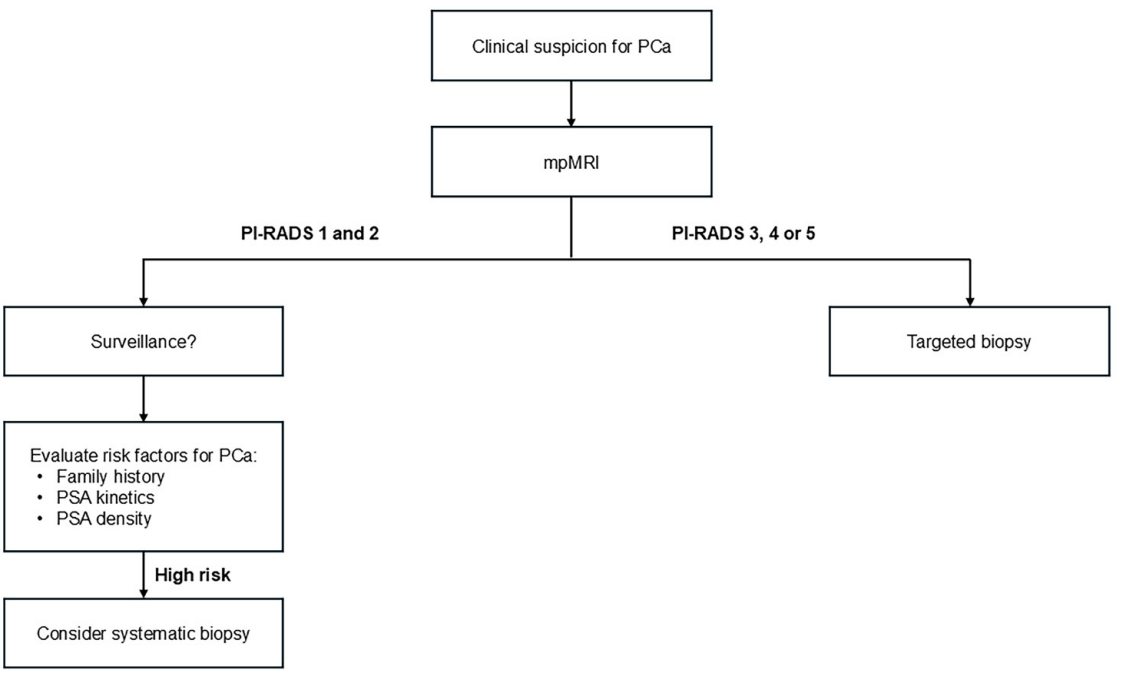
ACKNOWLEDGEMENTS

The authors would like to thank Rita Gomes and Joana Melo (W4Research) for the writing support during the preparation of this manuscript, and Miguel Cabral (W4Research) for the biostatistics analyses.

CONFLICT OF INTEREST

None declared.

Figure 1 - Clinical algorithm flowchart for PCa biopsy.



REFERENCES

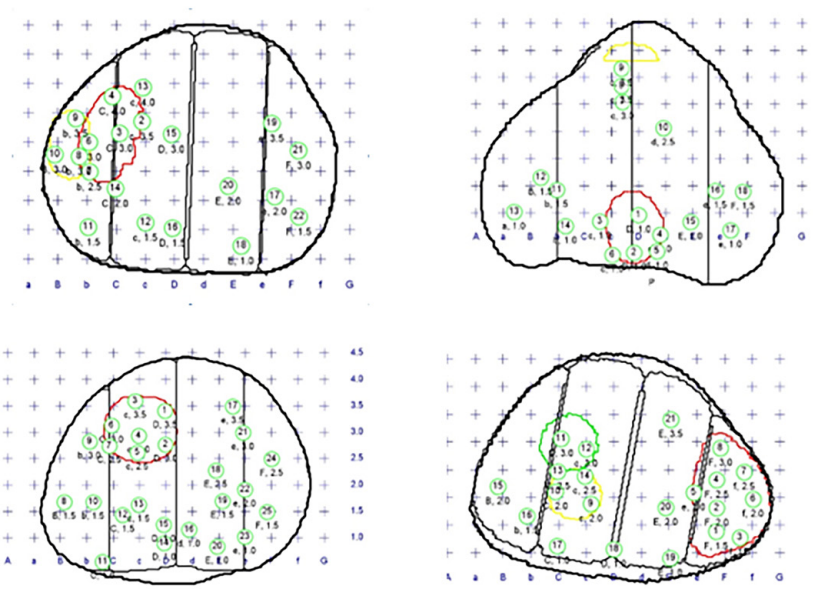
1. Rawla P. Epidemiology of prostate cancer. World J Oncol. 2019;10(2):63–89. doi: 10.14740/wjon1191
2. Sandhu S, Moore CM, Chiong E, Beltran H, Bristow RG, Williams SG. Prostate cancer. Lancet. 2021;398(10305):1075–1090. doi: 10.1016/S0140-6736(21)00950-8
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249. doi: 10.3322/caac.21660
4. Descotes JL. Diagnosis of prostate cancer. Asian J Urol. 2019;6(2):129–136. doi: 10.1016/j.ajur.2018.11.007
5. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol. 1989;142(1):71–74. doi: 10.1016/S0022-5347(17)38664-0
6. Kvåle R, Møller B, Wahlqvist R, Fosså SD, Berner A, Busch C, et al. Concordance between Gleason scores of needle biopsies and radical prostatectomy specimens: a population-based study. BJU Int. 2009;103(12):1647–1654. doi: 10.1111/j.1464-410X.2008.08311.x
7. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS prostate imaging – reporting and data system: 2015, version 2. Eur Urol. 2016;69(1):16–40. doi: 10.1016/j.eururo.2015.08.052
8. Correas JM, Halpern EJ, Barr RG, Ghai S, Walz J, Bodard S, et al. Advanced ultrasound in the diagnosis of prostate cancer. World J Urol. 2021;39(3):661–676. doi: 10.1007/s00345-020-03390-2
9. Paesano N, Catalá V, Tcholakian L, Alomar X, Barranco M, Trilla E, et al. The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies. Int Braz J Urol. 2024;50(3):296–308. doi: 10.1590/S1677-5538.IBJU.2023.0334
10. European Association of Urology. Prostate Cancer Guidelines 2025. Available from: https://uroweb.org/guidelines/prostate-cancer
11. Morote J, Paesano N, Picola N, Muñoz-Rodriguez J, Ruiz-Plazas X, Muñoz-Rivero MV, et al. Validation of the Barcelona-MRI predictive model when PI-RADS v2.1 is used with trans-perineal prostate biopsies. Int Braz J Urol. 2024;50(5):595–604. doi: 10.1590/S1677-5538.IBJU.2023.0441

12. Zhang S, Wan J, Xu Y, Huo L, Xu L, Xia J, et al. Predictive value of multiparametric MRI for pathological grading of prostate cancer: a meta-analysis. Int Braz J Urol. 2025;51(3):e20240509. doi: 10.1590/S1677-5538.IBJU.2024.0509
13. Ramacciotti LS, Strauss D, Cei F, Kaneko M, Mokhtar D, Cai J, et al. Transperineal versus transrectal MRI/TRUS fusion-guided prostate biopsy in a large, ethnically diverse cohort. Int Braz J Urol. 2024;50(5):616–628. doi: 10.1590/S1677-5538.IBJU.2023.0397
14. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med. 2020;382(10):917–928. doi: 10.1056/NEJMoa1910038
15. Günzel K, Magheli A, Busch J, Baco E, Cash H, Heinrich S, et al. Evaluation of systematic prostate biopsies when performing transperineal MRI/TRUS fusion biopsy with needle tracking. Int Urol Nephrol. 2022;54(10):2477–2483. doi: 10.1007/s11255-022-03185-5
16. Ahmed HU, Bosaily AES, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS). Lancet. 2017;389(10071):815–822. doi: 10.1016/S0140-6736(16)32401-1
17. Klotz L, Loblaw A, Sugar L, Moussa M, Berman DM, Van der Kwast T, et al. Active surveillance magnetic resonance imaging study (ASIST). Eur Urol. 2019;75(2):300–309. doi: 10.1016/j.eururo.2018.09.025
18. Oderda M, Dematteis A, Calleris G, Diamand R, Gatti M, Marra G, et al. MRI-targeted prostate fusion biopsy: what are we missing outside the target? Curr Oncol. 2024;31(7):4133–4140. doi: 10.3390/curroncol31070297
19. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al. MRI-FIRST: systematic and targeted biopsy based on mpMRI in biopsy-naive patients. Lancet Oncol. 2019;20(1):100–109. doi: 10.1016/S1470-2045(18)30569-2
20. Grivas N, Lardas M, Espinós EL, Lam TB, Rouviere O, Mottet N, et al. Prostate cancer detection percentages of repeat biopsy in patients with positive mpMRI and negative initial biopsy. Eur Urol. 2022;82(5):452–457. doi: 10.1016/j.eururo.2022.07.016
21. Exterkate L, Wegelin O, Barentsz JO, van der Leest MG, Kummer JA, Vreuls W, et al. Need for repeated systematic biopsies after previous negative biopsies in the MRI-targeted era? Eur Urol Oncol. 2020;3(2):216–223. doi: 10.1016/j.euo.2019.08.006
22. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, et al. Systematic review of complications of prostate biopsy. Eur Urol. 2013;64(6):876–892. doi: 10.1016/j.eururo.2013.05.049
23. Kalalahti I, Huotari K, Erickson AM, Petas A, Vasarainen H, Rannikko A. Infectious complications after transrectal MRI-targeted and systematic prostate biopsy. World J Urol. 2022;40(9):2261–2265. doi: 10.1007/s00345-022-04034-2
24. Truong M, Frye TP. Magnetic resonance imaging detection of prostate cancer in men with previous negative prostate biopsy. Transl Androl Urol. 2017;6(3):424–431. doi: 10.21037/tau.2017.03.69
25. Patel N, Cricco-Lizza E, Kasabwala K, Xu C, Robinson BD, Khani F, et al. The role of systematic and targeted biopsies in light of overlap on MRI-ultrasound fusion biopsy. Eur Urol Oncol. 2018;1(4):263–267. doi: 10.1016/j.euo.2018.04.007

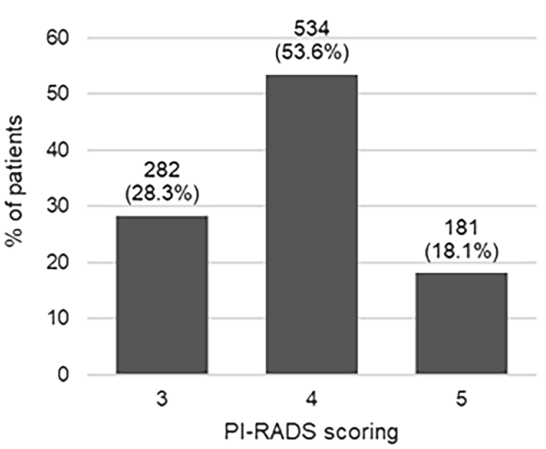
Correspondence address:
João Magalhães Pina, MD
Departamento de Urologia, ULS São José,
R. José António Serrano 1150-199
Lisboa, Portugal
E-mail: joaompina@gmail.com

APPENDIX

Supplementary Figure 1 - Examples of four sample grid mappings.



Supplementary Figure 2 - PI-RADS scoring of patients. Data are shown as absolute and relative frequencies.



Supplementary Table 1 - Lesions characterization following mpMRI.

	n=997
Lesion location	
By zonal anatomy, *n* (%)	
Central	267 (26.8)
Central/Peripheric	4 (0.4)
Peripheric	726 (72.8)
By prostate region, *n* (%)	
Apex	248 (25.0)
Base	204 (20.5)
Base/Middle	45 (4.5)
Base/Middle/Apex	6 (0.6)
Middle	436 (43.9)
Middle/Apex	55 (5.5)
Missing	3
Lesion size (mm)	
Median [P25; P75]	10.0 [8.0; 14.0]
Min / Max	1.0 / 49.0

Supplementary Table 2 - Histopathological features of PCa lesions.

	Total (***n*=**528)	No previous biopsy (***n*=**294)	Previous biopsy (***n*=**232)
Cribriform pattern, *n (%)*			
Yes	37 (7.1)	24 (8.3)	13 (5.6)
No	487 (92.9)	266 (91.7)	219 (94.4)
Missing	4	4	0
Lymphovascular invasion, *n* (%)			
Yes	1 (0.2)	0 (0.0)	1 (0.4)
No	524 (99.8)	291 (100.0)	231 (99.6)
Missing	3	3	0
Perineural invasion, *n* (%)			
Yes	117 (22.3)	78 (26.8)	39 (16.8)
No	408 (77.7)	213 (73.2)	193 (83.2)
Missing	3	3	0

Supplementary Table 3 - PI-RADS grading by biopsy approach.

		TB (n=997)		SB (n=997)	
		PCa	csPCa (ISUP ≥2)	PCa	csPCa (ISUP ≥2)
PI-RADS score	**3 (*n*=282)**	68 (24.1%)	35 (12.4%)	43 (15.2%)	18 (6.4%)
	4 (*n*=534)	272 (50.9%)	195 (36.5%)	113 (21.2%)	61 (11.4%)
	5 (*n*=181)	140 (77.3%)	117 (64.6%)	38 (21.0%)	24 (13.3%)

csPCa = PI-RADS 3; $X^2 = 5.33$; p=0.021; PI-RADS 4: $X^2=90.88$; p<0.001; PI-RADS 5: $X^2=104.65$, p<0.001

Supplementary Table 4 - Comparison between PI-RADS and ISUP grading after targeted biopsy. Relative frequencies relate to the number of PI-RADS patients in each category.

TB (n=997)		ISUP					
		No PCa (n=518)	ISUP 1 (n=132)	ISUP 2 (n=169)	ISUP 3 (n=93)	ISUP 4 (n=66)	ISUP 5 (n=20)
PI-RADS	**3 (n=282)**	214 (75.9%)	33 (11.7%)	24 (8.5%)	9 (3.2%)	2 (0.7%)	0 (0.0%)
	4 (n=534)	262 (49.1%)	77 (14.4%)	94 (17.6%)	53 (9.9%)	40 (7.5%)	8 (1.5%)
	5 (n=181)	41 (22.7%)	23 (17.7%)	50 (27.6%)	31 (17.1%)	24 (13.3%)	12 (6.6%)

Supplementary Table 5 - Comparison between PI-RADS and ISUP grading after systematic biopsy. Relative frequencies relate to the number of PI-RADS patients in each category.

SB (n=997)		ISUP					
		No PCa (n=803)	ISUP 1 (n=91)	ISUP 2 (n=61)	ISUP 3 (n=26)	ISUP 4 (n=14)	ISUP 5 (n=3)
PI-RADS	**3 (n=282)**	239 (84.8%)	25 (8.9%)	12 (4.3%)	4 (1.4%)	1 (0.3%)	1 (0.3%)
	4 (n=534)	421 (78.8%)	52 (9.7%)	35 (6.6%)	15 (2.8%)	9 (1.7%)	2 (0.4%)
	5 (n=181)	143 (79.0%)	14 (7.7%)	13 (7.2%)	7 (3.9%)	4 (2.2%)	0 (0.0%)

Supplementary Table 6 - ISUP grading after targeted and systematic biopsy, by prior biopsy status.

	TB			SB		
	No previous biopsy (n=496)	Previous biopsy (n=497)	P-value	No previous biopsy (n=496)	Previous biopsy (n=497)	P-value
ISUP score, n (%)						
ISUP 1	68 (13.7%)	65 (13.1%)		48 (9.7%)	43 (8.7%)	
ISUP 2	110 (22.1%)	57 (11.5%)		33 (6.7%)	27 (5.4%)	
ISUP 3	50 (10.1%)	43 (8.7%)	**<0.0001**	12 (2.4%)	14 (2.8%)	0.813
ISUP 4	36 (7.3%)	29 (5.8%)		8 (1.6%)	5 (1.0%)	
ISUP 5	11 (2.2%)	9 (1.8%)		2 (0.4%)	1 (0.2%)	
No PCa	221 (44.6%)	294 (59.1%)		393 (79.2%)	407 (81.9%)	
Significant PCa?, n (%)						
ciPCa (ISUP=1)	68 (13.7%)	65 (13.1%)		48 (9.7%)	43 (8.7%)	
csPCa (ISUP ≥2)	207 (41.7%)	138 (27.8%)	**<0.0001**	55 (11.1%)	47 (9.5%)	0.677
No PCa	221 (44.6%)	294 (59.1%)		393 (79.2%)	407 (81.9%)	

Supplementary Table 7 - PCa diagnosis and ISUP grading in patients with previous biopsy.

	Previous negative biopsy (n=497)			
	TB+SB	TB	SB	p-value
ISUP score				
ISUP 1	82 (16.5%)	65 (13.1%)	43 (8.7%)	
ISUP 2	64 (12.9%)	57 (11.5%)	27 (5.4%)	
ISUP 3	46 (9.3%)	43 (8.7%)	14 (2.8%)	**<0.0001**
ISUP 4	31 (6.2%)	29 (5.8%)	5 (1.0%)	
ISUP 5	9 (1.8%)	9 (1.8%)	1 (0.2%)	
No PCa	265 (53.3%)	294 (59.1%)	407 (81.9%)	
PCa				
ciPCa	82 (16.5%)	65 (13.1%)	43 (8.7%)	**<0.0001**
csPCa	150 (30.2%)	138 (27.8%)	47 (9.5%)	
No PCa	265 (53.3%)	294 (59.1%)	407 (81.9%)	

Supplementary Table 8 - Comparison of the PCa clinical significance between targeted fusion and systematic biopsy. Relative frequencies relate to the total number of patients. Values in bold represent csPCa cases. Values above gray shading indicates upgrading by TB, values below gray shading indicate upgrading by SB.

		SB		
		No PCa (n=803)	ciPCa (n=91)	csPCa (n=103)
TB	No PCa (n=517)	469 (46.9%)	34 (3.4%)	**14 (1.4%)**
	ciPCa (n=133)	106 (10.6%)	22 (2.2%)	**5 (0.5%)**
	csPCa (n=347)	**228 (22.9%)**	**35 (3.5%)**	**84 (8.4%)**

Supplementary Table 9 - Comparison of PCa diagnosis between targeted and systematic biopsies in patients with PCa positive fragments in at least one biopsy method.

	PCa positive patients (*n*=528)
PCa diagnosis between biopsy types	
Negative TB and positive SB	**48 (9.1%)**
ISUP 1 (SB)	34 (6.4%)
ISUP 2 (SB)	10 (1.9%)
ISUP 3 (SB)	3 (0.6%)
ISUP 4 (SB)	1 (0.2%)
ISUP 5 (SB)	0 (0.0%)
Positive TB and negative SB	**334 (63.3%)**
Positive TB, but less aggressive than positive SB	**12 (2.3%)**
ISUP 1 (TB) vs ISUP 2 (SB)	5 (0.9%)
ISUP 2 (TB) vs ISUP 3/4/5 (SB)	4 (0.8%)
ISUP 3 (TB) vs ISUP 4/5 (SB)	3 (0.6%)
ISUP 4 (TB) vs ISUP 5 (SB)	0 (0.0%)
Positive TB, with the same or greater aggressiveness than positive SB	**134 (25.4%)**

ORIGINAL ARTICLE

Vol. 52 (3): e20269901, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2026.9901

Correlation of Kidney Lenght and Body Parameters in CT Scans

Ana Raquel M. Morais [1], Carla M. Gallo [2], Luciano A. Favorito [2], Francisco J.B. Sampaio [2]

[1] Grupo Fleury, Rio de Janeiro, RJ, Brasil; [2] Unidade de Pesquisa Urogenital - Universidade do Estado do Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil

ABSTRACT

Purpose: To analyze the renal length in patients submitted to computed tomography (CT scans) and compare it according to age, gender, laterality and body parameters like height, weight and Body Mass Index (BMI).

Methods and Methods: We analyzed 74 patients (148 kidneys) submitted to CT scans and evaluated renal length in centimeters, gender, height, weight and BMI. The abdominal CT scans acquisition and image analysis was done using 16 and 64 slice multidetector computed tomography (MDCT) scanners to perform multiplanar reconstructions (MPR) and measure the kidney length (KL) in coronal plane. The statistical analysis was performed with the GraphPad Prism software (Version 9.2.0).

Results: The 74 patients analyzed (28 Males/37.83% and 46 females/62.17%) presented mean age of 54.1 years-old, right kidney length between 8.4 to 13.1cm (mean=10.79) and left kidney length between 8.3 to 13.1cm (mean=10.97). The kidney length on both sides was significantly greater in male sex ($p<0.001$). The length of the left kidney was significantly greater than that of the right kidney ($p=0.017$). The linear regression analysis showed non-significant correlation between both right kidney length and positive correlations between kidney length and BMI, weight and height.

Conclusions: CT scan accurately assessed renal length. We observed that renal length was greater in males and in the left side. Weight, age, height and body mass index showed a positive correlation with kidney length.

ARTICLE INFO

Luciano A. Favorito
https://orcid.org/0000-0003-1562-6068

Keywords:
Anatomy; Tomography, X-Ray Computed; Body Mass Index

Submitted for publication:
December 10, 2025

Accepted after revision:
January 15, 2026

Published as Ahead of Print:
January 29, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

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

INTRODUCTION

Knowledge of the normal sizes of the kidneys is important to radiologists and urologists when assessing the diagnosis and follow-up of renal diseases, using ultrasound scan (US) (1, 2). Renal length (kidney length) is an important parameter used in the clinical evaluation of renal growth and abnormalities and to estimate the renal cortex volume in chronic kidney disease (3-5). The kidney size can be affected by several diseases (6).

Renal size estimation most commonly incorporates renal length, renal volume and cortical thickness (3, 6, 7). The kidney length estimation is more solid because of its simple reproducibility, but the renal volume estimation is more precise (3, 6, 7).

During partial nephrectomies to treat kidney tumors the study of renal measurements and volume is very important and has great impact to surgical planning (8). The renal length is influenced by the overall body parameters, including age, height, weight and body mass index (BMI) (8-10). A few studies have been carried out on the normal dimensions of kidney size around the world (1, 2, 5, 11).

To our knowledge there are no studies that analyzed the length of the kidney with the measurements taken during CT scans and comparing the measurements with body parameters. Our hypothesis is that kidney length does not have important variations with age, genders, height, weight and BMI. The objective of the study was to analyze the kidney length in patients submitted to CT scans and compare it according to gender, age, laterality and body parameters.

MATERIAL AND METHODS

This study was approved by the Ethical Committee on Human Research, of our institution with the number (IRB: 76133 223.1.0000.5259) and we confirm that all methods used in this paper were carried out in accordance with relevant guidelines and regulation. The study has also been registered in the Brazil Plataform, Ministry of Health, National Health Council, National Research Ethics Commission for studies with human beings. We confirm that all methods used in this paper were carried out in accordance with relevant guidelines and regulation in compliance to the declaration of Helsinki.

We analyzed 74 patients (148 kidneys) submitted to abdominal computed tomography (CT) for various clinical indications in our institution between April 2024 and May 2025. We included patients up to 150 kg and evaluated the renal length in centimeters, age, gender, height, weight and Body Mass Index (BMI). We excluded patients with kidney anomalies, previous kidney surgeries, tumors and cysts; patients with urinary obstructive factors and patients with kidney Infection and renal failure.

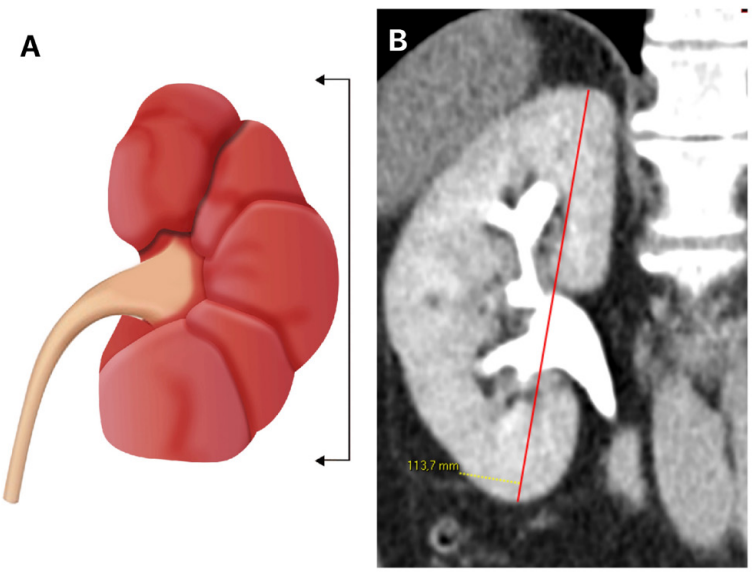
The abdominal CT scans and image analysis was done using 16 and 64 slice multidetector computed tomography (MDCT) scanners. The reconstruction slice thickness was 1.25mm and the contrast used was the Henetix® 350 /Contrast dose 1.3 mL/ Kg. An experienced radiologist evaluated the images acquired in the excretory phase using the commercially available Picture Archiving and Communication System software (PACS) Carestream® to perform multiplanar reconstructions (MPR) and measured the kidney length (KL) in coronal plane. The KL measurement was taken three times by the single observer (12, 13), and the average was calculated (Figure-1).

Statistical Analysis

All parameters were statistically processed and graphically described. The Shapiro-Wilk test was used to verify the normality of the data. Student-t test was used for comparison of quantitative data ($p < 0.05$), and the level of significance was adjusted by the correction of Bonferroni. Simple linear correlations were calculated for renal length according to patients age, height, weight and BMI.

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 kidney measurements, according to biometric parameters. The statistical analysis was performed with the GraphPad Prism software (Version 9.2.0).

Figure 1 - Kidney Length measurement.



A) Schematic drawing of kidney length measurement and B) Kidney length measurement in coronal plane (red line) in a CT scan image acquired during the excretory phase.

RESULTS

The 74 patients analyzed (28 Males - 37.83% and 46 females - 62.17%) presented ages between 19 and 79 years-old (mean=54.1), weight between 50 and 121kg (mean=74.35), height between 150 to 186cm (mean=166.6), body mass index between 15.2 to 38.19 (mean=26.72), right kidney length between 8.4 to 13.1cm (mean=10.79) and left kidney length between 8.3 to 13.1cm (mean=10.97). The summary of findings of the patients analyzed is reported in Table-1. The renal length on both sides was significantly greater in male sex (p<0.001). The length of the left kidney was significantly greater than that of the right kidney (p=0.017).

The linear correlation comparing renal length and the biometric parameters analyzed were assessed (Figure-2). The linear correlation comparing renal length and age were positive, but the r^2 values less than 0.4 in the right and left side indicates a very weak correlation. The linear regression analysis shows non-significant correlation between both right kidney length (r2=0.03041, p=0.1373, y=-0.01084x + 11.39) and left kidney length (r2=0.02422, p=0.1855, y=-0.01029x + 11.53) with age.

The linear correlation comparing renal length and BMI were positive, but the r^2 values less than 0.4 in right and left side indicates a very weak correlation. The linear regression analysis shows non-significant correlation between right kidney length and BMI (r2=0.05129, p=0.05123, y=0.05055x + 9.488) and a significant correlation between the left kidney length and BMI (r2=0.1004, p=0.0060, y=0.07521x + 8.961).

The linear correlation comparing renal length and height also indicates a weak correlation. The linear regression analysis shows a significant correlation between right kidney length and height (r2=0.1703, p=0.0003, y=0.04192x + 3.814) and a significant correlation between the left kidney length and height (r2=0.1926, p<0.001, y=0.04743x + 3.070).

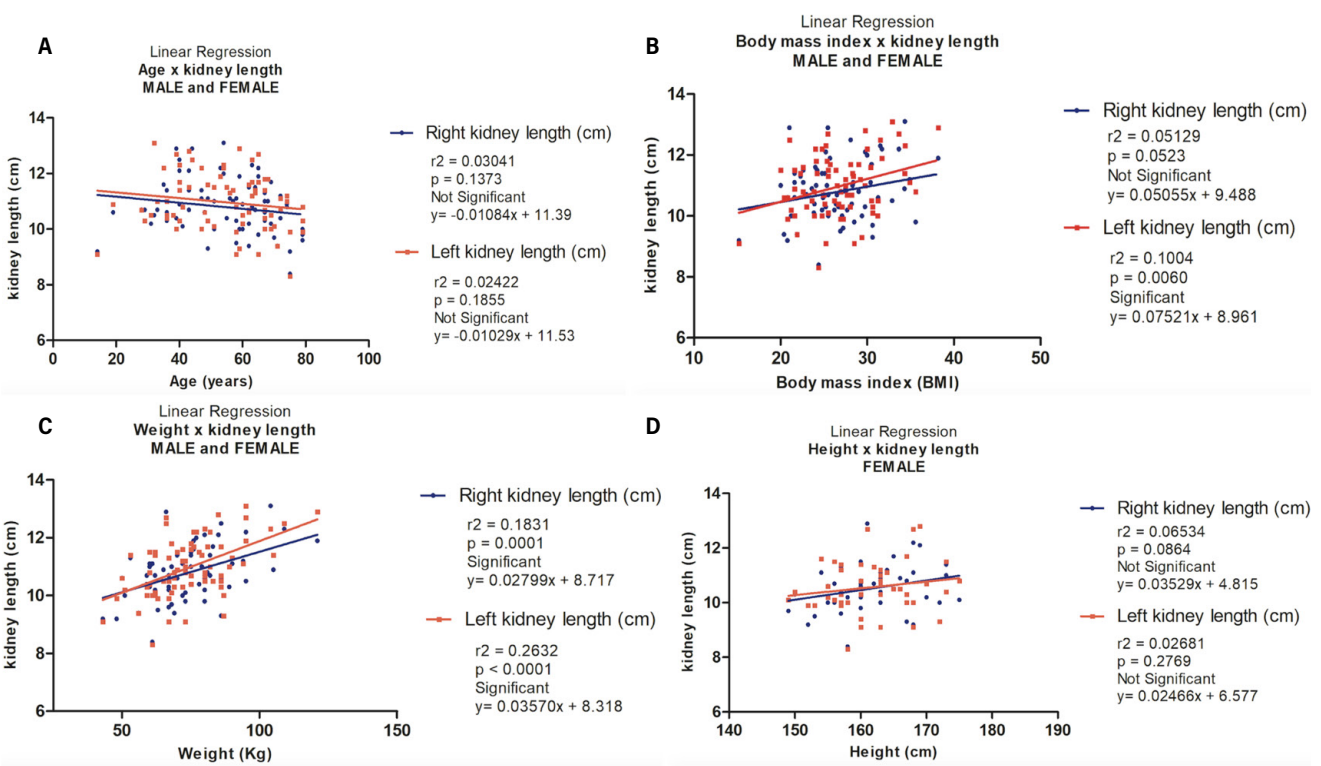
The linear correlation comparing renal length and weight also indicates positive correlation. The linear regression analysis shows a significant correlation between right kidney length and weight (r2=0.1831, p=0.0001, y=0.02799x + 8.717) and a significant correlation between the left kidney length and weight (r2=0.2632, p<0.001, y=0.03570x + 8.318).

Table 1 - The table shows the parameters of our sample (74 patients) analyzed in the present study.

Parameters	SEX	Sample	Mean	SD	IQR
Age(years-old)	F	46	56.7	15.168	24.50
	M	28	49.9	14.496	22.50
Weight (kg)	F	46	68.5	11.833	13.50
	M	28	83.9	13.337	13.50
Height_(cm)	F	46	161.6	6.234	9.75
	M	28	174.8	7.493	7.25
BMI	F	46	26.2	3.857	5.02
	M	28	27.6	4.725	6.13
RKL (cm)	F	46	10.5	0.861	1.07
	M	28	11.3	0.905	1.33
LKL (cm	F	46	10.6	0.939	1.17
	M	28	11.6	0.710	1.20

BMI = body mass index; RKL = right kidney length; LKL = left kidney length; SD = Standard deviation; IQR = Interquartile range

Figure 2 - The figure shows the linear regression analysis comparing the biometric data with renal length in CT scans.



A) Renal Length X Patients Age: The linear regression analysis shows non-significant correlation between both right kidney length (r2=0.03041, p=0.1373, y=-0.01084x + 11.39) and left kidney length (r2=0.02422, p=0.1855, y=-0.01029x + 11.53) with age; B) Renal Length X Body Mass Index (BMI): the linear regression analysis shows non-significant correlation between right kidney length and BMI (r2=0.05129, p=0.05123, y=0.05055x + 9.488) and a significant correlation between the left kidney length and BMI (r2=0.1004, p=0.0060, y=0.07521x + 8.961); C) Renal Length X Patients Weight: The linear regression analysis shows a significant correlation between right kidney length and weight (r2=0.1831, p=0.0001, y=0.02799x + 8.717) and a significant correlation between the left kidney length and weight (r2=0.2632, p<0.001, y=0.03570x + 8.318). D) Renal Length X Patients Height: the linear regression analysis shows a significant correlation between right kidney length and height (r2=0.1703, p=0.0003, y=0.04192x + 3.814) and a significant correlation between the left kidney length and height (r2=0.1926, p<0.001, y=0.04743x + 3.070).

DISCUSSION

The kidneys are located at the retroperitoneum, in contact with the major psoas muscle in each side, and therefore their longitudinal axis parallels the oblique direction of the psoas. The adult kidney has a length around 12 centimeters (cm) that vary among ethnic groups and are influenced by other factors such as body size, age and sex (14). The most accurate measurement of kidney size is estimated by the kidney volume, which could be correlated with biometric parameters like height, weight, and total body area (15, 16). The precise calculation of renal volume with US would be inappropriate, since it can underestimate the renal volume (17). Kidney volume is a better approximation of kidney size than renal length because of the shape of the kidney, but it is technically more demanding and needs four measurements in two different planes (15, 17, 18).

Renal length may not be an absolute predictor of overall kidney size, perhaps due in part to the fact that it measures only a single renal dimension, which may be associated with several inconsistencies and individual variations (17, 18). The renal volume has been emphasized by several authors as a true predictor of kidney size, however the renal length is easier to measure and is considered a good parameter for evaluating renal pathologies (19, 20).

Estimation of renal size could be a crucial step in the evaluation and treatment of several diseases, including cystic kidney diseases, chronic renal failure and renal masses (21, 22). US is the standard imaging modality in the investigation of renal diseases due to its noninvasive nature and easy availability; however it depends on the operator. CT scans are more commonly used for staging and characterization of renal cancer and could be an option for renal volume estimation because it has better accuracy in measurements (23).

Different studies have shown a correlation between renal measurements obtained via ultrasound and somatic parameters. In this paper for the 1st time in literature we studied the correlations between the anthropometric estimations with renal length using CT scans. Capaccioli and collegues (24) found a good correlation between age and kidney length. In a study with a larger sample size, Safak and collegues (25) examined 712 healthy school-age children and reported that weight best correlated with kidney length. The US reports are inconsistent on the relationship between body indices and renal morphology; some studies have found negative correlations between age and renal size (15,17,26). In our paper the linear correlation comparing renal length and age were positive, with a very weak correlation.

Several studies show that the renal length measurements were significantly associated with body mass index (BMI), weight, and body surface area (5, 8, 9). Emamian and collegues (27) reported evidence linking kidney length to weight, height, and body surface area, and BMI, while Han and Babcock (28) reported a correlation between kidney length and BMI. In our study, correlations show that weight, height, and BMI are significantly associated with renal length, especially for the left kidney. BMI and height were significant predictors for the right kidney, while sex and BMI were significant for the left kidney. The results indicate significant differences in kidney length between sexes, with men having larger kidneys, which may be related to anthropometric differences, such as greater weight and height.

Some studies have demonstrated no significant differences between the left and right kidney sizes. However, in our study the left kidney was significantly larger than the right kidney, which is similar to what was reported in other studies (5, 8, 9, 17, 26). The significant difference between the length of the right and left kidney suggests anatomical asymmetries, consistent with previous studies. The reasons to explain the difference between the length of the right and left kidney would be that the spleen smaller size compared to the liver, so the left kidney has more space to grow and the fact that the left renal artery is shorter than the right one, so increased blood flow in the left renal artery may result in a relatively increased size of the left kidney (14).

We should mention some limitations of this study: small sample size, study carried in a single institution, and we did not measure the renal volume.

In conclusion the CT scan accurately assessed renal length. We observed that kidney length was greater in males and in the left side. Weight, age, height and body mass index showed a positive correlation with kidney length.

ABBREVIATIONS

CT = computed tomography
BMI = body mass index
MDCT = multidetector computed tomography
PACS = Picture Archiving and Communication System software
MPR = multiplanar reconstructions
KL = kidney length
US = Ultrasound Scan

COMPLIANCE WITH ETHICAL STANDARDS

This study was supported by the National Council for Scientific and Technological Development (CNPQ – Brazil) (Grant number: 301522/2017) and The Rio de Janeiro State Research Foundation (FAPERJ) (Grant number: E26/202.873/2017).

This study was carried out in accordance with the ethical standards of the hospital's institutional committee on human experimentation. (IRB: 76133 223.1.0000.5259)).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Akinlade FT, Asaleye CM, Ayoola OO, Aremu AA. Ultrasound assessment of normal liver, spleen, and kidney dimensions in southwest Nigerian children: a bedside formula for sonologists. Acta Radiol. 2021;62(7):932-9. doi: 10.1177/0284185120948488
2. Al Salmi I, Al Hajriy M, Hannawi S. Ultrasound measurement and kidney development: a mini-review for nephrologists. Saudi J Kidney Dis Transpl. 2021 Jan-Feb;32(1):174-82. doi: 10.4103/1319-2442.318520
3. Nakazato T, Ikehira H, Imasawa T. Determinants of renal shape in chronic kidney disease patients. Clin Exp Nephrol. 2016;20(5):748-56. doi: 10.1007/s10157-015-1220-1
4. Nakazato T, Ikehira H, Imasawa T. An equation to estimate the renal cortex volume in chronic kidney disease patients. Clin Exp Nephrol. 2018;22(3):603-12. doi: 10.1007/s10157-017-1492-8
5. Mohtasib RS, Alshamri KM, Jobeir AA, Saidi FMA, Masawi AM, Alabdulaziz LS, et al. Sonographic measurements for kidney length in normal Saudi children: correlation with other body parameters. Ann Saudi Med. 2019;39(3):143-54. doi: 10.5144/0256-4947.2019.143
6. Chen Z, Jiang J, Gunda ST, Han X, Wu C, Ying MTC, et al. Ultrasonic renal length as an indicator of renal fibrosis severity in non-diabetic patients with chronic kidney disease. Clin Exp Nephrol. 2025 Apr;29(4):460-468. doi: 10.1007/s10157-024-02598-0.
7. Alyami AS, Majrashi NA, Elbashir M, Ali S, Shubayr N, Refaee T, Ageeli W, Madkhali Y, Abdelrazig A, Althobity AA, Alwadani B, AlShammari QT, Hendi AM. Normal sonographic measurements for kidney dimensions in Saudi adult population: A cross-sectional prospective study. Medicine (Baltimore). 2024 Jun 14;103(24):e38607. doi: 10.1097/MD.0000000000038607.
8. Son Y, Quiring ME, Dalton RM, Thomas B, Davidson N, DeVincentz D, Payne C, Parikh SH, Fink BA, Mueller T, Brown G. Renal mass imaging modalities: does body mass index (BMI) matter? Int Urol Nephrol. 2024 Aug;56(8):2483-2487. doi: 10.1007/s11255-024-03962-5.
9. Parmaksız G, Kekeç ŞD, Cengiz ND, Noyan A. The relationship between body mass index and renal length in obese children. Pediatr Nephrol. 2020 May;35(5):901-905. doi: 10.1007/s00467-019-04464-8.
10. Zewdu M, Kadir E, Berhane M. Variation of ultrasonic renal volume between hypertensive and non-hypertensive individuals in relation to body size parameters. Ethiop J Health Sci. 2021;31(5):857-64.
11. Diniz ALL, Rodrigues NCP, Sampaio FJB, Favorito LA. Study of the renal parenchymal volume during the human fetal period. Int Braz J Urol. 2019;45(1):150-60. doi: 10.1590/S1677-5538.IBJU.2018.0538
12. Tello C, Liebmann J, Potash SD, Cohen H, Ritch R. Measurement of ultrasound biomicroscopy images: intraobserver and interobserver reliability. Invest Ophthalmol Vis Sci. 1994;35(9):3549-52.
13. Bidra AS, Uribe F, Taylor TD, Agar JR, Rungruanganunt P, Neace WP. The relationship of facial anatomic landmarks with midlines of the face and mouth. J Prosthet Dent. 2009;102(2):94-103. doi: 10.1016/S0022-3913(09)60117-7

14. Alan JW, et al. Gray's anatomy: the anatomical basis of clinical practice. 41st ed. Edinburgh: Churchill Livingstone; 2016. p. 237-1253.
15. Abdullah MB, Garelnabi MB, Ayad CE, Abdalla EA. Establishment of reference values for renal length and volume for normal adult Sudanese using MRI disc summation method. Glob J Med Res. 2014;14:29-37.
16. Maravi P, Khan M, Kaushal L, Goyal S. Renal volumes by ultrasound and its correlation with body mass index and body surface area in adult population. Trop J Radiol Imaging. 2019;1:20-6.
17. Bakker J, Olree M, Kaatee R, et al. Renal volume measurements: accuracy and repeatability of US compared with that of MR imaging. Radiology. 1999;211(3):623-8.
18. Moorthy HK, Venugopal P. Measurement of renal dimensions in vivo: a critical appraisal. Indian J Urol. 2011;27(2):169-75. doi: 10.4103/0970-1591.82832
19. Egberongbe AA, Adetiloye VA, Adeyinka AO, Afolabi OT, Akintomide AO, Ayoola OO. Evaluation of renal volume by ultrasonography in patients with essential hypertension in Ile-Ife, south western Nigeria. Libyan J Med. 2010;5:4848. doi: 10.3402/ljm.v5i0.4848
20. Sanusi AA, Arogundade FA, Famurewa OC, Akintomide AO, Soyinka FO, Ojo OE, et al. Relationship of ultrasonographically determined kidney volume with measured GFR, calculated creatinine clearance and other parameters in chronic kidney disease (CKD). Nephrol Dial Transplant. 2009 May;24(5):1690-4. doi: 10.1093/ndt/gfp055. Epub 2009 Mar 4. PMID: 19264744.
21. Yadav SK, Yadav R, Chakradhar S, Karn A. Measurement of renal length and width in healthy adults and their association with various parameters. Int J Curr Res Rev. 2017;9:29-32.
22. Singla RK, Kadatz M, Rohling R, Nguan C. Kidney ultrasound for nephrologists: a review. Kidney Med. 2022;4(6):100464. doi: 10.1016/j.xkme.2022.100464
23. Saeed Z, Mirza W, Sayani R, et al. Sonographic measurements of renal dimensions in adults and its correlates. Int J Collab Res Intern Med Public Health. 2012;4:1626-41.
24. Capaccioli L, Stecco A, Vanzi E, Brizzi E. Ultrasonographic study on the growth and dimensions of healthy children and adults organs. Ital J Anat Embryol. 2000;105:1-50.
25. Safak AA, Simsek E, Bahcebasi T. Sonographic assessment of the normal limits and percentile curves of liver, spleen, and kidney dimensions in healthy school-aged children. J Ultrasound Med. 2005;24:1359-64.
26. Maravi P, Khan M, Kaushal L, Goyal S. Renal volumes by ultrasound and its correlation with body mass index and body surface area in adult population. Trop J Radiol Imaging. 2019;1:20-6.
27. Emamian SA, Nielsen MB, Pedersen JF, Ytte L. Kidney dimensions at sonography: correlation with age, sex, and habitus in 665 adult volunteers. AJR Am J Roentgenol. 1993;160(1):83-6. doi: 10.2214/ajr.160.1.8416654
28. Han BK, Babcock DS. Sonographic measurements and appearance of normal kidneys in children. AJR Am J Roentgenol. 1985;145(3):611-6. doi: 10.2214/ajr.145.3.611

Correspondence address:
Luciano Alves Favorito, MD, PhD
Unidade de Pesquisa Urogenital - Universidade do Estado do Rio de Janeiro - Uerj,
Rua Professor Gabizo, 104/201 – Tijuca
Rio de Janeiro, RJ, Brasil, 20271-320
Telephone: + 55 21 2264-4679
E-mail: lufavorito@Yahoo.com.br

ORIGINAL ARTICLE

Vol. 52 (3): e20250665, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0665

Factors Affecting Preserved Renal Volume and Function After Laparoscopic Partial Nephrectomy: A Long-Term 3D Volumetric Analysis

Onur Kalaycı [1], Ender Özden [2], Murat Gülşen [2], İlkay Çamlıdağ [3], Ertuğrul Köse [4], Mehmet Necmettin Mercimek [2], Yakup Bostancı [2], Yarkın Kamil Yakupoğlu [2], Şaban Sarıkaya [2]

[1] Department of Urology, Samsun City Hospital, Samsun, Turkey; [2] Department of Urology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey; [3] Department of Radiology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey; [4] Department of Urology, Gazi State Hospital, Samsun, Turkey

ABSTRACT

Objective: To assess long-term changes in renal volume and function after laparoscopic partial nephrectomy using 3D modeling and to identify key predictors.

Patients and Methods: This retrospective study included 187 patients who underwent laparoscopic partial nephrectomy between October 2012 and January 2023. Patients underwent the same cross-sectional imaging both pre- and postoperatively, with a minimum follow-up of one year. Pre- and postoperative volumes were reconstructed with 3D Slicer software.

Results: The median age of the patients was 58 years. The median Radius-Exophytic-Nearness-Anterior-Location (RENAL) score was 7. The median tumor volume was 15.8 cm^3. The median warm ischemia time was 14 minutes, and the median surgical time was 80 minutes. The mean tumor-free renal parenchymal volume before surgery was 168,87 ± 40,91 cm^3, which decreased to a mean operated renal parenchymal volume of 137.6 ± 41.7 cm^3 at 5 years postoperatively. The estimated glomerular filtration rate (eGFR) declined from a median value of 90.6 to 75.9 mL/min/1.73 m^2 over the same period.

The predictors of renal function decline were parenchymal volume loss, age, female gender, diabetes mellitus, and tumor-to-parenchyma contact surface area. Factors affecting parenchymal volume loss included age, RENAL score, comorbidities, Surface-Intermediate-Base (SIB) score, and operative time.

Conclusions: While the most influential factor on renal function in the early postoperative period was the preserved renal volume, diabetes mellitus (DM) emerged as the primary determinant of long-term functional outcomes.

Tumor resection technique and operative time are modifiable factors influencing parenchymal volume preservation. Enucleation-based approaches may enhance parenchymal preservation without compromising oncological outcomes.

ARTICLE INFO

Onur Kalayci
https://orcid.org/0000-0002-6898-7564

Keywords:
Kidney Neoplasms; Laparoscopy; Imaging, Three-Dimensional

Submitted for publication: November 14, 2025

Accepted after revision: January 28, 2026

Published as Ahead of Print: February 20, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

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

INTRODUCTION

Partial nephrectomy (PN) is the standard treatment modality for patients with cT1 renal tumors when technically feasible, as well as for cT2 tumors in patients with a solitary kidney or chronic kidney disease (CKD) (1).

Contemporary management of small renal masses increasingly emphasizes nephron-sparing strategies with a strong focus on long-term preservation of renal function rather than oncological control alone (2). Regarding functional outcomes, important determinants include warm ischemia time (WIT) and the volume of preserved functional renal parenchyma postoperatively. Previous studies have reported limited data on long-term functional outcomes assessed through kidney volumetry (3, 4).

Three-dimensional (3D) modeling techniques have become integral for obtaining precise and accurate measurements of renal parenchymal volume (RPV) with the help of current technological advancements. Moreover, 3D models facilitate more objective calculations of tumor volume, tumor-parenchyma contact surface area, and bilateral RPV in patients with renal tumors (5).

We hypothesized that preserved renal parenchymal volume is a primary determinant of long-term renal functional preservation after laparoscopic partial nephrectomy, independent of conventional clinical and nephrometry-based factors.

The novel contribution of this study lies in its long-term, three-dimensional volumetric–functional analysis performed in a homogeneous cohort of patients undergoing laparoscopic partial nephrectomy. By minimizing surgical heterogeneity through a single-surgeon, standardized approach, this study provides new insight into the relative impact of preserved renal parenchymal volume and tumor–parenchyma interaction parameters on postoperative renal functional preservation, beyond conventional clinical variables and nephrometry scores.

The primary aim of this study is to evaluate preserved RPV using three-dimensional modeling quantitatively and to examine its association with temporal changes in estimated glomerular filtration rate (eGFR). As a secondary objective, we aimed to identify preoperative and surgical factors influencing preserved RPV and postoperative renal function.

MATERIALS AND METHODS

This study was conducted with the approval of the Ondokuz Mayıs University Faculty of Medicine Clinical Research and Ethics Committee, dated February 14, 2024 (Decision No: B.30.2.ODM.0.20.08/84-134).

Data from patients who underwent laparoscopic partial nephrectomy (LPN) between October 2012 and January 2023 were prospectively collected and subsequently analyzed retrospectively. A total of 187 patients who had undergone evaluation using the same cross-sectional imaging modality both preoperatively and postoperatively (computed tomography [CT]/magnetic resonance imaging [MRI]) with a minimum follow-up period of one year were included in the study. Patients with a solitary kidney and those with bilateral renal masses were excluded from the study, as it focused on postoperative compensatory functional changes in the contralateral kidney. In the absence of a paired renal unit or in the setting of bilateral surgery, compensatory adaptation cannot be reliably distinguished from the direct effects of surgical intervention, thereby limiting the interpretability of volumetric–functional analyses. Demographic and clinical data such as age, sex, body mass index (BMI), presence of diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), CKD (defined as an eGFR below 60 mL/min/1.73 m^2), history of smoking, history of prior abdominal surgery, preoperative creatinine levels, and eGFR were recorded.

Preoperative radiological imaging was used to determine tumor size and the RENAL and Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) nephrometry score (6). Additionally, the lateral peripheral fat thickness at the level of the renal vein was measured in alignment with the renal capsule and renal vein. Posterior peripheral fat thickness was assessed by measuring the perpendicular distance from the midpoint of the posterior renal capsule to the posterior abdominal wall at the level of the renal vein. Previous studies have assessed the presence and thickness of perinephric linear soft tissue attenuation (stranding type), and the Mayo

Adhesive Probability (MAP) score was calculated based on these data.

A single surgeon performed all surgeries using a previously described technique.

A transperitoneal approach was preferred in all cases, with patients positioned in a modified lateral decubitus position. Pneumoperitoneum was established using a closed technique, and trocar placement was adapted according to patient anatomy. After mobilization of the colon and surrounding structures, Gerota's fascia was incised, and perirenal dissection was carried out to expose the renal hilum. The renal artery and vein were dissected separately and secured with vessel loops.

Tumor localization and resection margins were guided by intraoperative ultrasonography (USG), particularly in endophytic lesions. Tumor excision was performed using cold scissors along the tumor–parenchyma interface, aiming to preserve maximal healthy renal parenchyma and to avoid tumor capsule violation. Selective or global hilar clamping was applied when indicated.

Renorrhaphy was performed using a standardized two-layer technique. The inner layer consisted of absorbable sutures for closure of the collecting system or deep parenchymal defects, while the outer cortical layer was completed using absorbable braided sutures with a sliding-clip technique for parenchymal approximation and hemostasis. After completion of renorrhaphy, vascular clamps were released, and hemostasis was confirmed under reduced pneumoperitoneum pressure. The specimen was retrieved using an endoscopic retrieval bag, and Gerota's fascia was closed with absorbable sutures.

Perioperative variables were evaluated, including operative time, ischemia type and time, intraoperative ultrasonography (USG) use, and the Surface-Intermediate-Base (SIB) score. Complications were classified according to the Clavien-Dindo complication grading system. Postoperative eGFR values were recorded to assess renal function (RF).

Preoperative and postoperative radiological images of the patients were reconstructed into three-dimensional models using the 3D Slicer software (https://www.slicer.org). These models were used to calculate volume and surface area using the software.

Patients with missing clinical, functional, or volumetric imaging data at a given follow-up year were excluded from analyses corresponding to that specific time point. No data imputation was performed. Analyses were conducted on a year-specific basis, including only patients with complete imaging and renal function assessments available for the respective follow-up interval.

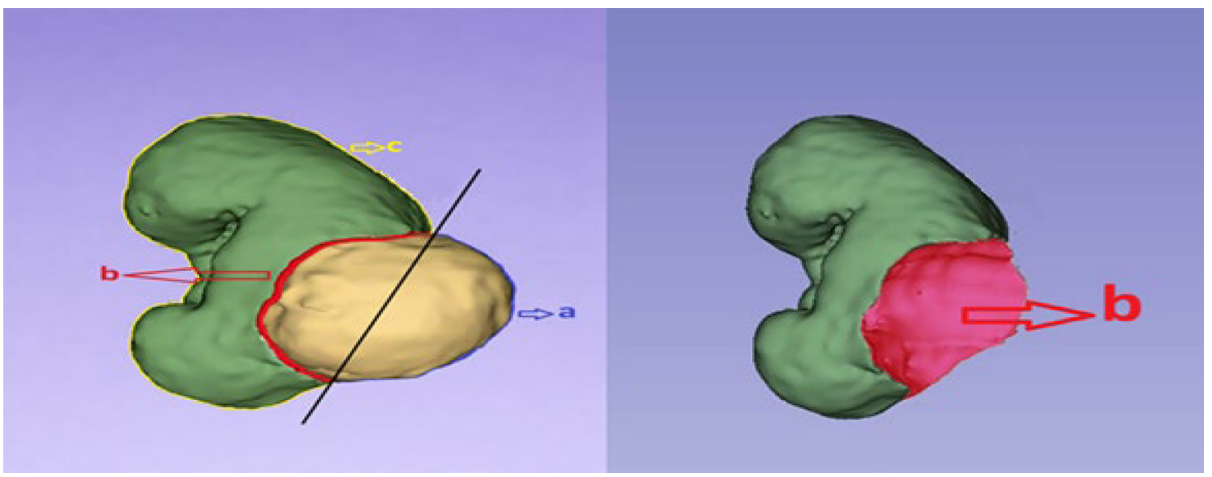
Volume and Surface Area Calculation

CT/MRI images were processed using the 3D Slicer software to identify the boundaries of the affected kidney, the tumor, and the contralateral kidney to generate 3D reconstructions. The 3D models revealed tumor volume, preoperative healthy RPV (excluding the tumor), contralateral renal parenchymal volume (CRPV), tumor surface area, and tumor-to-kidney contact surface area (as illustrated and described in Figure-1, the tumor-to-kidney contact surface area was calculated).

Imaging acquisition protocols were standardized to ensure volumetric accuracy and longitudinal consistency. Contrast-enhanced computed tomography scans were acquired using multiphasic protocols, and tumor assessment and volumetric analyses were performed on the nephrographic phase. Images were obtained with slice thicknesses ranging from 1 to 3 mm and reconstructed using isotropic voxels to enable accurate three-dimensional segmentation. In patients undergoing MRI, contrast-enhanced T1-weighted sequences with comparable slice thickness and reconstruction parameters were used. For each patient, preoperative and postoperative volumetric analyses were consistently performed using the same imaging modality to minimize inter-modality variability.

These measurements were performed as follows: tumor boundaries were delineated in all relevant slices using Hounsfield unit (HU) differences or intensity differences between the healthy parenchyma and the tumor in contrast-enhanced images. Optimal contouring was performed on the most detailed pixel scale in appropriate sequences that demonstrated intensity differences, ensuring precise delineation of tumor borders. Next, the preoperative healthy RPV, excluding the tumor, was measured. The tumor surface area was automatically calculated in square centimeters (cm^2) from the 3D models.

Figure 1 - Calculation of the Tumor-to-Kidney Contact Surface Area in Non-Endophytic Tumors



Suppose we define the exophytic surface area of the tumour as "a", the endophytic surface area as "b", and the outer surface area of the healthy parenchyma as "c". In that case, the 3D Slicer software allows us to calculate the values of "a + c", "a + b", and "b + c". Using these known values, the unknown "b" value, which represents the tumour-to-kidney contact surface area, was calculated using the following formula:

$$b = \text{tumour-to-kidney contact surface area} = \frac{(b + c) - (a + c) + a + b}{2}$$

Statistical Analysis

Data were analysed using Statistics Package for Social Sciences version 24 (IBM SPSS®, Armonk, NY) and Number Cruncher Statistical System (ICSS) 11 software. The normality of the distribution was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The Fisher's Exact Test, Yates Correction, and Pearson Chi-Square Test were used for categorical variables, while multiple comparisons were conducted using the Bonferroni-Corrected Z Test.

For group comparisons, the Independent Samples t-test was employed for normally distributed variables, whereas the Mann-Whitney U test was applied for variables that did not meet the assumption of normality. Linear Regression Analysis was used to examine factors affecting normally distributed dependent variables, while Robust Regression Analysis was applied to those not following a normal distribution.

Results were presented as frequencies (percentages) for categorical variables and as means ± standard deviations or medians (minimum-maximum) for quantitative variables. A p-value < 0.05 was considered statistically significant.

RESULTS

The demographic and perioperative data of the study are shown in Table-1. Of the patients, 52.9% (n=99) were male, and 47.1% (n=88) were female, with a median age of 58 years (IQR: 48-66). Among the study population, 17.6% (n=33) had DM, 45.5% (n=85) had HT, and 6.4% (n=12) had CKD. Additionally, 35.8% (n=67) had a history of previous abdominal surgery, and 26.2% (n=49) were active smokers.

The tumor was located in the left kidney in 43.9% of patients (n=82) and the right kidney in 56.1% (n=105). The mean tumor size was 36.76 ± 13.37 mm. The median RENAL score was 7 (IQR: 6-9), the median PADUA score was 8 (IQR: 7-10), and the median MAP score was 1 (IQR: 0-3).

Regarding ischemia types, 8.6% (n=16) underwent non-ischemic (off-clamp) surgery, 86.1% (n=161) underwent global ischemia, and 5.3% (n=10) underwent selective ischemia. The median WIT was 14 minutes (IQR: 11-18). The median SIB score was 4 (IQR: 2-5). The median operative time was 80 minutes (IQR: 65-100), with intraoperative USG used in 71% of patients (n=132). The median estimated blood loss was 100 mL (IQR: 50-160).

Table 1 - Demographic and Perioperative Features of the Cohort.

Demographic Data (n=187)	
Gender, n (%)	
Female	88 (47.1)
Male	99 (52.9)
Age (years), median (IQR)	58 (48 - 66)
BMI (kg/m^2), median (IQR)	28.52 (26.02 - 32.08)
Preoperative eGFR (mL/min/1.73m^2), median (IQR)	90.56 (73.99 - 103.16)
Radiological Characteristics (n=187)	
Tumor Side, n (%)	
Left	82 (43.9)
Right	105 (56.1)
Tumor size (mm), mean ± SD	36.76 ± 13.37
RENAL Score, median (IQR)	7 (6 - 9)
PADUA Score, median (IQR)	8 (7 - 10)
MAP Score, median (IQR)	1 (0 - 3)
Preoperative Volume and Surface Area Measurements (n=187)	
Tumor-Bearing Kidney Volume (cm^3), median (IQR)	188.5 (91 - 439)
Tumor Volume (cm^3), median (IQR)	15.8 (0.2 - 258)
Preoperative Tumor-Free RPV (cm^3), mean ± SD	168,87 ± 40,91
Preoperative CRPV(cm^3), mean ± SD	168.87 ± 40.91
Tumor Surface Area (cm^2), median (IQR)	35 (3 - 362)
Tumor-to-Parenchyma Contact Surface Area (cm^2), median (IQR)	16 (1 - 150)
Operative Data (n=187)	
Ischemia Type, n (%)	
Non-Ischemia	16 (8.6)
Global Ischemia	161 (86.1)
Selective Ischemia	10 (5.3)
WIT (min), median (IQR)	14 (11 - 18)
SIB Score, median (IQR)	4 (2 - 5)
Operative Time (min), median (IQR)	80 (65 - 100)
Intraoperative USG Use, n (%)	132 (71)
Estimated Blood Loss (mL), median (IQR)	100 (50 - 160)

Values are presented as median (interquartile range), mean ± standard deviation, or number (percentage), as appropriate.

BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; SD = standard deviation; RENAL = Radius–Exophytic/Endophytic–Nearness–Anterior/Posterior–Location score; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical score; MAP = Mayo Adhesive Probability score; RPV = renal parenchymal volume; CRPV = contralateral renal parenchymal volume; WIT = warm ischemia time; SIB = surface–ischemia burden; USG = ultrasonography

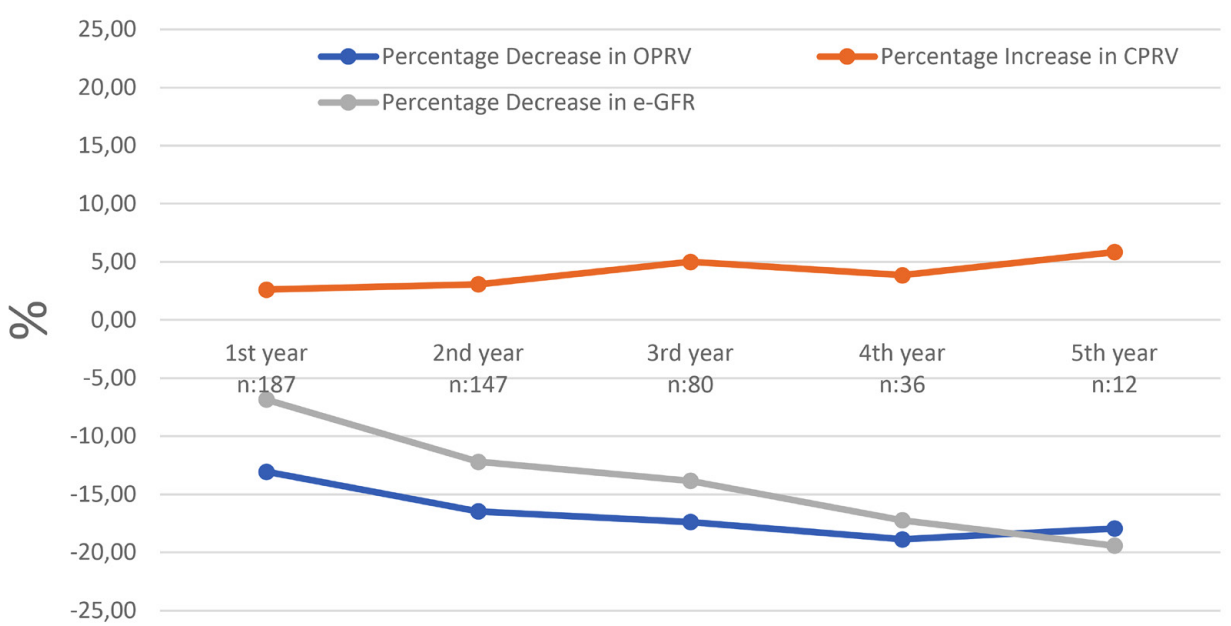
According to the Clavien-Dindo complication classification, among patients experiencing complications, 4.3% (n=8) had Grade 1 complications, 4.3% (n=8) had Grade 2 complications, and 3.2% (n=6) had Grade 3 complications. Grade 4-5 complications were not observed. Patients were followed for a mean duration of 30 months.

The median preoperative tumor-bearing kidney volume was 188.5 cm^3 (IQR: 91-439), the median tumor volume was 15.8 cm^3 (IQR: 0.2-258), and the mean tumor-free RPV was 168.87 ± 40.91 cm^3. The mean CRPV was 168.87 ± 40.91 cm^3. The median tumor surface area was 35 cm^2 (IQR: 3-362), and the median tumor-to-parenchyma contact surface area was 16 cm^2 (IQR: 1-150).

The duration of follow-up ranged from 1 to 5 years. The number of patients with complete imaging and renal function data decreased over time, reflecting the retrospective design of the study. Complete follow-up data were available for 187 patients at 1 year, 147 patients at 2 years, 80 patients at 3 years, 36 patients at 4 years, and 12 patients at 5 years. All analyses were performed on a year-specific basis, including only patients with complete data available for the respective follow-up interval.

Preoperative eGFR (mL/min/1.73m^2) was 90.56 (73.99–103.16), declining to 84.01 (13.22–121.46) at postoperative year 1, 81.19 (13.79–124.75) at year 2, 81.02 (17.55–118.92) at year 3, 77.66 (15.53–134.94) at year 4, 75.88 (16.81–116.96) at year 5. The operated renal parenchymal volume (ORPV) was measured to be 146 ± 40 cm^3 at postoperative year 1, 139.6 ± 40 cm^3 at year 2, 139.2 ± 39 cm^3 at year 3, 137.1 ± 36.4 cm^3 at year 4, and 137.58 ± 41.7 cm^3 at year 5. The CRPV was measured to be 173.5 ± 35.9 cm^3 at postoperative year 1, 175 ± 35.3 cm^3 at year 2, 180.9 ± 36 cm^3 at year 3, 178.3 ± 32.9 cm^3 at year 4, and 174.17 ± 23.77 cm^3 at year 5. The percentage changes in these volumetric data and in eGFR are presented in Figure-2. Robust regression analysis was

Figure 2 Relationship Between Δ ORPV, Δ CRPV, and Δ eGFR



Longitudinal percentage changes in operated renal parenchymal volume (OPRV), contralateral parenchymal renal parenchymal volume (CPRV), and estimated glomerular filtration rate (eGFR) over a 5-year follow-up period after partial nephrectomy. The graph demonstrates a progressive percentage decrease in OPRV and eGFR, accompanied by a gradual percentage increase in CPRV, indicating compensatory hypertrophy of the contralateral kidney in response to parenchymal volume loss in the operated kidney

n: Number of patients included in the analysis

performed to assess the independent variables influencing ΔeGFR (percentage change in eGFR), which is presented in Table-2. A one-unit increase in age caused a 0.164 decrease in the rate of preserved eGFR in the first postoperative year (p=0.045). Additionally, a one percent decrease in the first-year preserved ORPV led to a 0.197 unit decrease in the first-year rate of preserved eGFR (p<0.001). Furthermore, an increase of one unit in the tumor-to-parenchyma contact surface area resulted in a 0.876 unit decrease in the first-year rate of preserved eGFR (p=0.045).

A one-unit increase in age led to a 0.310 unit decrease in second-year rate of preserved eGFR (p=0.020). Similarly, a one percent decrease in the second-year preserved ORPV resulted in a 0.259 unit decrease in the second-year rate of preserved eGFR (p<0.001). Additionally, a 5.246 unit greater decrease in the rate of preserved eGFR was observed in female patients compared to male patients in the second year (p=0.027).

A one percent decrease in the third-year preserved ORPV was associated with a 0.229 unit decrease in the third-year rate of preserved eGFR (p=0.015). Furthermore, patients with DM had a rate of preserved eGFR decrease that was 12.154 units higher than those without DM (p=0.008) in the third year.

The robust regression analysis evaluating the independent variables associated with Δ ORPV (percentage change in OPRV) is presented in Table-2. It was determined that for each year increase in age, the first-year rate of preserved ORPV decreased by 0.284 units (p=0.034). Additionally, with an increase of one unit in operative time, the first-year rate of preserved ORPV decreased by 0.162 units (p=0.001). For each unit increase in the SIB score, the first-year rate of preserved ORPV decreased by 2.236 units (p=0.004). Patients without comorbidities had a first-year rate of preserved ORPV 6.166 units higher than those with comorbidities (p=0.014).

As the RENAL score increased, the second-year rate of preserved ORPV decreased by 4.409 units (p=0.002). Additionally, with an increase of one unit in operative time, the second-year rate of preserved ORPV decreased by 0.292 units (p=0.004). Each unit increase in the SIB score resulted in a 3.350 unit decrease in the second-year rate of preserved ORPV (p=0.022). Patients without comorbidities had a second-year rate of preserved ORPV 9.794 units higher than those with comorbidities (p=0.048).

DISCUSSION

This study identified preserved renal volume as the key modifiable factor influencing eGFR preservation. Tumor resection technique and operative time were additional modifiable factors affecting preserved renal volume. Unmodifiable predictors of eGFR preservation included age, gender, tumor-to-parenchyma contact surface area, and the presence of DM, whereas age, RENAL score, and comorbidities were identified as unmodifiable determinants of renal volume preservation. While the most critical factor on RF in the early postoperative period was the preserved renal volume, DM emerged as the primary determinant of long-term functional outcomes.

Acute kidney injuries secondary to surgery and warm ischemia lead to a renal recovery process. A larger preserved RPV post-surgery correlates with a higher compensatory capacity. Previous studies have emphasised that preserving RPV is the most statistically significant factor in eGFR decline (8, 9). Furthermore, in addition to factors that affect eGFR change by influencing postoperative RPV, other direct determinants of eGFR also exist.

It has been determined that eGFR declines annually as part of the natural ageing process, but the rate of decline slows with advancing age (10). However, postoperative renal functional changes represent a distinct process influenced by surgical and perioperative factors. Similar to our study, studies investigating eGFR decline following PN indicate that the rate of postoperative eGFR decline increases with age (11, 12). Potentially due to more effective compensatory mechanisms in younger patients and increased comorbidities in older individuals.

Furthermore, previous studies have suggested that women indicated a more rapid age-related decline in eGFR than men (13). Studies examining patient and disease characteristics that affect RF after PN have found a greater postoperative eGFR reduction in men than in

Table 2 - Robust Regression Analysis of Factors Associated with eGFR Decline and ORPV Loss Following LPN.

	Δ eGFR			Δ ORPV	
	Year 1 (n:187)	Year 2 (n:147)	Year 3 (n:80)	Year 1 (n:187)	Year 2 (n:147)
	β0 (95% CI) p	β0 (95% CI) p	β0 (95% CI) p	β0 (95% CI) p	β0 (95% CI) p
Patient Factors					
Age (years)	0.16 (0.00 –0.33) **p: 0.045**	0.31 (0.05 – 0.57) p:**0.020**	0.25 (-0.11 – 0.61) p:0.167	0.284 (0.02 – 0.55) p:**0.034**	0.46 (-0.16 – 1.1) p:0.138
Male Gender	-2.52 (-5.72 –0.69) p: 0.123	-5.25 (-9.87 – -0.62) p:**0.027**	1.05 (-5.74 – 7.85) p:0.757	-1.88 (-8.73 – 4.96) p:0.59	-7.22 (-22.8 – 8.4) p:0.350
Body Mass Index	—	—	—	-0.35 (-0.98 – 0.27) p:0.27	-0.57 (-1.71 – 0.58) p:0.320
Hypertension	0.72 (-2.52 – 3.97) p:0.660	2.38 (-2.2 – 6.95) p:0.306	3.21 (-2.85 – 9.28) p:0.293	—	—
Diabetes Mellitus	-0.34 (-4.76 – 4.08) p: 0.879	4.22 (-2.02 – 10.46) p:0.183	12.15 (3.24 – 21.07) p:**0.008**	—	—
Absence of Comorbidities	—	—	—	-6.17 (-11.1 – -1.25) p:**0.014**	-9.79 (-19.52 – -0.07) p:**0.048**
Smoking Status	-1.17 (-4.74 – 2.41) p:0.521	2,66 (-2,64 - 7,96) p:0.322	-1.79 (-9.55 – 5.96) p:0.645	—	—
Tumor Factors					
RENAL Score	—	—	—	0.33 (-2.12 – 2.78) p:0.790	4.41 (1.72 – 7.1) p:**0.002**
MAP Score	—	—	—	-0.82 (-2.48 – 0.84) p:0.331	-1.37 (-5.14 – 2.4) p:0.462
Preoperative Tumor-Free RPV (cm^3)	-0.04 (-0.08 – 0.01) p: 0.085	0 (-0.07 – 0.06) p:0.993	0.04 (-0.03 – 0.13) p:0.276	—	—
Tumor Volume (cm^3)	-0.02 (-0.09 – 0.05) p:0.570	-0.04 (-0.16 – 0.1) p:0.451	-0.06 (-0.19 – 0.07) p:0.346	0.01 (-0.10 – 0.12) p:0.898	-0.12 (-0.38 – 0.15) p:0.372
Contact Surface Area (cm^2)	0.88 (-0.44 – 2.20) p:**0.045**	1.37 (-0.89 – 3.63) p:0.233	1.72 (-1.08 – 4.52) p:0.225	1.64 (-0.65 – 3.94) p:0.159	-0.38 (-3.67 – 2.91) p:0.817
Surgical Factors					
Ischemia Type (Non/Sel)	—	—	—	-3.85 (-13.26 – 5.55) p:0.418	0.563 (-21.67 – 22.79) p:0.959
Warm Ischemia Time	—	—	—	0.01 (-0.59 – 0.62) p:0.960	-0.44 (-1.75 – 0.86) p:0.492
SIB Score	—	—	—	2.24 (0.75 – 3.72) p:**0.004**	3.35 (0.53 – 6.17) p:**0.022**
Operative Time (min)	—	—	—	0.162 (0.072 – 0.25) p:**0.001**	0.29 (0.10 – 0.48) p:**0.004**
Intraoperative USG	—	—	—	1.08 (-3.86 – 6.03) p:0.665	-2.11 (-10.82– 6.59) p:0.622
Outcomes					
Δ ORPV (%)	0.20 (0.09 – 0.30) p:<**0.001**	0.26 (0.12 – 0.4) p:<**0.001**	0.23 (0.05 – 0.41) p:**0.015**	—	—
Δ CRPV (%)	0.03 (-0.14 – 0.20) p:0.739	0.05 (-0.19 – 0.28) p:0.685	-0.17 (-0.49 – 0.15) p:0.293	—	—
Positive Margin	—	—	—	-10.61 (-33.84 –12.62) p:0.367	-7.68 (-41.86 – 26.49) p:0.648

women (14). However, our study's regression analysis revealed that the postoperative 2-year eGFR decline was 5.24% greater in women than in men. The absence of a gender difference in factors affecting postoperative 1-year eGFR decline, with a difference emerging in the second year, aligns to some extent with studies investigating gender-related eGFR decline in the absence of surgical intervention. This discrepancy highlights the absence of a clear consensus in the literature and suggests that observed sex-related differences may reflect temporal variability rather than a stable, sex-specific pattern of renal functional decline.

DM and HT are well-established risk factors of chronic and end-stage renal disease. Studies examining postoperative eGFR decline in patients with DM and HT have reported debatable outcomes (15, 16). In the literature, studies examining factors affecting RF after PN have demonstrated that baseline RF and DM are significant determinants. Specifically, DM has been highlighted as an independent factor influencing functional outcomes following surgery. These findings highlight the importance of personalised patient management strategies considering the long-term effects of DM on RF (17, 18). In our study, patients with DM exhibited a 12.1% greater eGFR decline than those without DM. At the same time, HT was not statistically significantly associated with RF decline or RPV loss.

Several volumetric analyses in the literature, predominantly conducted in robot-assisted partial nephrectomy cohorts, have emphasized the importance of preserved renal parenchymal volume in determining postoperative renal functional outcomes. These studies have demonstrated that volumetric parameters provide additional insight beyond traditional perioperative metrics. Although the majority of such data originate from robotic series, the volumetric–functional associations observed in our laparoscopic cohort appear to be directionally consistent with these reports. This suggests that the relationship between parenchymal preservation and renal function may be applicable across different minimally invasive approaches, while remaining influenced by technique-specific factors.

Complexity scores such as RENAL and PADUA can predict postoperative RPV changes independently of the surgical technique. Higher scores indicate greater surgical difficulty, making postoperative RF preservation more challenging (6, 19, 20). In our study, higher RENAL scores were associated with lower RPV preservation as well.

Lee et al. compared the predictive capabilities of the RENAL and PADUA scores with tumor contact surface area in assessing RPV changes following PN. They concluded that tumor contact surface area better predicted postoperative RPV changes than these scoring systems (21). Studies examining the relationship between eGFR decline and tumor-to-parenchyma contact surface area have found that patients with a smaller contact surface area experienced less RF decline (22, 23). Our study's regression analysis of independent variables affecting eGFR decline revealed that each 1-unit increase in tumor-to-parenchyma contact surface area resulted in a 0.876% decrease in eGFR ($p = 0.045$).

Our findings suggest that regression analysis showed that tumor-to-parenchyma contact surface area did not have a statistically significant effect on ORPV changes; however, its significant effect on eGFR decline suggests that even if the RPV is preserved, increased tumor contact surface area may lead to greater nephron loss and perfusion impairment.

MAP score has been linked to functional and oncological outcomes and is useful for predicting difficulties in tumor access and excision (24). However, no studies have examined the relationship between MAP score and postoperative ipsilateral RPV or eGFR change. In our study, no significant association was found between MAP score and eGFR or bilateral RPV changes, possibly due to the high experience of the primary surgeon and the use of laparoscopic USG in complex cases. In support of our findings, a study conducted in our clinic found that using intraoperative laparoscopic USG, specifically in patients with high MAP scores, significantly improved trifecta success rates (25).

Systematic reviews analyzing the effects of WIT on RF following PN have concluded that a limited WIT (<25 minutes) does not negatively impact long-term RF (26). Similar studies investigating different WIT suggest that WIT alone is not the primary determinant of RF loss; other factors play a role (4). Consequently, studies have

proposed various cutoff values for WIT, such as 10, 17, or 30 minutes, highlighting the greater impact of non-modifiable factors (e.g., age, DM, HT, BMI, tumor size, preoperative eGFR) on long-term RF (27). Our study's median WIT was 14 minutes, which was not identified as a statistically significant factor affecting RPV change or eGFR decline. This likely reflects that the WIT values in our cohort remained within the literature-defined safe range.

Studies comparing tumor enucleation and standard PN (tumor resection along with a margin of healthy parenchymal tissue) have reported that RF is better preserved in the tumor enucleation group (28, 29). Additionally, in terms of preserved RPV, tumor enucleation resulted in less parenchymal loss compared to standard PN (30). In our study, the SIB score was identified as a significant predictor of RPV change. This may be explained by the greater preservation of parenchymal tissue in enucleation-based PN.

When the SIB score is low, renorrhaphy is more likely to be performed in a relatively avascular area, reducing the amount of healthy parenchyma affected by suturing. This may be one of the factors contributing to better RF preservation. One possible explanation is that a larger tumor–parenchyma contact surface area may predispose to localized or segmental ischemic effects, which could impair renal function even in the absence of substantial measurable parenchymal volume loss. In this context, functional deterioration may occur despite preserved renal volume, reflecting microvascular or regional perfusion changes not captured by volumetric assessment alone.

Beyond surgical technique–specific considerations, preservation of renal function remains a central objective in the management of small renal masses. Minimally invasive alternatives such as thermal ablation have been increasingly adopted in selected patients with small renal masses, largely driven by their favorable renal functional profile and the absence of ischemic insult. Recent reports focusing on risk-adjusted outcomes after radiofrequency ablation have demonstrated acceptable oncological control with limited impact on renal function, underscoring the clinical relevance of parenchymal preservation across different treatment modalities (31).

Operative duration is influenced by patient factors, tumor complexity, surgical method, and the surgeon's expertise. In LPN, these factors influence operative time, leading to prolonged pneumoperitoneum, which can have physiological consequences. Factors contributing to longer operative time, such as tumor complexity, may not only directly impact eGFR and preserved RPV but also have indirect effects by prolonging pneumoperitoneum duration (32). In the present study, operative time emerged as a significant factor associated with postoperative renal outcomes. The reference to pneumoperitoneum should therefore be interpreted as a potential explanatory mechanism underlying prolonged operative duration, rather than as an independently analyzed variable, since the time spent with pneumoperitoneum was not evaluated separately and no direct statistical association was assessed.

Although the operative time in our study was within a reasonable range according to the literature, its effect on ORPV change was considered a consequence of these factors.

The limitations of this study include its retrospective design and the single-centre, single-surgeon experience, which may restrict the generalizability and reproducibility of the findings. However, the single-surgeon experience is also a strength, as it contributes to standardising surgical techniques and postoperative outcomes. Furthermore, volumetric analysis was conducted by a single reader, but minimised interobserver variability and enhanced measurement consistency.

Moreover historically, three-dimensional renal volumetry has been predominantly performed using CT, due to its earlier availability and more widespread clinical integration. Consequently, the majority of volumetric studies in the literature are based on CT datasets. Supplementary analysis demonstrated no statistically significant differences in renal parenchymal or tumor volume measurements between patients imaged with CT versus MRI. This suggests that MRI-based segmentation may serve as a reliable alternative to CT for volumetric evaluation when standardized protocols are applied. While these findings support the use of MRI in

this context, larger comparative studies are warranted to further validate its equivalence, particularly for applications involving perfusion or vascular modeling.

Despite these limitations, our study has notable strengths. Advanced three-dimensional volumetric analyses were conducted using a standardised methodology, ensuring the precise assessment of RPV changes. Furthermore, including long-term follow-up data reduces the risk of selection bias, enabling a more comprehensive analysis of RF preservation.

CONCLUSIONS

Based on the findings of this retrospective, single-center analysis, several clinical and surgical factors appear to influence renal functional outcomes following LPN. Determinants of RF change include patient age, gender, comorbidity burden, tumor-to-parenchyma contact surface area, and loss of ORPV. Renal volume loss was associated with age, comorbidities, RENAL score, operative time, and SIB score.

In selected cases, using the enucleation technique without compromising oncological and functional outcomes is the most modifiable factor for preserving healthy parenchymal volume. Long-term functional outcomes should be carefully monitored in patients with DM, given their potential risk for delayed renal function deterioration.

Declaration of Generative AI in Scientific Writing
"ChatGPT (OpenAI) was used solely for language editing during the preparation of this manuscript."

Ethical approval

This study was conducted with the approval of the Ondokuz Mayıs University Faculty of Medicine Clinical Research and Ethics Committee, dated February 14, 2024 (Decision No: B.30.2.ODM.0.20.08/84-134).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198(3):520-9.
2. Silvestri A, Gavi F, Sighinolfi MC, Assumma S, Panio E, Fettucciari D, et al. Management of small renal masses: literature and guidelines review. Int Braz J Urol. 2025;51(5):e20250203.
3. Kazama A, Attawettayanon W, Munoz-Lopez C, Rathi N, Lewis K, Maina E, et al. Parenchymal volume preservation during partial nephrectomy: improved methodology to assess impact and predictive factors. BJU Int. 2024 Aug;134(2):219-228. doi: 10.1111/bju.16300.
4. Campbell SC, Campbell JA, Munoz-Lopez C, Rathi N, Yasuda Y, Attawettayanon W. Every decade counts: a narrative review of functional recovery after partial nephrectomy. BJU Int. 2023;131(2):165-72.
5. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin J-C, Pujol S, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magn Reson Imaging. 2012;30(9):1323-41.
6. Veccia A, Antonelli A, Uzzo RG, Novara G, Kutikov A, Ficarra V, et al. Predictive value of nephrometry scores in nephron-sparing surgery: a systematic review and meta-analysis. Eur Urol Focus. 2020;6(3):490-504.
7. Gülşen M, Özden E, Yakupoğlu YK. Laparoscopic Partial Nephrectomy: Tips and Tricks. Bull Urooncol. 2020;18:96-7.
8. Beksac AT, Okhawere KE, Elbakry AA, et al. Measuring volumetric segmentation changes in the ipsilateral and contralateral kidney postpartial nephrectomy. Urol Oncol. 2020;38(10):798.e1-798.e7.
9. Marconi L, Desai MM, Ficarra V, Porpiglia F, Van Poppel H. Renal preservation and partial nephrectomy: patient and surgical factors. Eur Urol Focus. 2016;2(6):589-600.
10. van Rijn MH, Metzger M, Flamant M, Houillier P, Haymann J-P, van den Brand JA, et al. Performance of creatinine-based equations for estimating glomerular filtration rate changes over time. Nephrol Dial Transplant. 2020;35(5):819-27.
11. Wu Wensong, Chang Fan, Zhang Jianghui, Tang Shuai, Lv Zheng, Liu Xuehui, et al. Correlation between bilateral GFR in patients with localized renal cancer after partial nephrectomy. Int Urol Nephrol. 2024 May;56(5):1617-1625. doi: 10.1007/s11255-023-03901-w.

12. Saitta C, Garofano G, Lughezzani G, Meagher MF, Yuen KL, Fasulo V, et al. Preoperative Age and Its Impact on Long-Term Renal Functional Decline after Robotic-Assisted Partial Nephrectomy: Insights from a Tertiary Referral Center. Medicina (Kaunas). 2024;60(3):463. doi: 10.3390/medicina60030463.
13. Xu R, Zhang L-X, Zhang P-H, Wang F, Zuo L, Wang H-Y. Gender differences in age-related decline in glomerular filtration rates in healthy people and chronic kidney disease patients. BMC Nephrol. 2010;11:20. doi: 10.1186/1471-2369-11-20.
14. Kim NY, Lee HS, Park JH, Jeon S, Oh C, Kim SY. Influence of age on gender-related differences in acute kidney injury after minimally invasive radical or partial nephrectomy. Surg Endosc. 2022;36(5):2962-72. doi: 10.1007/s00464-021-08590-z.
15. Flammia RS, Anceschi U, Tufano A, Tuderti G, Ferriero MC, Brassetti A, et al. Is hypertension associated with worse renal functional outcomes after minimally invasive partial nephrectomy? Results from a multi-institutional cohort. J Clin Med. 2022;11(5):1243. doi: 10.3390/jcm11051243.
16. Beksac AT, Reddy BN, Martini A, Paulucci DJ, Moshier E, Abaza R, et al. Hypertension and diabetes mellitus are not associated with worse renal functional outcome after partial nephrectomy in patients with normal baseline kidney function. Int J Urol. 2019;26(1):120-5. doi: 10.1111/iju.13819.
17. Mercimek MN, Ozden E, Gulsen M, Yakupoglu YK, Bostanci Y, Sarikaya S. Which is the best predictor to achieve trifecta in patients undergoing elective laparoscopic partial nephrectomy with global hilar clamping? J Endourol. 2021;35(5):615-22. doi: 10.1089/end.2020.0758.
18. Yang Y, Meng L, Hu X, Li X. Renal functional outcomes after nephrectomy in patients with localized renal cell carcinoma and diabetes mellitus: a systematic review and meta-analysis. Int Urol Nephrol. 2024:1-10.
19. Bai N, Qi M, Shan D, Liu S, Na T, Chen L. Trifecta achievement in patients undergoing partial nephrectomy: a systematic review and meta-analysis of predictive factors. Int Braz J Urol. 2022;48:625-35.
20. Erkoc M, Besiroğlu H, Özbir S, Canat L, Değirmentepe B, Can O, et al. Influence of 3D-Calculated Parenchymal Volume Loss on Renal Function After Partial Nephrectomy. J Laparoendosc Adv Surg Tech. 2021;31(4):402-9.
21. Lee CH, Ku JY, Park YJ, Seo WI, Ha HK. The superiority of contact surface area as a predictor of renal cortical volume change after partial nephrectomy compared to RENAL, PADUA, and C-index: an approach using computed tomography-based renal volumetry. Scand J Urol. 2019;53(2-3):129-33.
22. Li Q, Zhang Y, Liu M, Li H, Guan W, Meng X, et al. Identification of predictive factors for outcomes after robot-assisted partial nephrectomy based on three-dimensional reconstruction of preoperative enhanced computerized tomography. Front Oncol. 2023;13:927582.
23. Takagi T, Yoshida K, Kondo T, Kobayashi H, Iizuka J, Okumi M, et al. Association between tumor contact surface area and parenchymal volume change in robot-assisted laparoscopic partial nephrectomy carried out using the enucleation technique. Int J Urol. 2019;26(7):745-51.
24. Kallidonis P, Spinos T, Zondervan P, Nyirády P, Backhaus MR, Micali S, et al. Predictive Value of the Mayo Adhesive Probability (MAP) Score in Laparoscopic Partial Nephrectomies: A Systematic Review from the EAU Section of Uro-Technology (ESUT). Cancers. 2024;16(8):1455.
25. Gülşen M, Özden E, Çamlıdağ İ, Öner S, Bostancı Y, Yakupoğlu YK, et al. Intraoperative Ultrasound Can Facilitate Laparoscopic Partial Nephrectomy in Adherent Perinephric Fat. J Laparoendosc Adv Surg Tech. 2023;33(5):480-6.
26. Rod X, Peyronnet B, Seisen T, Pradere B, Gomez FD, Verhoest G, et al. Impact of ischaemia time on renal function after partial nephrectomy: a systematic review. BJU Int. 2016;118(5):692-705.
27. Abdel Raheem A, Alowidah I, Capitanio U, Montorsi F, Larcher A, Derweesh I, et al. Warm ischemia time length during on-clamp partial nephrectomy: does it really matter? Minerva Urol Nephrol. 2022;74:194-202.
28. Patel HD, Koehne EL, Gali K, et al. Robotic-assisted tumor enucleation versus standard margin partial nephrectomy: Perioperative, renal functional, and oncologic outcomes for low and intermediate complexity renal masses. Urol Oncol. 2022;40(7):347.e9-347.e16.
29. Bertolo R, Pecoraro A, Carbonara U, Amparore D, Diana P, Muselaers S, et al. Resection techniques during robotic partial nephrectomy: a systematic review. Eur Urol Open Sci. 2023;52:7-21.

30. Dong W, Gupta GN, Blackwell RH, Wu J, Suk-Ouichai C, Shah A, et al. Functional comparison of renal tumor enucleation versus standard partial nephrectomy. Eur Urol Focus. 2017;3(4-5):437-43.
31. Li D YJ, Wang X, et al. Risk-adjusted trifecta outcomes in ultrasound-guided RFA of T1a renal masses: experience from a large tertiary cancer center. Int Braz J Urol. 2025;51(4):e20250034. doi: 10.1590/S1677-5538.IBJU.2025.0034
32. Demyttenaere S, Feldman LS, Fried GM. Effect of pneumoperitoneum on renal perfusion and function: a systematic review. Surg Endosc. 2007;21:152-60.

Correspondence address:
Onur Kalaycı, MD
Department of Urology,
Samsun Training and Research Hospital, Samsun, Turkey
Kadıköy, Barış Blv. No:199,
İlkadım/Samsun, 55090, Turquia
Telephone: + 90 506 807 2637
E-mail: dronurkalayci@gmail.com

EXPERT OPINION

Vol. 52 (3): e20269902, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2026.9902

Gonadotropin Stimulation Before Sperm Retrieval in Non-Obstructive Azoospermia: Myth, Magic, or Medicine?

Marina C. Viana [1], Arnold P. P. Achermann [1, 2], Danilo L. Andrade [1], Ricardo Miyaoka [1, 3], Sandro C. Esteves [1, 3, 4]

[1] ANDROFERT – Clínica de Andrologia e Reprodução Humana, Campinas, Brasil; [2] Programa de Pós-Graduação, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brasil; [3] Departamento de Cirurgia, Divisão de Urologia, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brasil; [4] Department of Clinical Medicine, Aarhus University, Denmark

INTRODUCTION

Hormonal stimulation prior to surgical sperm retrieval in men with testicular non-obstructive azoospermia (NOA) remains one of the most debated topics in reproductive urology (1). For some, it is an unproven intervention bordering on myth; for others, its outcomes appear almost magical when sperm retrieval succeeds after years of failure. Yet, between these extremes lies medicine—rooted in physiology, supported by emerging evidence, and refined through clinical experience. This Expert Opinion synthesizes pathophysiologic principles, contemporary clinical data, and our cumulative institutional experience in managing men with NOA. We argue that hormonal stimulation—when properly indicated and individualized—represents a biologically coherent and clinically meaningful medical strategy rather than belief or chance.

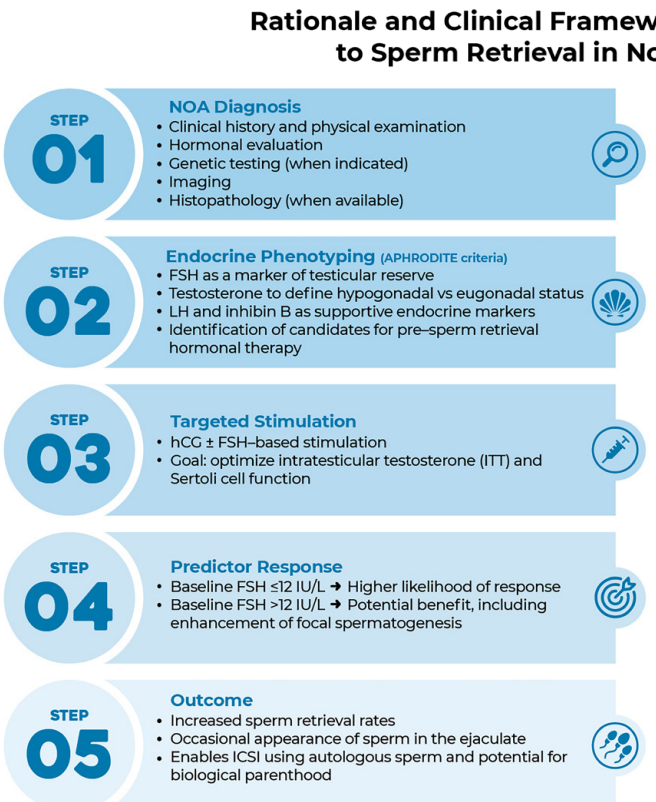
PHYSIOLOGIC BASIS: THE TESTICULAR ENDOCRINE MILIEU AND MECHANISTIC RATIONALE FOR HORMONAL MODULATION IN NOA

Spermatogenesis depends on tightly coordinated interactions between Leydig and Sertoli cells, driven respectively by luteinizing hormone (LH)-mediated testosterone production and direct follicle-stimulating hormone (FSH) stimulation (2-4). Intratesticular testosterone (ITT) concentrations are 50–100 times higher than serum levels and are indispensable for meiosis, spermiogenesis, and Sertoli-cell metabolic support (5).

In men with NOA, this endocrine equilibrium is frequently disrupted, as illustrated by the increased incidence of biochemical hypogonadism in this population (6). Although basal gonadotropin levels may be elevated, coordinated pulsatility of gonadotropin-releasing hormone (GnRH) and downstream gonadotropins may be dysregulated or insufficient to sustain optimal intratesticular endocrine dynamics (4, 7). The result is often a suboptimal microenvironment within the seminiferous tubules, leading to arrested or incomplete germ-cell maturation.

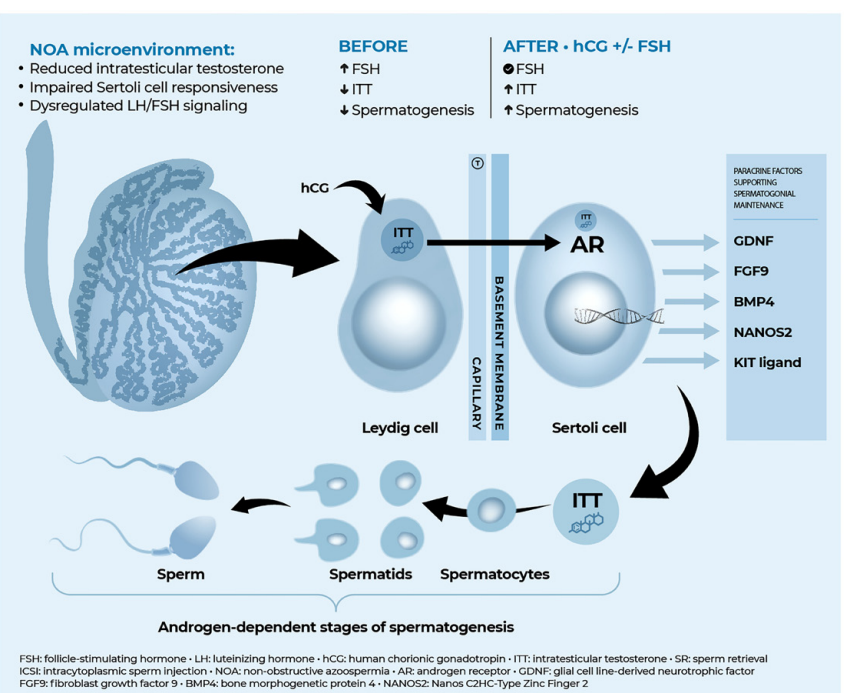
The mechanistic rationale for hormonal modulation is illustrated in Figure-1. In the untreated NOA state, elevated FSH often reflects impaired Sertoli-cell reserve, while reduced ITT compromises androgen receptor (AR)-

Figure 1 - Rationale and clinical framework for hormonal stimulation prior to sperm retrieval in non-obstructive azoospermia.



Clinical framework: Stepwise approach to hormonal optimization in men with non-obstructive azoospermia (NOA). Step 1 involves comprehensive NOA diagnosis, including clinical evaluation, hormonal assessment, genetic testing when indicated, imaging, and histopathology when available. Step 2 consists of endocrine phenotyping according to the APHRODITE criteria, using FSH as a marker of testicular reserve and testosterone to define biochemical hypogonadism, with LH and inhibin B as supportive markers. Step 3 includes targeted hormonal stimulation using hCG ± FSH to optimize intratesticular testosterone (ITT) and Sertoli-cell function. Step 4 highlights predictors of response, with baseline FSH ≤12 IU/L associated with higher likelihood of benefit, while men with FSH >12 IU/L may still experience enhancement of focal spermatogenesis. Step 5 illustrates clinical outcomes, including increased sperm retrieval rates, occasional appearance of sperm in the ejaculate, and facilitation of intracytoplasmic sperm injection (ICSI) using autologous sperm.

Physiologic mechanism: Depiction of the testicular microenvironment before and after hormonal stimulation. In the untreated NOA state, elevated FSH, reduced intratesticular testosterone (ITT), and impaired Sertoli-cell responsiveness contribute to compromised spermatogenesis. Administration of human chorionic gonadotropin (hCG) stimulates Leydig cells, increasing ITT. ITT activates androgen receptors (AR) within Sertoli cells, enhancing transcription of paracrine factors (e.g., GDNF, FGF9, BMP4, NANOS2, KIT ligand) that regulate germ-cell maintenance and differentiation. The later, androgen-dependent stages of spermatogenesis (spermatocytes → spermatids → spermatozoa) are particularly dependent on adequate ITT. Combined hCG ± FSH therapy aims to restore this endocrine balance, thereby increasing the probability of successful sperm retrieval.



mediated transcriptional activity within Sertoli cells. Because the later stages of spermatogenesis—from spermatocytes to spermatids and mature spermatozoa—are strongly androgen-dependent, insufficient ITT may critically limit progression through these stages.

Stabilization of ITT is central to preserving the androgen-dominant intratubular environment required for germ-cell survival and differentiation. Human chorionic gonadotropin (hCG) acts as an LH analogue and directly stimulates Leydig-cell LH receptors, enhancing ITT production beyond what may be achievable endogenously in men with Leydig-cell dysfunction or impaired hypothalamic–pituitary signaling, thus restoring androgenic signaling within the seminiferous tubules (8, 9).

FSH, in turn, acts directly on Sertoli cells to support proliferative capacity, promote inhibin B secretion, regulate tight-junction dynamics, and enhance androgen-binding protein expression (8-10). Chronic exposure to elevated endogenous FSH—common in NOA patients with primary testicular failure—may induce Sertoli-cell desensitization and downregulation of FSH signaling pathways (11, 12). Experimental and clinical observations suggest that transient suppression of chronically elevated endogenous FSH, followed by controlled re-stimulation with exogenous FSH, may restore Sertoli-cell function, as reflected by increases in inhibin B and potential improvement in spermatogenic activity (13).

When hCG stimulation is combined with exogenous FSH, Sertoli-cell stimulation may be enhanced, potentially reactivating residual spermatogenic foci. Improved AR activation promotes expression of paracrine factors such as glial cell line–derived neurotrophic factor (GDNF), fibroblast growth factor 9 (FGF9), bone morphogenetic protein 4 (BMP4), NANOS2, and KIT ligand—key regulators of germ-cell maintenance and differentiation. Accordingly, tailored gonadotropin stimulation may optimize the seminiferous microenvironment and facilitate germ-cell progression through mitotic and meiotic stages. Importantly, FSH alone cannot sustain spermatogenesis without adequate ITT; however, in combination with hCG, it may synergistically enhance Sertoli-cell responsiveness.

This mechanistic insight provides biological plausibility for combined hCG–FSH stimulation even in men with elevated baseline FSH levels, provided an FSH reset is achieved after hCG administration and residual Sertoli-cell function persists (14, 15). Taken together, these observations establish a coherent physiologic rationale: hormonal therapy in NOA does not create spermatogenesis de novo but seeks to reactivate and stabilize residual spermatogenic foci by reconstructing an optimized Leydig–Sertoli endocrine milieu.

THERAPEUTIC STRATEGIES AND DOSING CONSIDERATIONS

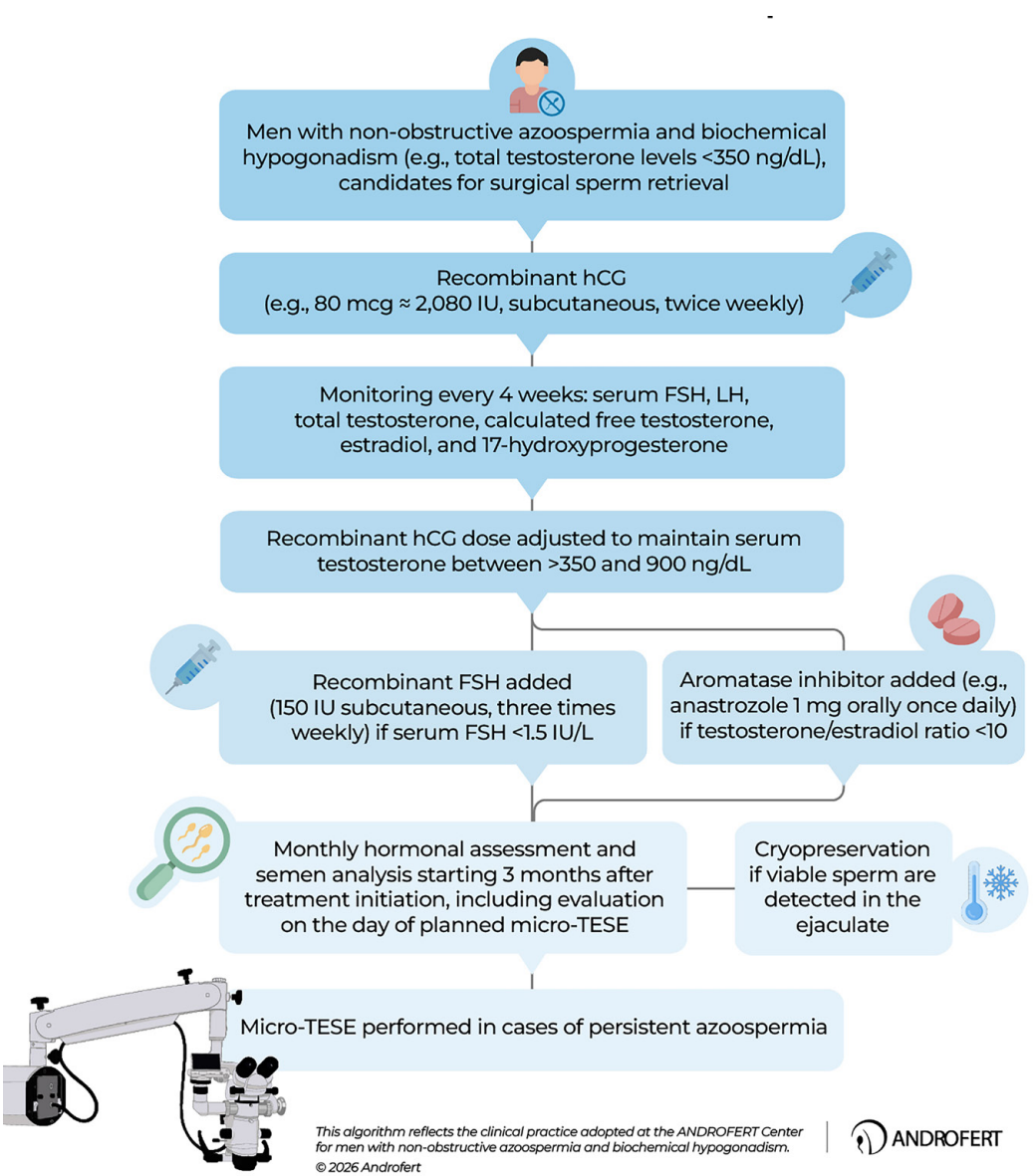
Given the heterogeneity of NOA and the absence of high-quality randomized trials, hormonal stimulation dosing regimens vary among centers. Most strategies are extrapolated from established protocols used in hypogonadotropic hypogonadism. Typically, hCG is administered at 1,000–3,000 IU subcutaneously or intramuscularly two to three times weekly, with dose titration guided by serum testosterone levels and clinical response. When added, exogenous FSH—either recombinant or highly purified urinary-derived FSH—is initiated at 75–150 IU two to three times weekly and adjusted according to hormonal dynamics, including inhibin B and FSH levels.

Therapy is generally maintained for three to six months, spanning at least one complete spermatogenic cycle before surgical sperm retrieval. Although largely empirical, this approach remains biologically coherent, aiming to stabilize ITT, enhance Sertoli-cell function, and improve the probability that microdissection testicular sperm extraction (micro-TESE) will identify viable spermatogenic foci.

HOW WE DO IT: A HORMONE-GUIDED OPTIMIZATION PROTOCOL

At our center, we employ a structured, physiology-driven protocol to maximize sperm retrieval success in carefully selected NOA patients. Treatment begins with recombinant hCG (80 μg ≈ 2,080 IU) administered twice weekly. Hormonal profiles—including FSH, LH, testosterone, and estradiol—are assessed every four weeks. Achieving and maintaining eugonadal

Figure 2 - Gonadotropin-based treatment algorithm for men with non-obstructive azoospermia and biochemical hypogonadism.



Endocrine optimization protocol developed and utilized at the ANDROFERT Clinic prior to surgical sperm retrieval in men with non-obstructive azoospermia (NOA) and biochemical hypogonadism (total testosterone <350 ng/dL). Treatment begins with recombinant human chorionic gonadotropin (hCG), with dose titration to maintain serum testosterone within the eugonadal range (≈350–900 ng/dL). Hormonal monitoring is performed every four weeks. Recombinant FSH is added if serum FSH falls below 1.5 IU/L, and an aromatase inhibitor is introduced when the testosterone-to-estradiol ratio is <10. Semen analysis is initiated after three months of therapy; sperm detected in the ejaculate should be cryopreserved. Microdissection testicular sperm extraction (micro-TESE) is performed in cases of persistent azoospermia.

testosterone serum levels (350–900 ng/dL) serves as a pragmatic surrogate for adequate ITT (Figure-2).

If FSH levels decline below 1.5 IU/L during hCG monotherapy—reflecting excessive suppression of endogenous gonadotropins and potential under-stimulation of Sertoli cells—recombinant FSH is introduced at 150 IU subcutaneously three times weekly. Anastrozole (1 mg daily) is added when the testosterone (ng/dL)-to-estradiol (pg/mL) ratio falls below 10 to prevent aromatase-mediated androgen depletion.

Monthly endocrine monitoring is maintained. Semen analysis begins after three months of therapy to detect possible reappearance of sperm in the ejaculate and is repeated on the day of planned sperm retrieval. In cases of persistent azoospermia despite hormonal optimization, which occurs in the vast majority of patients, micro-TESE is performed due to its superior capacity to identify isolated spermatogenic foci compared to conventional TESE. This individualized approach emphasizes endocrine reconstruction as a means of improving surgical outcomes.

FROM PHYSIOLOGY TO RESEARCH PRIORITY

The importance of endocrine modulation in male infertility has been underscored by the Fertility and Sterility "Top Priorities for Male Infertility Research" initiative, which explicitly asked whether endocrine stimulation can improve sperm retrieval outcomes (1). This question reflects growing recognition that testicular endocrine optimization may influence not only spermatogenic health but also sperm retrieval success and downstream assisted reproductive outcomes.

The clearest precedent comes from hypogonadotropic hypogonadism (HH), in which combined hCG and FSH therapy can reliably restore spermatogenesis and lead to natural conception (16-18). Although HH represents a distinct pathophysiologic entity, it demonstrates that appropriately targeted hormonal replacement can reinitiate sperm production—even after prolonged azoospermia (19). This precedent supports a biologically plausible hypothesis: if profound gonadotropin deficiency is reversible, milder endocrine dysfunctions frequently observed in NOA may also be modifiable (18, 20). Moreover, hypogonadal NOA patients exhibit lower sperm retrieval rates than eugonadal counterparts (6, 21), suggesting that intratesticular androgen status may influence surgical success.

CLINICAL EVIDENCE

Meta-Analysis

In 2022, Tharakan et al. published a systematic review and meta-analysis evaluating preoperative hormonal therapy in NOA (20). Pooled data from 10 controlled studies using various types of hormonal stimulation (hCG, selective-estrogen receptor modulators, aromatase inhibitors), including 1706 individuals, demonstrated a significant and clinically meaningful increase in sperm retrieval rates among hormonally treated men (odds ratio [OR]: 1.96, 95% confidence interval [CI]: 1.08–3.56, p=0.03), particularly in those with baseline FSH ≤12 IU/L (five studies, OR 2.13, 95% CI: 1.10–4.14, p=0.02). Despite heterogeneity across regimens and study designs, the overall signal suggested that endocrine optimization may benefit selected patients with residual testicular function.

Pilot Gonadotropin Study

In collaboration with Danish colleagues, we conducted a pilot study involving NOA patients with prior failed testicular sperm aspiration (TESA) (14). Following combined hCG ± FSH therapy, 4 of 8 men achieved viable sperm suitable for assisted conception, including two with sperm in the ejaculate and two with successful repeat TESA procedures, resulting in four live births via ICSI. Although small, this clinical signal supports the concept that endocrine modulation can convert prior failure into success in selected cases.

Contemporary Systematic Review

Our 2023 systematic review encompassing nearly 4,000 patients demonstrated a 6% absolute increase in sperm retrieval success with hormonal therapy, corresponding to a number needed to treat of 17 (95% CI 10.5 to 39.3) (9). Additionally, approximately 6% of men developed sperm in the ejaculate. These findings

highlight both promise and heterogeneity, reinforcing the need for structured phenotyping frameworks such as APHRODITE (22).

The controlled studies evaluating gonadotropin-based hormonal therapy prior to surgical sperm retrieval in NOA are summarized in Table-1. These investigations span more than two decades and include heterogeneous patient populations (normogonadotropic and hypergonadotropic phenotypes, men with prior failed TESE, and selected subgroups such as Klinefelter syndrome), diverse stimulation regimens (hCG alone, hCG combined with FSH or hMG, highly purified FSH, and mixed gonadotropin protocols), and variable treatment durations ranging from 2 to 9 months (7, 15, 23-30).

Despite methodological variability and the predominance of retrospective designs, several studies report higher sperm retrieval rates in hormonally treated men compared with untreated controls, particularly in selected endocrine phenotypes (7, 23-25, 28, 30). Some cohorts also demonstrate downstream reproductive benefits, including improved clinical pregnancy rates (24, 25), while others show neutral findings, especially in more severely hypergonadotropic populations or syndromic cases such as Klinefelter syndrome (27, 29).

Importantly, adverse events were generally mild and infrequent across studies. Collectively, these data suggest the existence of a biological signal supporting endocrine optimization in selected NOA patients, while simultaneously underscoring the need for prospective, phenotype-stratified randomized trials.

APHRODITE-BASED STRATIFICATION AND CLINICAL INSIGHTS

To address the heterogeneity of endocrine phenotypes in male infertility, the APHRODITE criteria were recently introduced as a physiology-driven framework to classify men with altered testicular function based on clinical characteristics, semen analysis results, gonadotropin dynamics and testosterone status (22). This new framework can be adopted to classify NOA men into clinically meaningful distinct endocrine phenotypes.

When applied to NOA men, the framework distinguishes patients with:

Group 2: FSH and testosterone levels within normal ranges (primary spermatogenic dysfunction without biochemical hypogonadism, typically seen in cases exhibiting maturation arrest on histopathology);

Group 3: FSH levels within normal ranges associated with biochemical hypogonadism (suggesting insufficient Leydig-cell activity despite preserved Sertoli-cell signaling);

Group 4: Elevated FSH with biochemical hypogonadism or compensated testosterone levels (combined Sertoli and Leydig dysfunction, representing more advanced testicular failure).

Collectively, men with NOA may span APHRODITE groups 2, 3, and 4, reflecting the biological diversity underlying this diagnosis. This heterogeneity may partly explain why hormonal stimulation yields variable clinical results across studies.

In our cohort of more than 600 NOA patients with biochemical hypogonadism, hormonal stimulation with exogenous gonadotropins—using the protocol depicted in Figure-2—significantly improved endocrine parameters and sperm retrieval rates (15). Approximately 80% of treated individuals reached an 'eugonadal' state (total testosterone levels >350 ng/dL) after hormonal stimulation. Treatment also promoted an FSH reset in most individuals. Pre-micro-TESE FSH levels were significantly lower (4.0 IU/L; 95% CI: 2.9-7.6) in patients with positive micro-TESE outcomes than those with failed retrievals (8.1; CI: 5.4-15.0; p<0.0001), supporting the idea that hCG may improve Sertoli cell function by counteracting FSH receptor desensitization. Importantly, sperm retrieval rates reached 62.5% in treated men versus 51.4% in untreated controls (p=0.006), with hormonal therapy emerging as an independent predictor of micro-TESE success (adjusted OR: 2.54; 95% CI: 1.64-3.93; p<0.0001) (15). When stratified according to APHRODITE, treatment benefit was not uniform. Patients classified as Group 3 (baseline FSH levels ≤12 IU/L with biochemical hypogonadism) demonstrated superior outcomes (67.9% vs. 50.1%; adjusted OR 3.20, 95% CI 1.59-6.44, p=0.001) compared to Group 4 (elevated FSH with biochemical hypogonadism) (58.1% vs. 51.9%; adjusted OR 1.46, 95% CI 0.74-2.88, p=0.27).

Table 1 - Characteristics and key outcomes of controlled studies primarily evaluating gonadotropin-based hormonal therapy before sperm retrieval in non-obstructive azoospermic men.

Study / Country / Design [ref.]	Population & Key Hormonal Profile	Intervention & Duration	Control & Sperm Retrieval Method	Key Outcomes (intervention vs. control)	Adverse Events
Aydos, et al. 2003 (Turkey) RC (23)	n=108 NG	hpFSH 75 IU 3x/ wk; 3 mo n=63	Yes; cTESE n=45	SR 64% vs 33%	NR
Shiraishi, et al. 2012 (Japan) RC (7)	n=48; NG+HGH; failed TESE	uhCG 5000 IU 3×/ wk ± rFSH; 3–6 mo n=28	Yes; mTESE n=20	SR 21.4% vs 0% (p<0.05)	Acne 10.7%; Gynecomastia 7.1%
Hussein, et al. 2013 (Turkey) RC (24)	n=612; NG/HG; TT <300 in 140	CC-based regimens ± hCG/ hMG; 3–9 mo n=496	Yes; mTESE n=116	SR ~11% vs 0%; CPR ~57% vs 33.6%	None
Cocci, et al. 2018 (Italy) PC (25)	n=50; NG	hpFSH 150 IU 3x/ wk; 3 mo n=25	Yes; cTESE n=25	SR 40% vs 28% (p<0.05) CPR: 28% vs 15% (p<0.05)	NR
Hu, et al. 2018 (China) RC (26)	n=35; HG; HYPO; failed TESE	Goserelin → + hCG + hMG; 6 mo n=25	Yes; cTESE n=10	SR 8% vs 0%	40% transient sexual AEs
Amer, et al. 2019 (Egypt) RC (27)	n=1395; HG	Mixed regimens; 3–9 mo n=426	Yes; mTESE n=969	SR 27.7% vs 34.3% (NS)	NR
Amer, et al. 2020 (Egypt) PC (28)	n=40; HG; failed mTESE	Testosterone → + hCG + FSH; 4 mo n=20	Yes; mTESE n=20	SR 10% vs 0%	NR
Guo, et al. 2020 (China) RC (29)	n=184; HG; KS	uhCG 2000 IU Q2D; 3 mo n=134	Yes; mTESE n=50	SR 43.3% vs 44%; LBR similar	NR
Peng, et al. 2022 (China) RC (30)	n=569; HG	hCG 2000 IU Q2D ± uFSH; 2–3 mo n=395	Yes; mTESE n=174	SR 31.2% vs 19.5% (p=0.006)	NR
Esteves & Achermann 2024 (Brazil) RC (15)	n=616; TT <350; NG & HG	rhCG 2080 IU 2×/ wk ± FSH ± AI; 3–8 mo n=291	Yes; mTESE n=325	SR 62.5% vs 51.4% (p=0.005)	Mild injection reactions (10.3%)

AI: aromatase inhibitor; CC: clomiphene citrate; CPR: clinical pregnancy rate; cTESE: conventional testicular sperm extraction; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HG: hypergonadotropic; hMG: human menopausal gonadotropin; hpFSH: highly purified human-derived follicle-stimulating hormone; IU: international units; KS: Klinefelter syndrome; LBR: live birth rate; mo: month[s]; mTESE: microdissection testicular sperm extraction; NG: normogonadotropic; NR: not reported; NS: non-significant; PC: prospective; RC: retrospective; rFSH: recombinant follicle-stimulating hormone; rhCG: recombinant human chorionic gonadotropin; SR: sperm retrieval; TT: total testosterone; uhCG: urinary human chorionic gonadotropin; wk: week[s].

This distinction is physiologically intuitive. Group 3 patients likely retain relatively preserved Sertoli-cell reserve, as reflected by normal FSH levels, while exhibiting potentially reversible Leydig-cell insufficiency. In contrast, Group 4 patients exhibit combined Sertoli and Leydig dysfunction, suggesting more advanced testicular impairment and reduced capacity for endocrine rescue. These findings reinforce a central message: hormonal stimulation should not be applied indiscriminately in NOA. Instead, endocrine phenotyping—such as that provided by the APHRODITE framework—may help identify men with residual functional reserve who are most likely to benefit from preoperative hormonal optimization.

PHARMACOGENOMICS AND DIFFERENTIAL RESPONSE TO GONADOTROPIN THERAPY

Inter-individual variability in response to hormonal stimulation may partly reflect genetic differences in gonadotropin signaling pathways. Functional polymorphisms in the FSH β-subunit gene (FSHB), particularly the −211 G>T promoter variant, are associated with reduced transcriptional activity and lower circulating FSH levels (31). Enrichment of this variant has been reported among infertile men, including azoospermic cohorts (32). Carriers may exhibit impaired endogenous FSH signaling despite apparently normal serum levels, potentially rendering them more responsive to exogenous FSH supplementation than to tablets such as selective estrogen receptor modulators and aromatase inhibitors.

Similarly, common FSH receptor (FSHR) polymorphisms—such as Asn680Ser and Thr307Ala—have been linked to differences in receptor sensitivity and intracellular signaling efficiency (33). Although data in male infertility remain heterogeneous, these variants may influence Sertoli-cell responsiveness to both endogenous and exogenous FSH.

These genetic insights offer a biologically plausible explanation for heterogeneous treatment responses. While routine genotyping is not currently standard practice, pharmacogenetic stratification represents a logical extension of precision andrology and warrants evaluation within prospective, APHRODITE-based clinical trials, particularly in NOA males.

FROM MYTH TO MEDICINE

When viewed collectively, physiologic rationale, meta-analytic data, and contemporary clinical evidence converge on a consistent conclusion: hormonal stimulation before sperm retrieval in NOA is neither myth nor magic—it is medicine. Its benefits are not universal, and patient selection remains essential. However, dismissing endocrine optimization outright ignores both biology and accumulating clinical data. The future lies not in debating whether hormones should be used, but in identifying which patients are most likely to benefit.

FUTURE DIRECTIONS

Future investigations should:

- Conduct prospective multicenter randomized trials with live birth as the primary endpoint
- Integrate biomarkers of testicular reserve and endocrine responsiveness
- Incorporate pharmacogenetic stratification
- Standardize treatment response definitions
- Evaluate cost-effectiveness relative to immediate surgical intervention

CONCLUSIONS

The journey of hormonal stimulation in NOA has evolved from skepticism to scientific plausibility. With advancing physiologic insight and growing clinical evidence, endocrine optimization should be regarded as a targeted medical strategy rather than conjecture. In selected men—particularly those with biochemical hypogonadism or low-normal FSH—reconstructing the testicular endocrine milieu may meaningfully improve sperm retrieval outcomes and expand reproductive opportunities.

NOTE FROM THE AUTHORS

'Is hormonal stimulation before sperm retrieval in NOA a myth? Clearly not — physiology explains it, and evidence supports it. Is it magic? Perhaps only in the joy of witnessing a patient once deemed hopeless achieve fatherhood. Above all, it is medicine — applied with logic, personalization, and purpose. The future does not lie in debating whether hormones should be used, but in understanding who will truly benefit.'

CONFLICT OF INTEREST

SCE has received unrestricted research grants and consulting fees for participation in advisory boards from Merck KGaA. He reports receipt of speaker's fees from Merck KGaA, and Med.E.A., and declares leadership roles as follows: Brazilian Society of Urology (Sao Paolo chapter; Head: Department of Male Reproductive Health and Contraception) and WHO (Topic Leader; Infertility guideline). MCV, APPA, DLA, and RM have no conflict of interest to declare.

REFERENCES

1. Duffy JMN, Adamson GD, Benson E, Bhattacharya S, Bofill M, Brian K, et al. Priority Setting Partnership for Infertility. Top 10 priorities for future infertility research: an international consensus development study. Fertil Steril. 2021 Jan;115(1):180-190. doi: 10.1016/j.fertnstert.2020.11.014
2. França LR, Hess RA, Dufour JM, Hofmann MC, Griswold MD. The Sertoli cell: one hundred fifty years of beauty and plasticity. Andrology. 2016 Mar;4(2):189-212. doi: 10.1111/andr.12165
3. Shiraishi K, Matsuyama H. Gonadotoropin actions on spermatogenesis and hormonal therapies for spermatogenic disorders. Endocr J. 2017;64(2):123-131. doi: 10.1507/endocrj.EJ17-0001
4. Oduwole OO, Peltoketo H, Huhtaniemi IT. Role of follicle-stimulating hormone in spermatogenesis. Front Endocrinol (Lausanne). 2018 Dec 14;9:763.
5. Coviello AD, Matsumoto AM, Bremner WJ, Herbst KL, Amory JK, Anawalt BD, et al. Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. J Clin Endocrinol Metab. 2005 May;90(5):2595-2602. doi: 10.1210/jc.2004-0802
6. Achermann APP, Esteves SC. Prevalence and clinical implications of biochemical hypogonadism in patients with nonobstructive azoospermia undergoing infertility evaluation. F S Rep. 2023 Nov 17;5(1):14-22. doi: 10.1016/j.xfre.2023.11.007
7. Shiraishi K, Ohmi C, Shimabukuro T, Matsuyama H. Human chorionic gonadotrophin treatment prior to microdissection testicular sperm extraction in non-obstructive azoospermia. Hum Reprod. 2012 Feb;27(2):331-339. doi: 10.1093/humrep/der404
8. Fink J, Schoenfeld BJ, Hackney AC, Maekawa T, Horie S. Human chorionic gonadotropin treatment: a viable option for management of secondary hypogonadism and male infertility. Expert Rev Endocrinol Metab. 2021 Jan;16(1):1-8. doi: 10.1080/17446651.2021.1863783
9. Esteves SC, Achermann APP, Simoni M, Santi D, Casarini L. Male infertility and gonadotropin treatment: What can we learn from real-world data? Best Pract Res Clin Obstet Gynaecol. 2023 Feb;86:102310. doi: 10.1016/j.bpobgyn.2022.102310
10. Huhtaniemi I. A short evolutionary history of FSH-stimulated spermatogenesis. Hormones (Athens). 2015 Oct-Dec;14(4):468-478. doi: 10.14310/horm.2002.1632
11. Themmen APN, Blok LJ, Post M, Baarends WM, Hoogerbrugge JW, Parmentier M, et al. Follitropin receptor down-regulation involves a cAMP-dependent post-transcriptional decrease of receptor mRNA expression. Mol Cell Endocrinol. 1991 Jul;78(3):R7-R13. doi: 10.1016/0303-7207(91)90130-K
12. Zhang S, Li W, Zhu C, Wang X, Li Z, Zhang J, et al. Sertoli cell-specific expression of metastasis-associated protein 2 (MTA2) is required for transcriptional regulation of the follicle-stimulating hormone receptor (FSHR) gene during spermatogenesis. J Biol Chem. 2012 Nov 23;287(48):40471-40483. doi: 10.1074/jbc.M112.383802

13. Foresta C, Bettella A, Spolaore D, Merico M, Rossato M, Ferlin A. Suppression of the high endogenous levels of plasma FSH in infertile men are associated with improved Sertoli cell function as reflected by elevated levels of plasma inhibin B. Hum Reprod. 2004 Jun;19(6):1431-1437. doi: 10.1093/humrep/deh255
14. Laursen RJ, Alsbjerg B, Elbaek HO, Povlsen BB, Jensen KBS, Lykkegaard J, et al. Recombinant gonadotropin therapy to improve spermatogenesis in nonobstructive azoospermic patients - A proof of concept study. Int Braz J Urol. 2022 May-Jun;48(3):471-481. doi: 10.1590/S1677-5538.IBJU.2022.9913
15. Esteves SC, Achermann APP, Miyaoka R, Verza S Jr, Fregonesi A, Riccetto CLZ. Clinical factors impacting microdissection testicular sperm extraction success in hypogonadal men with nonobstructive azoospermia. Fertil Steril. 2024 Oct;122(4):636-647. doi: 10.1016/j.fertnstert.2024.06.013
16. Ohlander SJ, Lindgren MC, Lipshultz LI. Testosterone and male infertility. Urol Clin North Am. 2016 May;43(2):195-202. doi: 10.1016/j.ucl.2016.01.006
17. Young J, Xu C, Papadakis GE, Acierno JS, Maione L, Hietamäki J, et al. Clinical management of congenital hypogonadotropic hypogonadism. Endocr Rev. 2019 Apr 1;40(2):669-710. doi: 10.1210/er.2018-00116
18. Esteves SC, Viana MC, Achermann APP, Santi D. Human chorionic gonadotropin-based clinical treatments for infertile men with non-obstructive azoospermia. Andrology. 2025 Feb 4. Epub ahead of print. doi: 10.1111/andr.70003
19. Fraietta R, Zylberstejn DS, Esteves SC. Hypogonadotropic hypogonadism revisited. Clinics (Sao Paulo). 2013;68 Suppl 1(Suppl 1):81-88. doi: 10.6061/clinics/2013(sup01)09
20. Tharakan T, Corona G, Foran D, Salonia A, Sofikitis N, Giwercman A, et al. Does hormonal therapy improve sperm retrieval rates in men with non-obstructive azoospermia: a systematic review and meta-analysis. Hum Reprod Update. 2022 Aug 25;28(5):609-628. doi: 10.1093/humupd/dmac016
21. Caroppo E, Colpi GM. Hormonal treatment of men with nonobstructive azoospermia: What does the evidence suggest? J Clin Med. 2021 Jan 20;10(3):387. doi: 10.3390/jcm10030387
22. Esteves SC, Humaidan P, Ubaldi FM, Alviggi C, Antonio L, Barratt CLR, et al. APHRODITE criteria: addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function. Reprod Biomed Online. 2024 Apr;48(4):103647. doi: 10.1016/j.rbmo.2023.103647
23. Aydos K, Unlü C, Demirel LC, Evirgen O, Tolunay O. The effect of pure FSH administration in non-obstructive azoospermic men on testicular sperm retrieval. Eur J Obstet Gynecol Reprod Biol. 2003 May 1;108(1):54-58. doi: 10.1016/S0301-2115(02)00412-8
24. Hussein A, Ozgok Y, Ross L, Rao P, Niederberger C. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. BJU Int. 2013 Mar;111(3 Pt B):E110-E114. doi: 10.1111/j.1464-410X.2012.11485.x
25. Cocci A, Cito G, Russo GI, Falcone M, Capece M, Timpano M, et al. Effectiveness of highly purified urofollitropin treatment in patients with idiopathic azoospermia before testicular sperm extraction. Urologia. 2018 Feb;85(1):19-21. doi: 10.5301/uj.5000253
26. Hu X, Ding Z, Hong Z, Zou Z, Feng Y, Zhu R, et al. Spermatogenesis improved by suppressing the high level of endogenous gonadotropins in idiopathic non-obstructive azoospermia: a case control pilot study. Reprod Biol Endocrinol. 2018 Sep 22;16(1):91. doi: 10.1186/s12958-018-0401-7
27. Amer MK, Ahmed AR, Abdel Hamid AA, GamalEl Din SF. Can spermatozoa be retrieved in non-obstructive azoospermic patients with high FSH level?: a retrospective cohort study. Andrologia. 2019 Mar;51(2):e13176. doi: 10.1111/and.13176
28. Amer MK, Ahmed HEH, GamalEl Din SF, Fawzy Megawer A, Ahmed AR. Evaluation of neoadjuvant gonadotropin administration with downregulation by testosterone prior to second time microsurgical testicular sperm extraction: a prospective case-control study. Urologia. 2020 Nov;87(4):185-190. doi: 10.1177/0391560320913401

29. Guo F, Fang A, Fan Y, Fu X, Lan Y, Liu M, et al. Role of treatment with human chorionic gonadotropin and clinical parameters on testicular sperm recovery with microdissection testicular sperm extraction and intracytoplasmic sperm injection outcomes in 184 Klinefelter syndrome patients. Fertil Steril. 2020 Nov;114(5):997-1005. doi: 10.1016/j.fertnstert.2020.05.043
30. Peng T, Liao C, Ye X, Chen Z, Lan Y, Fu X, et al. Gonadotropins treatment prior to microdissection testicular sperm extraction in non-obstructive azoospermia: a single-center cohort study. Reprod Biol Endocrinol. 2022 Apr 1;20(1):61. doi: 10.1186/s12958-022-00934-1
31. Busch AS, Kliesch S, Tüttelmann F, Gromoll J. FSHB -211G>T stratification for follicle-stimulating hormone treatment of male infertility patients: making the case for a pharmacogenetic approach in genetic functional secondary hypogonadism. Andrology. 2015 Nov;3(6):1050-1053. doi: 10.1111/andr.12094
32. Busch AS, Tüttelmann F, Cremers JF, Schubert M, Nordhoff V, Schüring AN, et al. FSHB -211 G>T polymorphism as predictor for TESE success in patients with unexplained azoospermia. J Clin Endocrinol Metab. 2019 Jun 1;104(6):2315-2324. doi: 10.1210/jc.2018-02249
33. Casarini L, Crépieux P, Reiter E, Lazzaretti C, Paradiso E, Rochira V, et al. FSH for the treatment of male infertility. Int J Mol Sci. 2020 Mar 25;21(7):2270. doi: 10.3390/ijms21072270

Correspondence address:
Sandro C. Esteves, MD, PhD
ANDROFERT, Clínica de Andrologia e Reprodução Humana
Av. Dr. Heitor Penteado, 1464,
Campinas, SP, 13075-460, Brasil
E-mail: s.esteves@androfert.com.br

ARTICLE INFO

Esteves, SC
https://orcid.org/0000-0002-1313-9680

Submitted for publication:
February 18, 2026

Accepted:
February 24, 2026

Published as Ahead of Print:
February 27, 2026

Editor in Chief
Luciano Alves Favorito

Associate Editor
Luciano Alves Favorito

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

UPDATE IN UROLOGY

UROANATOMY

Vol. 52 (3): e20269904, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2026.9904

Editorial Comment: Maximal anatomic bladder neck preservation at the prostatic origin (MANO) in robotic radical prostatectomy: does prostate size matter?

Deerush Kannan Sakthivel [1], Pushan Prabhakar [2], Mohamed Javid Raja Iyub [2], Manuel Ozambela Jr [2], Murugesan Manoharan [2]

[1] Department of Urology, Baptist Health South Florida, Miami, USA; [2] Department of Urology, Baptist Health South Florida, Miami, USA

J Robot Surg. 2025 Oct 22;19(1):707.

DOI: 10.1007/s11701-025-02880-7 | ACCESS: 41125940

Luciano A. Favorito [1, 2]

[1] Unidade de Pesquisa Urogenital - Universidade do Estado do Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil; [2] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil

COMMENT

IRobotic surgery has revolutionized the surgical treatment of prostate cancer, resulting in better outcomes and faster recovery (1-4). One of the most important aspects for the technical refinement of this surgical procedure is knowledge of pelvic anatomy. In tis paper of Sakthivel and collegues (5) we can observe the importance of the anatomy specially in large prostates. The authors described the maximal anatomic bladder neck preservation at the prostatic origin (MANO) technique, designed to enable safe circumferential dissection at the true bladder neck origin irrespective of gland size and concluded that larger prostates were associated with older age and higher preoperative, mean operative time increased with gland size and hospital stay was longer for > 50 cc prostates. The authros shows that the MANO technique enables safe bladder neck preservation across all prostate sizes. Despite increased operative complexity in larger glands, functional and oncological outcomes remain equivalent. This approach may standardize bladder neck management in RALP and support improved continence recovery irrespective of prostate volume. We congratulate the authors for the interesting paper.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Moschovas MC, Jaber A, Saikali S, Sandri M, Bhat S, Rogers T, Gamal A, Loy D, Patel E, Reddy S, Sighinolfi MC, Rocco B, Harvey T, Ficarra V, Patel V. Impacts on functional and oncological outcomes of Robotic-assisted Radical Prostatectomy 10 years after the US Preventive Service Taskforce recommendations against PSA screening. Int Braz J Urol. 2024 Jan-Feb;50(1):65-79. doi: 10.1590/S1677-5538.IBJU.2023.0530.
2. Jiao RD, Wang Z, Kong XG, Tang SY, Xia D, Wu ZJ, Liu JC, Liu LH. Clinical Outcomes and Cost-effectiveness between the Sentire® and da Vinci® systems in Robot-assisted Radical Prostatectomy. Int Braz J Urol. 2025 Jul-Aug;51(4):e20240706. doi: 10.1590/S1677-5538.IBJU.2024.0706.
3. Gamal A, Moschovas MC, Saikali S, Reddy S, Ozawa Y, Sharma R, Kunta A, Rogers T, Patel V. Comparing the Technological and Intraoperative Performances of Da Vinci xi and DaVinci 5 Robotic Platforms in Patients Undergoing Robotic-Assisted Radical Prostatectomy. Int Braz J Urol. 2025 Jan-Feb;51(1):e20240569. doi: 10.1590/S1677-5538.IBJU.2024.0569.
4. Pires RDS, Pereira CWA, Favorito LA. Is the learning curve of the urology resident for conventional radical prostatectomy similar to that of staff initiating robot-assisted radical prostatectomy? Int Braz J Urol. 2024 May-Jun;50(3):335-345. doi: 10.1590/S1677-5538.IBJU.2024.9909.
5. Sakthivel DK, Prabhakar P, Iyub MJR, Ozambela M Jr, Manoharan M. Maximal anatomic bladder neck preservation at the prostatic origin (MANO) in robotic radical prostatectomy: does prostate size matter? J Robot Surg. 2025 Oct 22;19(1):707. doi: 10.1007/s11701-025-02880-7.

Correspondence address:
Luciano A. Favorito, MD, PhD
Unidade de Pesquisa Urogenital
da Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

ARTICLE INFO

Luciano A. Favorito
https://orcid.org/0000-0003-1562-6068

Submitted for publication:
February 10, 2026

Accepted:
March 05, 2026

Published as Ahead of Print:
March 10, 2026

Editor in Chief	Associate Editor
Luciano Alves Favorito	Luciano Alves Favorito

Data Availability
Uninformed

VIDEO SECTION

Vol. 52 (3): e20250532, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0532

The Start of a Robotic Kidney Transplant Program: Institutional Step-by-Step Technique

Alessandro Antonelli [1, 2], Rostand Emmanuel Nguefouet Momo [2], Paola Donato [2], Gabriele Ugolini [2], Giovanni Corghi [1, 2], Simone Priolo [3], Cristina Buttazzoni [3], Francesco Nacchia [2], Riccardo Bertolo [1]

[1] Department of Surgical Sciences, Urology Unit, University Hospital of Verona, Verona, Italy; [2] Department of Surgical Sciences, Kidney Transplant Center, University Hospital of Verona, Verona, Italy; [3] Intensive Care and Anesthesia B Unit, University Hospital of Verona, Verona, Italy

ABSTRACT

Purpose: To report our institutional technique for robot-assisted kidney transplantation (RAKT) (1, 2) in a detailed, step-by-step manner.

Materials and methods: This is a case of RAKT from a living donor successfully performed at our institution. A 29-year-old male with end-stage renal disease secondary to focal segmental glomerulosclerosis, undergoing hemodialysis with a baseline serum creatinine of 1035 μmol/L at admission, received a left kidney donated by his 55-year-old mother. Preoperative evaluation confirmed one HLA mismatch (0-0-1) and ABO compatibility, making the patient suitable for living donation.

Results: The procedure was performed using the da Vinci Xi robotic system (Intuitive, Sunnyvale, CA, USA). The recipient was placed in a 23° Trendelenburg position. Four robotic ports were aligned above the umbilicus, and two additional ports were used for the assistant. Graft introduction was performed via a 7-cm Pfannenstiel incision using an Alexis O Wound Protector-Retractor with Laparoscopic Cap (Applied Medical, Rancho Santa Margarita, CA, USA). Following robotic living donor nephrectomy, extracorporeal bench preparation was performed (warm ischemia time = 4 min; cold ischemia time = 239 min). RAKT was then completed with intracorporeal vascular anastomoses using 5-0 Gore-Tex sutures (warm ischemia time = 45 min), and ureteral reimplantation according to the Lich-Gregoire technique, performed with 4/0 monofilament suture (3). The surgery was uneventful, with excellent graft reperfusion and no perioperative complications. Postoperative renal Doppler ultrasound and radionuclide renal scan were normal. Serum creatinine and eGFR at discharge were 1.45 mg/dL and 62 mL/min, respectively (4).

Conclusions: Our experience confirms the feasibility and safety of RAKT with a living donor in a selected setting, supporting further integration of robotic assistance into renal transplantation programs.

ACKNOWLEDGMENTS

We thank the surgical, anesthesiology, and transplant coordination teams for their contributions. We thank our residents Dr. Giuseppe Aronica and Dario Brunello for helping with photo and video shooting. We thank Dr. Claudio Brancelli for helping with the video voice-over.

CONSENT

Informed consent was obtained from both donors and recipient for publication of this case report.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Basile G, Pecoraro A, Gallioli A, Territo A, Berquin C, Robalino J, et al. Robotic kidney transplantation. Nat Rev Urol. 2024 Sep;21(9):521-33. doi: 10.1038/s41585-024-00865-z
2. Garisto J, Eltemamy M, Bertolo R, Miller E, Wee A, Kaouk J. Single port robot-assisted transperitoneal kidney transplant using the SP® surgical system in a pre-clinical model. Int Braz J Urol. 2020 Jul-Aug;46(4):680-1. doi: 10.1590/S1677-5538.IBJU.2019.191
3. Pulford C, Keating K, Rohloff M, Peifer D, Eames R, Maatman T. How we do it: robotic-assisted distal ureterectomy with ureteral reimplantation. Int Braz J Urol. 2021 Nov-Dec;47(6):1277-8. doi: 10.1590/S1677-5538.IBJU.2021.0207
4. Leite RRA, Leite M Jr, Einicker-Lamas M, Valverde RHF, Miranda LCD, Schanaider A. Clinical outcomes prediction in kidney transplantation by use of biomarkers from hypothermic machine perfusion. Int Braz J Urol. 2024 Jul-Aug;50(4):470-9. doi: 10.1590/S1677-5538.IBJU.2024.0166

Correspondence address:
Riccardo Bertolo, MD, PhD
Department of Urology, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy
Piazzale Aristide Stefani, 1, Verona, 37126
Telephone: +39 0458127701
E-mail: riccardogiuseppe.bertolo@univr.it

Submitted for publication:
September 15, 2025

Accepted after revision:
October 06, 2025

Published as Ahead of Print:
November 27, 2025

ARTICLE INFO

Riccardo Bertolo
https://orcid.org/0000-0003-0260-4601

Available at:

VIDEO

VIDEO SECTION

Vol. 52 (3): e20250660, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0660

Robotic-Assisted Laparoscopic Buccal Mucosal Graft Ureteroplasty and Ureteral Reimplantation for Repair of Complex Ureteral Strictures Using the Modular Carina™ System

Wencong Han [1, 2, 3], Zhihua Li [1, 2, 3], Zhenyu Li [1, 2, 3], Guanpeng Han [1, 2, 3], Zheng Zhang [1, 2, 3], Kunlin Yang [1, 2, 3], Xuesong Li [1, 2, 3]

[1] Department of Urology, Peking University First Hospital, Beijing, China; [2] Institution of Urology, Peking University, Beijing, China; [3] National Urological Cancer Center, Beijing, China

ABSTRACT

Purpose: Multifocal ureteral strictures pose significant challenges for reconstructive surgery due to their segmental distribution and the need to preserve the ureteral blood supply (1, 2). Robotic-assisted surgery, owing to its precision and minimally invasive advantages, has increasingly become a preferred approach (3). Although the da Vinci surgical system has long dominated this field, several novel robotic platforms have recently emerged with comparable safety and efficacy (4, 5). This study reports our experience with robotic-assisted laparoscopic buccal mucosal graft ureteroplasty combined with ureteral reimplantation for complex ureteral stricture repair using the modular Carina™ robotic surgical system.

Materials and Methods: A 32-year-old man presented with a one-month history of flank pain and was found to have both proximal and distal ureteral strictures. Using the modular Carina™ robotic system, the procedure was performed as follows: dissection of the proximal stricture, longitudinal ureterotomy, posterior augmented anastomosis, harvesting of buccal mucosa for ventral onlay grafting; followed by dissection of the distal ureteral stricture and bladder wall and completion of a side-to-side ureterovesical anastomosis.

Results: The procedure was completed successfully without conversion, with a total operative time of 272 minutes. The patient was discharged on postoperative day 7. Histopathological examination revealed granulomatous inflammation, and antituberculosis therapy was initiated. The double-J stent and nephrostomy tube were removed 2 months postoperatively. During an 8-month follow-up, the patient's symptoms resolved, imaging demonstrated improvement of hydronephrosis, renal function remained stable, and no postoperative complications were observed.

Conclusions: Robotic-assisted reconstructive surgery for complex ureteral strictures using the modular Carina™ robotic system is technically feasible. However, larger studies with longer follow-up are required to validate these preliminary findings.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bilotta A, Wiegand LR, Heinsimer KR. Ureteral reconstruction for complex strictures: a review of the current literature. Int Urol Nephrol. 2021;53(11):2211–2219. doi:10.1007/s11255-021-02985-6
2. Wang X, Meng C, Li D, Zhang Y, Liu Y, He Q, et al. Minimally invasive ureteroplasty with lingual mucosal graft for complex ureteral stricture: analysis of surgical and patient-reported outcomes. Int Braz J Urol. 2024;50(1):46–57. doi:10.1590/S1677-5538.IBJU.2023.0393
3. Biasatti A, Licari LC, Bologna E, Orsini A, Pearson MC, Autorino R. Iatrogenic ureteropelvic junction disruption from lumbar spinal fusion surgery: early repair using the SP robotic system. Int Braz J Urol. 2025;51(4):e20240690. doi:10.1590/S1677-5538.IBJU.2024.0690
4. Fan S, Chen S, Li X, Wang J, Zhang Y, Liu Z, et al. Totally intracorporeal robot-assisted bilateral ileal ureter replacement for the treatment of ureteral strictures using the Kangduo Surgical Robot 2000 Plus. Int Braz J Urol. 2024;50(6):781–782. doi:10.1590/S1677-5538.IBJU.2024.0360
5. Pokhrel G, Wang Z, Cui J, Zhang Y, Liu H, Li S, et al. Initial experience with the novel modular robotic system Carina in urology: a prospective study on safety, feasibility, and surgical settings. Sci Rep. 2025;15(1):12686. doi:10.1038/s41598-025-97411-7

Correspondence address:
Xuesong Li, MD
Department of Urology, Peking University First Hospital
No.8 Xishiku Street, Xicheng District,
Beijing, 100034, China
Telephone: + 86 10 8357-5101
E-mail: pineneedle@sina.com

Submitted for publication:
November 10, 2025

Accepted after revision:
November 21, 2025

Published as Ahead of Print:
January 16, 2026

ARTICLE INFO

Wencong Han
https://orcid.org/0009-0000-3556-586X

Available at:

VIDEO

VIDEO SECTION

Vol. 52 (3): e20250744, May - June, 2026
doi: 10.1590/S1677-5538.IBJU.2025.0744

Salvage Single-Port Transvesical Robotic Radical Prostatectomy Following High-Intensity Focused Ultrasound (HIFU) Therapy

Mohamad Watfa [1], Nicolas A. Soputro [1], Abdulrahman Al-Bayati [1], Karim Daher [1], Salim Younis [1], Samarpit Rai [1], Rui M. Bernardino [1], Lin Wang [1], Zeyad R. Schwen [1], Ruben Olivares [1], Riccardo Autorino [1], Jihad Kaouk [1]

[1] Glickman Urological Institute, Cleveland Clinic, Ohio, USA

ABSTRACT

Introduction: Focal therapy with high-intensity focused ultrasound (HIFU) has emerged as a treatment option for selected patients with localized prostate cancer; however, disease recurrence requiring salvage intervention remains a recognized challenge (1–5). Salvage radical prostatectomy is technically demanding due to post-ablative tissue changes, which may compromise oncologic and functional outcomes (6,7). Herein, we describe the surgical technique and clinical outcomes of salvage robotic-assisted radical prostatectomy (RARP) performed using a single-port (SP) transvesical approach following HIFU.

Materials and Methods: The index case was a 57-year-old man with a history of right hemigland HIFU for ISUP Grade Group 2 prostate cancer. During routine surveillance four years after HIFU, his PSA rose to 3.64 ng/mL, prompting repeat biopsy. Biopsy confirmed clinically significant recurrent prostate cancer both within and outside the prior treatment field, with bilateral involvement. Preoperatively, the patient reported satisfactory erectile function, with a Sexual Health Inventory for Men (SHIM) score of 25/25. After informed consent, salvage transvesical SP-RARP was performed. Dissection was carried out with anticipation of post-ablation tissue changes, and bilateral nerve-sparing was incorporated to optimize functional outcomes.

Results: The procedure was completed in 82 minutes without placement of additional ports and without intraoperative complications. Estimated blood loss was 75 mL. The patient was discharged home the same day (4.3 hours postoperatively). Foley catheter removal on postoperative day 6 was followed by immediate urinary continence. Erectile function remained satisfactory at 3 months, indicating preservation of baseline functional outcomes. Final pathology demonstrated pT3b ISUP Grade Group 2 prostate cancer with evidence of prior ablation and negative surgical margins. At the most recent follow-up (12 months), PSA remained undetectable, with no biochemical recurrence.

Conclusion: Transvesical SP-RARP appears to be a safe and effective salvage option following focal ablative therapy for prostate cancer. Leveraging the advantages of single-port robotic technology (8,9), this approach may facilitate outpatient surgery while maintaining favorable functional and oncologic outcomes.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Eastham JA, Auffenberg GB, Barocas DA, Chou R, Crispino T, Davis JW, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, part I: introduction, risk assessment, staging, and risk-based management. J Urol. 2022;208(1):10–18. doi: 10.1097/JU.0000000000002757
2. Stabile A, Orczyk C, Hosking-Jervis F, Giganti F, Arya M, Hindley RG, et al. Medium-term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using high-intensity focused ultrasonography for primary localized prostate cancer. BJU Int. 2019;124(3):431–440. doi: 10.1111/bju.14710
3. Aminsharifi A, Polascik TJ. Diagnosis and management of local recurrence after prostate focal therapy: challenges and solutions. Eur Urol Oncol. 2019;2(5):539–540. doi: 10.1016/j.euo.2019.07.008
4. Ezequiel B, Marcelo B, Polascik TJ, Rastinehad A, Rodriguez-Sanchez L, Sanchez-Salas R. Focal therapy: overcoming barriers for advances in prostate cancer treatment in South America. Int Braz J Urol. 2024;50(1):100–104. doi: 10.1590/S1677-5538.IBJU.2023.0539
5. Andrade GM, Manente FG, Barroso PJDD, Teles SB, Partezani AD, Baccaglini W, et al. Outcomes of ablative therapy and radical treatment for prostate cancer: a systematic review and meta-analysis. Int Braz J Urol. 2024;50(3):237–249. doi: 10.1590/S1677-5538.IBJU.2023.0628
6. Moschovas MC, Jaber A, Saikali S, Sandri M, Bhat S, Rogers T, et al. Impacts on functional and oncological outcomes of robotic-assisted radical prostatectomy 10 years after the US Preventive Services Task Force recommendations against PSA screening. Int Braz J Urol. 2024;50(1):65–79. doi: 10.1590/S1677-5538.IBJU.2023.0530
7. Thakker PU, Sandberg M, Hemal AK, Rodriguez AR. A comprehensive review of the current state of robot-assisted laparoscopic salvage prostatectomy. Int Braz J Urol. 2024;50(4):398–414. doi: 10.1590/S1677-5538.IBJU.2024.0126
8. Kaouk JH, Beksac AT, Abou Zeinab M, Duncan A, Schwen ZR, Eltemamy M. Single port transvesical robotic radical prostatectomy: initial clinical experience and description of technique. Urology. 2021;155:130–137. doi: 10.1016/j.urology.2021.05.022
9. Kaouk JH, Haber GP, Autorino R, Crouzet S, Ouzzane A, Flamand V, et al. A novel robotic system for single-port urologic surgery: first clinical investigation. Eur Urol. 2014;66(6):1033–1043. doi: 10.1016/j.eururo.2014.06.039

Correspondence address:
Jihad Kaouk, MD
Glickman Urological Institute
Cleveland Clinic Foundation
9500 Euclid Avenue, Q10, USA
Email: kaoukj@ccf.org

Submitted for publication:
December 19, 2025

Accepted after revision:
January 02, 2026

Published as Ahead of Print:
February 02, 2026

ARTICLE INFO

Mohamad Watfa
https://orcid.org/0009-0003-7744-6190

Available at:

VIDEO

INFORMATION FOR AUTHORS

Manuscripts submitted for publication should be sent to:

Luciano A. Favorito, MD, PhD
Editor, International Braz J Urol

Submit your article here:
https://www.intbrazjurol.com.br

Manuscripts must be written in current English or Portuguese. Non-native English speakers should ask a native specialist in medical English for checking the grammar and style. Either American or British English may be used but should be consistent throughout the manuscript.

A submission letter signed by all authors must accompany each manuscript. This letter must state that: a)- the paper or portion thereof have not been previously published and are not under consideration by another Journal, b)- that all authors have contributed to the information or material submitted for publication, and that all authors have read and approved the manuscript, c)- that the authors have no direct or indirect commercial financial incentive associated with publishing the manuscript, d)- that the source of extra-institutional funding, specially that provided by commercial companies, is indicated, e)- that the study had been reviewed and approved by a certified Ethical Board or Committee, including the nmeber of the approval dociment and the date of the approval, f)- a non-plagiarism statement (I (We) declare that all material in this assignment is my (our) own work and does not involve plagiarism). g)- Clinical trials must be registered on any Clinical Trials Registry and the letter must bring the number of registration and the name of the registry. After accepted for publication, the manuscript will become property of the **International Braz J Ur**ol.

Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, must be clearly disclosed when submitting a manuscript for review. If accepted, a disclosure will be published in the final manuscript.

The requirements for authorship and the general rules for preparation of manuscripts submitted to the **International Braz J Urol** are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med, 126: 36-47, 1997). An electronic version of the Uniform Requirements is available on various websites, including the International Committee of Medical Journal Editors web site: **www.icmje.org.**

In response to the concerns of the editors of scientific medical journals with ethics, quality and seriousness of published articles, a Committee on Publication Ethics (COPE) was established in 1997 and a guideline document was published. The International Braz J Urol signed, approved, and follows the COPE guidelines. The Editor strongly encourages the authors to carefully read these guidelines before submitting a manuscript **(www.publicationethics.org.uk/guidelines or www.brazjurol.com.br**, vol. 26 (1): 4-10, 2000).

Peer Review – All submissions are subject to editorial review. Typically, each manuscript is anonymously forwarded by the Editor to 4 Reviewers (at least 2). If the Editor receives conflicting or inconclusive revisions, the manuscript is always sent to 1 or 2 additional Reviewers before the Editor's decision. If considered necessary by the Editor or by the Reviewers, statistical procedures included in the manuscript will be analyzed by a statistician.

The International Braz J Urol contains six sections: **Original Article, Review Article, Surgical Technique, Challenging Clinical Case, Radiology**

Page and Video Section. The articles should be written in Portuguese or English official orthography.

Abbreviations should be avoided, and when necessary must be specified when first time mentioned. Unusual expressions may not be used. A list of abbreviations must be provided at the end of the manuscript.

Every manuscript submitted to publication should have a cover page containing the title, short title (up to 50 characters), authors and institution. Up to six key words should be provided. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine (**http://www.nlm.nih.gov/mesh/meshhome.html**). One of the authors should be designated as correspondent and the complete correspondence address, telephone and fax numbers and E-mail should be provided.

If any financial support has been provided, the name of the institution should be mentioned.

Original Article: Original articles should contain a Cover Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusions, References, Tables and Legends, each section beginning in a separate page and numbered consecutively. Original articles should cover contemporary aspects of Urology or experimental studies on Basic Sciences applied to urology. The manuscript text should contain no more than 2500 words, excluding the Abstract. The number of authors is limited to five. References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

Review Article: Review articles are accepted for publication upon Editorial Board's request in most of the cases. A Review Article is a critical and systematic analysis of the most recent published manuscripts dealing with a urological topic. A State of the Art article is the view and experience of a recognized expert in the topic. An abstract must be provided.

Surgical Technique: These manuscripts should present new surgical techniques or instruments and should contain Introduction, Surgical Technique, Comments and up to five References. An abstract must be provided. At least five cases performed with the technique must be included.

Challenging Clinical Case: These manuscripts should present relevant clinical or surgical situations which can bring or consolidate our understanding of genesis, natural history, pathophysiology and treatment of diseases.
Structure of the articles

Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario**: Description of case(s) relevant preceding and existing aspects;
- **Case(s) hypothesis and rational:** precepts, clinical and basic reasoning supporting the case(s) hypothesis and the raised scenario. Why is it important and is being reported?
- **Discussion and future perspectives:** what might it add and how does it relate to the current literature. 'Take-home message' - lessons learnt;
- **Table and/or Figure limits:** 2 (plates aggregating multiple images are encouraged) each exceeding table or figure will decrease 250 words of the full text;
- **Number of references:** 10-15.

Radiology Page: Will be published upon the Section Editor decision.

Video Section: The material must be submitted in the appropriate local, in the Journal's site, whe-

re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

ILLUSTRATIONS:

The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

ELECTRONIC SUBMISSION:

1) Do not embed the figures in the text, but supply them as separate files.
2) For Submitting Photographs Electronically, please:
Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not embed in Word or PowerPoint.
3) For Submitting Line Artwork Electronically please note that:
Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
4) IMPORTANT - Avoid - Do Not

a) **DO NOT** embed the images in the text; save them as a separate file
b) **DO NOT** supply artwork as a native file. Most illustration packages now give the option to "save as" or export as EPS, TIFF or JPG.
c) **DO NOT** supply photographs in PowerPoint or Word. In general, the files supplied in these formats are at low resolution (less than 300 dpi) and unsuitable for publication.
d) **DO NOT** use line weights of less than 0.25 point to create line drawings, because they will nor appear when printed.

TABLES: The tables should be numbered with Arabic numerals. Each table should be typed on a single page, and a legend should be provided for each table. Number tables consecutively and cites each table in text in consecutive order.
REFERENCES: The References should be numbered following the sequence that they are mentioned in the text. The references should not be alphabetized. They must be identified in the text with Arabic numerals in parenthesis. Do not include unpublished material and personal communications in the reference list. If necessary, mention these in the body of the text. For abbreviations of journal names refer to the "List of Journals Indexed in Index Medicus" (http://www.nlm.nih.gov). The authors must present the references according to the following examples; the names of all authors must be included; when exist more than six authors, list the first six authors followed by et al. The initial and the final pages of the reference should be provided:

Papers published in periodicals:

- Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

- Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

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

Chapters in Books:

- Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

THE EDITORS SUGGEST THE AUTHORS TO OBSERVE THE FOLLOWING GUIDELINES WHEN SUBMITTING A MANUSCRIPT:

The **Ideal Manuscript** may not exceed 2500 words.

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

NOTE:

Recent issues of the International Braz J Urol must be observed concerning the presentation form of the manuscript.

MANUSCRIPT CHECKLIST

The authors should observe the following checklist before submitting a manuscript to the International Braz J Urol

- The sequence of manuscript arrangement is according to the Information for Authors.
- The Article is restricted to about 2,500 words and 6 authors.
- Abbreviations were avoided and are defined when first used and are consistent throughout the text.
- Generic names are used for all drugs. Trade names are avoided.
- Normal laboratory values are provided in parenthesis when first used.
- The references were presented according to the examples provided in the Information for Authors. The references were numbered consecutively, following the sequence that they are mentioned in the text. They were identified in the text using Arabic numeral in parenthesis. The names of all authors were provided. When exist more than six authors, list the first sixauthors followed by et al. The initial and the final pages of the reference should be provided. The number of references must be accordingly to the informed in the Instructions for Authors, depending on the type of manuscript.
- The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.
- Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.
- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
- A corresponding author with complete address, telephone, Fax, and E-mail are provided.
- A submission letter and a disclosure form, signed by all authors, are included.
- The authors should included written permission from publishers to reproduce or adapt a previously published illustrations or tables.
- Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, is clearly disclosed in the manuscript.
- Check that each figure is cited in the text. The illustrations are not merged in the text.
- The photographs are supplied as TIFF or JPG files and saved at a resolution of 300 dpi (dots per inch) at final size.
- The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not embed in Word or PowerPoint.
- A list of abbreviations is provided.