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International Brazilian Journal of Urology is among the Top 10 urologic journals – the new Impact Factor is 3.7!

Luciano A. Favorito^{1,2}

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The September-October number of *Int Braz J Urol* is the 24th under my supervision and is very special. In July 23 the Web of Science released shows the 2022 impact factor and the *Int Braz J Urol* head the impact of 3.7 – the biggest in its history! A great reward for the hard work by the editorial team. With the new impact factor, the *Int Braz J Urol* today is one of the top 10 urologic journals (Figure-1), an unimaginable feat in 2019 when I took over as editor in chief. We will continue working for another 4 years to reach the top 5 of urology journals. In the cover of this edition, we can see the new impact factor of the International Brazilian Journal of Urology.

Figure 1: The top 10 impact factors in urology in 2023. International Brazilian Journal of Urology for the first time in his history is in the Top 10.

Journal	2022 Impact Factor
1. European Urology	23.4
2. Nature Reviews Urology	15.3
3. European Urology Oncology	8.2
4. Journal of Urology	6.6
5. European Urology Focus	5.4
6. Minerva Urology and Nephrology	4.9
7. Prostate Cancer and Prostatic Diseases	4.8
8. World Journal of Mens Health	4.8
9. BJU International	4.5
10. International Braz J Urol	3.7

In this number the *Int Braz J Urol* presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Overactive bladder, Endometriosis, Penile Cancer, Enuresis, Urolithiasis, BPH, Ureteroplasty and Varicocele. The papers came from many different countries such as Brazil, Italy, Russia, USA and China, and as usual the editor's comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. He and colleagues from China, presented in page 535 (1) a nice meta-analysis about the efficacy and safety of approved oral therapies for overactive bladder and concluded that solifenacin showed better efficacy. For safety, most anticholinergic drugs were more likely to cause dry mouth and constipation, lower doses were better tolerated. The choice of drugs should be tailored to the patient's specific situation to find the best balance between efficacy and safety.

Dr. Diniz and colleagues from the Urogenital Research Unit – Rio de Janeiro – Brazil, presented in page 564 (2) an important review about the Urological knowledge and tools applied to diagnosis and surgery in deep infiltrating endometriosis (DIE) and concluded that DIE in the urinary system is common, however the number of publications with high level of evidence is limited. The initial tools for diagnosis are ultrasonography and cystoscopy, but magnetic resonance is the most reliable tool. When the patient has voiding symptoms, the urodynamic examination is crucial. Laparoscopy improves lesion detection and anatomical understanding. This approach must be carried out by professionals with high expertise, since the surgery goes beyond the resection of lesions and includes the preservation of nerve structures and urinary tract reconstruction techniques.

Dr. Tobias-Machado and colleagues from Brazil performed in page 580 (3) a nice study about the long-term oncological and surgical outcomes after Video Endoscopic Inguinal Lymphadenectomy (VEIL) in patients with penile cancer and concluded that VEIL seems to offer appropriate long term oncological control with minimal morbidity. In the absence of non-invasive stratification measures such as dynamic sentinel node biopsy, VEIL emerged as the alternative for the management of non-bulky lymph nodes in penile cancer.

Dr. Dahan and colleagues from Brazil performed on page 590 (4) an interesting study about the asthma treatment in patients with enuresis: and the repercussions on urinary symptoms and concluded that controlling asthma in children with primary enuresis resulted in a significant increase in dry nights.

Dr. Xie and colleagues from China performed on page 599 (5) a nice study about a nomogram to predict the risk of adverse outcomes in patients with residual stones following percutaneous nephrolithotomy (PCNL) and concluded that larger diameter of residual stones, positive urine culture, and previous stone surgery were significant predictors associated with adverse outcomes in patients with residual stones after PCNL. This nomogram could help to assess the risk of adverse outcomes quickly and effectively in patients with residual stones after PCNL.

Dr. Maida and colleagues from Italy performed on page 608 (6) a nice study about the predictors of early catheter replacement after HoLEP and the results from a high-volume laser center and concluded that the presence of indwelling urinary catheter before surgery, bladder wall modifications and the maintenance of anticoagulants/antiplatelets therapy were shown to be independent predictors of early catheter replacement after HoLEP (Holmium Laser Enucleation of the Prostate).

Dr. Guliev and colleagues from Russia performed on page 619 (7) a nice study about the laparoscopic ventral onlay ureteroplasty with buccal mucosa graft for complex proximal ureteral stricture and concluded that patients with proximal ureteral strictures could be effectively treated by laparoscopic ventral onlay ureteroplasty with a buccal mucosa graft.

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

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CONFLICT OF INTEREST

None declared.

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ARTICLE INFO

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Comparative assessment of efficacy and safety of approved oral therapies for overactive bladder: a systematic review and network meta-analysis

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ABSTRACT

Purpose: To compare the effectiveness and safety of marketed oral drugs for overactive bladder based on a systematic review and network meta-analysis approach.

Methods: Pubmed, Embase, Web of Science, and the Cochrane Register of Clinical Trials databases were systematically searched. The search time frame was from database creation to June 2, 2022. Randomized controlled double-blind trials of oral medication for overactive bladder were screened against the protocol's entry criteria. Trials were evaluated for quality using the Cochrane Risk of Bias Assessment Tool, and data were statistically analyzed using Stata 16.0 software.

Result: A total of 60 randomized controlled double-blind clinical trials were included involving 50,333 subjects. Solifenacin 10mg was the most effective in mean daily micturitions and incontinence episodes, solifenacin 5/10mg in mean daily urinary urgency episodes and nocturia episodes, fesoterodine 8mg in urgency incontinence episodes/d and oxybutynin 5mg in voided volume/micturition. In terms of safety, solifenacin 5mg, ER-tolterodine 4mg, mirabegron, vibegron and ER-oxybutynin 10mg all showed a better incidence of dry mouth, fesoterodine 4mg, ER-oxybutynin 10mg, tolterodine 2mg, and vibegron in the incidence of constipation. Compared to placebo, imidafenacin 0.1mg showed a significantly increased incidence in hypertension, solifenacin 10mg in urinary tract infection, fesoterodine 4/8mg and darifenacin 15mg in headache.

Conclusion: Solifenacin showed better efficacy. For safety, most anticholinergic drugs were more likely to cause dry mouth and constipation, lower doses were better tolerated. The choice of drugs should be tailored to the patient's specific situation to find the best balance between efficacy and safety.

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INTRODUCTION

Overactive bladder (OAB) consists of four closely related symptoms: urgency, frequency, urge urinary incontinence (UUI) and nocturia, which have no significant impact on the patient's life safety but seriously reduce the quality of life. Studies have shown (1) that OAB can have varying degrees of impact on six aspects of daily life: recreational life, psychological problems, isolation, sexual desire, and work efficiency, causing a heavy economic burden on patients and society. The prevalence of OAB is high, ranging from 7% to 27% in men and 9% to 43% in women, and the prevalence of OAB increases with age (2, 3). However, the pathophysiological mechanisms involved in the symptoms of OAB syndrome are varied and treatment is difficult (4). For this reason, more and more scholars have been conducting research on the pathogenesis of OAB from different perspectives in recent years and are constantly exploring new treatments for OAB. Treatment options for OAB are divided by "lines of therapy" based on levels of invasiveness. Lifestyle modification and pelvic floor physical therapy are the tenets of the first line of therapy. Second line therapy consists of drug therapy with anticholinergics and/or beta-3 agonists. Third line therapies include intravesical botulinum toxin injection, sacral neuromodulation, and percutaneous tibial nerve stimulation (5, 6).

For decades, antimuscarinics such as tolterodine (TOL) and solifenacin (SOL) have been the main pharmacological treatment for OAB, but their lack of bladder specificity has led to a high incidence of adverse events such as dry mouth and constipation, ultimately limiting their effectiveness. In recent years, 3-adrenoceptor agonists, which are highly selective, have been developed as a potential treatment for OAB. Pharmacological assays have shown that 3-adrenoceptor agonists participate in beta adrenergic-mediated bladder relaxation, thus exerting their effect (5). They have been shown to be effective and well tolerated (7, 8).

Different treatment modalities have their advantages and limitations, and it is essential to choose the right treatment modality for the specific patient in clinical practice. The wide choice of drugs available for OAB treatment and the lack

of head-to-head clinical trials between drugs has led to controversy over the best drug choice. Given that one previously published study (9) had too many drug doses (including unapproved doses) grouped together, and the outcome indicators were not combined in a reasonable manner, the potential for bias is too high and the robustness of the final study results is questionable. Therefore, this study proposes to conduct a precise network meta-analysis of approved oral drugs, including only oral drugs with approved dosages and only outcome indicators with the same observation period, in order to reduce the heterogeneity of the introduced studies and provide a basis for the selection of therapeutic drugs in clinical practice.

MATERIALS AND METHODS

The software involved in this study included EndNote X8 (literature management and article writing) (Thomson Research Soft), Excel 2019 (data extraction and collation) (Microsoft Office), Review Manager 5.3 (methodological quality evaluation) (The Cochrane Collaboration, Copenhagen), and Stata 16.0 (network meta-analysis [NMA], heterogeneity assessment and inconsistency testing, surface under the cumulative ranking curve [SUCRA] plots) (Stata Corporation). The study was written according to the NMA extension for Priority Reporting Entry for Systematic Evaluation and Meta-Analysis (PRISMA). This study is registered with PROSPERO (registration number CRD42021233959).

Search strategies

Two reviewers searched independently in the following database: PubMed, Embase, Web of Science and Cochrane Library. Both mesh terms and free terms were used in the search. Details of search strategies are provided in [Supplementary Table-1 \(see Page 1\)](#).

Inclusion criteria

(1) Study population: patients ≥ 18 years of age with a diagnosis of OAB according to symptoms or urodynamic studies.

(2) Intervention: any drug approved for the treatment of OAB, or placebo as control, or ano-

ther drug for the treatment of OAB as control.

(3) Efficacy indicators: micturitions/d; incontinences/d; urgency episodes/d; urgency incontinences/d; nocturia episodes; mean voided volume/void.

(4) Safety indicators: dry mouth; constipation; nasopharyngitis; hypertension; cardiovascular AEs; urinary tract infection.

(5) Study type: randomized, controlled, double-blind trial with a follow-up period of ≥ 12 weeks.

Exclusion criteria

Trials without any access to full text (eg, conference abstracts, etc.), with incomplete data, lack of relevant outcome indicators, data not publicly available and duplicate publications were excluded. Studies with non-oral antimuscarinic or intravesical administrations were also excluded.

Literature screening and data extraction

(1) Literature Screening: the literature was screened using EndNote X8 software to electronically check the literature retrieved from the systematic search and the manual search to eliminate duplicate literature. Then, two investigators independently read the titles and abstracts of the literature to exclude those that did not meet the inclusion criteria. After that, the remaining literature was read further in full to exclude those that did not meet the inclusion criteria, and the reasons for exclusion were recorded. Finally, both sides cross-checked the included literature and jointly decided on the inclusion of the literature, and in case of disagreement, a third investigator was consulted to decide on the inclusion of the literature.

(2) Data extraction: data extraction was performed using Excel 2019 software, which included: authors and year of publication, sample size, interventions, baseline characteristics of the study population, and outcome indicators of the literature. Two researchers worked independently and discussed and resolved any disagreements or consulted a third researcher to decide. If incomplete information or disagreements were encountered in the literature study, the authors of the literature could be contacted for information.

Methodological quality evaluation

The risk of bias was assessed in the included literature using the Cochrane Risk of Bias Assessment Tool (10) in Review Manager 5.3 software, including seven aspects: random sequence generation, allocation concealment, blinding of investigators and subjects, blinded evaluation of study outcomes, completeness of outcome data, and selective reporting of study results and other biases. For each study element, the investigator made a risk of bias assessment profile according to “low risk”, “high risk” and “unclear”.

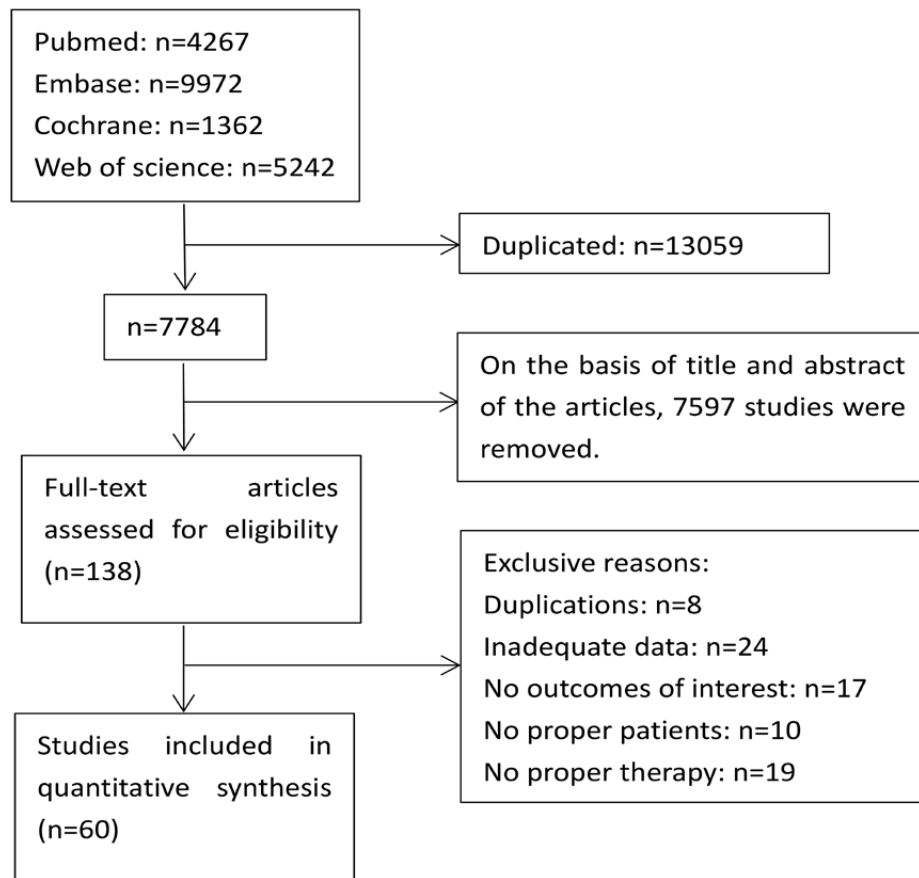
Statistical Analysis

We used the frequentist framework to perform a random effect network meta-analysis. The mean difference (MD) was used as an effect indicator for continuous variables, and odds ratio (OR) was used as an effect indicator for dichotomous variables. A 95% confidence interval (CI) was calculated for each effect size, and differences were considered statistically significant when $P < 0.05$. Uncertainty in the effect of heterogeneity was defined as the inconsistency between the CI of the relative treatment effect and its prediction interval (11). The global inconsistency model was used to assess the consistency of the entire network and was considered good at $p > 0.05$ (12). A loop-specific approach was used to assess the presence of local inconsistencies in each closed loop. The node splitting method was used to assess the inconsistency of the model with separating evidence on a particular comparison into direct and indirect evidence (13). Funnel plots were plotted to evaluate the presence of publication bias.

RESULTS

Study selection and basic characteristics

Through systematic search, 60 randomized, controlled, double-blind studies involving a total of 50,333 subjects were finally included. The literature search and screening process is shown in Figure-1, and the basic characteristics of the included studies are shown in Table-1.

Figure 1 - Flow Chart of Literature Search and Screening.

Evaluation of the quality of the included studies' literature

A total of 60 randomized, controlled, double-blind studies were included, including 7 four-arm studies, 18 three-arm studies and 35 double-arm studies. The overall risk of bias was generally low. The risk of bias was assessed as shown in [Supplementary Table-2 \(see Page 2\)](#).

Effectiveness indicators

Mean daily micturations

Forty-two RCTs (14-56) reported micturation's/d, including 2 studies in 4 arms, 12 studies in 3 arms and 30 studies in double arms, containing a total of 15 treatment measures and a total sample size of 32,317 cases (Figure-2). Initial overall inconsistency testing showed a p-value <0.05 and partial p-values <0.05 in ring inconsis-

tency, so subgroup regression analysis of the data according to the proportion of female patients showed that all inconsistency testing p-values were >0.05. For the subgroup with $\geq 50\%$ female, all interventions were significantly more effective than placebo compared to placebo, except for oxybutynin (OXY)5mg-TID, with SOL10mg-QD being the most effective and significantly better than the majority of interventions. For the subgroup with less than 50% women, SOL10mg-QD remained the most effective, with statistically significant differences in efficacy compared to propiverine (PRO) 20mg-QD, mirabegron (MIR) 50mg-QD, extended-release tolterodine (ER-TOL) 4mg-QD and PBO. Results of the NMA are reported in [Supplementary Table-3 \(see Page 5\)](#). Figure-3 shows the mean values of SUCRA for interventions on micturations.

Table 1 - Basic Characteristics of Included Study.

Study trial number	Study design	Country	Intervention	Population mean age	Female (%)	Numbers of patients (n)	Treatment duration (weeks)
Yoshida et al. (37) 2018 No. JapicCTI-152936	Phase IIb, RCT, double-blind, multicenter	Japanese	VIB 50mg, qd	58.0 ± 11.8	334 (90.3)	370	aged ≥ 20 years, patients experiencing OAB symptoms for ≥ 6 months
			VIB 100mg, qd	58.7 ± 11.1	330 (89.7)	368	
			PBO	58.9 ± 11.8	333 (90.2)	369	
			IMI 0.1mg, bid	59.7 ± 12.4	105 (89.7)	117	
Yamaguchi et al. (30) 2014a NCT00966004	Phase III, RCT, double-blind, multicenter	Japanese	MIR 50mg, qd	58.3 ± 13.88	58 (15.7)	379	aged ≥ 20 years, patients experiencing OAB symptoms for ≥ 24 weeks
			PBO	58.2 ± 14.18	58 (15.8)	379	
			TER 4 mg, qd	58.3 ± 13.96	64 (17.4)	375	
Yamaguchi et al. (38) 2014b NCT00527033	Phase II, RCT, double-blind, multicenter	Japanese	MIR 50mg, qd	56.2 ± 13.59	31 (14.9)	208	aged ≥ 20 years, patients experiencing OAB symptoms for ≥ 24 weeks
			PBO	55.7 ± 12.89	42 (19.9)	212	
Staskin et al. (43) 2020 NCT03492281	Phase III, RCT, double-blind, multicenter	Multinational	VIB 75mg, qd	63.0 ± 18.0	449 (85.4)	545	aged ≥ 18 years, patients experiencing OAB symptoms for ≥ 3 months
			PBO	61.0 ± 16.0	445 (85.6)	540	
			TER 4 mg, qd	61.0 ± 17.0	352 (84.4)	430	
Shin et al. (55) 2019	Phase IV, RCT, double-blind, multicenter	Korea	MIR 50mg, qd	66.40 ± 9.51	310 (100)	310	aged ≥ 20 years, patients experiencing OAB symptoms for ≥ 12 weeks
			PBO	65.23 ± 10.00	154 (100)	154	
Nitti et al. (40) 2013 NCT00662909	Phase III, RCT, double-blind, multicenter	United States and Canada	MIR 50mg, qd	59.2 ± 13.5	120 (27.1)	442	aged ≥ 18 years, patients experiencing OAB symptoms for ≥ 3 months
			PBO	60.1 ± 13.8	108 (23.8)	453	
Herschorn et al. (41) 2013 NCT00912964	Phase III, RCT, double-blind, multicenter	Europe and North America	MIR 50mg, qd	60.3 ± 12.22	137 (31.1)	440	aged ≥ 18 years, patients experiencing OAB symptoms for ≥ 3 months
			PBO	58.2 ± 13.73	132 (30.5)	433	
Kuo et al. (70) 2015 NCT01043666	Phase III, RCT, double-blind, multicenter	Taiwan, Korea, China, and India	MIR 50mg, qd	54.3 ± 14.21	110 (32.5)	366	aged ≥ 18 years, patients experiencing OAB symptoms for ≥ 3 months
			PBO	55.3 ± 13.63	98 (30.3)	366	
			TER 4 mg, qd	53.9 ± 14.50	120 (36.0)	371	
Khullar et al. (44) 2013 NCT00689104	Phase III, RCT, double-blind, multicenter	European–Australian	MIR 50mg, qd	59.1 ± 12.36	136 (27.6)	493	aged ≥ 18 years, patients experiencing OAB symptoms for ≥ 3 months
			MIR 100mg, qd	59.0 ± 12.71	141 (28.4)	496	
			PBO	59.2 ± 12.30	138 (27.9)	494	
			TER 4 mg, qd	59.1 ± 12.89	134 (27.1)	495	
Herschorn et al. (42) 2017 NCT01972841	Phase III, RCT, double-blind, multicenter	Multinational (42 countries)	MIR 50mg, qd	56.7 ± 13.3	99 (23.5)	422	aged ≥ 18 years, patients experiencing symptoms of wet OAB for ≥ 3 months
			PBO	57.9±13.0	102 (23.8)	429	
Chapple et al. (71) 2013 NCT00337090	Phase II, RCT, double-blind, multicenter	Multinational	MIR 50mg, qd	56.9 ± 12.5	18 (10.8)	169	aged ≥ 18 years, patients experiencing symptoms of OAB for ≥ 3 months
			PBO	57.1 ± 12.9	15 (9.0)	169	
			TER 4 mg, qd	56.6 ± 12.8	16 (18.8)	85	
Herschorn et al. (42) 2017 NCT01314872	Phase IIb, RCT, double-blind, multicenter	Multinational (18 countries)	MIR 50mg, qd	60.3 ± 8.7	129 (86.0)	150	aged ≥ 18 years and ≤ 75years, patients experiencing symptoms of OAB for ≥ 3 months
			PBO	57.8 ± 9.5	185 (90.2)	205	
			TER 4 mg, qd	58.5 ± 9.6	231 (89.9)	257	
Armstrong et al. (58) 2005	RCT, double-blind, multicenter	Multicenter	ER-OXY 10mg, qd	60 (18–92)	100%	391	aged ≥ 18 years, patients experiencing symptoms
			TER 4 mg, qd	60 (18–92)	100%	399	
Cardozo et al. (59) 2004	RCT, double-blind, multicenter	Multinational	SOL 5mg, qd	55.4 (13.8)	237 (82.9)	286	aged ≥ 18 years, patients experiencing symptoms of OAB for ≥ 3 months
			SOL 10mg, qd	55.9 (14.2)	238 (82.1)	290	
			PBO	56.1 (13.3)	227 (80.8)	281	

Chapple et al. (57) 2007a	RCT, double-blind, multicenter	Multinational	DAR 7.5/15 mg, qd	72 ± 5 (64–89)	206 (77.4)	266	aged ≥ 65 years with symptoms of OAB for at least 6 months
			PBO	73 ± 5 (64–87)	100 (75.2)	133	
Chapple et al. (60) 2014 NCT01302067	RCT, double-blind, multicenter	Multinational	FES 4 mg, qd	59.8 (21–94)	647 (82)	790	aged ≥ 18 years with OAB symptoms for ≥ 6 months
			FES 8 mg, qd	58.8 (18–89)	627 (80)	779	
			PBO	59.6 (19–85)	316 (82)	386	
Chapple et al. (15) 2007b	Phase III, RCT, double-blind, multicenter	Multinational	TER 4 mg, qd	57.7 ± 14.6	226 (78)	290	aged ≥ 18 years with OAB symptoms for ≥ 6 months
			FES 8 mg, qd	55.6 ± 14.1	223 (82)	272	
			FES 4 mg, qd	57.1 ± 13.2	232 (81)	287	
			PBO	56.0 ± 13.7	229 (81)	283	
Chapple et al. (61) 2005	RCT, double-blind, multicenter	European	SOL 5 mg/10mg, qd	56.5	493 (85.3%)	578	aged ≥ 18 years, patients experiencing OAB symptoms for ≥ 3 months
			TER 4 mg, qd	56.4	529 (88.3%)	599	
Chapple et al. (16) 2004	Phase IIIa, RCT, double-blind, multicenter	Multinational	SOL 5 mg, qd	58.1 (13.4)	194 (72.9)	266	aged ≥ 18 years, patients experiencing OAB symptoms for ≥ 3 months
			SOL 10 mg, qd	57.2 (13.4)	188 (71.2)	264	
			TER 2mg bid	56.9 (12.8)	200 (80.0)	250	
			PBO	57.8 (13.7)	193 (76.3)	253	
Choo et al. (17) 2008 NCT00189800	RCT, double-blind, multicenter	Korea	SOL 5 mg, qd	53.07 10.52	90 (84.11)	107	aged ≥ 18 years, patients experiencing OAB symptoms for ≥ 3 months
			SOL 10 mg, qd	52.65 (12.71)	83 (74.77)	111	
			TOL 2 mg, bid	53.05 (12.19)	88 (79.28)	111	
Chu et al. (20) 2009	Phase III, RCT, double-blind, multicenter	United States	SOL 10 mg, qd	59 (14)	272 (80.0)	340	aged ≥ 18 years with a diagnosis of OAB made by an investigator based on symptoms
			PBO	58 (13)	277 (83.4)	332	
Chua et al. (18) 2018 NCT01486706	RCT, double-blind, single center	Philippines	SOL 5 mg/10mg, qd	57.2 (9.36)	24 (77%)	31	18–79 years old, patients who are ambulatory, with defined history of OAB symptoms for ≥ 3 months
			PBO	53.9 (12.14)	23 (72%)	32	
Chuang et al. (19) 2020	RCT, double-blind, multicenter	Taiwan	IMI 0.1 mg, bid	59.84	23 (31.5%)	73	patients ≥ 20 years of age, with OAB symptoms for ≥ 3 months
			PBO	59.33	19 (48.7%)	39	
Diokno et al. (62) 2003	RCT, double-blind, multicenter	US	OXY 10 mg, qd	(23, 92)	100%	391	Women with OAB symptoms, aged 18 years and older
			TER 4mg, qd	(18, 85)	100%	399	
Dmochowski et al. (21) 2010	RCT, double-blind, multicenter	US	FES 4mg/8mg, qd	59.7 (13.7)	364 (83)	438	Aged ≥ 18 years patients experiencing OAB symptoms for ≥ 3 months
			PBO	60.1 (12.9)	368 (83)	445	
Dmochowski et al. (22) 2008	Phase III, RCT, double-blind, multicenter	US	TRO 60mg, qd	61.2 ± 0.7	230 (82.1)	280	Subjects aged 18 years or older with OAB of 6 months or longer duration
			PBO	58.4 ± 0.7	249 (87.7)	284	

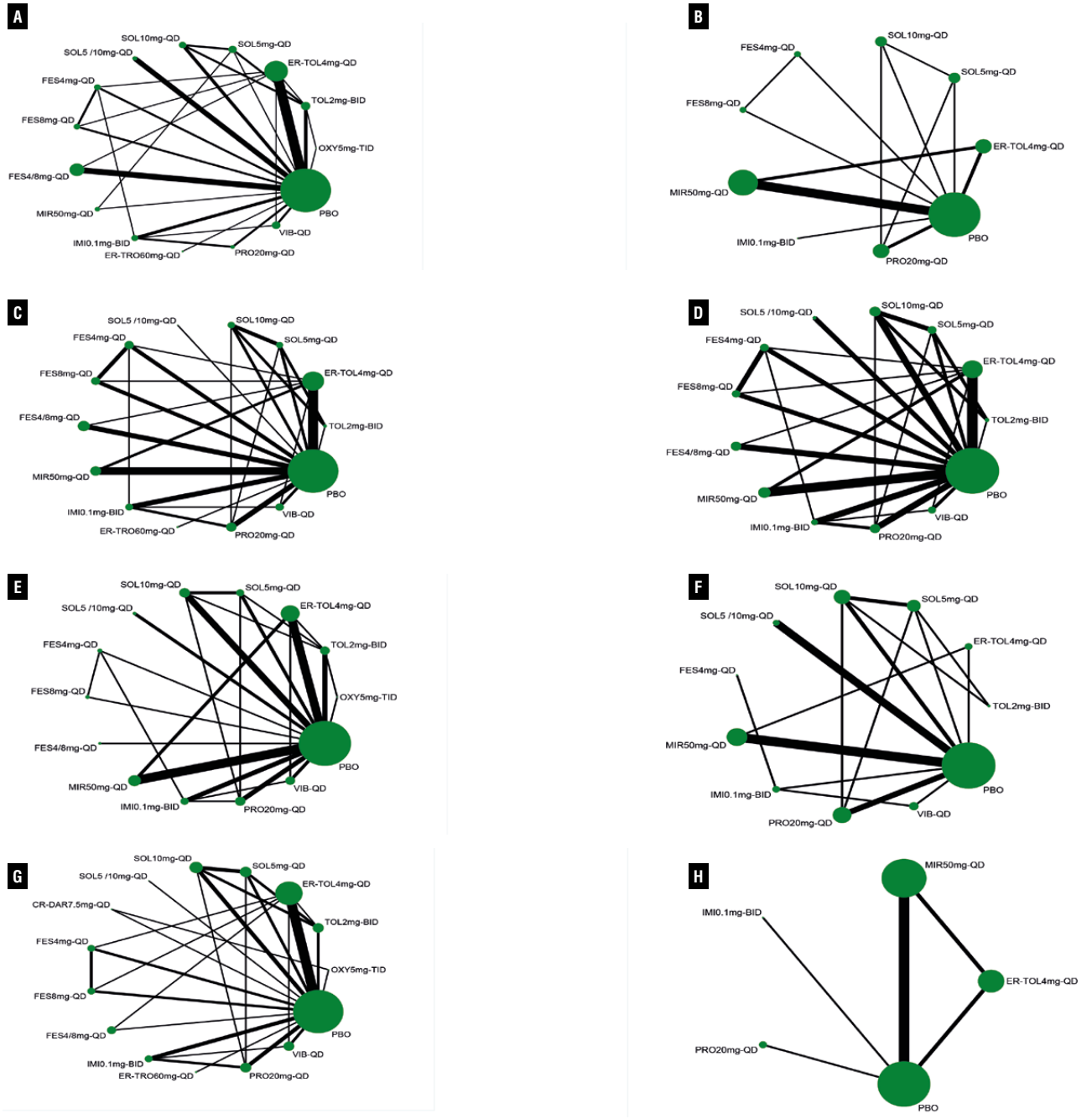
Drutz et al. (14) 1999	RCT, double-blind, multicenter	United States and Canada	TOL 2 mg, bid	63.0 (31–88)	88 (81)	109	aged ≥ 18 years, patients experiencing OAB
			OXY 5 mg, tid	66.3 (23–91)	81 (72)	112	
			PBO	62.1 (26–87)	45 (80)	56	
DuBeau et al. (23) 2014 NCT00928070	RCT, double-blind, multicenter	US	FES 4mg/8mg, qd	74.8 (65–91)	100%	103	65 years old or older with OAB symptoms for 3 or more months
			PBO	75.3 (65–90)	100%	77	
Ercan et al. (63) 2015	RCT, single center	Turkey	SOL 5 mg, qd	58.9 ± 11.5	UK	60	patients diagnosed with OAB
			FES 4 mg, qd	58.1 ± 10.258.1	UK	59	
Ginsberg et al. (64) 2013	RCT, double-blind, multicenter	Multinational	FES 4mg/8mg, qd	59.8 (14.3) 57.5 (13.0)	1374 (84)	1639	≥ 18 years old, had self-reported OAB symptoms for ≥ 3 months
			TER 4mg, qd	60.8 (14.1) 57.8 (13.4)	1382 (83)	1657	
			PBO	61.8 (13.9) 58.5 (13.2)	679 (84)	812	
Gotoh et al. (24) 2011	Phase III, RCT, double-blind, multicenter	Japan	PRO 20 mg, qd	56.6 (13.6)	216 (76.1)	284	≥ 20 years old with OAB symptoms for at least 12 weeks
			PBO	58.7 (14.1)	207 (76.7)	270	
Govier et al. (30) 2010	Phase III, RCT, double-blind, multicenter	US	SOL 10 mg, qd	60 ± 13	261 (82)	318	Aged ≥ 18 years with OAB symptoms
			PBO	59 ± 13	259 (82)	316	
Herschorn et al. (41) 2013 NCT01767519	Phase IIIb, RCT, double-blind, multicenter	North America and Europe	SOL 5 mg/10mg, qd	61.4 ± 12.8	134 (88.7)	151	Adults with symptoms of patients diagnosed OAB for ≥ 6 months
			PBO	62.9 ± 11.8	51 (85.0)	60	
Homma et al. (53) 2003	RCT, double-blind, multicenter	Japan and Korea	TER 4 mg, qd	61.2 (11.8)	162 (68)	239	aged ≥ 20 years with symptoms of OAB for ≥ 6 months
			OXY 3 mg, qd	57.9 (12.5)	177 (73)	244	
			PBO	58.4 (14.0)	84 (69)	122	
Homma et al. (25) 2009	Phase III, RCT, double-blind, multicenter	Japan	IMI 0.1 mg, bid	57.7 (12.7)	278 (87.4%)	324	≥ 20 years, who had OAB symptoms
			PRO 20 mg, qd	59.8 (11.9)	257 (84.3%)	310	
			PBO	58.0 (13.5)	125 (87.4%)	147	
Homma et al. (26) 2008	Phase II, RCT, double-blind, multicenter	Japan	IMI 0.1 mg, bid	64.5 (13.5)	63 (67.7)	93	≥ 20 years, who had OAB symptoms
			PBO	61.9 (11.8)	69 (72.6)	95	
Kaplan et al. (45) 2014 NCT01302054	RCT, double-blind, multicenter	Europe, North America, Asia, and Africa	FES 4mg/8mg, qd	57.3 (13.4)	253 (82)	308	aged ≥ 18 years, self-reported OAB symptoms for ≥ 6 months
			PBO	58.2 (13.2)	244 (81)	301	
Karram et al. (32) 2009 NCT00454896	Phase IIIb, RCT, double-blind, multicenter	USA	SOL 5 mg/10mg	57	84.20%	372	age 18 or older, OAB for at least 3 months
			PBO	57	84.20%	367	

Lee et al. (28) 2013 NCT01578304	Phase IV, RCT, double-blind, multicenter	Korean	IMI 0.1 m, bid	57.94 ± 10.81	57.94 ± 10.81	104	aged ≥ 20 years, with OAB symptom for ≥ 3 months
			FES 4 mg, qd	57.63 ± 12.63	57.63 ±12.63	102	
Nitti et al. (46) 2007	Phase III, RCT, double-blind, multicenter	US	FES 4 mg, qd	59 (21–85)	213 (76)	282	18 years or older with OAB syndrome for 6 months or greater
			FES 8 mg, qd	59 (23–91)	218 (78)	279	
			PBO	59 (24–88)	200 (74)	271	
Park et al. (47) 2014	Phase III, RCT, double-blind, multicenter	Korea	IMI 0.1 m, bid	58.31 ± 11.45	57 (85.07)	82	OAB patients aged ≥ 19 years for ≥ 3 months.
			PRO 20mg, qd	56.13 ± 11.29	55 (85.94)	80	
Rudy et al. (66) 2006	Phase III, RCT, double-blind, multicenter	US	TRO 40 mg, qd	61.1 ± 0.69	267 (81.2)	329	18 years or older with OAB symptoms for at least 6 months.
			PBO	61.0 ± 0.70	269 (81.8)	329	
Sand et al. (67) 2004	RCT, double- blind, multicenter	US	ER-OXY 10 mg, qd	58.4	100%	152	Participants with overactive bladder
			TOL 2mg, bid	58.8	100%	163	
Vardy et al. (33) 2009 NCT00573508	Phase IV, RCT, double-blind, multicenter	US	SOL 5 mg/10mg, qd	59 ± 13	306 (81)	377	(aged ≥ 18 years) were required to have OAB symptoms for ≥ 3 months
			PBO	60 ± 12	314 (84)	374	
Wagg et al. (34) 2013 NCT00798434	RCT, double- blind, multicenter	Multinational	FES 4mg/8mg, qd	72.6 ± 5.8	213 (54)	392	aged 65 and older with OAB symptoms for 3 months or longer
			PBO	72.8 ± 5.7	205 (52)	393	
Weiss et al. (50) 2013 NCT00911937	RCT, double- blind, multicenter	US	FES 4mg/8mg, qd	58.0 ± 14.7	313 (67.6)	463	age 18 years or older with self-reported OAB symptoms for 3 or more months
			PBO	57.5 ± 14.0	312 (65.8)	474	
Yamaguchi et al. (29) 2007	Phase III, RCT, double-blind, multicenter	Japan	SOL 5 mg, qd	60.4 (13.3)	318 (83.0)	398	aged ≥ 20 years and with symptoms of OAB reported for ≥ 6 months
			SOL 10 mg, qd	59.9 (13.0)	318 (85.7)	381	
			PRO 20 mg, qd	59.6 (13.6)	321 (83.6)	400	
			PBO	60.8 (12.5)	333 (84.3)	405	
Yamaguchi et al. (27) 2011 NCT00561951	Phase II, RCT, double-blind, multicenter	Japan, Taiwan, Korea, and Hong Kong	FES 4 mg, qd	57.2 (14.2)	251 (78.4)	320	≥ 20 years of age; a medical history of OAB symptoms for ≥ 6 months
			FES 8 mg, qd	58.8 (13.4)	255 (81.5)	313	
			PBO	56.7 (13.5)	251 (78.9)	318	
Yamaguchi et al. (38) 2014b JapicCTI-101309	RCT, double- blind, multicenter	Japan	PRO 20 mg, qd	55.6 (12.5)	478 (85.5)	576	Age ≥ 20 years, OAB symptoms for ≥ 24 weeks
			PBO	56.2 (13.2)	344 (92.2)	381	
Zinner et al. (68) 2004	Phase III, RCT, double-blind, multicenter	US	TRO 20 mg, qd	63 ± 0.8	203 (77.5)	256	aged ≥ 18 years with a history of OAB for ≥ 6 months
			PBO	61.5 ±0.8	186 (71.3)	256	

Zinner et al. (69) 2006	RCT, double-blind, single center	US	DAR 15 mg, qd	59.1 (20–93)	185 (86.4)	214	aged ≥ 18 years with a history of OAB for ≥ 6 months
			PBO	59.1 (18–89)	198 (88.0)	225	
Dmochowski et al. (54) 2003	RCT, double-blind, multicenter	UK	ER-TOL 4mg, qd	62.9[13.5]	117 (95.1)	123	at least 18 years of age taking current pharmacologic treatment for OAB
			PBO	64.5 [12.3]	109 (93.2)	117	
Haab et al. (72) 2004	RCT, double-blind, multicenter	Multinational	DAR 7.5 mg, qd	57.7 (22–88)	194 (84.7)	229	(aged 19–88 years, 85% female) who had suffered from symptoms of OAB for at least 6 months
			DAR 15 mg, qd	56.6 (24–81)	100 (87.0)	115	
			PBO	56.5 (19–81)	138 (84.1)	164	
Herschorn et al. (49) 2008 NCT00143377	RCT, double-blind, multicenter	Multinational	ER-TOL 4 mg, qd	58 (13)	290 (72)	408	aged ≥ 18 years with a history of OAB for ≥ 3 months
			PBO	57 (14)	143 (71)	204	
Hill et al. (73) 2006	RCT, double-blind, multicenter	Multinational	DAR 7.5 mg, qd	56.1 (23–88)	94 (87.04)	108	aged ≥ 18 years with a history of OAB for ≥ 6 months
			DAR 15 mg, qd	55.1 (24–82)	92 (85.98)	107	
			PBO	53.7 (21–85)	90 (82.57)	109	
Kaplan et al. (48) 2011 NCT00611026	RCT, double-blind, multicenter	Multinational	ER-TOL 4 mg, qd	58.1 (13.8)	818 (84)	960	(≥ 18 years) self-reported OAB symptoms for ≥ 3 months
			FES 4mg/8mg, qd	57.9 (13.5)	816 (85)	973	
			PBO	59.5 (13.2)	410 (86)	478	
Van Kerrebroeck et al. (35) 2001	RCT, double-blind, multicenter	Australasia, Europe and North America	ER-TOL 4 mg, qd	60 (20–89)	417(82.25)	507	aged ≥ 18 years with a history of OAB for ≥ 6 months
			TOL2 mg, bid	60 (22–92)	408(79.38)	514	
			PBO	61 (22–93)	410(80.71)	508	
Rogers et al. (51) 2008 NCT00143481	RCT, double-blind, multicenter	US	ER-TOL 4 mg, qd	49 (12)	100%	202	aged ≥ 18 years with OAB symptoms for ≥ 3 months
			PBO	47 (12)	100%	211	
Zinner et al. (36) 2002	RCT, double-blind, multicenter	Europe, United States, Canada, Australia, and New Zealand	ER-TOL 4 mg, qd	51 ± 10.5	417 (82.25)	507	aged ≥ 18 years with OAB symptoms for ≥ 6 months
			PBO	74 ± 6	410 (80.71)	508	
Batista et al. (56) 2015	Phase III, RCT, double-blind, multicenter	Multinational	MIR 50 mg, qd	56.7 (14.3)	712 (76.1)	936	aged ≥ 18 years old, with symptoms of OAB for ≥ 3 months
			SOL 5 mg, qd	57.4 (13.6)	709 (75.9)	934	

Abbreviations: OXY = Oxybutynin; ER-OXY = Oxybutynin chloride extended-release; TOL = tolterodine; ER-TOL = extended-release tolterodine; SOL = solifenacin; CR-DAR = darifenacin extended-release; FES = fesoterodine; IMI = imidafenacin; PRO = propiverine; TRO = trospium chloride; VIB = vibegron; MIR = mirabegron; PBO = placebo

Figure 2 - Evidence Network Plot for Micturitions with Female Proportion >50% (A), Micturitions with Female Proportion ≤50% (B), Incontinence (C), Urgency (D), Urgency Incontinence (E), Nocturia (F), Voiced Volume/micturition with Female Proportion >50% (G), Voiced Volume/micturition with Female Proportion ≤ 50%. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible randomized controlled trials. The width of the lines represents the cumulative number of randomized controlled trials for each pairwise comparison, and the size of every node is proportional to the number of randomized participants (sample size).



Mean daily incontinence episodes

Twenty-three RCTs (14-16, 25-44) reported incontinence episodes/d, including two 4-arm studies, eight 3-arm studies and 14 two-arm studies, comprising a total of 14 treatment measures and a total sample size of 15,632 cases (Figure-2). Among these studies, since the inclusion criteria for the Dmochowski 2003 et al. (54). study was “patients at least 18 years of age taking current pharmacologic treatment for OAB”, this study had significant clinical heterogeneity with other study populations, and the data were analyzed after excluding this study. The results showed that SOL10mg-QD was the most effective, followed by SOL5mg-QD and SOL5/10mg-QD. Results of the NMA are reported in [Supplementary Table-4 \(see Page 7\)](#). Figure-3 shows the mean values of SUCRA for interventions on micturitions.

Mean daily urgency episodes

Thirty-one RCTs (15-20, 23-34, 37-49) reported urgency episodes/d, including three 4-arm studies, nine 3-arm studies and 19 two-arm studies, containing a total of 13 treatment interventions and a total sample size of 23,764 cases (Figure-2). The results suggested that SOL5/10mg-QD was significantly more effective than other interventions in reducing the number of urinary urgency episodes, followed by SOL10mg-QD and SOL5mg-QD; while compared to placebo, TOL2mg-BID, VIB-QD, fesoterodine (FES) 4mg-QD, imidafenacin (IMI) 0.1mg-BID, MIR50mg-QD and ER-TOL4mg-QD's efficacy was improved, but the difference was not statistically significant. Results of the NMA are reported in [Supplementary Table-5 \(see Page 9\)](#). Figure-3 shows the mean values of SUCRA for interventions on micturitions.

Mean daily urgency incontinence episodes

Twenty-nine RCTs (15-19, 22-30, 37-51) reported urgency episodes/d, including three 4-arm studies, eight 3-arm studies and 18 two-arm studies, containing a total of 14 treatment measures and a total sample size of 17,859 cases (Figure-2). The results showed that FES8mg-QD was the most effective in reducing mean daily urgency incontinence episodes, followed by SOL10mg-QD, with no statistically significant difference between the

two, but both showed significant improvements in efficacy compared to most other interventions. FES8mg-QD was significantly more effective than FES4mg-QD and FES4/8mg-QD; while the difference in efficacy between SOL10mg-QD and SOL5mg-QD and SOL5/10mg-QD was not statistically significant. All interventions were significantly more effective than placebo and the differences were statistically significant, except for TOL2mg-BID which showed no significant improvement in efficacy differences compared to placebo. Results of the NMA are reported in [Supplementary Table-6 \(see Page 11\)](#). Figure-3 shows the mean values of SUCRA for interventions on micturitions.

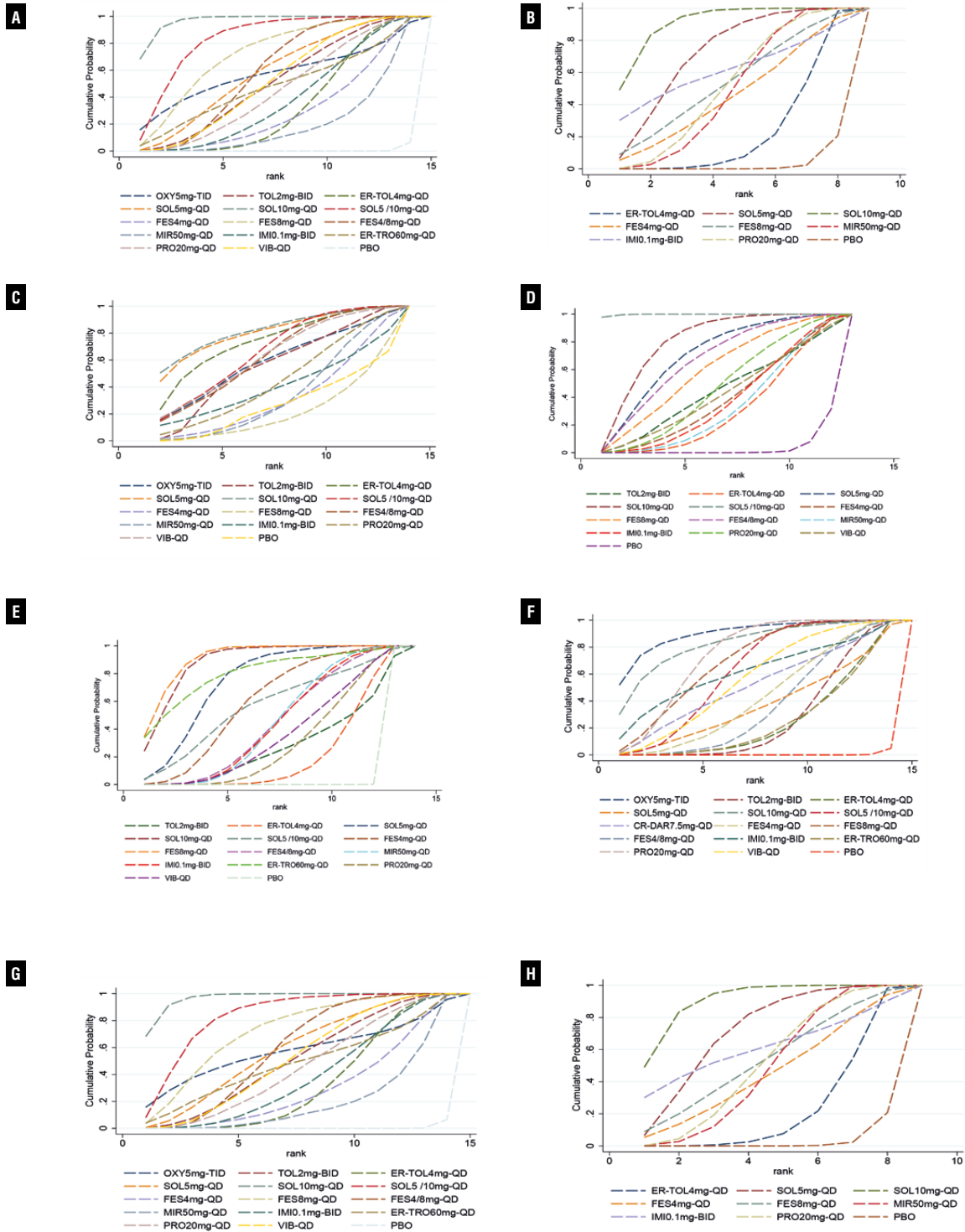
Mean daily nocturia episodes

Fifteen RCTs (17,18,24, 28-31,33, 37-42, 52) reported nocturia episodes/d, including one 4-arm study, three 3-arm studies and 12 two-arm studies, containing a total of 11 treatment interventions and a total sample size of 9,426 cases (Figure-2). The results showed that all interventions, except TOL2mg-BID, ER-TOL4mg-QD and FES4mg-QD, had significantly improved efficacy compared to placebo, and SOL5/10mg-QD had the best efficacy, followed by SOL10mg-QD and IMI0.1mg-BID. Results of the NMA are reported in [Supplementary Table-7 \(see Page 13\)](#). Figure-3 shows the mean values of SUCRA for interventions on nocturia.

Voided volume per micturition

Twenty-seven RCTs (14-19, 22, 24-26, 29-31, 35-38, 40-44, 46-48, 53, 54) reported voided volume per micturition, including three 4-arm studies, ten 3-arm studies, and fourteen two-arm studies containing 11 treatment measures with a total sample size of 9,426 cases (Figure-2). Initially, subgroup regression analysis was performed due to inconsistencies. The results showed a global inconsistency of p -value > 0.05 after subgroup analysis according to the percentage of females. In the subgroup with $\geq 50\%$ female, OXY5mg-TID had the best efficacy, followed by SOL10mg-QD and PRO20mg-QD, a result consistent with the initial overall results. In the subgroup with $< 50\%$ female representation, ER-TOL4mg-QD, MIR50mg-QD and PRO20mg-QD were significant-

Figure 3 - SUCRA Plot for Micturitions with Female Proportion >50% (A), Micturitions with Female Proportion ≤50% (B), Incontinence (C), Urgency (D), Urgency Incontinence (E), Nocturia (F), Voided Volume/micturition with Female Proportion >50% (G), Voided Volume/micturition with Female Proportion ≤ 50% (H). (SUCRA: surface under the cumulative ranking curve. The larger the surface area, the higher the ranking).



tly more efficacious than the placebo group, with only the IMIO.1 mg-BID group shared no significant difference with the placebo group. In contrast, compared to the placebo, IMIO.1mg-BID in the subgroup with $\geq 50\%$ female and the initial overall outcome posed a significant difference in efficacy. Results of the NMA are reported in [Supplementary Table-8 \(see Page 15\)](#). Figure-3 shows the mean values of SUCRA for interventions on voided volume per micturition.

Safety outcomes

Fifty-five RCTs (14, 16-18, 20-31, 33-41, 43-53, 56-73) reported dry mouth, and to exclude nocebo effect on study outcomes, two articles (14, 25) with significantly higher data in the placebo group than in other studies were excluded. Therefore, two 4-arm studies, 17 three-arm studies, and 34 two-arm studies, containing a total of 19 treatment measures and a total sample size of 45,756 cases, were considered (Figure-4). The results showed that the interventions with the lowest incidence of dry mouth were VIB-QD, MIR50mg-QD and PBO respectively. Constipation was reported in 50 RCTs, including two 4-arm studies, 18 three-arm studies, and 30 two-arm studies, containing a total of 19 treatment measures and a total sample size of 45,674 cases. The incidence of constipation was not significantly higher for FES4mg-QD, ER-OXY10mg-QD, TOL2mg-BID, and VIB-QD compared with placebo, while the incidence of constipation was higher for the remaining interventions than for the placebo group. A total of nine interventions were included for hypertension, of which only IMIO.1 mg-BID caused a significant difference in the incidence of hypertension compared with placebo and other treatments, and the remaining seven were not significantly different compared with placebo. For headache, 17 interventions were included, and only FES4/8mg-QD and CR-DAR-15mg-QD were found to exhibit a significantly higher incidence compared to placebo. A total of 18 interventions were included for urinary tract infections, and their incidence with only SOL10mg-QD differed statistically significantly from placebo. Figure-5 shows the mean values of SUCRA for interventions on AEs. Results of the NMA are reported in [Supplementary Tables 9-14 \(see Page](#)

[17-30\)](#). Figure-6 shows the mean values of SUCRA for interventions on safety outcomes.

Inconsistency and heterogeneity check

Initially, in improving mean daily micturition's and voided volume per micturition, overall inconsistency testing showed inconsistency (P value < 0.05) and inconsistency in individual rings (95% CIs not including 1), and subgroup analysis based on race, duration of disease, and other factors did not reveal significant improvement. Therefore, subgroup regression analysis of the data according to the proportion of female patients showed that the overall inconsistency and ring inconsistency p values were >0.05. In terms of reducing mean daily incontinence episodes, sensitivity analysis showed that the study by Dmochowski 2003 et al. (54). was significantly different from other studies, considering that the inclusion criteria for the study were "patients at least 18 years of age taking current pharmacologic treatment for OAB". Therefore, this study showed significant clinical heterogeneity with other study populations in the efficacy index of reduction in the number of incontinence episodes. Thus, analysis of the data upon excluding this study would show no inconsistency. The global inconsistency model showed well with $p > 0.05$ (Figures 6-8). The result of local inconsistency showed that most loops were consistent according to the 95%CI. The test for inconsistency using node-splitting model revealed no significant difference between direct and indirect comparisons ($P > 0.05$).

Publication bias

A funnel plot was established to assess the publication bias. There was no significant evidence of publication bias for outcomes based on a Begg funnel plot (Figure-9).

DISCUSSION

OAB is a chronic syndrome that is not life-threatening and does not progress to uncontrollable functional impairment but has serious impacts on the patient's quality of life. Therefore, current research is increasingly focused on the impact of interventions on the quality of life of patients

Figure 4 - Evidence Network Plot for Dry Mouth (A), Constipation (B), Nasopharyngitis (C), Hypertension (D), Urinary Tract Infection (E), Headache (F). Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible randomized controlled trials. The width of the lines represents the cumulative number of randomized controlled controlled trials for each pairwise comparison, and the size of every node is proportional to the number of randomized participants (sample size).

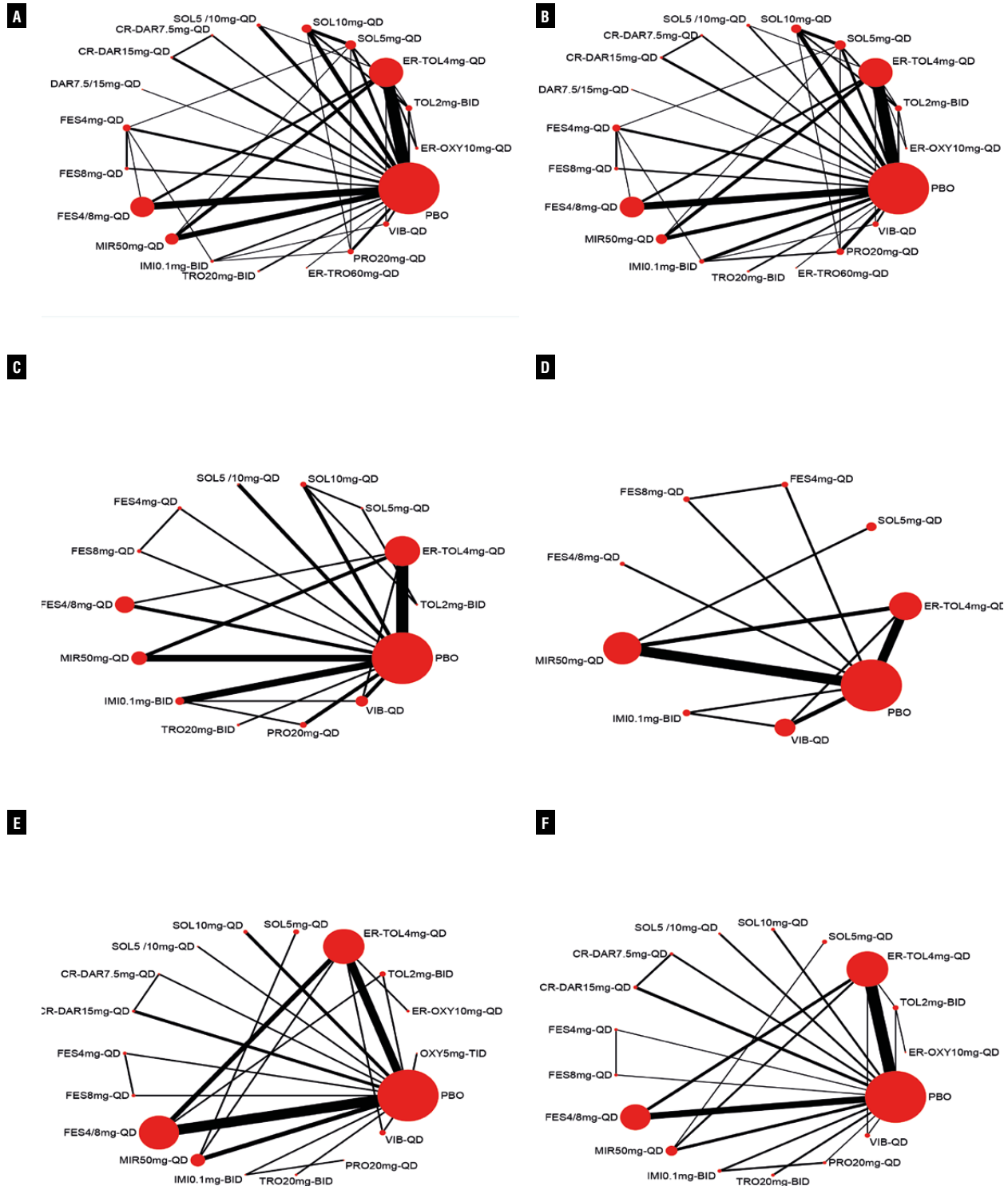
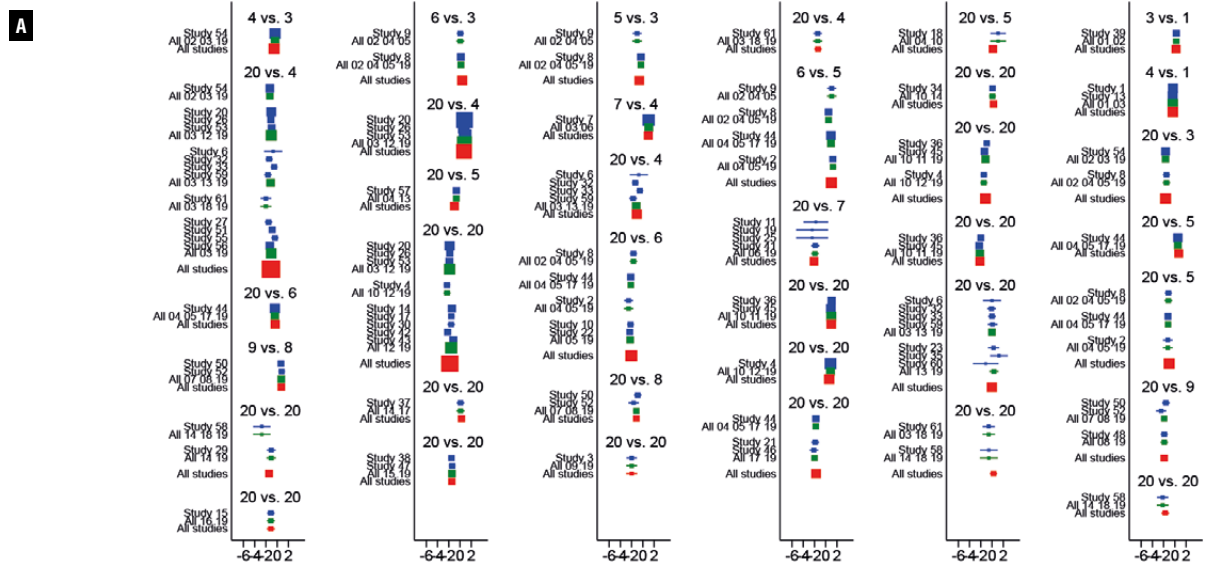
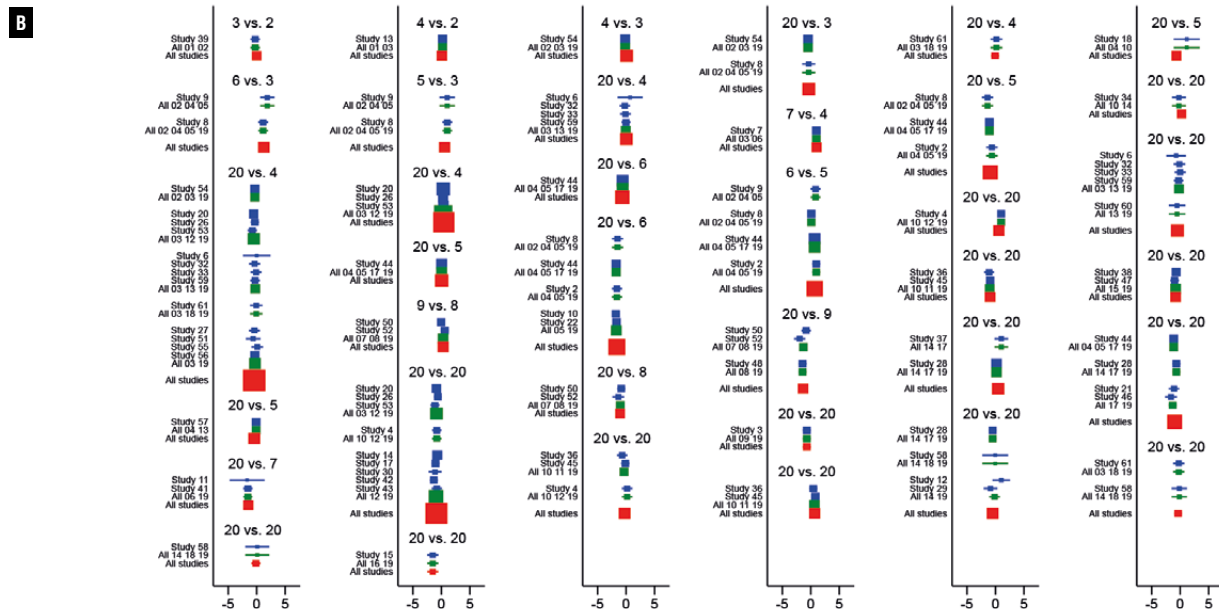


Figure 5 - NMA Forest Plot for Dry Mouth (A), Constipation (B), Nasopharyngitis (C), Hypertension (D), Urinary Tract Infection (E), Headache (F). (The consistency of the entire network and was considered good at $p > 0.05$).

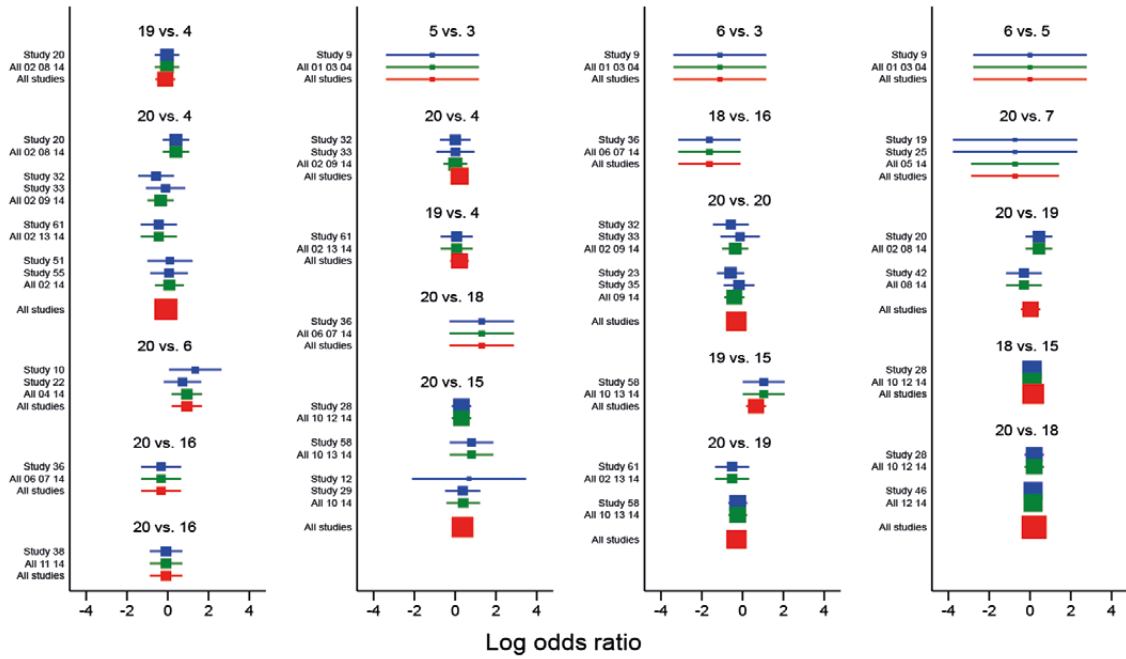


Test of consistency: $\chi^2(26)=30.75, P=0.238$



Test of consistency: $\chi^2(28)=19.90, P=0.868$

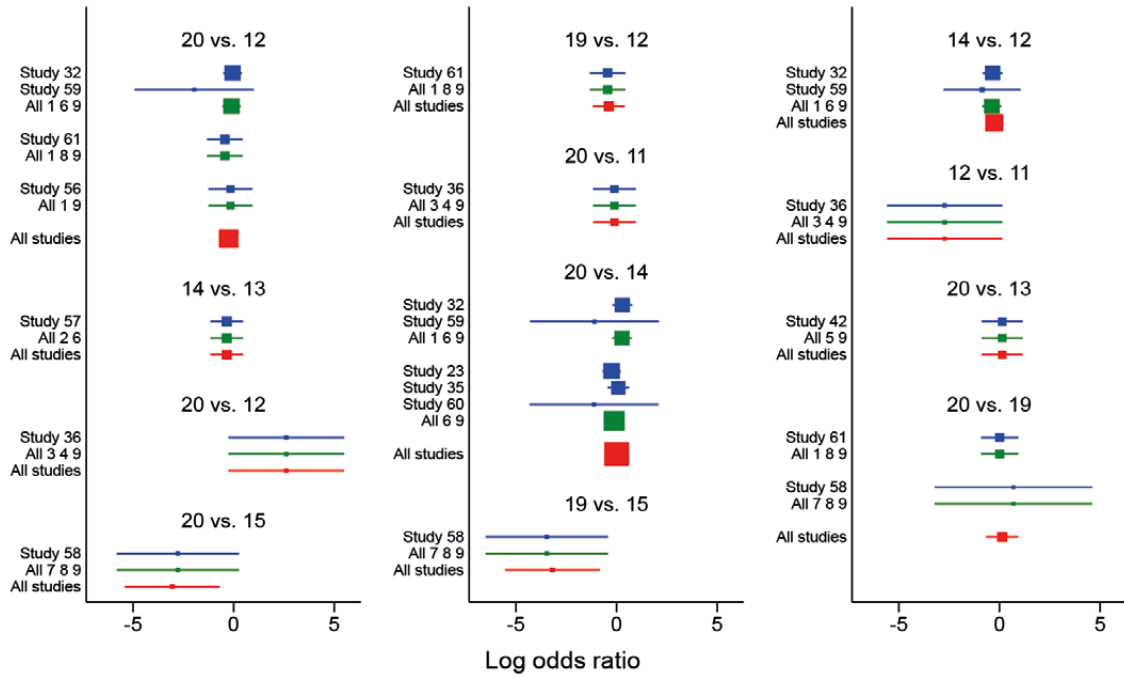
C



■ Studies ■ Pooled within design ■ Pooled overall

Test of consistency: $\chi^2(9)=5.50, P=0.788$

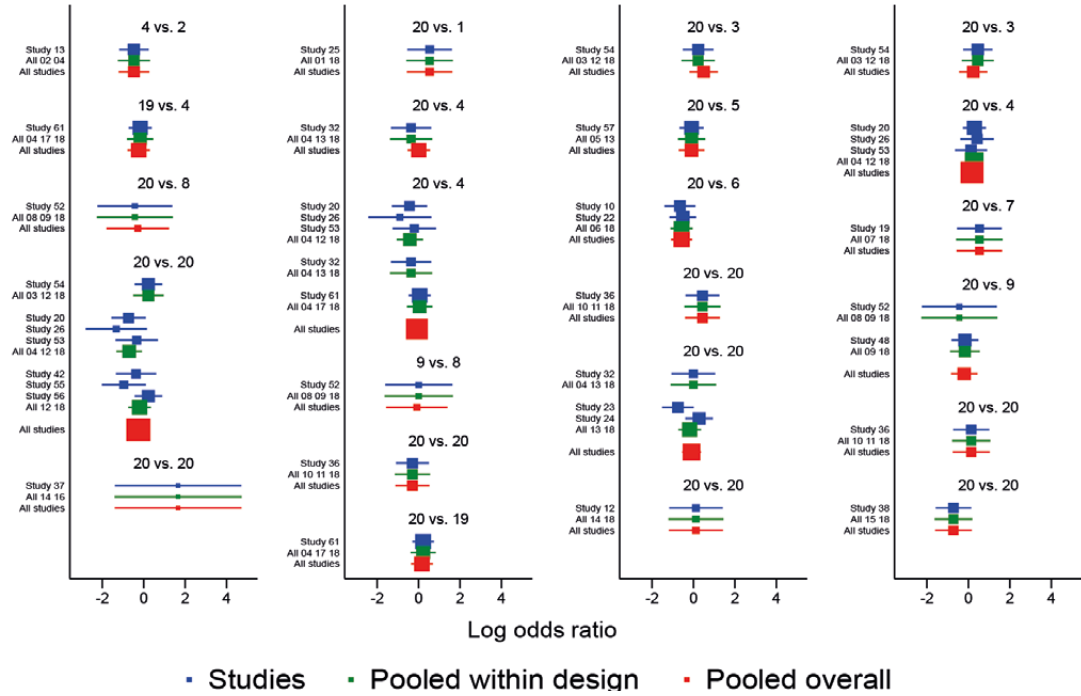
D



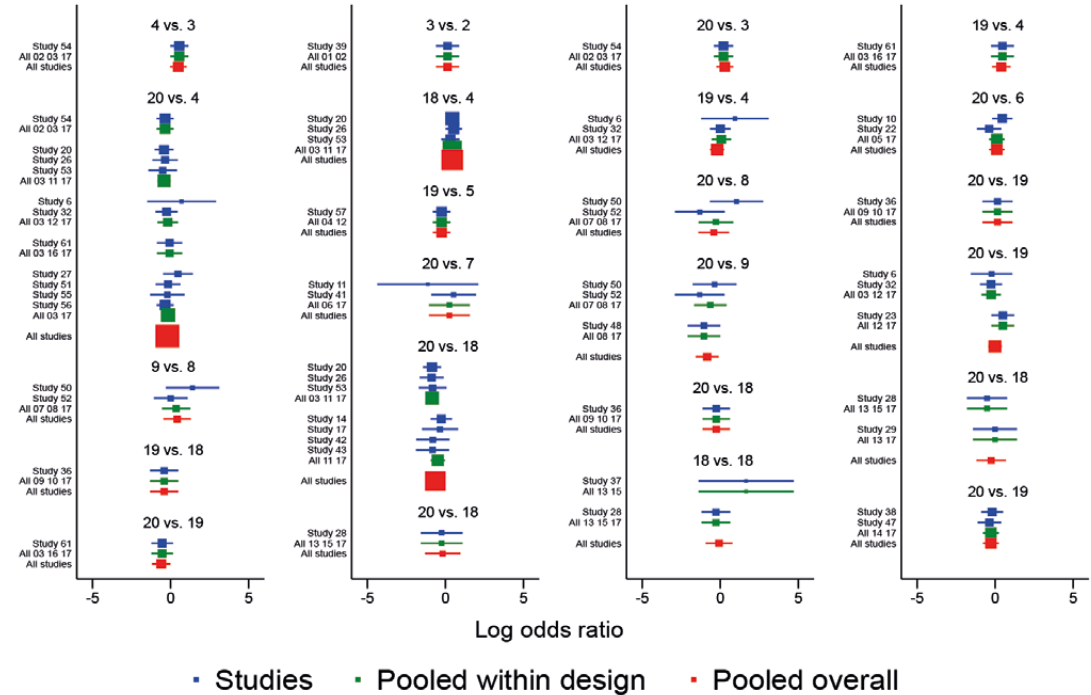
■ Studies ■ Pooled within design ■ Pooled overall

Test of consistency: $\chi^2(4)=1.96, P=0.744$

E

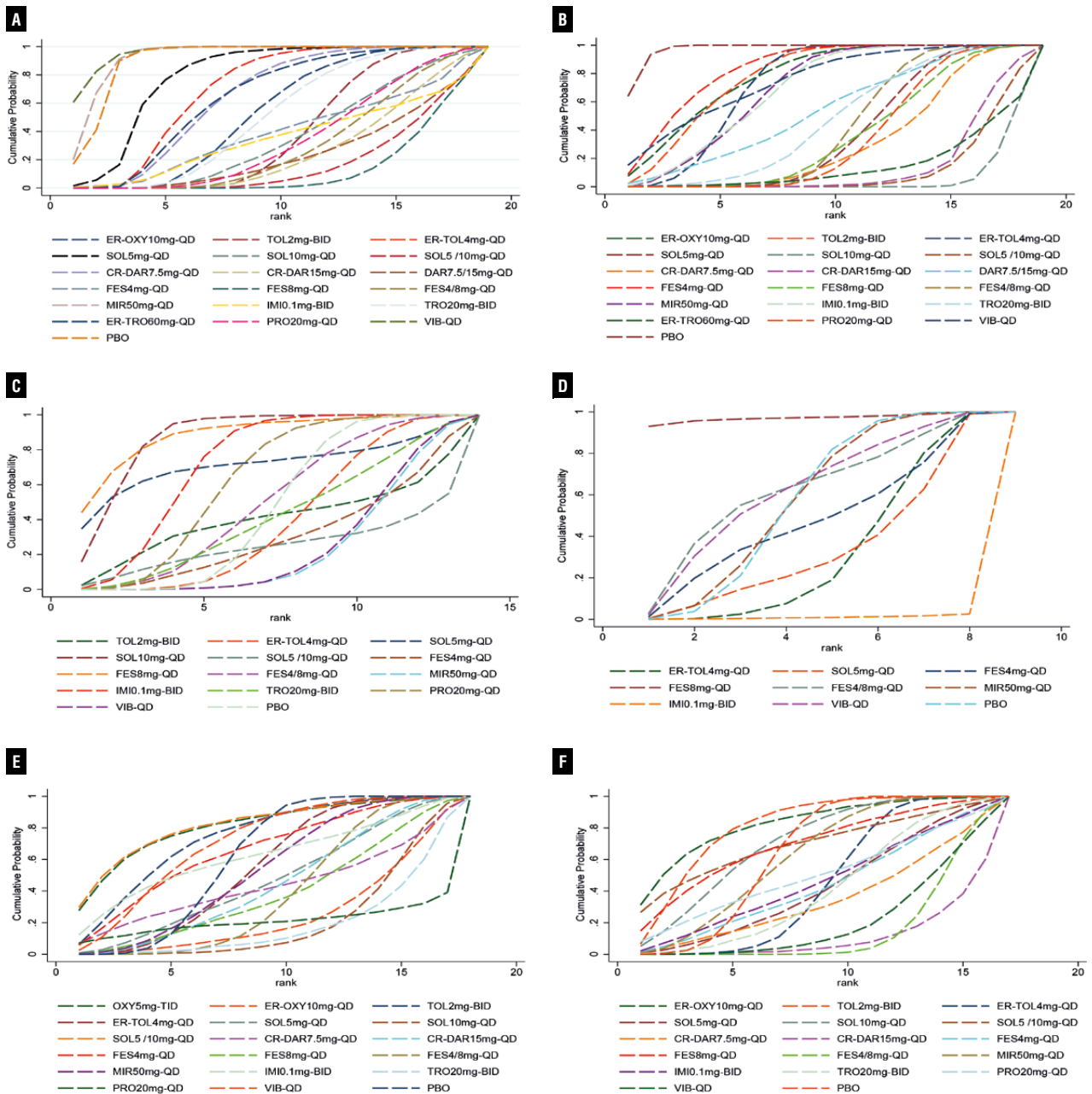


F



Test of consistency: $\chi^2(9)=6.59, P=0.680$

Figure 6 - SUCRA Plot for Dry Mouth (A), Constipation (B), Nasopharyngitis (C), Hypertension (D), Urinary Tract Infection (E), Headache (F). (SUCRA: surface under the cumulative ranking curve. The larger the surface area, the higher the ranking).

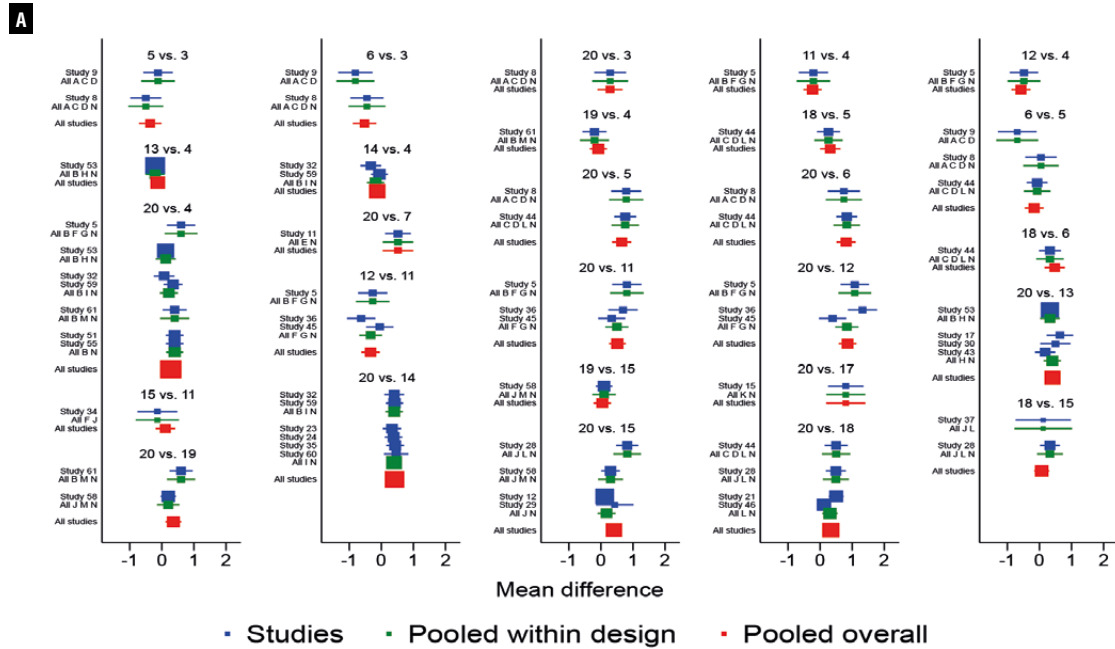


with OAB. For OAB treatment, improving patients' symptoms and reducing the incidence of adverse events are equally important for improving patients' quality of life and treatment compliance. This study aims to compare the therapeutic effects of different interventions in terms of efficacy and safety, and to identify the advantages and disadvantages of different drugs in the process of clinical

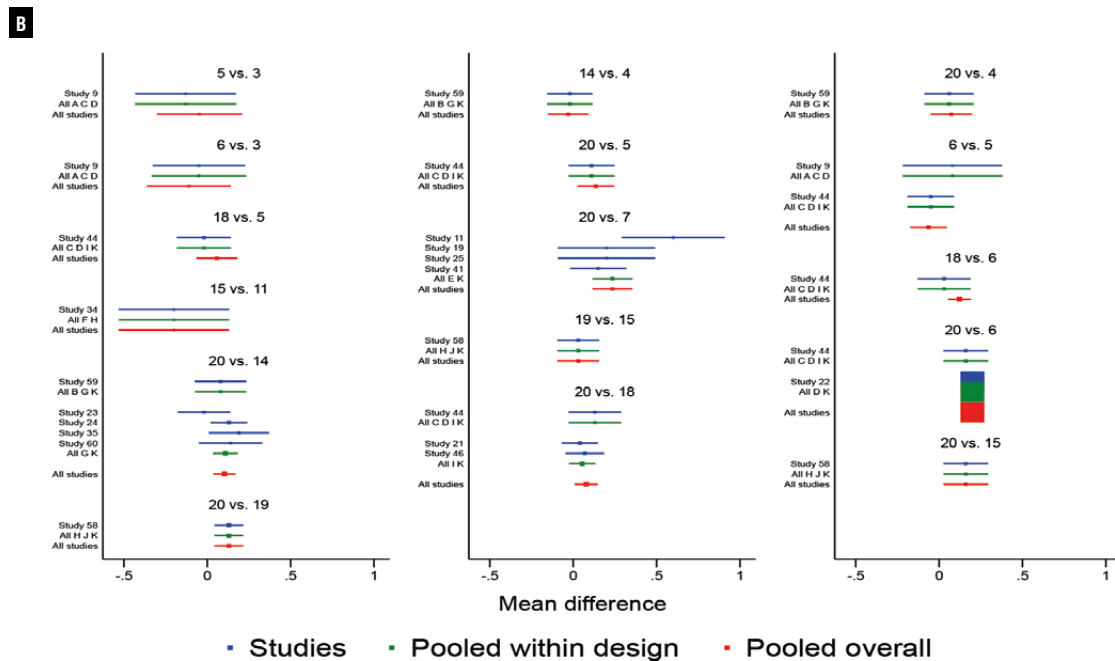
application, so as to provide more direct data support for the individualized treatment and drug use of different patients in the clinic.

Ten OAB therapeutic agents were included in this study, involving a total of 19 interventions grouped by different doses administered, and the NMA results show that solifenacin had a relatively good overall efficacy and a significant

Figure 7 - NMA Forest Plot for Urgency Incontinence (A), Nocturia (B), Voided Volume/micturition with Female Proportion >50% (C), Voided Volume/micturition with Female Proportion ≤50% (D). (The consistency of the entire network and was considered good at $p > 0.05$.)

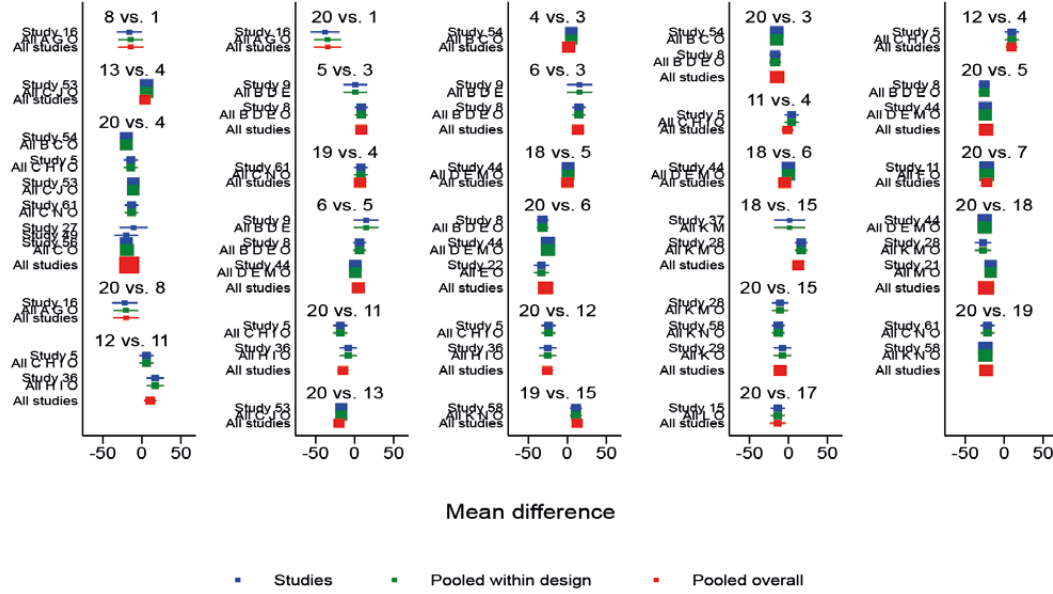


Test of consistency: $\chi^2(19)=16.37, P=0.632$



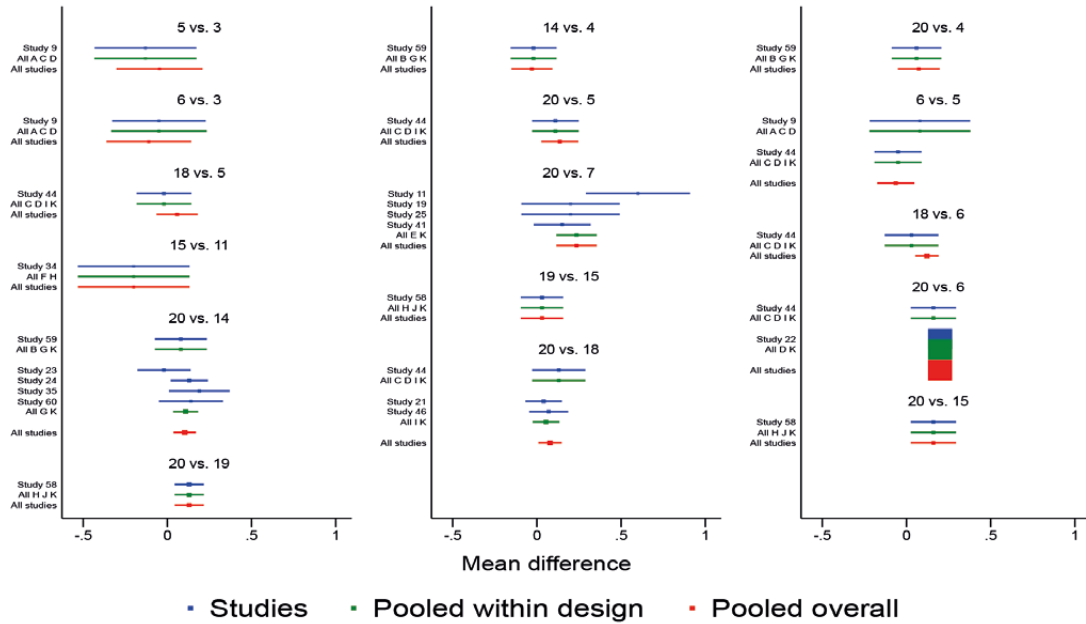
Test of consistency: $\chi^2(4)=2.76, P=0.599$

C



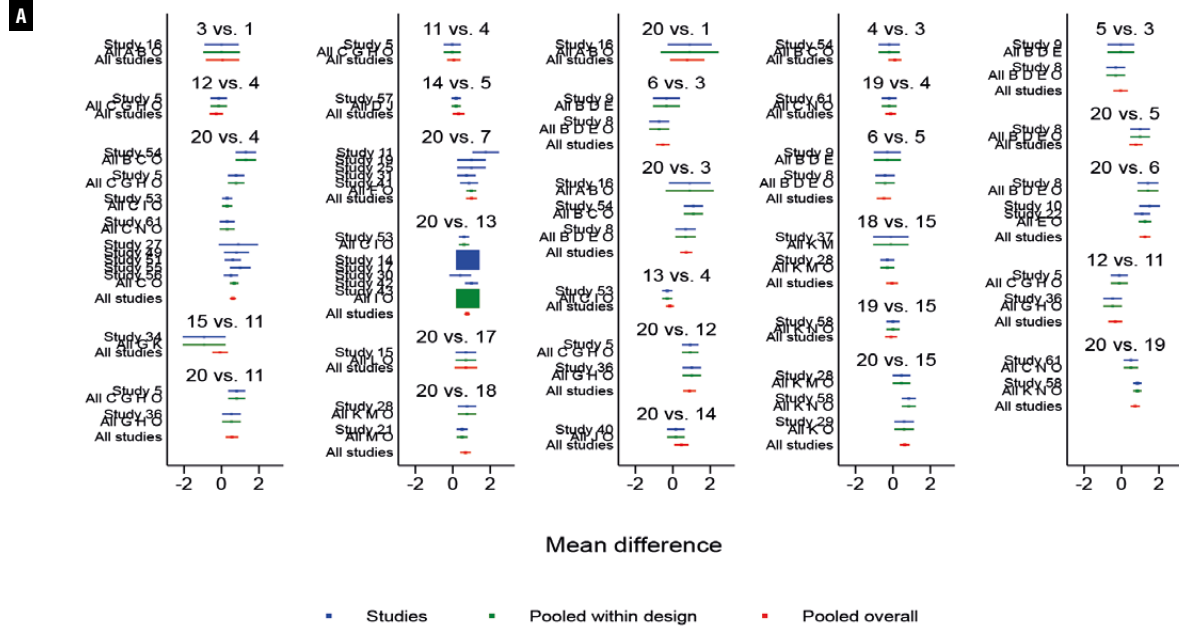
Test of consistency: $\chi^2(18)=23.38, P=0.176$

D

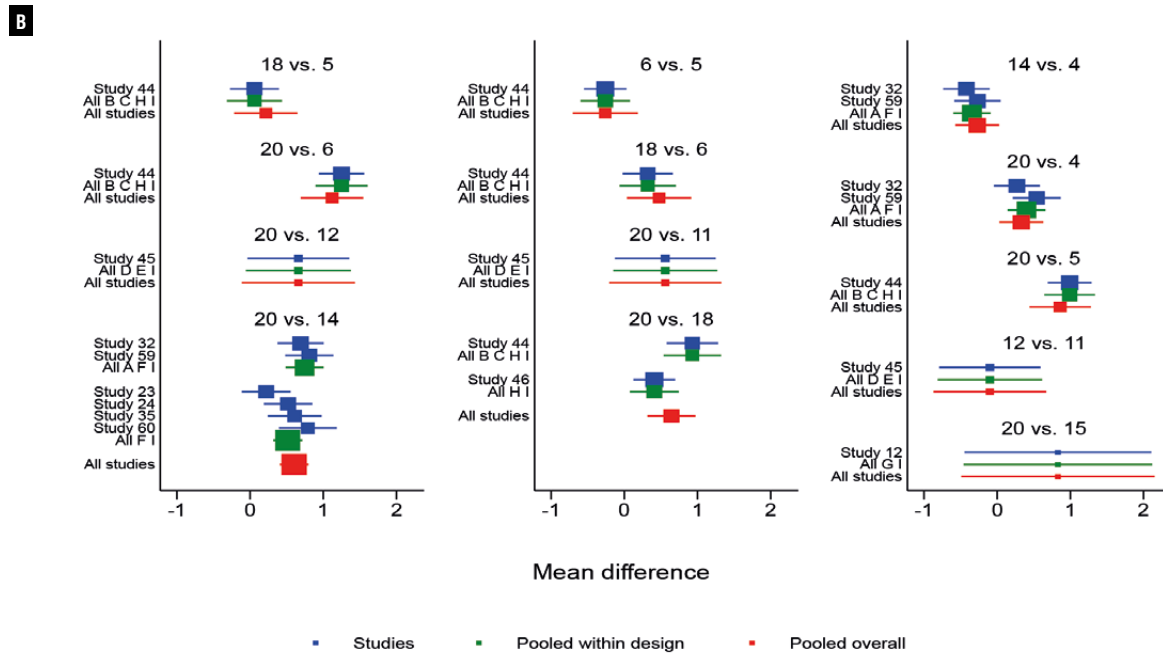


Test of consistency: $\chi^2(4)=2.76, P=0.599$

Figure 8 - NMA Forest Plot for Micturitions with Female Proportion >50% (A), Micturitions with Female Proportion ≤50% (B), Incontinence (C), Urgency (D). (The consistency of the entire network and was considered good at $p > 0.05$.)

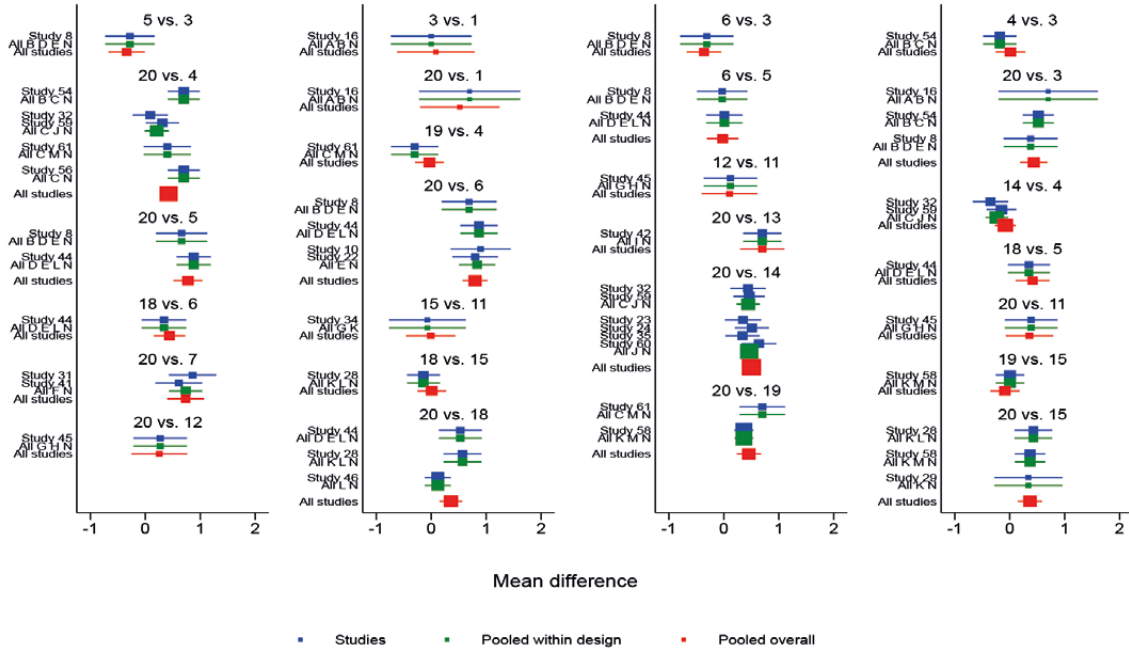


Test of consistency: $\chi^2(19)=26.93, P=0.106$

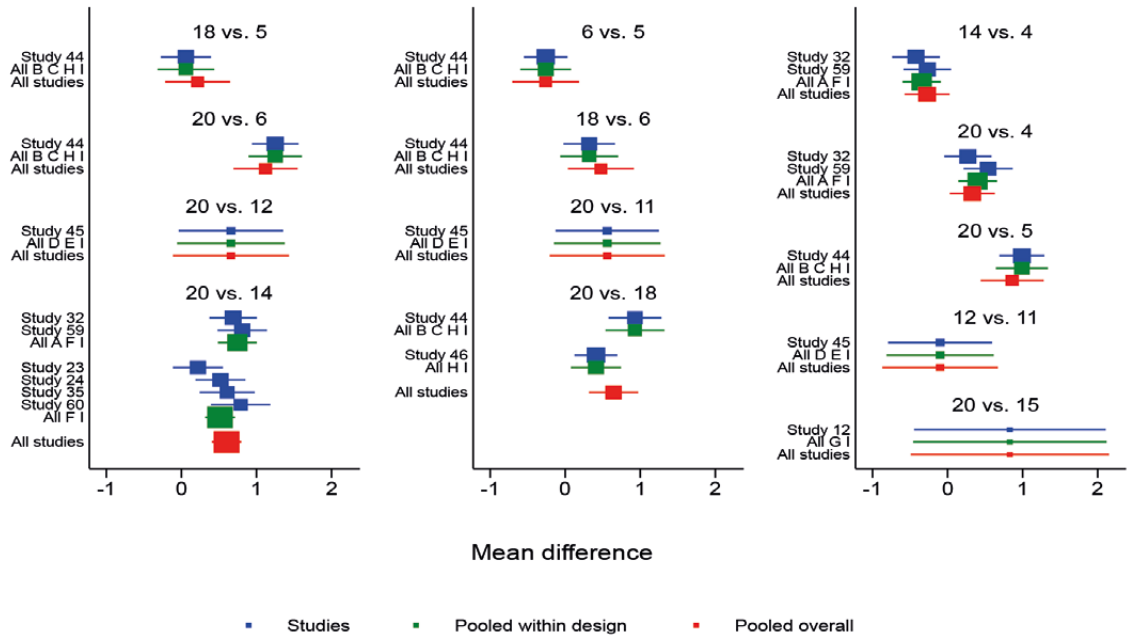


Test of consistency: $\chi^2(2)=5.81, P=0.055$

C

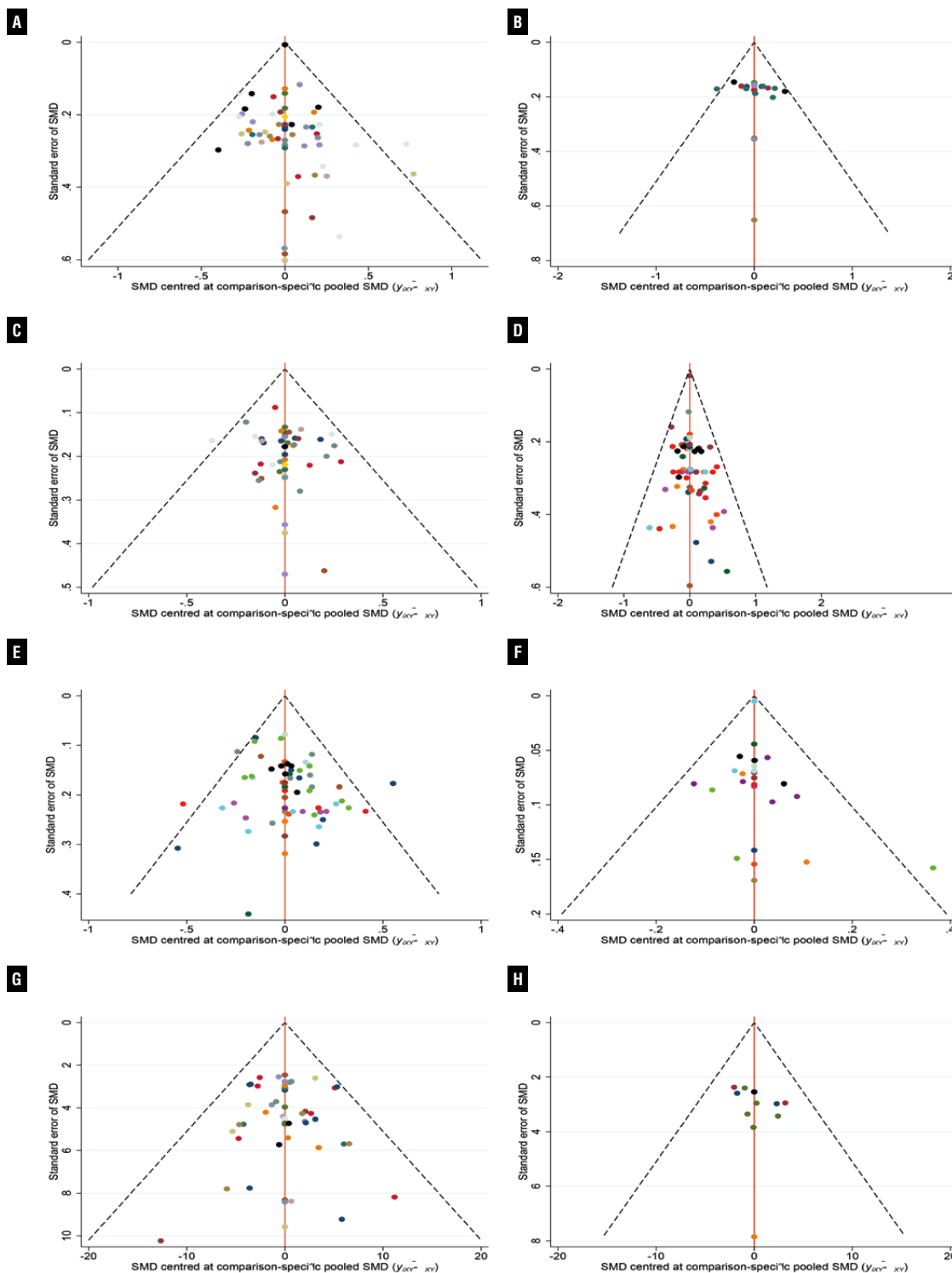


D



Test of consistency: $\chi^2(2)=5.81, P=0.055$

Figure 9 - Funnel Plot for Micturitions with Female Proportion >50% (A), Micturitions with Female Proportion ≤ 50% (B), Incontinence (C), Urgency (D), Urgency Incontinence (E), Nocturia (F), Voided Volume/micturition with Female Proportion >50% (G), Voided Volume/micturition with Female Proportion ≤ 50% (H). (The distribution of each point in the funnel plot is roughly symmetrical, suggesting that there is no publication bias or other bias in the studies).



advantage in improving patients' symptoms. Solifenacin 10mg was the most effective in reducing the number of voiding and incontinence; solifenacin 5/10mg was the most effective in reducing urinary urgency and nocturia; solifenacin 10mg ranked second in both urgency incontinence and voided volume. In terms of safety, the incidence of dry mouth events with solifenacin 5mg was not significantly different from placebo and was significantly lower than other anticholinergic drugs. Solifenacin is a competitive antagonist of M3 receptors and is highly specific and selective for bladder M3 receptors. The results of past studies have shown that solifenacin has a weaker blocking effect on salivary secretion than other anticholinergic drugs and that it inhibits salivary secretion at 3.6-6.5 times the effective concentration at which it produces an effect in the bladder (74, 75), which is consistent with the results of the present study. However, in the case of constipation, the results of this study showed that even a small dose of solifenacin (5mg) increased the incidence of constipation. Constipation has the greatest effect on patient satisfaction (76). Therefore, the results suggest that solifenacin is not recommended for the clinical treatment of patients with OAB who are prone to constipation.

Different interventions have different pharmacological characteristics, and different doses may affect the efficacy of treatment, in addition to their safety. Therefore, it is necessary to select the appropriate medication and dose according to the individual patient's condition so that the patient's quality of life can be maximized. This NMA analyzed the incidence of dry mouth, constipation, nasopharyngitis, headache, hypertension, and urinary tract infection in the included studies and showed that anticholinergic drugs may increase the incidence of dry mouth and constipation, while imidafenacin may increase the risk of hypertension, and FES4/8mg-QD and CR-DAR15mg-QD increase the incidence of headache compared to placebo. SOL10mg-QD may increase the risk of urinary tract infections.

Before choosing a treatment plan, the benefits of the treatment plan for the patient and the possible risks and complications should be fully considered, and decisions should be made after

weighing the pros and cons. In terms of efficacy, vibegron and mirabegron are superior to placebo and comparable to anticholinergics; although they do not show an efficacy advantage over anticholinergic drugs, their greatest advantage is in terms of safety, with both drugs showing good tolerability. In particular, vibegron and mirabegron have a significant advantage over cholinergic receptor antagonists with respect to dry mouth. As potent β_3 agonists, vibegron and mirabegron relax the detrusor muscle by activating β_3 receptors, thereby increasing bladder capacity and prolonging the interval between voiding without affecting bladder voiding activity. The selectivity for β_3 receptors over other β receptor subtypes also suggests that both drugs are effective and well-tolerated novel drugs for OAB patients (77, 78).

In the voided volume per micturition outcome indicator, there was inconsistency between the direct and indirect comparison results of SOL10mg-QD and PRO20mg-QD (p-value 0.017). Although the direct and indirect comparisons were significantly different, the results of the two interventions compared pointed towards the same direction, suggesting that SOL10 mg-QD was superior to PRO20 mg-QD, varying only in the degree of their difference, so the results were considered to be somewhat reliable.

Because of the overall inconsistency in this NMA study in terms of decreasing micturition/d and increasing voided volume/micturition, a subgroup regression analysis was performed. Despite the differences between male and female in the anatomy and physiology of the lower urinary tract system and the potential mechanisms of action that may lead to OAB-like symptoms (79), none of the clinical studies included "gender" as an analyzable data in detail, but simply expressed whether the proportion of women was $\geq 50\%$, so only subgroups of women \geq and $< 50\%$ were analyzed in this study. The results of the subgroup analysis suggest that the results of imidafenacin are opposite in the subgroups with greater than and less than 50% women, so it is speculated that the efficacy of imidafenacin in men and women may vary, which would need to be confirmed by the results of more single-sex studies.

To control for homogeneity in the included studies, strict entry row criteria were established, and all 12-week efficacy indicators were used as the endpoints examined in this study, which avoided the introduction of clinical heterogeneity due to different study periods. Some limitations still exist in this study: 1. Because the quality of life measurements used in different studies are not uniform, this indicator of quality of life has not been analyzed and compared. Clinical endpoints can assess the effectiveness of symptom treatment from an objective perspective, but further research is needed to determine whether these symptom changes are relevant to the improvement of patients' quality of life. 2. No subgroup analysis of age was performed in this study. Existing studies have shown differences in the effectiveness of solifenacin versus mirabegron in elderly and non-differentiated age groups (80). However, only 2 of the studies included in this study enrolled elderly subjects, so subgroup analysis could not be performed. 3. No comparative study of long-term medication use was conducted in this study. Overactive bladder requires long-term medication treatment, and the data from the 12-week study used in this study are not representative of its true efficacy and safety.

CONCLUSIONS

Individualized treatment based on the characteristics of the patient is crucial. Anticholinergic drugs carry a risk of increased incidence of dry mouth and constipation, with lower doses carrying a lower risk. Solifenacin (10mg, 5mg/10mg) has significant advantages in improving patient symptoms. However, even low doses of solifenacin (5mg) can increase the incidence of constipation. In addition, imidafenacin may increase the risk of hypertension, FES4/8mg and CR-DAR-15mg may increase the incidence of headaches, and SOL10mg-QD may increase the risk of urinary tract infections. These drugs should be used with caution in patients at risk for these side effects. Although the efficacy of mirabegron and vibegron is not superior to anticholinergic drugs, they are better tolerated by OAB patients.

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CONFLICT OF INTEREST

None declared.

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Urological knowledge and tools applied to diagnosis and surgery in deep infiltrating endometriosis – a narrative review

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ABSTRACT

Objectives: This review discusses deep infiltrating endometriosis (DIE) diagnosis and surgery using current urological knowledge and technologies.

Materials and Methods: Narrative review of deep infiltrating endometriosis that result in urological issues. We examined manuscripts from Pubmed, Embase, and Scielo's database using the following MeSH terms: ('endometriosis') AND ('urology' OR 'urological' OR 'urologist') AND ('bladder' OR 'vesical') AND ('ureteral' OR 'ureter'). Selection followed PRISMA guidelines. Sample images from our records were brought to endorse the findings.

Results: Thirty four related articles were chosen from 105. DIE may affect the urinary system in 52.6% of patients. Lower urinary tract symptoms may require urodynamic examination. Ultrasonography offers strong statistical yields for detecting urinary tract lesions or distortions, but magnetic resonance will confirm the diagnosis. Cystoscopy can detect active lesions, although any macroscopic visual appeal is pathognomonic. Endourology is utilized intraoperatively for bladder and ureteral assessment, however transurethral endoscopic excision of bladder lesions had higher recurrence rates. Laparoscopy is the route of choice for treatment; partial cystectomy, and bladder shaving were the most prevalent surgical treatments for bladder endometriosis. Regarding the ureteral treatment, the simple ureterolysis and complex reconstructive techniques were described in most papers. Using anatomical landmarks or neuronavigation, pelvic surgical systematization allows intraoperative neural structure identification.

Conclusions: DIE in the urinary system is common, however the number of publications with high level of evidence is limited. The initial tools for diagnosis are ultrasonography and cystoscopy, but magnetic resonance is the most reliable tool. When the patient has voiding symptoms, the urodynamic examination is crucial. Laparoscopy improves lesion detection and anatomical understanding. This approach must be carried out by professionals with high expertise, since the surgery goes beyond the resection of lesions and includes the preservation of nerve structures and urinary tract reconstruction techniques.

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INTRODUCTION

The presence of endometrial glands and stroma outside of their normal anatomic location was first described by Rokitansky in 1860 (1), and the first publications on this topic are about to complete their first centenary. In 1921, Sampson described the hemorrhagic chocolate cysts (2) and a few years later, in 1925, coined the name endometriosis (3). The disease is now understood as the presence of endometrial glands and stroma outside the uterine cavity.

According to epidemiological researches, the general prevalence is usually estimated to be 10% among women who are fertile (4) and despite the fact that it can afflict youngsters (5, 6), the highest occurrence is often documented between the ages of 25 and 35 years of age (7, 8). The average annual incidence rate is about 7.2 per 10,000 (9) and although this data may have variations, patterns show a reduction following the end of women's reproductive age, with a drop just after the age of 45 (8).

Usually related to pain, menstrual disorders, and infertility, it is a disease that can show up in different ways. It has the potential to stand as superficial implants on the peritoneal surface, been ovarian cysts called endometriomas or advance as lesions that infiltrate the muscularis propria of surrounding organs or even penetrate the peritoneal surface by more than 5 mm. Of these three possible phenotypes, this last one is the most aggressive; known as deeply infiltrating endometriosis (DIE) it is typically, but not solely, found in the pelvic compartment (10).

The anatomical obviousness would make the naivest observer relate this entity only to gynecology. Endometriosis is highly unpredictable and can manifest in the most random locations including head (11, 12), thorax (13-16), extra-pelvic abdominal organs (17-22) and the abdominal wall itself (23, 24). This wide range brings the newbie back to the real world, but it must be said that atypical DIE mostly affects the gastrointestinal and urinary tract (25). In this way, care will be better guided by a team composed by a gynecologist, coloproctologist/digestive system surgeon, and urologist. The purpose of this article is to describe

urological knowledge and tools applied to diagnosis and surgery in deep infiltrating endometriosis.

MATERIALS AND METHODS

In this study we carried out a review about the urological knowledge and tools applied to diagnosis and surgery in deep infiltrating endometriosis. We analyzed papers published in the past 20 years in the databases of Pubmed database (US National Library of Medicine, Bethesda, Maryland), Embase and Scielo, found by using the following combination of MeSH terms: ('endometriosis') AND ('urology' OR 'urological' OR 'urologist') AND ('bladder' OR 'vesical') AND ('ureteral' OR 'ureter'). The linked articles algorithm on Pubmed was used to identify English language and peer-reviewed journal articles published.

Original articles related to diagnosis, papers describing anatomy issues of the pelvis related to urological organs, descriptions of surgical techniques and outcomes were included if based on urinary tract matter. Clinical studies on complications functional urogenital disorders in endometriosis have also been analyzed. Studies with the following designs were included: randomized clinical trials, pre-post intervention studies and observational (cohort and case-control) studies assessing women of reproductive age with DIE involving urological structures. Clinical studies of non-urological complications were excluded. Related documents with communications in congress, reviews, opinions, case reports and case series with less than 10 patients have been also excluded. No attempt was made to identify the "gray literature". After screening, articles were first considered eligible by their title and abstract. Records were then evaluated in full articles before being included to the qualitative synthesis group. Bibliographies of essential articles were also studied to find papers of additional interest. PRISMA guidelines were followed during the selection process (26).

Authors provide sample imaging from his own database in support of the data found.

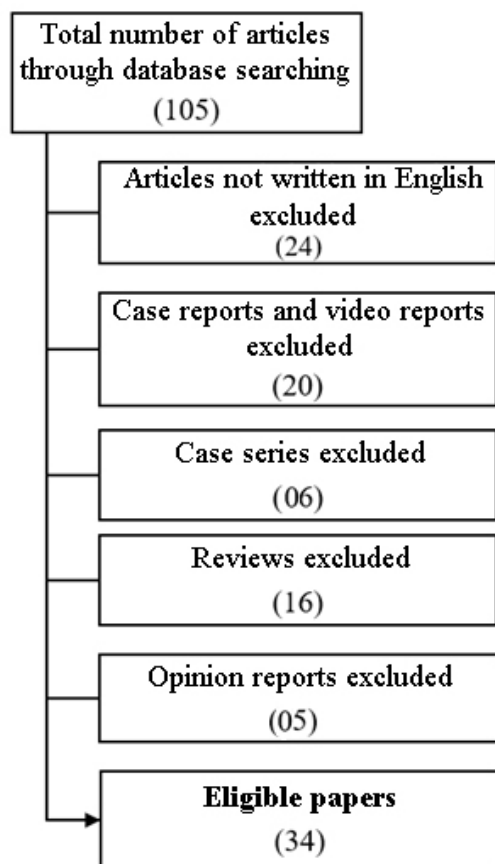
RESULTS

A total of 105 articles were identified as potentially relevant. In the first hand, 24 papers

were excluded for being written in other languages than English, of these four were case reports, one reported case with less than ten patients enrolled and one was a literature review. The following criteria disqualified English-language papers that did not meet the inclusion requirements. In this sense, 20 case reports—of which half had videos attached—were disregarded. Six studies reported series of cases involving less than ten participants, thus these were also eliminated. Sixteen studies were pure literature reviews; thus, they were eliminated. Finally, five publications describing expert opinions were disqualified according to the requirements. The flow diagram is depicted in Figure-1.

Considering the 34 publications selected, we organized the content by research design and issues pertinent to the prognosis of deep infiltrating endo-

Figure 1 - Flow diagram of the literature search.



metriosis. Our search yielded three retrospective studies and two prospective cohort studies that assessed radiological diagnostic techniques. One of them also analyzed the cystoscopy as a diagnostic tool and other three retrospective studies have detailed this endoscopic route employment. Three of those diagnostic studies also reported on clinical patient outcomes. Seven cohort studies, twelve retrospective analyses, and nine case series reported surgical procedures and/or clinical outcomes. There were no randomized clinical trials found, only observational research.

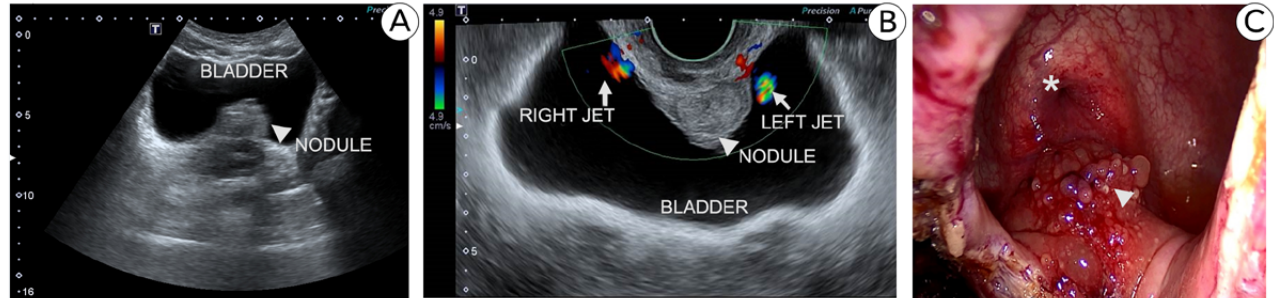
Descriptions of the radiological diagnostic techniques

Three of the five investigations on the radiological diagnosis of DIE included ultrasonography (US), while the other two involved magnetic resonance imaging (MRI).

The accuracy of transvaginal ultrasonography (TVUS) in predicting detrusor infiltration and ureteral meatus involvement in individuals with bladder endometriosis (BE) was examined by Ros and colleagues in 2021. TVUS detected bladder wall BE nodules and accurately predicted cystoscopic results in their sample; 21 of 22 women had uninvolved ureteral orifices at least 10 mm from the BE nodule (TVUS sensitivity, 95%). Authors concluded that cystoscopy may be unnecessary for partly muscular nodules seen at TVUS, as the example in Figure-2. Having said that, the researchers are aware of the limited statistical power of their findings related to the reduced number of participants enrolled (27). Years before, in a retrospective study, Hudelist et al. could evaluate the TVUS for preoperative detection of BE in a larger sample of which fifty of 207 patients with DIE had urinary endometriosis, including 30 patients with BE and 23 women with either isolated or multiple hydronephroses. TVUS was able to find bladder endometriosis with a sensitivity of 93%, a specificity of 99%, a positive and negative predictive value of 99% and 97% respectively and a test accuracy of 98.6% (28).

These authors' findings are in line with the conclusions of a cohort study conducted in 2015 by Pateman and coworkers who highlighted that US is an accurate test to diagnose urinary tract

Figure 2 – Nodule (arrowhead) identified at transabdominal US (A). Transvaginal US (B) was able to demonstrate bilateral urethral patency using doppler (arrows) despite the proximity to the nodule (arrowhead). Laparoscopic view (C) of the nodule (arrowhead) and bladder trigone (asterisk) just before partial cystectomy.



involvement in women with suspected pelvic endometriosis. Over the course of 14 months these researchers followed 848 women with chronic pelvic pain in whom suspicion of DIE was raised. One major concern of these researchers was to evaluate the effects of DIE on the upper urinary tract. So, in addition to USTV patients also underwent sonography of their kidneys. Given the service's tertiary nature, an unexpected epidemiology was found. US was able to show endometriosis in 335 women (39.5% 95% CI 36.2–42.8). Bladder seeds were observed in 6 women. Three patients had both, ureteric and bladder endometriosis. All bladder nodules were attached to the anterior uterus, above the trigone, medial to the ureters and distant from ostia; three were in the midline, two were to the left, and one was to the right. Ureteric endometriotic lesions were seen in 14 cases (8 on left, 6 on right). Of those fourteen women with ureteric involvement, two were referred to that specialized unity due to previous known hydronephrosis. The further statistical analysis was then made with a sample of 12 patients. Ten of these 12 subjects had ipsilateral upper urinary tract dilatation on transabdominal US and the other two women had distal ureteric distension without hydronephrosis. Pre-operative sonography for ureteral DIE showed a sensitivity of 92.3% (95% CI 63.9–99.8), specificity 100% (95% CI 97.6–100), PPV 100% (95% CI 73.5–100), and NPV 99.3% (95% CI 96.3–99.9%) (29).

Despite the previously demonstrated high statistical yields of ultrasonography, the recognition

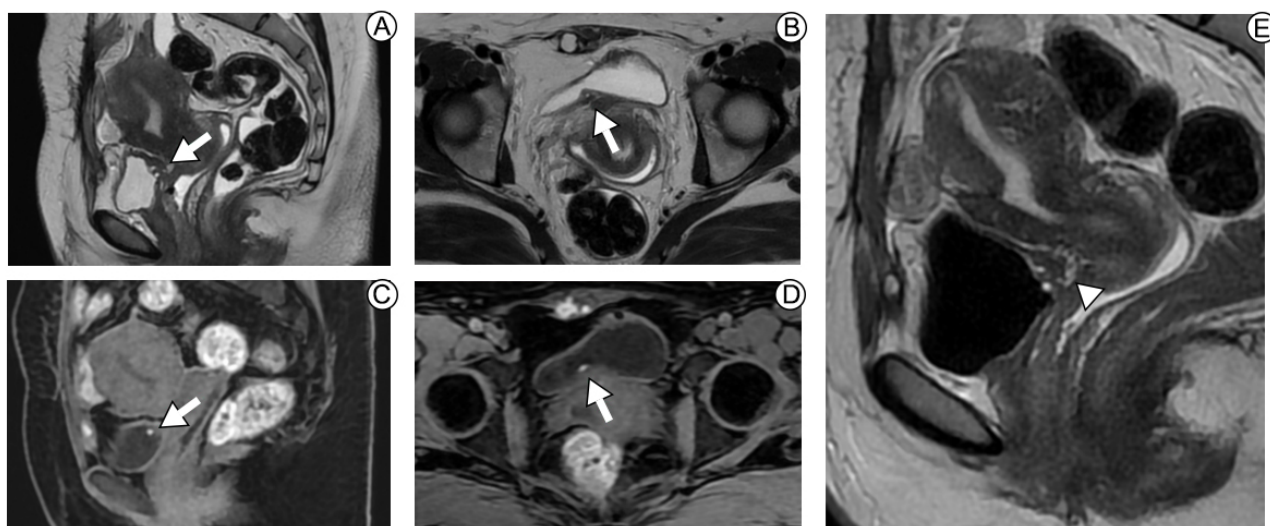
of a urinary tract lesion or distortion is simply a first step that alerts the surgeon to the disease's complexity. Data from Patemans's paper has shown that almost 58% of woman with endometriosis had lesions at two or more different locations using sonography (29). In this scenario, an MRI will then be critical to obtain a greater understanding and plan for the future of the procedure, since a US alone may not be quite enough.

Our search identified a retrospective study that evaluated the performance of MRI in locating endometriosis implants within the bladder wall with assessment of ureteral orifice extension using surgical findings as standard of reference. Researchers from academic medical centers had 39 exams by two senior members of the team. The mean size of the endometrioid foci was 30 ± 7 [SD]mm (range 19–41 mm); 56% were found in the median of the bladder wall, 26% left sided and 18% right sided. Still on the location of the lesion, 87% endometriosis implants were present in the two anterior thirds of the dome (sensitivity 100%; specificity 83%, accuracy 97%), 79% extended or were present in the posterior third pouch (sensitivity 100%; specificity 88%; accuracy 97%) and 64% extended into the bladder base (sensitivity 90%; specificity 87%, accuracy 89%). No extensive nodular endometriosis orifice infiltration was reported. The mean distance measured from the implant to the ureteral orifices was 9 ± 9 [SD] mm (range: 0–28 mm) at right, and 12 ± 12 [SD] mm (range: 0–55 mm) for the left one. Nine of these 25 patients with bladder base involvement, had a zero-distance

reported between endometriosis implants and ureteral orifices, all but one presenting with low-to-moderate bladder volume repletion; only two of those nine women had ipsilateral ureteral dilatation on MRI. In addition to demonstrating the high accuracy of the method, Rousset et al. point out that adequate bladder filling, as shows Figure-3, is needed to improve appropriate estimate of the distance between endometriosis implants and ureteral orifices to better predict requirement of ureteral resection-reimplantation (30).

tely by TVS in six individuals; however, the invasion depth was wrongly calculated in several instances (muscular vs submucosal or vice versa). However, the involvement of the bladder wall was appropriately identified on MRI in just two cases and was underestimated in one patient. Ureteral invasion was evaluated with IVU and MRI. The assessment of DE lesions in ureters was correct in 89,2% of patients based on IVU and 91,9% based on MRI. Pelvic ureteral encasement (i.e. narrowing with smooth wall lining) was not present in any of the patients at laparoscopy,

Figure 3 – MRI shows DIE at the posterior aspect of the bladder (arrows), in the trigone closer to the right ureteral ostium. MRI sequences are T2-weighted at images A, E (sagittal plane) and B (axial plane). MRI sequences are T1-weighted at images C (sagittal plane) and D (axial plane). Late MRI sequence was performed (E) to allow bladder distension (note the bladder hypointense signal intensity related to Gadolinium contrast media), improving the lesion - ureteral distance measurement. There is muscle and mucosal infiltration.



The importance of standardizing MRI studies highlighted by the previous author was also mentioned in a cohort study identified in our search. According to Bielen and colleagues, the capacity to determine the involvement of an organ system is highly dependent on the techniques adopted. In a tertiary care academic center 74 women were enrolled and the accurateness of the preoperative examination of specific organ systems using TVUS, double-contrast barium enema (DCBE), intravenous urography (IVU), and MRI was assessed. Regarding the urinary tract, the bladder involvement was detected in 10 individuals during laparoscopy. This was determined accurately

though it was suggested in two patients based on IVU and/or MRI. Pelvic ureteral displacement was present in 28 patients and was detected by IVU in 57.1% of patients while MRI detected the displacement in an additional nine patients, resulting in a detection score of 89.3% (31).

Descriptions of the endoscopy diagnostic techniques

At the previous session, data from Ros et al. were brought; in their institution, flexible cystoscopy was performed as routine for all women with US suspicion of BE affecting the bladder muscular layer.

In their study, it was concluded that cystoscopy may be unnecessary for partly muscular nodules seen at TVUS (27), but authors cite a publication in which recognizes that for infiltrative BE nodules, cystoscopy is able to detect the distance from the BE nodule to the ureteral meatus and the trigone (32), as demonstrated in Figure-4.

In a retrospective study which enrolled 22 patients, Schneider et al observed internal bladder endometriosis in 15 women (68.1%), cystoscopy revealed that its location was at the dome in nine patients (40.9%), at the base in five patients (22.7%), and multifocal in one patient (4.5%). In the same population, IVU only suggested the disease in four cases (18.1%). They quote a traditional statement from the

literature on the subject that reminds the reader to repeat cystoscopy at different times of the menstrual cycle, since endometriosis is best diagnosed before and during menstruation. Their study shows that cystoscopy is important for the potential diagnosis of DIE, the authors make it clear that the macroscopic aspect is not pathognomonic, even in cases as shown in Figure-5 (33).

Antonelli and cols. analyzed their database and found 1242 patients with surgically proved diagnosis of endometriosis within ten years; it was found that 31 patients (2.5%) had urinary tract involvement. The bladder was affected in 12 patients, the ureter in 15, and either the bladder or the ureter in 4. Cystoscopy was performed in all cases with bladder

Figure 4 – Cystoscopy shows bladder trigone (A), left (B) and right (C) ureteral ostia, left (D) and right (E) lateral walls free of lesions. A nodule (arrow) measuring approximately 1.5cm was found on the posterior wall of the bladder (F and G) at approximately 9mm from the right ureteral orifice and 11mm from the left ureteral orifice; bladder projection (arrowhead) suggests thickening of the left (H) and right (I) round ligaments.

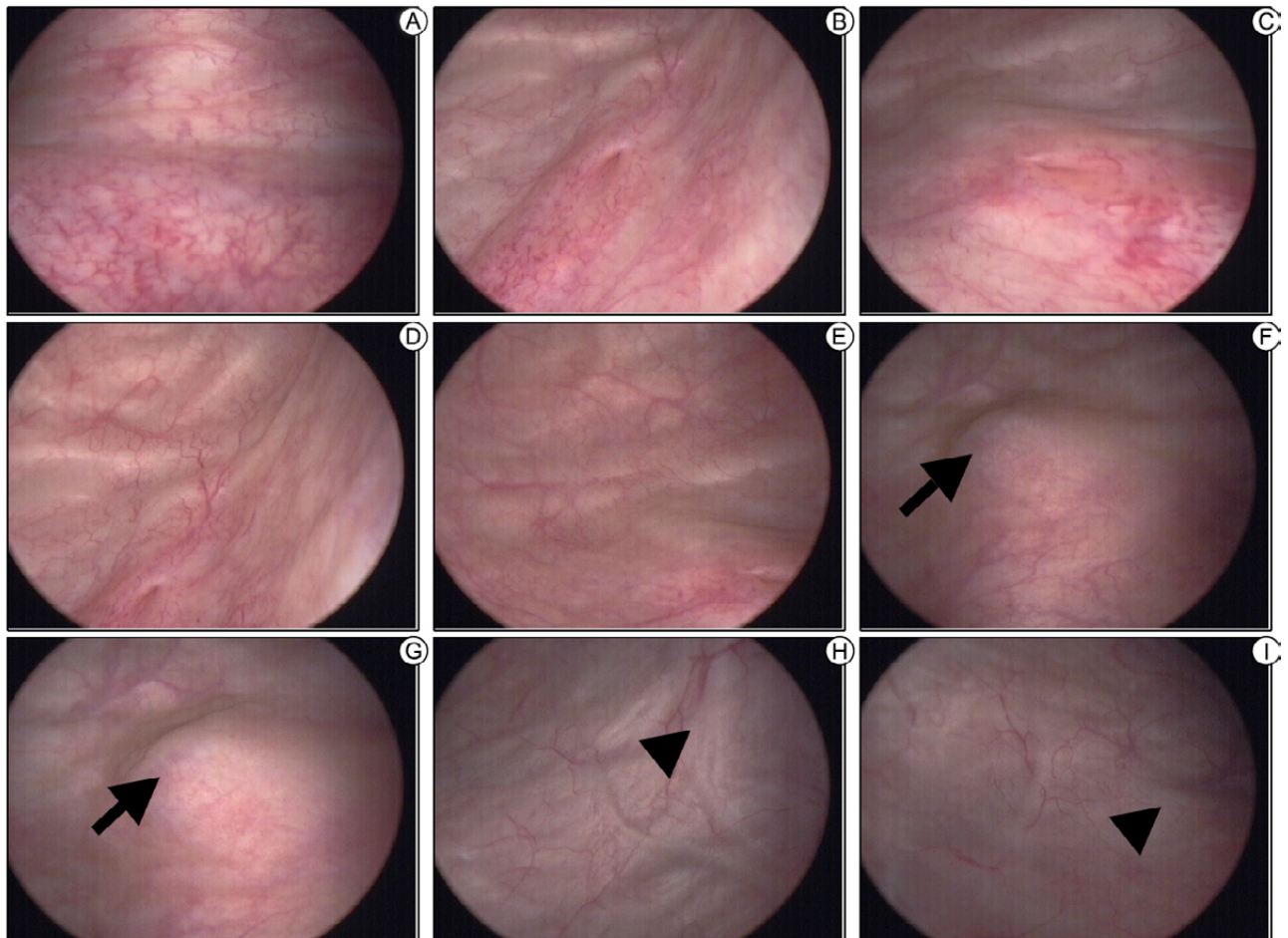
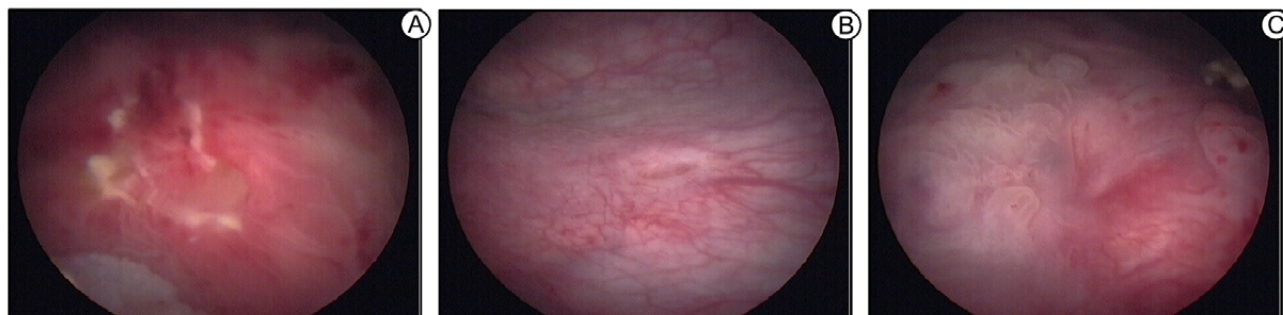


Figure 5 – Bladder infiltrative lesion at the bladder trigone (A), 1.5 cm far from left ureter orifice (B); right ureter orifice (C) with infiltrative lesion. Upon vaginal examination, it was possible to perceive the presence of a palpable intravaginal nodule, adhering to the right intramural ureter.



endometriosis and found the typical bluish irregular submucosal lesion on the dome (8 patients) or base (8 patients) of the bladder. Of the 16 cases in which cystoscopy corroborated the diagnosis of BE, transurethral endoscopic resection was performed in two patients with mean lesion size of 1.9cm, both women had bladder recurrence. Six individuals received open partial cystectomy and mean lesion size was 3.5cm; four cases were treated with laparoscopic partial cystectomy and mean lesion size was 3.6cm. Three patients underwent ureterocystoneostomy and partial cystectomy, bladder mean lesion size was 1.5cm. One woman was treated with laparoscopic bilateral ureterolysis and partial cystectomy, the lesion measured 3cm. None of these 14 subjects faced bladder recurrence. In face of their findings Antonelli et al. states that cystoscopy is advisable in women affected by endometriosis complaining LUTSs or haematuria; and reinforces that an ultrasonographic study of the upper urinary tract should be performed in all patients with pelvic endometriosis, even in the absence of urological symptoms (34).

By furthermore to the preoperative diagnostic, cystoscopy was found as an intraoperative method for bladder and ureteral evaluation. Some authors advocate the employment of cystoscopy during hysterectomy for benign causes as a tool for the prompt diagnosis of potential iatrogenic damage as perceived in Figure-6 (35 ,36).

Oliveira et al. described the perioperative cystoscopy in 47 patients just after pelvic surgeries, 26 women (55%) had laparoscopic hysterectomy and 21 (45%) underwent bladder endometriosis nodule resection; among these last, 13 patients had the shaving dissection (without the need to open the

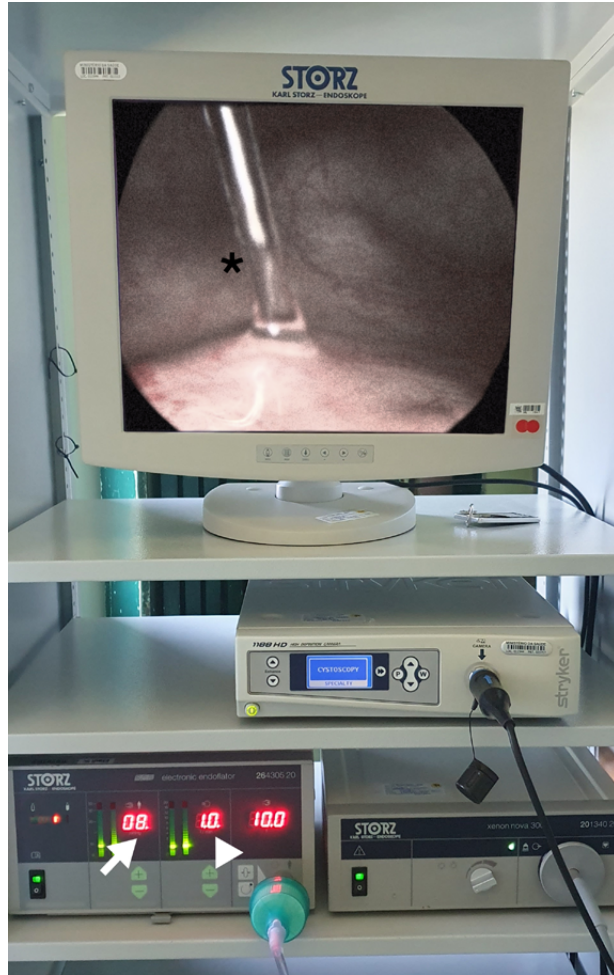
Figure 6 - Cystoscopy identifies bladder endometriosis (arrow) and thermal injuries related to hysterectomy (arrowhead: damage to the inner layer of the muscularis; asterisk: mucosal damage).



mucosa, but with detrusor suturing) and 8 patients underwent partial cystectomy. This cystoscopy was performed under CO₂ filling with constant pressure of 8 mmHg and flow of 1L/min; as demonstrated in Figure-7, kindly provided by Dr. Oliveira.

Regular cystoscopy filling the bladder with saline solution may impose some difficulty to jet identification due to the urinary density and the use of dyes may cause adverse effects. This cystoscopy using CO₂ allows the evaluation of the anatomy of ureteral orifices, the presence of ureteral jets and the integrity of bladder walls, with the same acumen as the regular fashion; the mean time between the onset of the cystoscopy and the observation of bilateral jets were 145 seconds, suggesting their patency. In face of their findings, Oliveira and colleagues stated that the cystoscopy technique using CO₂, was fast, easy, safe and efficient (37).

Figure 7 – CO₂ cystoscopy using a laparoscopic insufflator at pressure of 8mmHg (arrow), flow rate at 1L/min (arrowhead); urine jet identified (asterisk).



Descriptions of the surgical procedures and clinical outcomes

Six of the publications selected for the aforesaid purpose described diverse etiologies and/or therapy of urinary tract lesions. All these resources reported endometriosis, but without pushing our topic. Due to its worth, certain findings were brought to this study.

In a cohort study, Dallas et al. analyzed a sample of 296,130 women who underwent a hysterectomy procedure for benign conditions, which 18.8% were related to endometriosis. When such diagnosis was present, genitourinary injuries happened in about 2.3% of the women demonstrating an increased likelihood (OR 1.46; 95% CI 1.36-1.56) of

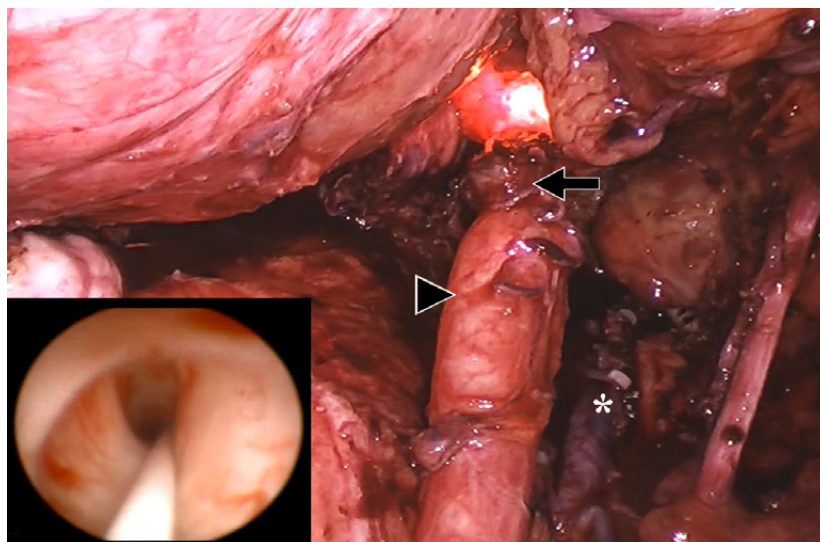
a genitourinary injury occur, with a delayed diagnosis happening in about 20.6% of the cases (36). These results were in accordance with a retrospective performed by Wallis and colleagues who similarly found that a primary post-operative diagnosis of endometriosis was associated with a significantly increased risk (OR 1.92, 95% CI 1.68-2.19) of urinary tract injury (35). Johnston et al. reported that 28% of their 1265 laparoscopic procedures were for endometriosis treatment, but happening only two urinary tract damages (38). With a smaller sample, Siow et al. studied 495 cases of laparoscopic hysterectomy, 25,1% due to endometriosis; urological lesions were found in 1.6% of patients; authors suggests that the most likely etiology was thermal damage from electrocautery used to secure hemostasis of the uterine artery pedicle and consider the endometriosis as one of the risk factors related (39). Inadvertent electrical conduction between instruments and tissues can also occur (Figure-8) and, when identified, should lead to revision of the affected tissue, as well as strict follow-up of the patient in the postoperative period, given the risk of late leakage.

Two case series documented ureteral stricture surgery for distinct causes. Five of our 44 patients experienced endometriosis-related ureteral stricture, similar to that shown in Figure-9. In four patients, the distal constriction was treated by ureteroneocystostomy (UNC) with a Boari flap and two with UNC

Figure 8 – Electrical conduction between monopolar scissor and grasper (arrow) during lymphadenectomy step. Grasper is pulling the ureter (arrowhead) away from the dissection area.



Figure 9 - Double endoscopic view of an extrinsic endometriotic lesion at the distal right ureter. A nitinol guidewire was used to allow safe progression of the semi-rigid ureteroscope as shown. The arrow shows laparoscopic aspect of the endometriosis, and the arrowhead shows the ureteral distension above the stricture point. Uterine artery, marked with asterisk, was ligated with Hem'O'Lock clips.



with the psoas hitch approach. UNC with a Boari flap was used to treat a 80mm lesion in the middle-inferior ureter transition. Both strategies work long-term without concerns (40, 41). This favorable outcome was also observed in a cohort study by Carmignani et al., who evaluated thirteen patients with deep endometriosis and ureteral involvement and concluded that the combination of bladder psoas hitch, ureteral resection, and ureteroneocystostomy had no negative effect on urodynamic parameters (42).

In order to increase understanding of the uro-neurology interaction, Chiantera et al. presented the use of neuronavigation methods for the treatment of deep endometriosis in a retrospective investigation. Involvement of deep lateral tissues was detected in 40% of women with central pelvic lesions and in 72.7% of patients with involvement of the hypogastric plexus. The authors concluded that complete laparoscopic excision of endometriosis tends to reduce recurrence rates without increasing surgical morbidity (43).

Twenty-two studies provided relevant evidence that primarily highlighted the proposed issue; however, the non-uniform description of clinical information, treatments, and results hinders the detailed analysis of the pooled data. Two of those papers referred exclusively to ureteral endometriosis.

For the treatment of bladder endometriosis, the techniques described were transurethral endoscopic resection (TURB), partial cystectomy with mucosal preservation (shaving) and partial cystectomy. Partial cystectomy was the most common surgical treatment for endometriosis of the bladder, as reported in twenty studies. A total of 1,355 patients were enrolled, and in addition to several further ureteral procedures, 598 partial cystectomies (44.13%) were done.

The use of TURB was documented in six studies with a total of 149 bladder endometriosis patients, and thus the endoscopic approach was adopted in 35% (52 patients). Recurrence was identified in 24 women, which corresponds to an estimated recurrence rate of 46.15%. Data are described in Table-1. The National Survey conducted by Hirata and colleagues stands out among the reported research, which cumulative recurrence rates were considerably greater with TURB than with partial cystectomy under statistical significance ($p < 0.05$).

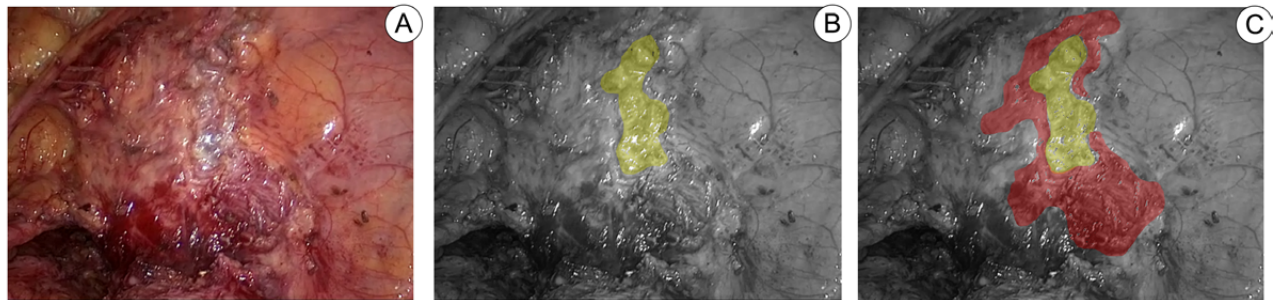
In several investigations, removal of bladder nodules maintaining the mucosa was also documented. This method has also been referred to as bladder shaving and bladder skinning, as demonstrated in the following series at Figure-10.

As described by Darwish et al., this technique begins with a detrusor incision around the bladder

Table 1 - Patients with bladder endometriosis treated by transurethral endoscopic resection.

Authors	Bladder endometriosis	TURB	Recurrences
Hirata et al.(44)	89	34	19
Freire et al. (45)	15	3	0
Schneider et al. (46)	15	5	0
Antonelli et al. (34)	16	2	2
Kumar et al. (47)	9	5	2
Perez et al. (48)	5	3	1
Total	149	52	24

Figure 10 – Image A shows bladder after laparoscopic resection of endometriosis, highlighted in yellow at Image B, the area delimits the resection performed up to the mucosa and marked in red at image C, we demonstrate the bladder resection in which it was possible to preserve the muscle layer.



lesion, followed by dissection to the nodule's macroscopic limits in the depth, and as resection appears complete prior to opening the bladder, muscular suture in one layer to reinforce the bladder wall is then performed (44). With data presented in Table-2, by examining these publications, there have been 109 people with vesical endometriosis; and 44 of them had bladder shaving, which corresponds to about 40.37 percent of cases; just one patient out of 44 experienced recurrences, which amounts to 2.27%. In these areas of weakening of the full thickness of the bladder, reinforcing suture is suggested, as shown in Figure-11.

Ureteral involvement by endometriosis foci may need various types of surgery; among the publications assessed, less invasive resection procedures such as ureteroscopic approaches to simple ureterolysis (N = 282), progressing to segmental ureterectomy with end-to-end anastomosis (N = 70), UNC as Lich-

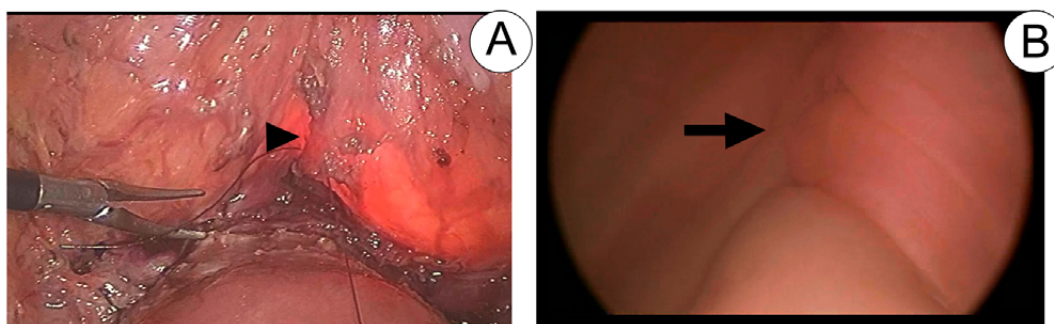
-Gregoir or Politano-Leadbetter (N= 271), UNC with Boari flap (N = 4), and UNC with psoas hitch (N = 17). Some combined procedures have been described, one ureteric stump was resected and a bladder cuff, two PC with ureterolysis, four PC plus ureterectomy with end-to-end anastomosis and four PC added to UNC as Lich-Gregoir. Six nephrectomies were performed due to loss of renal function related to ureteral obstruction by endometriosis.

DISCUSSION

Endometriosis reveals itself in a variety of clinical manifestations, and the urologist is rarely the first health care provider to interact with the patient. Menstrual disorders, chronic pelvic pain, and infertility are typically incorporated into the differential diagnosis for endometriosis. The combination of symptoms and signs enables us to properly demand

Table 2 - Patients with bladder endometriosis treated by bladder shaving.

Authors	Bladder endometriosis	Shaving	Recurrences
Maida et al. (50)	21	4	1
Alves et al. (51)	5	3	0
Darwish et al. (49)	50	15	0
Gabriel et al. (52)	33	22	0
Total	109	44	1

Figure 11 – Cystorraphy line (arrowhead) demonstrated by laparoscopy at Image A and by cystoscopy (arrow) at Image B. Bladder filling during cystoscopy also makes it possible to assess the watertightness of the suture performed.

imaging studies. As shown in the literature, sonographic evidence can eventually be used to make a presumptive diagnosis of the condition and evaluate the upper urinary tract; however, MRI scans are most often robust for the nonsurgical diagnosis of endometriosis.

However, if the patient discloses symptoms of the lower urinary tract during the interview and radiological findings corroborate the diagnosis of endometriosis, a urological consultation is required. Urodynamic and endoscopic examination may be requested in this case.

Researchers found that 96.7% of patients in a prospective study with 30 patients had one or more abnormalities at urodynamic examination; and those women with anterior compartment endometriosis had increased bladder sensation (90.0% versus 45.0%, $p=0.024$) and painful bladder filling (70.0% versus 30.0, $p=0.04$) compared to patients with posterior endometriosis only (45). In line with the results of this study, another team of investigators accessed data at a considerably larger population of 138 women with

radiological diagnosis of endometriosis and found that the harm of the bladder was a statistically significant independent predictor of low bladder compliance, whereas endometriosis in the parametrium was a statistically significant independent predictor of both abnormal residual urine and bladder outlet obstruction (46).

Even though it is invasive, cystoscopy is inexpensive, useful for estimating the distance between ureteral orifices and nodule boundaries and may allow biopsy if necessary. However, due to the intraperitoneal origin of the nodule, traditional outpatient cystoscopy is more usually normal; in only half of the instances, a classic adenomatous and nodular red or bluish mass expansion is visible, and ulcerations are more rarer (27, 47). In this sense, cystoscopy under sedation concomitant with physical examination of the pelvis, including bimanual palpation of the bladder, has been proposed to improve the accuracy of the method. By using this dynamic cystoscopy in a study of 157 participants, researchers perceived that the test's had a high specificity (97.78%) and low

sensitivity (58.21%) with substantial positive predictive value (95.12%) and negative predictive value (75.86%); this study has also shown that abnormalities during dynamic cystoscopy were associated with a higher ratio of bladder surgery for the treatment of deep endometriosis, and typical findings involving the mucosa tends to be associated with a higher ratio of partial cystectomy (48).

Depending on where the endometriotic lesions are located, deep pelvic endometriosis is anatomically classified as anterior, middle, and posterior compartments. The anterior compartment is the region just posterior to the pubic symphysis, where endometrial implants may happen within the vesicouterine pouch, vesicovaginal septum, bladder, and ureter. The middle compartment consists of the uterus, fallopian tubes, ovaries, mesovarium and broad ligaments. The posterior compartment is located between the posterior vaginal wall and the anterior rectal wall, it consists of the rectovaginal pouch, rectocervical space, the rectovaginal septum, uterosacral ligaments (USL), as well as the rectosigmoid (49). Disease distribution may also be classified as: Central Pelvic Endometriosis (CPE) when DIE involved one of these anatomic sites: cervix, vagina, uterosacral ligaments, rectum, bladder and pelvic peritoneum; superficial Lateral Pelvic Endometriosis (sLPE) when parametria, ureters or hypogastric plexus were involved; deep Lateral Pelvic Endometriosis (dLPE) in presence of sacral plexus and/or sciatic nerve infiltration (50).

The frequency of urinary tract involvement due to DIE may reach numbers as high as 52.6% as found in our search (51). The bladder is the most frequently affected organ in the urinary system and the endometriotic foci are usually found at the dome but it may extend to its base and even get close to the ureteric ostium (30, 31). During laparoscopy surgeries, a cystoscopy may assist partial laparoscopic cystectomy with a light-to-light methodology which enables appropriate intra- or extravesical detection of lesion boundaries (52). It may permit a sparing surgery in an effort to proceed the partial cystectomy or even a bladder shaving as described by Darwish (44). Still debating about minimally invasive approaches, the ureteroscopy may also be useful if ureteric lesions are presumed or suspected. Freire et al. reported 3 endoscopic management of ureteral lesions (53); in

the same sense, Kumar described the diagnosis of DIE of the ureter in one patient of his sample (54).

In the pelvis, endometriotic lesions are more frequently observed in the posterior compartment and on the left side (55). The uterosacral ligament and rectum are the most affected structures (43). The sigmoid colon promotes retrograde menstrual fluid stasis on the left, sheltering and inhibiting endometriotic cell diffusion from the left hemipelvis; hence, the left ureter is more often implicated than right, as shown by Ceccaroni et al. in his cohort study which found 151 patients with unilateral ureteral stenosis, 39 patients in the right ureter and 112 patients in the left (56). These lesions usually occur above the ureterovesical junction, where the ureter crosses the uterine artery. Large paracervical or pararectal lesions larger than 2 cm may involve the ureter (57).

An extensive ureteral involvement by DIE can result in hydronephrosis and asymptomatic loss of renal function, as demonstrated by Antonelli et al, who performed two nephrectomies for end-stage renal atrophy (34) and by Freire et al, whose patient populations with ureteral involvement had hydronephrosis, of which 41.2% (7/17) had partial and 17.7% (3/17) had total loss of renal function (53).

The surgeon who intends to act on the pelvis must comprehend ureteral fragility. This retroperitoneal tubular structure is harmed more frequently during gynecological pelvic operations (36, 37, 58). Not even the preemptive stenting is able to avoid harm as described by Siow et al. which states that the presence of the ureteric stents may actually make the ureter less pliable and more rigid thereby increasing the risk of injury during dissection to mobilize it (58).

The initial anatomical landmark in the systematic surgical treatment of endometriosis is the cranial pelvic point close to the promontory, below the split of the cava and aorta into iliac vessels. Access to the left ureter begins with sigmoid release from parietal peritoneal adhesions. Identification of the left ureter in the retroperitoneum in a healthy area, typically crossing the common iliac artery, enables ureterolysis in a distal direction, clearing the lateral aspect of the organ from the uterosacral ligament and the peritoneum of the ovarian fossa, which are frequently affected by endometriosis foci. Returning to that initial landmark, usually crossing the external iliac artery, we can find the right ureter covered by perito-

neum; and as with the contralateral one, the release of adhesions and endometriotic foci from the ovarian fossa and uterosacral ligament allows safe mobilization of the ureter. Ureterolysis of the medial face should be avoided since the vascularization of the distal portion may be compromised. Among the enrolled manuscripts, some provided a comprehensive explanation of surgical steps, with special mention to Abo et al., Darwish et al., and Maida et al.; the last adds supplemental video content to the paper (44, 59, 60).

Although they are extra-peritoneal structures, deep infiltrating endometriosis can harm the pelvic nerves. While this is not a signaling route unique to the urinary tract, it is imperative that the urologist be familiar with the treatment and dissection of these structures since those nerves are necessary for the proper functioning of the lower urinary tract.

The surgical systematization of the pelvis enables the intraoperative identification of neural structures based on knowledge of anatomical landmarks. On occasion, neuronavigation techniques may be advantageous, particularly when structures requiring neurolysis are at danger of being accidentally damaged during dissection (43). We can identify the motor response of a tissue that is thought to be a nerve by applying bipolar current to it, so that connections with S3 produce flexion of the hallux and contractions of the pelvic floor, rectum, and bladder, while connections with S2 cause flexion of the other toes. Damages to the superior hypogastric nerves may lead to urinary retention, urinary hesitancy, constipation, urinary and fecal incontinence, and sexual dysfunction; inferior hypogastric plexus harm is often related to urinary retention, constipation, and sexual dysfunction; the injury of pelvic splanchnic nerves may also cause urinary retention (61, 62). Mastering these concepts is essential for preventing bladder hypotonia or atony in the future, which is of utmost importance in urology.

CONCLUSIONS

Even experienced surgeons find pelvic surgery challenging. This paper emphasizes the role of the urologist in deep infiltrating endometriosis care.

The risk of inadvertent injury to urinary tract structures can be minimized with proper training and

anatomy understanding. The diagnostic methods of endometriosis are represented by USTV, MRI and cystoscopy. This endoscopic tool can also be useful during surgeries. Although bladder involvement is more common, ureteral injuries may be asymptomatic and cause long-term renal dysfunction. Surgical treatment of EID has been mainly performed by conventional and robotic-assisted laparoscopy. The use of systematic surgical steps allows the identification and preservation of nerves and surrounding tissues. Bladder sparing tactics may be relevant for the future voiding pattern of the patient, however the transurethral resection approach is related to high rates of recurrence. In order to effectively treat ureteral injuries, it is necessary to achieve a balance between gentle ureter manipulation and skillsets of urinary reconstructive procedures.

CONFLICT OF INTEREST

None declared.

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Long-term oncological and surgical outcomes after Video Endoscopic Inguinal Lymphadenectomy (VEIL) in patients with penile cancer

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ABSTRACT

Objective: To report outcomes from the largest multicenter series of penile cancer patients undergoing video endoscopic inguinal lymphadenectomy (VEIL).

Materials and Methods: Retrospective multicenter analysis. Authors of 21 centers from the Penile Cancer Collaborative Coalition-Latin America (PeC-LA) were included. All centers performed the procedure following the same previously described standardized technique. Inclusion criteria included penile cancer patients with no palpable lymph nodes and intermediate/high-risk disease and those with non-fixed palpable lymph nodes less than 4 cm in diameter. Categorical variables are shown as percentages and frequencies whereas continuous variables as mean and range.

Results: From 2006 to 2020, 210 VEIL procedures were performed in 105 patients. Mean age was 58 (45-68) years old. Mean operative time was 90 minutes (60-120). Mean lymph node yield was 10 nodes (6-16). Complication rate was 15.7%, including severe complications in 1.9% of procedures. Lymphatic and skin complications were noted in 8.6 and 4.8% of patients, respectively. Histopathological analysis revealed lymph node involvement in 26.7% of patients with non-palpable nodes. Inguinal recurrence was observed in 2.8% of patients. 10y- overall survival was 74.2% and 10-y cancer specific survival was 84.8%. CSS for pN0, pN1, pN2 and pN3 were 100%, 82.4%, 72.7% and 9.1%, respectively.

Conclusion: VEIL seems to offer appropriate long term oncological control with minimal morbidity. In the absence of non-invasive stratification measures such as dynamic sentinel node biopsy, VEIL emerged as the alternative for the management of non-bulky lymph nodes in penile cancer.

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INTRODUCTION

Penile cancer (PC) is a rare disease in developed countries with a reported incidence of 1-2 cases per 100,000 males (1). Squamous cell carcinoma, which has several subgroups with various clinical outcomes, accounts for 95% of instances of penile cancer. Penile cancer frequently has a relationship with chronic preputial inflammation brought on by phimosis or lichen sclerosus. Penile cancer risk is decreased by circumcision (hazard ratio: 0.33) (2). HPV was found to be involved in about 40% of penile malignancies (PCs), with HPV 16 being the most common genotype (3). Higher incidences are encountered in some areas of Latin America, Africa and Asia, where it can correspond to 1-2% of malignant diseases in men (4, 5).

Lymphatic spread to inguinal lymph nodes remains as the most important prognostic factor in patients with PC (6). Patients with low volume

disease undergoing radical inguinal lymph node dissection have an excellent cancer control and prolonged survival compared to surveillance followed by salvage surgery in case of clinical progression (7).

Despite being recommended by most clinical guidelines, early lymph node dissection in cases of intermediate/high-risk penile cancer is not frequently performed, probably due to high morbidity of the standard procedure (8). Open and VEIL approach have similar safety, overall survival and post-operative outcomes (9).

Over the last 40 years, modified templates, and dynamic sentinel node biopsy (DSNB) were proposed to decrease the morbidity associated with the standard lymph node dissection (10). DSNB false negative rates in large reference centers hangs around 5% (11). Nonetheless, other studies have shown false negative rates as high as 15% (12). In Latin America, DSNB is not com-

monly utilized, hence, false negative rates of 42% have been described (13).

Endoscopic approach for inguinal lymph node dissection was first described in cadaveric models in 2003 by Bishoff et al. (14). In 2006 Tobias-Machado et al. followed by Sotelo et al. published their first successful experience in patients (15, 16). In 2007, a pilot randomized trial demonstrated the oncological equivalence of VEIL when compared to the open counterpart (17).

After that, several other series and three systematic reviews with pure laparoscopic or robotic techniques have reported further evidence supporting the findings from that landmark comparative study (18-24).

In the present series our goal is to report the larger and longest surgical and oncological outcomes from Latin American patients with penile cancer undergoing VEIL.

MATERIALS AND METHODS

This is a retrospective and descriptive study of patients operated from 2006 to 2020 (CAAE:46451021.2.1001.5437).

All patients underwent partial or total penectomy and abdominal and pelvic computed tomography scan or magnetic resonance imaging before management of the lymph nodes. Results were reported following the American Joint Committee on Cancer TNM Classification (8th edition) (25). The study was approved by the central Ethics Committees

The indications for VEIL were clinically palpable nodes < 4 cm non-fixed or non-palpable nodes in patients with intermediate or high-risk penile cancer [12]. All patients underwent bilateral VEIL procedure. Patients with an American Society of Anesthesiologist (ASA) Score > 3 were excluded. No patients in this study received neoadjuvant treatments.

We selected 17 centers that routinely utilize a previously reported VEIL standardized technique (15). After training, each institution collects data according to a standardized questionnaire. A minimum of 5 (five) cases per institution was considered to enter in this study.

Patients were followed every 3 months in the first 2 years and twice a year for the following 3 years. Physical examination, laboratory testing, and imaging methods were performed according to the EAU guidelines (12).

Surgical Procedure

Preoperative workup

Palpable nodes are marked with a skin ink. When nodes are difficult to find, such as in obese patients, the node is marked guided by ultrasound. Intravenous second-generation cephalosporin is administered one hour before the procedure.

Surgical procedure

Patient is placed in supine position with thigh abducted. The video system must be placed on the opposite side of the limb that is under intervention at the level of the patient's waist. A 3-trocar configuration is applied distal to the femoral triangle. The working space is insufflated with CO₂ at 15 mmHg with quick space distention and kept as low as 5-10 mmHg for the duration of the procedure. The main landmarks are the adductor longus muscle medially, the sartorius muscle laterally and the inguinal ligament superiorly. The saphenous vein is located medially and the spermatic cord and the superficial inguinal ring superior-medially. The saphenous vein is dissected and preserved cranially up to the fossa ovalis close to the safeno-femoral junction. Modified template is recommended in order to reduce lymphatic complications. All cases underwent modified ILND technique. Following the fascia lata we identify the femoral vessels that constitute the deep limit for the dissection. All areolar tissue located medial to femoral artery must be removed. Small vessels are sealed with harmonic scalpel and control of larger lymphatics is obtained using clips. The specimen is totally dissected after ligation of the proximal portion of the lymphatic tissue at the deep portion of the femoral canal.

Perioperative care

Prophylactic intravenous antibiotics are administered routinely during hospital stay. In the 15 days postoperative period, patients can un-

dergo early walking and anti-embolic socks. Suction drain is removed when output is less than 50 mL/day. Hospital discharge does not depend on the drain output. It can be removed in the first 7-10 days post operative presentation. Postoperative use of low molecular weight heparin is not standard, as it is indicated according to each institution's protocol. Post operative antibiotics aren't needed.

Analyzed parameters

Perioperative data such as operative time, 90 postoperative days complications according to Clavien-Dindo classification, hospital stay, lymph node yield, days to remove drain, number of positive nodes, local and systemic recurrence and trocar recurrences were reported. Cancer specific (CSS) and overall survival (OS) were calculated for the pathological nodal stage (pN). Survival outcomes were compared with contemporary series of open surgery to estimate oncological control with VEIL.

Lymphedema was assessed by the same assistant physician according with physical exam and tonometer. Physiotherapy and compression rates also were evaluated.

Statistical Analysis

CSS was calculated using the Kaplan-Meier method, which was stratified by lymph node status (positive vs negative) and lymph node staging (pN1, pN2, or pN3). Survival time was calculated from the time of surgery to death or censored at the date of most recent follow-up for patients who did not die. Univariate Cox regression analysis was used to determine differences in cancer-specific death risk according to lymph node status and lymph node staging. All statistical analyses were performed using SPSS version 24 (IBM SPSS Statistics Subscription for Mac OS).

RESULTS

All 17 centers sent 127 cases to our database, however only 105 with complete follow-up were included in this report. Procedures were bilateral in 105 patients, with a total of 210 groins undergoing VEIL. Median follow-up was 10 years

(1-14 years). Clinical characteristics of our sample are shown in Table-1. Mean age of the patients included was 58 (45-68) years old.

Perioperative parameters are described in Table-2. VEIL was performed in 210 groins (105 patients). Mean operative time was 90 minutes (60-120). No conversions were reported. Mean hospital stay was two (1-3) days. Four (3.8%) hospital readmissions were necessary, one due to skin necrosis, two infected lymphoceles. Mean number of retrieved lymph nodes (range) was 10 (6-15).

Postoperative complications according to the Clavien-Dindo system are reported in Table-3. Skin complications corresponded to 4,8 % of the complications with only one (0.5%) severe case (Clavien-Dindo grade 3 or 4).

Lymphatic complications corresponded to 8.6% (14 lymphocele and 4 lymphedema). Three cases did not solve with manual compression, weight loss and exercises and needed further physiotherapy. Major complications in two (1.0%) severe cases needed surgical lymphocele drainage.

Sixteen patients (15.2%) died from penile cancer disease. Twelve (11.4%) died from other non-penile cancer causes. The median follow-up for cancer-free patients was 10 years. Four (3.8%) presented with pT1 disease, the majority (96.2%) presented with pT2 or pT3 disease. Seventy-one (67.6%) presented with no palpable lymph nodes, whereas 63 (88.7%) were high risk and eight (11.3%) had intermediate risk to develop regional metastasis, according with the EUA risk stratification. Similar results were observed in the Cubillas Risk Score.

Positive lymph nodes were observed in 26.7% of cN0 patients and negative lymph nodes were noticed in 41.1% in cN+ group. Cancer specific survival (CSS) and Overall Survival (OS) were reported in the Figure-1. In this series inguinal recurrence was 3,8% and disease progression were noticed in 41% of the pN+ group (16/39), with 3 cases in pN1 group, 3 cases in pN2 group and 10 in pN3 group. Ten year cancer specific survival was 84,8 % and 10-year overall survival was 73,3% (Figure-1). In this series inguinal recurrence was 3.8% and disease progression was noticed in 41% of the pN+ group (16/39), with 3 cases in pN1 group, 3 cases in pN2 group and 10 in pN3 group.

Table 1 - Patient characteristics (n = 105 patients).

		n
Age Mean (Range)	-	58 (45-68)
BMI	< 25	19
	25-30	63
	> 30	23
ECOG	0	85
	1	20
Tumor Pathological Classification (pT)	T1	4
Age Mean (Range)	-	58 (45-68)
BMI (%)	< 25	19 (18.1)
	25-30	63 (60)
	> 30	23 (21.3)
ECOG (%)	0	85 (81)
	1	20 (19)
Tumor Pathological Classification (pT) (%)	T1	4 (3.8)
	T2	23 (21.9)
	T3	78 (78)
Lymph Node Clinical Classification (cN)I(%)	N0	71 (67.6)
	N1	28 (26.7)
	N2	6 (5.7)
EAU Risk Group for NOI (%)	Intermediate	8 (11.3)
	High	63 (88.7)
Cubillas Risk ScoreI (%)	Intermediate	10 (14.1)
	High	61 (85.9)
CT ScanI (%)		90 (85.7)
MRI (%)		15 (14.3)

BMI = Body mass index; ECOG = Eastern Cooperative Oncology Group; EAU = European Association of Urology; CT = Computed tomography; MRI = Magnetic resonance imaging

Ten-year cancer specific survival was 84.8 % and 10-year overall survival was 73.3% (Figure-1).

Survival and histopathological analysis after bilateral VEIL are reported in Table-3. No portal seeding was documented. One-hundred-five patients with cN0-N2 underwent bilateral VEIL,

whereas after histopathological analysis, sixty-six revealed to be pN0, seventeen pN1, eleven pN2 and eleven pN3. The 10-year OS and CSS regarding regional lymph node disease are reported at Table-3. CSS for pN0, pN1, pN2 and pN3 were 100%, 82.4%, 72.7% and 9.1%, respectively.

Table 2 - Perioperative data and post operative complications according with Clavien-Dindo Classification of 210 VEIL procedures.

	Mean	Range			
Surgical time (minutes)	90	60-120			
Conversion	0	0			
Number of Lymph nodes retrieve	10	6-15			
Drainage time (days)	7	3-21			
Hospital Stay (days)	2	1-3			
Hospital Readmission (%)	4 (3,8)				
System	n	Overall (%)	Clavien 1 or 2 (n)	Clavien 3 or 4 (n)	Clavien 3 or 4 (%)
Skin	10	4.8%	9	1	0.5%
Lymphatic	18	8.6%	16	2	1.0%
Vascular	0	0	0	0	0
Overall	28	13.3%	25	4	1.9%

Table 3 - VEIL 10-year Overall and Cancer Specific (CS) Survival Rate according with Regional Lymph Node Disease (n = 105 patients).

Histopathological Stage (pN)	N	Overall Deaths (n)	Overall Survival (%)	CS* Deaths (n)	CS* Survival (%)
0	66	7	89.4%	0	100.0%
1	17	4	76.5%	3	82.4%
2	11	6	45.5%	3	72.7%
3	11	11	0.0%	10	9.1%
Total	105	28	73.3%	16	84.8%

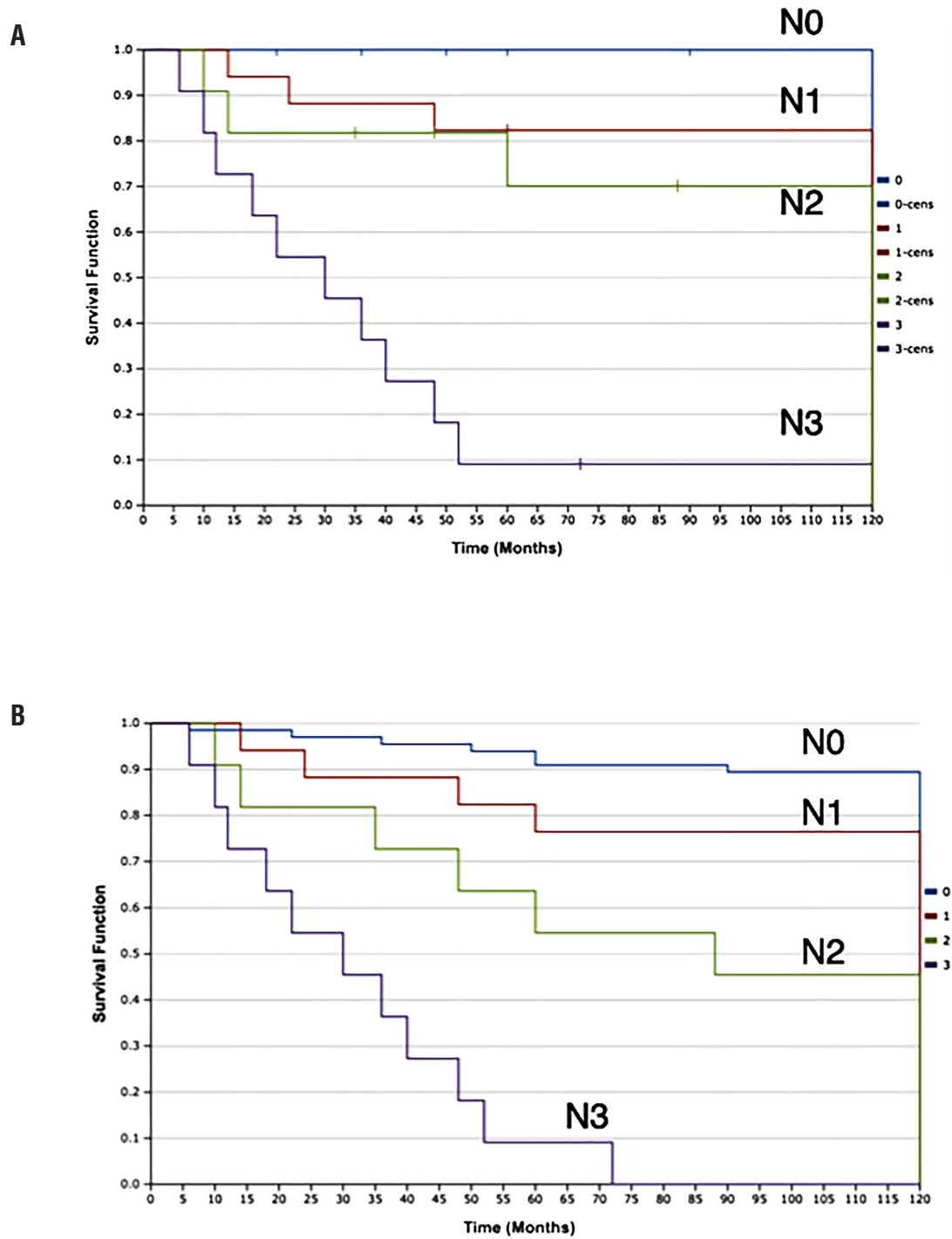
DISCUSSION

Inguinal management may vary according with the presence or absence of palpable lymph nodes. Those without palpable nodes and high risk of inguinal involvement need any kind of inguinal screening. In countries with high volume reference centers DNSL can achieve excellent oncological outcomes with false-negative rates of 5% regarding the low complication rates (10). In positive cases, ILND is mandatory. For patients with palpable nodes, EAU guideline recommends image staging with PET-CT and ILND as treatment (11). In Latin America there

is no report with good outcomes with DNSL (12) and PET-CT is not wide available to PC patients. In this scenario, the ILND is the standard of care in patients with risk of nodal spread.

After the period of the initial learning curve, VEIL has been gaining growing acceptance. One of the strengths of our study is that the pioneers of VEIL technique served as mentors for all surgeons performing the procedure in this study, ascertaining standardization of the technique across all participating centers. Our perioperative parameters showed acceptable operative time and no conversions at the 17 centers. The patients were discharged

Figure 1 - Kaplan-Meier curves of cancer specific survival and overall survival.



A) Ten-year cancer specific survival (CSS); B) Ten-year overall survival; The blue line represents the pN0 patients; The red line represents the pN1 patients; The green line represents the pN2 patients; The purple line represents the pN3 patients.

after a median of 2 (range 1- 5) days of hospital stay. A recent metanalysis including 290 patients in 10 comparative studies reports reduced morbidity of VEIL when compared to the open procedure. Oncological outcomes were similar in a short-term follow-up (25). Other two systematic reviews confirmed these results (26, 27).

Small number of subjects (since this is a rare disease) and absence of long term follow up is a major limitation of previous VEIL studies. So far, the studies with the longest follow-up reported good oncological outcomes after a median of 16 to 55 months (23, 24). In the present study we report the outcomes after a median of 120 months, which is the longest follow-up published so far.

Reduced skin morbidity is the most robust advantage observed in VEIL (4.8%) compared to open surgery series (30-60%) (5-8) followed by an important decrease in lymphatic morbidity. Some preliminary studies of VEIL reported higher incidence of lymphocele probably due to use of energy to seal lymphatic vessels. We refined our technique with caution to identify lymphatic vessels and clip the distal extremity instead of cauterizing it. This modification might have the potential to reduce the lymphatic events. Future comparative studies may prove this concept. Lymphedema and lymphocele are initially managed with conservative treatment with a low-fat diet, low hydric oral intake associated with compression and physiotherapy. A recent metanalysis shown reduced lymphoedema with VEIL vs O-ILND (OR=3.23, 95% CI [1.51, 6.88], P=0.002), however with no difference in lymphocele (OR=0.83, 95% CI [0.31, 2.23], P=0.720) (25). Surgical drainage along with third or fourth generation cephalosporin is administered when an infected lymphocele is suspected. Reoperation with surgical drainage and lymphatic control was carried out in only 2 cases.

Oncological principles include removal of all tissue superficial to the fascia lata inside the limits of the femoral triangle and medial to the femoral artery under fascia lata including the oval fossa and the femoral channel. To achieve complete removal of lymphatic nodes, ultrasound imaging and palpation before and after procedure were important to avoid leaving some "lost" nodes at the superficial area. Dissection of deep femoral triangle

was easier and vascular accidents were extremely rare and controlled laparoscopically, with no conversion needed. Mean number of retrieved nodes in this report was 10, which is comparable to the number of retrieved nodes reported in the open approach series. Most series showed that endoscopic techniques can remove an equivalent number of nodes when compared to the standard open surgery (4-8).

The number of metastatic lymph nodes reflects severity of the disease and influences survival. Some authors tried to discriminate between good and poor risk groups of patients. A significant difference was observed between 1 to 3 positive inguinal nodes vs. 4 or more nodes, in accordance with Li et al., in a 2018 retrospective series of 196 patients that demonstrated similar outcomes (28). In this current study we have found similar results. Most patients with pN3 disease had the worst CSS with early recurrence and poor survival two years after the surgery, with a CSS of only 10% after 5 years of follow up. Patients with pN1 and pN2 disease had similar OS and CSS rates.

Previous reports of open surgery showed positive lymph nodes in 20-30% of high-risk patients with no palpable nodes (cN0) (5-8). In the present series we found 26.7% of cN0 patients with positive inguinal nodes after histopathological analysis. In those with palpable nodes, a more intensive preoperative workup may be the key point to identify the high-risk patient in order to offer neoadjuvant (NAC) protocols to avoid upstaging ILDN/VEIL (29). In this series all NAC cases were excluded due lack of standardized protocols; some cases received taxane and others not, and different time to treat, many received NAC before and others after the penectomy. A future collaborative protocol from the Penile Cancer Collaborative Coalition-Latin America (PeC-LA) may answer this question.

Overall inguinal recurrence after VEIL was rare (3.8%). Pelvic and systemic recurrence are unfortunately higher in patients with extracapsular extension (pN3). Even when considering salvage chemo or radiotherapy mean survival in this situation was poor (6-9 months). No cases of trocar seeding were documented. We hypothesize that the outcomes were more correlated with aggressive biology of disease than with surgical technique.

The majority of patients of our series presented with low volume disease. Initial inguinal disease and adjuvant chemotherapy for positive inguinal nodes can explain the excellent survival curves observed in the present study. No patients with neoadjuvant treatment were considered in this study. Adjuvant chemotherapy was carried out for all pN2+ patients. Adjuvant radiotherapy was considered in the palliative care scenario and/or pN3 patients with local or systemic recurrence.

The findings of our study must be analyzed in light of some limitations. First, there are limitations due to the retrospective design of this study. Second, due to the rarity of PC, the study encompassed a long period of time with possible heterogeneity in the management of patients across different periods. Third, due to the learning curve of a new procedure, the initial cases at each participating center might have had a negative impact on the outcomes of our study. Fourth, despite standard follow-up protocol, retrospective studies may have underreported complications. We expect that with further dissemination of the technique to other centers that treat PC and with further improvements in the surgical technique we will see even better outcomes in the near future.

In the last few years, we have observed an increase in the adoption of a Robotic Assisted- VEIL (R-VEIL) approach, probably stimulated by a seemingly shorter learning curve when compared to pure laparoscopic VEIL (19, 27). Currently R-VEIL and conventional VEIL outcomes seem to be quite comparable. Further improvements associated with robotic platforms are expected for the near future. We speculate that R-VEIL will be standard of care in the next decade when inguinal lymph node dissection will be expanded for cases with N0-N2 disease. Future randomized studies will be important to demonstrate clinically important advantages of R-VEIL over pure VEIL.

CONCLUSION

In patients with low volume disease VEIL seems to offer excellent long term oncological control with reduced morbidity, specially the skin complications. In the absence of non-invasive stratification such as dynamic sentinel node bi-

opsy, VEIL emerges as an alternative staging tool with simultaneous nodal treatment to this aggressive disease.

CONFLICT OF INTEREST

None declared.

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Treating asthma in patients with enuresis: repercussions on urinary symptoms

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ABSTRACT

Background: Children presenting enuresis are more likely to be asthmatics. The association between enuresis and sleep-disordered breathing has already been demonstrated and several studies have shown at least partial improvement of two thirds or more of the cases of enuresis adenoidectomy. Studies have already described associations between enuresis and allergies but do not assess the repercussions of allergy treatment in enuretics.

Objective: This study aims to evaluate whether asthma treatment alters the course of enuresis and whether there is any predictive factor associated with this improvement.

Materials and Methods: Twenty patients (5 - 12 years old) with uncontrolled enuresis and asthma, received treatment for asthma. Children were also assessed for the presence of rhinitis and other allergies. The control of asthma was confirmed by a validated questionnaire and primary enuresis by clinical history and wet night diaries. Patients received only asthma treatment.

Results: At least partial improvement of enuresis was observed in 55% of the patients with an increase in 64.4% in the number of dry nights at the end of the study ($p=0.01$). The “presence of other allergies” and “obstruction seen in nasal endoscopy” positively influenced the improvement of urinary symptoms (OR = 3.350; CI 0.844–13.306) and (OR=1.272; CI 0.480–3.370), respectively.

Discussion: Until now, only patients presenting upper airway obstruction were known to benefit from the improvement of urinary symptoms when undergoing treatment for their respiratory problems. In our study, we found at least partial improvement in enuresis in 55% of our patients, with only clinical asthma treatment.

Conclusion: Controlling asthma in children with primary enuresis resulted in a significant increase in dry nights.

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INTRODUCTION

Enuresis is characterized by the involuntary loss of urine during sleep in children five years of age and older. According to the criteria of the International Children's Continence Society (ICCS), the definition of enuresis is established when there is at least one episode of urinary loss per month for at least three consecutive months, and after ruling out other organic diagnoses (1). The prevalence of enuresis is approximately 5 to 10% in children with seven years of age and 3% in adolescents with a great impact in quality of life (2).

Asthma is a heterogeneous disease caused by chronic inflammation of the lower airways (LOA) and clinically manifests with recurrent episodes of wheezing, dyspnea, tightness of the chest and coughing. The WHO lists asthma prevalence rates from 1 to 18% in different countries (3). Sleep-disordered breathing (SDB) are associated with upper airway obstruction (UAO). At the extremes are primary snoring, consisting only of respiratory noise, and Obstructive Sleep Apnea Syndrome (OSAS), in which there are repeated episodes of UAO collapse with drops in oxygen saturation (4). Epidemiological studies indicate a prevalence of 10 to 27% of primary snoring and 0.5 to 9% of apneas reported by parents (5).

The association between enuresis and SDB has already been demonstrated in several studies (6-9). Various studies have shown resolution of two thirds or more of the cases of enuresis following surgical resolution of SDB through an adenoidectomy, with or without tonsillectomy (6-9). Several pathophysiological mechanisms have been proposed to explain the association between enuresis and SDB. The main one is the release of brain natriuretic peptide (BNP) by cardiac cells after atrial wall distention due to increased negative intrathoracic pressure in upper respiratory obstruction. The increase in BNP levels is responsible for the increase in sodium and water excretion, in addition to inhibiting the release of vasopressin and the renin-angiotensin-aldosterone system (10). In addition, partial or complete UAO events in SDB, micro-recurrent awakenings caused by obstruction of the upper airways lead to an in-

creased threshold of awakening and stimulation such as bladder filling or contractions of the detrusor muscle become ineffective. (9, 10).

The association between enuresis and asthma at some point in life was described by Rawashdeh et al. (2002) (11). This association was also demonstrated by our group in schoolchildren from 6 to 14 years of age. We showed that children with enuresis are 2.8 times more likely to be asthmatic (8). Recently, a study carried out in Turkey confirmed a higher prevalence of enuresis in asthmatic children (12).

It is questioned whether this association found between enuresis and asthma is related to the concomitant presence of anatomic obstruction of the upper airway, as in OSAS. Abnormalities of the UAO and LOA can coexist according to the united airway hypothesis (13). Epidemiological studies have already confirmed the association between allergic rhinitis and asthma (14). Likewise, wheezing children have a higher incidence of snoring and nocturnal apnea. Apnea severity is associated with asthma severity, and the apnea-hypopnea index (AHI) is higher in children with uncontrolled asthma (15).

Since the association between asthma and enuresis is related to the presence of concomitant OSA, the resolution of UAO in enuretic and asthmatic patients would be the only determining factor for the resolution of urinary and asthma symptoms. This hypothesis, however, does not clarify the association between enuresis and a history of allergy confirmed by skin tests found by Rawashdeh et al. (2002) (11).

Several studies associate enuresis with allergic conditions such as urticaria, seasonal rhinitis, or drug or food allergy (11, 16, 17). The risk of enuresis is 1.7 times greater in patients with allergic rhinitis, and this risk was higher in boys and patients with comorbidities such as asthma and atopic dermatitis. (11, 18). These studies do not assess the repercussions of allergy treatment in enuretic patients with respiratory symptoms. Assuming that the treatment of respiratory allergies can influence the improvement of enuresis, we would have the possibility of shortening the approach in this group of patients with both diseases.

Therefore, this study aims to assess whether asthma treatment alters the course of primary enuresis in children from 5 to 12 years of age with both diseases, and whether “upper airway obstruction”, the “presence of rhinitis or other allergies reported by parents” and “obesity” are predictive of this improvement in urinary symptoms with asthma treatment.

MATERIAL AND METHODS

A prospective, uncontrolled interventional study was conducted, in which 20 patients from 5 to 12 years of age with uncontrolled asthma and with primary enuresis received inhaled treatment for asthma between September 2019 and April 2022.

This study was approved by the Human Research Ethics Committee (66961717.7./0000.51.03) and all parents and children signed a free and informed consent and ascent form, respectively.

The recruitment of participants with uncontrolled asthma and concurrent enuresis was carried out in pediatric pulmonology and pediatric urology outpatient clinics, in addition to an active search for patients at the level of public schools and basic health units, through posters placed with telephone contact. Only patients over 5 years and under 15 years of age, with current uncontrolled asthma and current enuresis were eligible to participate.

In order to define the presence of enuresis we followed the criteria of ICCS i.e., the answer “yes” by the parent to the question: “has your child wet the bed at night at least once a month for at least three consecutive months?”. Only children with primary enuresis (PE) participated in the project (1).

To define current asthma, parents initially answered the following question from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (19): “In the last 12 months, has your child had wheezing in the chest?” (20). Those who answered “yes” were then asked about the level of disease control in the last month. To select children with uncontrolled asthma, we used the Global Initiative for Asthma criteria (3).

The exclusion criteria were: age under five years, presence of diseases and/or use of medications that may interfere with the functioning of the bladder or urethral sphincter, diabetes, facial malformations and/or genetic syndromes with upper airway obstruction, secondary enuresis, controlled asthma, or refusal to participate in the study.

At the first consultation with the researcher, the selected patient and his/her guardian answered a detailed medical history for asthma prepared by the author herself, as well as for enuresis. The clinical diagnosis of allergic rhinitis was defined through the presence of symptoms such as nasal itching, nasal congestion, runny nose, sneezing, itchy eyes, or others, such as throat clearing. Other allergies such as urticaria without a defined cause, food or drug allergy, strophulus, anaphylactic shock, sudden swelling of the eyes and/or mouth and atopic dermatitis lesions were also questioned. The assessment of the level of asthma control in the last month was carried out in children from 5 to 11 years of age using the Childhood Asthma Control Test (c-ACT) questionnaire and the Asthma Control Test (ACT) questionnaire for children over 12 years of age.

The patients were then consulted at a pediatric urology outpatient clinic, where their guardians were instructed on the collection of the three-day voiding diary and the Dry Nights Diary, which corresponds to a record of dry or wet nights for 14 days. In the voiding diary, the child and their guardians recorded all episodes related to fluid intake and urination, as well as urgency and incontinence, for three days.

All patients underwent nasal endoscopy performed by the same otolaryngologist to diagnose and measure a possible cause of upper respiratory obstruction, such as adenoid hypertrophy. The examination was performed with a Pentax® 10RP3 fiber naso-pharyngo-laryngoscope and the classification of UAO described in percentage of UAO: from 0-25%; 25-50%; 50-75% and equal to or greater than 75% according to the Brodsky classification used to assess palatine tonsils (21).

Asthma treatment was started after the first interview, nasal endoscopy and collection of diaries. For that, inhaled beclomethasone was used at a dose of 200 mcg every 12 hours, admin-

istered through a spacer with mouthpiece, a device that allows for the application of the aerosol and minimizes problems of inadequate inhalation (22).

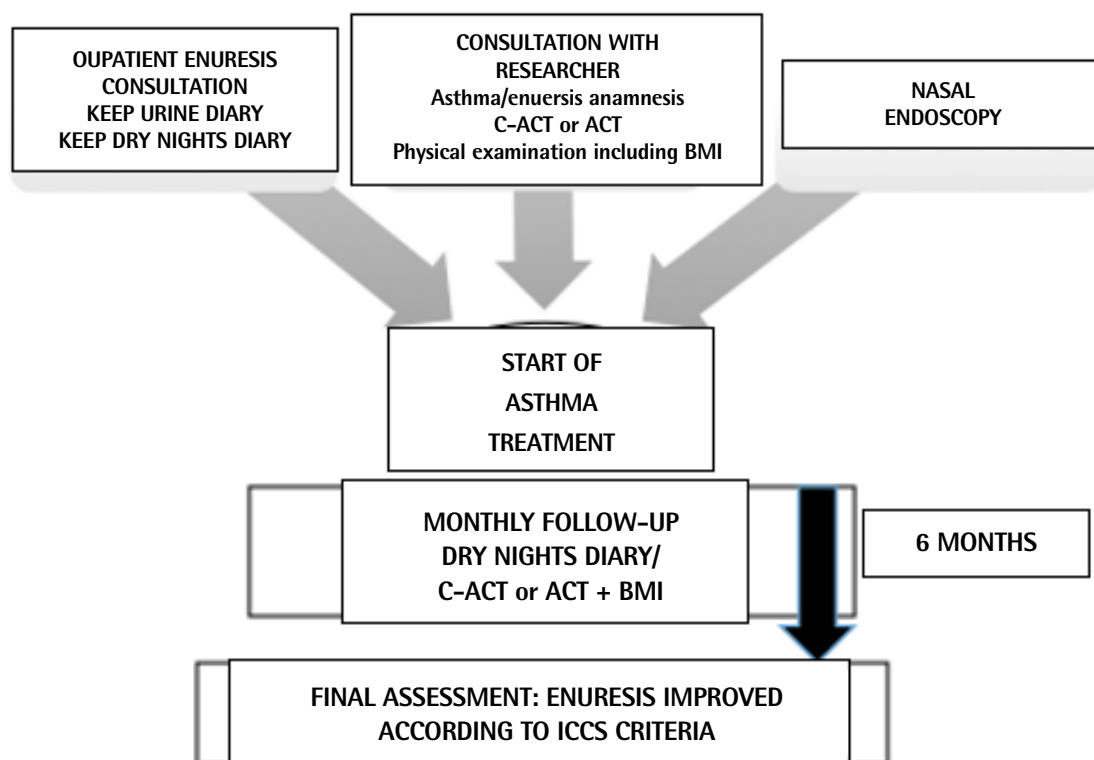
Subsequent consultations were monthly and, in addition to a physical examination (determination of BMI), it was included an assessment of the inhalation technique to avoid possible medication application errors, the patient's level of asthma control and the frequency of enuresis assessed by collecting a diary of continuous dry and wet nights. If the level of control indicated uncontrolled asthma (score less than 20 points on the c-ACT or ACT questionnaires) in any of the subsequent visits, even with continuous treatment and the inhalation mechanism performed properly, then the treatment was adjusted to a high dose of inhaled corticosteroid associated with a long-acting bronchodilator (salmeterol and fluticasone at a dosage of 25/125 mcg, two sprays every 12 hours) (21).

The project stages are listed in Figure-1.

Through a diary of dry and wet nights, we defined the number of dry nights over 30 days at the entrance and exit of the survey. We consider any improvement (partial and total improvement) above 50% improvement as per ICCS criteria (1).

Quantitative, continuous, or ordinal variables were described by their measures of central tendency (means or medians) while nominal or qualitative variables were described by their absolute values, percentages, or proportions. We used the Student's t test to compare the difference of the main continuous variable (number of dry/wet nights). In order to assess the measures of the effects of the independent variables (UAO; presence of allergies and obesity) with the binomial variable (improvement of enuresis according to ICCS criteria) we used logistic regression analysis. The statistical program Jamovi (Version 1.6) was used for the analyses. The strategy for selecting the

Figure 1- Description of the project stages from admission to the end of the survey.



variables was forward and the interpretation of the models was based on the analysis of the odds, AIC, deviance and R2 squared.

RESULTS

Thirty-two children with current primary enuresis and uncontrolled asthma who met the inclusion criteria for the study were recruited; of these, 12 dropped out of the study in the first months of treatment or even before starting it.

Therefore, a total of 20 children, 5 to 12 (7.4 ± 2.41) years of age, being 10 boys completed the entire six-month follow-up period. Five patients (25%), all boys, were obese for their age. All patients had symptoms of allergic rhinitis, as well as at least some other type of allergy (Table-1). The results of the nasal endoscopy described that 70% of the children had at least an UAO of 50% with 60% upper than 75%. A total of 15 children had non- monosymptomatic enuresis and the symptoms related were: urgency, urge incontinence, increased or infrequent micturition.

All patients presented control of their asthma symptoms in the first 2 months of treatment and 7 of the 20 patients (35%) required the addition of long-term bronchodilator (salmeterol) to the inhalation corticosteroid to achieve this control. There was no correlation between the need

for bronchodilator addition with improvement in urinary symptoms. After six months of asthma treatment and according to the ICCS classification, three patients had complete improvement of enuresis (improvement of urinary symptoms greater than 99%) and eight patients had partial improvement of enuresis (50 to 99% resolution of symptoms). Therefore, 55% of the patients had at least a partial response (50% or more reduction) in enuresis during the course of the study.

A mean increase in dry nights of 64.4% ($p < 0.01$) over 30 days was observed at the end of treatment (Figure-2).

Through logistic regression, the presence of other allergies and obstruction in nasal endoscopy positively influenced this improvement (OR=3.350; CI 0.844-13.306) and (OR=1.272; CI 0.480-3.370). The independent variable "obesity" did not influence the improvement in enuresis of the patients (OR = 0.361; CI 0.023-5.641) (Table-2)..

DISCUSSION

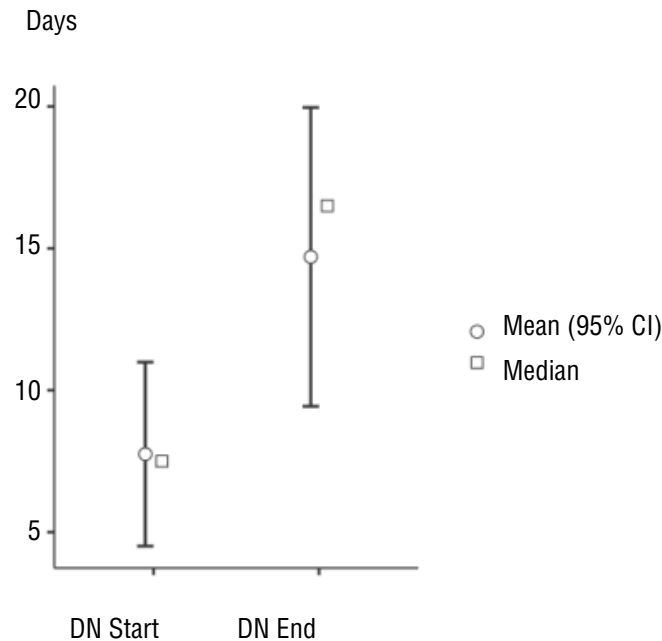
The results presented here show an improvement in enuresis with the treatment of asthma in patients with both diseases and, therefore, bring a new treatment perspective for this group of children presenting both enuresis and respiratory symptoms. Until now, only patients presenting upper airway obstruction were known to benefit from the improvement of urinary symptoms when undergoing treatment for their respiratory problems, as described that surgical intervention for UAO can treat up to two thirds of children presenting enuresis (6-9).

In our study, we found at least partial improvement in enuresis in 55% of our patients without any surgical intervention, with only clinical asthma treatment. The decrease in wet nights over 30 days, at the beginning and end of the study, was 35.6%.

Nocturnal enuresis has a spontaneous resolution rate of 15% per year. We followed our patients for about half a year and we were unable to differentiate spontaneous improvement from improvement with the proposed treatment. However, our results seem to be superior to spontaneous resolution (15% total resolution and 40% partial resolution in 6 months).

Table 1 - Characteristics of the population studied.

Characteristics assessed	n (%)
Obesity	5 (25%)
Male	5 (100%)
Female	0 (0%)
Presence of allergic rhinitis symptoms	20 (100%)
Non-monosymptomatic enuresis	15 (75%)
Report of other allergies (food, drug, etc.)	20 (100%)
One allergy	6 (30%)
Two allergies	7 (35%)
Three allergies	5 (25%)
Four or more allergies	2 (10%)

Figure 2 - Increase of the number of dry nights over 30 days at the entrance and exit of the survey.

DN start : Dry nights over 30 days at the entrance of the survey ; DN End: Dry nights over 30 days at the exit of the survey

We know that not all children with enuresis and SDB who undergo surgical correction of upper airway obstruction show improvement in urinary symptoms. Some authors have tried to elucidate the reason why some respond and others do not. It was observed that the response is better in those whose preoperative sleep study shows greater severity of apnea (greater number

of obstructive events and awakenings) (23). Due to the difficult access to the sleep study exam, we defined the degree of obstruction of the upper airways of our patients through flexible endoscopy and, therefore, we do not have information on the clinical repercussion of this obstruction during sleep (apnea and hypopnea index). The endoscopic evaluation is momentary and we assume that the

Table 2 - More stable binomial logistic regression model.

Binomial logistic regression		Deviance 21.4		AIC 31.4	R2 0.224	
Predictor	Estimate	95% Confidence Interval		SE	p	OR
		Lower	Upper			
Obesity	1.0201	-3.770	1.7301	1.4032	0.467	0.361
Allergies	1.2089	-0.170	2.5882	0.7037	0.086	3.350
Nasal endoscopy	0.2405	-0.734	1.2151	0.4973	0.629	1.272
WN in 30 days	0.1165	-0.279	0.0457	0.0828	0.159	0.089

Estimates represent the log odds of "CLASSIF. ICCS = 1" (improvement of enuresis) vs. "CLASSIF. ICCS = 0" (no improvement)
AIC=AKAIKE criteria; OR=Odds ratio; SE (Standard error); WN = wet nights

obstruction found may be overestimated by the edema found in situations of allergic rhinitis.

Among the factors that positively influenced the improvement of enuresis according to ICCS criteria, we had the presence of allergies other than rhinitis and asthma. All 20 patients reported symptoms of allergic rhinitis, which made it impossible to use this variable.

The association of enuresis with allergies is already well demonstrated in the literature (11, 12, 16-19). In a case-control study conducted in Turkey, 34% of enuretic patients presented with allergic illnesses, while these occurred in only 12% of the control group (24). Likewise, the association of enuresis with urticaria and food or drug allergies has been described in enuretic boys (16). These studies are observational and only show an association between atopy (allergic rhinitis, food allergies, urticaria, among others) with the presence of enuresis. There are no current reports of interventional studies to assess the repercussion of the treatment of allergic conditions on the symptoms of enuresis.

Likewise, we observed a positive association of the factor "obstruction seen in nasal endoscopy" with the improvement of enuresis after asthma treatment. This result initially surprised us since most studies that show an association between enuresis and obstructive sleep apnea in children also show improvement in urinary symptoms in most patients after a surgical procedure (adenoidectomy and/or tonsillectomy) (6-9). What may explain this positive association between the "obstruction seen in nasal endoscopy" and improvement in enuresis with asthma treatment would be the concomitant presence of allergic rhinitis (AR). In the literature, 60.8% of patients with adenoid hypertrophy have associated allergic rhinitis (25).

AR is associated with a higher risk of sleep disorders, such as insomnia or restless sleep, enuresis and SDB (both OSA and primary snoring) (25). It is now believed that rhinitis potentiates SDB and is even an independent predictor of unsuccessful adenotonsillectomy in children (26). In our study, 60% of the patients had an obstruction greater than 75% on nasal endoscopy and all pa-

tients reported symptoms of allergic rhinitis. The concomitant presence of AR was probably an aggravating factor in the results of the endoscopic examination.

As with asthma and enuresis, allergic rhinitis also compromises sleep (27). Some inflammatory mediators involved in this allergic process have been associated with sleep abnormalities verified in sleep studies: increased latency and decreased Rapid Eye Movement sleep time, as well as decreased latency for the onset of sleep (27). The sleep of enuretics is more fragmented, which leads to consequent sleep deprivation and collaborates to increase the awakening threshold of sleep (28). Likewise, sleep quality in asthma is inversely proportional to disease control. Worse objective measures of lung function, such as FEV1 (Forced Expiratory Volume in the first second), defined by spirometry, are associated with worse sleep quality (29). Therefore, asthma, AR, SDB and enuresis compromise patients' sleep in some way. It remains to be seen whether the control of any of these sleep disorders can retroactively interfere with the others, only through improved sleep quality.

A retrospective study in 393 children with primary enuresis monosymptomatic describe that winter season was associated with desmopressin treatment failure. We did not observe possible interference from colder weather due to the Covid-19 pandemic emergence and its protective measures during much time of the study (30).

Enuresis as a possible adverse effect of using topical corticosteroids for allergic rhinitis or long-acting bronchodilators for asthma has been described for the use of intranasal corticosteroids; enuresis was observed in a minority of children (3 cases in 106 children) and it does not correspond to the treatment route used in our study (31). Only 7 of the 20 patients required the combination of salmeterol with fluticasone to control their asthma. There was no correlation between the need for bronchodilator addition with improvement in urinary symptoms. All patients were instructed to use a spacer for asthma treatment and to perform posterior oral hygiene. These mechanisms decrease the systemic absorption of the medication.

One of the limitations found in the study was the high dropout rate (37.5%). We associate this occurrence with a behavior that is common to many patients with chronic diseases who require constant care (3). Another limitation was the impossibility of adding a control group: we understand that making a diagnosis of uncontrolled asthma and not providing the recommended treatment for it would be unethical.

Finally, it is clear that many studies are still needed to clarify the effectiveness of the clinical treatment of allergies on the repercussions of enuresis symptoms. However, we suggest that, in the future, a flowchart for the initial approach of enuretic patients with respiratory symptoms should be proposed. We could thereby direct the treatment of these patients, preventing them from being subjected to long and unsatisfactory treatments, generating frequent dropouts.

CONCLUSIONS

Treating and controlling asthma in children with primary enuresis resulted in a significant increase in dry nights. The presence of upper airway obstruction and other allergies positively improved results.

CONFLICT OF INTEREST

None declared.

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Nomogram to predict the risk of adverse outcomes in patients with residual stones following percutaneous nephrolithotomy

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ABSTRACT

Purpose: To investigate the risk factors associated with adverse outcomes in patients with residual stones after percutaneous nephrolithotomy (PCNL) and to establish a nomogram to predict the probability of adverse outcomes based on these risk factors.

Methods: We conducted a retrospective review of 233 patients who underwent PCNL for upper urinary tract calculi and had postoperative residual stones. The patients were divided into two groups according to whether adverse outcomes occurred, and the risk factors for adverse outcomes were explored by univariate and multivariate analyses. Finally, we created a nomogram for predicting the risk of adverse outcomes in patients with residual stones after PCNL.

Results: In this study, adverse outcomes occurred in 125 (53.6%) patients. Multivariate logistic regression analysis indicated that the independent risk factors for adverse outcomes were the diameter of the postoperative residual stones ($P < 0.001$), a positive urine culture ($P = 0.022$), and previous stone surgery ($P = 0.004$). The above independent risk factors were used as variables to construct the nomogram. The nomogram model was internally validated. The calculated concordance index was 0.772. The Hosmer-Lemeshow goodness-of-fit test was performed ($P > 0.05$). The area under the ROC curve of this model was 0.772.

Conclusions: Larger diameter of residual stones, positive urine culture, and previous stone surgery were significant predictors associated with adverse outcomes in patients with residual stones after PCNL. Our nomogram could help to assess the risk of adverse outcomes quickly and effectively in patients with residual stones after PCNL.

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INTRODUCTION

Percutaneous nephrolithotomy (PCNL) has been recommended as the primary modality or gold standard for renal stones more than 2 cm, with a high success rate (1, 2). Nevertheless, approximately 15%-25% of patients with large stones are left with stone fragments after initial PCNL (3). Residual stones less than 4 mm (or sometimes 5 mm), without urinary tract infection or obstruction, are typically referred to as clinically insignificant residual fragments (CIRF) and usually do not require special treatment (4). Tchey et al. also reported that stones can be eliminated naturally through lifestyle changes or medication when residual stones are less than 6 mm in diameter (5).

However, the latest studies have demonstrated that in some patients, small residual fragments or even CIRF are not expelled spontaneously after surgery and can lead to stone-related symptoms, including infection, hematuria, and back pain, and may require surgical treatment (6-9). In addition, the probability of stone growth in patients with upper urinary tract stones after surgery is 10% within 1 year, 35% within 5 years, and up to 50% within 10 years (10, 11). Consequently, the necessity of treating residual stones remains controversial.

Nomogram is a pictorial representation of a complex mathematical formula, employed for calculating probabilities of clinical events in the medical field. In recent years, it has been mentioned in various fields of researches including urolithiasis (12). For example, it can be used to predict urinary leakage complications after PCNL, as well as stone-free status following extracorporeal shock wave lithotripsy in pediatric patients (13, 14). However, to date, no study has focused on developing a nomogram to predict the risk of adverse outcomes in patients with residual stones following PCNL.

Therefore, this study aimed to investigate the risk factors related to adverse outcomes in patients with residual stones after PCNL and to construct a predictive model of adverse outcomes.

MATERIAL AND METHODS

Study design

We collected the clinical data of all patients who underwent PCNL for upper urinary tract

stones at First Affiliated Hospital of University of South China between January 1st, 2013, and May 31st, 2020. The inclusion criteria were as follows: (1) Patients who had residual stones after PCNL were included, (2) The postoperative residual stones were less than 7 mm in diameter. The exclusion criteria were as follows: (1) patients with incomplete clinical data; (2) patients lost to follow-up; (3) patients with malignant tumors; and (4) patients with obvious unilateral stenosis. A total of 233 cases were ultimately included according to the inclusion and exclusion criteria. The adverse outcome of residual stones was defined as an increase in the diameter of postoperative stones or the occurrence of stone-related symptoms, such as ipsilateral low back pain, fever, and gross hematuria, demanding rehospitalization (15). According to the presence or absence of adverse outcomes of postoperative residual stones, the patients were divided into an adverse outcome group ($n = 125$) and a control group ($n = 108$). Factors such as sex, age, body mass index (BMI), stone location (left or right), maximum stone diameter, serum creatinine, calcium in blood, urine pH value, maximum diameter of residual stones, urine bacterial and fungal culture, previous stone surgery, hypertension, and diabetes were compared between the two groups. All patients with positive urine cultures were treated with appropriate antibiotics for at least one week and underwent surgery only when the urine culture was negative. The other patients were treated with antibiotics 30 minutes before the beginning of the operation to prevent infection. All patients were treated by performing minimally invasive percutaneous nephrolithotomy (mPCNL) with an access sheath of 18F using a holmium laser for lithotripsy (No. SRM-H3B, Shanghai Ruikeen Laser Technology Co., Ltd.) for upper urinary tract stones. The holmium laser power was set as 50 W. At the end of the procedure, a 16 Fr drainage tube was inserted as a nephrostomy catheter in each patient. The study was approved by the Ethics committee of the First Affiliated Hospital of University of South China (IRB NO. 2022110114002). All the experiment protocol involving humans was in

accordance to guidelines of institutional and Declaration of Helsinki. Informed consent was received from all patients included in this study.

Data collection

All patients were diagnosed with renal or upper ureteral calculi by urinary computed tomography (CT) before the operation, and all patients were reexamined by urinary CT examination within 48 hours postoperatively. The maximum diameter of the stone was measured using CT by two radiologists at our institution. The average value of the two measurements was taken if the difference was within 1 mm; if the difference exceeded 1 mm, a third professional remeasured the stone diameter, and the average value of the two closest measurements was used. All patients were followed at least every 6 months during the first year and annually thereafter. Follow-up CT scans were typically performed annually or when a symptomatic episode occurred. Confirmation of an increase in residual stones and the incidence of stone-related symptoms was obtained by interview and CT examination. The rest of the clinical data were from the archived data of the medical records department of our institution.

Statistical Analysis

Data were analyzed using the software Statistical Package for Social Science version 25.0 (IBM, USA). The continuous variables were calculated as the mean \pm SD and analyzed by a two-sample *t* test. The chi-square test was used to analyze the categorical variables. In multivariate analysis, binary or multiple logistic regression analysis was used, and *P* values < 0.05 were considered statistically significant. According to the results of the multivariate logistic regression analysis model, the nomogram prediction model was created using the R software 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) *rms* package. Then, the bootstrap method was used for repeated sampling 1,000 times to internally validate the nomogram model, and a discrimination test was performed by calculating the consistency index (C-index) and area under the curve (AUC), drawing the calibration curve, and performing the Hosmer-Lemeshow goodness-of-fit test to assess the model accuracy.

RESULTS

Of the 233 patients with residual stones after PCNL for upper urinary tract calculi, adverse outcomes occurred in 125 patients (53.6%), including 64 males (51.2%) and 61 females (48.8%), with a mean age of 50.58 ± 11.39 years. Among them, 18 cases (14.4%) only had an increase in stone diameter without clinical symptoms, and 105 cases (85.6%) had stone-related symptoms. The median time post-PCNL until the development of adverse outcomes was 33.60 months (interquartile range [IQR] 20.50-48.75). There were 108 patients with no adverse outcomes (46.4%), including 70 male patients (64.8%) and 38 female patients (35.2%), with an average age of 53.01 ± 13.24 years. The median clinical follow-up period was 40.47 months (IQR 24.00-59.75).

Table-1 presents the univariate analysis of variables between the two groups of patients. Compared with the control group, more patients with positive urinary cultures ($P < 0.001$) and longer maximum diameter of residual stones (3.42 ± 1.61 vs. 2.12 ± 1.41 , $P < 0.001$) were found in the adverse outcome group. Female patients had a higher incidence of adverse outcomes than male patients ($P < 0.05$). Among patients with previous urinary stone surgery, the incidence of adverse outcomes of patients with residual stones after PCNL was higher in the adverse outcome group than in the control group ($P = 0.002$). Patients with residual stones in the renal pelvis or ureter had a higher rate of the adverse outcome than those with residual stones in the lower calyx ($P = 0.026$). Notably, there were no significant differences in age, maximum stone diameter, stone laterality, serum creatinine, calcium in blood, urine pH value, BMI, hypertension, or diabetes between the two groups.

Subsequently, the variables with $p < 0.05$ in the univariate analysis were enrolled in the stepwise multivariable logistic regression model based on maximum likelihood estimation. The risk factors such as residual stone size, urine culture, sex, previous stone surgery, and residual stone location were incorporated into this model. Finally, the results revealed that the independent risk factors included residual stone size (OR = 1.707, $P < 0.001$), positive urine culture (OR = 2.322, $P =$

Table 1 - Univariate analysis of variables between the two groups of patients.

Variables	Adverse outcome group (n = 125)	Control group (n = 108)	Statistical value	P
Age (years)	50.58 ± 11.39	53.08 ± 13.24	t = 1.554	0.122
Maximum stone diameter (cm)	2.03 ± 0.91	1.95 ± 0.88	t = -0.668	0.505
Serum creatinine (µmol/L)	97.14 ± 39.47	104.81 ± 53.31	t = 1.258	0.210
Calcium in blood (mol/L)	2.23 ± 1.96	2.21 ± 1.12	t = -0.689	0.386
Urine pH value	6.07 ± 0.70	6.09 ± 0.74	t = 0.031	0.763
Residual stone size (mm)*	3.42 ± 1.61	2.12 ± 1.41	t = 6.475	< 0.001
BMI (kg/m ²)	23.49 ± 3.49	22.76 ± 3.36	t = -1.622	0.106
Hypertension				
with/without	90/35	79/29	X ² = 0.038	0.845
Diabetes				
with/without	110/15	99/9	X ² = 0.843	0.359
Stone laterality				
left/right	66/59	49/59	X ² = 1.283	0.258
Gender				
male/female	64/61	70/38	X ² = 4.395	0.036
Urine culture				
positive/ negative	49/76	16/92	X ² = 17.128	< 0.001
Previous stone surgery				
Yes/No	51/74	24/84	X ² = 9.161	0.002
Residual stone location, n (%)			X ² = 9.242	0.026
Lower pole calix	58(46.4) ^a	68(63.0) ^a		
Middle pole calix	40(32.0) ^{a,b}	29(26.9) ^{a,b}		
Upper pole calix	14(11.2) ^{a,b}	8(7.4) ^{a,b}		
Renal pelvis/ureter	13(10.4) ^b	3(2.8) ^b		

* Residual stone size refers to its maximum diameter.

^{a,b} = No significant difference between the same superscripts.

0.022), and previous stone surgery (OR = 2.548, P = 0.04) (Table-2).

Based on the above results, we incorporated significant variables from the multivariate logistic regression analysis into R software to construct a nomogram (Figure-1). The bootstrap method was repeated 1000 times to verify the nomogram model internally. The superiority of the prediction model was tested by the Hosmer-Lemeshow goodness-of-fit

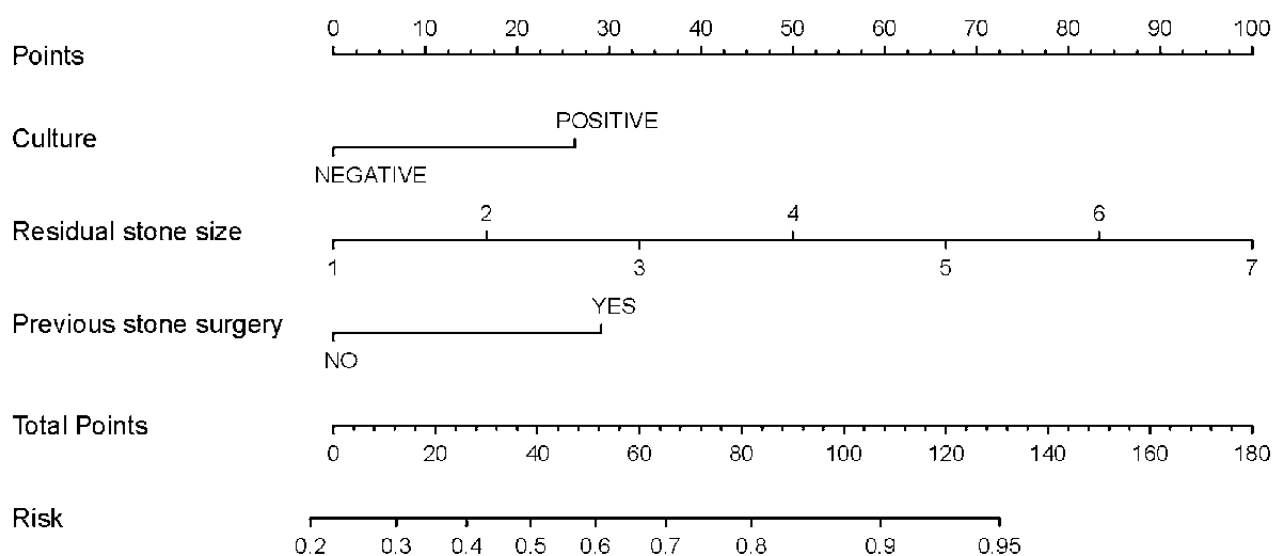
test (P = 0.055 > 0.05) and calibration curve (Figure-2A). The calibration curve of the nomogram model was close to the standard curve. The calculated C-index was 0.772. The effectiveness of the prediction model was further evaluated by the area under the ROC curve (Figure-2B). The area under the ROC curve was 0.772 (95% CI: 0.712 - 0.832), indicating that the model exhibits high accuracy in predicting the adverse outcome of residual stones after PCNL.

Table 2 - Multivariate logistic regression analysis of risk factors for the adverse outcome in patients with residual stones after PCNL.

Variables	Category	OR	95%CI	P
Residual stone size (mm)	-	1.707	1.370 – 2.127	<0.001
Urine culture	positive/ negative	2.322	1.132 – 4.765	0.022
Previous stone surgery	Yes/No	2.548	1.341 – 4.841	0.004

Abbreviations: OR = odds ratio; CI = confidence interval

Figure 1 - Nomogram for predicting the probability of the adverse outcome in patients with residual stones after PCNL.



Abbreviations: Culture: Preoperative urine culture; Residual stone size: the maximum diameter of residual stones; Previous stone surgery: Previous urinary stone surgery.

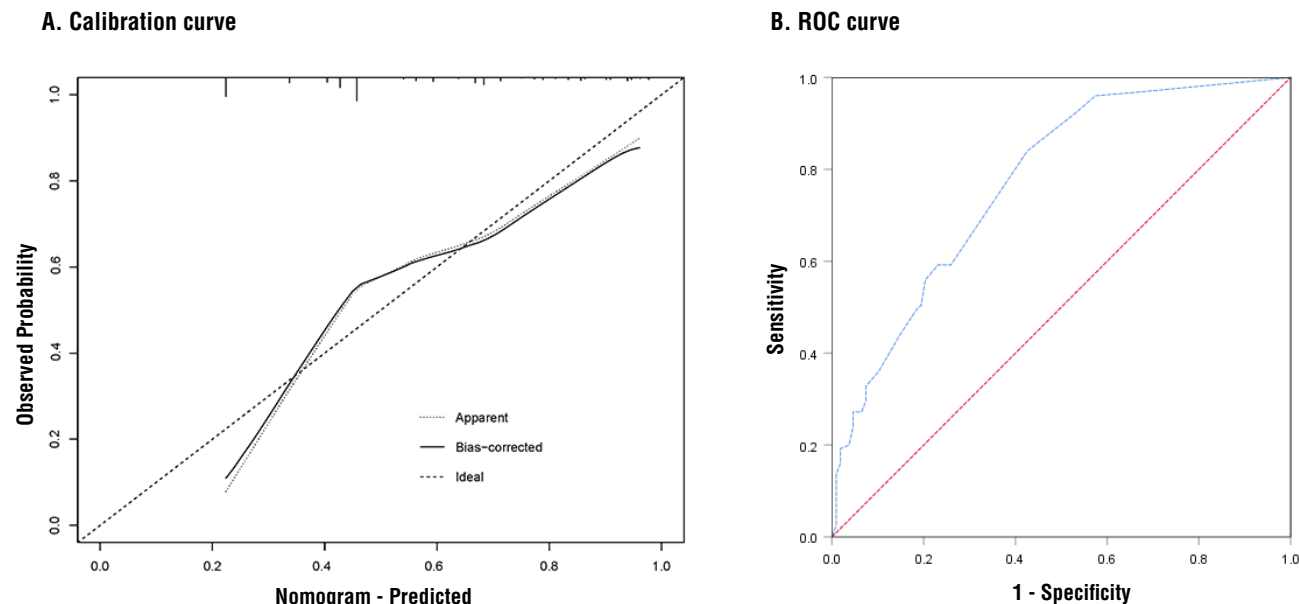
DISCUSSION

Upper urinary tract calculi are one of the most common diseases worldwide. In the past 30 years, the incidence of upper urinary tract calculi has been increasing continuously (16). The harm of upper urinary tract calculi to the human body is significant (17, 18). Although PCNL is one of the primary methods for the treatment of upper urinary tract calculi, PCNL cannot completely eliminate stone fragment residues. The primary aim of our study was to determine the risk factors associated with adverse outcomes in patients with residual stones after PCNL and to establish a nomogram based on these risk factors. This approach represents a completely new logistic regression analysis of patients with residual stones

after PCNL, and the risk factors can be obtained easily to assess the risk of adverse outcomes and provide appropriate follow-up plans and early treatment.

Based on previous studies (19, 20), we have concluded that postoperative residual stones may have the following hazards: (1) Postoperative residual stones may cause and perpetuate urinary tract infection. (2) New stones may form with residual stones as the core. (3) The movement of residual stones after surgery may cause obstruction and trigger new symptoms. A study revealed that stones larger than 7 mm exhibited a reduced rate of spontaneous elimination and are more likely to cause clinical symptoms or require surgical intervention (21). If the residual stone size following PCNL exceeded 7 mm, the operation was considered incompletely successful, and

Figure 2 - Evaluation of the predictive performance. (A) Calibration curve of prediction model for the adverse outcome in patients with residual stones after PCNL. (B) ROC curve of prediction model for the adverse outcomes in patients with residual stones after PCNL (AUC = 0.772)



Abbreviations: AUC = area under the curve; PCNL = percutaneous nephrolithotomy; ROC = receiver operating characteristic

further treatment would be necessary. Consequently, this study exclusively included patients with residual stones measuring less than 7 mm in diameter. Although many hazards can be caused by postoperative residual stones, it remains difficult to completely remove all stones due to limitations in surgical equipment, medical technology, and surgical experience. In the past, CIRF was not considered to require specific treatment. However, in recent years, the significance of these residual stones has become controversial. Olvera-Posada et al. evaluated 44 patients with residual stones after PCNL and found that 43% of patients had a stone-related event, with most of them undergoing surgical intervention (3). Osman et al. conducted a similar study, with a median follow-up of 36.2 months. Thirty-three percent of their patients experienced an increase in residual stone size (22). Therefore, in the future treatment of upper urinary tract stones, removing as many residual stone fragments as possible may become a new challenge for urologists. In this study, we found that residual stone size was an independent risk factor for predicting adverse outcomes in patients with residual stones after PCNL. Larger postoperative residual stone sizes were

associated with a greater possibility of adverse outcomes, highlighting the necessity of clinical intervention for relatively large postoperative residual stones.

Although there are controversies regarding the treatment of postoperative residual stones, we believe it is important for urologists to help every stone patient eliminate all stones completely in the future. Many researchers have developed novel techniques for the treatment of postoperative residual stones. Friedlander et al. developed a novel device that captures stones in a sealed polyethylene bag in vivo to prevent dispersion of stone fragments during PCNL. The authors reported that the use of this device significantly reduced the median time for stone fragmentation (23). Tan et al. developed a magnetic tool to improve the efficiency of lithotripsy under a ureteroscope. Compared with the traditional Ni-Ti alloy stone extraction basket, the time for magnetic stone extraction tools to extract residual stone fragments is reduced by 53%. Although the visual field of magnetic stone extraction tools is worse than that of traditional stone extraction tools, this design is under further development and improvement (24, 25). With the emergence, innovation, and application of new

technologies, the treatment of residual stones after upper urinary tract stone surgery will become much easier in the future of Urology.

In this study, we also found that bacterial or fungal infection in urine was an independent risk factor for adverse outcomes in patients with residual stones after PCNL. Among the cultured bacterial species, *Escherichia coli* was the most common, with 27 (55.1%) cases in the adverse outcome group and 10 (58.8%) cases in the control group. Previous studies have shown that in *Escherichia coli* infected kidneys, the expression of osteopontin is elevated in renal tubular epithelial cells, which leads to tubular epithelial cell damage and induces a renal inflammatory response that activates multiple immune response signaling pathways, thereby promoting stone formation (26). Furthermore, a study reported that urinary tract infections and stones potentiate each other (27). Therefore, to reduce the risk of adverse outcomes in patients with residual stones after PCNL, urinary tract infections should be avoided whenever possible.

Previous stone surgery was another risk factor. Similarly, Keskin analyzed 417 patients undergoing urinary surgery and found that readmission rates were significantly higher in patients with previous stone treatments than in patients with no history of stone treatments (9). Patients with a history of previous stone surgery are also at an increased risk of stone recurrence after another subsequent stone procedure (except for second stage surgery), likely because they are already recurrent stone formers. These patients may possess certain undetected risk factors, such as metabolic status, genetic factors, and eating habits, leading to the recurrence of stones, which eventually will require intervention (28). The specific mechanism involved deserves further study.

Based on the above three independent risk factors, residual stone size, positive urine culture, and previous stone surgery, we constructed a nomogram to predict the probability of adverse outcomes. Through internal verification, the C-index of the nomogram was 0.778, indicating a good consistency. The risk factors can be easily obtained. This prediction model can not only help in clinical decision-making but also provides a visual tool to assess the incidence of adverse outcomes in patients with residual stones after PNCL.

However, several limitations of this study must be highlighted: (1) The sample size of cases was relatively small. (2) The results were derived from a retrospective analysis, and a certain degree of selection bias was present. (3) This was a single-center study, and a multicenter study should be performed to further verify our results.

CONCLUSION

In conclusion, a larger residual stone diameter, positive urine culture, and previous stone surgery were significant predictors associated with adverse outcomes in patients with residual stones after PCNL. Our nomogram could help to simply and effectively assess the risk of adverse outcomes in patients with residual stones after PCNL.

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Doctors Feng Xie and Shidong Deng contributed similarly as first authors.

CONFLICT OF INTEREST

None declared.

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Predictors of early catheter replacement after HoLEP. Results from a high-volume laser center

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ABSTRACT

Introduction: The aim of the study was to investigate clinical and surgical factors associated with early catheter replacement in patients treated with Holmium Laser Enucleation of the Prostate (HoLEP).

Materials and Methods: Data of patients treated with HoLEP at our Institution by a single surgeon from March 2017 to January 2021 were collected. Preoperative variables, including non-invasive uroflowmetry and abdominal ultrasonography (US), were recorded. Bladder wall modifications (BWM) at preoperative US were defined as the presence of single or multiple bladder diverticula or bladder wall thickening ≥ 5 mm. Clinical symptoms were assessed using validated questionnaires. Only events occurred within the first week after catheter removal were considered.

Results: Overall, 305 patients were included, of which 46 (15.1%) experienced early catheter replacement. Maintenance of anticoagulants/antiplatelets (AC/AP) therapy at surgery ($p=0.001$), indwelling urinary catheter ($p=0.02$) and the presence of BWM ($p=0.001$) were more frequently reported in patients needing postoperative re-catheterization. Intraoperative complications ($p=0.02$) and median lasing time ($p=0.02$) were significantly higher in this group. At univariate analysis, indwelling urinary catheter ($p=0.02$), BWM ($p=0.01$), ongoing AC/AP therapy ($p=0.01$) and intraoperative complications ($p=0.01$) were significantly associated with early catheter replacement. At multivariate analysis, indwelling urinary catheter (OR: 1.28; $p=0.02$), BWM (OR: 2.87; $p=0.001$), and AC/AP therapy (OR: 2.21; $p=0.01$) were confirmed as independent predictors of catheter replacement.

Conclusions: In our experience the presence of indwelling urinary catheter before surgery, BWM and the maintenance of AC/AP therapy were shown to be independent predictors of early catheter replacement after HoLEP.

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INTRODUCTION

Latest European Guidelines on non-neurogenic male LUTS include Holmium Laser Enucleation of the Prostate (HoLEP) among treatment options for large benign prostatic hyperplasia (BPH). When compared to transurethral resection of prostate (TURP), HoLEP demonstrated similar long-term safety and efficacy, while being characterized by a slightly more favorable perioperative profile (1) Indeed, several studies reported that HoLEP is generally associated with shorter hospitalization and catheterization times, as well as lower transfusion and retreatment rates as compared to standard TURP (2, 3). Recent literature outlined similar findings in elderly and highly comorbid patients, thus making HoLEP a safe and valuable treatment option even in such subgroups (4, 5).

Despite the good perioperative profile, some patients still experience postoperative acute urinary retention (AUR) after catheter removal, thus leading to prolonged hospitalization, longer indwelling catheter time and higher readmission rates. However, to date only little evidence is available on perioperative variables associated with AUR following HoLEP (6, 7).

We hypothesized that several patient- and surgery-related features may act as adverse com-

peting factors in inducing postoperative AUR. To fill this gap, in the present study we retrospectively reviewed our data aiming to investigate clinical and surgical predictors of early catheter replacement in patients treated with HoLEP for BPH.

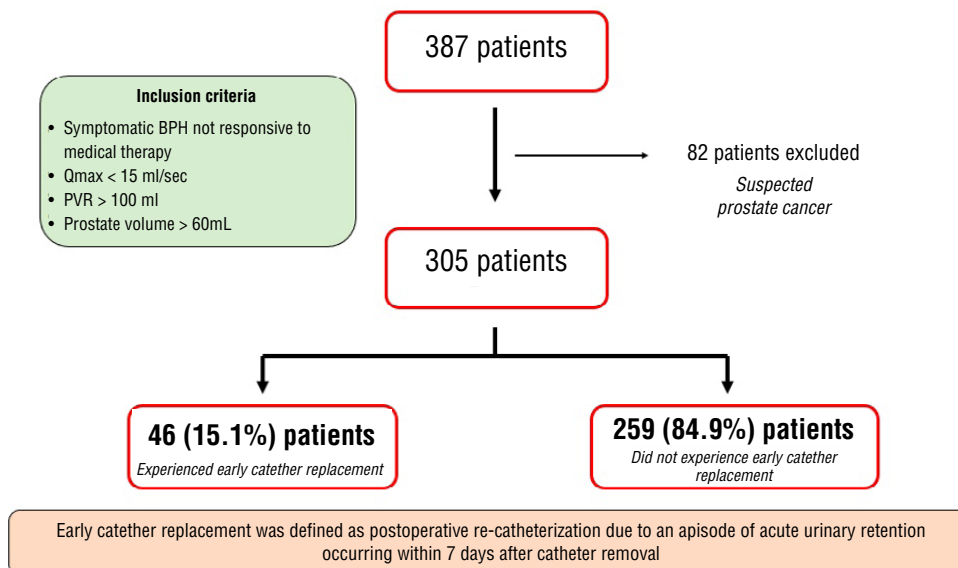
MATERIALS AND METHODS

Patient dataset

After Institutional Review Board approval, clinical and surgical data of patients treated with HoLEP at our center from March 2017 to January 2021 were collected. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all patients signed a written informed consent before enrollment.

Main inclusion criteria were: 1) symptomatic BPH not responsive to medical therapy, according to EAU guidelines (1); 2) Preoperative max flow rate (Qmax) at uroflowmetry < 15 mL/sec and/or post-voiding residual (PVR) > 100 mL; 3) Prostate volume > 60 mL. Patients with a prostate specific antigen (PSA) ≥ 4 ng/mL or suspect rectal examination underwent multiparametric magnetic resonance imaging (mpMRI) to rule out prostate cancer. Those with persistent suspect of prostate cancer were excluded from the study (Figure-1). All patients included in the study underwent pre-

Figure 1 - Flow chart depicting the study design.



operative non-invasive uroflowmetry with PVR examination and abdominal ultrasound (US) to assess prostate volume, presence of median lobe or bladder stones and bladder wall modifications (BWM), defined as the presence of either single or multiple bladder diverticula or bladder wall thickening ≥ 5 mm (1, 8).

Surgical-related variables included enucleation technique, overall operative time, enucleation time, morcellation time, lasing time, energy delivered and intraoperative complications. Since HoLEP relies on the contemporary use of laser and pulling movements, to be more accurate in quantifying the amount of energy delivered, we decided to separately report lasing and enucleation time. Particularly, enucleation time was defined as the time needed to enucleate the prostatic adenoma with both laser energy delivery and gentle mechanic traction, while lasing time referred to energy delivered for both enucleation and hemostasis. Overall surgical time included enucleation, morcellation and hemostasis time. Early and delayed postoperative complications were defined as any event occurring ≤ 30 th or > 30 th postoperative day, respectively, altering the normal postoperative course and/or delaying discharge. Postoperative complications were graded according to Clavien-Dindo classification.

A standard preoperative antibiotic regimen with Piperacillin-Tazobactam 4.5 gr was administered to all patients. In case of allergies, the alternative antibiotic therapy was Vancomycin 15 mg/Kg iv + Gentamicin 5 mg/Kg iv.

No special protocol was applied for patients taking AP/AC therapy. In case of suspension of coumadin, this was replaced with low molecular weight heparin (LMWH) 5 days before the procedure, while a suspension period starting from 48 hours before the procedure was generally applied for novel oral anticoagulants. The LMWH was therefore continued postoperatively before reintroducing AC therapy for a variable period defined by the anesthesiologists in relation to the individual risk profile. In case of AP therapy, a LMWH with prophylactic dose was routinely applied as in any other endoscopic surgery.

Surgical technique

All procedures were performed by a single surgeon, and enucleation was conducted according to operator's preference with either the three-lobes or the *en-bloc* with early apical release technique, as described in previous investigations (Figure-2) (9, 10).

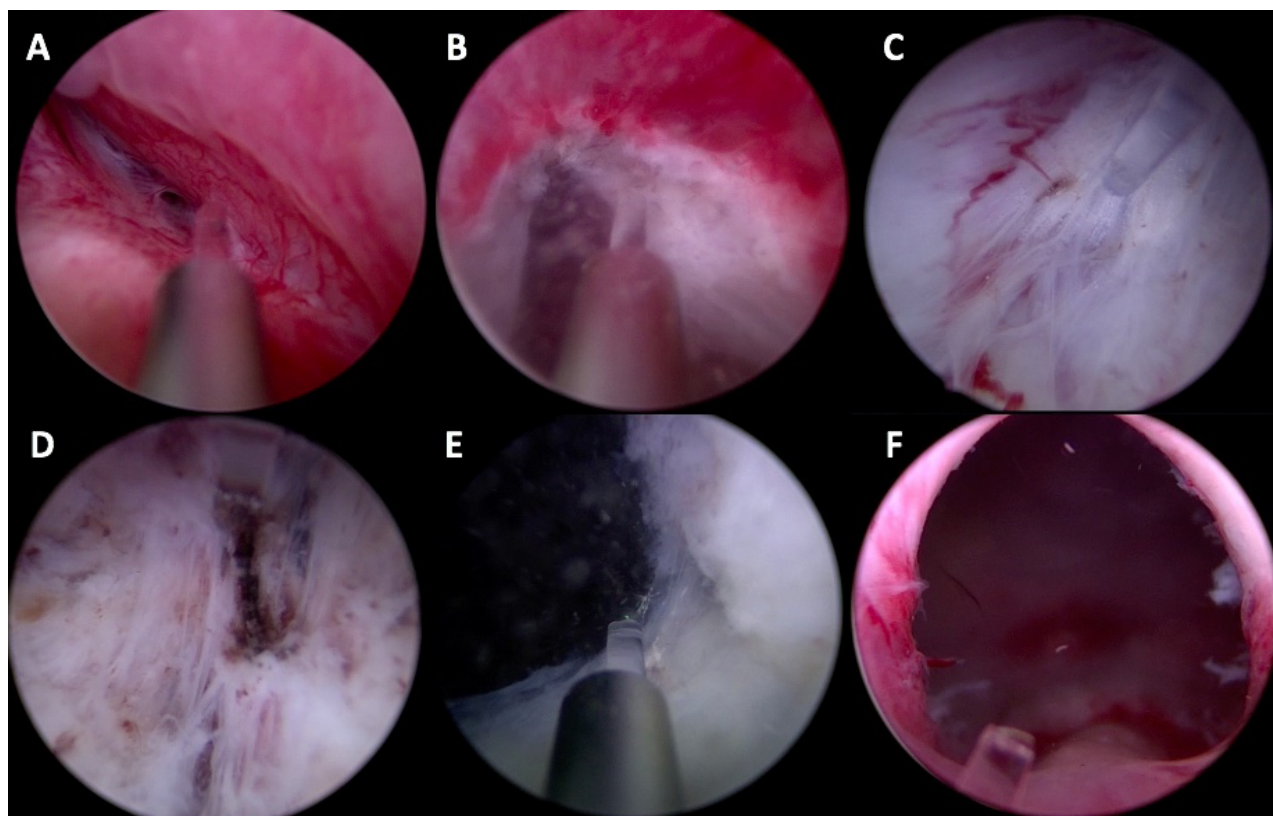
All procedures were carried out under general anesthesia using the 120W Versapulse holmium laser machine (Lumenis, Yokneam, Israel) with a 550- μ m end laser fiber (Boston Scientific, AccuMax 550 Laser Fiber). Laser energy was set at 2 J X 45 Hz, 90 W, for enucleation and 2 J X 30 Hz, 60 W, for coagulation. A 26F Storz continuous flow resectoscope sheath was modified by inserting the 26F inner sheath, and a laser bridge to stabilize the fiber. A 30° down lens was preferred. The enucleated prostatic adenoma was then morcellated using a morcellator (Lumenis, Versacut). After surgery, a 22F three-way catheter was inserted and bladder irrigation was performed using saline solution. We usually removed urethral catheter on 3rd postoperative day, in case of clear urine output.

Outcome measures and follow-up

Assessment visits, including uroflowmetry and PVR determination by abdominal US, were scheduled at screening visit on day 0 and then at 3 and 12-month follow up after the surgical intervention. Clinical evaluation was assessed using the Italian version of the following validated questionnaires: IPSS (international prostate symptom score) (11), OAB-q SF (Overactive Bladder Questionnaire-Short Form) (12), ICIQ-SF (International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form) (13) and the IIEF-5 (international index of erectile function) (14).

Endpoints

Patients were divided into two groups according to early catheter replacement, defined as postoperative re-catheterization due to an episode of AUR that occurred within 7 days after catheter removal. The primary endpoint of our study was to apprise any difference between the two groups in terms of perioperative and/or surgical variables.

Figure 2 - HoLEP surgical steps.

A) Identification of the anatomical dissection plane laterally at the level of the veru-montanum; B) Apical dissection at 12 o'clock position; C) Developing of the dissection plane circumferentially; D) Anterior dissection; E) Access to the bladder anteriorly; F) Final result.

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 not-normal distribution, respectively (normality of variables' distribution was tested by Kolmogorov-Smirnov test). Proportional data were assessed using the Chi-square test. To assess clinical differences from baseline to follow-up the median change and test for non-parametric differences were applied. All tests were two-sided. Statistical significance was set as $p < 0.05$. Statistical analysis was performed using SPSS v. 27 (IBM SPSS Statistics for Mac, Armonk, NY, IBM Corp).

RESULTS

Overall, 305 patients were included in our study and stratified into two groups according to

postoperative re-catheterization. Forty-six (15.1%) experienced early catheter replacement due to an episode of AUR. Particularly, 9 (19.6%) patients underwent postoperative re-catheterization within the first 24 hours after catheter removal. Preoperative characteristics are reported in Table-1. Particularly, patients needing catheter replacement showed a significantly higher use of anticoagulant (AC) or antiplatelet (AP) medications at surgery (11.5% vs 41.3%, $p = 0.001$) and a higher rate of BWM (6.9% vs 19.5%, $p = 0.001$), as well as a higher rate of indwelling urinary catheter before surgery (14.2% vs 34.7%, $p = 0.02$).

Intraoperative and surgical features are described in Table-2. Patients experiencing re-catheterization presented a longer median lasing time (30 min [IQR 29 - 40] vs 38 min [IQR 29 - 48], $p = 0.02$), while enucleation and morcellation time, total energy delivered during HoLEP and enucleation technique were comparable between the two co-

Table 1 - Preoperative characteristics of 305 patients treated with Holmium Laser Enucleation of the Prostate (HoLEP).

Variables	Group A (n=259; 84.9%)	Group B (n=46; 15.1%)	p-value	
Preoperative characteristics				
Age (years) (median, IQR)	69 (65 – 74)	70 (64 – 75)	0.13	
BMI (kg/m ²) (median, IQR)	26 (23.7 – 28.1)	26.1 (24.4 – 28.5)	0.73	
CCI age adjusted (median, IQR)	3 (1 – 4)	3 (1 – 4)	0.43	
ASA score (median, IQR)	2 (1 - 3)	2 (1 - 3)	0.21	
ACs/APs therapy at surgery (n, %)	30 (11.5)	19 (41.3)	0.001	
Bladder stone (n, %)	34 (13.1)	7 (15.2)	0.45	
Median prostate lobe (n, %)	101 (38.9)	19 (41.3)	0.23	
BPH therapy (n, %)	Alpha-blockers	136 (52.5)	27 (58.6)	0.30
	5-ARIs	41 (15.8)	9 (19.5)	
	Combination therapy	56 (21.6)	10 (21.7)	
AUR (n, %)	Overall	113 (43.6)	25 (54.3)	0.10
	Single/multiple episodes	76 (29.3)	11 (23.9)	
Indwelling catheter (n, %)	37 (14.2)	16 (34.7)	0.02	
BWM (n, %)	18 (6.9)	9 (19.5)	0.001	
Prostate volume (mL) (median, IQR)	100 (76 – 130)	109 (76 – 130)	0.39	
Creatinine serum level (mg/dL) (median, IQR)	1.0 (0.9-1.2)	0.9 (0.9-1.1)	0.91	
Hb blood level (g/dL) (median, IQR)	14 (13.1-15.2)	14.9 (13.7-15.3)	0.34	
Q-max (mL/s) (median, IQR)	8.2 (7.0 – 10.0)	8.7 (7.3 – 10.3)	0.47	
PVR volume (mL) (median, IQR)	160 (100 – 250)	150 (100 – 280)	0.17	
PSA serum level (ng/mL) (median, IQR)	5.6 (2.5 – 7.3)	4.8 (2.8 – 8.7)	0.25	
IPSS score (median, IQR)	24 (21 – 28)	24 (21 – 27)	0.63	
IIEF-5 score (median, IQR)	18 (12 – 22)	18 (10 – 21)	0.70	
OAB-q score (median, IQR)	44 (25 – 55)	39 (27 – 53)	0.76	
ICIQ-sf score (median, IQR)	0 (0 – 0)	0 (0 – 0)	0.42	
QoL score (median, IQR)	4 (3 – 5)	4 (4 – 5)	0.34	

Group A = catheter-free patients; Group B = patients experiencing early catheter replacement.

AC = Anticoagulants; AP = Antiplatelets; ASA = American Society of Anesthesiologists; AUR = Acute Urinary Retention; BMI = Body mass index; BPH = Benign Prostatic Hyperplasia; BWM = Bladder Wall Modification; CCI = Charlson Comorbidity Index; HB = Hemoglobin; ICIQ-q = International Consultation on Incontinence Modular questionnaire; IIEF-5 = International Index of Erectile Function; IPSS = International Prostate Symptom Score; OAB-q = Overactive Bladder questionnaire; PVR = Post-voiding residual; QoL = Quality of Life

Table 2 - Intraoperative features and surgical outcomes of 305 patients treated with Holmium Laser Enucleation of the Prostate (HoLEP).

Variables		Group A (n=259; 84.9%)	Group B (n=46; 15.1%)	p-value
Surgical Outcomes				
Enucleation Technique (n, %)	<i>Three-lobes</i>	105 (40.5)	22 (47.8)	0.17
	<i>En-bloc</i>	154 (59.5)	24 (52.2)	
Overall operative time (min) (median, IQR)		100 (67 – 120)	97 (65 – 115)	0.23
Enucleation time (min) (median, IQR)		52 (35 – 60)	45 (32 – 55)	0.24
Morcellation time (min) (median, IQR)		24 (16 – 35)	23 (16 – 32)	0.17
Lasing time (min) (median, IQR)		30 (29 – 40)	38 (29 – 48)	0.02
Energy delivered (kJ) (median, IQR)		120.1 (100.9 – 140.3)	131.3 (103.2 – 162.6)	0.48
Intraoperative complication, (n, %)		23 (8.8)	6 (13.0)	
Capsule perforation		14 (5.4)	5 (10.8)	0.02
Bladder mucosal damage		9 (3.4)	1 (2.2)	
Surgical Era (n, %)	≤ 50 procedures	41 (15.8)	9 (19.5)	0.39
	> 50 procedures	218 (84.2)	37 (80.5)	

Group A = catheter-free patients; Group B = patients experiencing early catheter replacement.

horts. Moreover, patients undergoing early catheter replacement reported a higher percentage of intraoperative complications (8.8% vs 13%, $p = 0.02$), including capsule perforation and/or bladder mucosal damage.

As regards postoperative variables (Table-3), patients experiencing early catheter replacement showed a significantly longer hospitalization compared to catheter-free patients (4 days [IQR 3 – 5] vs 6 days [IQR 4 – 7], $p=0.001$). Early and delayed postoperative surgical complication rates were comparable between the two cohorts ($p=0.21$). At 3-month assessment, median PSA, Q-max, urinary incontinence and clinical symptoms assessed by dedicated questionnaires did not significantly differ in the two study groups (all $p > 0.05$). On the contrary, median PVR appeared lower in catheter-free patients (30 mL [IQR 8 – 50] vs 60 [IQR 40 – 100], $p = 0.02$). Clinical assessment at 12-month follow-up did not reveal any significant differences between the two groups in terms of patient reported outcomes, with also difference

in PVR mitigating between the two groups (35 mL [10 – 55] vs 55 [40 – 80], $p = 0.12$).

At univariate analysis, indwelling urinary catheter before surgery ($p=0.02$), BWM ($p=0.01$), ongoing AC/AP therapy ($p=0.01$) and intraoperative complications ($p=0.01$) were significantly associated with early catheter replacement. At multivariate analysis, indwelling urinary catheter (OR: 1.28; CI 95%: 1.21 – 2.11 $p = 0.02$), BWM (OR:2.87; CI 95%:1.25–3.26; $p=0.001$) and AC/AP therapy (OR:2.21; CI 95%: 1.10–2.31; $p=0.01$) were confirmed as independent predictors of catheter replacement after HOLEP (Table-4).

DISCUSSION

While current available literature reports plenty of evidence investigating the safety and efficacy of different techniques for the surgical management of BPH (15), there is far less investigation into the HoLEP field in the setting of predictors of early catheter replacement. Indeed, although

Table 3 - Postoperative, functional and self-reported outcomes of 305 patients treated with Holmium Laser Enucleation of the Prostate (HoLEP).

Variables		Group A (n=259; 84.9%)	Group B (n=46; 15.1%)	p-value
Postoperative Outcomes				
Hospitalization time (days) (median, IQR)		4 (3 – 5)	6 (4 – 7)	0.001
Early events	36 (13.8)	8 (17.3)		
CD \leq 2	32 (12.3)	7 (15.2)		
CD $>$ 2	4 (1.5)	1 (2.1)		
Delayed events	4 (1.5)	1 (2.1)	0.21	
CD \leq 2	1 (0.3)	1 (2.1)		
CD $>$ 2	3 (1.2)	0 (0)		
Follow-up (month) (median, IQR)		18 (9-29)	17 (9-27)	0.19
Functional results and PROMs at 3-month follow up				
UI (n, %)		19 (7.3)	3 (6.5)	0.32
Q-max (mL/s) (median, IQR)		23 (17 – 27)	21 (17 – 26)	0.26
PVR volume (mL) (median, IQR)		30 (8 – 50)	60 (40 – 100)	0.02
PSA (ng/mL) (median, IQR)		0.9 (0.63 – 1.00)	0.9 (0.68 – 1.60)	0.17
IPSS (median, IQR)		9 (2 – 12)	6 (1 – 8)	0.19
IIEF-5 (median, IQR)		17 (12 – 20)	18 (11 – 20)	0.81
OAB-q (median, IQR)		15 (13 – 19)	13 (13 – 16)	0.06
ICIQ-sf (median, IQR)		1 (0 – 2)	0 (0 – 0)	0.08
QoL (median, IQR)		1 (0 – 2)	1 (0 – 1)	0.13
Functional results and PROMs at 12-month follow up				
UI (n, %)		7 (2.7)	0 (0.0)	0.29
Q-max (mL/s) (median, IQR)		22 (15 – 26)	21 (16 – 25)	0.34
PVR volume (mL) (median, IQR)		35 (10 – 55)	55 (40 – 80)	0.12
IPSS (median, IQR)		10 (2 – 11)	7 (1 – 9)	0.21
IIEF-5 (median, IQR)		16 (11 – 19)	18 (11 – 20)	0.78
OAB-q (median, IQR)		16 (12 – 18)	12 (10 – 16)	0.12
ICIQ-sf (median, IQR)		1 (0 – 2)	0 (0 – 0)	0.08
QoL (median, IQR)		1 (0 – 2)	1 (0 – 1)	0.13

Table 4 - Univariate and Multivariate logistic regression analysis for the predictors of Early catheter replacement.

Variates	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Indwelling catheter	1.32 (1.18-2.24)	0.02	1.28 (1.21-2.11)	0.02
Bladder wall modifications	2.51 (1.29-3.71)	0.01	2.87 (1.25-3.26)	0.001
On-going ACs/APs at surgery	2.23 (1.11-2.33)	0.01	2.21 (1.10-2.31)	0.01
Intraoperative complication	1.54 (1.45-2.11)	0.01	1.21 (0.94-2.13)	0.09
Lasing time (continuous variable)	1.11 (0.27-1.84)	0.53	-	-

AC = Anticoagulant; AP = Antiplatelet.

the surgical technique has already reached a high standardization, we still need finer tools to timely identify those patients eventually experiencing an early failure in resuming normal micturition after surgery. To address this unmet need, in the current paper we sought to analyze our high-volume single institutional series seeking for any clinical or surgical predictors of early catheter replacement. AUR after catheter removal was recorded in nearly 15% of cases and was associated either with blood clots or bladder neck spasm / postoperative oedema. Our data are consistent with current literature, since postoperative AUR was reported to range between 0% and 16% in previously published studies (16-18). Notably, we demonstrated that indwelling urinary catheter before surgery, AC/AP and BWM were independent predictors of early AUR after HoLEP, thus further highlighting three additional features worth of discussion at the time of preoperative counselling.

First key finding of our study is that the occurrence of AUR after catheter removal was not associated to the learning curve nor enucleation technique used, being no significant differences demonstrable between patients treated with “*en-bloc*” and “*three-lobes*” enucleation. Interestingly, median lasing time was significantly higher in those patients experiencing early catheter replacement, although the latter was not confirmed as an independent predictor of postoperative AUR at multivariable analysis. A longer lasing time could in fact hardly justify a greater risk of AUR, but may rather reflect a higher attention in hemostasis, since patients needing catheter replacement showed a significantly higher use of AC/AP at

baseline. The hypothetical risks carried by the ongoing AC/AP therapy during HoLEP was already confirmed by different previous studies (6, 19, 20), although it should be highlighted that the rate of postoperative bleeding even in case of AC/AP therapy is anyhow quite acceptable and makes HoLEP an excellent technique to treat also complex patients. In this regard, our group recently published a paper demonstrating that, in experienced hands, HoLEP represents an effective option for the treatment of BPH also for high comorbid patients (5). The observed benefit of HoLEP in maintaining hemostasis in AC/AP patients is likely due to the physics of the holmium laser (21). Indeed, due to the chromophore of water and minimal tissue depth penetration, holmium laser is able to achieve quick vaporization and coagulation of tissue without the disadvantage of deep tissue penetration. The safety of the surgical technique is further bolstered by the consideration that early and delayed postoperative complications did not differ between the two cohorts in our study, although a non-significant trend was observed in patients experiencing postoperative AUR.

Second key finding of the study is related to the influence of BWM in determining the resume of normal micturition after surgery. Indeed, BWM was the strongest independent predictor of AUR after HoLEP. To the best of our knowledge this is the first report correlating BWMs to risk for early catheter replacement after HoLEP. Indeed, bladder wall thickness had already been associated with risk of AUR before surgical management of obstructive BPH (22). BWM has been correlated with detrusor function. In this regard,

Oelke et al. found that detrusor wall thickness increases depending on the extent of bladder outlet obstruction (23). Therefore, measurement of bladder wall thickness has been proposed as a useful and simpler diagnostic parameter as it could act as a possible marker to replace conventional urodynamic pressure flow study in patients with bladder outlet obstruction (24). Indeed, as hypertrophy of the bladder musculature advances, there is an increase in the collagen component, gradually replacing the muscular fibers. The changes are coupled with a relative ischemia of the hypertrophic muscle fibers, being muscle hypertrophy not supported by a proportional neoangiogenesis. As a result, the increase in interstitial collagen reduces the distensibility of the bladder with consequent rise in intravesical pressure and leads to a progressive reduction in contractility of the detrusor. In this regard, in our experience indwelling urinary catheter before surgery was confirmed as an independent predictor of early catheter replacement after HoLEP, thus further highlighting the residual preoperative bladder contractility as a main key driver of resume of normal micturition after surgery.

Interestingly, in our study patients experiencing *de novo* catheter replacement still had a significantly higher PVR at 3-month evaluation, as compared to their counterpart. However, such difference was not statistically significant at 12-month assessment. Of note, our group first introduced the concept of “trifecta” in HoLEP (25). Multivariate analysis confirmed PVR \geq 250 mL as one of the independent predictors of Trifecta failure, further highlighting the decompensation of the detrusor as one the main key driver of postoperative outcomes. Based on these findings, it may be reasonable to offer urodynamic study to patients preoperatively presenting with BWM, as we could speculate those individuals could experience higher difficulties in resuming normal micturition after catheter removal. Nonetheless, the role of BPH surgery in case of concomitant detrusor underactivity remains controversial (26). Indeed, it is also true that in this context pressure/flow study would only add the benefit to better forecast the room for

improvement after BPH surgical management, thus further tailoring preoperative counselling, as it would hardly change the choice to relieve prostatic obstruction.

The present paper is not devoid of several limitations. This was a retrospective review of a prospectively collected database, thus the study design might have weakened itself the reliability of evidence reported. Second, all cases were performed by a single highly trained surgeon with an extensive experience in endoscopic surgery. As such, our findings could not be applicable to all surgeon- or center-related scenarios.

Despite of these limitations, the findings of the current series represent one of the largest series exploring predictors of *de novo* catheterization after HoLEP. Further studies with longer follow-up are eagerly warranted to validate the preliminary findings of the current series.

CONCLUSIONS

Indwelling urinary catheter before surgery, bladder wall modifications and maintenance of anticoagulant/antiplatelet therapy were shown to be independent predictors of early catheter replacement after HoLEP. Such features should be carefully discussed with patients at the time of preoperative counselling as they could eventually impair surgical outcomes after bladder outlet obstruction relief.

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STATEMENT OF ETHICS

The current study was approved by Institutional Review Board (IRB 1248/30). Informed consent was obtained from all individual participants included in the study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONFLICT OF INTEREST

None declared.

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Laparoscopic ventral onlay ureteroplasty with buccal mucosa graft for complex proximal ureteral stricture

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ABSTRACT

Introduction: There is lack of papers dedicated to the laparoscopic buccal mucosa graft (BMG) ureteroplasty of the complex upper ureteral stricture. The aim of this study is to evaluate the results of laparoscopic BMG ureteroplasty in patients with complex proximal ureteral stricture.

Material and methods: Twenty-four patients underwent laparoscopic ventral onlay BMG ureteroplasty for long or recurrent proximal ureteral stricture not amenable to uretero-ureteral anastomosis over 2019-2022. Patient demographics, operative time, estimated blood loss, length of stay, follow-up, intra- and postoperative complication rate and percentage of stricture-free at last visit were analyzed.

Results: The mean stricture length was 3.6 cm. The mean operative time was 208.3 min, while mean blood loss was 75.8 mL. The length of hospital stay was 7.3 days. No intraoperative complications were observed. Postoperatively, seven patients developed complications (29.2%). Five patients experienced a Grade II (according to Clavien nomenclature). Two patients developed a Grade IIIa complication, which included leakage of the anastomosis site. The mean follow-up was on the 22 months with stricture free rate 87.5%.

Conclusion: Patients with proximal ureteral strictures could be effectively treated by laparoscopic ventral onlay ureteroplasty with a buccal mucosa graft.

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INTRODUCTION

Long ureteral strictures represent a complicated dilemma that requires the significant experience and extensive surgical arsenal of urologists. The choice of surgical strategy depends on properties of the diseased ureter, mainly the localization and length of the stricture. Basically, the following procedures are proposed to be effective in the case of complex proximal ureteral stricture: ileal substitution of the ureter, ureterocalicostomy, downward nephropexy and auto-transplantation (1-3). However, associated drawbacks motivate urologists to seek new approaches to correcting such strictures, in particular with the help of grafts.

One of these is the buccal mucosa graft (BMG), which has been demonstrated over the past few decades to have excellent outcomes in patients with urethral strictures. The first BMG ureteroplasty in humans was described in 1999 (4). However, interest in this technique has renewed over the past decade, and the technique is now reported in numerous articles regarding its utility in open and robotic approaches (5-7). Unfortunately, there is a lack of papers dedicated to the laparoscopic BMG ureteroplasty of the complex upper ureteral stricture, being necessary to build a confident opinion on the pros and cons of different approaches (8, 9).

Therefore, we hypothesized that laparoscopic BMG ureteroplasty can be effectively and safely used for patients with complex proximal ureteral strictures, when ureteroureterostomy is impossible, or with recurrent ureteral strictures. Herein, we present the single-center experience in performing laparoscopic BMG ureteroplasty in 24 patients with a complex proximal ureteral stricture.

MATERIAL AND METHODS

Retrospectively, data from 24 patients who underwent laparoscopic BMG ureteroplasty between 2019 and 2022 at a single institution were collected and analyzed after local ethical committee approval (PG071). All subjects provided written informed consent for inclusion in the study. All procedures performed in studies involving human participants were in accordance with the 1964

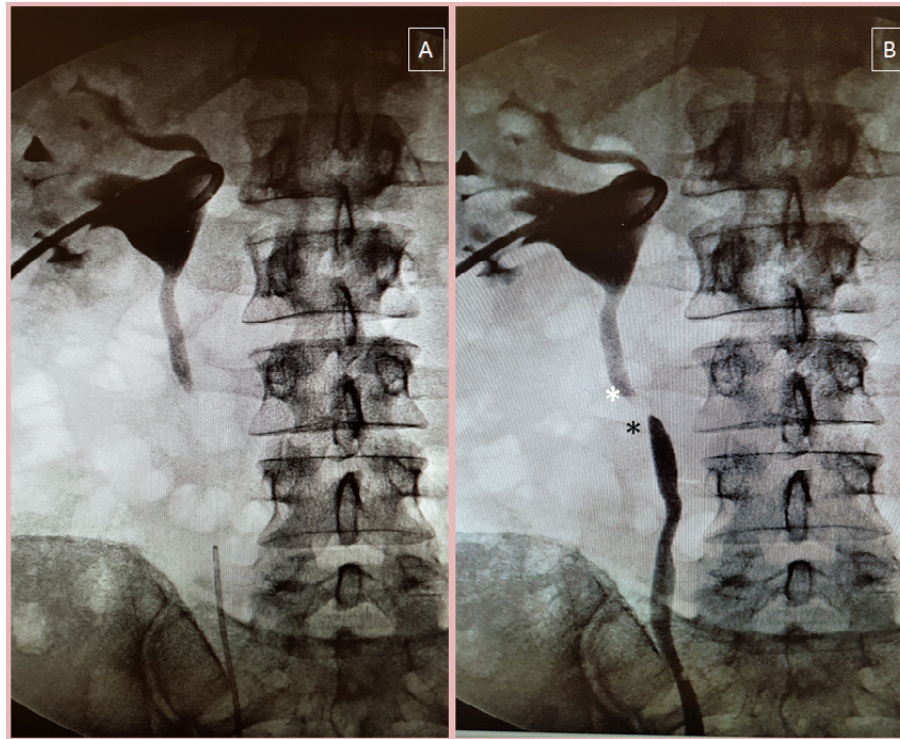
Helsinki Declaration and its later amendments or comparable ethical standards. The eligible criteria for this technique were a benign proximal ureteral stricture that was not amenable to primary anastomosis due to stricture length or extensive fibrosis. In all cases, the technique of choice was ventral onlay ureteroplasty, so patients were excluded if they had a complete absence of a large (>5 cm) portion of the ureter, such as after oncologic resection or ureteral avulsion. Those patients underwent alternative reconstructive techniques, such as a tapered bowel according to the Monti technique or tubular ileal segment substitution. Each patient underwent retrograde and antegrade (in the presence of a nephrostomy tube) pyelography to delineate stricture localization and length (Figure-1).

Patient demographics and preoperative characteristics are detailed in Table-1. Iatrogenic strictures were caused by lithotripsy and extraction of ureteral stones. The mean stricture length was 3.6 ± 1.3 cm. Five patients had previously undergone ureteroureterostomies.

SURGICAL TECHNIQUE

Procedures were performed in the lateral decubitus position, while the legs were placed in a modified lithotomy position to allow for simultaneous ureteroscopy. The endotracheal tube was fixed on the dependent side of the mouth, and the mouth was draped separately from the abdominal field in preparation for BMG harvest, which may be completed after laparoscopic dissection of the ureter and after defining the diseased ureter length.

After sterile preparation and draping, a 12-mm incision was made about two fingerbreadths lateral to the umbilicus. The dermis and subcutaneous tissues areas were dissected with electrocautery, the rectus fascia was identified and lifted, and a Veress needle was used to establish a pneumoperitoneum of 10-15 mm Hg. The camera was then inserted, and the abdomen was inspected for access-related injuries or bowel adhesions. The triangulation rule was followed to place two additional accessory trocars at least four fingerbreadths from the primary trocar. A 12-mm tro-

Figure 1 - Preoperative definition of ureteral stricture length and location.

A) Antegrade pyelography to define the proximal margin of stricture. B) Retrograde pyelography to define the distal margin of stricture. Notice that white and black asterisks indicate the proximal and distal margin of stricture, respectively.

car was placed cranially, and a 5-mm trocar was placed caudally and laterally at least four fingerbreadths away from the initial periumbilical trocar, also following the triangulation rule. Moreover, an additional 5-mm assistant trocar was placed four fingerbreadths caudally to the primary periumbilical trocar. The most cranial trocar was used for the camera while the other periumbilical and lower abdominal trocars were used to place working instruments.

Behind incision of the line of Toldt and medialization of the colon, Gerota fascia was exposed and opened. Intraoperative ureteroscopy was used to identify the stricture. The diseased ureter was dissected, paying attention to safe, healthy tissue as much as possible (Figure-2). The length of the stricture was determined using a ureteral catheter by placing it close to the stricture.

After the steps above, BMG harvesting was performed. First, the head was placed in the flank position, followed by cheek elevation,

and the Stenson's duct was identified. 1% lidocaine and epinephrine were used for hydrodissection of the buccal mucosa. The graft size was tailored to the length of the ureteral defect. The defect in the cheek mucosa was closed with a continuous suture.

Subsequently, the submucosal tissue was cleaned off the BMG, and the graft was passed through the trocar into the abdominal cavity. Vicryl 4/0 was used to sew apical angle of the graft to the superior aspect of the dissected ureter (Figure-3A). The graft was sutured distally to the ureteral defect (Figure-3B). A continuous suture was created between the buccal flap and the lateral margin of the ureter down to lower angle (Figure-3C).

Then, a 6Fr ureteral stent was introduced over the guidewire in distal ureter followed by guidewire removal (Figure-3D). The proximal aspect of the stent was inserted into the renal cavity (Figure-3E). Another vicryl 4/0 was used to suture the medial border of the dissected ureter with a

Table 1 - Patient demographics and preoperative characteristics.

Parameter	n (%)
Number of patients	24 (100)
Proximal ureteral stricture	24 (100)
Age, years, mean±SD (range)	44.8±14.7 (19-74)
Sex	
Male	16 (66.7)
Female	8 (33.3)
BMI, kg/cm ² , mean±SD (range)	26.7±2.8 (21.2-31.6)
Preoperative presence of nephrostomy tube	14 (58,3%)
Diseased side	
Left	13 (54.2)
Right	11 (45.8)
Stricture etiology	
Iatrogenic	18 (75)
Idiopathic	5 (20.8)
Impacted stone	1 (4.2)
Previous failed ureteroplasty	5 (20.8)
Stricture length, cm, mean±SD (range)	3.6±1.3 (2.5-8)

buccal flap (Figure-3F). The watertightness of the anastomosis was checked by filling the collecting system with sterile fluid through the ureteroscope (Figure-3G). Then, the ureteroplasty field was wrapped in omentum or perirenal fat to improve the vascularity of the graft (Figure-3H). The wrap was fixed with knotty sutures to the surgical zone. A drain was placed adjacent to the anastomosis. After surgery, the nephrostomy tube was not closed to keep the pressure in the upper urinary tract low.

In the early postoperative period, patients were monitored for blood tests and ultrasound. Patients received anti-inflammatory and antibacterial therapy. The ureteral stent was removed after 6-8 weeks. Patients with a nephrostomy tube under-

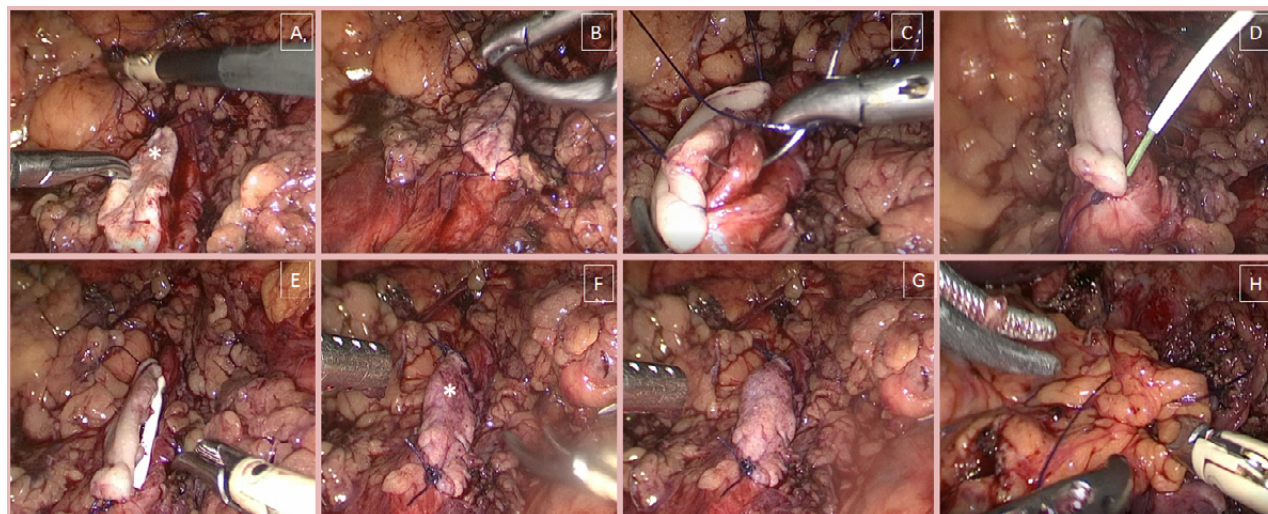
Figure 2 - Opened ureter in the site of stricture. Expanded proximally and distally to healthy tissues.

went antegrade pyelography. Then, the nephrostomy tube was removed. It should be noted that all procedures were performed by the same surgeon (G.B.) with experience in performing laparoscopic ureteroplasty in >100 cases (including ileal substitution, ureterocalicostomy, etc.).

Patient demographics, intra- and postoperative characteristics, follow-up duration, and percentage of stricture-free at the last visit, as well as complication rate according to Clavien-Dindo nomenclature, were calculated. The grade of hydronephrosis was assessed according to the SFU classification. A good postoperative outcome was considered to be the absence of any symptoms, the absence of hydronephrosis or grade 1, and the absence of nephrostomy drainage, provided that the contrast agent freely passes into the bladder through the ureter and the surgical site.

Statistical Analysis

SPSS statistical software version 26.0 (IBM, Chicago, USA) was used for statistical analysis. Continuous data were presented as a mean and standard deviation according to data distribution, which was assessed via the Kolmogorov-Smirnov test. A range of values was also presented. Nominal data were presented as number and percentage. Depending on the type of data, we used the paired-samples t-test or McNemar's

Figure 3 - Step-by-step technique to perform ventral onlay BMG ureteroplasty.

A) Graft is sutured to the upper aspect of the ureteral defect. The white asterisk indicates that in this step, the interior wall of BMG is outside. B) Graft is sutured to ureteral defect distally. C) Lateral border of ureter sutured via continue suture with the medial border of BMG (when the latter is placed with an interior wall outside) from the bottom to top. D) 6Fr ureteral stent is indwelled into ureter over guidewire distally up to the bladder. E) Guidewire is withdrawal, and the proximal end of the ureteral stent inserted up to the renal pelvis. F) BMG is sutured to the medial border of the ureter with continue suture from top to bottom. White asterisk corresponds to the exterior wall of the graft. G) Ureter is inflated to confirm BMG ureteroplasty watertightness. H) Ureteroplasty site is covered with omentum to improve vascularity.

test for statistical analysis. Nineteen patients with more than 1 year of postoperative follow-up at the time of publication were evaluated when comparing preoperative and 12 months or more later. Differences were considered statistically significant at a value of $P < 0.05$.

RESULTS

Operative characteristics are indicated in Table-2. The mean operative time was 208.3 ± 48 min., while the mean blood loss was 75.8 ± 28.9 mL. Omentum and perirenal fat were used to cover the graft in 21 and 3 cases, respectively, and the decision was made intraoperatively based on omentum accessibility. The length of the hospital stay was 7.3 ± 2.5 days. No intraoperative complications were observed. Postoperatively, seven patients (29.2%) developed complications. Five of the patients experienced urinary tract infections leading to the prescription of additional antibiotics (Grade II). Two patients developed a Grade IIIa complication, which included leakage of the anastomosis site. Anastomosis leaking was diagnosed as a result of profuse drainage. To correct this, temporary percutaneous nephrostomy tube

Table 2 - Operative and postoperative characteristics.

Parameter	Mean \pm SD (range)
Operative time, min	208.3 \pm 48 (140-300)
Estimated blood loss, mL	75.8 \pm 28.9 (50-150)
Wrap of the buccal graft, n (%)	
omental flap	21 (87.5)
perirenal fat	3 (12.5)
Length of stay, days	7.3 \pm 2.5 (3-13)
Follow-up, month	22 \pm 12.9 (4-45)
Stricture-free at last visit, n (%)	21/24 (87.5%)
Complication rate, n (%)	
Grade II	5 (20.8)
Grade IIIa	2 (8.3)

drainage was placed, and control of the leakage severity followed. On the 5th postoperative day, the nephrostomy tube was removed with no signs of leakage on antegrade pyelography.

Before discharge, all patients underwent excretory pyelography or antegrade pyelography

in the presence of a nephrostomy tube. As a follow-up, all patients were advised to see a doctor if even modest complaints appeared, as well as to perform computed tomography-urography (CTU) every six months during the first two years and annually after. Moreover, 12 months after the intervention, all patients underwent ureteroscopy to visualize ureteroplasty (Figure-4). The mean follow-up was 22 ± 12.9 (4-45) months. At the time of writing this study, the stricture-free rate was 87.5% (21 of 24). Notably, two patients with stricture recurrence on the 21st and 31st-month of follow-up had a previous failed uretero-ureteral anastomosis and were managed with balloon dilatation followed by double-J stent indwelling. The decrease in serum creatinine was statistically significant (Table-3). There was a difference between the frequency of grade 0/1 and grade 2/3 hydronephrosis in the pre- and postoperative periods ($p < 0.001$).

DISCUSSION

Long proximal ureter strictures remain challenging for surgeons (10, 11). End-to-end

anastomosis with a tension-free and watertight state is not always possible in these cases, and in the current literature, such cases are proposed to be cured via ureteral replacement with ileal, downward nephropexy or auto-transplantation (12-14).

Ileal substitution of the ureter is a challenging procedure with a significant rate of complications due to intestinal resection and postoperative metabolic changes. Nephropexy and auto-transplantation of the kidney in a downward fashion are also not easy-to-perform surgical procedures and are often associated with complications, such as pseudoaneurysms and vascular thrombosis, which results in their relatively rare use (15, 16). Given the current modality drawbacks, developing surgical techniques that may facilitate the management of proximal ureteral strictures is recommended.

Buccal mucosa graft is actively used for reconstructive urethral surgery (17). The buccal mucosa is readily available for harvesting, less prone to immune reactions, and tolerates urinary

Figure 4 - A) Antegrade pyelography indicates patency of ureter after removal of the ureteral stent. B) Three-dimension reconstruction of CTU on 12 months postoperatively. On both pictures, the white asterisk indicates ureteroplasty site. C) Endoscopic view of BMG after 12 months postoperatively. The interrupted and solid line indicates the graft and health ureter in the distal level of BMG ureteroplasty, respectively. D) Endoscopic view of BMG in the stricture site. The white and black asterisk indicates BMG and health ureter, respectively.

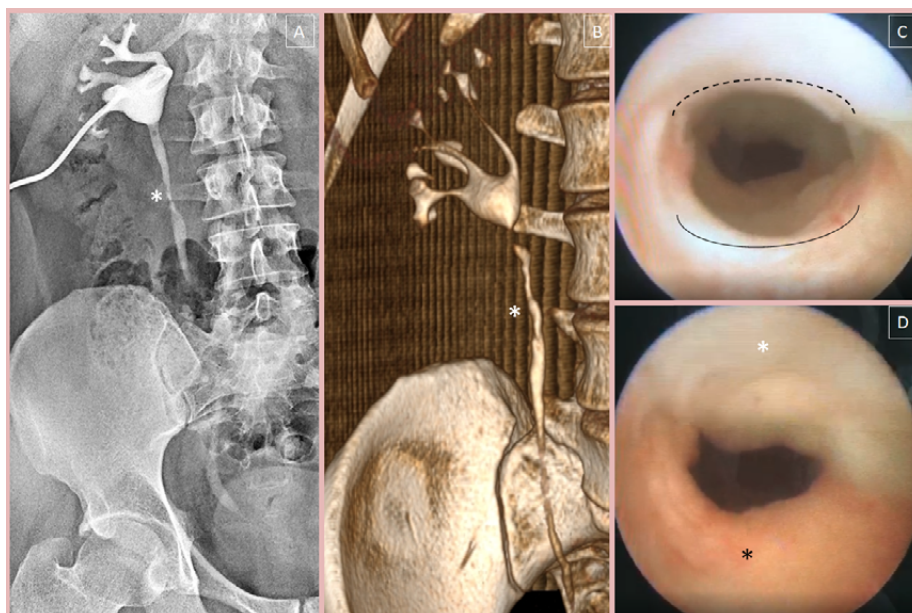


Table 3 - Pre- and postoperative parameters.

Parameter	Before surgery, n=24 (a)	after removal of drains, n=24 (1,5-2 months)	Follow up after 12 months or more, n=19 (b)	P-value (a vs b)
Serum creatinine ($\mu\text{mol/L}$)	86.6 \pm 22.8	82 \pm 17.9	80.3 \pm 19.5	0.021*
Pain, n (%)				
Yes	18 (75)	3 (12.5)	2 (10.5)	<0.001*
No	6 (25)	21 (87.5)	17 (89.5)	
SFU grade of hydronephrosis, n (%)				
Grade 0	0	14 (58.3)	13 (68.4)	<0.001*
Grade 1	0	7 (29.2)	4 (21.1)	
Grade 2	17 (70.8)	2 (8.3)	2 (10.5)	
Grade 3	7 (29.2)	1 (4.2)	0	
Grade 4	0	0	0	

Values are mean \pm SD.

* Statistically significant difference.

tract pathogens. BMG ureteroplasty also becomes more and more popular, especially when a tension-free anastomosis is difficult to achieve via ureteroureterostomy or for patients with recurrent ureteral strictures who previously underwent failed ureteroplasty associated with peri-ureteral scarring and poor ureteral vascularization (18). According to the recent review, the overall reported success rate was reported to be 66 out of 72 (91.6%), 32 out of 34 (94.1%) and 34 out of 38 (89.5%) open and robotic cases, respectively. The complication rate was reported in 60 cases, being 15 out of 60 (25%) for all complications, with a 5% (3/60) rate for complications graded as Clavien–Dindo score \geq III (19).

Most of the current studies on minimally invasive ureteroplasty in BMG have focused on the robot-assisted procedure (6, 7, 18, 19). Arora et al. reported no data for recurrence during the 6-month follow-up period (20). More recently, Zhao et al. published the results of robot-assisted BMG ureteroplasty in 19 patients recruited from three clinics in the United States. In 74% of these cases, the stricture was localized in the upper third, while the remaining 24% of patients had a middle ureteral stricture. The length was about 4 cm (2–8 cm). The onlay technique cured 79% of patients,

and the rest underwent augmented anastomotic ureteroplasty. The total success rate was 90% for an average 26-month follow-up period (7).

Despite the encouraging results of performing BMG ureteroplasty via robotic surgery, it has a downside. On the one hand, robot-assisted surgery is not as popular as desired. The international community recognized that the optimal use of robotic technology requires the development of dedicated training pathways and that outcomes during the learning curve should be scrutinized (21). Data not only on open and robotic but also laparoscopic BMG ureteroplasty should be available in literature. On the other hand, most hospitals throughout the globe have just shifted their armamentarium from open to laparoscopic surgery, and the latter should not be omitted even for challenging procedures. However, it should be noted that performing reconstructive operations of the urinary tract using laparoscopic access requires expert mastery of laparoscopic techniques, including intracorporeal suturing.

To expand the current data on laparoscopic BMG ureteroplasty, we conducted a retrospective study on 24 patients with proximal ureteral stricture who were amenable to laparoscopic surgery. According to our results, even this challenging

procedure could be performed via laparoscopy. The operative time, complication rate and intra-operative parameters were optimal. There was no significant difference compared with previously published results of robotic BMG ureteroplasty.

Our study has several limitations that should be noted. First, the retrospective nature may lead to some bias compared to a prospective study. Second, we reported only results from ventral onlay because it is more convenient for laparoscopic surgery. In contrast, previous data on robotic results comprise the mixed data on dorsal and ventral onlay, and some maneuvers accessible for the robotic ureteroplasty are challenging in laparoscopy. Third, we collected data from one hospital, which could also lead to bias associated with the surgeons' experience in this field. Nevertheless, this study is valuable because it helps to reveal the theoretical feasibility of laparoscopic BMG ureteroplasty. Additional experience and multi-clinical studies are needed to clarify the role of laparoscopic BMG ureteroplasty in ureteral reconstructive surgery.

CONCLUSION

Laparoscopic ventral onlay ureteroplasty with a buccal mucosa graft could effectively treat patients with proximal ureteral strictures. However, it should be noted that in order to perform this type of ureteroplasty effectively, a careful approach to patient selection is necessary. Also, have experience in various reconstructive surgeries on the upper urinary tract, including ileal ureter substitution, and be prepared to perform them. Since the final decision on the type of reconstructive surgery is made intraoperatively.

ABBREVIATIONS

BMG = buccal mucosa graft

LOS = length of stay

SD = standard deviation

SFU = The Society for Fetal Urology

CTU = computed tomography – urography

BMI = body mass index

CONFLICT OF INTEREST

None declared.

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Predictive histopathological factors of nodal metastasis in penile cancer

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INTRODUCTION

Penile cancer (PC) is a neoplasm with variable incidence depending on geographic location, with higher prevalence in underdeveloped countries when compared with developed countries (1). Moreover, the poorest regions of Brazil have the highest incidence of PC, according to the literature (2-4). Because PC mainly affects a socially disadvantaged population from underdeveloped countries, knowledge of its pathology, clinical management, and treatment is still limited. However, it has been revealed that the presence and extent of inguinal lymph node metastasis are the most important prognostic factors of PC (5-7).

PC often metastasizes first to the superficial inguinal lymph nodes, then extends to the deeper nodes, and, finally, to the iliac lymph nodes (8). Enlarged lymph nodes >1.5cm in diameter, pathological stage T2 and above, low-to-middle differentiation, and lymphatic vascular infiltration were independent predictive factors that worsened the prognosis of patients with PC (9). Lymphadenectomy can interrupt this process and acts as a curative treatment for PC, avoiding radical procedures that may further impact quality of life and sexual function (10). Moreover, recent studies have revealed

better survival outcomes in patients with microscopic metastases who undergo prophylactic inguinal lymphadenectomy (IL) compared with those whose physical examination initially showed no metastasis to the lymph nodes but who later had recurrent disease (11-15). Clinical and radiological assessments are insufficient to detect early lymph node metastasis. Therefore, prophylactic lymphadenectomy is a viable procedure for selected patients at high risk of metastasis, although, IL has a high rate of short- and long-term complications. Accordingly, several histological factors have been explored with regard to their potential to reliably predict the occurrence of metastasis in inguinal lymph nodes.

This study aimed to provide pathologists, oncologists, and urologists with a review of the main histopathological parameters that should be considered when deciding to perform lymphadenectomy, along with observations from the region with the highest incidence of PC worldwide (2).

Histological type

Squamous cell carcinoma (SCC) constitutes 95% of PCs. The remaining 5% are classified as sarcoma (leiomyosarcoma, Kaposi's sarcoma, angiosarcoma, rhabdomyosarcoma, epithelioid sarcoma, and Ewing's sarcoma, melanoma, adenocarcinoma,

or sebaceous carcinoma) (16). Although there is less evidence to support the use of lymphadenectomy in these other neoplasms, aggressive approaches should be considered in appropriate patients. Furthermore, it is important to consider tumor stage and nodal status when predicting the outcome of patients with non-SCC neoplasms (17).

In cases of penile melanoma, sentinel lymph node evaluation is similar to the established protocol for melanoma in other sites (18). Penile sebaceous carcinoma has a strong tendency to metastasize to regional lymph nodes; thus, it is usually treated with wide local excision and regional lymphadenectomy. Regional lymphadenectomy is performed only if clinically significant nodes are found. In a previous study, three of five patients with sebaceous carcinoma presented with bilateral palpable inguinal lymph nodes and underwent IL. In two of these three patients, a biopsy revealed nodal metastasis (19).

Histological subtype

Penile SCC is classified into several subtypes that demonstrate varying rates of inguinal lymph node involvement and survival. The most recent World Health Organization classification divided SCC into two categories: human papillomavirus (HPV)-associated and non-HPV-associated SCC (20). Unlike in SCC of the head and neck, the presence of HPV in penile SCC does not necessarily dictate prognosis or therapeutic approach. Thus, classifying tumors as HPV+ or HPV- may not be as useful as grouping them into histological subtypes of low risk or high risk for developing lymph node metastasis.

The frequency of SCC subtypes varies according to geographic location. In northeastern Brazil, HPV was detected in approximately 89.1% of penile SCC cases (21), a rate higher than that observed in other regions, which have a prevalence of 1.3–72.9%. In our previous study, we showed many HPV-associated subtypes, differing from other regions, characterized by a large predominance of the usual variant (HPV-) (22).

Given the importance of the SCC histological subtype, it is vital that adequate tissue representation is used in macroscopy for the correct subclassification of these tumors. This is especially true for regions of high incidence, where patients seek medical assistance at a very advanced stage, with an average

of almost 2 years after the first signs of the disease and large tumors measuring approximately 4.5 cm (3). In these cases, more than one pattern is often observed macro and microscopically, and each of them may have different degrees of differentiation and a different prognostic profile, considering the high frequency of mixed subtypes in our cases, particularly in advanced tumors. Given these peculiarities regarding morphological criteria, we recommend that the same professional should conduct all diagnostic steps, from macroscopy to microscopy. In the next section, we group the subtypes based on the risk of developing lymph node metastasis.

Low-risk group

In this section, we group the PC subtypes according to the risk of developing lymph node metastasis. Verruciform neoplasms constitute one class of PC that is at low risk of metastasis, regardless of the presence or absence of HPV. The prototype of this exophytic pattern is verrucous carcinoma, an HPV-*in-situ* neoplasm that is rarely invasive. Therefore, *in-situ* tumors and verrucous SCC are not recommended for IL, even when there is clinical suspicion of nodal involvement. In fact, there are no reports of metastasis in patients with these tumors. Usually, antibiotic treatment is initiated for enlarged nodules, and the nodule is excised if enlargement persists (23). Other subtypes of verruciform carcinoma that are not associated with HPV and exhibit low rates of lymph node metastasis include pseudohyperplastic, papillary, and cuniculatum SCC.

Condylomatous carcinoma is a form of verruciform carcinoma that is associated with HPV and demonstrates a low rate of inguinal metastasis of approximately 17% (24). Nevertheless, more advanced tumors with a higher level of infiltration are more likely to lead to lymph node metastasis. In our country, where the neoplasm is diagnosed after 2 years of disease progression, the lesions are large, often forming part of a mixed-pattern neoplasm, especially with the usual type. In these cases, the patient faces a less favorable prognosis, usually with a more aggressive carcinoma component.

High-risk group

We classified tumors as high-risk if they demonstrate a risk of lymph node metastasis at a diag-

nosis rate of > 50%. Like low-risk tumors, there are representatives of both HPV+ and HPV- tumors in this category. Non-HPV-associated subtypes include the usual (pattern solid), pseudoglandular and sarcomatoid, showing a risk of nodal involvement above 85% (25).

Among the subtypes associated with HPV are basaloid, clear cell, and mixed forms of SCC such as warty-basaloid. The risk of lymph node metastasis in these subtypes ranges from 50% to 66% in basaloid SCC to 100% in clear cell SCC (26). Other HPV+ forms of PC, such as lymphoepithelioma-like and medullary cancer, are high-grade neoplasms rich in inflammatory cells, but their prognosis has not yet been established.

Hybrid, warty-basaloid, and papillary-basaloid carcinomas should be further evaluated according to the percentage of the highest risk component. Thus, the tissues of the lesions should be accurately represented and observed to detect different subtypes. At our institution, lesions are well represented, with those smaller than 3.0 cm being fully represented, and the larger lesions being prepared with at least 30 blocks of paraffin.

Histological grade

Tumor histological grade is the most important prognostic factor in PC patients with clinically negative lymph nodes that do not undergo regional lymphadenectomy (27). The National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) have published guidelines on the management of PC based on the histological grade and staging of the primary tumor (pTNM, AJCC). In epithelial tumors, it is generally more difficult to define the histological grade of squamous carcinomas than in adenocarcinomas. Moreover, classification criteria vary according to the institution, resulting in high interobserver variability in the grading of PC (28). Additionally, it is important to note that knowledge of SCC in other sites does not necessarily apply to SCC of the penis.

The morphological features commonly used to assess SCC grade are keratinization; cell atypia/anaplasia calculated by the nucleus to cytoplasm ratio; thickness of the cell membrane; nuclear pleomorphism and chromatin pattern; pattern of tumor growth and expansion in nests, cords, solid blocks,

and detached cells; and presence of nucleolus, mitotic activity, intercellular bridges, and tumor edge (29). Tumor grading is classified as follows: G1: well-differentiated, tumors with minimal changes and morphological proximity to a normal or hyperplastic epithelium, and atypia in the most basal layer; G2: moderately differentiated, tumors with alterations between G1 and G3; and G3: poorly differentiated, tumors with any percentage of cell anaplasia (8). This classification system demonstrates the importance of accurate sampling to detect small areas of undifferentiated cells.

The risk of nodal involvement, as well as tumor invasiveness and aggressiveness increase with histological grade. Specifically, nodal metastasis is found in approximately 8%, 50%, 60% of G1, G2 and G3 tumors respectively (30, 31).

Tumor location and measurement

The glans is the most frequent site of involvement in PC, followed by the foreskin. Tumors of the foreskin have a better prognosis than those of the glans because they are of a lower grade and are more superficial, thus demonstrating less potential for nodal metastasis.

Although tumor size is not a good predictive factor for penile SCC, tumors 2–4 cm in size are more likely to be associated with nodal metastasis, in contrast to tumors smaller than 2 cm or larger than 4 cm. This is due to tumors with superficial dissemination (verruciforms) that reach large proportions (32, 33).

It is important to determine advanced loco-regional disease to define its management. Primary radical inguinal surgical debulking alone for these cases is unlikely to promote long-term survival and is related to a high incidence of complications (34)

Presence of koilocytosis/HPV

Koilocytosis is a morphological parameter indicative of the presence of HPV that should be included in the histopathological report. Through polymerase chain reaction, HPV has been identified as an important prognostic biomarker for penile neoplasia because of its tumorigenic pathway in SCC and its occurrence in tumor tissues (35). At least two Brazilian studies have identified an association between koilocytosis and a low incidence of lymph

node metastasis (36, 37). However, further research is warranted for confirmation.

Perineural invasion

Perineural invasion is characterized by infiltration of the clear space surrounding the nerve bundle under the epineurium and should not be confused with the nerve trapped within the tumor mass. The role of perineural invasion in PC is controversial. Some researchers have declared the presence of perineural invasion to be associated with a high risk of inguinal lymph node metastasis in PC patients (30, 38). Others, including studies from Brazil, have found different results (36, 38-40). In 2009, the EAU guidelines identified perineural invasion as an important prognostic factor in lymph node metastasis (41), although the same recognition was not given to the 2014 EAU, 2017 NCCN, or the eighth edition of the AJCC TNM staging guidelines.

Lesion depth/tumor thickness

The depth of invasion and tumor thickness are often confused, and although they represent different measurements, they have equivalent significance. The depth of invasion is measured from the intact basement membrane of the tumor edge to the deepest tumor cell. Tumor thickness, in turn, is measured from the top of the neoplasm to the deepest tumor cell. In exophytic and keratinizing lesions, tumor thickness is measured from the surface, excluding the keratin layer; in ulcerated lesions, tumor thickness is measured from the surface of the ulcer (3, 6, 32).

The mean thickness of neoplasia-free penile tissue to the lamina propria is 3 mm (T1), to the corpus spongiosum is 5 mm (T2), and to the corpus cavernosum is 10 mm (T3). In the foreskin, the thickness from the skin to the mucosa is approximately 10 mm (30).

Studies have shown a correlation between tumor thickness and lymph node metastasis index. Additionally, higher tumor infiltration and histological grade are correlated with a greater likelihood of lymph node metastasis. Thus, tumors with a thickness of <5 mm have a minimal risk of metastasis, those with a thickness of 5–10 mm have an intermediate risk of metastasis, and those with a thickness of >10 mm have a high risk of metastasis (appro-

ximately 80–86%). Nevertheless, due to anatomical variation in thickness, we believe TNM staging classification (based on anatomical structure) to be more efficient in assessing of depth of invasion than the measurement in millimeters (11).

Growth pattern and invasion front

Neoplasm growth patterns can be horizontal or vertical and correspond to the form of tumor spread and the relationship with the host tissue. Some studies have determined the vertical growth pattern to be associated with a more unfavorable prognosis compared to the horizontal growth pattern (42, 43). Moreover, the horizontal growth pattern is typically found in exophytic verruciform tumors.

Recently, researchers have turned their attention to the assessment of the so-called “invasion front” (44). Translocation of neoplastic cells is a well-known feature at the invasion front of malignant tumors. The change in the phenotypic pattern of invasion with the absence of epithelial biomarkers and the presence of mesenchymal biomarkers may be associated with invasion and lymph node involvement (45, 46). Unlike in colorectal and head and neck tumors, no studies have yet assessed tumor budding in PC. Thus, future study of this topic is warranted.

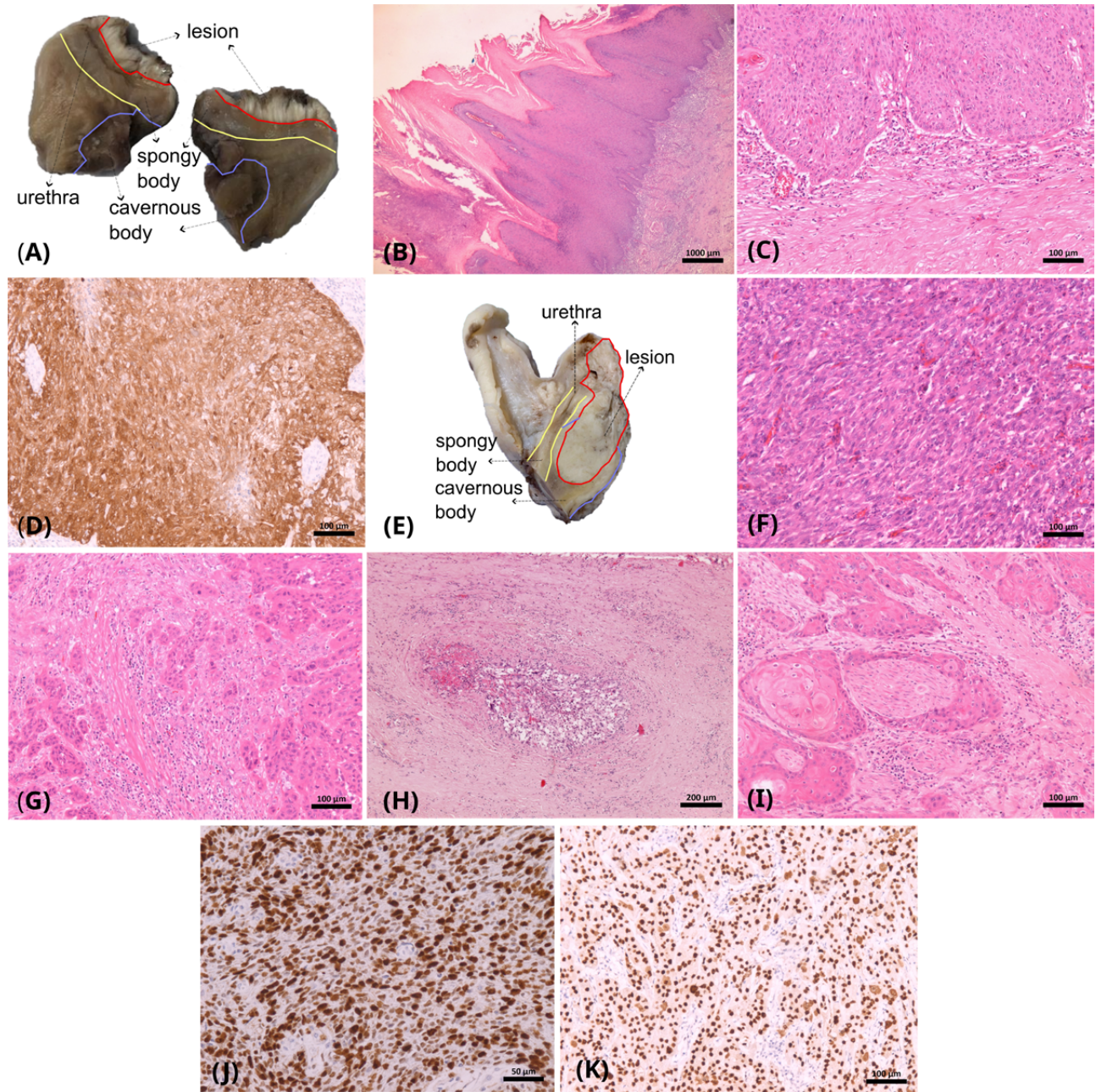
Nomograms

Several nomograms have been created to predict lymph node metastasis (29, 47, 48). However, the diverging importance of each individual histological parameter results in poor performance of the combination of these parameters in nomograms. Another challenge of using these nomograms is the lack of independent external verification and validation. Nomograms applied by different groups to the same population did not obtain the same results (49, 50).

Ki67, p53, and p16

Ki67, p53, and p16 have been evaluated as potential biomarkers of prognosis and lymph node metastasis in PC (51). Although p53 demonstrated the best predictive ability among the three biomarkers, it was not shown to be better than that of other predictive factors, such as tumor stage, and there are no consistent results concerning its use in the ma-

Figure 1 - Pathological features associated with low risk (A, B, C, D) and high risk (F, G, H, Y, Z) lymph node metastases.



(A) Superficial infiltration restricted to the lamina propria. (B) Verruciform subtype histological grade 1. (C) Tumor pushing border. (D) Diffuse p16 immunostain. (E) Corpus cavernosum infiltration. (F) Sarcomatoid subtype histological grade 3. (G) Infiltrative border. (H) Angiovascular invasion. (I) Perineural invasion. (J) High proliferation index (Ki67 immunostain). (K) High expression of p53 protein. B, C, F, G, H, I: HE stain; J, K, D: immunohistochemistry.

nagement of PC (52). Moreover, Brazilian studies have found good results with the evaluation of p53 (53, 54). Furthermore, a strong association between high Ki67 expression and lymph node metastasis in PC has been reported (55, 56). Other studies have confirmed this association (57, 58). Although the absence of p16 may be associated with poor survival, most studies did not find an association between p16 and lymph node metastasis (21, 59, 60).

Immunohistochemical biomarkers require further investigation as they are simple to employ and are widely used. Moreover, in Brazil, the use of immunohistochemical biomarkers is funded by the public health system. Finally, it is noteworthy that the three biomarkers listed above can be assessed in any basic pathology laboratory. Our group will soon present the results of a study using these biomarkers.

CONCLUSIONS

No definitive predictive biomarker of inguinal lymph node metastasis has yet been established. There are many challenges to achieving this goal: the disease is most prevalent in regions with low socioeconomic conditions, there is difficulty in standardizing the criteria for inguinal lymph node metastasis, there is difficulty in accessing radiological exams and medical monitoring of patients, there is varying prevalence of HPV and histological subtypes according to geographic location, there is interobserver variation, and there is the need for extensive tissue sampling in advanced tumors. However, several studies and international guidelines demonstrate that the strongest predictors of inguinal lymph node metastasis are the stage of the primary tumor, the histological grade, and the presence of angiolymphatic invasion.

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CONFLICT OF INTEREST

None declared.

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Can we recommend varicocele surgery for men with hypogonadism?

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COMMENT

Varicocele is a frequent finding, identified in 15% of the male general population and, among those with infertility, the prevalence is around 35% for primary infertility and 80% for secondary infertility (1, 2). This pathology can be defined as an abnormal tortuous dilation of internal spermatic veins and pampiniform plexus in spermatic cord. Some risk factors such as age, height, lifestyle habits are associated with the presence of varicocele, however it seems that an increase of body mass index decreased risk of varicocele (3). The early diagnosis and treatment aim to avoid the possible progressive duration-dependent reduction in testicular function, demonstrated as impaired semen parameters, low testosterone (TT) levels and increased sperm DNA fragmentation levels, particularly stress-induced sperm DNA damage (1, 4, 5).

Many hypotheses have been proposed to explain the consequences of varicocele in testicular function, such as testicular hyperthermia, hypoxia, hormonal dysfunction, decreased blood flow, back-flow of metabolites from the adrenal gland, impairment of Leydig cells (6-8). Furthermore, Weiss et al. reported a reduced testosterone synthesis in individuals with varicocele (9). Another study suggests that Leydig cell hyperplasia, commonly seen in patients with varicocele, is a compensatory reaction to Leydig cell dysfunction and impaired testosterone synthesis (10).

In men presenting with both hypogonadism and varicocele, the stimulation of hypothalamic-pituitary-gonadal axis with gonadotropins or clomiphene citrate is feasible. If combined with varicocelectomy, the serum levels of TT can be further improved. However, the real benefit of this treatment remains unclear (11, 12). The treatment of the varicocele will at least stop possible further varicocele-induced testicular damage and, in a majority of men, lead to improved semen parameters (13), enhanced Leydig cell function in association with increased TT levels and as a consequence, improved quality of the semen due to the reduction in DNA damage (10, 14).

The present review compiles the effects of varicocelectomy in men with hypogonadism on TT serum levels.

MATERIALS AND METHODS

We selected articles published from 1975 to 2022. Studies were obtained using PubMed. The search terms “varicocele”, “hypogonadism” and “testosterone level” were used as filters. The

language of publication was set only to English. In total, 595 potential articles were found. Through screening of titles and abstracts, 36 articles were identified. After full-text reading, 15 original studies and 2 meta-analyses were included in this review (Figure-1).

RESULTS

Several studies demonstrated that varicocele might be associated with decreased testosterone production and impaired sperm synthesis, corroborating with the hypothesis that varicocele may be linked with hormonal dysfunction. The first study published by Comhaire et al. in 1975 demonstrated that 10 of the 33 men with varicocele analyzed had decreased testosterone levels and erectile dysfunction, and both symptoms were improved in those submitted to surgery (12). In 1978 Rodriguez-Rigau et al. reported that individuals with varicocele and normal serum levels of TT submitted to varicoectomy showed decreased Leydig cell counts on testicular biopsy (15).

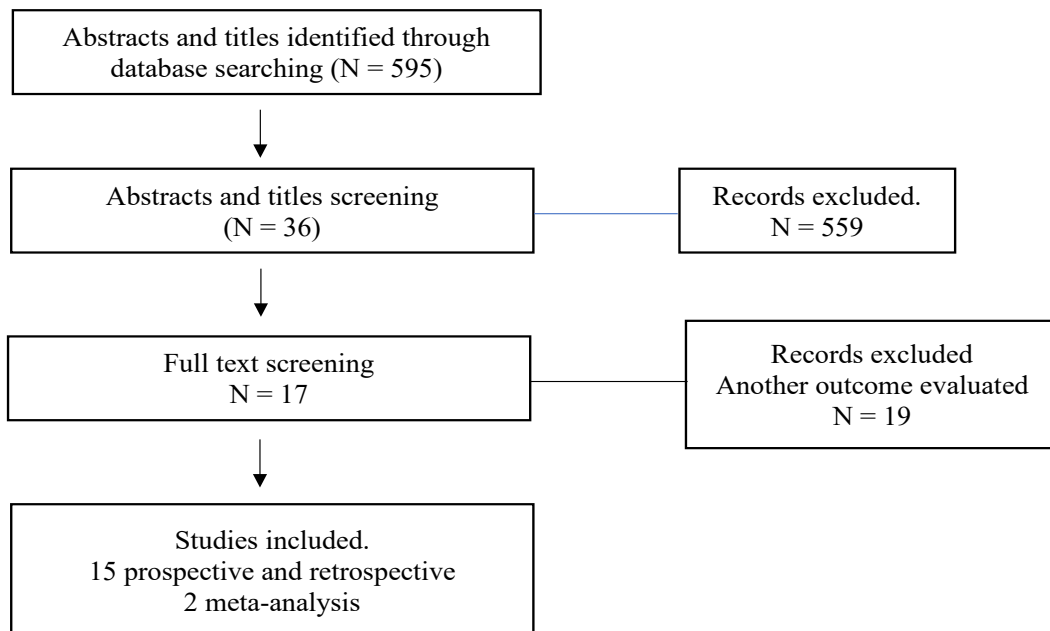
Su et al. reviewed the effect of varicoectomy on TT levels in 53 men and showed a mean TT level increase from a preoperative level of 319

(± 12 ng/dL) to 409 (± 23 ng/dL) in the post operative period ($p < 0.0004$). These findings demonstrated a direct positive correlation of varicoectomy with spermatogenic function (16).

In 1999, Cayan et al. analyzed the effects of varicoectomy on FSH and TT levels. They retrospectively evaluated 78 infertile patients who underwent microsurgical inguinal varicoectomy. The mean FSH levels decreased from 15.21 mIU/mL to 10.82 mIU/mL after surgery, and mean TT levels increased from 563 ng/dL (± 140) to 837 ng/dL (± 220) (17).

Pierik et al. demonstrated the impact of varicoectomy on serum inhibin B levels, TT levels, FSH and LH levels. Within the 30 men analyzed, there were no significant changes in serum levels of FSH, LH and testosterone levels, but, instead, a significant increase in inhibin B was observed, from 133.9 (± 13.4 pg/mL) to 167.8 (\pm pg/mL) (18). Similarly, Di Bisceglie et al. performed sclerotherapy in 38 patients with varicocele and compared inhibin B and FSH levels with 40 untreated patients with varicocele. A significant increase ($p < 0.01$) in serum inhibin B levels and a significant decrease ($p < 0.05$) in FSH levels were observed at 6 months

Figure 1 - Flow chart of screened and excluded publications.



after treatment. However, there was no significant increase on TT levels (660 ng/dL before procedure and 650 ng/dL after) (19). Likewise, Ozden et al. studied thirty men presenting with varicocele and infertility associated with oligoasthenospermia. All hormone analysis were performed preoperatively and at a 6-month postoperative follow up. There was no statistically significant difference between the mean serum FSH, luteinizing hormone (LH), prolactin and testosterone levels before and after treatment ($p > 0.05$). However, they showed a significant improvement in sperm concentration, forward progressive motility, and serum inhibin B levels after treatment ($p < 0.05$) (20). Furthermore, Rodriguez Peña et al. studied the effects of varicolectomy in hormone levels and seminal parameters in 202 patients. They did not find any difference between pre and post operative on TT levels (preoperative 648 ± 156 ng/dL, post operative 709 ± 232 ng/dL) (21).

Gat et al. performed a study on internal sperm vein embolization in patients with varicocele and reported that mean serum TT concentration rose after embolization by 43%, from 12.07 to 17.22 nmol/L ($p < 0.001$). Also, the author demonstrated a significant decrease in the mean serum FSH levels, improving Leydig and Sertoli cell functions (22).

Lee et al. evinced that the mean TT levels of 18 men submitted to microsurgical varicolectomy and vasectomy increased from 348 ng/dL preoperatively to 416 ng/dL postoperatively (23).

In 2011, Zohdy et al. analyzed 141 infertile men with varicocele. They compared the International Index of Erectile Function score (IIEF-5) and total serum testosterone. The patients were divided into two groups according to surgical intervention; 103 individuals were submitted to varicolectomy and 38 were the control group (assisted reproduction procedures). They showed that the serum TT significantly increased from 379.1 ± 205.8 before varicolectomy to 450.1 ± 170.2 ng/dL 6 months after and the IIEF-5 increased from 17.1 ± 2.6 in the initial visit to 19.7 ± 1.8 after the surgery. Interestingly, there was a non-significant negative correlation between the mean change

in TT and the mean change in IIEF-5 in the control group (24).

Hsiao et al. retrospectively reviewed 272 patients who underwent subinguinal microsurgery varicolectomy between 1996 and 2009 and compared serum TT levels before and after treatment. Patients who had baseline TT lower than 400 ng/dL had a greater increase in serum levels (309 ± 7.4 to 431 ± 16.2 ng/dL, $p 0.001$). And this elevation occurred even in individuals over 40 years old. (25).

Tanrikut et al. measured preoperative TT levels in 325 men with palpable varicocele and in 510 men with vasectomy reversal without varicocele who served as a control group. The TT level increased significantly from 358 ± 126 ng/dL to 454 ± 168 ng/dL after varicolectomy. Within the subgroup of patients with postoperative TT level improvement, the mean increase was 178 ng/dL. Also, they evidenced that varicocele was a risk factor for androgen deficiency and the microsurgical repair increased hormonal levels (26).

Sathya Srini et al. evaluated 200 men diagnosed with clinical varicocele. They were divided into two groups, one submitted to microsurgical varicolectomy and the other to assisted reproduction procedures. The group that underwent surgery had an increase in mean TT (177 ± 18 ng/dL before varicolectomy to 301 ± 43 ng/dL after) and in testicular size (+ 1.508 cc) that was associated with mean TT change. Out of the 100 patients of the varicolectomy group, 78 had postoperative normalization of TT levels, while only 16 of the control group had the same outcome (27).

Abdel-Meguid et al. performed a prospective controlled study in 171 men divided into four groups: varicocele-infertile treatment group, varicocele-infertile control group, varicocele-fertile treatment group and the normal-control group. They compared TT levels at 6 and 12 months. Significantly lower hormonal level was evidenced in men with varicocele compared with normal men. Varicolectomy increased TT levels in 102.3 ng/dL among hypogonadal men, however showed no improvement in eugonadal men (28).

Najari et al., in 2016, analyzed 34 patients retrospectively who had undergone microsurgical varicolectomy and had both pre and post-operative

rative Male Sexual Health Questionnaire (MSHQ). Most men in the study had bilateral varicocele and left grade III varicocele. Significant improvement in the total MSHQ score (3.9 ± 8.7 , $p=0.027$), the MSHQ erectile function (1.2 ± 2.3 , $p=0.007$), and the MSHQ ejaculatory function (1.4 ± 3.1 , $p=0.018$) domains were seen. Fifteen (44%) men reported improvement in their erectile function and 18 (53%) noticed better improvement in ejaculatory function. The mean baseline testosterone level in the 20 men who had post-operative levels assessed was 379.4 ± 164.7 ng/dL and post-operatively mean TT level increased to 515.3 ± 231.6 ng/dL ($p=0.007$) (29).

Ji et al. conducted a prospective comparative study from 2014 to 2015, comparing 130 men who had varicocele and complained of either infertility or scrotal pain, and 130 controls. All participants were further classified based on hypogonadism status using a serum testosterone cut-off value 300 ng/dL. They could see a correlation of grade II and III varicocele with an increased risk of hypogonadism as well as a correlation of impaired sexual function with TT levels (30).

Recently, Saylam et al. retrospectively analyzed 202 infertile men with hypogonadism and varicocele who underwent microsurgical sub-inguinal varicocele repair. Their hormonal and sexual function after surgery were assessed. Mean serum TT levels increased from 255 ± 66 ng/dL to 372 ± 134 ng/dL ($p = 0.000$), while serum FSH ($p=0.198$), LH ($p=0.207$) and prolactin ($p=0.345$) levels did not significantly change from pre to post-operative period. Also, IIEF-EF score significantly increased from 27.47 ± 2.96 (15–30) to 28.61 ± 2.02 (18–30), after surgery ($p=0.000$) (31).

Bernie et al. compared men who underwent varicolectomy versus testosterone therapy in patients in their 5th and 6th decades of life, and those submitted to the procedure improved as much as younger men. For those with TT < 400 ng/dL larger changes in serum testosterone with baseline normal levels were observed. Also, the improvement may not be clinically meaningful and may not be enough to improve symptoms in some men (32).

A meta-analysis done by Chen et al. in 2017, included eight studies and 712 patients who

underwent varicolectomy. The mean TT levels of patient's post-operation improved by 34.3 ng/dL ($p < .00001$) compared with their pre-operative levels. In a subgroup analysis, TT improvement in hypogonadal men was more significant (improvement of 123 ng/dL, $p<.00001$) than in eugonadal men, or in the untreated controls. In an analysis of surgery versus untreated controls (three studies included), results showed that mean testosterone levels among hypogonadal men increased by 105.65 ng/dL, favoring varicolectomy, as the between groups difference was statistically significant ($p < .00001$). There were insignificant differences in the eugonadal control group ($p = 0.36$) (33).

Another recent meta-analysis conducted by Russo et al. comprised fifteen studies, nine were retrospective and six observational. They showed that the mean difference of TT levels was statistically significant in men before and after varicolectomy (mean difference = 106.76 ng/dL; $p < 0.0001$). Although a high heterogeneity was present among the studies (34).

Below, we summarized on Table 1 all the studies in this review, reporting the effects of varicolectomy in total serum testosterone level in hypogonadal men.

DISCUSSION

Herein, the evidence that the surgical correction of varicocele improves the TT levels is seen in many studies and is corroborated by recent meta-analysis published. As we can observe, an increase of around 106 ng/dL could be achieved by the microsurgical technique (33, 34).

Furthermore, varicocele seems to cause pantesticular injury that leads to an impairment of both Sertoli and Leydig cell function, resulting in hypogonadism and altered seminal parameters and spermatogenesis. Whereas adequate intragonadal TT levels are necessary to ensure spermatogenesis (35). For example, Sirvent et al. analyzed testis biopsies from 31 men with varicocele. In addition to the atrophy of seminiferous tubules, they observed multiple changes in the characteristics of the Leydig cell population. Curiously, men with varicocele had Leydig cell hyperplasia. Sirvent et al. went further by functionally testing

Table 1 - Literature studies evinced the correlation between microsurgery varicocelectomy and serum testosterone levels.

Author	Year	Study type	N. of patients	Surgical Approach	Mean pre-op TT (nd/dL)	Mean post-op TT (nd/dL)
Su et al. (16)	1995	O	53	Microsurgical	319 ± 12	419 ± 23
Cayan et al. (17)	1999	R	78	Microsurgical	563 ± 140	837 ± 220
Pierik et al. (18)	2001	O	30	Conventional	460 ± 160	470 ± 190
Di Bisceglie et al. (19)	2007	O	38	Sclerotherapy	660 ± 50	650 ± 50
Ozden et al. (20)	2008	O	30	Conventional	660 ± 130	720 ± 130
Rodriguez Pena et al. (21)	2009	O	202	Conventional	648 ± 156	709 ± 232
Lee et al. (23)	2007	O	18	Microsurgical	360 ± 191	416 ± 358
Zhody et al. (24)	2011	O	141	Microsurgical	379 ± 205.8	450 ± 170.2
Hsiao et al. (25)	2010	R	272	Microsurgical	309 ± 7	431 ± 170
Tanrikut et al. (26)	2011	R	325	Microsurgical	200 ± 7	454 ± 168
Sathya Srini et al. (27)	2011	O	200	Microsurgical	177 ± 18	301 ± 43
Abdel-Meguid et al. (28)	2014	O	28	Microsurgical	233.8 ± 50.7	327.5 ± 53.2
Najari et al. (29)	2016	R	34	Microsurgical	379.4 ± 164.7	515.3 ± 231.6
Ji et al. (30)	2016	O	260	Microsurgical	310 ± 179	669 ± 180
Saylam et al. (31)	2020	R	202	Microsurgical	255 ± 66	372 ± 134

O = Observational; R = Retrospective.

the expanded population of Leydig cells with the peroxidase-antiperoxidase method and demonstrated a decreased number of cells expressing testosterone. It is interesting that all men had normal peripheral levels of LH and testosterone, leading to conclude that men with varicoceles must compensate via Leydig cell hyperplasia in order to remain eugonadal (36).

Also, some trials demonstrated the improvement in seminal parameters such as motility,

sperm concentration and Total Motile Sperm Count (TMSC) (20, 31) after correction of varicocele. The benefit related to improvement of FSH and LH levels remains uncertain (18, 19, 21, 31). On the other side, when the erectile function was analyzed, data show that IIEF was significantly improved by the correction of varicocele in infertile men. Consequently, these results must be interpreted cautiously given the complex interplay between infertility and sexual dysfunction (37, 38).

CONCLUSION

Varicocele is associated with an important impairment in men's testicular function, a decreased testosterone production and a significantly increased risk for hypogonadism. Infertile men presenting with hypogonadism may benefit substantially from varicocelectomy in terms of postoperative improvements in hormonal and seminal parameters. Nevertheless, the modest rise of TT levels may not manifest clinically, and patients must be counseled not to have high expectations.

CONFLICT OF INTEREST

None declared.

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Editorial Comment: Penile revascularization utilizing the lateral femoral circumflex artery after pelvic fracture urethral injury

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COMMENT

The present paper shows how the anatomy is important to urology. The authors demonstrate the use of an alternative arterial donor vessel for penile revascularization.

Using an operating microscope the dorsal penile artery was ligated and the distal end was anastomosed to the donor artery and an end-to-end fashion with the lateral femoral circumflex artery. Penile vascular anatomy is basic for this procedure. The penis is irrigated by two internal pudendal arteries, branches of the internal iliac (hypogastric) artery. After its various perineal branches, the pudendal arteries combine to form the so-called common penile artery, which divides into three branches: the bulbourethral artery, the dorsal penile artery and the cavernosal artery. The cavernosal artery is located inside the corpus cavernosum, the bulbourethral artery is responsible for irrigating the corpus spongiosum and urethra, and the dorsal penile artery is located between the tunica albuginea and Buck's fascia (1, 2).

The authors concluded that this case demonstrates an excellent result from penile revascularization utilizing the lateral femoral circumflex artery. This artery can be considered an alternate donor for penile revascularization procedures following pelvic fracture urethral injury when there is a contraindication to the use of the inferior epigastric artery.

CONFLICT OF INTEREST

None declared.

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Laparoscopic Pyelolithotomy for treating urolithiasis in ectopic pelvic kidneys

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ABSTRACT

Introduction: The management of urolithiasis ectopic pelvic kidneys (EPK) can be challenging because of the aberrant anatomy (1-4). We demonstrate the step-by-step technique of the laparoscopic approach for treating urolithiasis in EPK. **Patients and methods:** Three men with EPK (2 left, 1 right) underwent laparoscopic pyelolithotomy through a transperitoneal approach. After establishing the pneumoperitoneum, the parietal peritoneum was opened at the parietal colic sulcus and the bowel displaced medially. The kidney was identified in the retroperitoneum and the renal pelvis exposed after removal of the perirenal adipose tissue. The renal pelvis was opened, and the stones were identified and retrieved with forceps in 2 cases and with a flexible nephroscope in 1 case. The renal pelvis was closed with a 3/0 running barbed suture. A DJ stent was placed in all patients.

Results: For the first time, a laparoscopic technique for treating stones in the ectopic kidney is demonstrated in detail. Mean patient age was 52.6 years (44-58). The mean stone size was 22.3 mm (20-24 mm). Stones were in the renal pelvis in 2 cases and in the inferior calyx in 1 case. Mean operative time was 146 minutes (135-155 min). Mean estimated blood loss was 116 ml (60-140 ml). No complications were observed. The mean hospital stay was 3 days. The DJ stents were removed after 3 weeks. All patients were stone free at the postoperative CT scan with a mean follow-up of 3.3 months (1-6 months).

Conclusions: Laparoscopic pyelolithotomy can be an effective and reproducible minimally invasive technique for treating urolithiasis in EPK.

CONFLICT OF INTEREST

None declared.

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Robotic partial nephrectomy for large renal Leiomyoma: first case report

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ABSTRACT

Aim: Renal leiomyoma is a rare benign mesenchymal tumor arising from the smooth muscle cells of the kidney. Renal capsule is its most common location (1). Large tumor may require surgical excision which can be challenging in case of proximity to major vessels (2). Indications of robotic partial nephrectomy (RPN) have exponentially expanded over the past few years (3). We aim to report a case of large renal leiomyoma successfully managed with RPN.

Methods: A 59-year-old female patient with BMI 51 presented with chief complaint of abdominal discomfort. The patient underwent a CT scan that revealed a massive circumscribed exophytic complex solid cystic mass of 4.5 x 7.7 x 6.2 cm, arising from the lower pole of right kidney and abutting the inferior vena cava. RENAL score was 11ah (high complexity). Past surgical history included mid-urethral sling, breast reduction, and hysterectomy with salpingectomy. Preoperative creatinine and eGFR were 0.9 (mg/dL) and 77 (mL/min), respectively. A robotic excision of this mass was successfully performed by using Da Vinci Xi platform. Main steps of the procedure are illustrated in the present video.

Results: Dissection and isolation of the tumor were carefully performed after identifying key anatomical structures such as the ureter, the IVC and the renal hilum. Intraoperative ultrasound was used to confirm the margins of the mass. The renal artery was clamped and then the tumor was resected/enucleated. Renal parenchyma was re-approximated with a single layer of interrupted CT-1 Vicryl 0 with sliding clip technique. Warm ischemia time was 19 min. Estimated blood loss (EBL) was 250 ml. Operative time was 165 min. No intraoperative complications occurred. No drain was placed. Patient was discharged on postoperative day 2. Post-operative hypotension was managed with fluid bolus. Postoperative creatinine and eGFR were 1,0 (mg/dL) and 69 (mL/min/1.72m²), respectively. Pathology revealed a leiomyoma of genital stromal origin with hyalinization and calcification.

Conclusions: To the best of our knowledge, this is the first description of RPN for the management of a large (about 8 cm) renal leiomyoma. Robotic assisted surgery allows to expand the indications of minimally invasive conservative renal surgery whose feasibility becomes even more clinically significant in case of benign masses which can be managed without sacrificing healthy renal parenchyma.

CONFLICT OF INTEREST

None declared.

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Robotic assisted radical nephrectomy with Inferior vena cava tumor thrombus

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ABSTRACT

Purpose: Surgery for renal cell carcinoma (RCC) with an inferior vena cava (IVC) tumor thrombus can be done via a robotic approach. While this approach is thought to minimize blood loss, it may still result in significant losses (1) and current publications indicate that it can require upwards of 3-day hospital stays (1, 2). However, innovative surgical techniques, such as the split and roll, may curtail this. The purpose of this video is to present the case and surgical technique of robotic assisted radical nephrectomy with IVC thrombectomy.

Materials and Methods: The patient was a 77-year-old male found to have a right upper pole renal mass on CT urogram. On MRI (Figure 1), a renal mass and level II thrombus was seen. For this case, the Da Vinci Xi Intuitive robotic system was used, with four robotic 8-millimeter (mm) metallic trocars, two 5 mm assistant trocars, and one 12 mm air seal port. The split and roll technique were utilized to access the IVC and lumbar veins. This surgical method uses the adventitia of the IVC as a plane of dissection and safely identifies all branches/tributaries of the IVC to minimize the chance of vascular injury (3).

Results: Robotic console time was 150 minutes. The patient had an excellent outcome, with all tumor thrombus removed, less than 50cc of blood loss, and was discharged within 24 hours of the operation. The tumor pathology came back as papillary, high grade, and was stage pT3bN1.

Conclusions: The robotic approach with split and roll technique is a great surgical option for urologists to consider in patients with RCC and a level I or II thrombus, which can minimize blood loss and expedite discharge.

Figure 1 - MRI of abdomen.



On an axial view of the abdomen, the level II thrombus was seen pre-operatively. This was determined to be a level II thrombus.

CONFLICT OF INTEREST

None declared.

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ChatGPT for medical applications and urological science

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To the editor,

A Generative Pre-Trained Transformer (GPT) is an artificial intelligence (AI) algorithm designed to understand and generate human-like language. ChatGPT is a free and publicly available large language model developed by OpenAI. It uses advanced natural language processing algorithms, is trained on a vast corpus of data, and is not free of limitations and biases. AI is in its infancy and there is enough potential to be developed that will undoubtedly change our practices and human life. As an impactful tool, it can be used for the good and for the bad, and its responsible and moderated use is critical.

What is chatGPT

A Generative Pre-Trained Transformer (GPT) is an artificial intelligence (AI) algorithm designed to understand and generate human-like language. ChatGPT is a free and publicly available large language model developed by OpenAI. It uses advanced natural language processing algorithms, trained on a vast corpus of data (1).

Training data includes a wide range of questions and prompts and a diverse set of texts, such as books, articles, and websites, allowing knowledge in many different domains. As an AI language model, its goal is to assist and provide useful responses to users who interact (2).

A PubMed search on March, 03, 2023 using the word “chatGPT” displayed 5 publications in 2022 and 72 in the first 2 months of the year of 2023 and another search on March, 09, 2023 retrieved additional 22 new documents. The studies range from literature reviews on the issue to clinical case reports that used chatGPT as a writing tool.

ChatGPT for medical applications

ChatGPT has several potential applications in the field of medicine and healthcare. As an AI language model, ChatGPT has been trained on a vast amount of medical text data, including research papers, clinical reports, and electronic health records. This means that it has a deep knowledge base on medical topics and can generate text that may be instructive (3).

One potential application of ChatGPT in medicine is clinical decision support. By inputting patient data and symptoms, ChatGPT can generate recommendations for diagnosis and treatment based on the latest medical research and clinical guidelines. As any tool, when complementary to human expertise it can help improve the accuracy and efficiency of medical diagnosis and treatment, with potential to lead to better patient outcomes (4).

Another application of ChatGPT in medicine is natural language processing of electronic health records (EHRs). EHRs contain a vast amount of unstructured text data, and extracting meaningful information from these records can be time-consuming and challenging. ChatGPT can help automate this process by analyzing EHRs and identifying key information, such as patient diagnoses, treatments, and outcomes (5).

ChatGPT can also assist with patient education by generating easy-to-understand explanations of medical conditions and treatments. This can be particularly helpful for patients who may have difficulty understanding complex medical terminology or who may feel overwhelmed by the amount of medical information available online (6).

Overall, ChatGPT has several potential applications in medicine and healthcare, and its ability to generate text on a wide range of medical topics makes it a valuable tool for medical professionals, researchers, and patients alike. However, it's important to note that ChatGPT should be used as a complementary tool to human expertise and should not be relied upon as a substitute for professional medical advice or diagnosis.

CHATGPT FOR MEDICAL WRITING

ChatGPT can be a valuable resource for medical writing in several ways. As an AI language model, ChatGPT has been trained on a vast amount of data, including medical literature, research articles, and clinical reports. This means that it has a vast knowledge base on medical topics and can generate text that is precise (7).

One way ChatGPT can help with medical writing is by providing assistance with grammar and syntax. Medical writing often involves complex terminology and jargon, and ChatGPT can help ensure that the language used in a medical document is grammatically correct and easy to understand (8).

ChatGPT can also help with writing medical reports, research papers, and other types of medical documents by providing suggestions for structure, formatting, and organization. For example, it can suggest appropriate headings and

subheadings, provide examples of effective introductions and conclusions, and help ensure that the document flows logically and coherently (9).

Furthermore, ChatGPT can help with summarizing complex medical information in a way that is easy to understand for a lay audience. This can be particularly helpful for medical writers who are creating patient education materials or other types of health-related content (10).

Overall, ChatGPT's ability to generate grammatically correct text on a wide range of medical topics can be a valuable resource for medical writers looking to improve the quality and effectiveness of their work.

ChatGPT for urological science

ChatGPT can be a useful resource for urological science in several ways. As an AI language model, ChatGPT has been trained on a vast amount of text data, including scientific research papers, medical textbooks, and other authoritative sources on urological science. This means that it has a deep knowledge base on urological science (11).

One way ChatGPT can help with urological science is by providing assistance with writing research papers and clinical reports. Urological science involves complex medical terminology and jargon, and ChatGPT can help ensure that the language used in a research paper or clinical report is scientifically accurate (12).

ChatGPT can also help urological scientists with analyzing and interpreting data. By inputting data from urological studies or clinical trials, ChatGPT can generate text that provides insights into the findings, significance, and implications of the data. This can be particularly helpful for urological scientists who need to communicate their research findings in a clear and concise way (13).

Furthermore, ChatGPT can assist with creating patient education materials on urological topics. Urological conditions can be complex and difficult to understand for patients, and ChatGPT can generate text that explains urological conditions and treatments in a clear and understandable way (14, 15). Overall, ChatGPT can be a valuable resource for urological scientists looking to improve the quality and effectiveness of their work.

ChatGPT and references

ChatGPT is an AI language model that generates text based on patterns and statistical models learned from a large corpus of text data. While it can provide accurate and informative information, it does not have the ability to add exact references or citations to its writing.

However, as an AI language model, ChatGPT is trained on a vast amount of text data, including scientific research papers, academic journals, and other authoritative sources. This means that the information it provides is typically based on reliable and credible sources.

It's important to note that it is ultimately up to the user to ensure that the information is properly cited and referenced in any written work. If you are using ChatGPT to generate content for a research paper, article, or other type of written work, it's important to carefully review and fact-check the information it provides and to include proper citations and references to any sources used.

In summary, ChatGPT is a powerful tool that can provide information on a wide range of topics, but it is the user's responsibility to ensure that the information is properly cited and referenced in any written work.

Ethics in the use of chatGPT

As an AI language model, ChatGPT has the potential to be a powerful tool for many different applications. However, there are important ethical considerations that must be taken into account in the use of ChatGPT (16).

First and foremost, the data that is used to train ChatGPT is critical. To ensure that ChatGPT is ethical and unbiased, the data that is used to train the model must be carefully selected and scrutinized. Training data that includes biased or discriminatory language can result in a model that perpetuates those biases and reinforces harmful stereotypes (17).

Another important ethical consideration is the potential misuse of ChatGPT. While ChatGPT can be used to provide helpful information and support to users, it can also be used to spread misinformation, hate speech, and other harmful content. It is important for developers and users

of ChatGPT to be aware of this potential and take steps to mitigate it, such as implementing content moderation tools and educating users on responsible use.

There are also privacy and security concerns associated with the use of ChatGPT. Conversations with ChatGPT can contain sensitive personal information, and it is important for developers to take steps to protect this data from unauthorized access or use. Overall, ethics in the use of ChatGPT requires careful consideration of the data used to train the model, responsible use of the model to prevent harmful content, and safeguarding user privacy and security (18).

Researchers using AI tools should document this use in the methods or acknowledgements sections of the created manuscript, and AI tools cannot take any attribution of authorship, since it carries with responsibility and accountability for the work (19, 20).

AI is in its infancy, is not free of limitations and biases, and there is enough potential to be developed that will certainly change our practices and human life. As any impactful tool, it can be used for the good and for the bad, and its responsible and moderated use is key.

ChatGPT limitations

Researchers are actively working to improve the capabilities and to address limitations that are common to most language models and AI systems in general.

While it is continually being updated with new data and fine-tuned by researchers and developers to improve its performance, the specific level of updating and the frequency of updates can vary depending on the resources and priorities of the team or organization responsible for maintaining ChatGPT. The current version was trained on a dataset that had a knowledge cutoff date of September 2021.

In addition to biases based on the sources of the data or the people who wrote it or programmers' orientation, algorithmic bias may create systematic and repeatable errors with "unfair" outcomes in ways different from the intended algorithm.

Artificial intelligence hallucination may generate plausible sounding but incorrect or non-sensical answers that does not seem to be justified by its training data, such as claim to be human.

Limited access to the human commonsense knowledge, and inability to reason and learn and create like humans may generate struggle to understand the full context of a conversation or a piece of text, providing illogical, out of context, not relevant or not accurate responses (21).

The Author

CONFLICT OF INTEREST

None declared.

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