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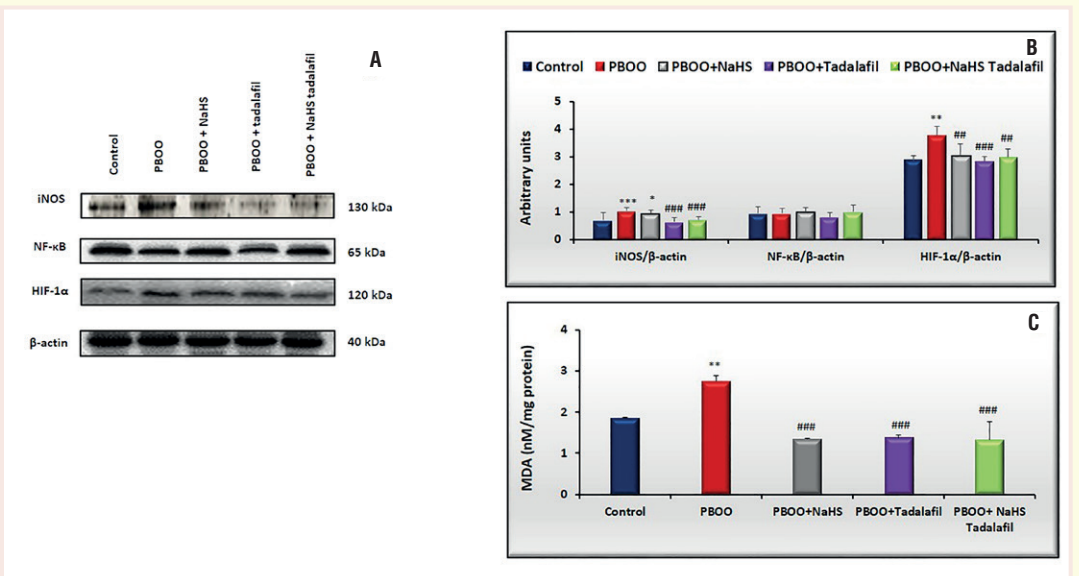

A) semi-quantification of iNOS, NF-κB, and HIF-1α protein expression levels in rat bladder tissues from all groups (control=5, PBOO=6, PBOO+NaHS=6, PBOO+tadalafil=5; PBOO+NaHS+tadalafil=6). B) bar graphs show the ratio of iNOS, NF-κB, and HIF-1α protein expression to β-actin expression. C) MDA content in the bladder tissue of rats from all groups(control=5, PBOO=5, PBOO+NaHS=5, PBOO+tadalafil=5; PBOO+NaHS+tadalafil=5). (page 977)

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EDITORIAL
IN THIS ISSUE

Primary monosymptomatic nocturnal enuresis highlighted in this number of International Brazilian Journal of Urology

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The November-December number of Int Braz J Urol, the 19th under my supervision, presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Prostate Cancer, Bladder Outlet Obstruction, BPH, Translational Research, Primary monosymptomatic nocturnal enuresis and UPJO. The papers came from many different countries such as Brazil, USA, Turkey, India, China, Italy, Argentina and Singapure and as usual the editor´s comment highlights some of them.

In the present issue we present two important papers about Primary monosymptomatic nocturnal enuresis. Dr. Ribeiro and colleagues from Brazil in page 937 (1) evaluated the hormone profile (brain natrituretic peptide -BNP and anti-diuretic hormone - ADH) and improvement in dry nights in a sample of children before and after surgical treatment of the Upper airway obstruction (UAO) and concluded that surgery for airway obstruction contributed to an increase in BNP without increasing ADH. A total of 85.8% of the children presented partial or complete improvement of their enuresis. Dr. Carvalho and colleagues from Brazil performed in page 944 (2) a interesting study about the relationship between the toilet training process (TT) and Primary monosymptomatic nocturnal enuresis (PMNE) and concluded that the age of onset of TT, acquisition of daytime continence, and the type of equipment were not associated with higher occurrence of PMNE. On the other hand, the Child-Oriented approach was a protective factor for the occurrence of PMNE. The editor in chief would like to highlight the following works too:

Dr. Hu and colleagues from China, presented in page 891 (3) a nice systematic review about the feasibility of 68Ga-PSMA PET/CT in diagnosing primary prostate cancer and concluded that compared with conventional imaging examinations, 68Ga-PSMA PET/CT had higher sensitivity and specificity in detecting primary prostate cancer. At present, most of the studies that used 68Ga-PSMA PET/CT for detecting prostate cancer are retrospective studies. Based on its advantage of high detection rate, the use of 68Ga- PSMA PET/CT in the detection of primary prostate cancer is worthy of promotion.

Dr. Gauhar and colleagues from Singapure and Brazil performed in page 903 (4) a interesting systematic review about the perioperative outcomes, complications, and survival in studies comparing ureteral stent and percutaneous nephrostomy in malignant ureteral obstruction and concluded that stents as the preferred choice as these are easier to maintain and ureteral stent placement should be recommended whenever feasible. If the malignant obstruction precludes a stent placement, then PCN is a safe alternative.

Dr. Guo and colleagues from China, presented in page 915 (5) a nice systematic review about the prevalence and clinical risk factors in patients diagnosed with incidental prostate cancer (IPC) during certain surgeries (transurethral resection of the prostate [TURP], open prostatectomy [OP], and holmium laser enucleation of the prostate [HoLEP]) after clinically suspected benign prostatic hyperplasia (BPH) and concluded that the prevalence of IPC was similar amongst patients undergoing TURP, HoLEP, and OP for presumed BPH. Interestingly, increased PSA level was the only independent predictor of increasing risk of IPC after BPH surgery rather than age and prostate volume. Hence, future research should focus on predictors which accurately foretell the progression of prostate cancer to determine the optimal treatment for managing patients with IPC after BPH surgery.

Dr. Favorito and colleagues from Brazil performed in page 930 (6) a interesting translational research about the anatomical aspects of the kidney surface in human fetuses during the second gestational trimester and concluded that the number of renal clefts has a great variation, weak correlation and no tendency to decrease during the 2nd gestational trimester. The number of clefts in right kidney of total sample and female fetuses has a significant development with age.

Dr. Carneiro and colleagues from Brazil and USA performed in page 952 (7) an interesting study about the role of remote proctoring during the initial training phases of a robotics curriculum using surgical robot skills simulator exercises and concluded that robotic performance increased significantly over three attempts for simulation exercises of low, medium, but not high-complexity. Proctoring, either in-person or remotely, has a positive impact on approval performance, particularly in intermediate tasks.

Dr. Gonzalez and colleagues from Brazil and Argentina performed in page 961 (8) a nice study about the surgical techniques (open- OP vs laparoscopic –LP - vs robotic -RALP pyeloplasty) to treat ureteropelvic junction obstruction and concluded that minimally invasive surgery for the management of UPJO in children is gaining more acceptance, even in patients younger than 1-year-old. Operative time continues to be significantly shorter in OP than in LP and RALP. Hospital stay was shorter in RALP compared to the other techniques. No differences were found in com- plication rates, type of complications, and reoperation rate.

Dr. Yilmaz-Oral and colleagues from Turkey performed in page 971 (9) a nice experimental study about the possible healing effect of combination treatment with a hydrogen sulfide (H2S) donor, sodium hydrosulfide (NaHS) plus tadalafil on partial bladder outlet obstruction (PBOO)-induced bladder dysfunction and concluded that the combination therapy has beneficial effects on bladder dysfunction via regulating both H2S and nitric oxide pathways as well as downregulation of oxidative stress and hypoxia. The synergistic effect of H2S and nitric oxide is likely to modulate bladder function, which supports the combined therapy for enhancing clinical outcomes in men with BPH/LUTS.

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

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REVIEW ARTICLE

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Performance of ^{68}Ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography in the diagnosis of primary prostate cancer: a systematic review and meta-analysis

Xianwen Hu [1], Yan Wu [1], Peiqing Yang [1], Ju Wang [1], Pan Wang [1], Jiong Cai [1]

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ABSTRACT

Objective: To explore the feasibility of ^{68}Ga-PSMA PET/CT in diagnosing primary prostate cancer.
Materials and Methods: Embase, PubMed and Cochrane Library databases were searched for studies published before July 2020. The studies that used ^{68}Ga-PSMA PET/CT for detecting primary prostate cancer, and pathological biopsy as the reference standard were included. The selecting process used preferred reporting items for systematic reviews and meta-analyses (PRISMA). The quality of enrolled studies was assessed by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.
Results: According to our search strategy, 9 studies were included for analysis. A total of 547 patients with primary prostate cancer and 443 lesion segments that underwent ^{68}Ga-PSMA PET/CT scans were included and their pathological biopsies were compared. The results of these studies showed some differences. For instance, the lowest sensitivity of ^{68}Ga-PSMA PET/CT in diagnosing primary prostate cancer was 67%, while the highest sensitivity recorded was 97%.
Conclusions: Compared with conventional imaging examinations, ^{68}Ga-PSMA PET/CT had higher sensitivity and specificity in detecting primary prostate cancer. At present, most of the studies that used ^{68}Ga-PSMA PET/CT for detecting prostate cancer are retrospective studies. Based on its advantage of high detection rate, the use of ^{68}Ga-PSMA PET/CT in the detection of primary prostate cancer is worthy of promotion.

ARTICLE INFO

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INTRODUCTION

Prostate cancer poses a serious threat to the health of men all over the World and its detection rate is increasing year by year with the development of medical technology. Imaging plays an important role in early and accurate diagnosis of prostate cancer (1). Conventional imaging tests for prostate cancer diagnosis include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), 2-deoxy-2-[fluorine-18]fluoro-D--glucose positron emission tomography/computed tomography (18F-FDG PET/CT), etc. Previous studies have demonstrated high specificity of trans-

rectal ultrasound biopsy and multi-parameter MRI in diagnosing prostate cancer. However, the sub--rectal ultrasound biopsy has increased the risk of overdiagnosis and overtreatment of indolent prostate cancer (2), and the sensitivity, accuracy and specificity in diagnosing prostate cancer by multi-parameter MRI varied greatly (3).

The physical half-life of positron radionuclide ^{68}Ga prepared by ^{68}Ge/^{68}Ga generator is 67.71 min. The positron decay accounts for 89% of the decay process, and the remaining 11% involves electron capture, considering that it is suitable for the pharmacokinetic study of small-molecular drugs and labeling of radioactive tracers (4). More than 90% of patients with prostate cancer have had high expression of prostate-specific membrane antigen (PSMA) in their cell membranes (5), and thus it might be an ideal drug target to treat radiation. Based on the above characteristics, ^{68}Ga-labeled PSMA has been successfully developed as a nuclear medicine clinically, and has been reported in the diagnosis of liver cancer and kidney cancer in addition to prostate cancer (6, 7). In recent years, ^{68}Ga-PSMA PET/CT was proved to be highly sensitive and specific in diagnosing prostate cancer. But, whether ^{68}Ga-PSMA PET/CT completely replaces invasive biopsy by transrectal ultrasound in diagnosing prostate cancer in the future has become a hot research topic (8). Therefore, a meta-analysis and systematic review was conducted to evaluate the diagnostic performance of ^{68}Ga-PSMA PET/CT in detecting prostate cancer.

MATERIALS AND METHODS

According to the preferred reporting items of the systematic review and meta-analysis (PRISMA) guidelines, the present meta-analysis was conducted. The studies that compared the diagnostic performance of ^{68}Ga-PSMA PET/CT in primary prostate cancer with histopathology were included.

Literature search strategy

In July 2020, a systematic search of the EMBASE (including MEDLINE), PubMed, and Cochrane Library databases was conducted according to the PRISMA guidelines. The search criteria were as follows: (["^{68}Ga-labeled prostatic membrane antigen"] or ["^{68}Ga-PSMA"] or ["gallium-PSMA"] or ["gallium-68 prostatic membrane antigen"]) and (["PET/CT"] or ["Positron Emission Tomography-Computed tomography"] or [PET] or ["Positron Emission Tomography"]) and (["prostat* neoplasm"] or ["prostat* cancer"] or ["prostat* carcinoma"] or ["prostat* tumor"]) and ([detection] or [detectability] or [positivity] or [accuracy] or [diagnosis] or [specificity] or [sensitivity] or [performance]). The search was limited to human studies, and in vitro and animal studies were excluded. As no patients were included in this study, informed consent or ethical review board (ERB) approval was not required.

STUDY SELECTION PROCESS

Inclusion criteria

The inclusion criteria were as follows: studies (I) that used The inclusion criteria were as follows: studies (I) that used ^{68}Ga-PSMA PET/CT for diagnosing primary prostate cancer; (II) that used histopathological examination as reference standard for comparison; (III) in which prostate cancer was confirmed by biopsy or postoperative histopathological examination; (IV that included true positive, false positive, true negative, and false negative data to construct a 2x2 quadrilateral contingency table; (V) with at least 10 patients; and (VI) that were originally published.

Exclusion criteria

The exclusion criteria were as follows: (I) study population with metastatic or recurrent prostate cancer (however, if the study provides diagnostic performance for each stage of prostate cancer including primary prostate cancer should be included); (II) review articles, case reports/series, diagnostic guides, short surveys, letters, consensus statements, study registrations, and conference summaries; (III studies with less than 10 patients; (IV) if the data included in the study was insufficient to construct a 2x2 quadrilateral table; and (V) ^{68}Ga-PSMA PET/CT was used for diagnosing prostate cancer, but its diagnostic performance was not emphasized.

The establishment and literature selection process of this study was conducted by two independent authors with more than 10 years of scientific research experience. In case of any disagreements, consensus was reached by consulting the reviewers.

Data extraction

The following data were extracted from the included studies in a standardized form: (I) characteristics of patients-number of patients, median age, median value of prostate specific antigen, Gleason score median and range; (II) features of studies included- origin of research (first author, nation), year of publication, study design (prospective or not, multicenter or not), reference criteria, blinding to reference criteria, and (III) PET/CT characteristics-PET/CT manufacturers, minimum scan layer thickness, radioactive tracer dose, uptake time, and CT technique and the mean maximum standard uptake value (SUVmax) for lesion images collected from the patients with PET/CT.

Quality assessment of diagnostic accuracy studies-2 (QUADAS-2) was used for assessing the quality of enrolled studies (9). Data extraction and critical evaluation were carried out independently by two authors, and any disputes between them were resolved by reaching a consensus with the third reviewer.

Data integration and analysis

The primary purpose of this meta-analysis was to evaluate the diagnostic performance of ^{68}Ga-PSMA PET/CT in diagnosing primary prostate cancer. Secondly, the heterogeneity between the included studies was also analyzed and attempted to explore its underlying causes.

True positive, false positive, false negative, and true negative data of ^{68}Ga-PSMA PET/CT in diagnosing primary prostate cancer were extracted from the included studies (some of the data were deduced according to the paper) to make a 2x2 quadrellar contingency table, and the sensitivity and specificity were also calculated. If the included studies were given grades according to the prostate-specific antigen (PSA) values, then the detection rate was synthesized from it. When multiple reference indicators such as PSA value, maximum standard uptake value and Gleason score were given, then the results with the highest accuracy were used. The hierarchical logistic regression model was used to calculate the general estimates of sensitivity and specificity of the included study, which included the hierarchical summary receiver operating characteristics (HSROC) model and concomitant variables. HSROC curves with 95% confidence and prediction regions were used to map the results for their sensitivity and specificity. Cochran's Q test and Higgins I2 test were used to examine their heterogeneity. In Cochran's Q test, $p < 0.05$ was taken as the test standard, which indicated the existence of heterogeneity. Higgins I2 test was used to evaluate the degree of heterogeneity using the following criteria: inconsistency index (I2) <50% was considered as heterogenous; I2=50-80% represents the possibility of moderate heterogeneity, and I2>80% represents the possibility of significant heterogeneity. Stata software 14.0 was used for statistical analysis, and $p < 0.05$ was considered to be statistically significant.

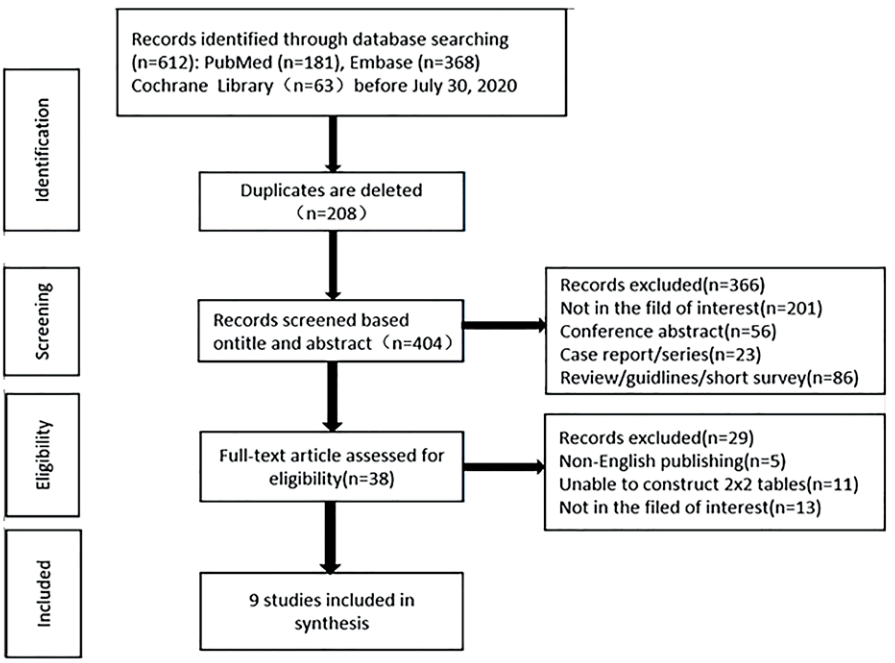
RESULTS

Studies and study design

Literature search initially yielded 612 articles that diagnosed prostate cancer by ^{68}Ga--PSMA PET/CT. After gradually removing the overlapping, irrelevant, reviews, case reports and other articles, there were 38 potentially eligible original texts. Due to non-English publications (n=5), the 2x2 quadrilingual table (n=11) could not be constructed by the data extracted from these papers, and the papers that were not the field of interest (n=13) were further excluded. Finally, 9 papers were included for meta-analysis, and the detailed process of literature search is presented in Figure-1.

The characteristics of patients in the enrolled studies (10-18) are presented in Table-1. Seven of the 9 included studies assessed the diagnostic performance of ^{68}Ga-PSMA PET/CT for prostate cancer based on the number of patients (a total of 547 patients) and 3 studies (one of the article included studies on both patients as well as lesion segments) evaluated the diagnostic performance

Figure 1 - The literature screening flow chart of the inclusion study.



based on lesion segments (a total of 443 lesion segments). The study population size ranged from 24 to 173, and the average age, PSA values and Gleason scores were recorded from 8 of the 9 studies. The patients included in this study presented with clinical symptoms, had increased PSA, or pathologically confirmed prostate cancer.

Three of the 9 studies were conducted in Germany, 2 in India and the others in Italy, Australia, Egypt and China, and were published from 2016 to 2020. Among these studies, 3 studies were prospective studies, and the remaining were retrospective studies. Pathological tissue biopsy was used as the reference, and 5 of the 9 studies were blinded with the reference criteria.

Four studies were scanned by Siemens, 2 by GE, 2 by Philips PET/CT scanners, and the other one was not recorded. Four of the 9 studies recorded minimum thickness of the scan, and 6 studies recorded the dose of radioactive tracer and uptake time, while 2 studies did not record the CT technique used and the maximum standard uptake value of the lesion.

Quality evaluation

The QUADAS-2 tool was used to evaluate the quality of the studies included as shown in Figure-2. In an objective assessment, the quality of these studies was shown to be medium to high, and 6 of the 9 studies met at least 4 of the 7 QUADAS-2 indicators. Of the 6 retrospective studies, one had high risk of bias due to discontinuous study design (11), and one retrospective study did not explicitly mention whether the patient registry was continuous or not (16), and so the risk of bias could not be determined. With respect to the index test, except for the two studies (15, 18), there was an ambiguous risk of bias in the remaining studies (10-14, 16, 17), and this is because there were no records of whether PET/CT was blinded to the reference criteria. With regards to reference criteria, several studies did not record whether the interpretation of reference standard results was made without understanding the results of the indicator tests (11, 14, 16), but all the studies used pathological biopsy as reference criteria and were therefore considered as low risk. Regarding the flow and timing, we believed that there is a high risk because one study did not include all enrolled patients in the analysis (12).

Accuracy evaluation of ^{68}Ga-PSMA PET/CT

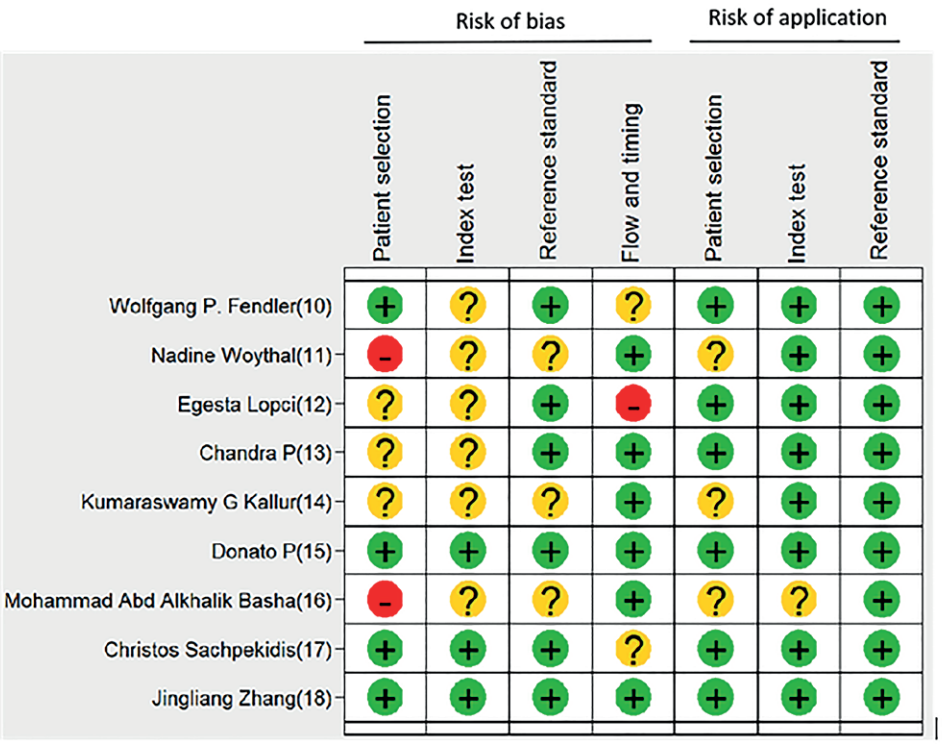
Of the 9 studies, 2 studies did not record the evaluation by ^{68}Ga-PSMA PET/CT (15, 16),

Table 1 - Features of the included studies.

First Author, Nation, Ref.	PY	Sample size(n)	Mean age	Mean PSA ng/mL	GS		Study design		RS	Blind	Vendor	STmin mm	RTD (mBq)	UT (min)	CT technique	Mean SUVmax
					Mean	Range	PD	MC								
Fendler et al., Germany (10)	2016	126(lesion)	NR	NR	7	6-9	Yes	No	biopsy	NR	Siemens	5.0	104-276	45-80	Non-CE and CE	11.8
Woythal et al., Germany (11)	2018	31	67.2	17.49	NR	6-10	No	No	biopsy	Yes	Philips	4.0	117.23± 19.86	60.90±26.13	Non-CE	14.06
Lopci et al., Italy (12)	2020	168(lesion)	74.7	7.6	NR	6-10	Yes	No	biopsy	Yes	NR	NR	NR	NR	NR	4.29
Chandra et al., India/(13)	2019	41	69.1	13.7	8	6-10	No	No	biopsy	NR	GE	NR	NR	NR	Non-CE	8.53
Kallur et al., India (14)	2017	76	68	25.5	7	5-9	No	No	biopsy	Yes	GE	3.75	M=111 R=74-185	60	Non-CE and CE	>4.0
Donato et al., Australia (15)	2020	144 (149,lesion)	67	8.6	7	6-8	No	No	biopsy follow-up	NR	Siemens	NR	150±7.5	60	Non-CE	NR
Basha et al., Egypt (16)	2019	173	68	17.7	8	6-10	Yes	Yes	biopsy	Yes	Philips	NR	NR	NR	NR	NR
Sachpekidis et al., Germany (17)	2016	24	69	24.1	7	7-9	No	Yes	biopsy	Yes	Siemens	NR	M=268 R=69-352	55-60	Non-CE	14.3
Zhang et al. China (18)	2019	58	70	15.46	NR	6-10	No	Yes	biopsy	Yes	Siemens	5.0	1.8–2.2 MBq/kg	60	Non-CE	8.76

Notes: Ref = Reference; **PY** = Publication year; **M =** Median; **R** = Range; **NR** = Not reported; **STmin** = Minimum slice thickness; **CT** = Computed tomography; **GS**=Gleason score; **PD** = Prospective design; **MC** = Multicenter; **RS**= Reference standard; **CE** = Contrast-enhanced; **Non-CE** = None contrast-enhanced; **RTD** = Radioactive tracer dose; **UT** = Uptake time.

Figure 2 - Risk of bias and applicability concern summary: Review the authors' judgments of each of the areas covered in the study by QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2 tool).

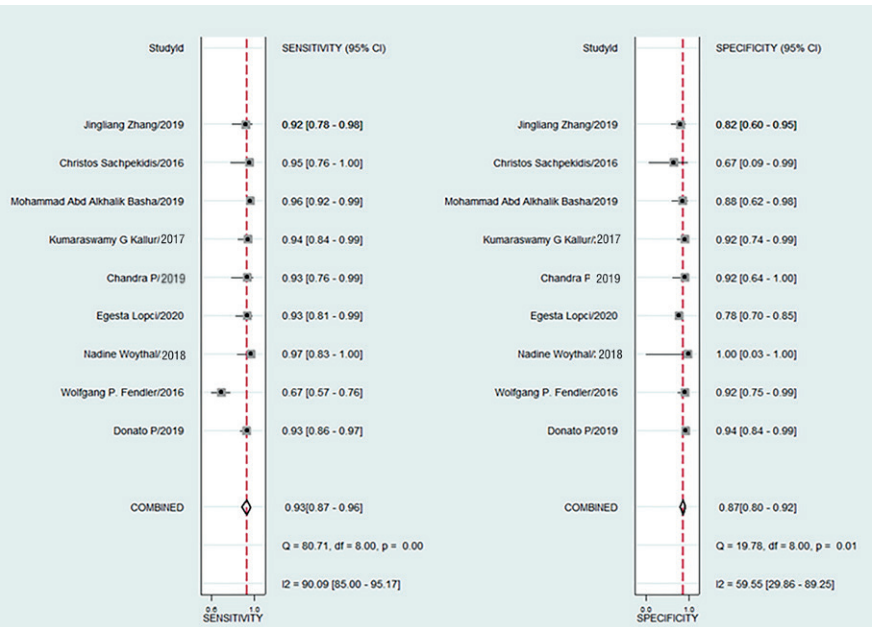


and the other studies evaluated the positive PSMA uptake of PET/CT further by quantitative comparative analysis of SUVmax value of suspicious lesions and SUV uptake value of normal PSMA biodistribution region. The sensitivity and specificity of ^{68}Ga-PSMA PET/CT in diagnosing prostate cancer in 9 studies are shown in Figure-3. The sensitivity and specificity ranges of 9 enrolled studies were 67-97% and 67%-100%, respectively. The Higgins I2 statistics showed heterogeneity in terms of sensitivity and specificity were (90.09 [95%CI, 85.00-95.17) and (59.55 [95%CI, 29.86-89.25). The pooled sensitivity and specificity in all 9 studies were 93% (95%CI=0.87-0.96) and 87% (95%CI=0.80-0.92), and the positive likelihood ratio, negative likelihood ratio and diagnostic advantage ratio were 7.4 (95%CI, 4.6-11.9), 0.08 (95%CI, 0.05-0.15) and 89 (95%CI, 42-187), respectively. The summary receiver operating characteristic (SROC) curve of the included studies is shown in Figure-4A. A significant difference was observed between the 95% confidence interval (CI) and the prediction interval, further indicating heterogeneity among studies within this group. The area under the SROC curve was 0.95, wherein the 95%CI was 0.93-0.97. Deeks' funnel plot is presented in Figure-4B. The P value of slope coefficient was 0.84, which was greater than 0.05, and so it is considered as low possibility of publication bias.

Predictors of ^{68}Ga-PSMA PET/CT positivity

The relationship between ^{68}Ga-PSMA PET/CT positive and other factors in patients, such as PSA level, patient stage, GS, etc., was explored in 9 included studies. Some of these studies suggested that the positive diagnosis of prostate cancer by ^{68}Ga-PSMA PET/CT showed association with PSA level, Gleason score and SUVmax (10, 15-18). Sachpekidis et al. (17) have found that the PSA level in prostate cancer patients showed significant correlation with the mean standard uptake value (SUVmean) and SUVmax of ^{68}Ga-PSMA uptake in tumor tissues (r=0.6, r=0.57, respectively), and the

Figure 3 - Coupled forest plots of the combination sensitivity and specificity of the inclusion study. Numbers are pooled estimates of the 95% CIs in parentheses. The lower right corner provides the corresponding statistics of heterogeneity. The horizontal lines represent the 95%CIs. CI=confidence interval. I2=heterogeneity.



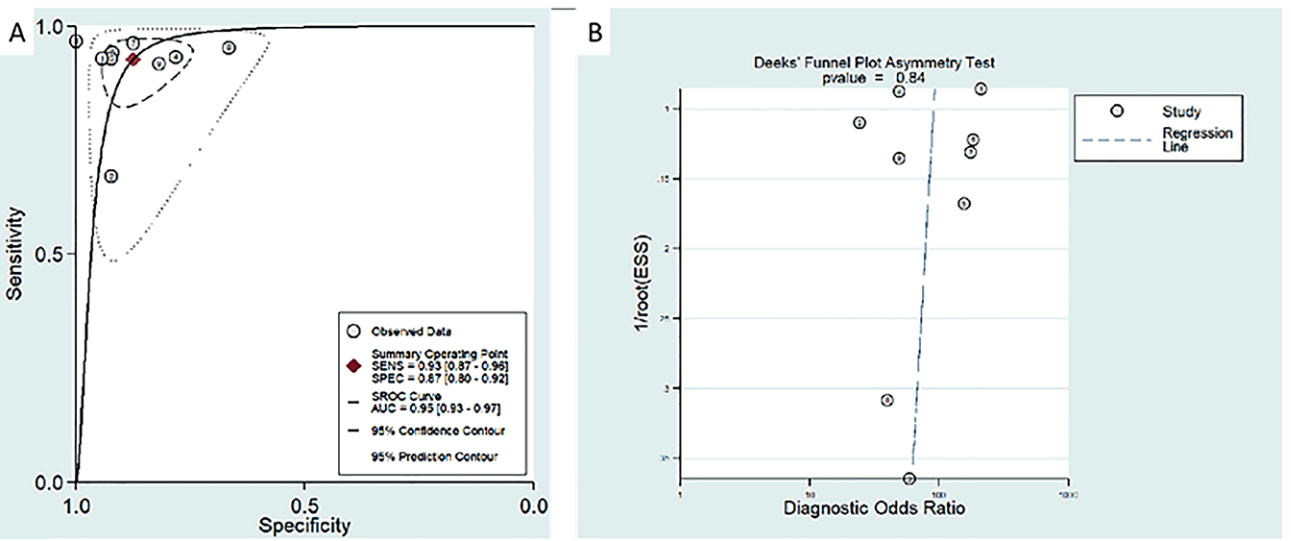
Gleason score remained weak but showed marked correlation with SUVmean (r=0.33) and SUVmax (0.28). Furthermore, Lopci et al. (12) have concluded that SUVmax and SUVratio of ^{68}Ga-PSMA showed obvious correlation with the accuracy of clinical diagnosis of prostate cancer in a study conducted on a total of 168 tumor tissue fragments. Moreover, Kallur et al. (14) have found that the accumulation of ^{68}Ga-PSMA in tumor tissues was gradually increased with increasing prostate volume and Gleason score, but showed no distinct correlation. In another study conducted by Woythal et al. (11) on diagnostic performance of ^{68}Ga-PSMA PET/CT for primary prostate cancer revealed that the SUVmax of tumor tissue was evidently higher in patients with Gleason score ≥8 than in patients with Gleason score <8, but showed no confirmed and evident correlation.

Exploration of heterogeneity

Meta-regression analysis results show that there are significant heterogeneity in Gleason score, and in the uptake of ^{68}Ga-PSMA SUVmax in the tumor tissues of prostate cancer patients (P<0.01). To be specific, the sensitivity of prostate cancer patients with Gleason score ≥8 (0.95 [95%CI 0.93-0.98]) was slightly higher than those with PSA<8 (0.93 [95%CI 0.90-0.97]), but in contrast, the specificity of the former was 0.79 ([95%CI 0.73-0.86]), which was significantly lower than that of the patients with Gleason score <8 (0.92 [95%CI 0.87 - 0.98]), and the difference was statistically significant (P <0.01). In addition, the sensitivity of mean SUVmax ≥10 (0.88 [95%CI 0.75-1.00]) was slightly lower than that of mean SUVmax <10 (0.93 [95%CI 0.86-1.00]), and the specificity of the former (0.88 [95%CI 0.73-1.00]) was greater than that of the latter (0.80 [95%CI 0.73-0.88]), but the difference between the two showed no statistical significance (P=0.26 and P=0.82, respectively).

The forest plot of the sensitivity analysis is presented in Figure-5. In addition to low pooled sensitivity estimates shown in both subgroups - contrast - enhanced CT techniques and based on lesion analysis - the sensitivity estimates were comparable in most of the remaining subgroups,

Figure 4-A) Hierarchical summary receiver operating characteristic curve for the diagnostic performance of 68Ga-PSMA PET/CT in patients with primary prostate cancer. B) Deeks' funnel plot was used for each patient analysis. The p value was 0.44>0.05, indicating a low possibility of publication bias. ESS=effective sample size. AUC=area under the curve; SROC=summary receiver operating characteristic; 68Ga-PSMA=Gallium (68) labeled prostate-specific membrane antigen; PET/CT=Positron emission computed tomography/computed tomography.

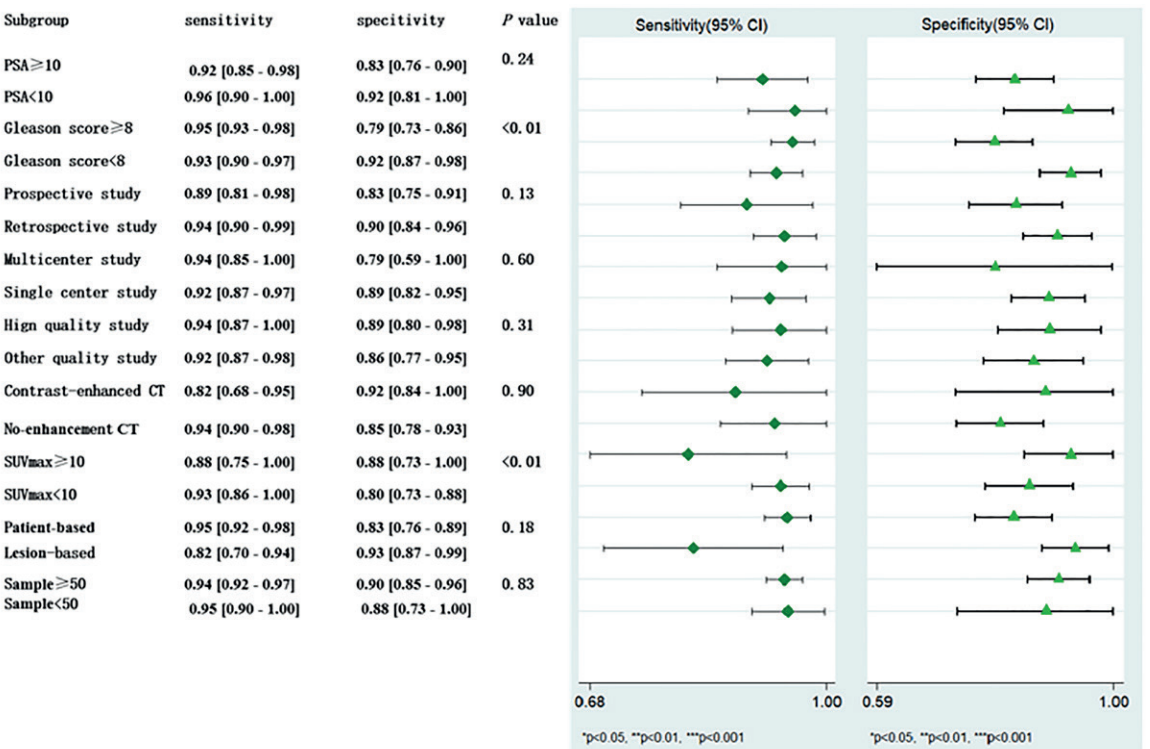


and their pooled sensitivity ranged from 0.88 to 0.96. Nevertheless, the pooled specificity estimates were relatively low in several subgroup analyses, specifically in those subgroups that included multicenter studies (0.79 [95%CI, 0.59-1.00]), Gleason score of ≥8(0.79 [95%CI, 0.73-0.86]), and SUVmax of <10 (0.80 [95%CI, 0.73-0.88]), and this might be due to smaller sample sizes, as only two of the 9 included studies were included in the analysis of multicenter studies and Gleason score ≥8. Moreover, only 3 of the 9 studies were prospective, thus showing an estimated specificity of 0.83 with a 95%CI of 0.81-0.98.

DISCUSSION

Prostate cancer is the most common malignancy in men after lung cancer, with nearly 430.000 new cases and more than 360.000 deaths reported each year worldwide (19). There are no specific clinical manifestations in the early stage of prostate cancer, and many patients have metastasized at the time of first diagnosis and lost the best time for treatment, leading to treatment failure. Therefore, finding effective diagnostic methods and indicators for early diagnosis of prostate cancer is the key to improve the cure rate as well as the survival rate (20, 21). Imaging examination plays an important role in the clinical diagnosis and staging of malignant tumors. However, traditional imaging examination is limited due to reduced accuracy of early diagnosis of prostate cancer (22). ^{68}Ga-PSMA PET/CT, a non-invasive examination technology, has ideal application prospects, provides diagnostic performance as that of traditional imaging examination, and at the same time can detect distant metastasis, achieving "one-stop" detection efficiency and achieving early diagnosis and treatment, finally improving the prognosis of patients (23, 24). Meanwhile, ^{68}Ga can be obtained by leaching with gallium germanium generator, so it is easy to produce, low cost, easy to label, and conforms to GMP (Good Manufacturing Practice) production requirements, so it is easy to clinical conversion (25). Meta-analyses have confirmed that ^{68}Ga-PSMA PET/CT had dominant advantages in detecting the recurrence and staging of prostate cancer (26, 27), and the pooled sensitivity and

Figure 5 - Forest plot of the sensitivity analysis, showing estimates of the pooled sensitivity and specificity of the various subgroups and the corresponding 95%CI.



specificity for detecting prostate cancer recurrence was 70% and 97%, as well as the pooled sensitivity and specificity of prostate cancer staging/restaging studies was 92% and 94%, respectively. However, our study is the first meta-analysis to use ^{68}Ga-PSMA PET/CT for the detection of primary prostate cancer. The objective of the current meta-analysis was to explore the accuracy of ^{68}Ga-PSMA PET/CT in diagnosing primary prostate cancer.

Among the enrolled studies, one study showed lower sensitivity and specificity respectively, which may be related to the small number of patients included in the analysis (21 and 24 patients included, respectively). However, the pooled sensitivity and specificity of the prostate cancer detection rates in the included 9 studies in this meta-analysis were 93% and 87%, respectively, and the results of the diagnosis of primary prostate cancer suggests that ^{68}Ga-PSMA PET/CT can be used as one of the main screening methods for patients suspected with prostate cancer (with increased PSA levels, elderly patients with frequent urination, urgency, progressive urinary tract drainage and other clinical symptoms), and help determine the best treatment regimen. We did not directly compare the diagnostic performance of ^{68}Ga-PSMA PET/CT and MRI in primary prostate cancer. But in a recent meta-analysis on the diagnostic performance of MRI in primary prostate cancer, Liang et al. (28) have concluded that its sensitivity and specificity was 0.77 (95%CI: 0.73-0.81) and 0.81 (95%CI: 0.76-0.85), respectively. Therefore, we believed that ^{68}Ga-PSMA PET/CT had more advantages in diagnosing primary prostate cancer. As our meta-analysis results were based on a combination of patient and lesion segments, there are very few research studies on ^{68}Ga--PSMA PET/CT based on the lesion fragments of prostate cancer (10, 12, 15), and we only included them in the subgroup analysis instead of studying them separately. So, it is necessary to evaluate the

diagnostic effects of ^{68}Ga-PSMA PET/CT in prostate cancer from patient-based and lesion-based aspects in the future work.

In terms of predicting the risk factors of patients with ^{68}Ga-PSMA PET/CT positive, multiple studies have confirmed that PSA levels and Gleason scores showed close correlation. The uptake of ^{68}Ga-PSMA on PET/CT in patients with prostate cancer with Gleason score of ≥8 or PSA level of ≥10ng/mL was significantly higher than those in patients with prostate cancer with Gleason score of <8 or PSA level <10 (5-18), and similar results were presented in a meta-analysis study conducted by Afshar-Oromieh et al. (29) on the prediction of ^{68}Ga-PSMA PET/CT for prostate cancer recurrence. Moreover, few studies have suggested that greater the prostate volume or the higher the stage of the patients with prostate cancer, the greater is the risk of predicting ^{68}Ga-PSMA PET/CT positive (11, 14).

In this meta-analysis, significant heterogeneity was observed among the 9 included studies. From meta-regression analysis, it was observed that the PSA level and average SUVmax for quantitative detection of tumor tissues by PET/CT contributed to this heterogeneity. With regard to type of study design, the quality of the included study and CT techniques used in the included study (whether contrast-enhanced scanning technology is used) showed no significant heterogeneity ($P > 0.05$). As for the scan thickness, the uptake time and dose of the tracer, only a few articles in the 9 included studies recorded their values and were therefore not included in this meta-regression analysis. Therefore, further studies might be needed to explore additional value of slice thickness and dose and uptake time of tracers in detecting primary prostate cancer. In terms of the characteristics of the included studies, whether it is a multicenter study, prospective study, and whether the sample size is greater than 50 patients showed higher sensitivity and specificity in diagnosing prostate cancer were recorded.

One of the major limitations of our meta-analysis is that there were few studies included, and many studies in the literature regarding the diagnosis of primary prostate cancer by ^{68}Ga-PSMA PET/CT were excluded due to lack of effective specific data. Secondly, most of the studies included had retrospective study designs and were non-multicenter institutional studies. Another limitation is that the sample sizes in some of the studies are smaller and the inter-study heterogeneity is large, which might in turn affect the general applicability of the results.

CONCLUSIONS

As a new radioactive tracer of PET/CT, ^{68}GA-labeled PSMA ligand had good sensitivity and specificity in detecting primary prostate cancer, and showed superior diagnostic performance in both pooled as well as subgroup analysis estimates.

FUNDING

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Nephrostomy tube versus double J ureteral stent in patients with malignant ureteric obstruction. A systematic review and meta-analysis of comparative studies

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ABSTRACT

Purpose: We aimed to perform a systematic review to assess perioperative outcomes, complications, and survival in studies comparing ureteral stent and percutaneous nephrostomy in malignant ureteral obstruction.

Materials and Methods: This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses framework. Meta-analyses were performed on procedural data; outcomes; complications (device-related, accidental dislodgement, febrile episodes, unplanned device replacement), dislodgment, and overall survival. Continuous variables were pooled using the inverse variance of the mean difference (MD) with a fixed effect, and 95% confidence interval (CI). The incidences of complications were pooled using the Cochran-Mantel-Haenszel method with the random effect model and reported as Odds Ratio (OR), and 95% CI. Statistical significance was set two-tail p-value <0.05

Results: Ten studies were included. Procedure time (MD -10.26 minutes 95%CI -12.40-8.02, p<0.00001), hospital stay (MD -1.30 days 95%CI -1.69 - -0.92, p<0.0001), number of accidental tube dislodgments (OR 0.25 95% CI 0.13 – 0.48, p<0.0001) were significantly lower in the stent group. No difference was found in mean fluoroscopy time, decrease in creatinine level post procedure, overall number of complications, interval time between the change of tubes, number of febrile episodes after diversion, unplanned device substitution, and overall survival.

Conclusion: Our meta-analysis favors stents as the preferred choice as these are easier to maintain and ureteral stent placement should be recommended whenever feasible. If the malignant obstruction precludes a stent placement, then PCN is a safe alternative.

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INTRODUCTION

Malignant ureteral obstruction is the consequence of secondary, extrinsic compression/infiltration of the ureter causing obstruction in different cancers. Mechanisms include intraluminal ureteral tumour invasion, ureteral entrapment or compression by retroperitoneal/pelvic lymphadenopathy or metastasis, and as a consequence of retroperitoneal fibrosis induced by surgery, chemotherapy, and radiotherapy (1).

The primary reason for referral to urologists is to evaluate the most appropriate type of urinary diversion and its feasibility accounting for both disease and patient characteristics.

Urologists aim to relieve urinary obstruction, reduce symptoms, and improve renal function while preserving patient quality of life and potentially prolonging overall survival as many of these patients have ongoing treatments (2). Urinary diversion can be achieved externally via a percutaneous nephrostomy tube or internally using a double J ureteral stent (3).

The endoscopic approach may be technically difficult and at times even impossible in advanced pelvic or retroperitoneal disease with high failure rates particularly in pelvic malignancies. Indeed, the success of retrograde ureteral stenting in patients with pelvic malignancy is usually significantly lower in patients with extrinsic ureteral obstruction compared with those with internal ureteral obstruction due to non-progression of the hydrophilic guide and non-identification of the ureteral meatus (4). On the other hand, the percutaneous approach may negatively affect patient quality of life being more invasive and often associated with a greater incidence of infection, bleeding, discomfort, and accidental tube displacement (5). Frail patients may be even more reluctant in accepting long indwelling nephrostomy tubes that need regular change with further worsening of quality of life (2). The choice must be balanced according to operator experience and patient's choice whilst evaluating the patient clinical condition and life expectancy. Unlike temporary urinary diversion in acute urinary obstruction, there are currently no guidelines or consensus for the optimal approach in malignant ureteral obstruction.

The present study aimed to systematically review the literature to assess perioperative outcomes, complications, and survival in studies comparing double J ureteral stent and percutaneous nephrostomy in malignant ureteral obstruction to help clinicians in taking an informed decision on urinary diversion choices by understanding the nuances of both interventions.

EVIDENCE ACQUISITION

Literature search

We aimed to perform a meta-analysis comparing outcomes in patients with ureteral obstruction secondary to malignancies. This systematic review was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. A comprehensive literature search was performed on 6th December 2021, using MEDLINE, EMBASE, and Cochrane Central Controlled Register of Trials (CENTRAL). The following term and Boolean operators were used: (ureteral stent OR urinary diversion OR double-J) AND (nephrostomy tube OR external urinary drainage) AND (extrinsic ureteral obstruction OR ureteral obstruction OR cancer ureteral obstruction). No date limits were imposed. The search was restricted to English papers, searching comparative studies between the two urinary diversions. Animal and paediatric studies were excluded. Additional articles were sought from the reference lists of the included articles. The review protocol was registered in PROSPERO (CRD42022297668).

Selection criteria

The PICOS (Patient Intervention Comparison Outcome Study type) model was used to frame and answer the clinical question. P: patients with external ureteral obstruction due to malignancy; Intervention: ureteral stent; Comparison: nephrostomy tube; Outcome: procedural time, fluoroscopy time, post-procedural complications, hospital stay, decrease in creatinine, episodes of accidental dislodgment, and overall survival; Study type: prospective randomized studies, retrospective, or prospective non-randomized studies.

Study Screening and Selection

Two independent authors screened all retrieved records through Rayyan Intelligent Systematic Review (https://www.rayyan.ai/). Discrepancies were solved by a third author. Studies were included based on PICOS eligibility criteria. Meeting abstracts, case reports, reviews, letters to editor, and editorials were excluded. The full text of the screened papers was selected if found relevant to the present review. The screening was further expanded by performing a manual search based on the references of the full-text relevant papers.

Data Synthesis and Statistical Analysis

Outcomes were split into three main domains: i) procedural data (operative time, fluoroscopy time, and the number of device replacements); ii) outcomes (postoperative creatinine, hospital stay, and overall survival); iii) complications (device-related, accidental dislodgement, febrile episodes, and unplanned device replacement).

Continuous variables (procedural time, fluoroscopy time, length of stay, creatinine, overall survival) were pooled using the inverse variance of the mean difference (MD) with a random effect, 95% confidence interval (CI), and p-values. The incidences of complications and accidental tube dislodgment were pooled using the Cochran--Mantel-Haenszel method with a random effect model and reported as Odds Ratio (OR), 95% CI, and p-values. Statistical significance was set two--tail p-value <0.05. Study heterogeneity was assessed utilizing the I^2 value. Substantial heterogeneity was defined as an I^2 value between 75% and 100%. Significance was set at p-value <0.05 (two tails) and 95%CI. Meta-analysis was performed using Review Manager (RevMan) 5.4 software by Cochrane Collaboration. The quality assessment of the included studies was performed using the ROBINS-I for non-randomized studies (6).

EVIDENCE SYNTHESIS

Literature screening

Literature search retrieved 596 papers. After title and abstract screening, 575 records were excluded because they were not related to the study purpose. The full texts of the remaining 21 studies were assessed for eligibility. Eleven studies were further excluded due to missing data. Finally, ten studies were accepted and included (7-16). Among these, only one was prospective (7) while the others were retrospective studies (8-16). No randomized study was found. Figure-1 shows the 2020 PRISMA flow diagram. Study characteristics are summarized in Table-1.

Study quality assessment

Supplementary Figure-1 demonstrates the details of the quality assessment. Seven studies exhibited a moderate risk of bias for all quality criteria, while three showed a serious risk of bias. The most common risk factor for quality assessment was the risk of bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, and bias in the measurement of outcomes as the studies were retrospective in design.

Procedural data

Meta-analysis from 3 studies (145 cases in stent and 60 cases in nephrostomy) showed that the mean procedure time was significantly shorter in the stent group (MD -10.26 minutes, 95% CI -12.40 -8.02, p<0.00001). Study heterogeneity was substantial (I^2 97%) (Figure-2A).

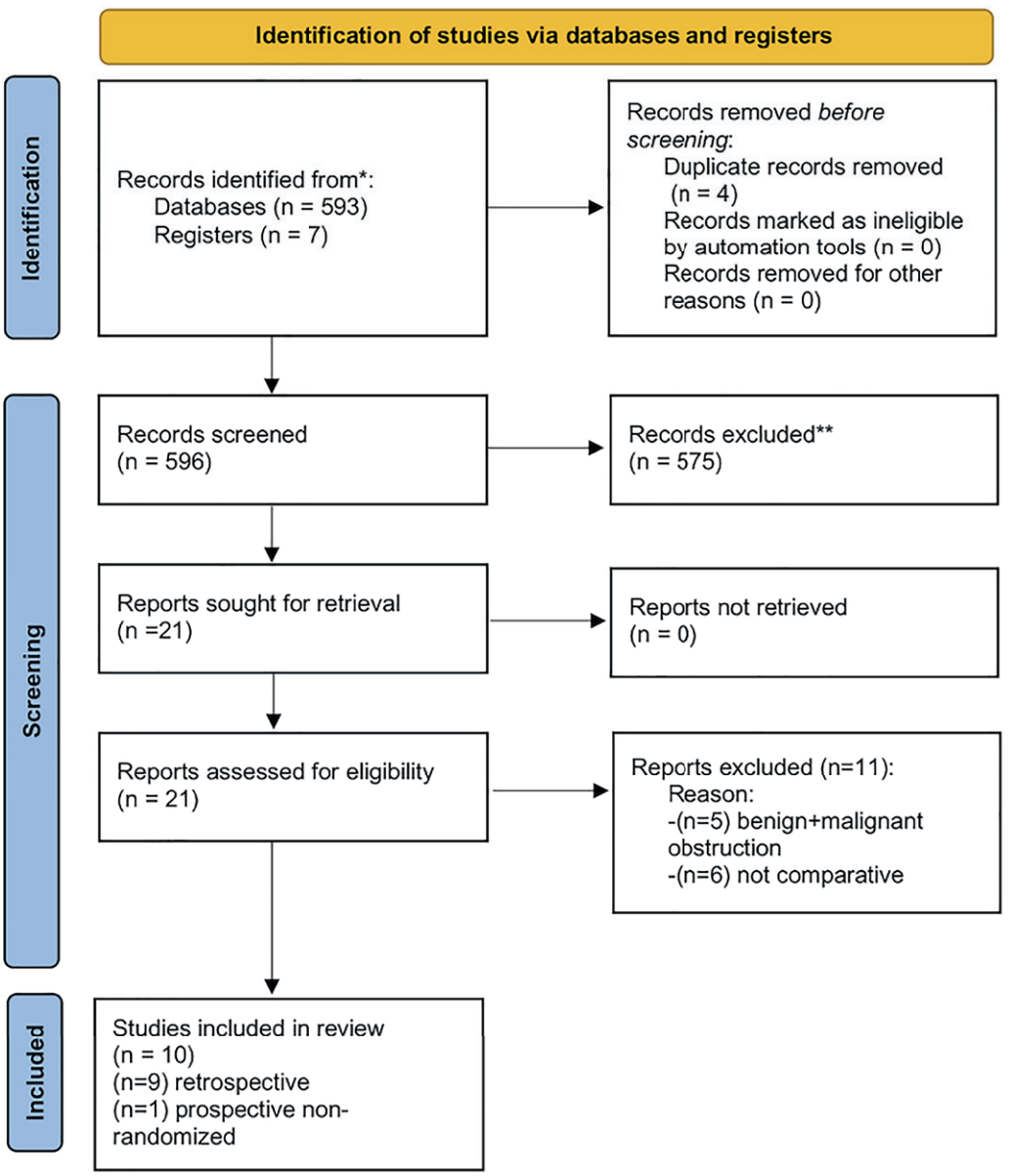
Meta-analysis from 2 studies (65 cases in stent and 40 cases in nephrostomy) showed no difference between the two groups in mean fluoroscopy time (MD -0.61 minutes, 95% CI -4.05 – 2.84, p=0.73). Study heterogeneity was not significant (I^2 0%) (Figure-2B).

Meta-analysis from 2 studies (65 cases in stent and 40 cases in nephrostomy) showed no difference between the two groups in the mean interval time between the change of drainage tubes over time (MD 1.52 months, 95% CI -4.55 – 7.59, p=0.62). Study heterogeneity was substantial (I^2 96%) (Figure-2C).

Outcomes

Meta-analysis from 3 studies (126 cases in stent and 130 cases in nephrostomy) showed no difference between the two groups in the decrease of the creatinine level after the procedure (MD -0.35

Figure 1 - PRISMA flow diagram of the study.



mg/dL, 95% CI -1.19 - 0.49, p=0.41). Study heterogeneity was substantial (I^2 99%) (Figure-3A).

Meta-analysis from 3 studies (146 cases in stent and 69 cases in nephrostomy) showed a significantly shorter hospital stay in the stent group compared to the nephrostomy tube group (MD -1.30 day, 95% CI -1.69 - -0. 92, p<0.0001). Study heterogeneity was substantial (I^2 70%) (Figure-3B).

Meta-analysis from 3 studies (84 cases in stent and 64 cases in nephrostomy) showed no difference in the mean overall survival between the two groups (MD 2.72 months 95% CI -1.15 - 6.59, p=0.17). Study heterogeneity was substantial (I^2 89%) (Figure-3C).

Complications

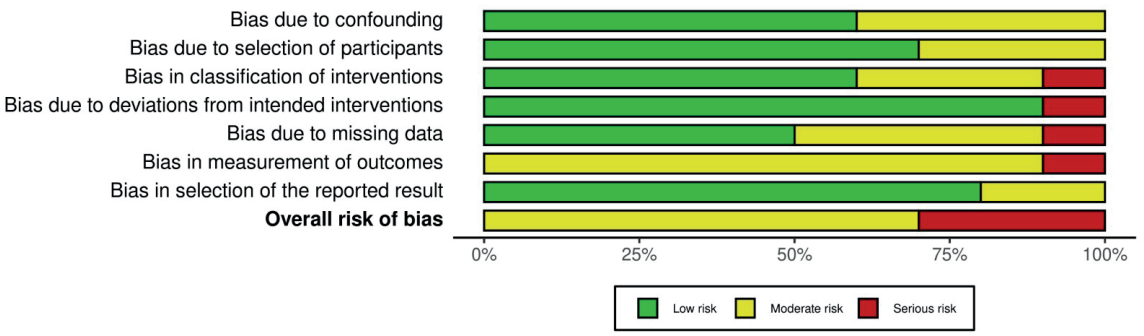
Meta-analysis from 4 studies (140 cases in stent and 135 cases in nephrostomy) showed no difference in the number of febrile episodes after diversion between the two groups (OR 1.04

Table 1 - Characteristics of the included studies.

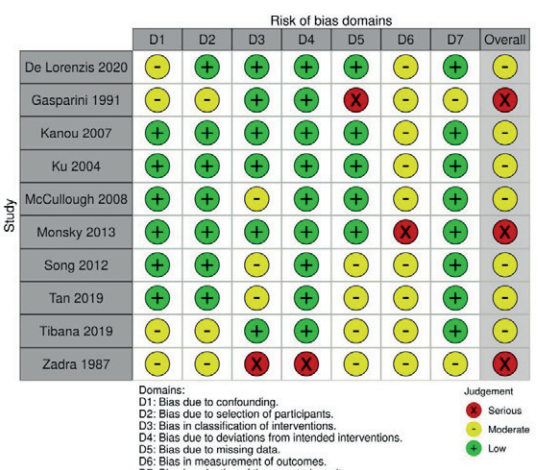
Authors	Type of study: 1 RCT; 2 retrospective; 3 prospective	Ureteral stent patients (n)	Nephrostomy patients (n)	Total (n)	Type of cancer (absolute number) in ureteral stent	Type of cancer (absolute number) in nephrostomy tube
De Lorenzis et al. 2020 (8)	Retrospective	27	24	51	Upper Gastrointestinal tract (n=5); Lower Gastrointestinal tract (n=22)	Upper Gastrointestinal tract (n=4); Lower Gastrointestinal tract (n=20)
Gasparini et al. 1991 (9)	Retrospective	7	15	22	Ovarian cancer (n=2); cervical cancer (n=2); gastric cancer (n=1); colon cancer (n=1); prostate cancer (n=1)	Prostate cancer (n=1); Cervical cancer (n=3); Gastrointestinal (n=3); Ovarian cancer (n=1); Lymphoma (n=2); Unknown tumor (n=1); Bladder cancer (n=4)
Kanou et al. 2007 (10)	Retrospective	51	24	75	Cervix cancer (n=7); Rectal cancer (n=4); Prostate cancer (n=7); Bladder cancer (n=3); Ovarian cancer (n=2); Retroperitoneum tumor (n=1)	Lymphoma (n=2)
Ku et al. 2004 (11)	Retrospective	68	80	148	Not available	Not available
McCullough et al. 2008 (12)	Retrospective	31	26	57	Prostate cancer (n=5); bladder (n=5); colon (n=4); gynecological (n=7); breast (n=3); lymphoma (n=2); lung (n=1); others (n=4)	Prostate cancer (n=15); Bladder (n=7); Colon (n=3); gynecological (n=1)
Monsky et al. 2013 (7)	Prospective non randomized	15	15	30	Bladder (n=4); cervical (n=6); prostate (n=1); ovarian (n=2); endometrial (n=1); fallopian tube (n=1)	Bladder (n=5); cervical (n=3); uterine (n=2); prostate (n=2); colon (n=1); lymphoma (n=1); sarcoma (n=1)
Song et al. 2012 (13)	Retrospective	50	25	75	Cervical cancer (n=26); Endometrial cancer (n=22); Ovarian cancer (n=20); Uterine leiomyosarcoma (n=4); Vaginal carcinoma (n=1); Choriocarcinoma (n=2)	
Tan et al. 2019 (14)	Retrospective	69	20	89	Cervical cancer	Cervical cancer
Tibana et al. 2019 (15)	Retrospective	26	15	41	Bladder cancer (n=7); Uterine cancer (n=6); Metastatic colorectal cancer (n=4); Adenocarcinoma of the prostate (n=3); Sarcoma of the prostate (n=3); Colorectal adenocarcinoma (n=1); Retroperitoneal neuroendocrine tumor (n=1)	Uterine cancer (n=5); Bladder cancer (n=5); Prostate adenocarcinoma (n=3); Metastatic colorectal cancer (n=1); Ovarian cancer (n=1)
Zadra et al. 1987 (16)	Retrospective	27	53	80	Not available	Not available

Supplementary Figure 1. Risk of bias in non-randomized controlled trials (ROBINS-I)

A) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



B) Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



95% CI 0.19 - 5.60, p=0.96). Study heterogeneity was moderate (I^2 55%) (Figure-4A).

Meta-analysis from 4 studies (140 cases in stent and 135 cases in nephrostomy) showed no difference in the overall number of complications after diversion between the two groups (OR 1.46 95% CI 0.72 - 2.95, p=0.30). There was no study heterogeneity (I^2 0%) (Figure-4B).

Meta-analysis from 8 studies (328 cases in stent and 251 cases in nephrostomy) showed that the number of accidental tube dislodgments was significantly lower in the stent group compared to the nephrostomy tube group (OR 0.25 95% CI 0.13 – 0.48, p<0.0001). Study heterogeneity was not important (I^2 16%) (Figure-5A).

Meta-analysis from 3 studies (134 cases in stent and 119 cases in nephrostomy) showed no difference in unplanned device substitution between the two groups (OR 0.41 95% CI 0.06 – 2.98, p=0.38). Study heterogeneity was moderate (I^2 43%) (Figure-5B).

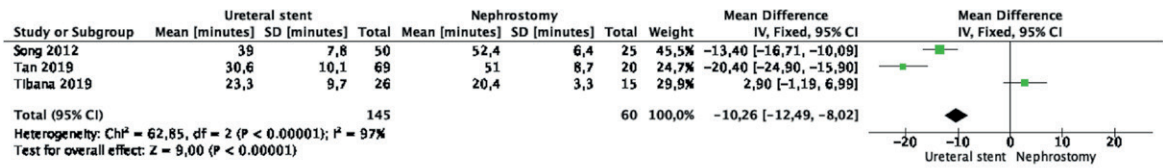
DISCUSSION

Malignant ureteral obstruction commonly affects patients with advanced cancers. Development of ureteral obstruction is slow and insidious, typically causing dull pain, associated with fatigue and lethargy. Malignant ureteral obstruction is often an ominous sign frequently associated with poor survival (17).

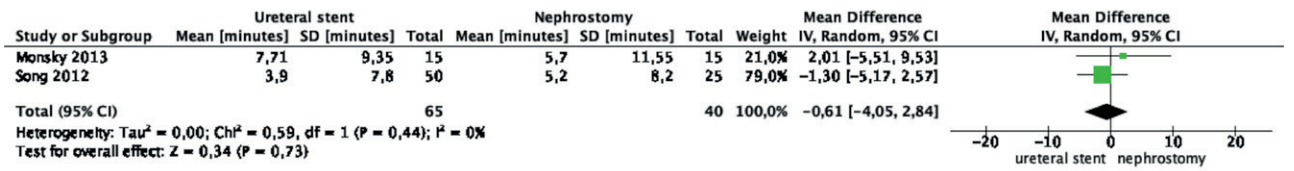
Patients are usually referred when clinical or

Figure 2 - Meta-analysis of procedural data. A) procedure time; B) fluoroscopy time; C) interval time between the change of drainage tubes over time

A) Procedural time, minutes



B) Fluoroscopy time, minutes



C) Interval time between the change of tube, months

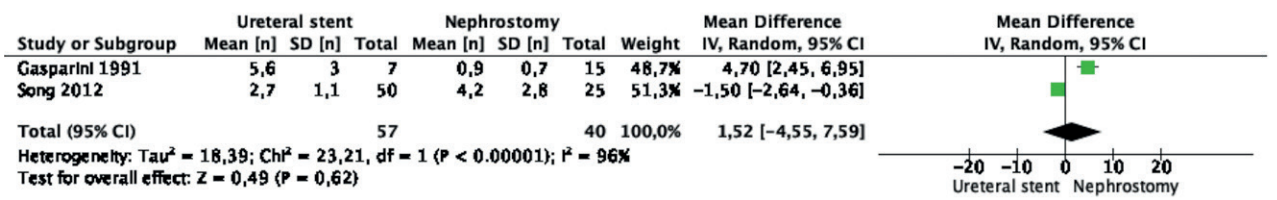
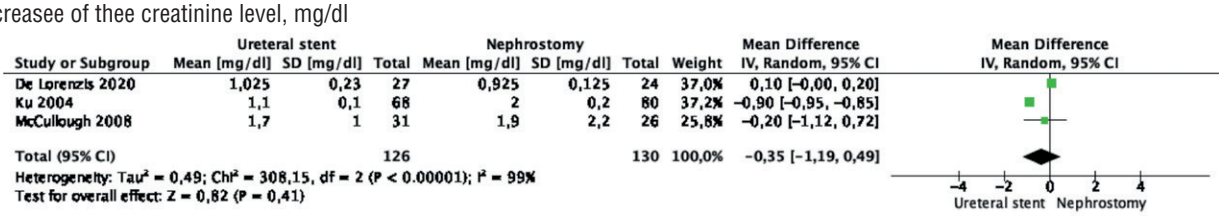
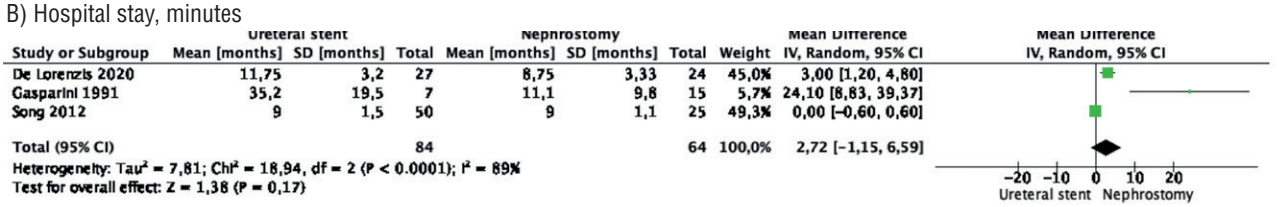


Figure 3 - Meta-analysis of outcomes. A) decrease of the creatinine level after the procedure; B) hospital stay; C) overall survival.

A) Decreasee of thee creatinine level, mg/dl



B) Hospital stay, minutes



C) Overall survival, months

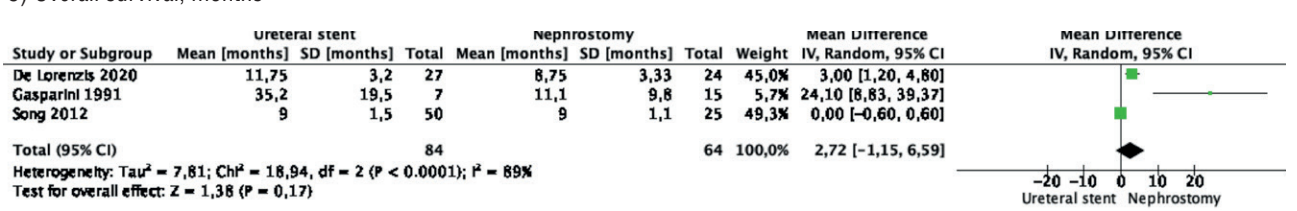
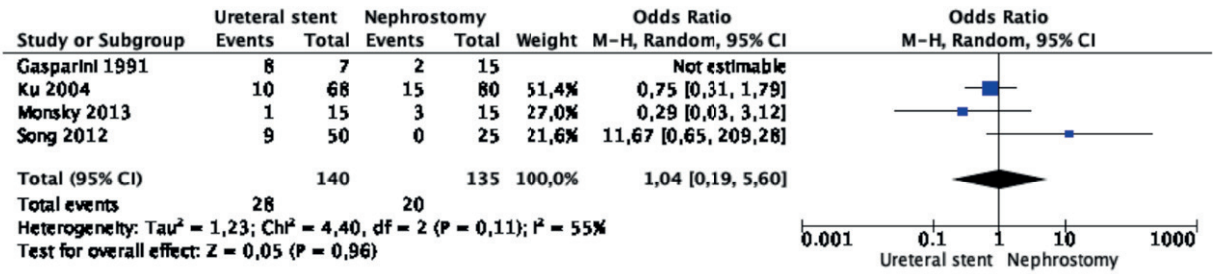
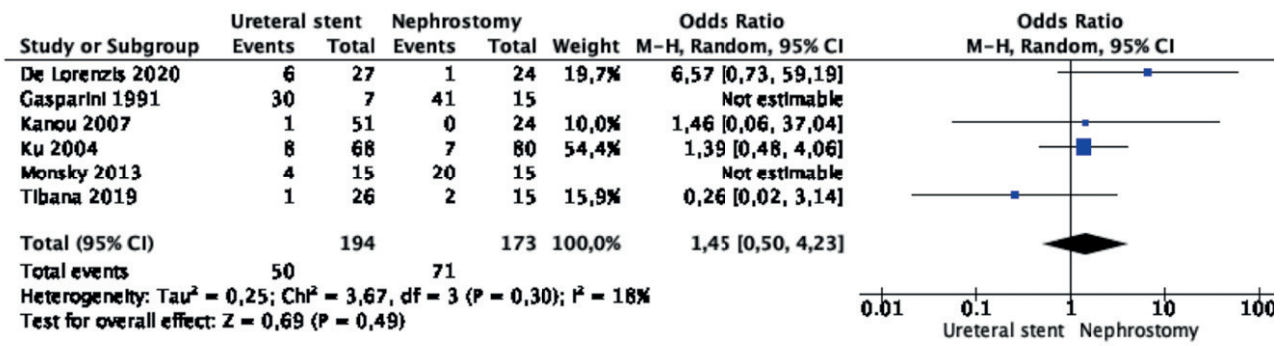


Figure 4 - Meta-analysis of complications. A) number of febrile episodes after diversion; B) overall number of complications after diversion.

A) Number of febrile episodes after diversion



B) Overall number of complications after diversion

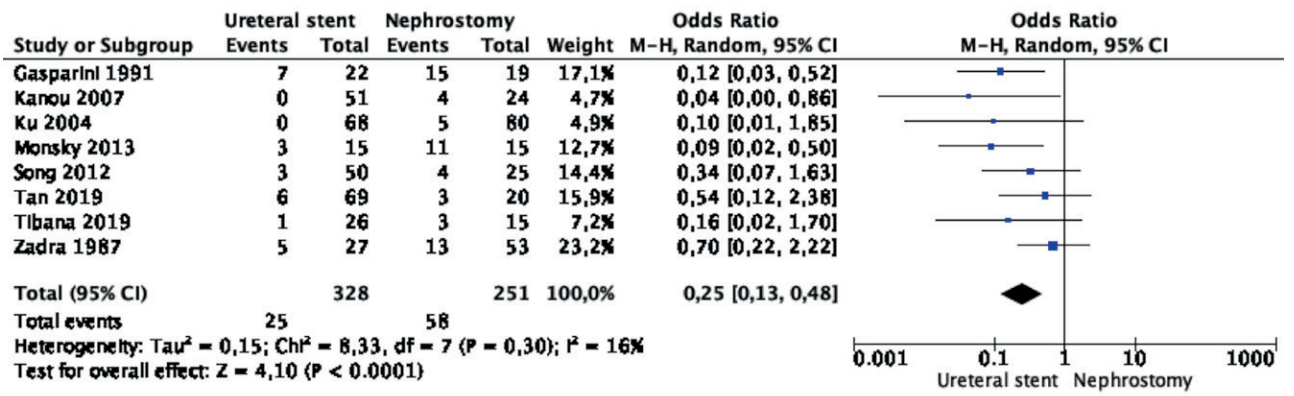


radiological evaluation resulting from urinary stasis often with worsening kidney function is observed as a consequence of ureteral obstruction. Occasionally, acute symptoms may occur such as fever due to urinary infection or renal colic with nausea and vomiting due to a sudden increase in pressure or stretch of the ureteral lumen with the hypercontractility of the ureteral smooth muscle and subsequent activation of nociceptors of renal afferent nerves fibers by prostaglandins (18). Sometimes, *de novo* acute obstructive uropathy can be the first presenting sign of advanced pelvic cancers (19).

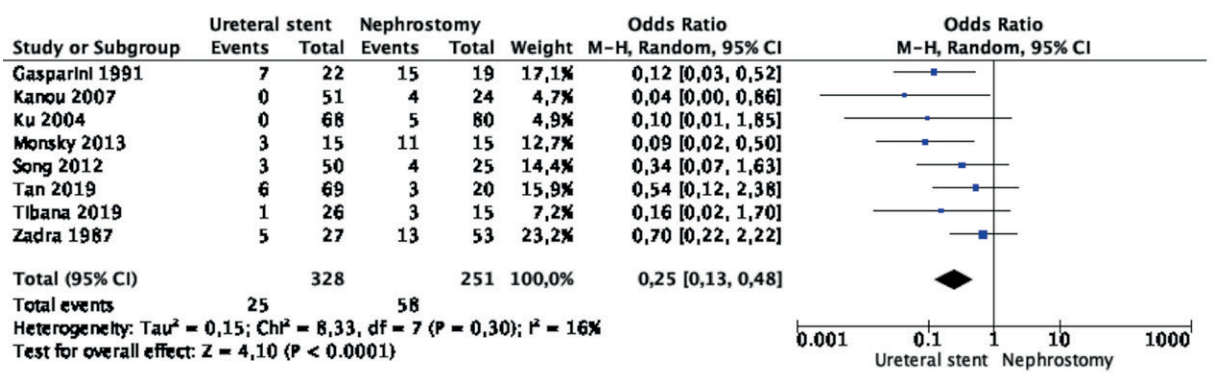
The management of patients with ureteral obstruction needs a multi-disciplinary approach involving urologists, oncologists, palliative care physicians, interventional radiologists, along with patients and caregivers. In most cases, obstruction is primarily asymmetrical. In the case of bilateral involvement, it is common practice to drain only the symptomatic kidney or the kidney with better function in asymptomatic patients. Although there are recommendations within cancer-specific guidelines, there is a lack of consensus as well as a strong piece of evidence to support the decision process on which modality of decompression has a better outcome (20). Often, at this late stage of malignancy, the quality of life is poor and therefore the ethics of palliative decompression have often been questioned (19). Patients with advanced malignancy are poor surgical candidates, and the option of no intervention should also be discussed since the procedures themselves are not without potential morbidity (3). Indeed, the mean survival has been reported to be 120-140 days even with decompression (19, 21). Considerable variability in survival time has been reported in the literature and it is therefore important to identify objective criteria that can be used to estimate a patient's prognosis. Lapitan et al. followed up a cohort of patients who had a malignant ureteral obstruction and assessed the outcomes of those who were decompressed and those who were not (22). The authors found that the 6-month survival of patients who underwent diversion was 38% compared with 28% of those who did not. By 12 months, both groups had the same survi-

Figure 5 - Meta-analysis of complications. A) number of accidental tube dislodgments; B) unplanned device substitution.

A) Number of accidental tube dislodgments



B) Unplanned device substitution



val of 16%. In our analysis, we found no difference in mean survival between the two groups, pointing out that the type of urinary diversion does not impact the overall survival.

Since considerable variability in survival time has been reported in the literature, it is therefore important to identify objective criteria that can be used to what type of diversion will probably minimize the impact on patients' quality of life.

Our study showed that stent placement had a shorter operative time and hospital stay but mean change interval trend over time did not differ. The overall complication rate was also not different between the two approaches, but the accidental displacement was significantly higher in the nephrostomy group. We also found no differences in creatinine level decrease after decompression or complication rates between the two procedures. Therefore, the ureteral stent placement had better procedural results, similar efficacy, and fewer handling issues than percutaneous nephrostomy tube placement. Indeed, the endoscopic approach, which represents a less invasive procedure, ensured a faster discharge of patients and a lower risk of tube displacement. This last point is very relevant because ureteral stent placement avoided repeated and unnecessary treatments, which can be very troublesome in frail patients. For all these reasons, physicians should be inclined to treat patients with malignant ureteral obstruction first with a ureteral stent, whenever possible. However, the decision to choose either should rely more on identifying risk factors associated with disease progression and resource availability at the place of practice.

The prognostic stratification model by Lienert et al. and Ishioka et al. have identified some risk factors to help decision-making for percutaneous

nephrostomy placement with a 3-month to one-year benefit seen only in low or favourable risk and intermediate-risk group (19, 21). In addition, survival has been demonstrated to differ among cancers causing ureteral obstruction. For instance, tumours that originate outside the true pelvis (such as breast, pancreatic and gastric cancers) have a worse prognosis whereas patients with prostate and gynaecological cancers have longer survival times (2). For patients predicted to have relatively long survival, conversion to an internal ureteral stent may be recommended for a better quality of life [6]. In our meta-analysis, ureteral stenting had a significant advantage over the percutaneous nephrostomy cohort in terms of fewer device dislodgements (OR 0.25 95% CI 0.13 – 0.48, p<0.0001), an important consideration in patients needing a longer duration of diversion, especially in the modern era where metallic stents are available and superior to conventional polymeric stents and can stay up to 1 year before the next change (23).

As per our meta-analysis, the stent group showed better procedural results, similar efficacy, and fewer handling issues than the percutaneous nephrostomy group, however, it is not uncommon to face ureteral stent insertion failure, particularly in those cases with cystoscopy evidence of bladder or ureteral invasion (2, 4). Bladder cancer and prostate cancer-causing ureteral obstruction have shown a far higher failure rate than that caused by colon or breast cancer, probably due to the former directly invading the trigone, causing both intrinsic and extrinsic obstruction, making stent insertion, not possible (24). We also found that there was no difference in unplanned intervention for a device substitution either due to a mechanical device malfunction or for clinical reasons such as increasing febrile episodes secondary to the implants. These have a significant bearing on quality of life and hence it may be easiest for a patient to manage a ureteral stent than a percutaneous nephrostomy tube. Moreover, our meta-analysis significantly favoured ureteral stent insertion as this minimized the hospital stay (MD -1.30 day 95% CI -1.69 - -0. 92, p<0.0001) with a similar procedure-related fluoroscopy time for both procedures. These factors can influence decision-making for clinicians when faced with malignant ureteral obstruction especially as these patients are a critically vulnerable cohort. In addition, the procedural cost can also be taken into account. Only one study reported data on cost analysis and showed that the average cost of stenting was significantly lower than percutaneous nephrostomy (US$164.10 vs. US$552.20 , respectively) (15).

Specific to malignant ureteral obstruction related to genitourinary malignancies, Shekarriz et al. analysed 103 patients with advanced malignancies treated with palliative urinary diversion (stent or percutaneous nephrostomy) and found that prostate cancer patients had the longest median survival, although the difference did not reach significance (25). Instead, gynaecological cancer patients survived approximately 4-fold longer than those with bladder cancer. Among patients with bladder cancer, those presenting *de novo* with ureteral obstruction survived significantly longer than those in whom obstruction developed after diagnosis and treatment already administered (26). These are important considerations as often in these patients if there is any difficulty in cystoscopic access for stent placement a percutaneous nephrostomy should be the best consideration for immediate diversion in advanced malignancies (11). However, a concern for percutaneous nephrostomy is that tube may need to be changed more frequently due to blockage with a reported incidence of 0.4-37% in various studies and can lead to more febrile episodes due to infection with a reported incidence of 2-8% in various studies (27). This can make clinicians and patients reluctant for this intervention, but our meta-analysis showed no significant difference between the two groups in the mean interval time between change of drainage tubes or the number of febrile episodes.

Our study pointed out two important take-home messages. First, ureteral stenting represents a less invasive procedure and has more appeal for patients, ensuring a faster discharge of patients, a longer exchange interval, and a lower risk of tube displacement. This last point is very relevant because ureteral stent placement avoided repeated and unnecessary interventions, which can save costs and precious time for other palliative procedures. Second, if stent placement is technically not possible, since no differences were noted in complication rates and unplanned need for device substitution, patients can be safely advised that percutaneous nephrostomy is not an inferior choice as a primary drainage procedure,

especially in the presence of a pelvic malignancy or in patients with shorter survival that requires only palliative relief of ureteral obstruction.

The present review has some limitations. The study is based only on retrospective studies and one prospective study with no randomized data and the number of patients in each study is relatively small. We argue that this reflects two reasons. First of all, a randomized study may not be feasible, because the choice of kidney decompression is mostly patient-tailored. Second, the few comparative studies could also reflect the low interest of the scientific community in this field that, conversely, deserves attention as a pivotal role in the palliative management of end-life cancer patients. We were not able to assess the quality of life after urinary diversion due to different tools to evaluate it in the studies included in this meta-analysis and this can be considered another study limitation. We also could not assess the materials of stent as this was not reported in the studies included in our review.

CONCLUSIONS

While both forms of urinary diversion can be utilized in malignant obstruction, our meta-analysis favours stents as the preferred choice as these are easier to maintain, and ureteral stent placement should be recommended whenever feasible. If the malignant obstruction precludes a stent placement, then percutaneous nephrostomy tube is a safe alternative. The findings of our review can help clinicians in using a personalized approach to choose either option in malignant ureteral obstruction.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Prevalence and risk factors of incidental prostate cancer in certain surgeries for benign prostatic hyperplasia: A systematic review and meta-analysis

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ABSTRACT

Background: This study aimed to explore the prevalence and clinical risk factors in patients diagnosed with incidental prostate cancer (IPC) during certain surgeries (transurethral resection of the prostate [TURP], open prostatectomy [OP], and holmium laser enucleation of the prostate [HoLEP]) after clinically suspected benign prostatic hyperplasia (BPH).

Materials and Methods: Literature search of the MEDILINE, Web of Science, Embase, and Cochrane Library databases was performed to identify eligible studies published before June 2021. Multivariate adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) of the prevalence and clinical risk factors of IPC were calculated using random or fixed-effect models.

Results: Twenty-three studies were included in the meta-analysis. Amongst the 94.783 patients, IPC was detected in 24.715 (26.1%). Results showed that the chance of IPC detection (10%, 95% CI: 0.07-4.00; P<0.001; I2=97%) in patients treated with TURP is similar to that of patients treated with HoLEP (9%, 95% CI: 0.07-0.11; P<0.001; I2=81.4%). However, the pooled prevalence estimate of patients treated with OP was 11% (95% CI: -0.03-0.25; P=0.113; I2=99.1%) with no statistical significance. We observed increased incidence of IPC diagnosis after BPH surgery amongst patients with higher prostate-specific antigen (PSA) level (OR: 1.13, 95% CI: 1.04-1.23; P=0.004; I2=89%), whereas no effect of age (OR: 1.02, 95% CI: 0.97-1.06; P=0.48; I2=78.8%) and prostate volume (OR: 0.99, 95% CI: 0.96-1.03; P=0.686; I2=80.5%) were observed.

Conclusions: The prevalence of IPC was similar amongst patients undergoing TURP, HoLEP, and OP for presumed BPH. Interestingly, increased PSA level was the only independent predictor of increasing risk of IPC after BPH surgery rather than age and prostate volume. Hence, future research should focus on predictors which accurately foretell the progression of prostate cancer to determine the optimal treatment for managing patients with IPC after BPH surgery.

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INTRODUCTION

Prostate cancer is the most common malignant tumor amongst ageing male patients, with an estimated 41.000 Americans dying from prostate cancer annually (1). Incidental prostate cancer (IPC) is defined as a tumor incidentally diagnosed after surgery for benign prostatic hyperplasia (BPH) (prostate cancer was not suspected before) or found after autopsy or incidentally detected after radical cystoprostatectomy for patients with bladder cancer (2-4). Moreover, patients with BPH are usually screened for prostate cancer before surgery to rule out the presence of IPC that may ultimately change the treatment strategy (5). Thus, previous studies have revealed that IPC detection after BPH surgery has declined in the prostate--specific antigen (PSA) era (4, 6). Some studies have shown that the prevalence of IPC between patients diagnosed with BPH undergoing TURP is between 5% and 14% (7, 8). A recent study has indicated that the clinical course of IPC has become aggressive, although most IPCs are not clinically obvious (9). The decision 'treatment or not' should be determine by predictive factors that can accurately foretell IPC after BPH surgery (10). However, the best clinical management of IPC has remained controversial for decades.

In the present study, we conducted a systematic review and meta-analysis of previous literature to explore the prevalence and clinical risk factors in patients diagnosed with IPC for surgery after clinically suspected BPH. We also performed subgroup and meta-regression analyses to determine how the potential variables affected the merged results and the level of heterogeneity of the meta-analysis.

MATERIALS AND METHODS

The methods of this meta-analysis were conducted in accordance with the Cochrane Collaboration criterion (11). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was utilized for reporting our study (Supplementary Material 1) (12). Thus, no ethical approval and patient consent were required.

Search strategy

Literature search of the MEDILINE, Web of Science, Embase, and Cochrane Library databases were performed to identify eligible studies on the prevalence and clinical risk factors in patients diagnosed with IPC during surgery after clinically suspected BPH published before June 2021. Each database was searched without restrictions in language, publication type, or region by using the following combination of Medical Subject Headings (MeSH) and non-MeSH search terms: ('prostate cancer' OR 'prostate neoplasm') AND ('incidental') AND ('benign prostatic hyperplasia'). Moreover, a freehand search was conducted for additional relevant articles of interest in journals not listed in these databases. Any discrepancy was settled by consulting amongst investigators.

Inclusion and exclusion criteria

All publications regarding the prevalence and risk factors in patients diagnosed with IPC after BPH surgery were included if they met the following eligibility criteria: (1) original studies regarding the relevant topic; (2) the primary endpoint was IPC prevalence and/or associated risk factors amongst IPC patients (as previously defined) after BPH surgery (transurethral resection of the prostate [TURP], open prostatectomy [OP], and holmium laser enucleation of the prostate [HoLEP]); and (3) studies reporting sufficient data of prevalence and risk estimates with corresponding 95% confidence intervals (CIs) or sufficient data to calculate them. The exclusion criteria were as follows: (1) non-English articles; (2) case reports, editorial comments, and review articles; and (3) patients have been diagnosed with prostate cancer preoperatively. Furthermore, repeat publications from the same authors or the same centre were excluded to avoid duplication of information, and we retained only the most recent or largest study (where appropriate). Disagreements were resolved through discussion amongst investigators.

Data extraction and methodological-quality assessment

Data extraction was conducted by two independent investigators using a pre-established data extraction form, and another investigator

checked the correctness of all extractions. Any disagreement was resolved by the adjudicating senior authors. The following data were extracted using a standardized Excel (Microsoft Corporation) file: first author, publication year, country, database source and duration, study design, participants characteristics (i.e., mean age, mean prostate volume, mean PSA, sample size, and number of patients diagnosed with IPC), prevalence, and risk estimates with their corresponding 95% CIs or sufficient original data. Moreover, if potentially eligible records did not provide sufficient information, we contacted the primary authors to acquire missing data.

The quality of the included studies was assessed by two independent reviewers according to the Newcastle-Ottawa scale (NOS) (13), which comprises nine items. Each item was evaluated as either 'yes', 'no', or 'unclear', which corresponded to '1', '0', or '0' in accordance with the information provided by the studies. The total score ranged from 0 to 9 and was categorized as follows: a score of 8 to 9 was considered high quality, a score of 6 to 7 was considered moderate quality, and a score of 5 or below was considered low quality. Disagreements were resolved by discussion amongst investigators.

Data synthesis and analysis

The overall prevalence of IPC and risk estimates of the predictors were calculated through the prevalence and odds ratios (ORs) with their corresponding 95% CIs by using STATA software (version 15.0; serial number: 10699393; StataCorp Wyb). The I-square (I2) test was applied to evaluate the study heterogeneity, with I2 values of 0%, 25%, 50%, and 75% representing no, low, moderate, and high heterogeneity, respectively. Heterogeneity amongst the studies was evaluated by random or fixed-effect models, and a considered severe heterogeneity of I2≥50% was evaluated by random-effect models. Otherwise, a fixed-effect model was used. Statistical significance was set at $P < 0.05$ through two-sample t-test. To explore the influence of various clinical characteristics on heterogeneity, we performed subgroup analyses stratified by different geographic distributions. Sensitivity analysis was conducted by omitting each study individually to assess the quality and consistency of the results. To investigate the possible sources of heterogeneity, a meta-regression analysis was conducted and the restricted maximum likelihood method was applied for analysis. Finally, the test of Egger et al. (14) and Begg & Mazumdar (15) were performed to assess publication bias, and the funnel-plot symmetry was examined.

RESULTS

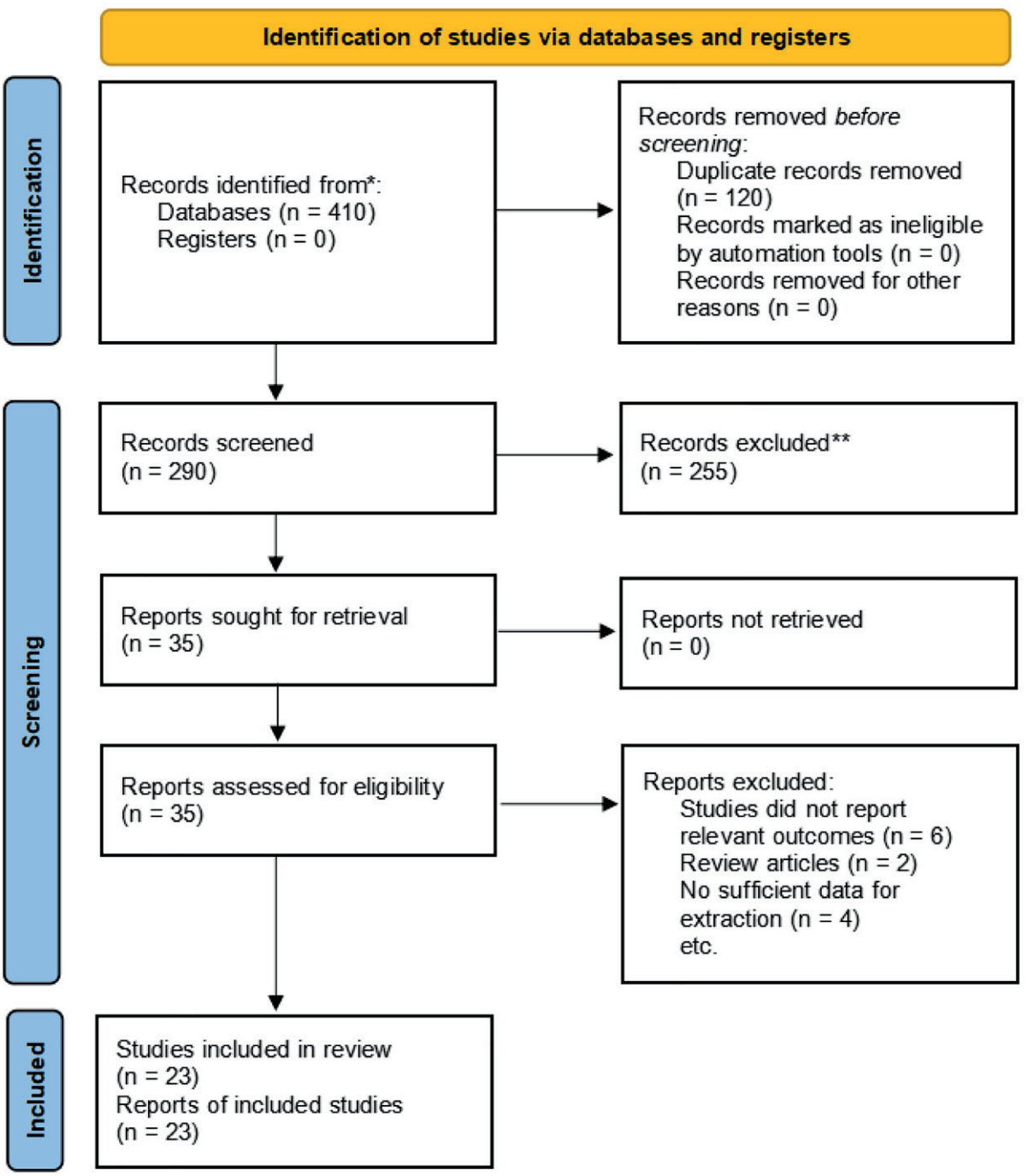
Study identification and selection

A total of 410 records were identified initially based on the comprehensive search strategy described at the search stage. Figure-1 presents the process of study selection. After removing 120 duplicates, only 290 unique articles remained. Then, 35 articles were further assessed through their full texts after screening the titles and abstracts of 290 articles in detail. However, 12 articles were excluded for the following reasons: 6 studies did not report relevant outcomes, 2 studies were reviews, and 4 studies had insufficient data for extraction. Amongst them, 23 observational studies (8, 16-37) comprising 94.783 patients with 24.715 (26.1%) IPC were included in the meta-analysis in accordance with the eligibility criteria.

Study characteristics and methodological-quality assessment

Overall, the basic characteristics of the included studies are illustrated in Table-1. The included studies (21) were retrospective studies (8, 16, 18-30, 32-37), 1 was a prospective study (31), and 1 was a cross-sectional study (17) that were published between 2005 and 2021, with sample sizes ranging from 120 patients to 76.788 patients. Furthermore, mean age ranged from 66 years to 75.8 years, mean prostate volume ranged from 44.2mL to 110mL, and mean PSA level ranged from 2.9ng/mL to 21.47ng/mL. Amongst the included studies, twelve were performed in Europe (17-19, 21, 23, 25, 26, 32-34, 36, 37), six in Asia (8, 16, 24, 28, 29, 35), two in Africa (20, 22), two in North America (27, 30), one in Oceania (31). Importantly, 18 studies reported clinical stage of IPC (T1a and T1b) (8, 18-23, 25-27, 30-37). All studies

Figure 1 - Flow diagram of literature searches according to the preferred reporting items for systematic reviews and meta-analyses statement.



were published in English. Finally, three surgical methods (TURP, OP, and HoLEP) for BPH were reported amongst all included studies.

In general, the methodological quality of the included studies was evaluated on the basis of the NOS. One study (31) acquired eight points and were considered high quality, twenty one studies (8, 16, 18-30, 32-37) acquired six or seven points and were considered moderate quality, and the remaining study (17) scored three and was considered low quality (Supplementary Material 2).

Prevalence of IPC after BPH surgery

All included studies reported sufficient data on IPC prevalence (8, 16-37). Overall, patients diagnosed with IPC after BPH surgery was detected in 24,715 of 94.783 patients. Results showed that the chance of IPC detection (10%, 95% CI: 0.07-4.00; P <0.001; I2=97%) in patients treated with TURP is similar to that of patients treated with HoLEP (9%, 95% CI: 0.07-0.11; P <0.001; I2=81.4%). However, the pooled prevalence estimate of patients treated with OP was 11% (95% CI: -0.03-0.25; P=0.113; I2=99.1%) with no statistical significance. However, significant heterogeneity was observed, so a random--effect model was applied for pooled analysis (Figures 2A-2C).

In the subgroup analysis stratified by different geographic distributions in patients with IPC after TURP, a higher prevalence was observed in Oceania (26%, 95% CI: 0.23-0.29; P <0.001) and Africa (22%, 95% CI: 0.15-0.28; P <0.001), followed by Asia (9%, 95% CI: 0.06-0.13; P <0.001), Europe (8%, 95% CI: 0.06-0.10; P <0.001), and North America (1%, 95% CI: 0.01-0.02; P=0.001). We also conducted a meta-regression analysis to further investigate the possible sources of heterogeneity, and results revealed that none of the covariate (geographic distribution, P=0.958) resulted in heterogeneity amongst the included studies. Moreover, sensitivity analysis demonstrated that the stability of the results exhibited no significant change by omitting each study individually (Table-2). Finally, potential publication bias was likely to exist according to inspection of formal statistical tests (Begg test, P=0.044; Egger test, P=0.022).

Risk factors of IPC after BPH surgery

Nine retrospective cohorts comprising 6.241 patients reported data on risk factors of IPC (8, 19, 20, 22-24, 28, 34, 35). We observed increased incidence of IPC diagnosis after BPH surgery amongst patients with increased PSA level (OR: 1.13, 95% CI: 1.04-1.23; P=0.004; I2=89%) in multivariate analysis. However, no effect of age (OR: 1.02, 95% CI: 0.97-1.06; P=0.48; I2=78.8%) and prostate volume (OR: 0.99, 95% CI: 0.96-1.03; P=0.686; I2=80.5%) were observed possibly due to the limited number of included studies. Moreover, a random-effect model was utilized due to the significant heterogeneity (Figures 3A-3C).

DISCUSSION

Main findings

Uncertainty currently exists about the prevalence and risk factors of IPC with conflicting opinions based on single institutional research. Accordingly, we performed this systematic review and meta-analysis to address these issues. Our results revealed that the prevalence of IPC was similar amongst patients undergoing TURP, HoLEP, and OP for presumed BPH. Higher prevalence was also observed in Oceania and Africa, followed by Asia, Europe, and North America. Notably, sensitivity analysis indicated that the stability of the results had no significant change by omitting each study individually, although the subgroup and meta-regression analyses could not identify the potential factors that may affect the level of heterogeneity between studies. However, potential publication bias was likely to exist according to inspection of formal statistical tests. Interestingly, increased PSA level was significantly associated with increased risk of IPC after BPH surgery rather than age and prostate volume.

Although our results showed that PSA was a highly sensitive predictor for IPC detection, it may have a higher rate of false positives because its specificity was not high. Indeed, almost all included studies reported a significant association between PSA and IPC detection, whereas two studies yielded conflicting results (24, 28). Kim et al. (24) retrospectively analyzed 458 consecutive patients who underwent HoLEP. They found that

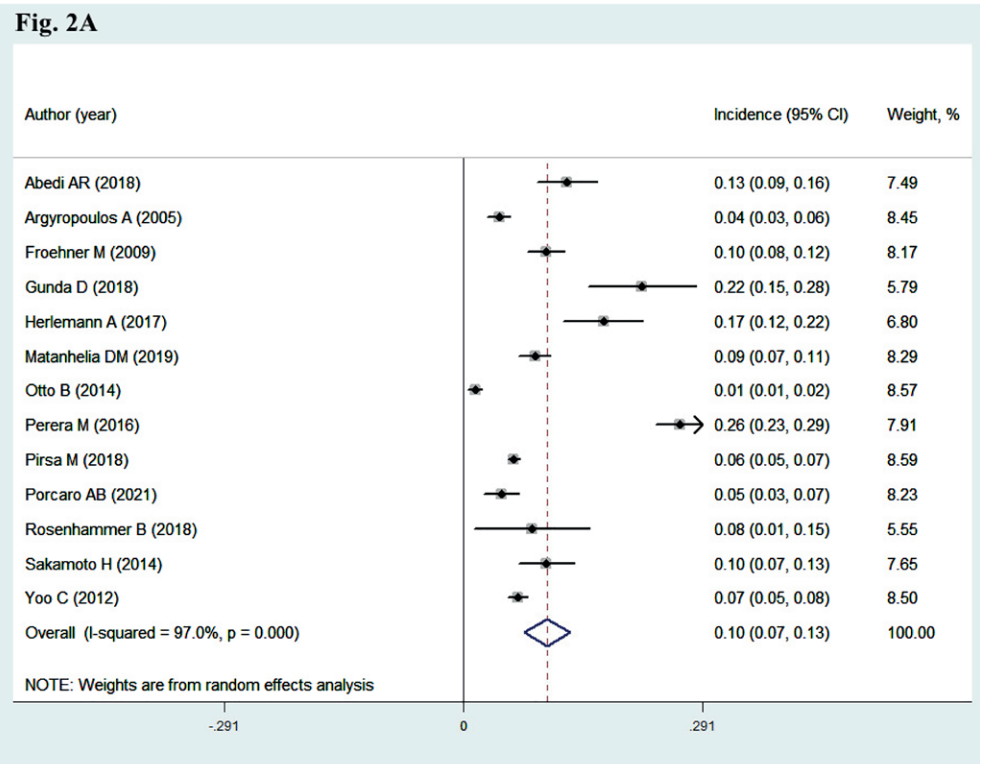
Table 1 - Characteristics of the included studies.

First author year	Study design	Country	Database source (Duration)	Sample size (No. IPC)	Stage
Abedi AR. 2018 (16)	Retrospective study	Iran	Shohada-e-Tajrish Hospital database (2006-2016)	TURP:315 OP:108 (TURP:40, OP:44)	NA
Andrèn O. 2009 (17)	Cross-sectional study	Sweden	Swedish National Inpatient Register (1970-2003)	TURP:72322 OP:4456 (23.288)	NA
Argyropoulos A. 2005 (18)	Retrospective study	Greece	Athens General Hospital (1999-2003)	TURP:786 (34)	T1a:17 T1b:17
Capogrosso P. 2018 (19)	Retrospective study	Italy	European academic center (2007-2016)	OP:139 TURP:498 HoLEP:540 (74)	T1a:64 T1b:10
Elkoushy MA. 2015 (20)	Retrospective study	Egypt	HoLEP database (1998-2014)	HoLEP:1242 (70)	T1a:54 T1b:16
Froehner M. 2009 (21)	Retrospective study	Germany	NA (1997-2006)	TURP:693 (70)	T1a:52 T1b:18
Gunda D. 2018 (22)	Retrospective study	Tanzaia	Bugando University Hspital in Tanzania (2015)	TURP:152 (33)	T1a:11 T1b:22
Herlemann A. 2017 (23)	Retrospective study	Germany	Department of Urology of the Ludwig-Maximilians-University of Munich (2013-2014)	TURP:229 HoLEP:289 (TURP:39, HoLEP:43)	T1a:14 T1b:68
Kim M. 2014 (24)	Retrospective study	Korea	Seoul National University College of Medicine (2008-2011)	HoLEP:458 (27)	NA
Matanhelia DM. 2019 (25)	Retrospective study	Ireland	Mater Misericordiae University Hospital (2007-2016)	TURP:826 (72)	T1a:37 T1b:35
Misraï V. 2019 (26)	Retrospective study	France	Rennes Hospital (2013-2018)	OP:393 HoLEP:345 (OP:33, HoLEP:34)	T1a:28 T1b:39
Nunez R. 2011 (27)	Retrospective study	America	Department of Urology of Mayo Clinic (2007-2010)	HoLEP:240 (28)	T1a:14 T1b:14
Ohwaki K. 2017 (28)	Retrospective study	Japan	St. Luke's International Hospital (2008-2014)	HoLEP:654 (41)	NA
Otsubo S. 2015 (29)	Retrospective study	Japan	Southwest Urological Clinic of Japan (2006-2011)	HoLEP:365 (25)	NA
Otto B. 2014 (30)	Retrospective study	America	New York-Presbyterian Hospital (2006-2011)	TURP:760 (11)	T1a:9 T1b:2
Perera M. 2016 (31)	Prospective study	Australia	Ludwig Institute for Cancer Research, Austin Hospital (2010-2013)	TURP:923 (243)	T1a:109 T1b:134
Pirša M. 2018 (32)	Retrospective study	Croatia	Department of Urology in Sestre milosrdnice University Hospital Center (1997-2017)	TURP:4.372 (265)	T1a:119 T1b:146
Porcaro AB. 2021 (33)	Retrospective study	Italy	Department of Urology of University of Verona (2017-2019)	TURP:389 (18)	T1a:11 T1b:7
Rosenhammer B. 2018 (34)	Retrospective study	Germany	University of Regensburg (2016-2017)	TURP:60 HoLEP:60 (TURP:5, HoLEP:14)	T1a:12 T1b:7
Sakamoto H. 2014 (35)	Retrospective study	Japan	Tokyo Saiseikai Central Hospital (2006-2011)	TURP:307 (31)	T1a:18 T1b:13
Skrzypczyk MA. 2014 (36)	Retrospective study	Poland	Centre of Postgraduate Medical Education in Warsaw (2004-2010)	OP:145 TURP:823 (34)	T1a:19 T1b:15
Tonyali S. 2021 (37)	Retrospective study	Turkey	Turkiye Yuksek Ihtisas Training and Research Hospital (2008-2018)	OP:36 TURP:281 (21)	T1a:10 T1b:11
Yoo C. 2012 (8)	Retrospective study	Korea	Yonsei University College of Medicine (2004-2008)	TURP:1.613 (78)	T1a:32 T1b:46

Note: HoLEP = holmium laser enucleation of the prostate; NA = not available; OP = open prostatectomy; PSA = prostate-specific antigen; PV = prostate volume; TURP = transurethral resection of the prostate.

Mean age, years	Mean PV, mL	Mean PSA, ng/mL	Risk factors	Prevalence, %
68.74±9.87	80.56±25.12	21.47±13.44	NA	TURP:12.6 OP:40.7
NA	NA	NA	NA	OP:30.3
69.7	NA	5.1	NA	TURP:4.3
66	76	3.2	PV, age and PSA	OP:6.4
75.8±8.7	NA	NA	Age and PSA	HoLEP:5.64
NA	NA	NA	NA	TURP: 10.1
69±9.4	92.7	8.5	PV, age and PSA	TURP:21.71
71	80	5.5	Age and PSA	TURP:17 HoLEP:15
68.4±6.6	NA	3.38±4.16	Age and PSA	HoLEP:5.9
73.3	44.2	5.25	NA	TURP:8.7
69	110	6.6	NA	OP:8.5 HoLEP:9.9
73	71.2	3.3	NA	HoLEP:11.7
70	66	6.1	PV and PSA	HoLEP:6.3
68	55.5	4.5	NA	HoLEP:6.8
71	92.4	NA	NA	TURP:1.4
NA	65	NA	NA	TURP:26.3
74.5	56	NA	NA	TURP:6.1
70	55	2.9	NA	TURP:4.6
71.5±7.9	74.2±13.9	4.99±3.12	PV, age and PSA	TURP:8.3 HoLEP:23.3
69.2	61	5.4	PV, age and PSA	TURP:10.1
71	70	3.36	PSA	OP:3.5
69	NA	3.24	NA	OP:6.6
71.1±7.6	59.5±30.5	4.7±4.2	PV, age and PSA	TURP:6.6

Figures 2A-2C: Meta-analysis on the prevalence of IPC after BPH surgery. CI, confidence interval. 2A: TURP group; 2B: HoLEP group; 2C: OP group.



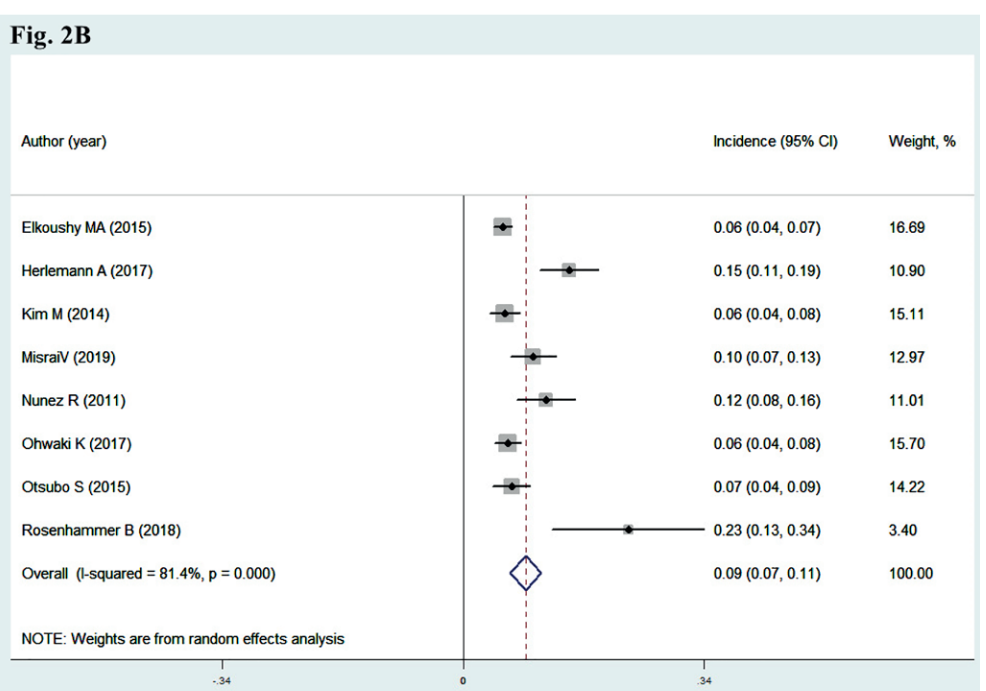


Fig. 2C

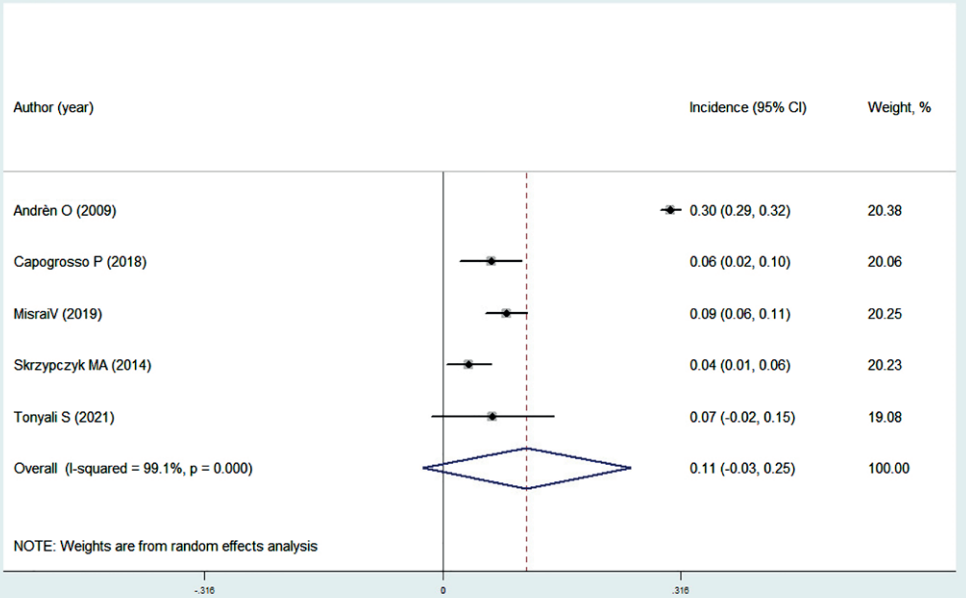


Table 2 - Results of sensitivity analyses.

Study omitted	OR	95% CI	
Abedi AR (2018) (16)	0.1	0.07	0.13
Argyropoulos A (2005) (18)	0.11	0.1	0.14
Froehner M (2009) (21)	0.1	0.07	0.13
Gunda D (2018) (22)	0.09	0.07	0.12
Herlemann A (2017) (23)	0.1	0.07	0.12
Matanhelia DM (2019) (25)	0.1	0.07	0.13
Otto B (2014) (30)	0.11	0.08	0.14
Perera M (2016) (31)	0.08	0.06	0.11
Pirsa M (2018) (32)	0.11	0.07	0.14
Porcaro AB (2021) (33)	0.11	0.07	0.14
Rosenhammer B (2018) (34)	0.1	0.07	0.13
Sakamoto H (2014) (35)	0.10	0.07	0.13
Yoo C (2012) (8)	0.11	0.07	0.13
Combined	0.1	0.07	0.13

OR = odds ratios; CI = confidence interval

Figures 3A-3C: Meta-analysis on the risk factors of IPC after BPH surgery. OR, odds ratios; CI, confidence interval. 3A: PSA; 3B: Age; 3C: Prostate volume.

Fig. 3A

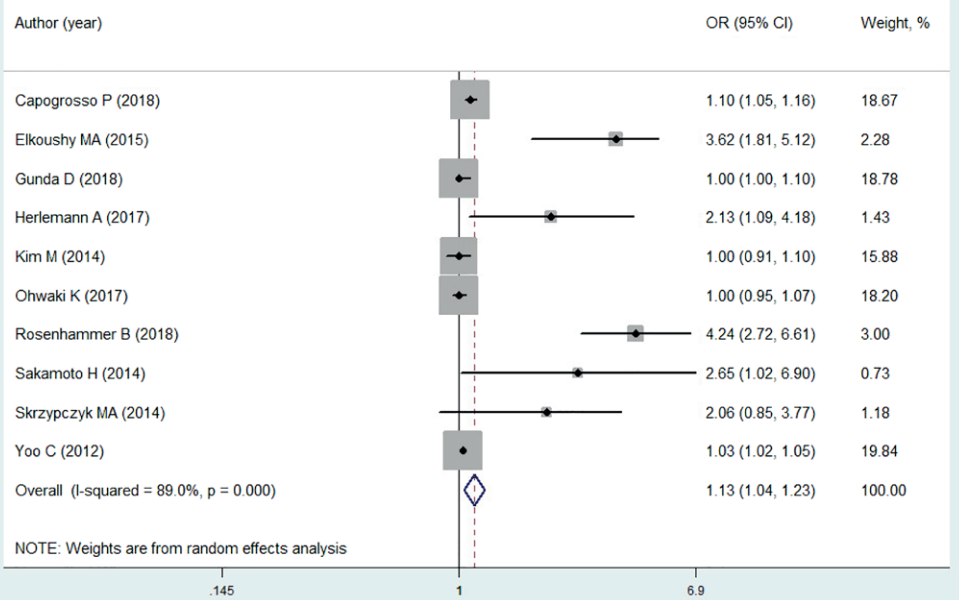


Fig. 3B

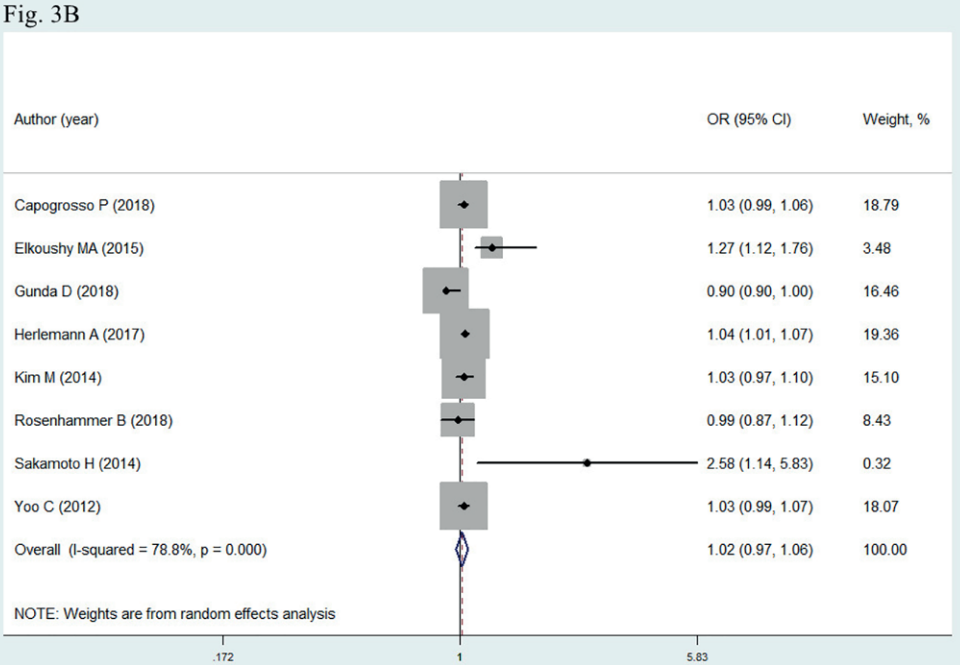
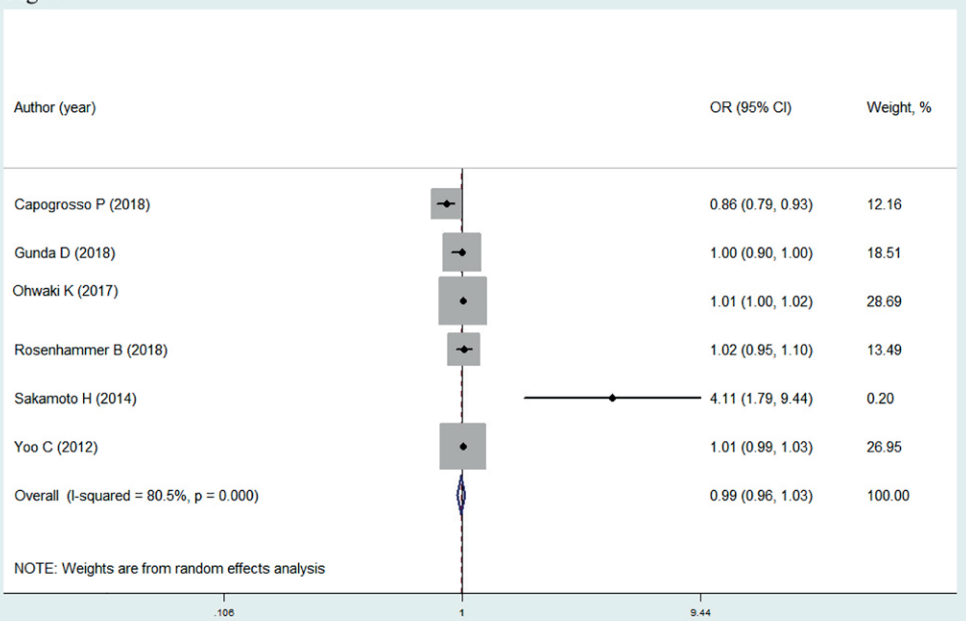


Fig. 3C



PSA does not affect the detection rate of IPC after HoLEP (OR: 0.999, 95% CI: 0.908-1.098; P=0.976) in multivariate analysis. Additionally, Ohwaki et al. (28) performed a retrospective study comprising a consecutive group of 688 patients who were diagnosed with BPH and underwent HoLEP. They observed no effect of PSA. Interestingly, diabetes may be an important factor for predicting IPC (OR: 3.15, 95% CI: 1.06-9.43; P=0.04) in men diagnosed with BPH who have undergone HoLEP. When we discarded these two studies from the meta-analysis, the results showed no significant changes, thereby validating the rationality and reliability of our analysis.

Implications for clinical practice

A significant increase has been observed in the number of minimally invasive surgical treatments for BPH, which is considered to be a factor affecting the incidence of IPC detection after BPH surgery (38). In fact, these surgical methods may not provide a sufficient amount of prostate tissue for pathological examinations. We found that the proportion of patients receiving HoLEP treatment significantly increased compared with those receiving TURP and OP. Unexpectedly, patients treated with TURP were more likely to be diagnosed with IPC rather than HoLEP and OP according to our meta-analysis. Therefore, these results should be interpreted rigorously. Generally, the surgical concepts of prostate tissue removal for the three types of BPH surgeries are similar. The previous literature demonstrated that HOLEP have a higher total detection rate of incidental PCa when compared with TURP due to more efficient tissue removal (34), which was inconsistent with our results. However, other previous studies indicated that the probability of IPC detection and the quality of the tissue retrieved after surgery were not significantly different among TURP, HoLEP, or OP (23, 39). One of the reasons may be that some prostatic tissue retrieved by HoLEP is lost due to coagulative and vaporizing effects. Therefore, it is more difficult to find biological reasons to explain the different detection rate of IPC between them. Future research should pay attention to the quality of prostate tissue retrieved through different BPH surgical methods to further determine the reasons for the different prevalence of IPC except for the sample size (39). Moreover, the best treatment for IPC remains controversial. Active surveillance for every patient with IPC subclassified as clinical sta-

ge T1a or T1b after BPH surgery is unacceptable. Thus, patients who do not meet the criteria for active surveillance can be recommended for radiotherapy or radical prostatectomy. Radiotherapy is safe for patients with a history of BPH surgery and is related to an acceptable quality of life. However, undergoing radical prostatectomy is technically challenging for patients with a history of TURP (40). Our analysis showed no significant difference in terms of patients age and prostate volume rather than PSA level. However, other potential risk factors such as PSA density, PSA velocity, or underlying diseases could not be investigated due to the limited data obtained from the included studies. Nevertheless, one previous research indicated that higher preoperative PSA density and velocity, preoperative treatment with 5-alpha reductase inhibitors, and diabetes was identified to have a significant correlation with the diagnosis of IPC after surgery for BPH (41-44). Future study regarding more important risk factors of IPC with sufficient data are still needed for early screening and identification of IPC patients. Abedi et al. (18) indicated that the cut-off point of PSA for detecting IPC was 3.8ng/mL, which showed low sensitivity and high specificity. The relevant information regarding this issue was limited reported in all the included studies. Hence, future studies with high--quality should focus on the PSA referral cut-off value for the diagnosis of IPC after BPH surgery, so as to improve the early recognition of IPC.

Strengths and limitations

Our meta-analysis exhibited crucial strengths in several ways. Firstly, to our knowledge, the present meta-analysis is the first one focusing on the prevalence and clinical risk factors of IPC after BPH surgery. Moreover, sensitive and meta--regression analyses were performed to determine the potential factors that moderated the level of heterogeneity and results of the meta-analysis according to the PRISMA guidelines. Secondly, multivariate-adjusted risk estimates were applied to minimize the other relevant confounding factors that may influence the overall results. Lastly, the results of the sensitivity analysis and meta--regression validated the rationality and reliability of this meta-analysis.

However, some limitations should also be addressed and merit further discussion when interpreting our results. Firstly, significant heterogeneity was observed. Therefore, the introduction of potentially significant heterogeneity was imminent even though meta-regression was conducted. The reason may be that all included studies were observational design with the disadvantages of heterogeneity and variations in terms of histopathological examination. Secondly, we did not evaluate data regarding the cancer clinical stage (TNM system) of patients because few studies have reported related information. Thirdly, potential publication bias is likely to exist, although our data search included a number of databases combined with freehand search. Moreover, related results may be affected with the continuous advancement of surgical techniques. Finally, our understanding of predictors which accurately foretell prostate cancer progression remains insufficient because related data have been investigated inadequately.

CONCLUSION

The prevalence of IPC was similar amongst patients undergoing TURP, HoLEP, and OP for presumed BPH. Moreover, increased PSA level was an important predictor of the presence of IPC after BPH surgery. However, no effect of age and prostate volume was observed. Therefore, further prospective studies should be conducted in a multicentric population to evaluate other relevant variables that can accurately predict the progression of prostate cancer to determine the optimal treatment for IPC patients after BPH.

Trial and protocol registration: PROSPERO CRD42021268051.

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AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

CONFLICT OF INTEREST

None declared.

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Kidney surface development in human fetuses: study applied to radiological diagnosis

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ABSTRACT

Objective: To evaluate the anatomical aspects of the kidney surface in human fetuses during the second gestational trimester.
Material and Methods: We studied 108 kidneys obtained from 54 human fetuses (29 males and 25 females). The kidney was dissected and the number of clefts was counted. The renal volume was also assessed. To compare the quantitative data in both sexes, the Students-t-test was used ($p < 0.05$). Simple linear correlations were calculated for all kidney measurements, according to fetal age. Statistical analysis was performed with the R program (Version 3.5.1).
Results: The fetuses ranged in age between 11.4 to 23 weeks post-conception. The renal volume of the right kidney ranged from 0.09 to 2.397 cm (mean=0.8479) and the renal volume of the left kidney ranged from 0.07 to 2.416 cm (mean=0.8036). The mean number of renal clefts in fetuses studied was 15.25 (7 to 28). There was no statistical significant difference in renal clefts between the sides either in males ($p = 0.646$) or in females ($p = 0.698$). Also, there was no significant difference in the mean number of renal clefts between male and female fetuses in right kidney ($p = 0.948$) and in left kidney ($p = 0.939$).
Conclusions: The number of renal clefts has a great variation, weak correlation and no tendency to decrease during the 2nd gestational trimester. The number of clefts in right kidney of total sample and female fetuses has a significant development with age.

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INTRODUCTION

The 2nd gestational trimester is very important for the embryonic development of the kidneys, renal pelvis, ureter and bladder (1, 2). An important branching of the ureteric bud occurs between the 5th and 14th weeks post conception, leading to formation of the major and minor renal calyces, renal pelvis and collecting tubules (3, 4). This branching will be important to the renal lobulations development.

The surface of the fetal kidney is divided by a number of clefts into lobes and lobules. Fetal kidney lobes (clefts) are fine, linear demarcations indenting the renal surface, separating normal lobes, consisting of a central pyramid, and surrounding cortex (5, 6). The interlobular boundary lines are apparent as grooves on the surface of the fetal kidney but are rarely visible in the mature kidney (7). The persistent fetal kidney lobulation is a rare anatomic variant and can mimic a renal neoplasm leading to a wrong

radiological diagnosis. This condition is denominated as renal pseudotumors (8).

Studies of the renal clefts development in human fetuses are rare. We hypothesized that the renal clefts are observed during the 2nd gestational trimester without differences between the genders and sides and showing a lower incidence at the end of this period. The objective of this work is to evaluate the anatomical aspects of the kidney surface in human fetuses during the 2nd gestational trimester.

MATERIALS AND METHODS

The study was approved according to the ethical standards of the hospital's institutional committee on experimentation with human beings (IRB: 4.088.773, CAAE:31780419.0.0000.5259).

We studied 108 kidneys obtained from 54 human fetuses (29 males and 25 females) ranging in age from 11.4 to 23 weeks post-conception (WPC). The fetuses were macroscopically well preserved, with no signs of malformation, and the stillbirth was due to hypoxia. Gestational age was determined at WPC according to the length of the foot. Currently, this criterion is considered the most acceptable parameter for estimating gestational age (9-11). The fetuses were also evaluated regarding total length (TL), crown-rump length (CRL) and body weight immediately before dissection with the aid of a digital pachymeter. The same observer made all the measurements (12, 13). The fetuses were donated by the hospital's obstetrics department. All data were collected from July 2018 to November 2021.

Using a standardized technique, the fetuses were carefully dissected with extraction of the kidneys and ureters with the aid of a stereoscopic lens with 16/25X magnification. All fetuses were dissected under identical conditions by the same researcher, who has practical experience in microsurgery. After kidney dissection, we evaluated the following measurements with the aid of a digital pachymeter: renal length, width of the superior pole, width of the inferior pole, and renal thickness (Figure-1). The data were expressed in centimeters. The fetal renal volume was calculated using the ellipsoid formula (14): Renal volume (RV) = [renal length x renal thickness x renal width (lower pole + upper pole)/2] x 0.523.

After the measurements the kidney was dissected in our laboratory with the aid of a microscope (Zeiss Discovery V8 microscope with stereoscopic lens with 16/25X magnification) and the number of clefts was counted (Figure-1). We observed the fetal kidneys in anterior position, lateral position, and posterior position and to facilitate the clefts number identification we marked each cleft with a color pen (Figure-1).

Statistical Analysis

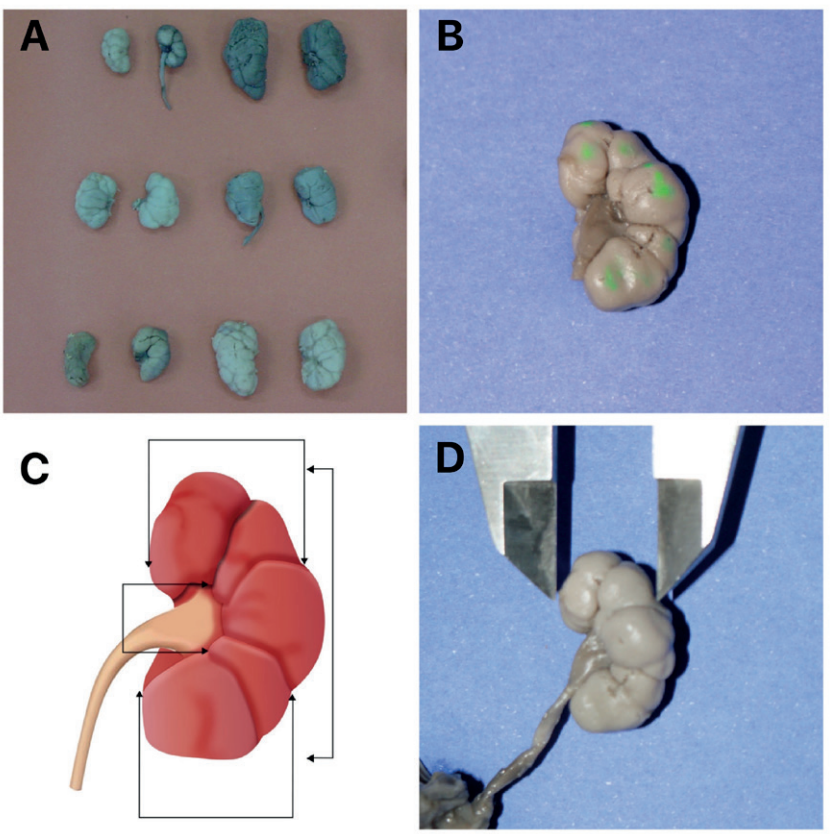
All parameters were statistically processed and graphically described. To compare the quantitative data in both sexes, the students--t-test was used ($p < 0.05$). Simple linear correlations (where r^2 values less than 0.4 reflect very weak correlation, r^2 between 0.4 and 0.7 reflect moderate correlation and r^2 greater than 0.7 indicate strong correlation) were calculated for all kidney measurements, according to fetal age. The statistical analysis was performed with the R program (Version 3.5.1).

RESULTS

The fetuses ranged in age between 11.4 to 23 WPC, weighted between 60 and 780g, and had crown-rump length between 7.3 and 22.2 cm. The mean number of renal clefts in fetuses studied was 15.25 (7 to 28). The statistical analysis of all kidneys biometric parameters measurements is reported in Table-1.

There was no statistically significant difference in renal clefts between the sides either in males ($p = 0.646$) or in females ($p = 0.698$). Also, there was no significant difference in the mean number of renal clefts between male and female fetuses in right kidney ($p = 0.948$) and in left kidney ($p = 0.939$). The renal volume of the right kidney ranged from 0.09 to 2.397 cm (mean = 0.8479) and the renal volume of the left Kidney ranged from 0.07 to 2.416 cm (mean = 0.8036). The analysis of the fetal kidney volume showed no significant statistical difference between side and sex comparisons (Volume of right kidney x left kidney (males and females): $p = 0.057$; Volume of right kidney x left kidney (males): $p = 0.067$;

Figure 1 - Renal clefts and kidney measurements.



A) The figure shows some units of our sample after the fetal kidney dissection; B) Fetal kidney of a male fetus with 16 weeks post-conception in anterior position, we marked each cleft with a green color pen; C) Schematic drawing of kidney measurements: Renal length, lower pole width, hilar width and upper pole width and D) The figure shows the measurement of the upper pole width with the aid of a digital pachymeter.

Volume of right kidney x left kidney (females): p = 0.333; Males x females (volume of right kidney): p = 0.381 and Males x females (volume of left kidney): p = 0.359).

The linear correlation was performed to enable analysis of morphological data at different gestational ages. Results for male fetuses' renal volume (Right kidney: r = 0.763, p < 0.001 and Left kidney: r = 0.755, p < 0.001) and female fetuses' renal volume (Right kidney: r = 0.698, p < 0.001 and Left kidney: r = 0.751, p < 0.001), indicated that the renal volume increased significantly during the fetal period studied in males and females fetuses.

The linear correlation of renal lobes was performed to enable analysis of morphological data at different gestational ages. The linear correlation of the 54 fetuses renal clefts is shown in Figure-2. The linear correlation indicated that the fetal renal lobes number increased with age both in total sample, female and male fetuses, but the differences were not statistically significant, and the correlation was weak. The exception was the renal right clefts in total sample and female fetuses that has a significant development with age.

DISCUSSION

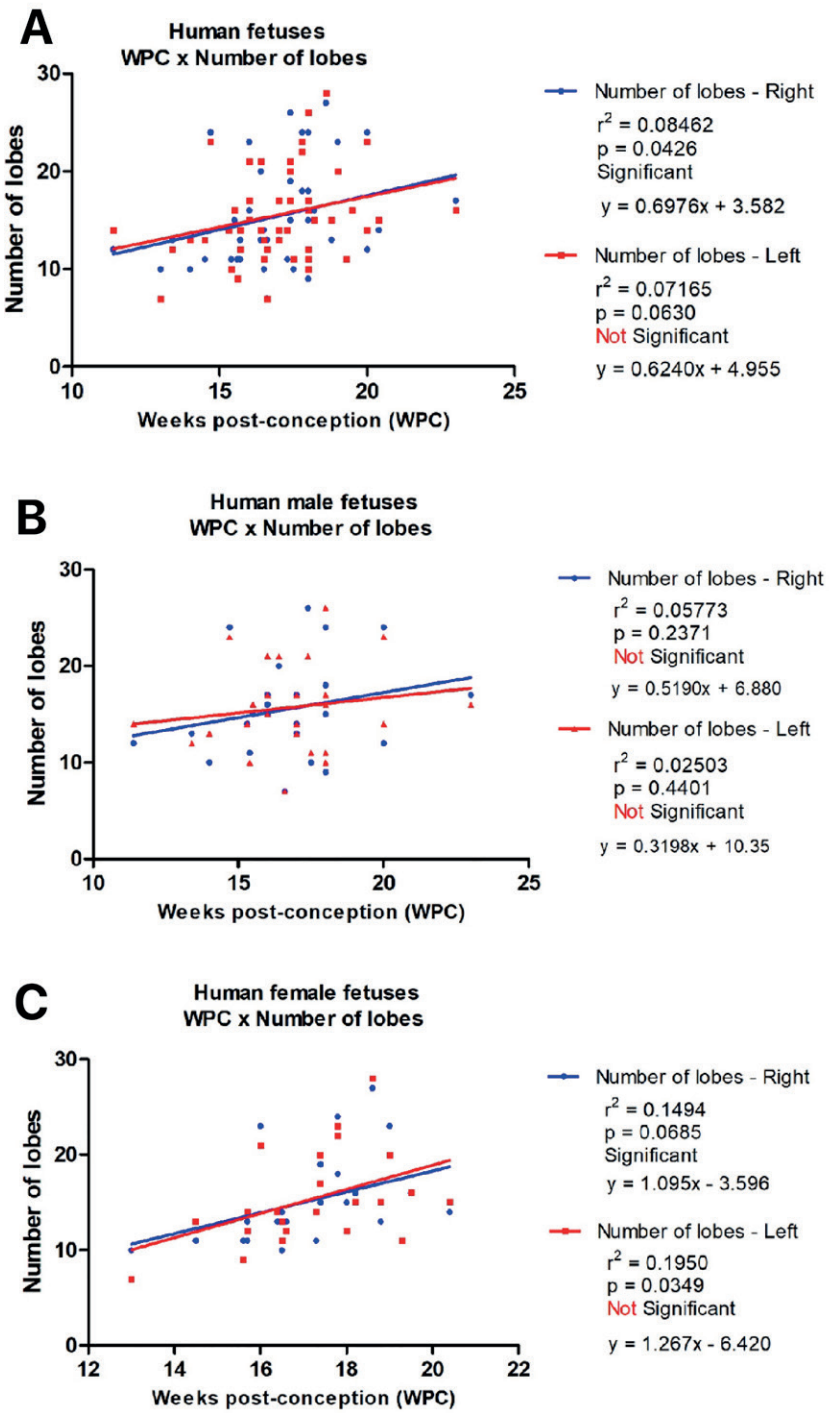
In the beginning of the 5th week of development, the ureteral buds originate at the distal portion of the mesonephric ducts and merges with the metanephrogenic blastema (15, 16). In this paper we studied fetuses of the 2nd trimester of gestation. At this age, the kidneys are expected

Table 1 - The table presents the statistical analysis of the main fetal parameters and the renal clefts in 54 fetuses studied.

	GENDER																	
	MALE						FEMALE						TOTAL					
	n	Mean	Median	SD	Min	Max	n	Mean	Median	SD	Min	Max	n	Mean	Median	SD	Min	Max
Age (WPC)	29	16.628	16.60	2.327	11.40	23.00	25	17.304	17.40	1.680	13.00	20.40	54	16.941	17.00	2.063	11.40	23.00
Total length (cm)	29	22.841	23.00	3.528	15.00	32.00	25	23.480	24.50	3.100	13.50	28.00	54	23.137	23.50	3.321	13.50	32.00
Weight (g)	29	261.207	245.00	133.568	60.00	780.00	25	275.600	285.00	102.045	60.00	455.00	54	267.870	270.00	119.134	60.00	780.00
Nº of Clefts (R)	29	15.207	15.00	4.924	7.00	26.00	25	15.120	14.00	4.711	10.00	27.00	54	15.167	14.00	4.781	7.00	27.00
Nº of Clefts (L)	29	15.379	15.00	4.648	7.00	26.00	25	15.280	14.00	4.792	7.00	28.00	54	15.333	14.50	4.670	7.00	28.00
Vol. RK (cm)	26	0.7887	0.6640	0.5099	0.2340	2.3970	23	0.9148	0.8300	0.4853	0.0900	2.1600	49	0.8479	0.7080	0.4974	0.0900	2.3970
Vol. LK (cm)	26	0.7399	0.5995	0.4946	0.1630	2.4160	23	0.8757	0.7800	0.5316	0.0700	2.4100	49	0.8036	0.6570	0.5115	0.0700	2.4160
CRL (cm)	29	14.659	15.00	3.399	7.30	22.20	25	15.884	16.00	2.059	9.50	19.30	54	15.226	15.75	2.899	7.30	22.20

SD = Standard Deviation; **WPC**= weeks post conception**; cm** = centimeters; **RK** = right; **LK** = left kidney; **CRL** = Crown rump length.

Figure 2 - Linear regression analysis comparing the correlation of the renal clefts and fetal age (WPC).



The points plotted represent the mean values obtained for each week studied. A) Correlation for renal clefts in right side (blue point) and left side (red points) in male and female fetuses X fetal age (WPC). Linear regression indicated a weak and positively correlation of renal clefts with age (Right kidney: r2 =0.08462, p=0.046 and Left Kidney: r2 =0.07165, p=0.0630); B) Correlation for renal clefts number in male fetuses X fetal age (WPC) (Right side: blue points and left side: red points). Linear regression indicated a weak and positively correlation of male renal clefts with age (Right kidney: r2 =0.05773, p=0.2371 and Left Kidney: r2 =0.02503, p=0.4401) and C) Correlation for renal clefts number in female fetuses X fetal age (WPC) (Right side: blue points and left side: red points). Linear regression indicated a weak and and positively correlation of female renal clefts with fetal age (Right kidney: r2=0.1494, p= 0.0685 and Left Kidney: r2=0.1950, p=0.0349).

to have reached their final position and from then on they will only develop in size, representing an ideal moment for this study. In our sample we observed that the renal parenchymal volume had a strong and positive correlation with fetal age during the 2nd gestational trimester.

The branching of the ureteral buds will determine the pyelocaliceal pattern and the corresponding renal lobules (2, 17, 18). The kidney fetal lobe is made up of medullary pyramid surrounded by cortex, separated by interlobar grooves and drained by single calyx. The kidney interlobar grooves disappear during the third gestational trimester (5).

The persistence of kidney fetal clefts is a rare anatomic variant characterized by fine, linear demarcations indenting the renal surface between normal renal lobes and consisting of normal central pyramids and surrounding cortex which are mistaken as tumor and can lead a difficulty radiological diagnosis. This condition is called renal pseudotumor (8, 19). Renal pseudotumor is a term that include persistent fetal lobulation, hypertrophy of Bertin columns and dromedary humps (8, 19).

Radiological confirmation of persistent fetal lobulation of kidney can be made by documenting the presence of renal pyramid in the bulge bounded by septa of Bertin on either side (20). Radiologist can make potential errors during image interpretation of persistent fetal lobulation especially on conventional and power Doppler ultrasound scan and to reach a secure diagnosis, a CT or MRI should be done (7).

The fetal kidney grooves become invisible during the third trimester resulting in smooth renal surface (5, 21). This paper presents the first normative parameters of fetal renal clefts development during the 2nd gestational trimester, and we observed that the renal clefts number increased with age, however the correlation was weak in the fetal period analyzed, except in the right side of total sample and in the right side of female fetuses where the number of clefts has a significant development with age. We observed that the differences of the development of renal clefts number were not statistically significant between genders and side.

Renal clefts showing no tendency to decrease during the 2nd gestational trimester and this finding may justify the persistence of renal lobulations during the 3rd gestational trimester and after birth, however the absence of 3rd gestational trimester fetuses in our sample to determine the moment when the lobulations begin to disappear is an important limitation of this work.

CONCLUSIONS

The number of renal clefts has a great variation, weak correlation, and no tendency to decrease during the 2nd gestational trimester. The number of clefts in right kidney of total sample and female fetuses has a significant development with age.

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An earlier version of this paper has been presented in the European Urology Congress according to the following link: https://resource-centre.uroweb.org/resource-centre/eau19/189800/Poster?

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CONFLICT OF INTEREST

None declared.

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Enuresis and upper airway obstruction: BNP and ADH hormones behavior before and after airway surgery

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ABSTRACT

Introduction: Upper airway obstruction (UAO) is a common condition in all pediatric population, with a 27% prevalence. Primary monosymptomatic nocturnal enuresis (PMNE) is a condition related to UAO in 8% to 47% of these children. The specific pathophysiological mechanism of this bond is not well understood. Some authors suggest a connection between brain natriuretic peptide (BNP) and anti-diuretic hormone (ADH) during sleep. The aim of this study was to evaluate hormone profile (ADH and BNP) and improvement in dry nights in a sample of children before and after surgical treatment of the UAO.

Methods: This is a longitudinal prospective interventionist study in children, 5 to 14 years of age, with UAO and PMNE recruited in a specialty outpatient clinic. Children presenting UAO and PMNE were evaluated with a 30-day dry night diary and blood samples were collected to evaluate ADH and BNP before and after upper airway surgery. Data were analyzed prior to surgery and 90-120 days after surgery.

Results: Twenty-one children with a mean age of 9.7 years were included. Mean BNP before surgery was 116.5 ± 126.5 pg/mL and 156.2 ± 112.3 pg/mL after surgery ($p<0.01$). Mean ADH was 5.8 ± 3.2 pg/mL and 14.6 ± 35.4 before and after surgery, respectively ($p=0.26$). The percentage of dry nights went from 32.3 ± 24.7 before surgery to 75.4 ± 33.4 after surgery ($p<0.01$).

Conclusion: Surgery for airway obstruction contributed to an increase in BNP without increasing ADH. A total of 85.8% of the children presented partial or complete improvement of their enuresis.

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INTRODUCTION

Upper airway obstruction (UAO) is a common condition affecting 27% of the pediatric population (1). It is related to anatomical nasal and/or pharyngeal alterations, being adenotonsilar hypertrophy the most incident cause (2).

Primary monosymptomatic nocturnal enuresis (PMNE), which is defined by an intermittent urinary incontinence that occurs during sleep in children from the age of 5 years or more (3), can be related to UAO in an estimated prevalence of 8 to 47% (4). In these cases, surgery to treat upper airway obstruction

is associated with a complete PMNE resolution in 31 to 76%, in a follow-up period of 30 to 90 days after surgery (4).

The exact mechanism that controls this improvement remains unknown. The main hypothesis is that UAO causes an increase in negative intrathoracic pressure that causes atrial distension, which will lead to an increase in atrial natriuretic peptide (ANP) release; this would increase the brain natriuretic peptide (BNP) secretion, which induces a release of water and sodium excretion, inhibiting secretion of anti-diuretic hormone (ADH) (4), leading to an increase of nocturnal polyuria.

Some prospective studies have been published (4-7) evaluating UAO and PMNE, but in all of them the criteria to describe upper airway obstruction were not clear, which may have impacted in their results.

We hypothesized that after treating upper obstruction in those children, intrathoracic negative pressure would decrease as so as atrial distention and BNP secretion. In consequence, the water-sodium-ADH secretion mechanism would normalize leading to improvement in enuresis.

The aim of this study was to evaluate the hormone profile (ADH and BNP) and improvement in dry nights in a sample of enuretic children presenting moderate to severe upper airway obstruction before and after surgical treatment of upper airway obstruction.

MATERIALS AND METHODS

This is a longitudinal prospective interventionist study in a sample of 21 children. The study was approved by the hospital ethics committee (resolution number 2.630.758) and all parents and children signed a free an informed consent and ascent form, respectively. The study was registered in clinical trial (RBR-5pwcs47).

We included children from 5 to 14 years of age with UAO and PMNE that were recruited voluntarily in a tertiary outpatient clinic from May 2018 to November 2020, and whose parents agreed to participate. To confirm that enuresis was monosymptomatic, all children answered a structured questionnaire and fulfilled a voiding diary. Children who presented neurological, psychiatric, metabolic or kidneys illness and presented non monosymptomatic and/or secondary enuresis were not included.

Children presenting UAO and PMNE were evaluated with a 30-day dry night diary and blood samples were collected to evaluate ADH and BNP prior and after surgery of the upper airway. Blood samples were collected early in the morning, about 90 minutes after the child was awaken and a 10 to 12 hours of fasting. All blood samples were collected until 7:30 AM. If, for any reason, children arrived in the laboratory after this time, parents would be instructed to return another day. After arriving in laboratory, the child remained lying down for thirty minutes prior to collecting the blood samples. For both BNP and ADH, blood sample was collected from a peripheral venous puncture. For BNP, 0.8 mL of blood was centrifuged for 10 minutes with 2,200 grams of gravity in 18 Celsius degrees; after separation in serum, clot and gel, serum was submitted to eletrochemiluminescence technique. For ADH, 2.5 mL of blood was separated in a test tube with EDTA - *Ethylenediamine tetraacetic acid* and was centrifuged for 10 minutes in 3,000 rpm and then, frozen to minus 20 Celsius degree. ADH was dosed from frozen plasma by radioimmunoassay technique.

After completing the evaluation, upper airway surgery was scheduled and was done by only one surgeon. The surgery was performed under general anesthesia and oral intubation.

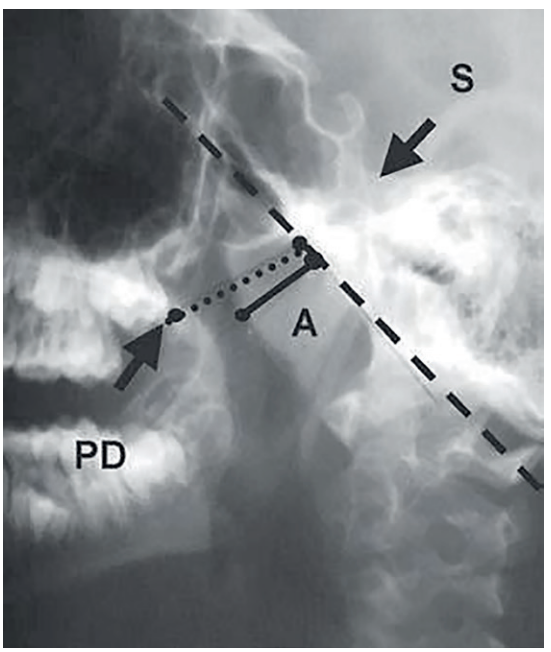
All data were analyzed prior to airway surgery and 90-120 days after it.

Children were not submitted to any other kind of treatment for enuresis, as urotherapy, alarm or medication.

Upper airway obstruction was objectively defined using cavum x-ray and nasal endoscopy. The criteria used was adenoid nasopharynx ratio (ANR) greater than 0.66 in the X-ray (8) and Brodsky 3 or 4 for nasal endoscopy (9) (Figures 1 and 2).

The Apnea / Hypopnea Index (AHI) is a way of classifying the degree of sleeping apnea. In children, up to 5 events per hour is classified

Figure 1 - Cavum X-Ray - adenoid nasopharynx ratio (ANR) – black line is the measure of the adenoid / dotted line is nasopharynx measure; ANR is the result of the division of the measures of the black line by the dotted line.



as mild apnea, from 5 to 15 as moderate and severe if more than 15 events per hour (10).

To predict the Apnea / Hypopnea Index (AHI) we used the formula of Klijajic Z et al. AHI = 3.2 x modified Mallampati score + 1.13 tonsillar size – 1.65 (10).

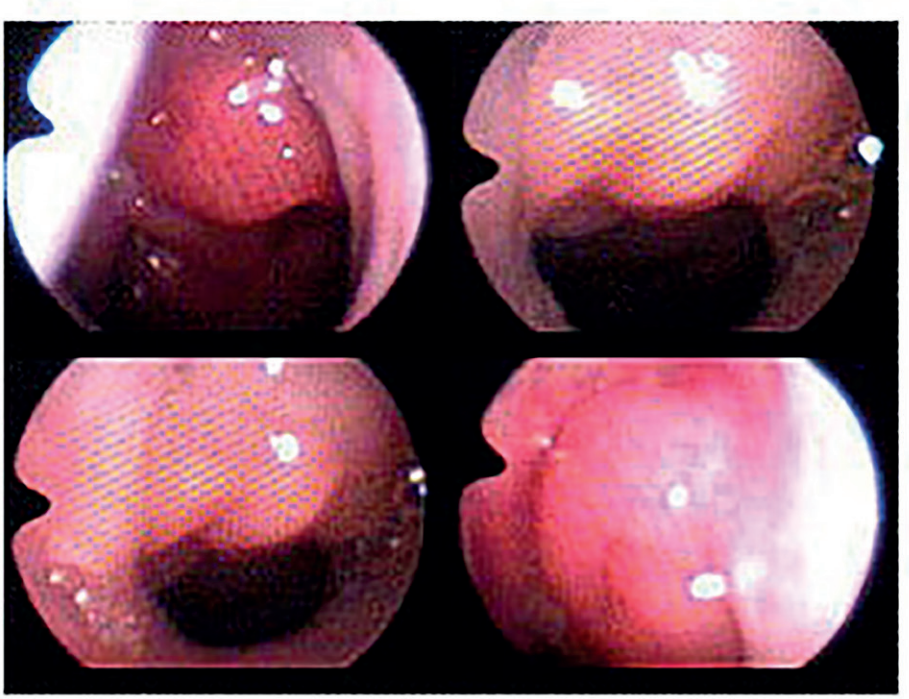
Sample calculation was made based on Kovasevic et al. study (4) using www.biomath.info/power/ttest.htm (11) for a 80% power of study and an Alfa of 0.05.

For statistical analysis we used JASP free platform (12). For assumption checks we used Shapiro-Wilk test. Parametric data was analyzed using t-test and for non-parametric data we used Wilcoxon test. Central trend and dispersion measures were used for the analysis. Significance was considered when p-value was ≤ 0.05.

RESULTS

A total of 30 children presenting PMNE and UAO that filled inclusion criteria were re-

Figure 2 - Choana nasal endoscopic view – Grades I (up to 25% of choana obstruction), II (25% to 50% of choana obstruction) , III (50% to 75% of choana obstruction) and IV (more than 75% of choana obstruction) - from left to right and from top to bottom.

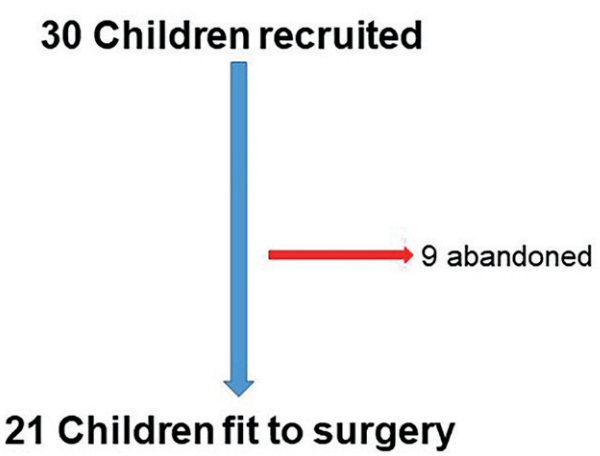


cruited. Of those, 9 discontinued follow-up due to fear of surgery and it`s possible complications and also claiming difficulty to continue follow-up after surgery. These patients received other clinical treatments for UAO and PMNE. Therefore, a total of 21 children, 6 to 14 (9.7 ± 2.49) years of age, being 13 boys, have completed all the protocol (hormones tests and dry night diary before and after surgery) (Figure-3).

After completing all the protocol an increase in BNP levels (p=0.001) and in the number of dry nights (p=0.001) were found. No difference was found for ADH levels (p=0.26) as demonstrated in Table-1.

According to the International Children's Continence Society criteria (ICCS), of the 21 children, 9 presented total improvement of enuresis, 9 presented partial improvement, and 3 did not present any improvement (Table-2).

Figure 3 - Patient recruitment flowchart.



DISCUSSION

The present study is one of the few that have evaluated BNP and ADH profile in children presenting PMNE and UAO. The results presented herein demonstrated an increase in BNP levels and no difference in ADH levels after correction of UAO in those children. Considering the ICCS criteria (13, 14) it was observed an 85.8% improvement in enuresis, being half of those (42.9%) a complete response. These findings show an improvement better than 68% described by Lehmann et al. in their systematic review (15).

Perhaps the increase of BNP levels has a relationship with the blood collection time, as we will describe further. The ideal time for blood collection is exactly the moment child is urinating, during the night; but it is virtually impossible for logistical reasons.

To avoid selection and analysis bias, only PMNE children were included in the present study.

Some studies suggests that upper airway obstruction causes negative intrathoracic pressure, leading to cardiac wall distension, which results in the release of atrial natriuretic peptide – ANP which induces BNP secretion (16). These hormones cause increase in water and sodium excretion, which inhibit vasopressin secretion. Therefore, it was hypothesized that releasing upper airway could normalize serum levels of these hormones (BNP would fall and ADH would increase), leading to improvement of enuresis. This is what was proposed by some studies (4-7). Differently from those findings, we observed an increase in

Table 1 - Mean variation from before and 90 to 120 days after airway surgery.

	Before surgery	After surgery	p value
BNP (pg/mL)	116.5 ± 126.5	156.2 ± 112.3	< 0.01
ADH (pg/mL)	5.8 ± 3.2	14.6 ± 35.4	0.26
Dry nights %	32.3 ± 24.7	75.4 ± 33.4	< 0.01

Table 2 - Improvement of Enuresis based on the International Children's Continence Society (ICCS) criteria.

ICCS Criteria	Absolute Frequency	Relative Frequency
<50% of improvement	3	14.2%
50% - 99% of improvement	9	42.9%
100% of improvement	9	42.9%

BNP levels and no changes in ADH after airway surgery; although our ADH mean increases almost three times, we have some outliers that possibly interfered in ours results. But even if we analyze data excluding outliers, we would find the following results of ADH hormone: mean before surgery 4.59 ± 1.83 and 17.03 ± 39.18 after surgery (p 0.19). These differences in our findings may also be related to a higher mean age or the moderate to severe upper airway obstruction of our series.

As we present different results than what we expected, related to BNP and ADH, we have to infer that hormonal mediation of PMNE was not valid in our sample. We expected a decrease in BNP and an increase in ADH, both with statistical significance.

The mean age of our sample is a bit higher than others prospective studies (4-7) which may have influenced our results, since it has been shown that 15% of enuretic children improves their symptoms every year regardless of any treatment. Another factor that can be associated with our better results with the UAO surgery is the degree of obstruction in our patients. The mean ANR found our sample was 0.78 (0.68-0.88), which means that the children had a moderate to severe obstruction, other than that, we used the formula of Klijajic Z. et al. (10) to predict the Apnea / Hypopnea Index (AHI) (AHI = 3.2 x modified Mallampati score + 1.13 tonsillar size – 1.65); in our sample the average of this estimated index was 7.8, which is considered moderate. A greater degree of obstruction may have a greater impact on the cascade of events related to enuresis in this population and also a greater impact on their sleep quality.

Enuretic children are considered to be *deep sleepers* (17). Children presenting UAO are oral breathers which makes them hyperexcited. This hyper excitation is related to a non-physiological breathing mechanism during sleep, caused by UAO, which increases muscular effort and norepinephrine levels. This condition causes a constant stimulus increasing their excitation threshold and making it difficult for them to wake up. In order to catch up deep sleep phases, as REM (rapid eyes movement), these children would develop inhibition afference mechanisms to effectively rest at night, other than that, if there is a constant arousal stimulus (from the airways) the arousal thresholds will increase in order to preserve sleep. The problem is, these children will keep high norepinephrine levels during the day (because of a bad sleep night that will prevent them to sleep well next night), which will keep them with high excitation threshold, consequently increasing afference inhibition, perpetuating this vicious cycle.

Besides that, recently Sun et al. (18) proposed that the winter season and high severity of initial symptoms are two high risk factors for desmopressin treatment failure; this is corroborated by Bastos Netto and Bessa Junior (19) in their editorial comment paper; they also describe some differences in sleeping architecture which could cause influence in this multifactorial and very complex mechanism of nocturnal urinary production. Just another piece of this complex puzzle.

Our follow up (90 to 120 days) was longer than Kovasevic et al. study - 30 days - (4, 5), but shorter than Fakhim et al. (7) - 180 days. In our point of view, this extended follow up allowed a better adaptation of circadian cycle of patients, contributing for an 85.8% improvement of enuresis.

So, the results presented herein are applicable to those children with more severe upper airway obstruction. This demonstrates that in a group of enuretic children with severe upper airway obstruction, surgery to release airway has to be tightly considered as a therapeutic option.

Although our sample is small, it exceeds the sample calculation for a clinical trial with a comparative group (14 patients in each group), which is being constituted in continuity of our research; this part of the major study already shows how airway surgery is an effective treatment for these specific enuretic children. The pathophysiology of enuresis in children with UAO remains unknown. Comparative studies, especially prospective ones are necessary to check the role of hormones in the control of enuresis for what we can definitively include or exclude BNP and ADH from this chain of events.

Therefore, the ideal study design would be one in which we could collect blood samples during night at the exact moment the child was urinating but unfortunately, we could not do so but only after the child had wakened; eventually this could explain the absence of changing in ADH measures. Although our sample size was within the sample previously calculated we believe that a large number of children could demonstrate different results, especially regarding ADH, which was almost three times greater after surgery and no significant difference was found; other than that, as we focused on the hormones behavior, we didn't consider nocturnal urine production as a variable; this can be considered another weakness of our research. To better understand these differences, future studies are needed, including a comparative group.

CONCLUSIONS

Evaluation of hormones profile in children presenting PMNE and upper airway obstruction showed high levels of BNP and low levels of ADH before airway surgical treatment. After that, there is an increase in both BNP and ADH levels, although mean variation of ADH was not statistically significant.

Clinically, upper airway surgery was able to improve the number of dry nights in 85.7% these children, with complete response in 42.8 %.

Improvement of enuresis after surgery could not be explained by the variations in BNP and ADH.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval number

UFJF - 2.630.758

Clinical trial registration number

RBR-5pwcs47.

Access: <https://ensaiosclinicos.gov.br/rg/RBR-5pwcs47>

Data Availability Statement

Access: <https://repositorio.ufjf.br/jspui/>

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Relationship between primary monosymptomatic enuresis and process toilet training: a case-control

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ABSTRACT

Objective: Primary monosymptomatic nocturnal enuresis (PMNE) is a prevalent condition in childhood, and the pathophysiology is multifactorial. This study investigated the relationship between the toilet training process (TT) and PMNE in children and adolescents.

Patients and Methods: A case-control study was carried out from 2015 to 2020. The presence of PMNE was identified according to International Children's Continence Society criteria. A semi-structured questionnaire was applied to assess TT.

Results: The study included 103 children and adolescents with PMNE and 269 participants with normal psychomotor development without PMNE (control group [CG]). Readiness signals were more remembered and less frequent in participants with PMNE (p=0.001) when compared to control group. No differences were found between the groups regarding the onset age of the daytime TT (p= 0.10), the nocturnal TT (p=0.08), the acquisition of daytime continence (p=0.06), and the type of equipment used for the TT (p=0.99). The use of Child-Oriented approach in group of children with enuresis was lower than in controls [87.4% (90/103) versus 94% (250/266)], respectively (OR= 0.44, 95% CI 0.21-0.94, p = 0.039).

Conclusions: The age of onset of TT, acquisition of daytime continence, and the type of equipment were not associated with higher occurrence of PMNE. On the other hand, the Child-Oriented approach was a protective factor for the occurrence of PMNE.

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INTRODUCTION

Monosymptomatic nocturnal enuresis is defined by the International Children's Continence Society (ICCS) as isolated urinary incontinence during sleep in children aged five years and older, with no associated clinical condition to justify it. Primary monosymptomatic nocturnal enuresis (PMNE) occurs in children and adolescents who have never achieved a period greater than six continuous months of nighttime dryness (1, 2). PMNE is more prevalent in male gender with a 2:1 ratio at any age and affects about 5-10% of 7-year-old children (3). The prevalence in adolescents is around 3% and from 0.5 to 1% in adults (2, 4, 5). The spontaneous remission rate is about 15% (2, 3).

PMNE often leads to loss of self-esteem, compromised school learning, and difficulties in relationships with peers and family (2, 3, 6). The etiology is multifactorial, and the main pathogenic mechanisms include nocturnal polyuria, detrusor overactivity, increased arousal threshold, and genetic predisposition (2, 7). However, the pathophysiology is not fully understood (2, 7-9). Some aspects of the toilet training (TT) process have been associated with the occurrence of PMNE (10, 11).

TT is an important milestone in child development, which can be affected by anatomical, physiological, behavioral, and cultural conditions (12, 13). Over 50 years, the average age to start TT has been delayed from 18 to 24-36 months in children with normal neuropsychomotor development. The same happened concerning the average age to complete the TT, which went from 24 to 36-39 months (13-15). On the other hand, in some Asian and African countries, very early TT is commonly used, starting from two to three weeks of age, and finishing around 12 months of age (16, 17). Girls, more frequently, start and complete the TT earlier than boys (18). The method of TT can be categorized as the Child-Oriented approach and the Structured Behavioral approach (13, 19). The American Academy of Pediatrics (AAP) recommends the Child-Oriented approach, based on Brazelton's Method (20), for children with normal neuropsychomotor development. This approach recommends the start of TT only when the child shows signs of readiness (12, 13, 20). On the other hand, the Structured Behavioral approach is guided by the parents (Azrin and Foxx Method (21), Infant Assisted Training (16), and Elimination Communication (17) and does not consider the child's need for readiness to initiate TT (19).

There are still a lot of discussion about when to start the TT, what would be the best approach and its possible repercussions on the lower urinary tract. We hypothesize that the TT process might be related to the occurrence of PMNE in children and adolescents. In this sense, the present study aimed to evaluate the relationship between the occurrence of PMNE, the age of beginning and completion of the TT, the approach, and the type of equipment used in this process.

PATIENTS AND METHODS

Ethical approval

The institution Ethics Committee approved the study CAAE 86171118.0.0000.514, under protocol number 2.625.013 (April 27, 2018). The legal guardians of the patients signed an informed consent form.

Study design

This is a case-control study with prospectively collected data in which 133 children and adolescents with PMNE were initially evaluated as cases. Thirty were excluded for the following reasons: five had spina bifida occulta, ten had intellectual development disorders, one had diabetes mellitus, one had sickle cell disease and 13 had non-monosymptomatic enuresis. Therefore, the case group consisted of 103 children and adolescents with PMNE, aged between five and 12 years, who regularly attended an Enuresis Outpatient Clinic from February 2015 to February 2020. The control group (CG) consisted of 266 children and adolescents with normal neuropsychomotor development and without lower urinary tract symptoms matched by sex, age and socioeconomic status that attended a primary healthcare unit.

Exclusion criteria

Children and adolescents with intellectual development disorder, congenital anomalies of

the nervous system, urogenital malformations, presence of diseases and/or use of medications that interfere with the functioning of the bladder or urethral sphincter, diabetes, sickle cell disease, non-monosymptomatic diseases and/or enuresis secondary school or who refused to participate in the study were excluded

Study protocol

The diagnosis of PMNE was based on the ICCS criteria, defined as urinary incontinence during sleep in children aged at least five years with at least one episode per month and a minimum duration of three months, excluding organic causes. (1, 2). Following the care protocol of the Enuresis Outpatient Clinic based on the ICCS (1, 2) and the Brazilian Consensus on Enuresis (22), guided anamnesis, urinalysis, urine culture, renal and bladder ultrasound and calculation of nighttime urinary volume were performed. In addition, a bladder and bowel diary and a calendar of dry nights were requested. The Dysfunctional Voiding Symptom Score (DVSS) adapted for this population was used to diagnose PMNE. The cutoff values to indicate the presence of lower urinary tract symptoms (LUTS) were greater than six for girls and nine for boys (23).

A semi-structured questionnaire not yet validated was developed and applied to parents to assess the TT process. The questionnaire was based on previous studies (19, 24). It included the signs of readiness, the age at which the child started and completed the TT, the approach (Child-Oriented or Structured Behavioral), and the type of equipment (potty chair, regular toilet, toilet with seat reducer, toilet with footrest, toilet with a seat reducer) used (Appendix A). TT completion was defined as the age at which the child achieved complete bowel and bladder control without failing to retain urine or stool during the day and night (14). The pediatricians were trained to apply the instruments and conducted the interviews with the subjects and their parents in a confidential environment.

Statistical Analysis

The software GraphPad Prism, version 9.0.3 (GraphPad Prism®, San Diego-CA, USA) was used for statistical analysis. The Shapiro Wilk test evaluated the distribution of the numerical variables. Continuous quantitative variables were expressed as means and standard deviations. Categorical variables were shown as absolute values or proportions. Student's t-test or Mann-Whitney test compared continuous variables according to distribution, whereas chi-square test was used for categorical variables comparisons. Odds Ratio (OR) with 95% confidence interval (95% CI) evaluated the magnitude and precision of the association between categorical variables. Values of $p<0.05$ were considered statistically significant.

RESULTS

The case group was composed of 63.1% of male gender (65/103) with a mean age of 7.5 ± 3.11 years. Control group (CG) had a mean age of 7.3 ± 2.88 years, with 57.1% of male gender (152/266). As shown in Table-1, no significant differences were found concerning age, gender and socioeconomic status when comparing the groups.

Readiness signs were reported in 42.7% (44/103) of children and adolescents with PMNE and in 54.1% of the CG (144/266). These signs were absent in 40.8% (42/103) of the PMNE patients and 15% (40/266) of the CG. Only 16.5% (17/103) of the parents of PMNE cases did not remember if there were signs of readiness, while, for the parents of controls, the percentage was significantly higher reaching 31% (82/266) (p=0.001, Table-1). The main signs of readiness reported by parents are described in Figure-1. No differences were found in cases and controls (p=0.98).

The prevalence of the enuretic group and controls trained by the Child-Oriented approach was 87.4% (90/103) and 94% (250/266), respectively (OR= 0.44, 95% CI 0.21 a 0.94) (p = 0.039, Table-1).

There was no difference between the groups when evaluating the type of equipment used during the TT (p=0.99). Few cases and controls used a toilet with a seat reducer, footrest, or both. All participants in this study used disposable diapers during the TT. The type of equipment is described in Table-1.

Table 1 - Baselines and characteristics of toilet training in children and adolescentswith primary monosymptomatic nocturnal enuresis and the control group.

Characteristics	Children and adolescentswith PMNE (n=103)	Control group (n=266)	p
Gender Male	63.1% (65/103)	57.1% (152/266)	0.09
Age mean (SD)	7.3 ± 2.88	7.5 ± 3.11	0.10
Toilet Training Readiness			0.001
Present	42.7% (44/103)	54.1% (144/266)	
Absent	40.8% (42/103)	15% (40/266)	
Not remembered	16.5% (17/103)	31% (82/266)	
Approach			0.03
Child-oriented	87.4% (90/103)	94% (250/266)	
Structural Behavior	12.6% (13/103)	7.1% (19/266)	
Type of equipment			0.99
Potty Chair	65% (67/103)	66.5% (177/266)	
Regular toilet	26.2% (27/103)	25.2% (67/266)	
Toilet with seat reducer	4.9% (5/103)	4.5% (12/266)	
Toilet with footrest	1.9% (2/103)	2.3% (6/266)	
Toilet with a seat reducerand footrest	1.9% (2/103)	1.5 % (4/266)	
Time	Age mean (SD) months		
Started the daytime TT	18.6 ± 8.7	17.4 ± 4.9	0.10
Acquisition of daytime continence	23.2 ± 11.3	21.4 ± 6.1	0.06
Started the nighttime TT	22.3 ± 3.1	20.1 ± 5.5	0.08

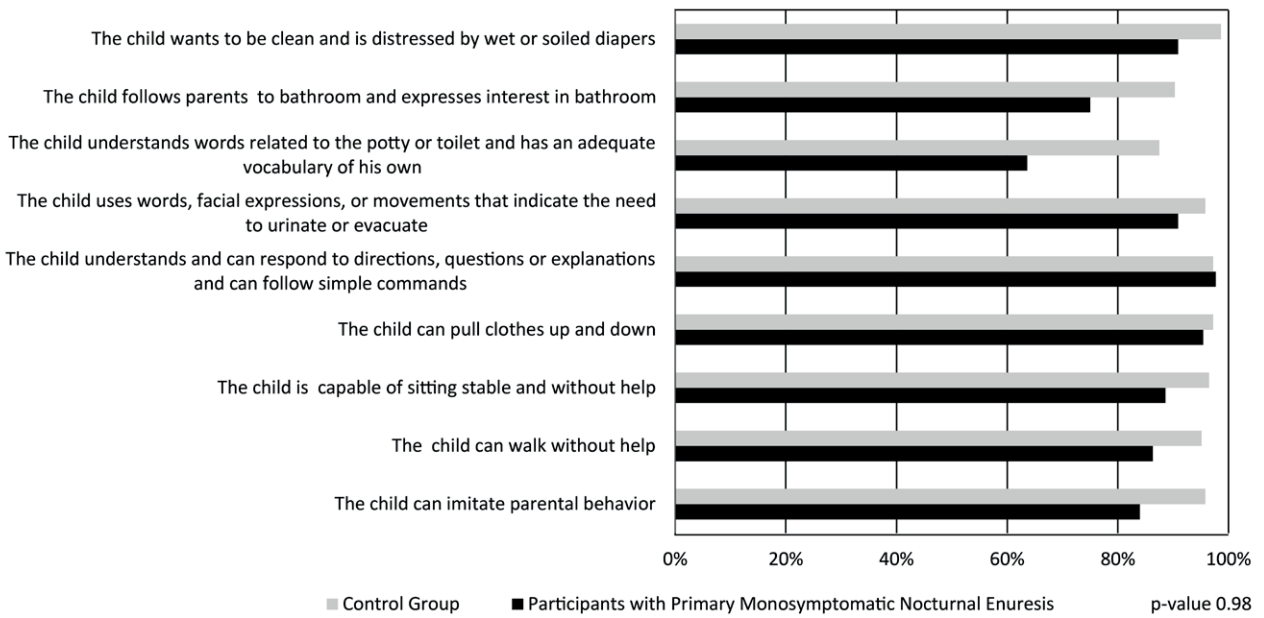
PMNE = Primary monosymptomatic nocturnal enuresis; SD = Standard Deviation; TT = Toilet training.
p value < 0.05.

Participants with PMNE started the daytime TT at 18.6 ± 8.7 months and those without PMNE at 17.4 ± 4.9 months (p=0.10). The average age of acquisition of daytime continence was 23.1 ± 11.3 months for cases and 21.4 ± 6.1 months for controls (p=0.06). Nocturnal TT's onset age was 22.3 ± 3.1 months in cases and 20.1 ± 5.5 months in the CG (p=0.08). The mean age of acquisition of nocturnal continence in controls was 27.34 ± 9.23 months (Table-1).

DISCUSSION

We started our investigation by assessing whether parents identified specific skills to initiate the TT process in their children named readiness signs. These signs comprise three pillars of the child's neuropsychomotor development: physiological maturation, external feedback, and development of self-esteem and motivation (13, 20). Our study showed that parents of children and

Figure 1 - Main readiness signs described by parents/caregivers



adolescents with PMNE remembered more signs of readiness than the parents of CG. A possible explanation would be that the parents of children and adolescents with PMNE usually try to identify the cause of enuresis. In contrast, the parents of healthy controls do not have the same motivation. Usually, parents of children with a disease or condition remember more related facts, in this case, a son or daughter with PMNE (25). There was no difference in the main signs of readiness found in the two groups. The same signals found in this study were the most frequently reported in two recent reviews (19, 26). The authors reported approximately twenty-one readiness signs, but both reviews considered the absence of knowledge about which and how many readiness signs are needed to start the TT (19, 26). On the other hand, we emphasize that the absence of signs of readiness was more frequent in participants with PMNE than in the CG, which may corroborate the Child-Oriented approach as a protective factor for PMNE occurrence in our series described below.

There is no consensus on the best method to be used for TT. The chosen approach depends on cultural differences, parental preferences, and expectations (13, 19). The approach should be individualized based on how the child learns best and the family's needs (13). In our study, children trained with the Child-Oriented approach had significantly less chance of exhibiting PMNE. Two studies showed an increase in the prevalence of PMNE, in children who received a threatening method of TT (27, 28). In one of them, PMNE was found 2.24 times more often in children submitted to a coercive and threatening approach (28). A recent study in Indonesia showed that if the TT quality is not good enough, the risk of enuresis is increased by 5.4 times compared to properly trained children. (29). In sharp contrast, Hackett et al. (30) showed an association between relaxed parental attitudes during TT with the occurrence of enuresis. However, the literature is very scarce regarding TT approaches and the occurrence of enuresis.

Before starting the TT process, parents must decide which equipment to use, usually the potty or toilet. The potty is preferred in the early stages because it is safe. Children feel more comfortable, do not need foot support or a seat reducer, and can be moved to other environments. The potty also offers the best biomechanical position for the child. Although the potty is preferred, some children like to imitate their parents and choose the toilet (10, 12, 20, 24). In the present sample, when

evaluating the type of equipment used during the TT, about two third of children in both groups used the potty. The potty is the equipment indicated for approaching children and is considered a tool that helps assess readiness signs (13, 20). Notably, 24.9% of the enuresis group and 26.2% of the CG used the regular toilet without a seat reducer and/or footrest. It is important to reinforce that incorrect posture when urinating or defecating may lead to bowel bladder dysfunction (BBD), including enuresis (24). Although we did not find any association between the equipment used and the occurrence of enuresis, we suggest that children always use a toilet with a seat reducer and footrest or potty. The proper equipment results in a feeling of safety and a more physiological position to facilitate evacuation and urination and prevent BBD. We did not find in the literature studies that evaluated the relationship between the TT equipment and the presence of enuresis.

In our series, PMNE children and adolescents started daytime TT at 18.6 months and nighttime TT at 22.3 months, achieving daytime continence at 23.1 months, therefore earlier than recommended. Most studies suggested the beginning of TT between 24 and 36 months (13, 15) and showed that the age for staying dry during the day would be 32.5 to 35 months (18) and for complete acquisition of continence around 36 to 39 months (13, 15). Despite this, we found no statistical difference between cases and controls. The literature is still controversial about the relationship between the age at the beginning and end of the TT and its association with PMNE. The early onset of nocturnal TT (<30 months) was associated with early nocturnal continence and a lower rate of enuresis (31). Acikgoz et al. (11) reported a relationship between urinary incontinence only during the day, monosymptomatic and non-monosymptomatic enuresis, and initiation of the TT process after one year of age. In this regard, Akis et al. (32) showed that if the age of TT was late (> 24 months), the risk of enuresis was 3.04 times higher than in controls. Tokar et al. (33) showed an association between enuresis and age at the beginning of TT. They reported a higher reported likelihood of PMNE in children who began TT at four to six years or later. On the other hand, one recent study described that the onset of TT training after 24 months was not associated with isolated enuresis but strongly related to isolated daytime urinary incontinence, delayed bladder control, and school-age urinary incontinence (34).

We are aware of the limitations of this study. First, recall bias concerning TT data must be considered, especially in the control group. Caregivers of children with a disease or condition tend to be more accurate in describing it, and the opposite may occur in the CG (25). A second point concerns the TT. The assessment of the TT is challenging due to heterogeneity and methodological flaws, including bias, lack of standardization, differences in terminology and cultural definitions of successes and failures. Finally, this study has a relatively small sample size that precludes the detection of statistical differences, as for instance, regarding gender.

However, this study shows the importance for the healthcare team and family members to discuss the TT process. In general, healthcare professionals are only sought out for advice on TT when problems occur. The role of the healthcare team in the TT process is multifaceted. It includes the assessment of the child's signs of readiness, the investigation of family dynamics, the development of short- and long-term follow-up goals, and the identification of risk factors for failure.

In conclusion, the age of onset of TT and acquisition of daytime continence and the type of equipment were not associated with a higher occurrence of PMNE. On the other hand, parents of the children and adolescent with PMNE remembered more frequently of the signs of readiness than parents of the controls. The Child--Oriented approach was a protective factor for the occurrence of PMNE.

ABBREVIATIONS

ICCS - International Children's Continence Society
PMNE - Primary monosymptomatic nocturnal enuresis
TT - Toilet training
AAP - American Academy of Pediatrics
CG - Control Group

DVSS - Dysfunctional Voiding Score Symptom
LUTS - Lower urinary tract symptoms
OR - Odds ratio
BBD - Bowel bladder dysfunction

COMPLIANCE WITH ETHICAL STANDARDS

Institution where the research was carried out Universidade Federal de Minas Gerais (UFMG).

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ETHICAL APPROVAL

The institution Ethics Committee approved the study under the protocol CAAE 86171118.0.0000.5149. The legal guardians of the patients signed an informed consent form.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author. Data will be made available upon reliable request.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Can remote assistance for robotic surgery improve surgical performance in simulation training? A prospective clinical trial of urology residents using a simulator in south america

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ABSTRACT

Introduction: We aimed to evaluate the role of remote proctoring during the initial training phases of a robotics curriculum using surgical robot skills simulator exercises.
Materials and Methods: Prospective randomized study comprising 36 urology residents and junior staff urologists without previous robotic training. Group 1 (G1) performed exercises without any assistance or support, group 2 (G2) received support from in-person proctor, and group 3 (G3) from a remote proctor through a telementoring system. Qualitative and quantitative analyses were conducted for each exercise and group.
Results: The overall score approval rates (OSA) for the different skill exercises were Ring Walk 2 (RW2) 83%, Energy Dissection 2 (ED2) 81%, and Ring Walk 3 (RW3) 14%. RW2 OSA was higher on attempt 3 than on attempt 1 (83.3% vs. 63.9%, p=0.032). ED2 OSA rate was higher in attempt 3 than in attempt 1 (80.6% vs. 52.8%, p=0.002). RW2 OSA was similar among the groups. In ED2, both remote and live assistance were significantly related to upper OSA (G1=47.2%, G2=75.0%, G3=83.3%, p=0.002). RW3 had similar OSA among the groups, which can be explained by the high level of difficulty and low OSA in all the groups. However, in a sensitive quantitative analysis, the mean overall score of the participants in RW3 was higher in both proctored groups (G1=24, G2=57.5, G3=51.5, p=0.042).
Conclusion: Robotic performance increased significantly over three attempts for simulation exercises of low, medium, but not high-complexity. Proctoring, either in-person or remotely, has a positive impact on approval performance, particularly in intermediate tasks.

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INTRODUCTION

Robotic technology has been used during surgery for approximately 30 years. However, its use during urologic surgery has grown significantly over the last decade due to improvements in visualization and precision compared to standard laparoscopy (1).

Robotic training programs in developing countries differ from those in the United States and Europe. For example, there are few or no uniform or well-established resident or fellowship training programs for young surgeons interested

in robotics. Busato et al. demonstrated that robotic surgery is still largely uncharted territory for far from Brazilian residents (2). Meanwhile, in other countries, robotic knowledge is currently at urology objective structured clinical examinations (OSCEs) stages (3). Surgical education has recently undergone a paradigm shift towards competency--based frameworks, highlighting the need for surgical training, evaluation, and certification (4).

In developing countries, higher-volume robotic centers are mainly concentrated in large cities, forcing most expert surgeons to travel for proctoring, which is a strain on already limited time and resources and, even worse, this limits the dissemination and development of robotic surgery in these countries (5, 6).

To reduce inequalities in health resources in Brazil, programs such as the Institutional Development Program of the Unified Health System (*Programa de Desenvolvimento Institucional do Sistema Único de Saúde – PROADI-SUS*) have been developed since 2008. Among these programs, telemedicine stands out, in which high-tech hospitals remotely connect with health units to support them through the exchange of knowledge, information, and experiences. De Souza et al. demonstrated that telemedicine is an excellent tool for disseminating knowledge about these services (7). As our service is part of the PROADI-SUS project from an important robotic surgery center, we saw the opportunity to combine these fronts.

Inanimate and virtual reality simulations have played a significant role in robotic surgery training, and studies have shown that basic robotic skills can be transferred from simulators to the operating room (3, 8). The da Vinci Surgical Skills Simulator (dVSSS) of the da Vinci robotic surgical system™ (Intuitive Surgical, Inc.) is a validated virtual training system that allows repetitive skill training at different pre-determinate proficiency levels. It provides trainees with timed scores (9), which can help enhance the learning curve.

A user-friendly telementoring platform may play an essential role as a tool to share expertise and spread knowledge (10), allowing larger centers to assist smaller ones in improving safety and shortening the learning curve. Our institution currently has an established program of telementoring in emergency and critical care medicine, and we sought to build on that expertise.

The telementoring platform we describe herein could provide a final "testing" for the surgical trainee prior to embarking on actual live surgery. Moreover, it can be used as a means to share experiences in complex and rare cases.

We hypothesized that remote guidance using the dVSSS exercises would positively impact the performance score required by urology residents and young urologists. We aimed to validate a telementoring system using the dVSSS with the specific goal of hastening the training process with simulators for novice and intermediate surgeons.

Objective

This study aimed to evaluate the role of remote proctoring during the initial training phases of a robotic curriculum using dVSSS exercises performed by urological residents and junior attending-level urologists.

MATERIAL AND METHODS

A prospective, randomized study of remote proctoring in simulation training was conducted at the *Hospital Israelita Albert Einstein*, São Paulo, SP, Brazil, from March 2016 to August 2017. The study was approved by the Research Ethics Committee of the *Hospital Israelita Albert Einstein* (IRB number 62289516.0.0000.0071). Each participant enrolled in this study signed an informed consent form for the survey and agreed to the use of the related data for research purposes.

The participants were urology residents and junior staff urologists who had no previous contact with the robotic platform. Thirty-six participants were included in the study; 12 in each group. Of the participants, 18 were residents of the first and second years of medical residency in urology, and 18 were residents of the third year of medical residency in urology or junior staff urologists. Two surgeons were excluded from the study because of previous contact with the robotic platform. Only one proctor was included in the study who participated as an in-person proctor (Group 2) and telementoring proctor (Group 3).

All participants enrolled in the study received a standardized oral orientation and demonstration of the management and use of the robotic platforms, with details on the correct management of the console and simulator. Subsequently, participants completed an initial basic training protocol consisting of five exercises in the dVSSS (Camera Targeting 1, Camera Targeting 2, Ring Walk 1, Energy dissection 1 and Play Ground). Each exercise was performed thrice (11). To set the exercises and number of repetitions, a pilot study was conducted with five urology residents without any familiarity with the robotic platform, and three experts. Based on the results of this study, we selected the exercises and number of repetitions in consensus among the authors. We determined the difficulty level, exercises, and repetitions for this study based on the literature and our experience (9).

The participants underwent simple randomization by lottery into three groups. Group 1 (G1) performed the exercises without assistance or support. Group 2 (G2) had support from an in-person proctor. Group 3 (G3) was supported by a remote proctor through a telementoring system, as described below (AdobeConnect®).

Only one proctor was proficient in performing dVSSS exercises and was consistent throughout the training exercises. He only provided oral advice.

After randomization, three exercises were performed three times each to evaluate skill progression. These were the low-difficulty Ring Walk 2 (RW2), intermediate-difficulty Energy Dissection (ED2), and high-difficulty Ring Walk 3 (RW3).

Outcomes and Performance evaluation

Qualitative (the participant reaches proficiency or not, "overall score approval rate") and quantitative (overall score: 0–100 points) proficiency evaluations were performed for each attempted exercise using the dVSSS scoring system. In addition, the time taken to complete the exercise, economy of motion, instrument collisions, excessive force applied to an instrument, instruments out of view, master workspace range, and drops were recorded and analyzed.

Telementoring system

The telemonitoring system consisted of two stations: a compatible computer and high-quality internet connection for the remote proctor, and a telemonitoring cart connected to the robot for the surgeon. The image from the robot went to the cart, which was connected via AdobeConnect®. Through the internet, the proctor could access this image and provide remote support, which consisted of the same oral advice as in G2.

AdobeConnect® was the system used for communication between the research candidate and the remote proctor. It provides a very good image quality with a short delay (1 s). This system is commonly used in Brazil and elsewhere for teaching conferences, and an additional advantage is that only one center is required to own the software.

Basic IT hardware was employed: a PC running Windows 7 (Intel i3, 4 GB RAM, HD 80 GB), graphics board set at 1280 × 1024 resolution, network card with a minimum connection speed of 100 Mbps, Internet Explorer version 9.0, monitor with a resolution of 1280 × 1024, and audio system with a microphone and headset.

Statistical Analysis

We used the chi-square test to compare the groups regarding participants' degree of training. To investigate the effects of the attempt, group, and degree of training, we used generalized estimation equations. We compared the performance in the different groups separately, using the Friedman and Kruskal–Wallis tests. In cases of significant differences, multiple comparisons were performed using the Bonferroni's method. The analyses were carried out on SPSS, version 24.

RESULTS

Table-1 summarizes the data of the study participants. The participants were predominantly men, and only one participant had a left-predominant hand. The groups studied had similar levels of training (p=0.717, chi-square test), number of surgeries performed per month (p=0.913, Fisher's exact test), and age (p=0.986, variance analysis).

Table 1 - General characteristics of the participants according to groups.

Variables	Group 1 (no proctor)	Group 2 (in person proctor)	Group 3 (telementoring proctor)
N	12	12	12
Gender			
Male	11 (91.7%)	12 (100.0%)	8 (66.7%)
Female	1 (8.3%)	0 (0.0%)	4 (33.3%)
Dominant hand			
Right	11 (91.7%)	12 (100.0%)	12 (100.0%)
Left	1 (8.3%)	0 (0.0%)	0 (0.0%)
Degree of training 1			
R3	0 (0.0%)	5 (41.7%)	2 (16.7%)
R4	6 (50.0%)	2 (16.7%)	3 (25.0%)
R5	3 (25.0%)	3 (25.0%)	6 (50.0%)
Urologist	3 (25.0%)	2 (16.7%)	1 (8.3%)
Degree of training 2			
R3+R4	6 (50.0%)	7 (58.3%)	5 (41.7%)
R5 + Urologist	6 (50.0%)	5 (41.7%)	7 (58.3%)
Numbers of surgeries performed per month			
≤ 4	3 (25.0%)	6 (50.0%)	6 (50.0%)
≥ 5 or ≤ 7	5 (41.7%)	3 (25.0%)	2 (16.7%)
> 7	4 (33.3%)	3 (25.0%)	4 (33.3%)
Age			
Mean (SD)	31 (2)	31 (4)	31 (2)
Min-Max	28 - 37	26 - 40	28 - 36

R3 = First year of medical residency in Urology; **R4** = second year of medical residency in Urology; **R5** = Third year of medical resindecy in Urology.

The most common corrections were to improve the use of the Endowrist manipulation, improve the use of both hands, keep the instruments close to each other, avoid leaving the camera too close, and avoid keeping the instruments out of view.

We observed differences in difficulty between the exercises. We observed differences in difficulty between the exercises. Considering the attempts, the first attempt showed RW2=64%, ED2=53% and RW3=8%; the second attempt showed RW2=69%, ED2=72% and RW3=11%; and the third attempt showed RW2=83%, ED2=81% and RW3=14%; respectively. Based on the overall score approval rate (OSA), RW3 provided a significantly greater degree of difficulty than other exercises on the third attempt (OSAs: RW2= 83%, ED2=81%, RW3=14%) (Appendix: Supplementary Table-1).

We also observed different levels of performance regarding the number of attempts. The

OSA increased significantly with the number of attempts only in RW2 and ED2. The RW2 OSA was higher on attempt 3 than on attempt 1 (83.3% vs. 63.9%, p=0.032). The ED2 overall score approval rate was higher in attempt 2 than in attempt 1 (72.2% vs. 52.8%, p=0.048) and in attempt 3 than in attempt 1 (80.6% vs. 52.8%, p=0.002). There was no significant difference in the OSA with respect to different attempts at RW3 (Table-2).

We found different performance levels between the groups in the analysis of telementoring impact (Table 3). On ED2, both remote and live assistance were significantly related to upper OSA (G1 = 47.2%, G2=75.0%, G3=83.3%, p=0.002). The RW2 and RW3OSAs were similar among the groups. However, in a sensitive quantitative analysis, the mean overall score of the participants in RW3 was higher in both proctored groups (G1=24%, G2=57,5%, G3=51,5%, p=0,042).

DISCUSSION

Significant technological progress has been achieved in minimally invasive surgery using the Da Vinci® robot, and robotic surgery is successfully and reliably applied in the treatment of urological cancers (4, 11-13). Robotic prostatectomies have been introduced with the expectation of minimizing perioperative and postoperative complications, providing three-dimensional magnification and tools with seven degrees of freedom that can duplicate hand movements. However, the absence of tactile feedback and high costs are disadvantages that still need to be overcome (11).

In developing countries, this robotic platform is restricted to a few large centers (5), and the system costs and time required for robotic surgery training are major challenges that likely limit the expansion of robotic surgery (13). Telemedicine has been used to overcome distance barriers and improve access to medical services that are not consistently available in distant communities (7).

This study aimed to evaluate the role of remote proctoring during the initial training phases of a robotic curriculum using dVSSS exercises performed by urology residents and junior attending-level urologists. We observed that telementoring for novice robotic surgeons, either in-person or remotely, positively impacted performance

Table 2 - Overall score for all participants along multiple attempts in each exercice.

Overall score	Attempt			p-value	
	1st	2nd	3rd	1st x 2nd	1st x 3rd
RW2 approval	23 (63.9%)	25 (69.4%)	30 (83.3%)	0.528	0.032
ED2 approval	19 (52.8%)	26 (72.2%)	29 (80.6%)	0.048	0.002
RW3 approval	3 (8.3%)	4 (11.1%)	5 (13.9%)	0.705	0.417

ED2 = Energy Dissection 2; RW2 = Ring Walk 2; RW3 = Ring Walk 3

Table 3 - Impact of the Telementoring.

Overall Score Approval	Groups			p-value	
	G1	G2	G3	G1 vs. G2	G1 vs. G3
RW2	26 (72.2%)	27 (75.0%)	25 (69.4%)	0.769	0.703
ED2	17 (47.2%)	27 (75.0%)	30 (83.3%)	0,005	0.002
RW3	3 (8.3%)	1 (2.8%)	8 (22.2%)	0.387	0.086

ED2: Energy Dissection 2; RW2: Ring Walk 2; RW3: Ring Walk 3.

score required by, particularly when learning intermediate simulation tasks. In ED2, both remote and live assistances resulted in significantly upper OSA (G1=47.2%, G2=75.0%, G3=83.3%; p=0.002).

Proctoring (in-person or remote) had no impact on high- and low-difficulty tasks. The RW2 OSA was similar between groups. RW3 had similar OSA among the groups, which can be explained by the high level of difficulty and low OSA in all groups, suggesting that telementoring may be helpful for beginner surgeons in allowing for more rapid attainment of higher skill levels.

We believe that by using telemedicine equipment and platforms as a means to spread knowledge, telementoring may play an essential role in the vital early step of the learning process (14). This early step is one where novice surgeons develop habits, whether helpful or harmful, that can persist throughout their learning process and even, conceivably, throughout their careers. Our study suggests that this system can augment the positive effects of simulators on the learning curve (9).

A recent review of telementoring and telesurgery categorized 38 studies into four advancing levels: verbal guidance, guidance with telestration (indicating target areas on the local monitor screen), guidance with tele-assisted surgery (controlling the operative camera or an instrument via robotic arms), and telesurgery (performing surgery remotely). Eight studies on telementoring with verbal guidance were included which reported the following related advantages: low-cost, widely available equipment, mature technology, and lower network bandwidth requirements (15). This is the first prospective and randomized study to evaluate telementoring with verbal guidance in robotic surgery training using objective dVSSS data. Additionally, we found that it is possible to build a useful mentoring system using basic infrastructure and widely available Internet services.

One prospective but not randomized trial of endovascular surgery evaluated verbal guidance (16), and other studies involved a series of patients who underwent laparoscopic and robotic procedures (17-22). Our easy-to-reproduce telementoring system allowed us to demonstrate that simple instruction from a mentor in the form of verbal guidance can be effective in teaching surgical skills remotely. Hung et al. concluded that safety, legal, financial, economic, and ethical concerns persist, for more advanced interactions (through surgical telementoring and telesurgery) to be fully adopted and clinically integrated (16).

Despite the efforts of numerous organizations, a consensus for training, credentialing, and assessment of competency in robot-assisted urologic surgery has not yet been achieved, even in developed countries (23). One of the main barriers to expanding robotic expertise in Brazil is because of its limited number of surgical simulators and proctors. Most of the 60 da Vinci robots in Brazil are concentrated in the São Paulo area. Moreover, proctors must travel to assist surgeons throughout the country; this implies a significant strain on resources.

The limitations of our study include the small number of participants in each group and the number of exercises performed. Additional information could have been obtained by adding cameras showing the actual movements of the trainees at the console, and/or recording the actual advice given by the proctor. Moreover, the participation of only one proctor can have influence in the results, by some inherent biases from this professional, such as bias in surgical practice, teaching and communication skills, due to proctor medical training, and others. A larger number of students and proctors are recommended in future studies.

Telementoring assistance can be used to provide support and increase surgeon confidence during either primary proctoring or follow-ups (24). This might allow for greater access to the limited number of trained robotic surgeons and improvements in mentoring for unusual surgeries (4).

CONCLUSIONS

As expected, repetitive training increases the success rate of surgical robot skills. Our study showed that proctoring through telementoring, either in-person or remotely, positively impacts performance, especially with the intermediate-difficulty tasks of the dVSSS simulator. Telementoring proved to be as efficient as in -person proctoring.

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CONFLICT OF INTEREST

None declared.

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APPENDIX: Supplementary Table-1. dVSSS scores.

		OSA (%) RW2			OSA (%) ED2			OSA (%) RW3		
ID	Group	First attempt	Second attempt	Third attempt	First attempt	Second attempt	Third attempt	First attempt	Second attempt	Third attempt
1	3	84	91	84	79	95	100	71	85	62
2	3	96	98	99	95	89	96	90	73	72
3	2	94	99	100	86	95	93	70	77	18
4	1	31	27	67	59	69	62	0	0	36
5	1	92	76	94	83	79	89	42	41	42
6	2	67	68	74	78	99	96	44	35	70
7	3	77	84	90	80	69	82	43	29	59
8	1	81	67	78	65	78	84	25	37	49
9	2	59	75	88	51	82	88	50	42	68
10	2	44	88	95	83	94	98	73	63	65
11	2	88	96	86	98	48	73	70	61	73
12	1	85	82	51	86	96	97	21	44	37
13	1	58	87	90	48	64	52	0	29	62
14	3	97	94	93	91	95	95	86	79	94
15	3	94	95	90	79	83	88	23	48	54
16	2	68	91	87	63	77	87	67	41	73
17	1	85	92	99	69	71	85	23	73	91
18	2	89	91	98	94	96	99	57	50	63
19	1	88	92	96	81	89	96	40	61	41
20	1	86	91	87	92	100	95	22	48	53
21	2	80	67	85	78	80	68	18	48	39
22	2	96	91	90	97	96	98	82	79	75
23	3	80	86	95	53	90	95	45	80	70
24	2	93	91	98	71	86	96	58	65	62
25	1	93	92	97	79	79	79	33	87	79
26	3	59	68	59	86	88	93	0	7	31
27	3	40	68	63	78	100	95	0	14	68
28	1	88	94	91	75	74	77	78	74	80
29	3	96	98	94	88	88	89	73	77	85
30	3	75	96	91	78	82	85	58	76	57
31	3	70	79	92	81	100	86	15	51	16
32	1	90	92	94	81	98	87	60	67	66
33	3	77	94	89	86	90	98	73	88	87
34	2	94	70	98	97	89	95	45	25	30
35	1	36	42	80	71	87	79	12	0	26
36	2	80	88	89	86	95	100	53	76	46

ID = Participant identification; Group 1 = no proctor; Group 2 = in person proctor; Group 3 = telementoring proctor; OSA = overall score approval; ED2 = Energy Dissection 2; RW2 = Ring Walk 2; RW3 = Ring Walk 3.

ORIGINAL ARTICLE

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Multicenter comparative study of open, laparoscopic, and robotic pyeloplasty in the pediatric population for the treatment of ureteropelvic junction obstruction (UPJO)

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ABSTRACT

Introduction: Dismembered open pyeloplasty described by Anderson and Hynes is the "gold standard" for the treatment of ureteropelvic junction obstruction. The aim of our study was to compare the results of open (OP) vs laparoscopic (LP) vs robotic (RALP) pyeloplasty.

Material and Methods: A multicenter prospective review was conducted of pyeloplasty surgeries performed at five high-volume centers between 2014 and 2018. Demographic data, history of prenatal hydronephrosis, access type, MAG3 renogram and differential renal function, surgery time, length of hospital stay, and complication rate (Clavien-Dindo) were recorded. Access type was compared using the Kruskal-Wallis, Chi-square, or Fisher's exact tests.

Results: A total of 322 patients were included: 62 OP, 86 LP, and 174 RALP. The mean age was 8.13 (r: 1-16) years, with a statistically significant lower age (mean 5 years) in OP ($p < 0.001$). There were no significant differences in the distribution of the side affected. Operative time was 110.5 min for OP, 140 min for LP, and 179 min for RALP ($p < 0.0001$). Hospital stay was significantly shorter in the RALP group than in the other groups ($p < 0.0001$). There were no differences in postoperative complications and reoperations between the three groups.

Conclusions: Minimally invasive surgery for the management of UPJO in children is gaining more acceptance, even in patients younger than 1-year-old. Operative time continues to be significantly shorter in OP than in LP and RALP. Hospital stay was shorter in RALP compared to the other techniques. No differences were found in complication rates, type of complications, and reoperation rate.

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INTRODUCTION

Open dismembered pyeloplasty (OP), originally described by Anderson and Hynes, is the most commonly performed surgical procedure for the treatment of ureteropelvic junction obstruction (UPJO), with long-term success rate of around 95% (1, 2). Over the last two decades, however, minimally invasive surgery (MIS) techniques such as laparoscopic pyeloplasty (LP) and robot-assisted laparoscopic pyeloplasty (RALP) have been developed and popularized as a standard of care in common practice.

Since its first description by Peters et al., laparoscopic pyeloplasty has not been as popular in pediatric urology as in the adult population possibly due to its technical difficulty and long learning curve, and better recovery in children compared to adults (3, 4).

Although MIS techniques are associated with a longer operative time compared to open procedures, they have shown benefits in terms of shorter postoperative hospital stay and lower morbidity (4-6). Nevertheless, LP is technically demanding and has a long learning curve (7, 8). RALP has reduced the technical difficulty of this procedure with a shorter learning curve compared to LP (9-13). Therefore, we believe that the three techniques should have similar outcomes.

The aim of this study was to compare outcomes in safety and effectiveness between OP, LP, and RALP in a large, multicenter cohort of pediatric patients with UPJO.

MATERIAL AND METHODS

The study was approved by the Ethics Committee of each Hospital (IRB: 18967819.8.0000.5327).

A multicenter retrospective cohort study was conducted with prospectively collected data. We included pyeloplasty surgeries (including redo cases) performed in children younger than 16 years of age between 2014 and 2018. The choice of OP, LP, and RALP were due to the surgeon and center preference, and the techniques were compared in terms of safety and effectiveness.

After IRB approval, medical records of all patients with a history of UPJO were reviewed evaluating the following characteristics: age at surgery, sex, affected side, history of urinary tract infection (UTI), flank pain, operative time (skin incision to skin closure -port removal in LP and RALP -, in minutes), type of stent placement during the surgery and length of hospital stay (determined by the computerized time recorded on hospital admission and discharge records).

Indications for surgical intervention were impairment of differential renal function (< 40%) by nuclear scan or a decrease in split renal function of > 10% on subsequent studies, obstructive drainage curve on diuretic renogram, symptomatic obstruction (recurrent flank pain, UTI), and progressive worsening of hydronephrosis on ultrasound images (urinary tract dilation - UTD - classification system) (14). Each institution's registered technique is routinely performed outside the learning curve.

Complications were assessed using the Clavien-Dindo grading system (15). Post-surgical patients were followed-up with ultrasonography every 3 months during the first year of surgery, every 6 months in the second year, and then on an annual basis. Patients were defined as having a good outcome when SFU grade hydronephrosis improved without symptom recurrence. In patients in whom SFU grade decreased but was still greater than 2, we performed a MAG3 renal scan to rule out obstruction.

Continuous variables are expressed as mean, or median and range and categorical variables are expressed as absolute value and/or percentage. For comparison between techniques, the Kruskal-Wallis, Chi-square, or Fisher's exact tests were used depending on the case. In the case of multiple comparisons, they were adjusted using the Bonferroni correction method. In all cases, a p-value of less than 0.05 was considered as a cut--off for a significant value. SPSS 22.0™ software was used.

Surgical technique

a. OP: a subcostal flank or dorsal lumbotomy approach was used. Conventional dismem-

bered pyeloplasty was performed with a running polydioxanone (6/0 PDS® II) anastomotic suture. The bladder catheter was removed 24 hours later. A ureteral stent or nephrostomy tube was used only in select cases and a perirenal drain was left in place in all patients.

b. LP: transperitoneal dismembered pyeloplasty was performed using 3 ports (one 5- or 10-mm port for the 30-degree optics and two 3- or 5-mm ports for the instruments). A running (5/0 PDS® II) anastomotic suture was placed, and a ureteral double J stent was placed in an antegrade fashion in all patients. The Foley catheter was removed on postoperative day 1 or on the next morning.

c. RALP (4 trocars): an infraumbilical port was used for the optics (8.5–12 mm), an 8-mm working port in the epigastric region, another 8-mm working port below the optic port laterally to the midline in the right / left iliac fossa, and an assistant port (5 mm) was placed between the optic port and the lower working port (left pyeloplasty) or between the optics and the upper working port to lift the liver (right pyeloplasty) for the introduction of the suture, retraction, or suction.

RALP (3 trocars): 3 midline trocars (8 mm) were used, one for the camera at the umbilicus and the others at least 4 cm above and below the umbilicus, respectively.

The bladder catheter was removed 24 hours later. Ureteral stents, when placed, were removed approximately 4 weeks postoperatively via cystoscopy using short-acting anesthesia. In a group of patients in whom the stent was placed in a retrograde fashion and a string was left in the genitalia, the stent was removed in the clinic 2-3 weeks postoperatively.

RESULTS

A total of 322 patients were included in the study: 62 OP, 86 LP, and 174 RALP. The mean age was 8.1 years (range 1-16). Children that underwent OP were younger than those undergoing procedures with the other techniques ($p < 0.001$ – Table-1). Demographic data analysis showed that in the RALP group female patients prevailed ($p < 0.001$). There were no significant differences regarding the distribution of the affected side between the three groups (Table-1).

The majority of the patients were older than 6 years (64%, 206 patients). Table-1 shows the most used technique according to age

Table 1 - Sex, Age and Side of UPJO of patients submitted to open, laparoscopic and robotic pyeloplasty.

	OP (n=62)	LP (n=87)	RALP (n= 161)	p
Sex: Female (%)	18 (29)	31 (36)	95 (54,6)	0.0001
Age: mean (range)	5 (1 – 15)	10.5 (1-16)	8.9 (1 – 16)	0.0001
< 1 year (%)	20 (32.3)	2 (2.3)	9 (5.2)	
1-6 years (%)	22 (35.5)	13 (15.1)	50 (28.7)	
> 6 years (%)	20 (32.3)	71 (82.6)	115 (66.1)	
Side (%)				0.469
Right	27 (43.5)	29 (33.7)	74 (42.5)	
Left	35 (56.5)	57 (66.3)	98 (56.3)	
Bilateral	0	0	2 (1.1)	

OP = Open Pyeloplasty; **LP** = Laparoscopic Pyeloplasty; **RALP** = Robotic-assisted laparoscopic pyeloplasty

group; OP was more commonly used in children younger than 1 year and LP in patients older than 6 years. In the intermediate group, OP and RALP were more commonly used than LP.

Operative time was shorter in the OP group (110.48 min vs 140 min for LP and 179 min of RALP). On the other hand, hospital stay was shorter in the RALP group in comparison with the LP and OP groups ($p < 0.0001$). There were no significant differences in postoperative complications or reoperation rate. A ureteral stent was placed during surgery in almost all patients undergoing MIS, exceeding the rate of stent placement in OP ($p < 0.0001$) (Figure-1 and Table-2).

In only 5 patients (1.55%) UPJO recurred after a median follow-up of 42.3 months. In these patients, SFU grade decreased but was still greater than 2. MAG3 renal scan confirmed the obstruction (Table-2).

When analyzing complication rate (n=51) according to initial vs redo procedures, Clavien-Dindo grades IIIb to V were found to be mostly associated with redo surgeries with a statistically significant difference.

DISCUSSION

In our study, RALP and LP proved to be safe and successful methods, with several advantages over OP. While operative time was longer, hospital stay was shorter. As shown in previous studies (16, 17) operative time was longer in RALP than in LP and OP. A contributing factor may have been older age, which has been shown to be associated with operative time (16) in the RALP group.

The first important outcome to be considered after minimally invasive pyeloplasty is the success of the procedure. In a meta-analysis, Cundy et al. compared RALP, LP, and OP in children. Twelve articles were included of which five were cohort and seven case-controlled studies. Success rates of higher than 95% were reported for RALP and LP, whereas in the comparative studies of RALP and OP included, success rates were higher than 87% and the procedures were found to be comparable (18). Another meta-analysis by Huang et al. compared the outcomes of LP and OP in children. One randomized controlled trial and 15 comparative studies were included in the analysis. Success rates of both procedures were between 83 and 100% and were found to be comparable (19). In our series, the success rates were higher than 95% and no statistically significant difference was observed regarding success between the procedures.

In infants, the operation may be more challenging due to the limited space; (19) however, RALP has recently been successfully performed in infants, with an operative time that was even shorter than that of OP (20, 21). Other techniques such as the Flexdex® articulating needle driver may facilitate the procedure (22).

Postoperative hospital stays of patients undergoing RALP and LP were shorter compared to open surgery. Since the children had no underlying conditions (comorbidities), the length of hospital stay was a reasonably good measure of the trauma caused by the surgery. A reduced length of hospital stay with RALP/LP has previously been shown and is of major importance, both for the patient and caregivers and for the hospital (23).

No statistical difference was found between the three groups regarding complication rate. Compared to other studies reporting complication rates of 0–33% for RALP (24), our results were in the lower range (0-18%). In addition, most complications were stent-related and transient, with only 14/322 (4.3%) patients requiring a second surgical intervention. It seemed that postoperative complications, especially those related to pyelonephritis and stent morbidity, increase the risk of needing secondary repair. On the other hand, it is possible that not the complications per se increased the risk for reoperation, but that the complications were an indication of an already distorted healing process related to either the surgery or factors inherent to the patient. Complications rates were higher in the redo surgeries group, but some studies showed that other techniques such as endopielolitotomy have a greater failure rate (25).

In a prospective comparative case-control study (OP vs LP), Piaggio et al. (26) described four

Figure 1 - Comparison of surgical time and hospital stay in open, laparoscopic and robotic pyeloplasty.

Figure 1A. Surgical Time.

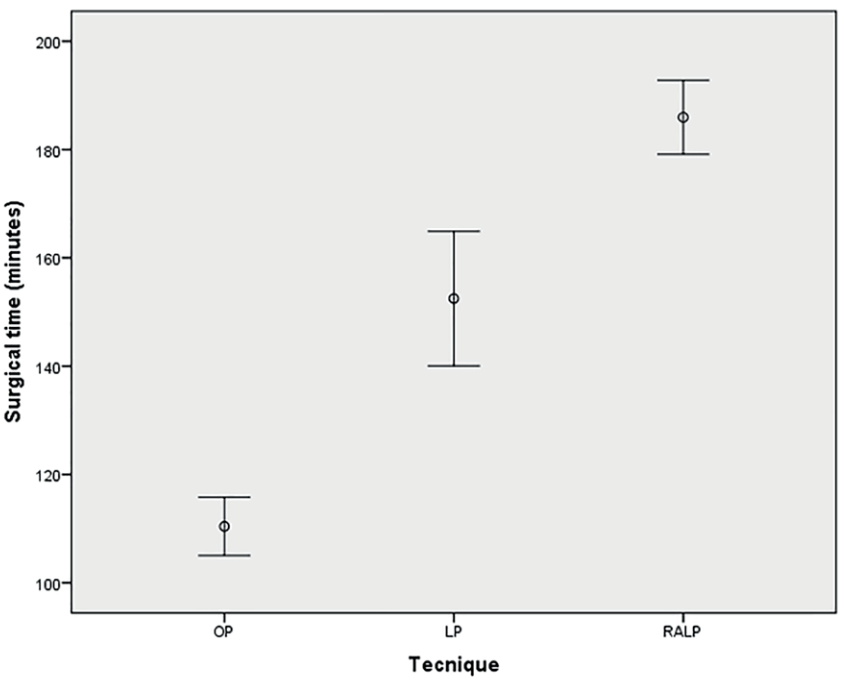
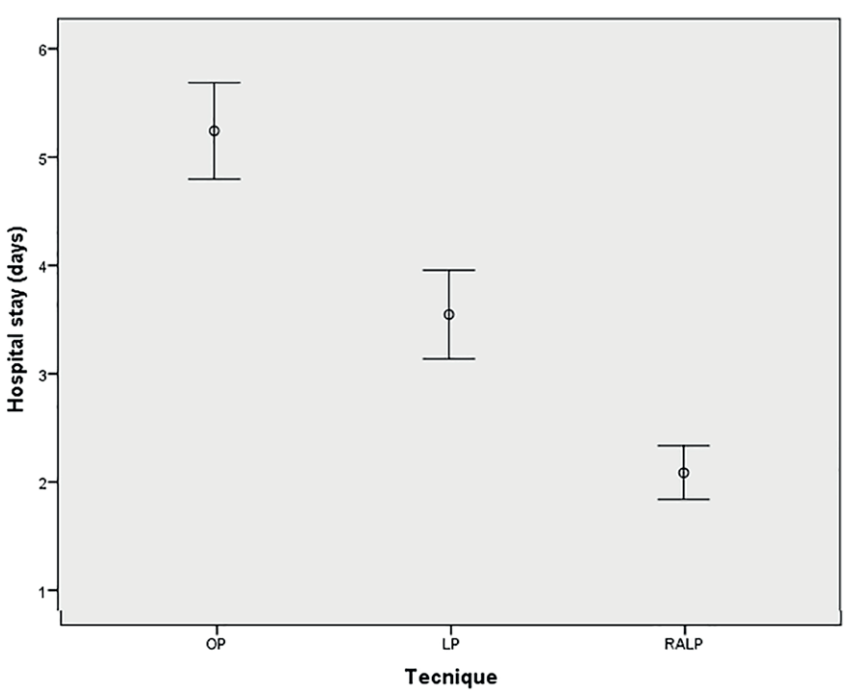


Figure 1B. Hospitay Stay



OP = Open Pyeloplasty; LP = Laparoscopic Pyeloplasty; RALP = Robotic-assisted laparoscopic pyeloplasty

Table 2 - Surgery outcomes and complications' rate of patients submitted to open, laparoscopic and robotic pyeloplasty.

	OP (n=62)	LP (n=86)	RALP (n=174)	p
Transfusion (%)	0	0	0	NS[1]
Operative time, median (min.)	110 (60-210)	140 (60-316)	179 (108-361)	p = 0.0001
Stent (%)	22 (35.5%)	83 (96.50%)	174 (100%)	p = 0.0001
Length of hospital stay, median (days)	5 (3 – 13)	3 (1-12)	1 (1-11)	p = 0.0001
UPJO recurrence (n)	1	2	2	NS
Follow-up months median (range)	57.8 (7-136)	41.1 (3-87)	44.6 (3-140)	

OP = Open Pyeloplasty; LP = Laparoscopic Pyeloplasty; RALP = Robotic-assisted laparoscopic pyeloplasty; UPJO = Ureteropelvic Junction Obstruction
NS = non-significant

complications in the LP group: febrile UTI (two), double J stent disruption, and meatal stenosis (one each); and three in the OP group: febrile UTI, flank pain due to stent displacement, and persistent gross hematuria (one each). Two patients in the LP group and one in the OP group needed additional procedures (p > 0.05): meatoplasty and ureteroscopy for stent removal (LP) and stent repositioning (OP).

The optimal age is one of the concerns for the use of LP in children. It is generally believed that it is difficult to perform LP in small children due to the risk of pelvic perforation when introducing the trocars. Excellent intracorporeal laparoscopic suturing skills are imperative in limited spaces (27). In our series, no significant differences were found when comparing reoperations and/or complications according to age.

In a systematic review, only two studies presented the age of the patient as mean +- SD (28). The analysis showed that patients who underwent LP were significantly older (50.90 months) than those who underwent OP. The authors of the seven remaining studies also found that patients in the LP group were older than those in the OP group. Other authors, however, reported similar or even younger ages in the LP group compared to the OP group (29, 30).

The main strength of this international multicenter study is the large number of patients showing good effectiveness of the procedure regardless of the technique (OP, LP, or RALP) or age. No significant differences were found when comparing with reoperations and/or complications according to age.

This study has some limitations, especially due to the retrospective design, but this is a multicenter study in the Ibero-american scenario with a significant number of patients. The difference in age between the groups could be a selection bias that could affect the results. Also, in pediatric urology controversy remains regarding what patients with hydronephrosis require surgery and what clinical and imaging methodology should be selected to define recurrence of UPJO.

CONCLUSIONS

Open, laparoscopic, and robotic-assisted pyeloplasty in the pediatric population have similar success rates and are safe to perform, even in children less than 1-year-old where traditionally open pyeloplasty is more performed. No differences were found in complication rates, type of complications, and reoperations between the three groups. Operative time was shorter in the OP. Severe complications required a greater number of reoperations.

More studies are needed to evaluate RALP, especially in infants. In addition, aspects,

such as surgical costs and patient satisfaction, should be further assessed.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Minimally invasive surgery for pyeloplasty poised to become The preferred surgical technique irrespective of age

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COMMENT

For a minimally invasive surgery (MIS) technique to become mainstream and perhaps overtake the open technique as the gold standard it must achieve a couple of goals. First and foremost, it must have a similar or better success rate, after all, adequate treatment of the condition is the main goal. If the success rate is at least similar, it must provide an advantage either by a decrease in the complication rate or the recovery period. Finally, providing a benefit from the cosmetic endpoint can also lead to it becoming the preferable approach. By using a multi-institutional approach, with a large number of patients, the present study highlighted the main reasons why the minimally invasive is becoming the preferable option to perform a pyeloplasty (1). This study showed that the MIS approach both laparoscopically and robotically achieved similar success and complication rates but provided a benefit in the recovery with a shorter hospital length of stay.

While using this multi-institutional approach is a significant strength of the manuscript, it does add one possible weakness. The different institutions likely have different post-operative protocols mostly based on the surgeon's preference. They may or may not be using enhanced recovery after surgery (ERAS) protocols. Furthermore, it is not clear in the manuscript that the techniques were evenly distributed among institutions. These differences could partly influence the findings regarding hospital stay, specifically the fact that robotic technique had a shorter hospital stay than even laparoscopy. It would be expected that both MIS techniques to have similar recovery as shown in a recent single institutional series (2). Nevertheless, the findings in this manuscript described above are on par with another multi-institutional series showing that improved hospital length of stay is associated with the robotic technique (3). These findings appear to also hold even for the younger patients, making MIS for pyeloplasty poised to become the preferred surgical technique irrespective of age.

CONFLICT OF INTEREST

None declared.

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Co-administration of sodium hydrosulfide and tadalafil modulates hypoxia and oxidative stress on bladder dysfunction in a rat model of bladder outlet obstruction

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ABSTRACT

Purpose: This study aimed to assess the possible healing effect of combination treatment with a hydrogen sulfide (H2S) donor, sodium hydrosulfide (NaHS) plus tadalafil on partial bladder outlet obstruction (PBOO)-induced bladder dysfunction.

Materials and Methods: A total of 75 male Sprague-Dawley rats aged 10-wk and 300-350g were divided into five groups; control; PBOO; PBOO+NaHS (5.6mg/kg/day, i.p., 6-wk); PBOO+tadalafil (2mg/kg/day, oral, 6-wk) and PBOO+NaHS+tadalafil. PBOO was created by partial urethral ligation. 6 weeks after obstruction, the in vitro contractile responses of the detrusor muscle and Western blotting, H2S and malondialdehyde assay were performed in bladder tissues.

Results: There was an increase in bladder weight($p<0.001$) and a decrease in contractile responses to KCl ($p<0.001$), carbachol ($p<0.01$), electrical field stimulation ($p<0.05$) and ATP ($p<0.001$) in the detrusor smooth muscle of obstructed rats which was normalized after the combination treatment. Cystathionine -lyase and cystathionine -synthase, and nuclear factor kappa B protein levels did not significantly differ among groups. The obstruction induced decrement in 3-mercaptopyruvate sulfur transferase protein expression($p<0.001$) and H2S levels($p<0.01$) as well as increment in protein expressions of neuronal nitric oxide synthase (NO, $p<0.001$), endothelial NOS ($p<0.05$), inducible NOS($p<0.001$), hypoxia-inducible factor 1-alpha ($p<0.01$), and malondialdehyde levels ($p<0.01$), when combined treatment entirely normalized.

Conclusions: Combination therapy has beneficial effects on bladder dysfunction via regulating both H2S and nitric oxide pathways as well as downregulation of oxidative stress and hypoxia. The synergistic effect of H2S and nitric oxide is likely to modulate bladder function, which supports the combined therapy for enhancing clinical outcomes in men with BPH/LUTS.

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INTRODUCTION

Lower urinary tract symptoms (LUTS), including storage, voiding and postmicturition symptoms, are widespread clinical conditions in older men and concurrent with bladder outlet obstruction (BOO) as a consequence of benign prostatic hyperplasia (BPH) (1). Tadala-

fil is the only phosphodiesterase type-5 inhibitor (PDE5i) approved for treating moderate to severe LUTS/BPH (2). A previous study showed that tadalafil improved blood flow of the bladder as well as functional and histological alterations in the partial BOO (PBOO) rat bladder (3).

A gasotransmitter, hydrogen sulfide (H_2S) is endogenously synthesized by cystathionine β-synthase(CBS), cystathionine γ-lyase(CSE) and 3-mercaptopyruvate sulfurtransferase(3-MST) (4). H_2S has various roles, including neuromodulation, smooth muscle cell regulation with its antioxidant activity and anti- or pro-inflammatory effects (5). H_2S displays a species-specific difference or diverse site-specific effects on bladder contractility (5). Studies reported that H_2S and its donors induced relaxation in the human and rat bladder (6, 7).

The precise mechanisms leading to improving pathological components in LUTS remain unclear. Previous data suggest that obstruction leads to structural and functional changes, including urodynamic parameters (8). Furthermore, numerous studies assessed the effects of PBOO on morphologic changes and physiologic mechanisms in the bladder without *in vivo* urodynamic data (9, 10).

Previous data revealed that PDE5i could act through several mechanisms to suppress LUTS. It has also been demonstrated that H_2S was an endogenous inhibitor of PDE (11).In addition, a PDE5i, sildenafil relaxes human bladder strips and, at similar doses, induces H_2S production in a concentration- and time-dependent manner (7).

We hypothesized that the improvement in the nitric oxide(NO)/cGMP and H_2S signaling could ameliorate bladder dysfunction secondary to the obstruction. This study is aimed to elucidate the effects of either a donor of H_2S, sodium hydrogen sulfide (NaHS) or a PDE5i, tadalafil treatment alone or in combination on bladder dysfunction in rats with obstructed bladder.

MATERIALS AND METHODS

Animals

All experimental procedure of the animals was approved by the Ethics Committee of Ankara University(approval no:2015-16-184). Rats were housed in separate cages and provided food and water ad libitum in a temperature-controlled room(22±1°C) artificially lit from 7:00 a.m. to 7:00 p.m. daily.

Male Sprague-Dawley rats(n=75, 10wk, 330.9±3.1g) were obtained from Bilkent University (Ankara, Turkey). Rats were divided into five groups;1:control, 2:PBOO, 3:PBOO+NaHS, 4:PBOO+tadalafil and 5:PBOO+NaHS+tadalafil. After the operation, each rat was treated with NaHS(300µL, 5.6 mg/kg/day) (12) or/and tadalafil(300µL, 2mg/kg/day) (3, 13) once a day for 6wk. Tadalafil tablets(Cialis™ 20mg film-coated tablets, Eli Lilly and Company, Indianapolis, USA) were crushed, freshly suspended in water as a vehicle, and administered orally by gavage feeding after surgery. A total of 5.6mg/kg NAHS(diluted in saline(0.9%); Sigma-Aldrich) was intraperitoneally injected after surgery. The body weights of all rats were calculated via a precision scale before the sacrifice of animals. The bladder and prostate tissues were excised and weighted by an electronic scale after sacrifice.

Surgical induction of PBOO

Obstruction was induced based on a previous study (14). After a longitudinal incision, the prostatic urethra and bladder were revealed. A 3-0 polypropylene non-absorbable suture was tied around the proximal urethra with a 4F urethral catheter to initiate the obstruction in the anesthetized rats. Following the suture was guaranteed, the catheter was carefully removed, and the incision was closed in layers. Sham rats underwent similar procedures without placing a ligature around the urethra.

Metabolic Cages

Metabolic cage experiments were conducted 6wk after obstruction to record total water intake and the total amount of urine. Rats were placed in a metabolic cage with free access to water, and food and the voided urine was collected for 24h. Total water consumed and the total amount of urine were noted (14).

Organ Bath Experiments

Six weeks after the surgery, the rats were killed under anesthesia(ketamine/xylazine;

100/10mg/kg, ip), and bladder tissues were removed for organ bath experiments. Following the removal of connective tissues, the bladder was cut into strips(2×10 mm) along the longitudinal axis isolated from the posterior face to perform *in vitro* functional studies. The strips were mounted under a resting tension(1g) in an organ bath including Krebs solution with 95%O2/5%CO2 at 37°C. The isolated strips were attached to a metal hook and a force transducer. For electrical field stimulation(EFS), an electrical pulse (5ms pulse width, amplitude 90V) was delivered for 15 seconds at increasing frequencies (1- 40Hz) using two platinum electrodes(Grass Instruments, Quincy, MA, USA).After equilibration time (1hr), bladder strips were contracted with 60mmol/L KCl and, cumulative concentrations 10^{-7}-10^{-4}M of carbachol, EFS(1–40Hz), and ATP(0.1-1mM).The maximum force of KCl depolarization was taken as 100%, and the contractile response was standardized to a percentage of this value(14).

Western Blot and Quantitative Analysis

Western Blot analysis was performed based on previous studies(14, 15). Approximately half of the bladders were homogenized in RIPA with a protease inhibitor cocktail (Cell Signaling Technology, MA, USA). After centrifugation, total protein quantification was performed by the bicinchoninic acid method (BCA). Equal amounts(40 µg) of protein were fractioned on 10% sodium dodecyl sulfate-polyacrylamide gel and then transferred onto polyvinylidene difluoride membranes for 1h at 100V. The membrane was incubated with blocking solution and then probed with 1:1000 diluted primary antibodies, including endothelial and neuronal NOS (eNOS; 610297 and nNOS; 610308) [BD Transduction Labs,CA, USA], inducible NOS (iNOS; sc-7271), CSE (sc-374249), CBS (sc-133154) [Santa Cruz Biotechnology,Dallas,TX,USA], 3-MST (NBP1-82617)[Novus Biologicals, Littleton,CO,USA], nuclear factor kappa B(NF-κB, 8242), hypoxia-inducible factor 1 alpha (HIF-1α, 36169), and β-actin (4970) [Cell Signaling Technology] at 4°C overnight. Following incubation with secondary antibodies, the visualization of protein bands was performed by a chemiluminescence substrate (Merck, Darmstadt, Germany) and Odyssey Fc system(LI-COR Biosciences, Lincoln, USA). The intensity of protein bands was quantified by Image J software(National Institutes of Health, Bethesda, Maryland, USA).

Determination of H_2S and malondialdehyde (MDA) levels in the bladder

H_2S and MDA levels in bladder tissues were assessed with commercial kits[H_2S assay kit (kit code:E-BC-K355-M; Elabscience Biotechnology Co.Ltd, Wuhan, China) and MDA assay kit(kit code:700870; Cayman Chemical, Ann Arbor, MI, USA)] based on the instructions. Approximately half of the bladder was homogenized in RIPA. The homogenate was centrifuged at 10,000g and 1,600g for 10min at 4°C to collect the supernatant. The absorbance at 665nm for H_2S measurement and 540nm for MDA measurement was calculated via a microplate reader(Thermo Scientific, Waltham, MA, USA). Bladder H_2S and MDA concentrations are expressed as nmol per mg protein by determining protein concentrations in bladder tissue samples using the BCA assay kit.

Data analysis

The findings were analyzed by Prism v.4(GraphPad Software, San Diego, CA, USA) and expressed as mean± standard deviation (SD). Multiple groups were compared via a one-way analysis of variance(ANOVA) followed by Bonferroni analysis. The minimum level of significance was set at $p<0.05$.

RESULTS

Characteristics of animals

There was no difference in body weight between groups (Table-1). The bladder weight of rats with PBOO was considerably greater than controls($p<0.001$). Monotherapies reduced increased bladder weight, however, there were no statistical differences in the decrement compared to PBOO rats ($p<0.05$ vs. controls and $p<0.01$ vs. controls). The combined therapy with NaHS and tadalafil decreased the bladder weight to control levels($p<0.05$ vs. PBOO). There were no significant differences in prostate weight, 24-hour water intake, or urine volume between all groups (Table-1).

Table 1 - Characteristics of animals in the control, partial bladder outlet obstruction and treated groups at 6 weeks.

	Control	PBOO	PBOO+ NaHS	PBOO+ Tadalafil	PBOO+ NaHS Tadalafil
Body weight (g)	430.50±44.38	407.86±26.46	422.83±37.66	412.72±58.02	400.72±22.41
Bladder weight (g)	0.21±0.05	0.61±0.22***	0.44±0.22*	0.47±0.22**	0.39±0.12#
Prostate weight (g)	0.96±0.19	1.03±0.28	1.03±0.29	0.99±0.25	0.88±0.19
Total urine volume/24 h (mL)	16.85±4.45	17.86±6.44	14.66±7.58	13.81±4.60	12.72±4.12
Total water intake/24 h (mL)	**37.50±7.27**	**45.33±11.87**	**39.16±12.40**	**46.81±12.3**	**47.27±11.03**

Abbreviations: NaHS:sodium hydrogen sulfide and PBOO:partial bladder outlet obstruction. Values are the mean ± SD (control=14, PBOO=15, PBOO+NaHS=12, PBOO+Tadalafil=11; PBOO+NaHS+Tadalafil=11).
*P < 0.05; **P < 0.01; ***P < 0.001 vs control group; # P < 0.05 vs PBOO group.

Contractile responses of the urinary bladder

The membrane depolarizing agent KCl--induced contraction in PBOO bladders was 58% lower than controls(p<0.001),and the combination treatment, but not monotherapies improved this reduction in the obstructed bladder(p<0.001 vs. PBOO, Figure-1A).

Carbachol (10 and 100 µM)-induced contractile responses in obstructed bladder strips were decreased compared to controls(maximal response:51.3%, p<0.01 vs controls). Decreased contractile responses were reversed by combination therapy of NaHS plus tadalafil, NaHS, or tadalafil treatment (Figure-1B).

PBOO decreased EFS-induced contractile response in bladder strips(p<0.05 vs. controls) except at 1Hz frequency. Also, the reduction was normalized by the combination therapy and each monotherapy (Figure-1C).

PBOO induced a considerable reduction in the contractile response to a purinergic agonist, ATP(p<0.001 vs. controls). Contractile responses to ATP(1mM) in obstructed rats receiving tadalafil alone were significantly higher than in control and PBOO rats(p<0.001 vs. controls and p<0.001 vs. PBOO). There were no significant differences in contractile responses to ATP among the combination and NaHS treatment groups (Figure-1D).

The protein expression of eNOS, nNOS, CSE, CBS, and 3-MST and measurement of H_2S levels in the bladder tissue

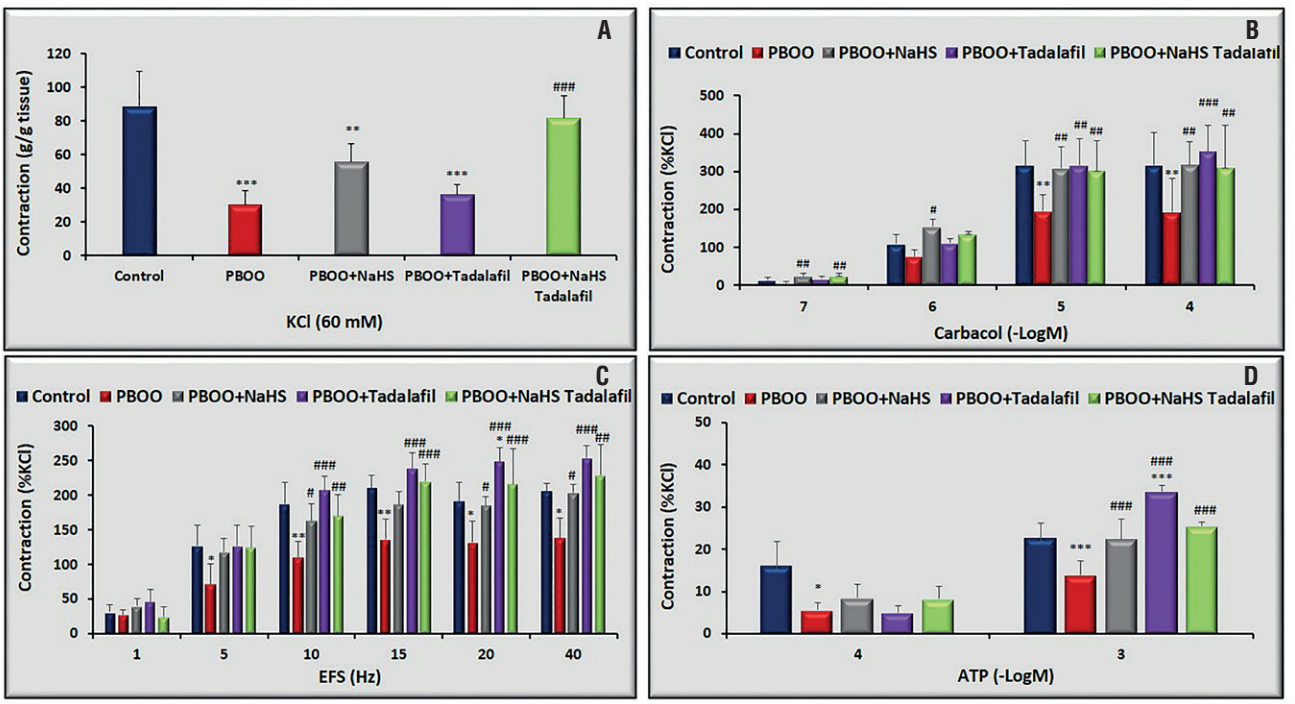
There was no difference in CSE and CBS protein expression between all groups. 3-MST protein expression was reduced in PBOO rats compared to controls (p<0.001), while was returned after combination treatment (p<0.01 vs. PBOO, Figures 2A and B).

eNOS protein expression in the obstructed bladder was higher than in controls, which was decreased by both monotherapies and the combined treatment (p<0.05 vs. controls, Figures 2A and B).

The protein expression of nNOS was significantly enhanced in the PBOO group and decreased in PBOO with tadalafil treated group(p<0.001 vs. controls), which was reduced by the combined treatment (p<0.001 vs. PBOO Figures 2A and B).

H_2S levels in obstructed bladders were lower than in controls (p<0.01). The reduction in H_2S levels in PBOO rats was enhanced by the combination treatment(p<0.001 vs. PBOO) and to a greater extent by NaHS(p<0.05 vs. controls; p<0.001 vs. PBOO), or tadalafil (p<0.05 vs. controls; p<0.001 vs. PBOO) treatment alone compared to controls(Figure-2C).

Figure 1 - Contractile dose-response curves for A) KCl, B) carbachol, C) electrical field stimulation and D), ATP in bladder strips from all groups.



Data are presented as mean ± SD (control=14, PBOO=15, PBOO+NaHS=12, PBOO+tadalafil=11; PBOO+NaHS+tadalafil=11). *P< 0.05, **P< 0.01, and ***P< 0.001 versus the control group; #P< 0.05, ##P< 0.01, and ###P< 0.001 versus the PBOO group (ANOVA with Bonferroni post hoc test).

The protein expression of inflammation and hypoxia-related markers (iNOS, NF-κB, HIF-1α) and MDA levels in the bladder tissue

iNOS protein expression was increased in the obstructed group (p<0.001 vs. controls), while was diminished by tadalafil alone and combination treatment (p<0.001 vs. PBOO, Figures 3A and B).

NF-κB protein levels did not alter in all groups(Figures 3A and B).

HIF-1α protein expression in PBOO bladders was greater than in control bladders(p<0.01), which was reduced by both monotherapies and the combined therapy(p<0.01 vs. PBOO, Figures 3A and B).

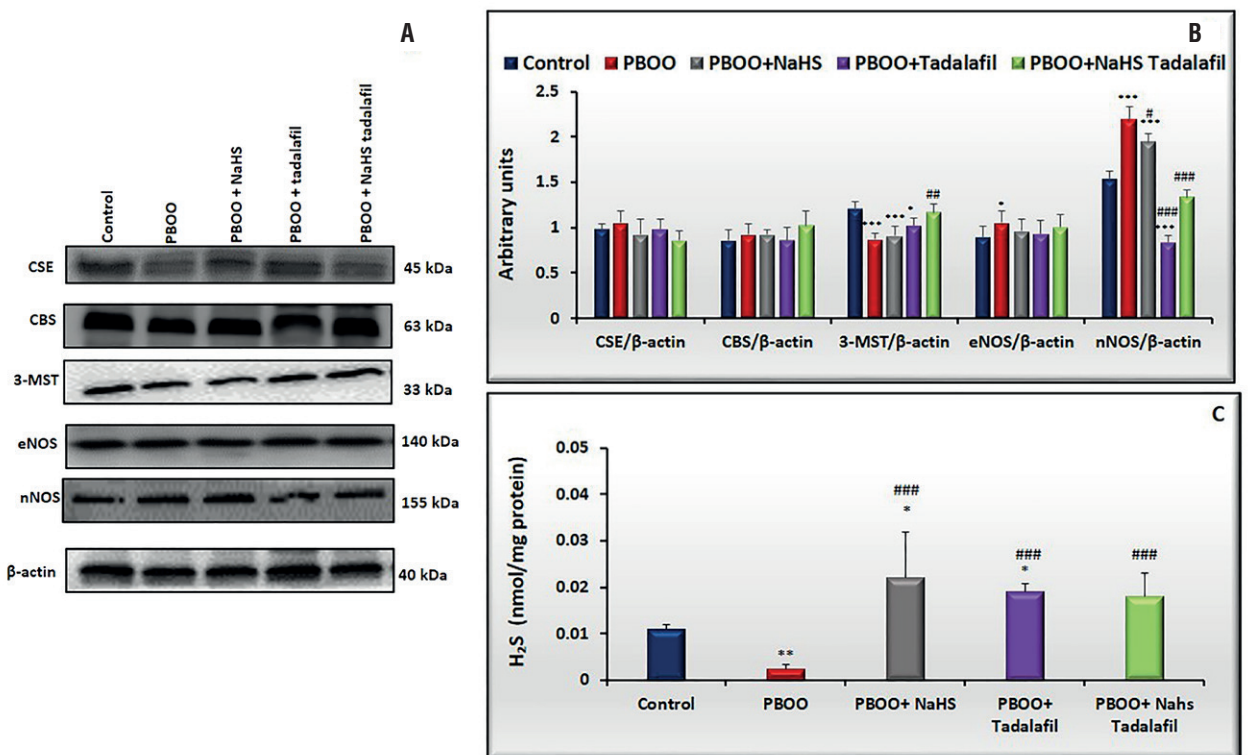
MDA levels in PBOO rats were 1.2-fold higher than in controls (p<0.01), which was prevented by all treatments (p<0.001 vs. PBOO, Figure-3C).

DISCUSSION

The current data confirmed that: (a)carbachol-, EFS- and ATP-caused contraction were lower in the obstructed group than in the control group, and the reduction in responses was improved by the combined treatment, (b)the co-administration of NaHS and tadalafil completely reversed PBOO-induced decrease in 3-MST levels and increase in eNOS,nNOS, iNOS and HIF-1α expression in bladder tissues, and (c) decreased H_2S levels and raised MDA levels in bladder tissue samples were normalized by the combination treatment.

The obstruction led to an increase in bladder weight compared to the sham-operated group, similar to previous data (16). In the present study, the augmentation in bladder weight was moderately restored in rats receiving monotherapy, when the combination treatment returned this increase. A previous study showed partial improvement in PBOO-induced increase in bladder weight after tadalafil treatment (16). Another study demonstrated that long-term tadalafil treatment prevented functional and histological alterations even though did not reduce bladder weight in the obstruc-

Figure 2 – A) semi-quantification of CSE, CBS, 3-MST, eNOS, and nNOS protein expression levels in rat bladder tissues from all groups (control=5, PBOO=6, PBOO+NaHS=6, PBOO+tadalafil=5; PBOO+NaHS+tadalafil=6). B) bar graphs show the ratio of CSE, CBS, 3-MST, eNOS and nNOS protein expression to β-actin expression. C), H_2S levels in the bladder tissue of rats from all groups (control=5, PBOO=5, PBOO+NaHS=5, PBOO+tadalafil=5; PBOO+NaHS+tadalafil=5).



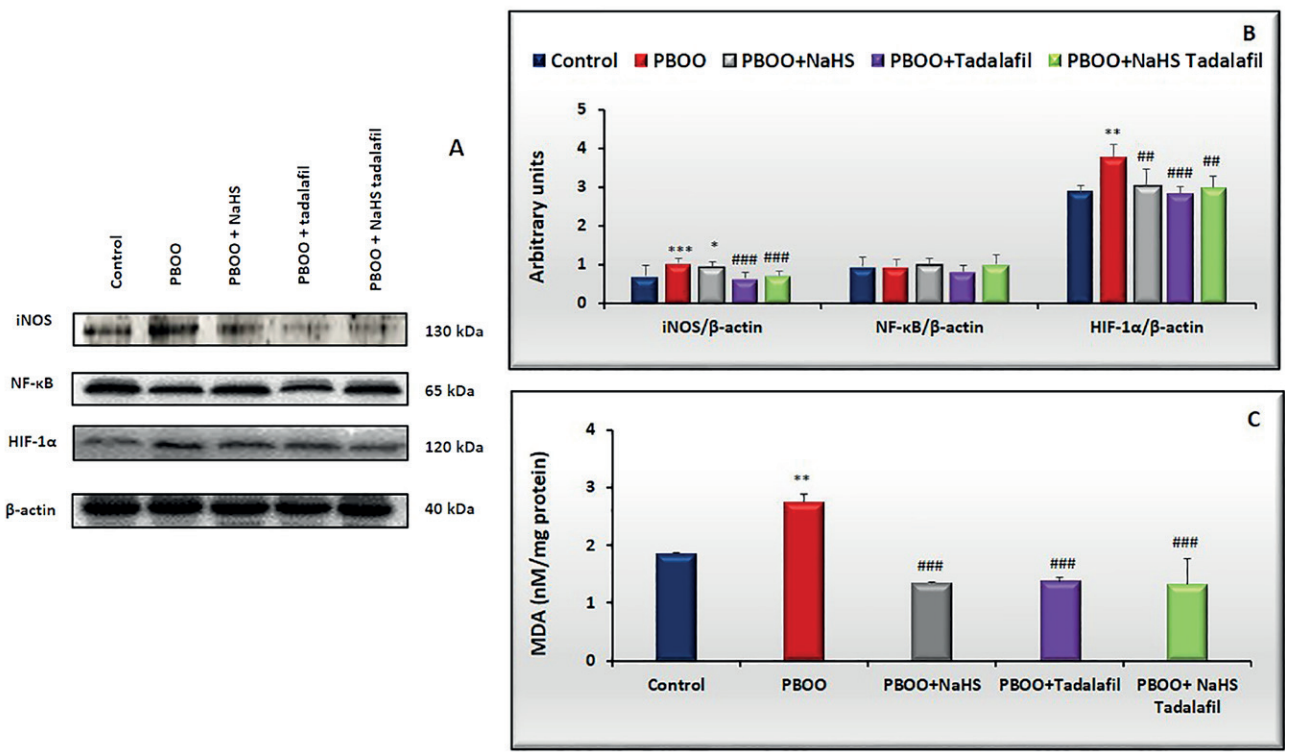
Data are presented as mean ± SD.

*P<0.05; **P<0.01; ***P<0.001 versus the control group; #P< 0.05; ##P< 0.01; ###P< 0.001 versus the PBOO group (ANOVA, Bonferroni post hoc).

ted rat bladder (3). However, there are no previous data to assess the impact of NaHS on the obstruction-caused increase in bladder weight. Previous data indicated that NaHS dose-dependently induced relaxation in the rat bladder (5), and the relaxation was impaired by hypertension and aging-induced decreased H_2S levels (17, 18). In addition, there is an interaction between NO and H_2S signaling systems. Sildenafil increased levels of H_2S in the human bladder (7), and H_2S enhanced eNOS phosphorylation and xanthine oxidase activity, caused NO production and enhanced NO bioavailability in endothelial cells (19, 20). So, it can be indicated that the combination treatment with NaHS and tadalafil causes additive effects to reduce bladder mass in PBOO rats when compared with monotherapy.

In the present study, urethral ligation reduced in vitro contraction responses in detrusor smooth muscle to carbachol, EFS, ATP and KCl. Furthermore, in the current study, tadalafil treatment partially prevented reduced contractile responses in the obstructed bladder, similar to an earlier study (3). On the other hand, decreased contractility of isolated bladder strips was considerably potentiated by NaHS alone. The previous data showed that PBOO caused a decrease in several parameters of detrusor contractility (14, 21). There was a high correlation between increasing obstructed bladder weight and decreased contractile responses (22). Contrary to our findings, the contractility to carbachol stimulation of PBOO bladder was increased in both rats and human bladder (9). After obstruction, the bladder undergoes

Figure 3 – A) semi-quantification of iNOS, NF-κB, and HIF-1α protein expression levels in rat bladder tissues from all groups (control=5, PBOO=6, PBOO+NaHS=6, PBOO+tadalafil=5; PBOO+NaHS+tadalafil=6). B) bar graphs show the ratio of iNOS, NF-κB, and HIF-1α protein expression to β-actin expression. C) MDA content in the bladder tissue of rats from all groups(control=5, PBOO=5, PBOO+NaHS=5, PBOO+tadalafil=5; PBOO+NaHS+tadalafil=5).



Data are presented as mean ± SD. *P<0.05; **P<0.01; ***P<0.001 versus the control group; ##P< 0.01, ###P< 0.001 versus the PBOO group (ANOVA, Bonferroni post hoc).

a 'compensated stage' or 'decompensated stage', and the contractile response changes accordingly. In the compensated state, the detrusor muscle undergoes hypertrophy and becomes hypercontractile (23). However, in the decompensated stage, the bladder becomes unable to properly compensate with decreasing bladder contraction (24). The difference between these results could be associated with the obstructed bladders being obtained in different stages of compensation/decompensation (9). A reduction in detrusor contractility in isolated bladders is a characteristic feature of bladder decompensation (25). It can be suggested that PBOO can cause underactive bladder symptoms together with decreased contractile responses of bladder strips.

In our study, CSE and CBS protein expressions did not differ between all groups. Protein expression of 3-MST in the bladder of PBOO and mono-treated groups was lower than in the control group, which was improved by NaHS plus tadalafil treatment. Furthermore, H_2S concentration in obstructed rat bladder was lower than in controls, which was reversed by combined treatment. Surprisingly, each monotherapy induced significantly higher levels of H_2S than controls. In a previous study, Fusco et al. (7) demonstrated that sildenafil increased H_2S levels in the human bladder through the activation of both CSE and CBS enzymes, and the combination of CBS and CSE inhibitors significantly reduced relaxant response to sildenafil in the human bladder (7). It seems that there is a connection between PDE5 activity and the H_2S pathway in the regulation of bladder function.

NO has a crucial physiological role in the proliferation and differentiation of several cell

types and can act as a neurotransmitter in the urothelium and affect bladder function (3, 26). However, the relation between the expression levels of NOS isoforms in bladder function remains unclear. In this study, eNOS and nNOS protein expression were greater in PBOO bladders than in controls. Numerous previous animal studies have demonstrated that the NOS expression increased in the rat obstructed bladder (9, 27), which is responsible for bladder dysfunction. In our study, this increase in nNOS and eNOS expression was further normalized by the combined treatment. It can be suggested that PBOO increased the production of NO by upregulating eNOS and nNOS, but the combination therapy may have a compensatory role for NOS expression in obstruction-induced bladder dysfunction.

In our data, NF-κB protein expression did not differ in all groups. Also, an increment in iNOS protein expression and MDA levels was observed in the obstructed rat bladder. Similarly, previous studies demonstrated no significant differences in total protein expression of NF-κB between the control and obstructed rat bladders (14), and iNOS expression and MDA levels were significantly enhanced by PBOO in rat bladder tissue (28). In addition, iNOS and MDA levels returned to control levels by combination with NaHS and tadalafil in the present study. In an animal model for metabolic syndrome, tadalafil decreased the mRNA levels of inflammatory, pro-fibrotic, and hypoxia indicators in the bladder of rabbits (29). Moreover, treatment with NaHS decreased the renal ischemia/reperfusion-caused overexpression of iNOS and lowered levels of MDA (30).

The protein expression of HIF-1α, a marker of hypoxia, was significantly enhanced in obstructed rats compared to controls, which was normalized by all treatments. PBOO leads to the upregulation of HIF-1α protein expression in the bladder (31). Previous studies showed that the protein expressions of HIF-1α decreased by NaHS in the PBOO rat penis and tadalafil in the PBOO rat bladder (13, 15). The combination of H_2S donor and PDE5i can recover PBOO-induced bladder dysfunction via decreasing oxidative stress and hypoxia.

The limitations of the study regarding some features of experimental design could affect the interpretation of the outcomes. One of the limitations of the current study is the lack of control treatment groups. Therefore, without these groups, it may be difficult to know if the results were from balanced effects or if the treatments prevented the negative effects of the obstruction. Previous studies demonstrated that NaHS and tadalafil treated control rats displayed similar responses in bladder function, inflammation and oxidative stress markers compared to control rats (32, 33). The current use of a sulfide salt, NaHS is likely to be regarded as a limitation for the application of our study to urological practice, but numerous studies have revealed that H_2S is effective on bladder function (5, 34). We have shown, for the first time, that the combined treatment with H_2S and tadalafil is likely to remedy PBOO-induced bladder dysfunction. As obstruction can lead to bladder dysfunction, H_2S donors and PDE5i may be a new treatment strategy for improving urinary symptoms in BPH patients. The current work supports further clinical studies to focus on developing controllable H_2S donor drugs, such as AP39, ATB-346 and SG1002, in clinical trials (35, 36).

CONCLUSIONS

In conclusion, combination therapy involving H_2S and NO signaling pathways has additive beneficial effects on obstruction-induced bladder dysfunction compared with NaHS or tadalafil alone through an improvement in oxidative stress and hypoxia in the bladder tissue. Collectively, our data suggest that the combination of H_2S donors and PDE5i might contribute to the improvement of urinary symptoms in BPH patients.

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CONFLICT OF INTEREST

None declared.

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EXPERT OPINION

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Testicular involvement in pediatric acute lymphocytic leukemia: what to do about it?

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INTRODUCTION

Acute lymphocytic leukemia (ALL) represents 30% of childhood cancers (1) and relapsed ALL is the leading cause of death caused by cancer in childhood (2).

Relapse of ALL typically arises from the bone marrow. Extramedullary relapse most commonly involves the central nervous system but may also present as a testicular isolated or concomitant relapse in males (3).

Information about testicular leukemia is difficult to analyze, considering difficulties to compare patients treated with protocols that are not in use contemporaneously to children treated nowadays, the different results of leukemia treatment in developed and low/medium income countries (LMIC) results referring to multiple age groups, the relative rarity of the disease and the limited quality of the literature.

MATERIALS AND METHODS

We made an analytic descriptive non-systematic literature review about testicular recurrence after ALL in childhood. The key words "leukemia AND (testis OR testicle)" were used to find papers through PUBMED, limited to children (0-18 years old), in Portuguese, Spanish, English, or French. The abstracts were then reviewed. Papers dealing primarily with TR after ALL were reviewed. The selected papers were then read in toto. Any other papers of interest retrievable from the references were also reviewed. Gray literature was not included.

RESULTS

Testicular involvement in pediatric ALL is rare in patients from developed countries being treated with modern protocols, where more than 90% survive (4), with a proportion of 15-20% relapses after first remission, mostly bone marrow disease (5-6). Lower prevalence of testicular ALL is strongly dependent on modern chemotherapy protocols: testicular recurrences (TR) affected 5.8 to 16.2% of the patients in the '70s, versus 0-2% in contemporaneous cohorts from developed countries (0-2%), equally divided between early, intermediate and late occurrences (2, 3, 6, 7). Data from 308 ALL autopsies on leukemia patients from 1958-1982 (88 children) showed involvement of the testes in 15% of the most recent cases (1977-1982) versus 49% of those treated between 1958-1964 (8). Later and intermediate TR usually occurs 2-3 years after remission but has been reported up to 10 years after treatment of myeloid leukemias (9).

TR incidence in LMIC persists similar to that described in the '70s, mainly due to late diagnosis and irregular or inadequate chemotherapy,

despite the adoption of intermediate/high-dose methotrexate (MTX) protocols. In India, almost a quarter of ALL children recur (half of those early), and a quarter of the relapses present TR (equally divided between isolated and concurrent) (10).

Timing of TR (early/< 18 months, intermediary/18-35 months or late/≥ 36 months after remission), kind of relapse (isolated versus concurrent TR), and the number of relapses presented by the patient are directly related to the prognosis. Early, concurrent, and successive relapses are related to a worse prognosis. TR is partially responsible for the worse prognosis of ALL in males as compared to females (11).

Studies from autopsies of ALL patients, obviously biased towards severe and/or irresponsive cases, report frequent testicular involvement (25-48.5% of the patients) associated with other disease foci (12, 13), suggesting that the testis may be frequently involved in disseminated uncontrolled disease and that testicular leukemia that is associated to severe disseminated early or recurrent leukemia may be different from TR, especially if isolated.

Three different clinical patterns of TR may be seen:

1. Isolated TR;
2. Concurrent relapse associating TR to disease attaining other loci;
3. Advanced/out of control severe leukemia.

The efficacy of chemotherapy on the testicles is limited due to insufficient penetration of some drugs in the blood-testicular barrier ("pharmacological sanctuary"). Although the physiological basis for a blood-testis barrier is unclear, it has been demonstrated that some systemic medications do not distribute equally to the testes. The concentrations of methotrexate (MTX) are 2-4 times lower in the testicular interstitial space (the typical site of tumoral invasion) and 18-50 times lower in the tubules (typically associated with late tumoral invasion) than in the patient's blood MTX (6, 14). This can be resolved with higher doses of MTX (14), prolonged chemotherapy, and usage of vincristine and/or cyclophosphamide (drugs that surpass the blood-testicular barrier) associated with steroids. Departing from this information, the usage of intermediate/high intravenous doses of MTX from the 1980s significantly lowered the incidence of TR. Some authors also suggest that the lower temperatures typical for normally located testis may also be related to the lower pharmacological activity of some drugs (15).

Prepubertal and peripubertal testicles may respond differently to neoplastic invasion, as compared to mature gonads (16). Cases presenting next to puberty may be more prone to TR than pre- or post-pubertal patients (6, 11). Immunological tolerance to neoplastic cells may also differ in the testicles as compared to other organs, locally "protecting" and "harboring" leukemia cells (4, 11). Two possibilities involving relapses have been suggested: (1) development from original clones that survived chemotherapy and are probably chemoresistant; (2) isolated or non-isolated TR developing from cells from a common ancestral clone previously protected from chemotherapy as a testicular nidus (2). This has obvious implications for treatment, with potentially worse results with rescue chemotherapy for chemotherapy-resistant disease, and calls for more studies (4, 16).

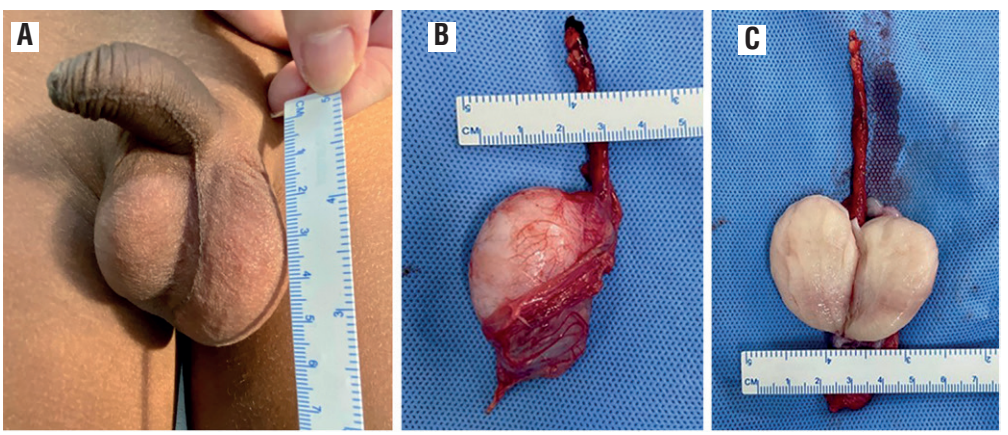
The involvement of the testicle in ALL cases is more frequent in high-risk patients (< 1-year-old, ≥ 10 years old, patients presenting higher peripheral blasts counts at the moment of the diagnosis, T-cell leukemia cases showing significant hepatomegaly/splenomegaly or > 2 cm lymph nodes, unfavorable genetic patterns (BCR-ABL1 and KMT2A), and multiple recurrences) (1, 4, 10). Those need aggressive treatment, frequently including bone marrow transplantation (4).

Testicular ALL may (1) be simultaneous to the diagnosis of the primary disease (1.1 to 2.4% of the patients), and (2) present after treatment and remission of the primary disease (TR).

Clinically, the involved testis is usually augmented (Figure-1), irregular, firmer than a normal testicle, and usually painless. Bilateral enlargement is typically asymmetric. Discoloration may be rarely seen. The growth rate is quite rapid: some authors report that many of the involved testicles doubled in volume in 15 days (3).

In ultrasound, the testis is diffusely hypoechogenic or presents hypoechogenic nodules that are hypervascular on Doppler (17). The role of 18F

Figure 1 - Early left testicular recurrence in a 4-year-old boy.



A) testicular enlargement at physical examination; B) surgical specimen; C) surgical specimen, longitudinal section showing almost complete substitution of testis parenchyma for tumor cells.

FDG PET/CT to detect extramedullary leukemia is still being studied. Most data are available from relapsed patients, with sensitivity, specificity, and accuracy of, respectively, 93.3%, 71.4%, and 79.7%. The exam was able to detect all 4 cases of TR in Zhou´s paper, 3/4 as diffuse uptaking/involvement. No false positives (usually related to inflammatory or infectious complications) were reported (9).

Fine needle and core needle biopsies are both accurate for diagnosis. Needle biopsy specimens provide results that are similar to open wedge biopsies (18-21). Microscopically the involved testicle shows focal or diffuse infiltration of leukemic blasts with effacement of the normal architecture (22), frequently arranged in a concentric fashion around tubules or vessels in the interstitial tissue (7). Tubular involvement is a late event (4). The specimen should be handled with care to avoid crushing artifacts and should be promptly fixed. There is some controversy about what concerns the fixative (formaldehyde, Bouin´s, or Zenker´s) (23).

"Isolated" TR should be considered a systemic disease: exclusive local treatment is associated with early systemic recurrence, including 10-20% with central nervous system invasion. Concerning treatment:

1. Clinically apparent testicular involvement simultaneous to primary diagnosis/treatment is rare (less than 2% of the patients) and is treated as "common" cases. This clinical presentation is related to severe disease at presentation (hepatosplenomegaly, lymphonodomegaly, high number of peripheral blasts), but the results of treatment are similar to those in other cases in modern cohorts: testicular involvement in the initial clinical presentation is not an individual predictive factor (24, 25). Testicular irradiation is used only if the testicular abnormalities persist after chemotherapy. This is controversial and some authors advocate for local radiotherapy depending on the moment of the diagnosis, the bulk of testicular disease, and initial response to chemotherapy or for post-chemotherapy "control" biopsies by protocol (1). Subclinical testicular involvement normally responds to routine modern chemotherapy protocols. So, there is no need to actively search for testicular foci in ALL patients presenting clinically normal testicles and a normal ultrasound examination (4, 26).

   a. Systematic testicular biopsy just before discontinuing maintenance therapy in patients in remission was routine till the 1980s. Positive biopsies led to bilateral testicular irradiation and extension of chemotherapy in positive cases) (23). This was abandoned, considering the better results

of modern chemotherapy protocols, the relative rarity of TR, the possibility of false negatives, late diagnoses of TR despite negative biopsies, and results similar to those found in patients diagnosed departing from clinical symptoms/signs of TR (4, 27-30).

b. Prophylactic testicular irradiation has been abandoned, in order to minimize gonadal dysfunction and infertility (14, 31), as no improvement in survival has been demonstrated in patients that received adequate systemic chemotherapy (32).

2. Post-remission TR:

a. Local treatment: bilateral gonadal irradiation (24 Gy/2500 rads distributed in 2 weeks, 12 sessions, applied to the testis and spermatic cords (31, 33) or orchiectomy (generally reserved for unilateral cases and patients who refuse radiotherapy) + contralateral prophylactic irradiation (15 Gy), trying to preserve Leydig function and the potential for spontaneous puberty. However, lower testosterone levels in response to HCG stimulation, as compared to normal children/adolescents, have been proved after testicular irradiation (34), as well as delayed or arrested spontaneous puberty, and high serum FSH (31). Contralateral irradiation is needed even if the contralateral testicle seems normal clinically, as microscopic involvement is common: unilateral orchiectomy is not sufficient, but may be done with lower doses (15 Gy) (3). The penis is taped away from the irradiation field in order to protect the urethra. The responsive testes reduce to the normal size during the first month after treatment (3). Associated intensive re-induction chemotherapy with high doses of MTX is mandatory.

b. Late TR after bone marrow transplantation: orchiectomy is mandatory (4, 35), but other treatments are controversial, considering previous exposures to chemotherapy and bad prognosis (36).

c. There is no published protocol specifically considering the technique for orchiectomy in ALL TR. The concept of avoiding lymphatic spreading of the tumor via scrotal incisions seems to apply, and trans-inguinal radical orchiectomy seems appropriate, as done in primary testicular tumors.

Immunotherapy using CD19-specific chimeric antigen receptor T (CAR-T) cells has shown good results and complete remission in 6/7 patients with isolated TR (5-23 months follow-up), without radiotherapy or orchiectomy. One patient re-recurred (bone marrow), but all showed a complete testicular response (37).

The prognosis varies with the timing of TR: 5 years of survival varies from 13.6% in early recurrences (< 18 months) to 52.2% (18-36 months) and 60% (late recurrences, ≥ 36m after treatment), with modern treatment protocols (4).

DISCUSSION

The quality of the information about TR after ALL is a serious problem. Most papers about the TR are from the '80s and the '90s and report on retrospective descriptive cohorts. Many mix children and adults, leukemias and lymphomas, and different types of leukemia together. Also, papers from LMIC are scarce. Most information available comes from developed countries, which usually present more favorable results, and provide easy access to state-of--the-art treatments. This is directly related to the high indexes of TR in LMICs when compared to developed countries, but the effect of worse treatments is difficult to separate from the effect of late diagnoses and the predominance of more advanced cases in LMICs. Also, the protocols may have to be adjusted to the circumstances. Considering the relatively high incidences of TR, would it be useful to adopt post-remission testicular biopsies in LMICs, despite this having been eliminated from developed countries' protocols?

Would it be useful to frequently follow up the testis with imaging after remission? As some suggest, testicular "harbored" blasts may be the origin of systemic leukemia relapse. Would early detection of subclinical testicular nodules facilitate treatment?

Some clinical situations are exceedingly rare (e.g. TR after bone marrow transplantation), making it difficult to evaluate and compare the

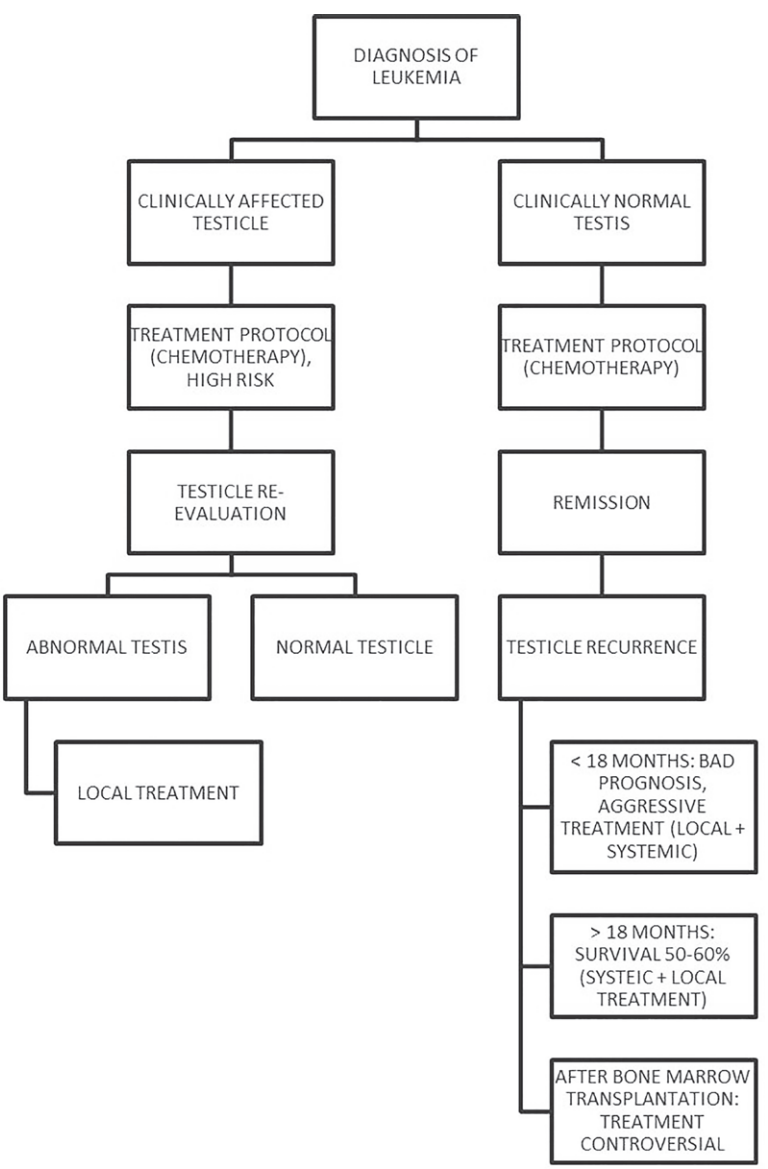
treatment strategies and establish reasonable treatment protocols.

Basic research is needed to understand the testicular-blood barrier in detail. This may deepen our understanding of the immunological response of the testis to leukemic cells and, potentially, suggest new methods of treatment and avoidance of future TR.

A recent paper describing excellent results of immunotherapy may be a first suggestion that this may also be used to avoid future TR in the future (37). TR, despite being treatable, leads to prolonged chemotherapy, high risks of infertility, and frequent need for external androgens in young adults. Survival after early TR remains dire. New protocols to avoid and treat TR are needed. We suggest herein a treatment algorithm, based on the current state of the art (Figure-2).

In conclusion, testicular affection by ALL is not rare in LMICs, despite being very uncommon

Figure 2 - Treatment algorithm suggested by the authors to treat ALL cases, according to the clinical situation and response to treatments, considering primary testicular affection and testicular recurrence. Local treatment in this context means either ipsilateral orchiectomy or radiotherapy with contralateral biopsy.



in developed nations. Data about this condition are mainly based on results from developed countries in the 20th century, which may not apply to the contemporaneous circumstances found in LMIC. TR worsens prognosis, and is related to late diagnosis of ALL, suggesting that better pediatric health care may help to get earlier diagnoses and to diminish the incidence of testicular ALL. Also, more research is needed on this subject, especially concerning physiopathology and the role of the testes as "leukemia sanctuaries" and about the promising new proposals for the immunological treatment of ALL testicular relapses.

ABBREVIATIONS

ALL = acute lymphocytic leukemia
LMIC = low and middle-income country
TR = testicular recurrence

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

NEURO-UROLOGY

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Editorial Comment: Solifenacin treatment after intradetrusor injections with botulinum toxin in patients with neurogenic detrusor overactivity

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COMMENT

This prospective study evaluated whether adding solifenacin to the intradetrusor injection of botulinum toxin A (BoNT) could boost the effect of BoNT in patients with neurogenic detrusor overactivity (NDO) due to multiple sclerosis or spinal cord injury refractory to antimuscarinics alone (1). Thirty-nine patients who achieved total continence after BoNT injections were included in the analysis (group A: BoNT injections; group B: BoNT + solifenacin) and were followed for a minimum of 24 months. Data from urodynamic testing and questionnaire assessments before and 3 months after injections and reinjections were gathered.

Reinjection was needed after a mean 8.2 months for group A and 11.7 months for group B. Patients receiving solifenacin also presented greater OABq score improvement (A = 17.25 ± 5.07, B = 20.44 ± 4.51, P = 0.0485), as well as maximum bladder capacity (A = 11.05 ± 7.04 mL, B = 19.39 ± 6.43 mL, P = 0.0005). However, differences in Pdet change (A = 51.72 ± 16.57 cmH2O, B = 50.80 ± 16.33 cmH2O, P = 0.7635) and post-void residual change (A = 17.67 ± 12.63 mL, B = 12.30 ± 8.32 mL, P = 0.126) were not statistically significant.

Authors concluded that adding solifenacin to BoNT improved patient satisfaction and increased the interval between reinjections. Nevertheless, this is a non-randomized trial, which lacked a placebo control group. Further well-designed studies (e.g. RTCs) are still warranted before definitive conclusions may be drawn concerning the role of adding antimuscarinics to patients receiving BoNT to treat NDO.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

MALE HEALTH

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Editorial Comment: Intra-cavernous injection of BOTOX ® (50 and 100 Units) for treatment of vasculogenic erectile dysfunction: Randomized controlled trial

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COMMENT

Onabotulinum toxin-A (BTX) is widely used to treat various medical conditions such as striated and smooth muscle disorders. In urologic disorders, the use of BTX has been approved to treat detrusor overactivity (1).

Despite the various therapeutic options for the treatment of erectile dysfunction (ED), there is a need for a new effective and safe treatment for patients who are refractory to noninvasive therapies. Some studies have suggested the possible role of intracavernosal injection (ICI) of BTX for the treatment of ED, which has aroused interest in the area of sexual medicine (2-4).

BTX inhibits sympathetic adrenergic or cholinergic vasoconstriction, sensory nerves, decreasing the tone of penile resistance vessels, blood flow, and cavernosal smooth muscle tone, which are involved in the pathophysiology of DE (5).

In this interesting study, the authors compared the safety, efficacy and durability of ICI of BTX at different doses (50 and 100μ) against placebo (saline) in the management of vasculogenic ED non-responsive to pharmacological therapy (phosphodiesterase type 5 inhibitors and/or ICI of trimix). They conducted a prospective randomized double-blind placebo-controlled trial involving 176 patients, who were randomly assigned to one of the treatments. All patients were monitored for six months. Significant improvements in all parameters (Sexual Health Inventory for Men Score, Erection Hardness Score, Sexual Encounter Profile, Global Assessment Score, and Doppler parameters) were observed in patients in the BTX-100μ and BTX-50u groups, with maximum improvement in the third month of treatment. BTX-100U was more dura-

ble with statistically significant difference between the aforementioned groups in favor of BTX-100U. They observed some adverse events, such as injection site penile pain and hematoma. Interestingly, four patients developed prolonged sustained erection during penile Doppler examination at three months, which was managed conservatively, and at six months, one patient from the BTX-100μ group had priapism, which was resolved by ICI of ephedrine. On the other hand, no systemic side effects were observed. According to the authors, BTX can promote a safe, effective and relatively durable improvement of ED.

The present study has some limitations, such as failure to stratify the different causes of vasculogenic ED and measure psychological problems that can have an important impact on the response to treatment. In addition, the study was conducted in a single institution and with a short follow-up. However, the authors presented one of the pioneering works evaluating the effects ICI of BTX on the treatment of ED. Congratulations to the authors for their contribution with this important and interesting report.

ICI of BTX is a promising second-line treatment option of ED. However, unfortunately we have more questions than answers on this topic. Which profile makes patients candidates for this therapy? Is long-term ICI of BTX safe? What is the ideal dose to start? What is the duration of the effect of BTX on erectile function? Thus, larger-scale human multicenter prospective randomized double-blind placebo-controlled studies with a long follow-up period are needed to determine the therapeutic efficacy and clinical safety of BTX for the treatment of ED.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ENDOUROLOGY

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Editorial Comment: Flexible Ureterorenoscopy Versus Shockwave Lithotripsy for Kidney Stones ≤ 2 cm: A Randomized Controlled Trial

Andrea Bosio [1], Eugenio Alessandria [2], Ettore Dalmasso [2], Simone Agosti [2], Federico Vitiello [2], Eugenia Vercelli [2], Alessandro Bisconti [2], Paolo Gontero [2]

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COMMENT

Bosio et al. conducted a randomized controlled trial to compare the outcomes of flexible ureterorenoscopy (RIRS) versus shockwave lithotripsy (SWL) for kidney stones up to 2 cm. The primary endpoint was stone-free rate (SFR) at 1 month (1). Secondary endpoints were SFR at 6 months and 1 year, complications and secondary treatments. True SFR (zero residual fragments) at 1 month favors RIRS (50.0% vs. 26.5%; p=0.004). In the long run, the authors state that this difference tends to reduce at 6 months 59.4% vs. 40.9%; p=0.032 and no longer be significant at 1 year 55.9% vs. 48.4%; p=0.392 (1). Although it is very difficult to control variables for 1 year, authors suggests that clearance of residual fragments after SWL persists longer than after RIRS. Clearance rate of residual stone fragments ≤ 2 mm after RIRS is about 80% during the first 3 months whereas less than 12% of the residual stone fragments > 2mm (2). Another important point is that patients in the SWL arm were submitted to further treatments during one-year follow-up more than patients in the RIRS arm, including flexible ureterorenoscopy, which could had artificially increased the success of shockwave lithotripsy.

This study also compared the outcomes of each treatment from the patient point of view. 87.1% of the patients of the RIRS arm vs. 88.2% of the SWL arm; p=0.845 were satisfied with their own treatment. Despite these good satisfaction rates, there is room for improvement. Patients would not choose the

same treatment again in 22.9% of RIRS arm vs. in 13.2% of SWL arm; p=0.142. Patients of the RIRS arm that would choose another treatment reported stent-related symptoms as the reason in 56.3% and patients of SWL arm reported negative outcome in 77.7% (1). Improvements in ureteral stents and better patient selection seem to be the keys to increase patient's satisfaction with the treatment.

One limitation of this study is the image evaluation. Only stones 16-20 mm on ultrasound (US) and kidney-ureter-bladder X-ray (KUB) preoperative evaluation were submitted to computed tomography (CT) and none postoperative image evaluation used CT. Although CT is the gold standard image modality to determinate true SFR and US + KUB are not a reliable tool to identify residual stone fragments 0-2 mm, authors used only US + KUB for both groups (2).

To sum up, SWL remains a viable alternative for the treatment of kidneys stones, particularly for selected patients. Also, every effort should be made at the time of flexible ureterorenoscopy to leave no stone fragment behind and to maintain high SFR. Mitigation of stent-related symptoms is crucial to increase patient's satisfaction with RIRS.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic excision of vaginal pouch in ovotesticular disorder of sexual development

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ABSTRACT

Purpose: Ovotesticular disorder of sexual development (DSD) is the rarest of DSDs with an incidence of 1:20000 (1). Management of vaginal pouches in such cases is warranted for symptomatic presentations and laparoscopy is considered the gold standard treatment (2). We report a rare case of robotic excision of a large symptomatic vaginal pouch in a 19-year-old boy with ovotesticular DSD.

Material and Methods: A 19-year-old boy with ovotesticular DSD post hypospadias repair in early childhood presented with complaints of recurrent UTIs, ballooning of urethra during micturition and post-void dribbling. Ultrasound, voiding cystourethrogram (VCUG) and magnetic resonance imaging (MRI) were suggestive of a vaginal pouch. The patient underwent endo-evaluation followed by robot-assisted excision of the vaginal pouch. Endo-evaluation showed two orifices in the posterior urethra. The posterior orifice was leading into a blind-ending rudimentary uterus and the true urethra was lying anteriorly. The DaVinci Xi Robotic Surgical System was used and the entire pouch was dissected free of the surrounding tissues using monopolar scissors. The pouch was transected just a few millimetres from its junction with the urethra. The urethra was then closed with V-loc 4-0 suture. The patient was discharged on postoperative day 2 and the catheter was removed on day 21.

Results: Follow-up VCUG at 6 weeks did not show any residual pouch. There was no complaint of post-void dribbling or UTI at 30 months of follow-up.

Conclusion: Robot-assisted laparoscopy should be considered as an alternative to laparoscopy for the primary treatment of a large symptomatic vaginal pouch.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Three-dimensional reconstruction and intraoperative ultrasonography: Crucial tools to safely approach highly complex renal masses

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ABSTRACT

Purpose: Robot-assisted partial nephrectomy (RAPN) is rapidly increasing its role in the nephron-sparing surgery setting (1). The recent introduction of technological advancements is leading more experienced surgeons to approach complex renal mass with a conservative intent (2, 3).
In particular, three-dimensional reconstruction and the use of intraoperative ultrasonography are gaining attention as crucial tools to safely and effectively approach complex cases (4, 5).
We aimed to video-report the management of highly complex renal mass treated with RAPN, focusing on preoperative surgical planning and intraoperative technical nuances.
Materials and methods: A 73-year-old male patient was referred to our institution for an incidental detection of a 70 mm diameter, completely endophytic, hilar renal mass (PADUA score 13, RENAL score 11a). Contrast-enhanced CT scan images were processed by M3DICS (Turin, Italy) and used to obtain a 3D virtual model. RAPN was performed by a highly experienced surgeon using Da Vinci Si robotic platform with a three-arm configuration.
Results: The overall operative time was 114 min, with a warm ischemia time of 16 min. No intraoperative or postoperative complications were recorded. According to the SIB score, the pure enucleation excision strategy was performed. Histopathological analysis revealed a pT3a low-grade oncocytic kidney tumor with negative surgical margins. with negative surgical margins. At 24-months follow up, no local or systemic recurrence was detected.
Conclusions: Conservative management of complex renal masses is challenging with a highly nuanced decision-making process. In this regard, preoperative 3D models and intraoperative ultrasound (US) guidance play a pivotal role to develop a tailored surgical strategy according to patient' and tumor's characteristics.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study. All the procedures 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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