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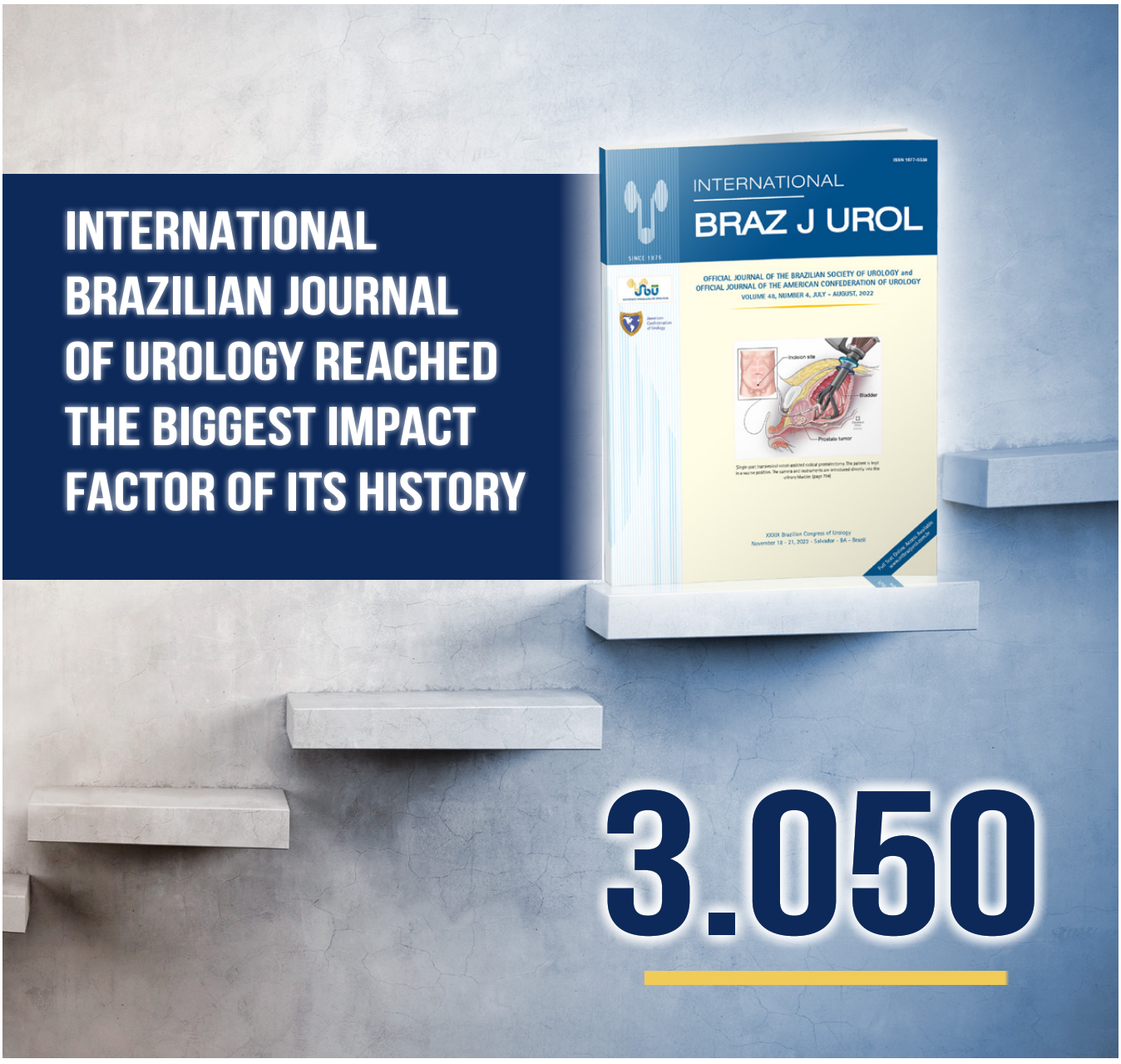

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LETTER TO THE EDITOR

Vol. 48 (5): 739-741, September - October, 2022
doi: 10.1590/S1677-5538.IBJU.2022.05.01

EDITORIAL
IN THIS ISSUE

International Brazilian Journal of Urology reaches the highest impact factor in its history (3,050) and changes level in this current management

Luciano A. Favorito [1, 2]

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The September-October number of Int Braz J Urol, the 18th under my supervision is special. The International Brazilian Journal of Urology new impact factor just been released and we have a spectacular result: 3.050. We are now on the same level as the traditional urology journals. In less than three years of our tenure as editor-in-chief, we have achieved through hard and serious work tripling the journal's impact factor and making the journal one of the most important in the field in the world. We must celebrate this achievement and continue with our work. We are on the right track and we will surely increase even more our impact factor and our relevance in the academic environment.

In this number the Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Ureteral stones, male breast cancer, Fournier's Gangrene, Reconstructive urology, Renal cancer, Bladder pain syndrome, Renal stones, Renal Cysts, Hypogonadism, Robotic Surgery, Prostate Cancer. The papers came from many different countries such as Brazil, India, Indonesia, China, Turkey and USA and as usual the editor's comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. Sharma and colleagues from India, presented in page 739 (1) a nice systematic review about the efficacy of alpha-blockers as medical expulsive therapy (MET) and concluded that among the three commonly used alpha-blockers silodosin is the most efficacious drug as MET for lower ureter stones followed by alfuzosin and tamsulosin.

Dr. Makdissi and colleagues from Brazil performed in page 760 (2) a interesting narrative review about the male breast cancer (MaBC) urological aspects and concluded that despite its rarity, MaBC represents an impor- tant problem in men's health that can be neglected if professionals who have higher access to this popu- lation are uninformed. Therefore, urologists can play an important role in the early diagnosis of MaBC because their work involves a broader scenario in which the focus is greater than sexual dysfunction and screening for prostate cancer.

Dr. Raizandha and colleagues from Indonesia performed in page 771 (3) a interesting systematic review about the role of Hyperbaric oxygen therapy (HBOT) in management of Fournier's Gangrene and concluded that the adjunctive therapy of Hyperbaric Oxygen possessed a significantly lower mortality rate compared to conventional therapy. However, the effect of HBOT on the length of stay and number of debridement was not proven in this study.

Dr. Cao and colleagues from China performed in page 784 (4) a nice study to confirm the hypothesis that a Nomogram can be built to predict the pathological T3a upstaging from clinical T1a in patients with localized renal cell carcinoma before surgery and concluded that older age, higher ratio of the tumor maximum and minimum diameter (ROD), increased fibrinogen level (FIB), and larger tumor size were independent risk factors for upstaging. The ARFS model (Age, ROD, FIB, tumor Size) has a high prediction efficiency for pT3a upstaging in patients with cT1a Renal cell carcinoma.

Dr. Hacad and colleagues from Brazil performed in page 807 (5) a interesting study about the effects of biofeedback (BF) and manual therapy (MT) associated with transcutaneous electrical nerve stimulation (TENS) or postural exercises (PE) in the treatment of bladder pain syndrome (BPS) in women regarding pain and urinary symptoms and concluded that biofeedback and manual therapy associated with postural exercises showed a significant improvement in perineal and suprapubic pain and urinary symp- toms after treatment and during follow-up. Both results suggest a possible role for the use of this physiotherapy technique to treat BPS patients.

Dr. Sahan and colleagues from Turkey performed in page 817 (6) an important study about a novel nomogram and a simple scoring system for urinary leakage after percutaneous nephrolithotomy and concluded that the novel scoring system is easy to use and repeatable. The efficacy of the factors predicting urinary leakage in the scoring system was demonstrated to be in agreement with the literature. In addition, this scoring system can be used as a predictive method to determine which patients should receive a DJ catheter intra-operatively to shorten the length of hospital stay by estimating the risk of urinary leakage and to decrease additional anesthesia exposure due to postoperative DJ catheter requirement.

Dr. Caglayan and colleagues from Turkey performed in page 830 (7) a interesting study about a deep learning model in detecting kidney stones in different planes according to stone size on unenhanced computed tomography (CT) images and concluded that the use of deep learning algorithms for the detection of kidney stones is reliable and effective. Additionally, these algorithms can reduce the reporting time and cost of CT-dependent urolithiasis detection, leading to early diagnosis and management.

Drs. Meng and Mi from China performed in page 842 (8) a study about the clinical efficacy and safety of transurethral flexible ureteroscopic incision and drainage with holmium laser in the treatment of parapelvic renal cysts and concluded that transurethral flexible ureteroscopic incision and drainage with holmium laser in the treatment of parapelvic renal cysts has obvious advantages over traditional surgery, and is worthy of advancement and application, but its long-term effect needs further follow-up studies.

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

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Int Braz J Urol. 2022; 48: 739-41

REVIEW ARTICLE

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Comparison of efficacy of three commonly used alpha-blockers as medical expulsive therapy for distal ureter stones: A systematic review and network meta-analysis

Gopal Sharma [1], Tarun Pareek [1], Pawan Kaundal [1], Shantanu Tyagi [1], Saket Singh [1], Thummala Yashaswi [1], Sudheer Kumar Devan [1], Aditya Prakash Sharma [1]

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ABSTRACT

Introduction: The efficacy of alpha-blockers as medical expulsive therapy (MET) is well established. However, it is not known which of the three most commonly used alpha-blockers (tamsulosin, alfuzosin and silodosin) is the most efficacious. With this study we aimed to assess the efficacy of the three commonly used alpha-blockers as MET for distal ureter stones.

Materials and Methods: For this review, we searched multiple databases such as PubMed/Medline, Scopus, Embase, OviD SP, CINAHL, and web of science to identify all the relevant randomized studies comparing the efficacy of tamsulosin, alfuzosin, and silodosin. Preferred reporting items for systematic reviews for network meta-analysis (PRISMA-NMA) were followed while conducting this review and the study protocol was registered with PROSPERO (CRD42020175706).

Results: In this review, 31 studies with 7077 patients were included. Compared to placebo all the treatment groups were more effective for both stone expulsion rate (SER) and stone expulsion time (SET). For both SER and SET, silodosin had the highest SUCRA (94.8 and 90.4) values followed by alfuzosin (58.8 and 64.9) and tamsulosin (46.2 and 44.5). The incidence of postural hypotension was similar with all the drugs, whereas, the incidence of retrograde ejaculation was significantly higher for silodosin. Overall confidence for each comparison group in this review ranged from "very low" to "moderate" according to the CINeMA approach.

Conclusion: Among the three commonly used alpha-blockers silodosin is the most efficacious drug as MET for lower ureter stones followed by alfuzosin and tamsulosin.

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INTRODUCTION

The worldwide prevalence of stone disease is gradually increasing in recent times and presently it is estimated to be 5-10% (1). Ureteric stones, as a subset of urinary stones, demand prompt diagnosis and treatment due to their propensity to cause back pressure changes leading to obstructive uropathy, if not relieved timely.

Spontaneous expulsion of ureteric stones depends on diverse factors, of which stone size and location remain the most pertinent predictors for stone passage (2). Failure of spontaneous passage of ureteric stones necessitates intervention.

The current treatment modalities for ureteric stones include conservative measures such as medical expulsive therapy (MET) and extracorporeal shockwave lithotripsy (ESWL) and surgical interventions including endoscopic, open surgery, laparoscopic surgery, and robot-assisted surgery. As per the latest American and European guidelines, MET remains a feasible management option for ureteric stones less than 10mm, given its non-invasive and comparatively inexpensive features (3-5).

Multiple drugs such as α-blockers (tamsulosin, silodosin, alfuzosin, and naftopidil) (6-8), calcium channel blockers (CCB) (nifedipine) (9) and phosphodiesterase inhibitors (PDEI) (sildenafil and tadalafil) (10, 11) have been found to be effective in facilitating the expulsion of ureteric stones compared to general measures such as the use of non-steroidal anti-inflammatory drugs (NSAIDS), hydration, antispasmodics, diuretics, and placebo. Most of the evidence has been published with alpha-blockers (6, 7). However, among various available alpha-blockers the comparative efficacy and safety has been a matter of debate. Few studies have compared different alpha-blockers to each other (12) and there is a paucity of studies evaluating the relative efficacy of individual alpha--blockers specifically for "distal" ureteric stones, as MET has been reported to be most efficacious for this subgroup compared to proximal ureteric location (4). Thus, with this study we aimed to compare the relative efficacy of three commonly used alpha-blockers (alfusozin, silodosin and tamsulosin) as MET for distal ureteric stone.

MATERIALS AND METHODS

This systematic review and network meta--analysis were performed with a frequentist approach. A pre-specified study protocol was registered with PROSPERO (CRD42020175706) and standard Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines for conducting network meta-analysis (NMA) were followed (13).

Literature search

Systematic literature search for various electronic databases such as PubMed/Medline, Scopus, Embase, OviD SP, CINAHL and web of science was conducted by two study authors independently (GS & ST). A literature search was conducted from the time of inception of these databases until March 2020. Literature search was limited to English only. The search string used for literature search was based on Patient, Intervention, Control and Outcome (PICO) guidelines. The following keywords and strategy were used: Patient: Lower ureteric stone OR Lower ureteric calculi OR Distal ureteric stone OR Distal ureteric calculi. Intervention: alfuzosin OR silodosin OR tamsulosin. Control: No treatment. Outcome: Stone expulsion OR medical expulsive therapy.

The search results thus obtained from various databases were transferred on to a citation manager and additional articles were also sought from various review articles on same topic and hand searches of references selected for full-text review were also undertaken.

Study eligibility criteria

Following a comprehensive literature search, initial title and abstract screening were conducted by two authors independently (GS & ST) to screen the articles for possible inclusion into the study based on the below mentioned exclusion and inclusion criteria.

Inclusion criteria:

1 - Randomized studies containing data on the number of stone expulsion or time to stone expulsion in adult patients with lower ureteric stones with the use of any of the three alpha- blockers being studied. Comparison could be against control group or with each other.

Exclusion criteria:

1. Non-randomized studies
2. Case reports, editorials, letters, reviews and conference abstracts
3. Not containing data on above mentioned drugs i.e. silodosin, alfuzosin ortamsulosin.
4. Studies in the pediatric age group (age <18 years).
5. Not containing data on the stone expulsion rate (SER) or stone expulsion time (SET) at the completion of study.

Studies were then selected for full-text review and those satisfying the inclusion and exclu-

sion criteria were included in review. In case of disagreement between two study authors, arbitration with the other authors was done.

Data extraction

Two study authors independently (GS & ST) extracted data from the studies on a pre-determined format including following variables such as first author, year, type of study, country, type of treatment, duration of treatment, baseline comparability according to age, sex, stone size, SER and SET. The discrepancy of data was resolved after arbitration with other study authors.

Outcome

The primary outcome studied was SER at the end of study period in the treatment and the control groups. We also provided data for ranking of the three alpha-blockers on their efficacy for the expulsion of distal ureteric stones in terms of SER Data on SET and complications such as postural hypotension and premature ejaculation was also analyzed in this study and various alpha-blockers were ranked accordingly (secondary outcome).

Statistical analysis and certainty of evidence

This network meta-analysis (NMA) was performed using frequentist approach that determines the probability of an event to occur if the same process is repeated multiple times (14, 15). This NMA was designed to compare three treatment groups (alfuzosin, silodosin and tamsulosin) for the primary and secondary outcomes. This NMA is aimed to combine both direct and indirect evidence into a single effect size for the two comparisons i.e. stone expulsion rate and time to stone expulsion. Relative rankings of various alpha--blockers i.e. alfuzosin, silodosin and tamsulosin were estimated for both the outcomes using the distribution of ranking probabilities and surface under the cumulative ranking area curves (SUCRA). For publication, bias visual interpretation of comparison adjusted forest plots was done. All the statistical analysis was performed using Stata (version 16; StataCorp, College Station, TX, USA) (16) using "network (14)" and "network graph" packages (17).

Inconsistency

Inconsistency evaluation was done using both global and local approaches. Loops specific approach was also used to detect loops of evidence for inconsistency (18, 19).

Quality or certainty of evidence was determined by using methodology as described by Salanti et al. (20) using Confidence in Network Meta-analysis (CINeMA) web application (21) for the primary outcome. CINeMA requires data formatted in terms of study level outcome, risk of bias and indirectness. Data was then configured and network plot was created. Nodes were colored green, yellow or red according to risk of bias (low, unclear and high, respectively). Edges of plot were colored according to average risk of bias across all the studies. Edging with was according to sample size and node size by number of studies. Then random-effect analysis with risk ratio as effect measure was used. A bar graph depicting contributions of each study to network estimate was generated. For this given network estimate risk of bias across contributions was summarized by selecting "Average" command. For assessing imprecision, a risk ratio of 1.25 was set as clinically important size of effect. Relative effect estimates below 0.8 and above 1.250 were considered clinically important. Judgment for imprecision was formulated as "very serious", "serious" and "not serious" depending upon whether the confidence interval (CI) values cross both, one or neither limits of clinically important effect zones. Prediction intervals were generated to make judgments on heterogeneity and its implications on quality of treatment effects.

Incoherence or inconsistency was assessed according to methods described on separate section. Finally, results of all comparisons were graded as high, moderate, low or very low according to this framework.

RESULTS

Literature search and study characteristics

The literature search of various databases yielded a total of 573 citations that were imported on a citation manager. Of these 214 duplicate

Table 1 - Characteristics of the studies included in this review.

S. no	Author / Country	Treatment	Control	Duration of treatment	Age mean (SD) / (Treatment) (Years)	Age mean (SD) (Control) / (Years)	Male/ Female (Treatment)	Male/ Female (Control)	Stone size less than 10 mm	Mean stone size (Treatment) (mm)	Mean stone size (Control) (mm)
1	Al-Ansari et al., (22), 2010, Qatar	Tamsulosin 0.4mg	Placebo	4 weeks	37.1(9.4)	36.1 (9.3)	32/18	35/15	Yes	5.8 (2.4)	6 (2.5)
2	Aldemir et al., (23), 2011, Turkey	Group I- Tamsulosin 0.4mg	Diclofenac 100 mg	10 days	42.4 (16)	43.5 (16.6)	22/9	19/10	Yes	6.7 (1.4)	6.6 (1.7)
		Group II- Rowatinex 100 mg thrice daily			46.5 (16.5)		17/13			6.8 (2)	
3	Alizadeh et al., (24), 2014, Iran	Tamsulosin 0.4 mg	Placebo	4 weeks	-	-	29/21	32/14	3-6 mm	-	-
4	Bajwa et al., (25), 2013, Pakistan	Tamsulosin 0.4 mg	Diclofenac 50 mg	4 weeks	32.4 (8.3)	33.8 (9.6)	18/12	19/11	Yes	6.9 (1.4)	6.6 (1.4)
5	Cervenakov et al., (26), 2002, Slovakia	Tamsulosin 0.4 mg	Tramadol 50 mg / Diazepan and Veral 50	-	-		32/19	33/18	Yes	-	-
6	El-Gamal et al., (27), 2011, Egypt	Group II Tamsulosin 0.4mg Group IV Uralyt-U plus tamsulosin	Group I Placebo control Group III UralytU	4 weeks	35.3(5.7)	36.2 (6)	32/16	34/12	Yes	7.9 (1.9)	7.7 (1.6)
7	ElGalaly et al., (28), 2017, Egypt	Group I Tamsulosin 0.4 mg	-	4 weeks	35.5 (11)	-	32/19	-	Yes	5.6(1.2)	-
		Group II Silodosin 8mg			33.6 (9.9)		35/17			5.4(1.5)	
8	Vincendeau et al., (29), 2010, France	Tamsulosin 0.4 mg	Placebo	6 weeks	38.9 (12)	39 (11)	43/18	52/9	2-7 mm	2.9 (1)	3.2 (1.2)
9	Yilmaz et al., (30), 2005, Turkey	Group II Tamsulosin 0.4mg Group III Terazosin 5mg Group IV Doxazosin 4mg	Group I No treatment	4 weeks	40.6(10)	41.6(12)	9/20	19/9	Yes	6(1.2)	6(1.4)

10	Aggarwal et al., (31), 2009, India	I – Tamsulosin II – Alfuzosin	III -Placebo	4 weeks	(31.4) (38.7)	(35.3)	26/8 28/6	24/10	Yes	6.17 6.7	6.35
11	Ahmad et al., (32), 2015, Pakistan	I -Tamsulosin	II- Placebo	4 weeks	-	-	4-10mm		<8mm	5.78mm	-
12	Cha et al., (33), 2012, Korea	ITamsulosin - 0.2mg OD II Tamsulosin - 0.2 mg BD III Alfuzosin IV Trospium	-	4 weeks	(45.07)	-	31/10	-	4-10mm	5.49	-
13	Dell'Atti et al., (34), 2015, Italy	I Tamsulosin II - Silodosin	-	3 weeks	(35)	-	39/27		4-10mm	5.37	-
14	Furyk et al., (35), 2016, Australia	I -Tamsulosin	II-Placebo	4 weeks	> 18	>18	156/42	164/31	Yes	4	3.7
15	Ochoa-Gomez et al., (36), 2011, Mexico	I- Tamsulosin	II-Placebo	4 weeks	(38.5)	(38.2)	15/17	21/12	5-10mm	5.3	5.2
16	Hermanns et al., (37), 2009, Switzerland	I-Tamsulosin	II-Placebo	3 weeks	(36)	(41)	39/6	36/9	7mm or less	4.1	3.8
17	Itoh et al., (38), 2013, Japan	II- Silodosin	I -Placebo	4 weeks	(56.3)	(55.8)	All male	-	Yes	4.87	5.07
18	Kumar et al., (12), 2015, India	I - Tamsulosin II – Silodosin III- Tadalafil	-	4 weeks	(36.4)	-	62/28	-	5-10mm	7.44	-
19	Sameer et al., (39), 2014, India	I-Nifedipine II- Alfuzosin	III- Control	4 weeks	(32.74)	(33.06)	19/16	23/12	Yes	6.5	6.37
20	Ahmad et al., (40), 2010, Saudi Arabia	I = Tamsulosin 0.4mg II - Alfuzosin 10mg	III- control-Diclofenac 75mg	30 days	40.7(14.8)	38.9(13.3)	9/10	19/09	Yes	4.97 (2.24)	5.39 (1.81)
21	Elsaid et al., (41), 2015, Egypt	Alfuzosin 5mg BD	control - Diclofenac + Hydration	4 weeks	32.8(9.5)	32.1(9.2)	18/10	16/10	Yes	6.3 (2.1)	5.9 (1.9)
22	Nuraj et al., (42), 2017, Kosovo	I-Tamsulosin 0.4mg	Control-Diclofenac	4 weeks	35.5(11.0)	35.4(10.8)	34/18	35/17	4-10mm	6.5 (1.6)	6.6 (1.5)
23	Pedro et al., (43), 2008, USA	I- Alfuzosin	Placebo	4 weeks	36.69(13.6)	42.03(12.8)	28/6	27/8	Up to 8mm	3.83 (0.94)	4.07 (1.13)

24	Pickard et al., (44), 2015, UK	I - Tamsulosin 0.4mg III - Nifedipine 30 mg	III- Placebo	4 weeks	43.1(11.5)	48.2(12.3)	315/68	299/85	Yes	4.6(1.6)	4.5(1.7)
25	Rahman et al., (45), 2018, India	I - Tamsulosin 0.4mg OD II - Silodosin 8 mg OD III- Silodosin 8mg + Tadalafil 5 mg	-	4 weeks	38(10)	-	24/16	-	5-10mm	7.5(1.20)	
26	Sur et al., (46), 2015, USA	I- Silodosin 8mg OD	II- Placebo	4 weeks	47 (13)	47 (15)	72/53	80/37	4-10mm	5.4 (1.4)	5.5 (1.6)
27	Wang et al., (47), 2008, Taiwan	I- Tamsulosin 0.4 mg OD II- Terazosin 2 mg OD	III- control	2 weeks	50.4(9.7)	50.9(9.6)	22/10	23/08	Yes	6.5(1.3)	6.5(1.4)
28	Ye et al., (49), 2018, Wuhan, China	I- Tamsulosin 0.4mg	II- Placebo	4 weeks	40.1(11.6)	40.7(12.3)	556/1086	605/1049	Yes	5.8(1.9)	5.7(1.8)
29	De Sio et al., (50), 2006, Italy	Diclofenac 100mg/day + Aescin 80mg/day Diclofenac 100mg + Aescin 80mg + Tamsulosin 0.4 mg	-	2 weeks	44.5(11.3)	-	26/20	-	Yes	6.4(1.3)	-
30	Wang et al., (48), 2016, Taiwan	I- Silodosin 8mg	II- control	2 weeks	51.4(8.6)	51.5(10.5)	40/22	43/18	Yes	6.4(1.4)	6.4(1.3)
31	Yuksel et al., (51), 2015, Turkey	Group II Silodosin 4 mg/day	Group I Placebo	3 weeks	35.31 (11.55)	35.23 (11.2)	19/16	20/15	4-10mm	6.40(1.61)	6.34(1.57)

articles were removed and another 309 articles were removed after initial title and abstract screening due to various reasons (Figure-1). Fifty articles were selected for full-text review. For the final analysis 31 articles were included and the remaining 19 articles were excluded due to non-randomized nature of the study.

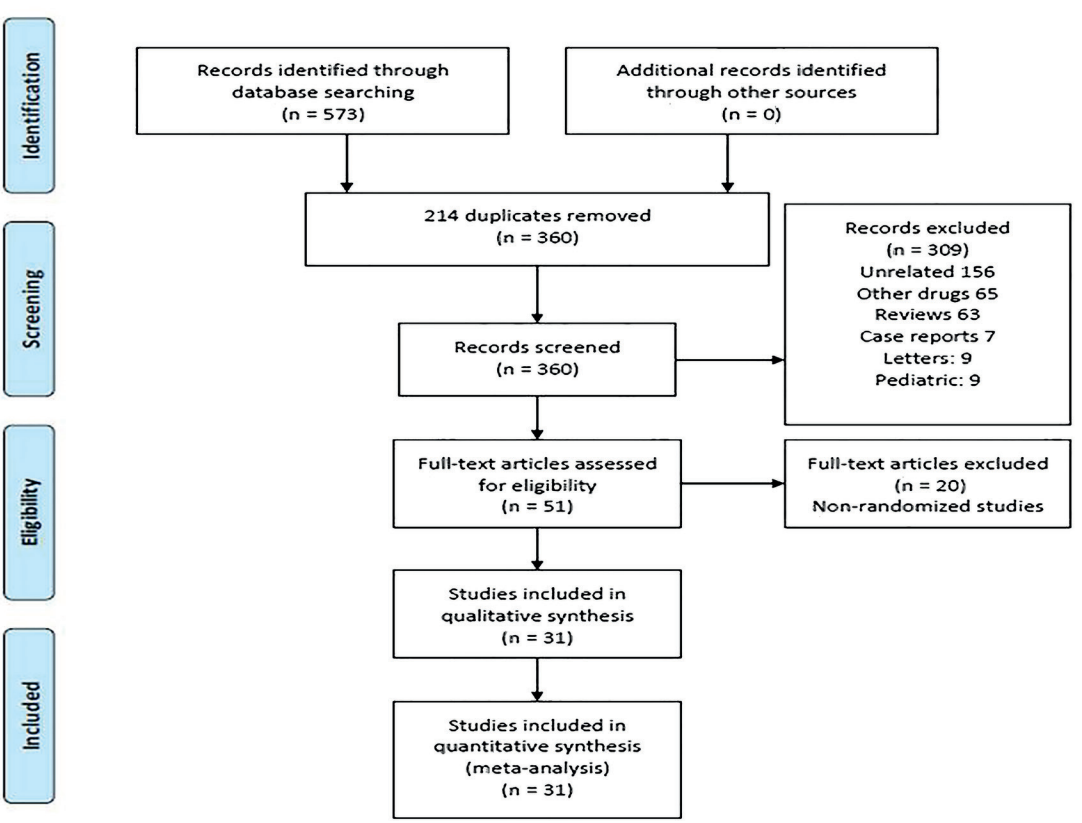
In this review, 31 RCT's (12, 22-51) across various countries with 7077 patients were included.

The intervention group included the three alpha-blockers with or without best medical therapy i.e. adequate hydration and analgesic use. The control group was variable with 14 studies containing placebo groups and others containing best medical therapy and analgesics. Duration of treatment ranges from 10 days to 6 weeks. The duration of treatment was 4 weeks in 21 studies, 3 weeks in one study and 2 weeks in 3 studies. All the studies compared well for various demographic factors such as age and sex. The mean stone size was similar in the two groups in all the studies (Table-1).

NETWORK

Data for primary outcome i.e. SER was available from all the 31 studies. Mixed evidence was available for 5 comparisons (alfuzosin vs. control, silodosin vs. control, tamsulosin vs. control, alfuzosin vs. tamsulosin and silodosin vs. tamsulosin) whereas indirect evidence was available for alfuzosin vs. silodosin. The network plot for the primary outcome is shown in APPENDIX 1. As described previously, nodes were colored green, yellow or red according to risk of bias (low, unclear and high, respectively). Edges of the plot were colored according to the average risk of bias across all the studies. Edge width was according to the sample size and node size by the number of studies. The number of studies for each comparison are alfuzosin vs. con-

Figure 1 - PRISMA flow-chart depicting search strategy used for conducting this study.



trol (5), silodosin vs. control (4), tamsulosin vs. control (19), alfuzosin vs. tamsulosin (3) and silodosin vs. tamsulosin (4). For other outcome i.e. SET network consists of 19 studies with 4 treatments and 5 comparisons (alfuzosin vs. control (3), silodosin vs. control (2), tamsulosin vs. control (11), alfuzosin vs. tamsulosin (2) and silodosin vs. tamsulosin (3).

Stone expulsion rate

Compared to placebo all the treatment groups were more effective. Relative risk (RR) of stone expulsion rate for silodosin, alfuzosin and tamsulosin were 1.55 (95% confidence interval (CI) 1.31, 1.83), 1.33 (95% CI 1.06, 1.67) and 1.29 (95% CI 1.16, 1.43) respectively. Compared to alfuzosin RR of silodosin and tamsulosin were 1.16 (95% CI 0.9, 1.51) and 0.97 (95% CI 0.78, 1.19) respectively.

Comparison of tamsulosin with silodosin had RR of 0.83 (95% CI 0.70, 0.98) (Figure-2).

Global approaches for inconsistency models revealed no violation of consistency assumption for direct and indirect assumptions. Loop specific approach revealed two treatment loops without inconsistency. Local approaches using node splitting revealed inconsistency for two comparisons i.e. alfuzosin-silodosin and alfuzosin-tamsulosin. SUCRA values were calculated to estimate the rank of efficacy according to stone expulsion rate (Table-2). According to the SUCRA values obtained silodosin had the highest rank followed by alfuzosin and tamsulosin.

Time to stone expulsion

Data on the time to stone expulsion was available from 18 studies. Comparison of silodosin to other treatment modalities such as control, alfuzosin and tamsulosin favored silodosin with mean difference (MD) of -6.0 (95% CI, -8.1, -3.9) `days, -1.28 (95% CI -4.4, -1.8) days, 2.73 (95% CI 0.73, days respectively. Comparison of tamsulosin with control favored tamsulosin with MD of -3.35 (95% CI -4.6, -2.1) and comparison to alfuzosin favored alfuzosin with MD of 1.45 (95% CI -1.07, 3.96) Comparison of alfuzosin with control group favored alfuzosin with MD of -4.8 (95% CI -7.25, -2.3) (Figure-3).

Loop-specific heterogeneity estimates and inconsistency models (global and local) revealed no violation of consistency assumption for direct and indirect assumptions SUCRA values obtained for time to stone expulsion estimate revealed highest values for silodosin i.e. silodosin was best with lowest SET followed by alfuzosin and tamsulosin (Table-2).

Complications

Data for analysis into network meta-analysis has been inconsistently reported. For this study, we extracted data for two commonly reported and clinically relevant side-effects i.e. postural hypotension and retrograde ejaculation. Data for postural hypotension and retrograde ejaculation was available from 14 studies. For postural hypotension there was no significant difference between all the treatment and control groups (Figure-4). According to SUCRA values alfuzosin had the highest ranked and silodosin the lowest ranked i.e. silodosin had lowest incidence of postural hypotension (Table-2). For retrograde ejaculation, silodosin had significantly higher incidence as compared to all the other treatment groups (Figure-5). According to SUCRA values, silodosin had the highest incidence of retro-

Table 2 - Surface under cumulative ranking area (SUCRA) values according to various outcomes.

TREATMENT	SUCRA for SER	SUCRA for SET	SUCRA for Postural hypotension	SUCRA for retrograde ejaculation
Control	0.1	0.2	35.7	32.1
Alfuzosin	58.8	64.9	**86.1**	6.8
Silodosin	**94.8**	**90.4**	17.6	**98.6**
Tamsulosin	46.2	44.5	60.6	62.6

SER = Stone expulsion rate; **SET** = Stone expulsion time

Figure 2 - Interval and Forest plot for various drugs for stone expulsion rate (SER).a

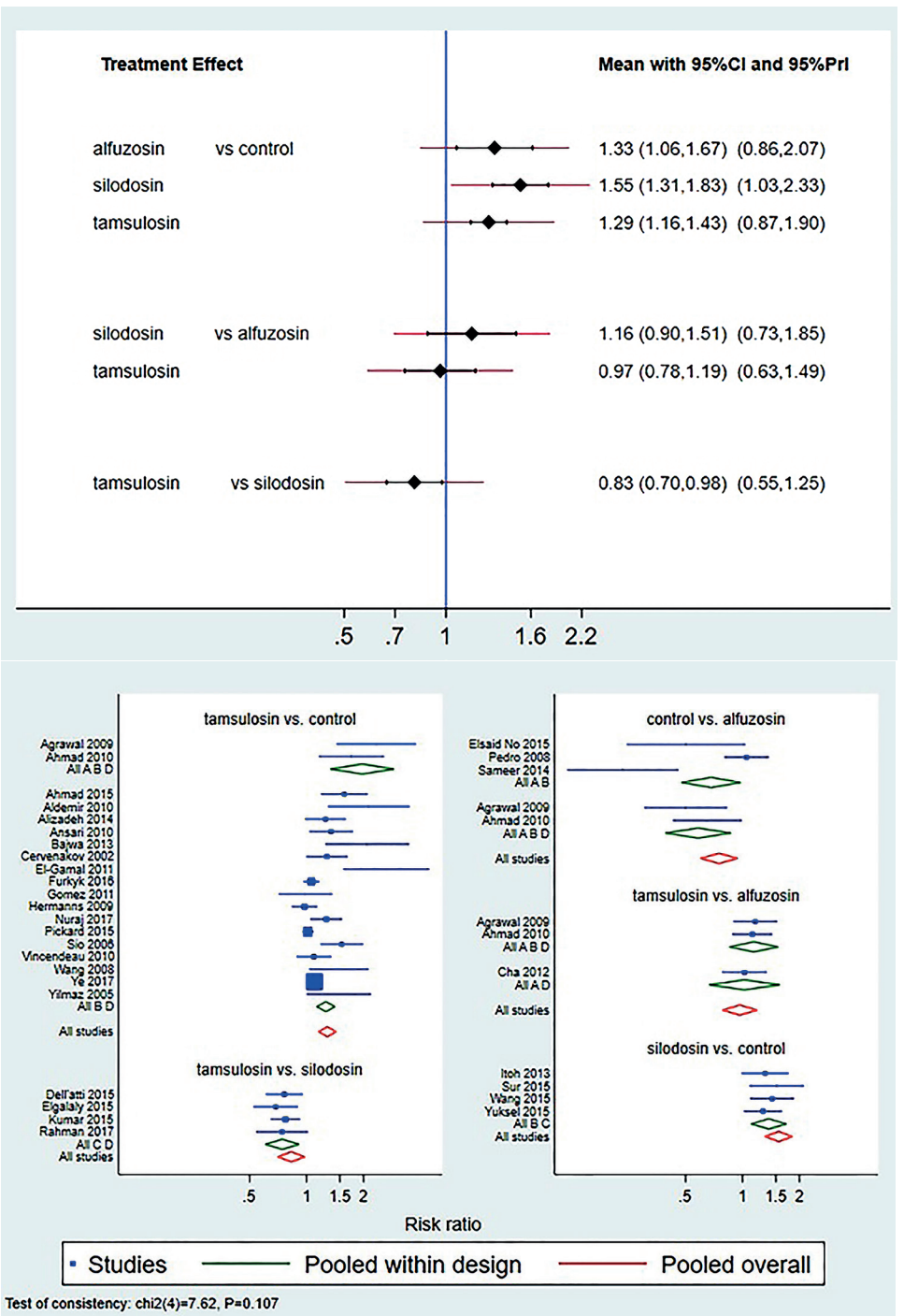


Figure 3 - Interval and Forest plot for various drugs for stone expulsion time (SET).

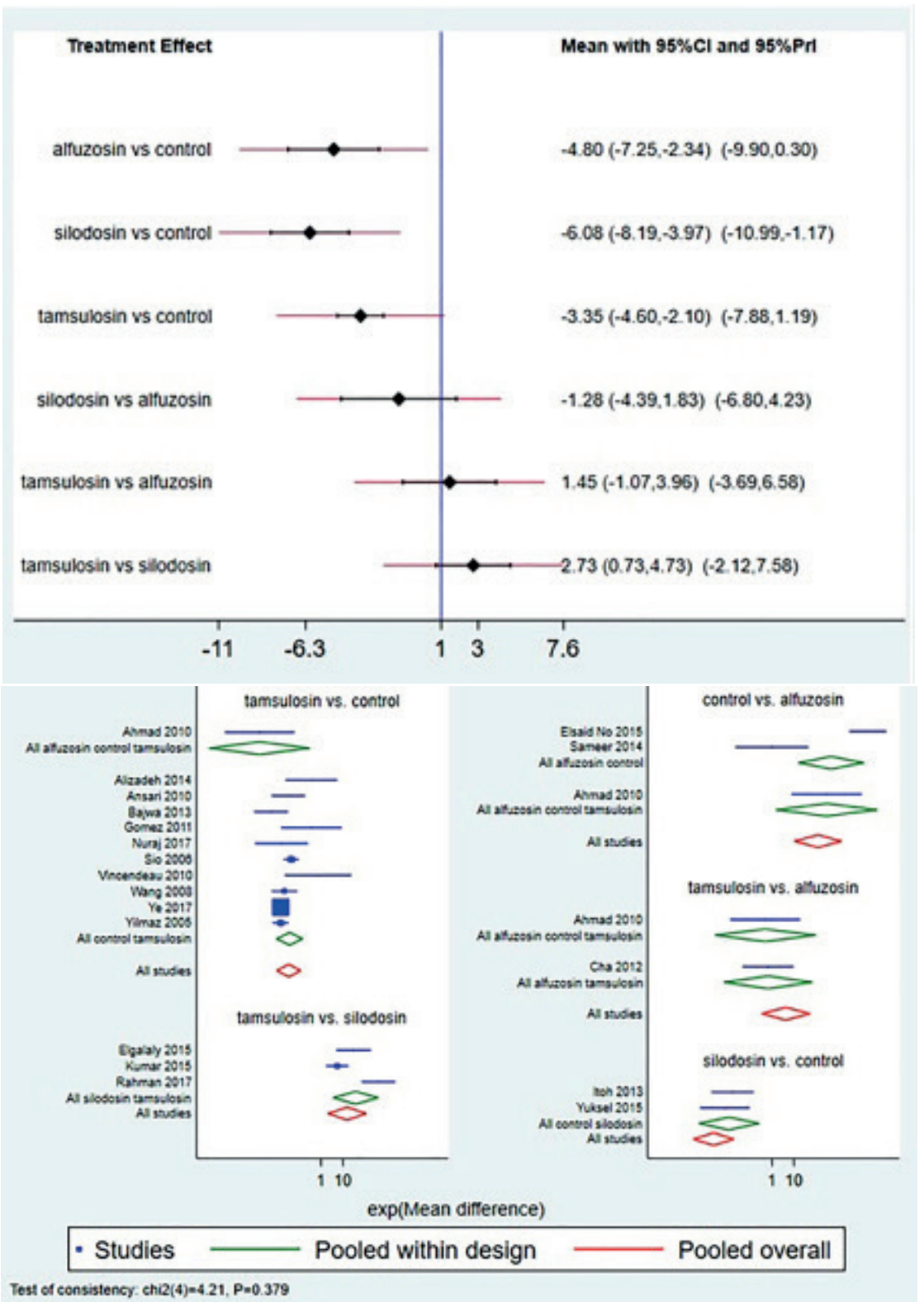


Figure 4 - Interval and Forest plot for various drugs for postural hypotension.

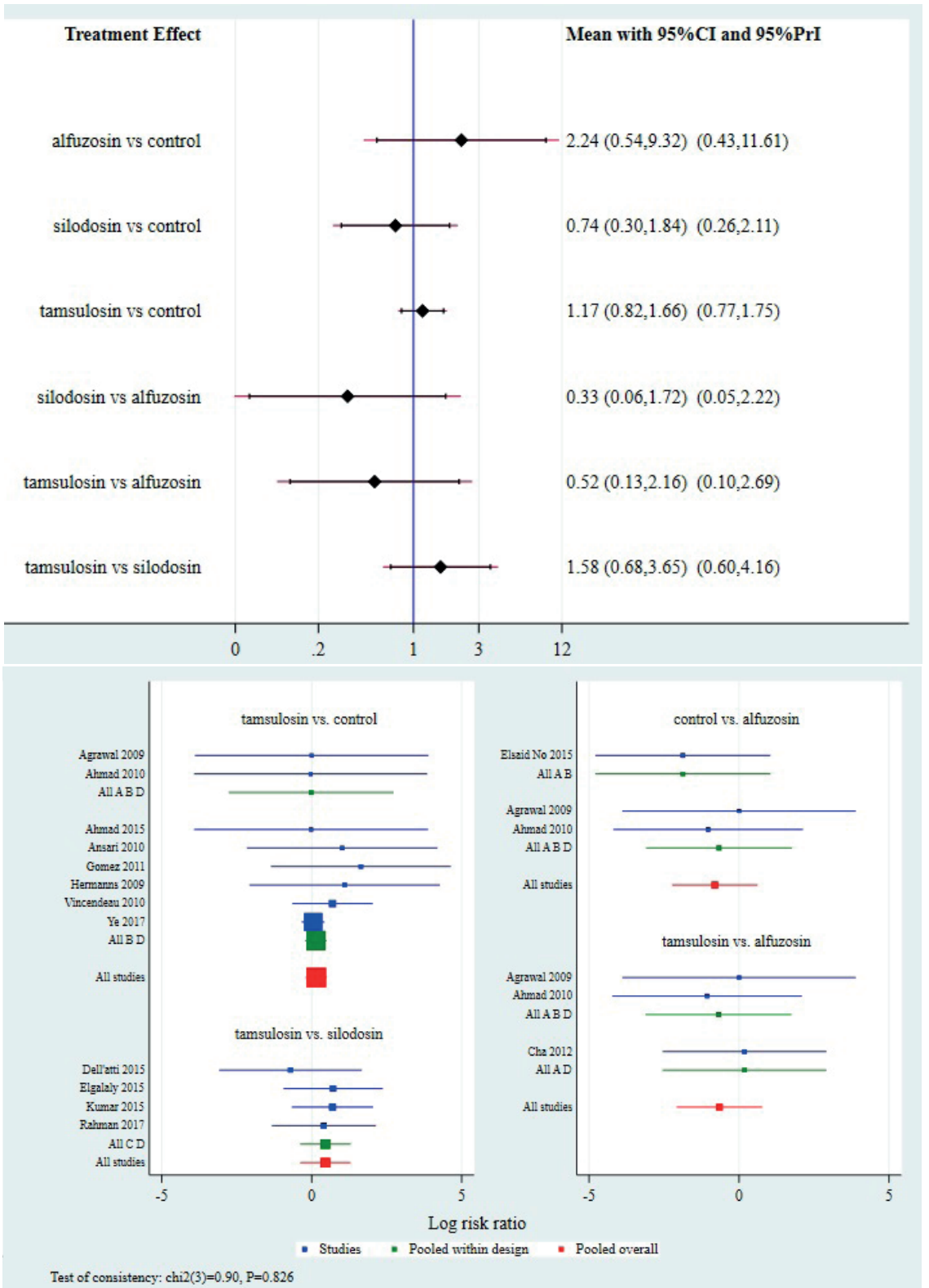
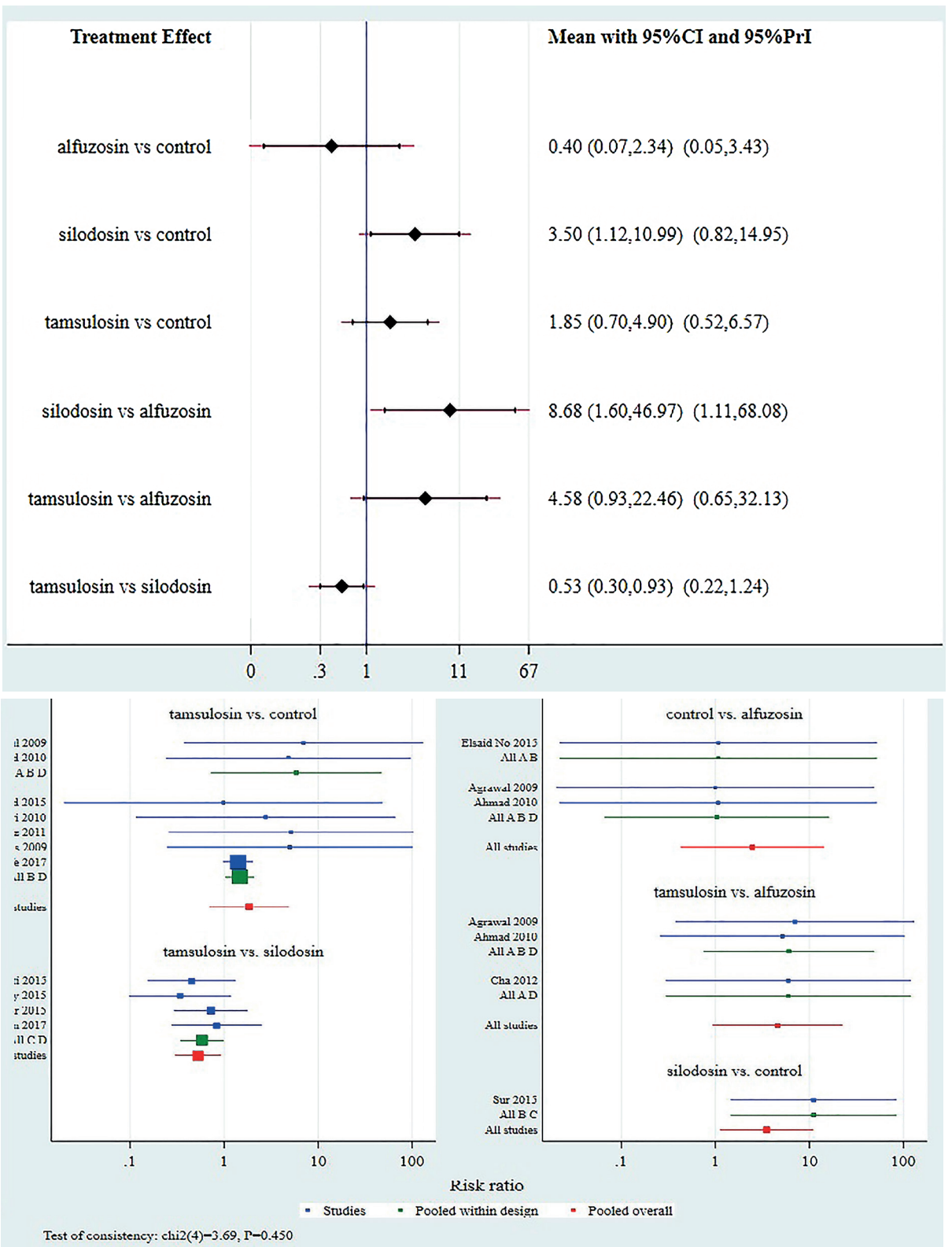


Figure 5 - Interval and Forest plot for various drugs for retrograde ejaculation.



grade ejaculationand alfuzosin the least (Table-2).

Sensitivity analysis

Sensitivity analysis was performed according to risk of bias and duration of treatment. Analysis after excluding studies at high risk bias was performed and we found RR of 1.48, 1.12, 1.18 for silodosin, tamsulosin and alfuzosin respectively as compared to placebo. Again, silodosin was the highest ranked drug followed by alfuzosin.

Separate analysis for studies with treatment duration for 4 weeks was also performed including 21 studies. SUCRA values obtained again revealed similar results. Similar results were obtained when analysis of studies with 4 weeks of follow-up at low or unclear risk of bias was performed (excluding studies at high risk of bias) Visual interpretation of comparison adjusted funnel plots revealed mild asymmetry for both the outcomes (Supplementary APPENDIX 2).

Certainty of evidence

Study level risk of bias assessment as per Cochrane risk of bias tool revealed 13 studies at low risk bias, 4 at unclear risk and 14 at high risk of bias. Mixed evidence for all the comparisons was obtained except for alfuzosin-tamsulosin for which only indirect evidence was available. Overall assessment of results of confidence in certainty of evidence for each comparison group is presented in the supplementary file S3.

DISCUSSION

For the last few decades, MET has been routinely used for conservative management of ureteric stones owing to its increased expulsion rate, accelerated "time to expulsion", and decreased severity of colic episodes (7). Studies in the past have shown that various types of pharmacotherapy like alpha- blockers, CCB, PDE-5 inhibitors, and steroids have better efficacy than placebo in management of the ureteric calculi (52). Few meta-analyses have also examined the role of various combinations of drug interventions in the management of ureteric stones (53), however, there is a paucity of studies specifically comparing the different alpha-blockers for treatment of distal ureteric calculi. Moreover, due to lack of studies comparing "head-to-head" interventions the most appropriate choice to treat ureteric stones remains unknown. This drawback can be circumvented by a "Network meta-analysis", in which both direct and indirect comparisons are analyzed with a common control within a network framework. With NMA approach researchers could acquire direct and indirect evidence through the comparison with a common comparator, thus making it possible to assess the actual effectiveness ranking of numerous interventions (54). Therefore, we did the present network meta-analysis to evaluate the relative efficacy of the commonly used alpha-blockers in the management of distal ureteric calculi.

Quality of the evidence and implications for research

One important concern in this review is that there were 14 studies at overall high risk of bias due to inadequate data in the allocation concealment and the detection bias domains. Overall confidence for each comparison group in this review ranged from "very low" to "moderate" according to CINeMA approach. Same care was taken during our sensitivity analysis by excluding studies at a high risk of bias and we still found our results to hold true.

In this large network meta-analysis, 31 randomized controlled trials enrolling 7077 patients with lower ureteric stones less than 10mm were incorporated in our final analysis. We compared SER and SET to assess the comparative efficacy of the commonly used alpha-blockers (alfusozin, silodosin and tamsulosin) for the treatment of distal ureteric stones. Previously, numerous meta-analyses have been published evaluating different alpha-blockers like tamsulosin (55), silodosin (56), and alfuzosin (57) and all have reported that the studied alpha-blockers are more efficacious than the control or placebo in improving stone clearance and time to stone expulsion. However, few multi-centre RCTs have demonstrated no significant favourable efficacy of alpha-blockers on the clearance rates as compared to placebo (35, 44, 46). But, majority of these trials (35, 44), have nearly two-thirds of the patient with stones smaller than 5mm and since smaller stones have more

likelihood of spontaneous expulsion, even in the absence of MET, the potential favourable effect of MET for smaller stones seems non-significant. Our study has concluded that alpha-blockers are definitely superior to placebo or control in terms of better SER and lesser time to stone expulsion.

Regarding the differences amongst the individual alpha-blockers, a meta-analysis completed by Sridharan et al. (52), concluded that silodosin was superior to others for SET and terazosin has the highest SER. While, a systematic review published by Campschroer et al. (58) concluded that the efficacy of alpha-blockers does not depend on the type of alpha-blocker used. Therefore, the results of this meta- analysis are different from the previous meta-analysis and silodosin appears to be the most efficacious drug in terms of SER and SET. From the side effect profile, all the drugs in this meta-analysis had similar incidence of postural hypotension, whereas silodosin had significantly higher incidence of retrograde ejaculation. Thus, silodosin may be the most efficacious drug in terms of SET and SER for the distal ureter stones; however, it may not be suitable for patients who are concerned about sexual function.

Alfuzosin seems to be suitable alternative for such patients.

Limitations

The present study is not without limitations. Firstly, we did not perform a subgroup analysis based on stone size as data was lacking from most of the studies. Secondly, many studies in the present analysis were not placebo-controlled and were at high risk of bias. Thirdly, apart from postural hypotension and retrograde ejaculation other adverse events were not explicitly studied in the included studies. Lastly, the literature search was limited to English language only.

CONCLUSIONS

Our NMA suggested that silodosin has highest SER followed by alfuzosin and tamsulosin. The time to stone expulsion is lower with silodosin followed by alfuzosin and tamsulosin. Therefore, silodosin appears to be the most efficacious drug of the three for lower ureteric stones less than 10mm.

ABBREVIATIONS

CCB = Calcium channel blockers
CINeMA = Confidence in Network Meta-analysis
NMA = Network meta-analysis
MET = Medical expulsive therapy
PDEI = Phosphodiesterase inhibitors
SER = Stone expulsion rate
SET = Stone expulsion time
SUCRA = Surface under cumulative ranking curve

CONFLICT OF INTEREST

None declared.

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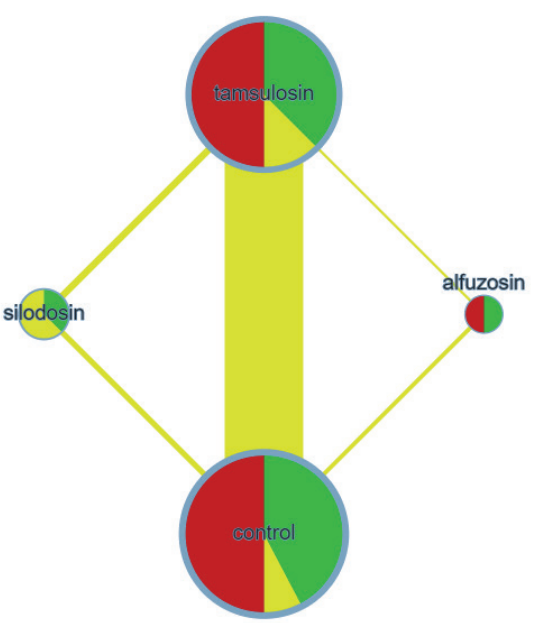
APPENDIX 1

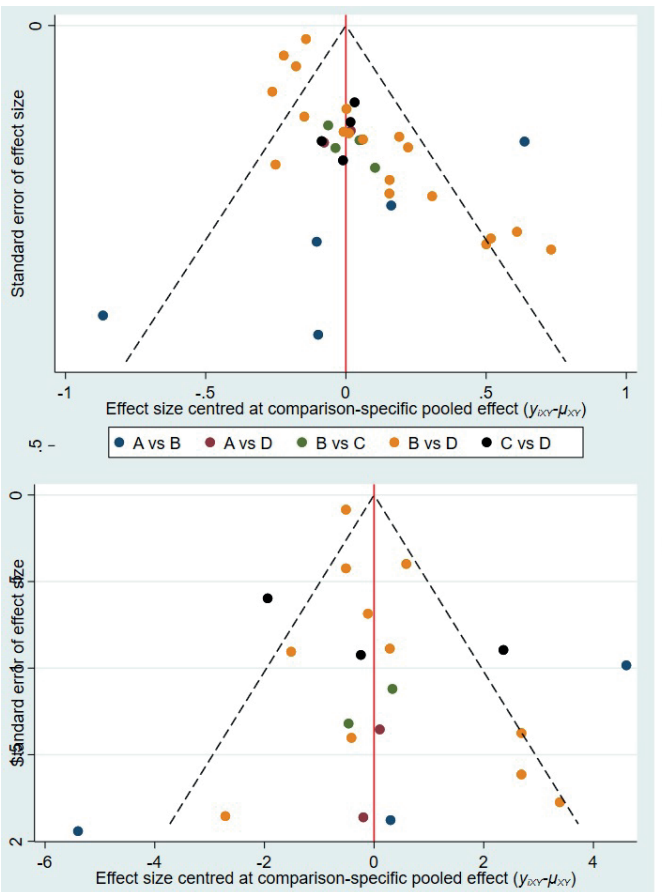
S1: Network plot the comparison of the three alfa-blockers and control group for primary outcome stone expulsion rate.



Nodes were colored green, yellow or red according to risk of bias (low, unclear and high respectively). Edges of plot were colored according to average risk of bias across all the studies. Edge width was according to sample size and node size by number of studies.

APPENDIX 2

S2: Comparison adjusted funnel plots for the two study outcomes



A- Alfuzosin, B= control, C= silodosin, D= Tamsulosin

REVIEW ARTICLE

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An introduction to male breast cancer for urologists: epidemiology, diagnosis, principles of treatment, and special situations

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ABSTRACT

Breast cancer (BC) is mainly considered a disease in women, but male BC (MaBC) accounts for approximately 1.0% of BC diagnoses and 0.5% of malignant neoplasms in the western population. The stigmatization of MaBC, the fact that men are less likely to undergo regular health screenings, and the limited knowledge of health professionals about MaBC contribute to men being diagnosed at more advanced stages. The aim of this article is to increase the visibility of MaBC among urologists, who have more contact with male patients. This review highlights key points about the disease, the risk factors associated with MaBC, and the options for treatment. Obesity and increased population longevity are among the important risk factors for MaBC, but published studies have identified family history as extremely relevant in these patients and associated with a high penetrance at any age. There is currently no screening for MaBC in the general population, but the possibility of screening in men at high risk for developing BC can be considered. The treatment of MaBC is multidisciplinary, and, because of its rarity, there are no robust clinical studies evaluating the role of systemic therapies in the management of both localized and metastatic disease. Therefore, in current clinical practice, treatment strategies for men with breast cancer are extrapolated from information arising from studies in female patients.

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INTRODUCTION

Breast cancer (BC), despite being commonly considered a disease in women, can also affect men. However, male BC (MaBC) is rare, accounting for approximately 1.0% of BC cases and 0.5% of malignant neoplasms in the general western population (1, 2). It was estimated that 2650 men in North America will be diagnosed with BC in 2021, and 530 men are expected to die from the disease (1). Data on the incidence of MaBC in other countries, especially in developing countries, are scarce.

In Brazil, the most common cancers in men, excluding non-melanoma skin cancer, are prostate and colorectal cancers. Despite its rarity, it is estimated that MaBC accounts for at least 1% of all BC cases in the country (3). As 66,680 women are expected to be diagnosed with BC in 2021, it is estimated that more than 600 men will be diagnosed with BC in Brazil. Although we do not have information on

incidence trends in Brazil, it is known that the incidence of MaBC has increased worldwide. In 1975, there were 0.85 cases per 100,000 men in the general population, and in 2011, this number had increased to 1.43 (4).

Older studies have shown that the interval between symptom onset and the diagnosis of BC in men can reach 21 months, whereas more recent studies have shown that this duration can still be as long as 12 months (5). Historically, men have greater resistance to accessing medical services and health prevention programs, which leads to greater diagnostic delays and higher overall mortality than in women (6). In the case of BC, in addition to peculiar male behavior toward health (no diseases prevention or regular routine exams), the stigmatization of MaBC and the lack of knowledge by health professionals contribute to diagnosis at more advanced stages in men (5). In a Brazilian study conducted among university students and professors about their knowledge about cancer, when asked about the possibility of men developing BC, 30.6% believed that men could not develop BC. When asked which cancers were the most prevalent in men, only 3.0% of responses included breast as a possible site (7). In another study, 25.8% of men had no knowledge about MaBC. Only 8.1% had received any professional guidance about the disease, 61.0% did not know about the need for self-examination, and 39.0% did not know how to perform self-examination (8).

The objective of this article is to increase the visibility of MaBC among urologists, as they have more contact with male patients. Here, we highlight key points about MaBC, the associated risk factors, and the options for treatment. In addition to individual factors, an increasing number of studies have shown that genetic predisposition seems to play a very important role in these patients, and this knowledge is essential for professionals to improve care for patients and their families. By expanding the information to these professionals, we hope to improve access to information and promote quality primary care for the entire population (9).

Epidemiology and Risk Factors

The risk factors for female BC (FBC) are widely known. The most well-known risk factors are those that increase the time and concentration of female hormones active in the breast tissue over time. These include age (with increased incidence from 40 years old and peak incidence over 50 years old), early menarche, late menopause, indiscriminate use of hormone replacement therapy, nulliparity, late age at first pregnancy (over 30 years old), and contraceptives (10). In addition, chest exposure to ionizing radiation and a family history of BC are important risk factors associated with FBC.

There are also known risk factors for MaBC, including obesity and increased population longevity (3, 10); however, the impact of risk factors is less known, as MaBC is less frequent than FBC and less studied.

Factors associated with an increased risk of MaBC that should be known by healthcare professionals who see these patients on a regular basis are: general (gynecomastia, increased blood estradiol, liver disease, obesity, testicular abnormalities, Klinefelter syndrome, ionizing radiation, longevity) and familiar/hereditary (family history for BC, hereditary cancer-related syndromes). However, some men without these risk factors still develop CM, although in some cases there may be uninformed, unknown or incorrectly collected data. There was an increase in the incidence of MaBC in the United States from 1973 to 1998; however, associated risk factors were not analyzed (11). In a study of 49 American patients at a single institution (12), 75.5% of patients did not have any of the general risk factors listed above, but 44.0% had a family history of MC.

The existing studies indicate that risk factors linked to family history are highly relevant in this group of patients, and this information has the potential to change the entire approach when a man is diagnosed with BC, including assessing risk with the patient's family (11, 12). When a patient is diagnosed with cancer, treatment planning and follow-up are centered on the individual; however, the family approach generates changes in the care protocol when considering the possibility of identifying a genetic alteration that increases the risk of disease.

According to the National Comprehensive Cancer Network (NCCN) criteria (10) (2021), MaBC is a criterion for testing high-penetrance genes at any age, especially *BRCA1*/2, CDH1, PALB2, PTEN, and p53. According to this increased risk, there is an indication for self-examination and clinical examination

of the breasts starting at age 35. According to the recommendations followed by the AC Camargo Cancer Center do Brasil (13) for MC testing, it is necessary to refer for genetic counseling:

a) Breast cancer ≤45 years
b) Breast cancer ≤50 years and one of the following:
  b 1) Second primary breast cancer
  b 2) Family with breast cancer at any age
  b 3) ≥1 family member with pancreatic cancer
  b 4) ≥1 family member with prostate cancer (Gleason score ≥ 7)
  b 5) Limited family history (<2 1st- or 2nd-degree female relatives alive up to 45 years old)
c) Triple-negative breast cancer ≤60 years
d) Breast cancer at any age if:
  d 1) ≥2 family members with breast, pancreatic, or prostate cancer (Gleason score ≥7)
  d 2) ≥1 family member with breast cancer <50 years
  d 3) ≥1 family member with ovarian cancer
  d 4) ≥1 family member with male breast cancer
  d 5) Ashkenazi ancestry
e) Male breast cancer
f) Patient without breast cancer, but based on family history (discuss interpretation limitations for the family):
  f 1) 1st- or 2nd-degree relative meeting the testing criteria

Epigenetic events also play an important role in CMM carcinogenesis, often associated with earlier age at diagnosis, and these changes are associated with worse prognosis (3).

ATM, BRCA1, PALB2, RAD51B, and *XRCC3* have epigenetic signatures in MaBC that are absent in corresponding normal tissue and gynecomastia samples obtained from patients without cancer or with a family history of BC. The *RAD51B* and *XRCC3* signatures can accurately discriminate MaBC from gynecomastia, with normal breast tissues showing methylation of these gene promoters at lower levels than in MaBC, suggesting the existence of a tumorigenesis pathway (3, 14).

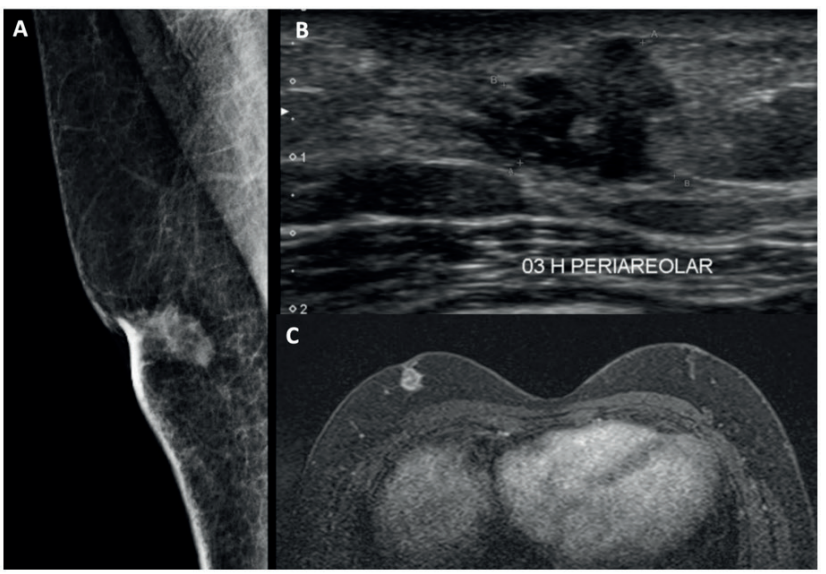
Unlike *BRCA1* mutation, *BRCA2* alteration is more common in MaBC than in FBC. In high-risk families, about 60-70% of MaBC cases have a *BRCA2* alteration. The risk of BC in patients with such alterations is 5.0-10.0%, whereas the risk of MaBC in the general population is 0.1%. The MaBC phenotype in carriers of this mutation includes high-grade, progesterone receptor-negative, HER2-enriched tumors, and patients tend to be younger (< 50 years) (3, 15).

DIAGNOSIS

For women, the lifetime risk of BC is one in eight, whereas for men, the lifetime risk is one in a thousand (4, 5). Mammography (16) plays a key role in routine screening and reducing mortality in women, especially when performed annually; however, the low incidence of MaBC does not allow the indication of periodic examinations (see Figure-1). However, the possibility of screening in men at high risk for developing BC, such as those with mutations in the BRCA genes, is currently being discussed (17). Currently, the NCCN guidelines recommend that men with BRCA mutations receive training and education in breast self-examination and undergo annual clinical breast examination starting at 35 years of age. Therefore, annual screening mammography can be considered in men with gynecomastia starting at age 50 or in men with a family history of BC 10 years before the age at diagnosis of the youngest known case in the family (10).

In a study of 3,806 MaBC cases and 571,115 FBC cases, the mean age at diagnosis was higher in men than in women (64.2 years vs. 59.1 years, p<0.01) (18). Further, men were more likely to have lymph node metastasis than women (N1mic: 5.9% vs. 4.0%; N1-3: 12.1% vs. 8.7%; N0: 73.3% vs. 80.1%; all p<0.01). Invasive ductal carcinoma was more common in men than in women (87.6% vs. 81.3%, p < 0.01), as was papillary BC (4.4% vs. 0.7%, p < 0.01). By contrast, the classic lobular subtype was more common in women (1.2% vs. 8.2%, p < 0.01) (3, 18). Most tumors were hormone receptor-positive and histological grade 2 (19). The 5-year overall survival (OS) was lower in men than in women (82.8% vs. 88.5%), and the risk of death from BC was 43.0% higher in men. This difference cannot be explained by diagnosis at advanced stages, because even among patients with stage I and II disease, men had worse OS than women (82.0% and 61.0% in men, respectively, and 90.0% and 79.0% in women, respectively) (3, 20, 21).

Figure 1 - An irregular mass in the retroareolar region of the right breast in a 44-year-old man, seen on mammography (A), ultrasonography (B), and magnetic resonance imaging (C).



Symptoms

The common complaints associated with FBC are often addressed in cancer prevention campaigns and are among the main motivations for seeking medical evaluation. However, as male breast complaints are rare, they are rarely commented upon, so they appear as a concern only in their occurrence, not as reasons for preventive conduct. As in women, breast complaints in men, including pain or enlargement of the mammary gland, are generally associated with benign issues (gynecomastia secondary to the use of medication) or physiological issues (teenager or senile gynecomastia). However, the presence of breast complaints, as well as misinformation on MaBC, can cause great discomfort and fear about the diagnosis (Table-1) (22, 23).

The main symptom of MaBC is the presence of a painless retroareolar mass (12). Depending on the time of disease onset and evolution, other symptoms may occur, such as nipple retraction, skin ulceration, local bleeding, and palpable axillary lymph nodes. However, imaging tests at the time of symptom onset are essential for the differential diagnosis or confirmation of the suspicion of MaBC.

The current recommendation of the American College of Radiology (ACR) for the assessment of palpable changes in the male breast differs in relation to the age at onset of symptoms (24). In patients younger than 25 years, ultrasonography should be the imaging method for the initial assessment. In patients older than 25 years, mammography should be the initial imaging method, followed by ultrasonography if the mammographic findings are inconclusive or suspicious of malignancy. Magnetic resonance imaging (MRI) is usually of little use in the routine investigation of changes in the male breast and should be restricted to individual cases, especially in the staging of confirmed malignant neoplasms.

The main differential diagnosis is gynecomastia, which can be differentiated from carcinoma using imaging methods. As fibroadenomas and cysts are very rare in men due to the lack of development of terminal ducto-lobular units in the male breast, any solid mass identified on imaging should be considered suspicious for malignancy (BI-RADS 4). In these cases, ultrasonography-guided percutaneous biopsy followed by histological examination of the biopsy specimen is necessary. Because of the small breast dimensions, the indication for mammography-guided biopsy is very rare (24).

MaBC usually presents on mammography as irregular, dense masses, with microlobulated, indistinct or spiculated margins, and eccentric in relation to the nipple-areola complex. Calcifications are less

Table 1 - Possible causes of gynecomastia in men (22, 23).

AGE-RELATED Newborns, puberty, elderly	FAT-RELATED Obesity, increased body fat
IDIOPATHIC	END-ORGAN ABNORMALITY
DRUG-RELATED Cannabis abuse; Use of anabolic steroids; occupational exposure to embalming fluids or oral contraceptives; contact with environmental phytoestrogens or phthalates; amlodipine, atorvastatin, benserazide, captopril, cimetidine, cladribine, combination, cytotoxic agents, cyclosporine, dasatinib, diazepam, didanosine, diethylproprion, digoxin, diltiazem, domperidone, D-penicillamine, etritinate, ffavirenz (HIV), fenofibrate, finasteride, fluoresone, fluoxetine, gabapentin, HAART, imatinib, indinaver (HIV), isoniazid, ketoconazole, marinol, methotrexate, metronidazole, nettle, nifedipine, omeprazole, paroxetine, phenytoin, pregabalin, ranitidine, rosuvastatin, saquinavir (HIV), spironolactone, stavudine, sulindac, sulperide, sunitinib, tandospirone, thalidomide, theophylline, venlafaxine, verapamil, vincristine.	

HIV = Human Immunodeficiency Virus; **HAART** = antiretroviral therapy

common than in women and present in approximately 30% of cases. On ultrasonography, the typical appearance is hypoechoic, solid, round or oval masses, with non-circumscribed margins (Figure-1). The higher frequency of papillary carcinomas results in a greater number of complex solid-cystic masses on ultrasonography (25).

Therapeutic Approaches to Breast Cancer in Men

The treatment of BC is multidisciplinary, and recognition of the histopathological subtype, as well as the initial staging, are the first steps toward optimal treatment.

Surgery

Surgical treatment of MaBC, whether upfront or after neoadjuvant chemotherapy, generally employs total mastectomy combined with sentinel lymph node dissection or axillary emptying because of the small breast volume and the presence of tumors close to the nipple-areola complex in most cases. Leone et al. (20) found that even patients with early-stage locoregional disease (81.2%) or tumors smaller than 1 cm (T1a or T1b) (74.0%) preferentially underwent total mastectomy. However, there was no difference in OS between patients undergoing mastectomy and those undergoing conservative surgeries (Table-2).

The indication for sentinel lymph node dissection in these patients follows the recommendation for FBC, i.e., patients with no initial clinical or radiological signs of axillary metastasis (N0) or those with N1 disease with clinical and radiological complete response after neoadjuvant chemotherapy. According to Leone et al., only patients who did not undergo axillary dissection had poorer survival (20).

An ongoing study with patients treated at the *A.C.Camargo Cancer Center* between 2000 and 2021

Table 2 - Studies of MaBC surgical treatment.

	Mastectomy	Conservative Surgery
Srour et al., 2020, 49 cases (12)	87.8%	4.1%
Yadav et al., 2018, 81 cases (19)	86.0%	14.0%
Leone et al., 2016, 1263 cases (20)	81.2%	17.6%
Campos et al. 2021, 65 cases (unpublished data)	89.0%	4.6%

MaBC = male breast cancer

included 65 men with MC, 61 of whom underwent surgical treatment, including total mastectomy (58/61) and breast-conserving surgery (3/61). Of the patients for whom we had information about the axillary approach, 38 underwent axillary dissection and 21 underwent exclusive resection of the sentinel lymph node (unpublished data).

Adjuvant therapy

Because of the rarity of MaBC, there are no robust clinical studies evaluating the role of systemic therapies in the management of both localized and metastatic disease. Hence, in current clinical practice, treatment strategies for men with BC are extrapolated from information arising from studies of FBC (26-28).

Since most BCs in men are hormone receptor-positive, endocrine therapy is the mainstay of treatment in these patients. The effectiveness of hormone deprivation, which initially involves orchiectomy, has long been established in the metastatic disease setting (5). Currently, the medication of choice to block estrogenic action is tamoxifen, a selective estrogen receptor modulator (26). In the adjuvant setting, observational studies show a benefit in OS with tamoxifen for at least 5 years after surgery (29). A recent meta-analysis with real-world data showed a significant increase in OS for patients receiving tamoxifen (HR 0.62, 95% confidence interval [CI] 0.41-0.95) (30). Therefore, for men with stage I–III hormone receptor-positive BC undergoing surgical treatment, adjuvant tamoxifen for 5 years is the therapy of choice, and it can be individually extended to 10 years based on tolerance and the risk of recurrence (26, 31).

Aromatase inhibitors (anastrozole, letrozole, and exemestane) perform better in the adjuvant setting than tamoxifen for postmenopausal women and are therefore the standard adjuvant therapies for FBC (29). However, their effectiveness is less evident in men. Population-based studies show poorer survival for men with BC treated with adjuvant aromatase inhibitors compared to those who received tamoxifen (29). Therefore, aromatase inhibitors should not be the routine choice in this setting, although they can be administered in combination with GnRH agonists or antagonists in patients with contraindications to tamoxifen (26).

Adjuvant endocrine therapy in men with BC has potential adverse effects that, as in women, can lead to treatment dropout. Up to 50% of men do not complete tamoxifen for 5 years after surgery. Sexual dysfunction/loss of libido and weight gain are the most common adverse effects, and hot flashes, mood alterations/depression, cognitive deficits, and thrombotic events may also occur (32).

Although the role of adjuvant chemotherapy in MaBC has not been established by prospective randomized clinical studies, observational studies have shown that it increases OS (33, 34). However, not all patients benefit from adjuvant chemotherapy. A study of 514 men with stage I–III BC in the Surveillance, Epidemiology, and End Results (SEER) database concluded that chemotherapy may not be necessary for patients with stage I and IIA disease (34). In general, the indications for adjuvant chemotherapy should take into account, especially, the tumor size, the histological grade, and the lymph node involvement. As in FBC, the use of the 21-gene recurrence score for male patients with hormone receptor-positive T1–T3/N0–N1 tumors may be useful to guide the decision regarding the administration of chemotherapy (26).

Treatments developed with the aim of overcoming endocrine resistance primarily in the female population, such as fulvestrant, mTOR inhibitors, and more recently CDK4/6 inhibitors and PI3K inhibitors, have also been indicated for the treatment of men with BC (26, 27, 35). In the rare cases of HER2-positive and triple-negative MaBCs, targeted therapies with anti-HER2 and anti-PD1 monoclonal antibodies, respectively, follow the same treatment recommendations for women with these tumor subtypes (26).

Considering the non-negligible prevalence of pathogenic germline variants in genes involved in DNA repair mechanisms in men with BC, especially *BRCA2*, the use of poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPi) is of particular interest. In patients with these alterations, PARPi (olaparib and talazoparib) are an important therapeutic option for metastatic disease (36, 37). Recently, a phase 3 study of 1836 patients, including 6 men, with high clinical-risk BC and germline variant pathogenic or likely patho-

genic mutations in *BRCA1/2* had increased invasive disease-free survival with adjuvant olaparib for 1 year (38).

SPECIAL SITUATIONS FOR UROLOGISTS

Testicular Tumors and Gynecomastia

Gynecomastia could be a first presentation in several neoplasms (39):

- ✓ Testicular: originating from germ (secreting forms), Leydig or Sertoli Cells;
- ✓ Adrenal: androgen - or estrogen - secreting tumors; mainly carcinomas (gynecomastia usually of recent onset and progress rapidly);
- ✓ Ectopic production of HCG (human chorionic gonadotropin), such as choriocarcinoma;

Leydig cell tumors are the most common of the 5% of sex cord-stromal tumors; they are generally benign lesions, with only 5-10% being considered malignant. Due to Leydig cells' hormonally active properties, they can present with gynecomastia (the most common hormone-related presentation), precocious puberty, breast tenderness, reduce libido, erectile dysfunction, azoospermia, primary infertility, or even Cushing syndrome (40).

Sertoli cells tumors are often hormonally active, secreting estrogen. Males present with gynecomastia, advanced bone age, and rapid growth with short stature (41). These tumors typically emerge in syndromes such as Peutz-Jeghers (39).

In the case of enlargement of the breast and palpable glandular breast tissue, it is necessary to investigate the suspected tumor, through testicular palpation, ultrasound and referral to a urologist. Likewise, breast tissue hard, non-tender and/or joining underlying structures, the need for biopsy, referral to a breast cancer specialist and oncologic treatment (if malignant) should be evaluated (39).

Prostate Cancer and Breast Cancer

Steroid hormones play an important role in the tumorigenesis of both MBC and prostate cancer. Prostate cancer is androgen-dependent and responsive to androgen blockade, whereas MaBC is estrogen--dependent and responsive to estrogen blockade in the vast majority of cases (19). Despite this divergence regarding hormonal risk factors, a possible relationship between prostate cancer and MaBC has been hypothesized for several decades (42).

Men with BC are at an increased risk of developing second primary neoplasms. In a multicenter study that included 3409 men with BC, 426 (12.5%) developed a second cancer (42). Small bowel cancer was the most common second cancer (standardized incidence ratio [SIR] = 4.95), followed by myeloid leukemia (SIR = 3.42). The SIR for prostate cancer was 1.61 (95% CI 1.34-1.93). Another study that analyzed data from 1788 men with BC from the SEER database found a non-significant increase in the incidence of prostate cancer (SIR = 1.09; 95% CI 0.85-1.37) (43), which is in agreement with the results of more recent studies [44]. Absolute data show that the incidence of prostate cancer in men with previously diagnosed BC ranges from 3.5% to 17.4% (Table-3), which is higher than that in the general population.

BC accounts for approximately 0.09% of second primary cancers in men previously diagnosed with prostatic adenocarcinoma (48, 49). A 2003 study that analyzed data from all prostate cancer patients in the Swedish Cancer Registry (135,713 men from 1958 to 1996) showed an increased risk of MaBC (SIR = 2.01, 95% CI 1.44–2.74) (50). The authors concluded that this increased risk of BC after the diagnosis of prostate cancer could be explained by the estrogen therapy administered in the treatment of these patients, although this therapy is in decline. More recent population-based studies have not found an increased association of BC in men previously diagnosed with prostate cancer and instead show an overall lower incidence of a second neoplasm in prostate cancer patients (50, 51).

Risk of BC in transgender patients

Little is known about the risk of BC in transgender patients because of the small number of studies, the underestimation of the number of cases, and the lack of recommendations for specific screening. However, BC diagnoses in transgender individuals are becoming more common, and knowledge on the subject is necessary for proper care (52). To properly discuss BC in these patients, it is important to define the following terms:

- **Cisgender man (or cis man):** an individual designated male at birth who identifies and lives as someone of the male gender.

Table 3 - Studies evaluating the incidence of prostate cancer in male patients with breast cancer.

Author, year	Institution/Data Source	Period	Number of participants with MBC	Patients with PC (%)	Patients with prior PC
Lee et al., 2009 (42)	Cleveland Clinic	1990–2006	69	12 (17.4)	6
Leibowitz et al., 2003 (45)	Dana-Farber Cancer Institute	1977–2000	161	10 (6.2)	2
Hemminki et al., 2005 (46)	Multi-institutional	1941–1997* 1978–1998	3409	119 (3.5)	0
Dawood et al., 2016 (47)	SEER	1990–2012	6970	644 (9.2)	NI
Satram-Hoang et al., 2006 (48)	California Cancer Registry	1988–2003	1926	69 (3.6)	0
Campos et al., ongoing**	Brazilian Cancer Center	2000–2021	65	11 (16.9)	3

MaBC = male breast cancer; **PC** = prostate cancer; **SEER** = Surveillance, Epidemiology, and End Results; **NI** = not informed.
* The period varied according to the institution. The longest and shortest periods are presented.
** Ongoing study, unpublished data.

- **Cisgender woman (or cis woman):** an individual designated female at birth who identifies and lives as someone of the female gender.
- **Transgender man (or trans man):** an individual designated female at birth who identifies and lives as someone of the male gender.
- **A transgender woman (or trans woman):** an individual designated male at birth who identifies and lives as someone of the female gender (53).

BC in trans men

The risk of BC in these patients is considered to be similar to the risk of BC in cis men. Trans men frequently undergo breast reduction surgeries, similar to risk-reducing surgeries for patients with hereditary syndromes, and these surgeries, in addition to the administration of testosterone, reduce the risk of BC by approximately 90% (54). However, those who do not undergo breast reduction should be advised to maintain mammographic screening as indicated for women, with an annual mammogram starting at age 40. The recommendation is to follow the premise of "always track and track what you have" (53).

BC in trans women

It is expected that the risk of BC in this group is higher than FBC, as these patients receive female hormones; however, this increase does not reach the risk of BC in cis women (54). There is an estimated 46-fold increase in risk of BC for trans women compared to cis men, but their risk is still lower than that of cis women, most likely explained by lower hormone levels (albeit prolonged hormone exposure) (55).

In relation to screening, despite the insufficient literature on the subject, biannual mammography is indicated from the age of 50 onwards, or from 5 to 10 years after the start of female hormone administration. We also lack data to support case management of trans women with a *BRCA1* mutation. However, a *BRCA1* mutation increases the risk of BC 6% in cis men and more than 78% in cis women. Therefore, if the patient does not want preventive removal of the breasts, they should be screened as high-risk cis women (56) (Table-4).

CONCLUSIONS

Despite its rarity, MaBC represents an important problem in men's health that can be neglected if professionals who have higher access to this population are uninformed. Therefore, urologists can play an important role in the early diagnosis of MaBC because their work involves a broader scenario in which the focus is greater than sexual dysfunction and screening for prostate cancer. The promotion of care, whether for cis men, trans men, or their families, is the responsibility of these professionals.

Table 4 - BC risk and screening for trans men and women (13, 53-55).

Subject	Risk	Management
Cis men	1:1000; 1% of cancer cases in the male population	Not indicated
Cis wmen	1:8; 10-12% lifetime risk	Annual mammogram beginning at age 40
Cis men with BRCA mutation	> 6%	If the patient has gynecomastia, screening starts at age 50 or 10 years before the age of onset in the youngest individual in the family
Cis women with BRCA mutation	>78%	Earlier-onset mammography according to the type of mutation, and MRI is included in the screening
Trans men with both breasts	Lower risk than cis women due to the administration of testosterone	Biannual mammogram beginning at age 50; annual recommendation from the age of 40 [13].
Trans men without breasts (after mastectomy)	Risk similar to that of cis men because the breasts were removed	Mammography does not need to be performed; encourage education and self-knowledge
Trans women	46 times higher risk than cis men	Biannual mammogram beginning at age 50 or from 5-10 years of the start of female hormones

BC = breast cancer; **BRCA** = Breast Cancer Gene; **MRI** = Magnetic Resonance Imaging

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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The role of hyperbaric oxygen therapy in Fournier's Gangrene: A systematic review and meta-analysis of observational studies

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ABSTRACT

Purpose: Management of Fournier's Gangrene (FG) includes broad-spectrum antibiotics with adequate surgical debridement, which should be performed within the first 24 hours of onset. However, this treatment may cause significant loss of tissue and may delay healing with the presence of ischemia. Hyperbaric oxygen therapy (HBOT) has been proposed as adjunctive therapy to assist the healing process. However, its benefit is still debatable. Therefore, this systematic review and meta-analysis aimed to evaluate the effect of HBOT as an adjunct therapy for FG.

Materials and Methods: This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocol to obtain studies investigating the effect of HBOT on patients with FG. The search is systematically carried out on different databases such as MEDLINE, Embase, and Scopus based on population, intervention, control, and outcomes criteria. A total of 10 articles were retrieved for qualitative and quantitative analysis.

Results: There was a significant difference in mortality as patients with FG who received HBOT had a lower number of deaths compared to patients who received conventional therapy (Odds Ratio 0.29; 95% CI 0.12 – 0.69; p = 0.005). However, the mean length of stay with Mean Difference (MD) of -0.18 (95% CI: -7.68 – 7.33; p=0.96) and the number of debridement procedures (MD 1.33; 95% CI: -0.58 – 3.23; p=0.17) were not significantly different.

Conclusion: HBOT can be used as an adjunct therapy to prevent an increased risk of mortality in patients with FG.

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INTRODUCTION

Fournier's Gangrene (FG) is a progressive infectious disease marked by necrotizing fasciitis of the perineum and external genitalia (1, 2). It is considered an emergency in Urology due to its tendency to develop into a severe soft tissue infection associated with systemic sepsis. In several cases, it also required amputation of the penis (3). FG mortality rate ranges from 18 to 50%, with an average of 20 to 30% (4). Management of FG includes aggressive resuscitation, broad-spectrum antibiotics, and surgical debridement, which should be done in under 24 hours

(5). Despite this current standard therapy, FG still causes high mortality. It is possibly due to poor local blood supply in FG patients, causing infection and damage to the blood vessels, thus may delay healing. Aggressive debridement, in this case, may cause significant loss of tissue which prolongs the healing process causing long hospital stays and a high mortality rate (6).

This problem leads to Hyperbaric Oxygen Therapy (HBOT) as adjunctive therapy for FG. Hyperbaric oxygen therapy (HBOT) is a therapeutic option involving inhaling pressurized 100% oxygen in sealed chamber (7). HBOT allows the speeding up of the healing process, which increases tissue oxygen tension, and inhibits and kills anaerobic bacteria. HBOT possessed a bactericidal effect on anaerobic infection due to aerobic or anaerobic bacteria. Recent studies have reported the role of HBOT in significantly decreasing mortality in Fournier Gangrene patients (8). There is no consensus regarding the role of adjunctive therapy of HBOT in FG, and it is still debated whether it can be used to manage FG (4, 9). Therefore, this study aims to evaluate the effect of HBOT as an adjunct therapy for FG.

MATERIALS AND METHODS

This study was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol. Preliminary searching was performed to ensure that the PICO characteristics were yet to be investigated and avoid duplication of meta-analysis. Literature searches were conducted through MEDLINE, EMBASE, and Scopus databases. Applied key words were specified as ("Fournier Gangrene" or "penile necrotizing fasciitis") and ("hyperbaric oxygen" or "hyperbaric oxygen therapy" or "hyperbaric oxygen treatment"). The expanded searching terms are presented in Table-1. The protocol of this study was registered on PROSPERO (CRD42021283421).

Inclusion and Exclusion Criteria

Articles permitted for inclusion must have been a randomized controlled trial or observational research, written in English, comprising a minimum of two arms, reporting the number of debridement, length of stay, and mortality rates in patients with FG who were treated with HBOT as opposed to only conventional therapy. Experimental trials in animals, unpublished articles, and abstract-only findings were excluded. Hyperbaric oxygen therapy (HBOT) is an adjunctive treatment in which the patients inhale 100% O^2 fraction while being exposed to rising atmospheric pressure. The interventional arm was compared to the standard conventional therapy without HBOT.

Data Extraction

Two independent investigators retrieved the data according to the extraction template. Any discrepancies and disagreements regarding data extraction would be discussed and decided by a third investigator as needed. The extracted items included study characteristics (authors, time of publication, number of samples, study design, inclusion and exclusion criteria, duration of follow-up); baseline characteristics of the subjects (age, type of intervention, affected anatomical region, and location of the study); and quantitative outcomes (length of stay, number of debridement procedures, and number of deaths).

Table 1 - Systematic search using relevant keywords.

Database	Keywords	Articles (n)
PubMed/MEDLINE	((((Fournier Gangrene) OR (Penile necrotizing fasciitis)) AND (Hyperbaric oxygen)) OR (Hyperbaric oxygen therapy)) OR (Hyperbaric oxygen treatment)	90
Scopus	((((Fournier Gangrene) OR (Penile necrotizing fasciitis)) AND (Hyperbaric oxygen)) OR (Hyperbaric oxygen therapy)) OR (Hyperbaric oxygen treatment)	191
EMBASE	((((Fournier gangrene) OR (penile necrotizing fasciitis)) AND (hyperbaric oxygen)) OR (hyperbaric oxygen therapy)) OR (hyperbaric oxygen treatment)	173
	TOTAL	**454**

Quality Assessment

The risk of research bias was assessed using The Newcastle-Ottawa Scale (NOS), including selection, comparability, and exposure parameters. This scoring system was used to assess the risk of bias in non-randomized studies. The result from NOS instrument assessment is classified into three categories. A score of 0-3 indicates a low-quality study, while 4-6 indicates a medium quality study, and 7-9 indicates a high-quality study.

Statistical Analysis

The measured endpoints were the mean number of debridement, mean length of stay, and mortality rate. The dichotomous variable was analysed using Odds Ratio (OR) at 95% Confidence Interval (CI), with a p-value below 0.05 regarded as statistically significant. Secondary outcomes were measured as a continuous variable with Weighted Mean Difference (WMD). Analysis of heterogeneity between studies was calculated using I^2. Heterogeneity is considered high if the I^2 is above 50%. Subsequently the random-effects model will be applied for pooled analysis. Otherwise in I^2 <50%, the statistical fixed-effects model will be used. Statistical analysis was performed using RevMan 5.4 for Windows software and presented in the form of forest plots and descriptive narratives.

RESULTS

Systematic search results

The initial search of the study database using specific key words (Table-1) yielded 454 studies. However, we removed 194 studies with irrelevant abstracts or titles and 230 duplicate studies. A total of 30 full-text studies were then assessed for eligibility. Finally, ten eligible studies were included in the analysis of this study (Figure-1).

Baseline characteristics of the included studies

The characteristics of each included study are presented in Supplementary Table-1, which consists of the author and year of published studies, study design, description of the intervention, the mean age, comorbidities, and FGSI score. All included studies were retrospective studies that were published between 1998 and 2021. The total number of patients analysed in this meta-analysis was 657 patients consisting of 268 in the HBOT group and 369 in the non-HBOT group, with the average age of each study ranging from 46.13 to 68.3 years old. The intervention groups of each study were given a different dose of HBOT. However, only three studies mentioned the mean FGSI score of the included studies, ranging from 7.38 to 9 (10-12). Fournier gangrene patients were associated with several comorbidities such as diabetes, alcoholism, hypertension, and smoking. The assessed outcome of this study includes mortality, mean length of stay, and mean number of debridement, as described in Table-2.

Risk of bias assessment

We used the NOS instrument to assess the risk of bias in this meta-analysis. The result from the assessment using NOS instrument of the included studies ranged from 6 to 8 which indicates a moderate to a high-quality assessment of the risk of bias (Table-3).

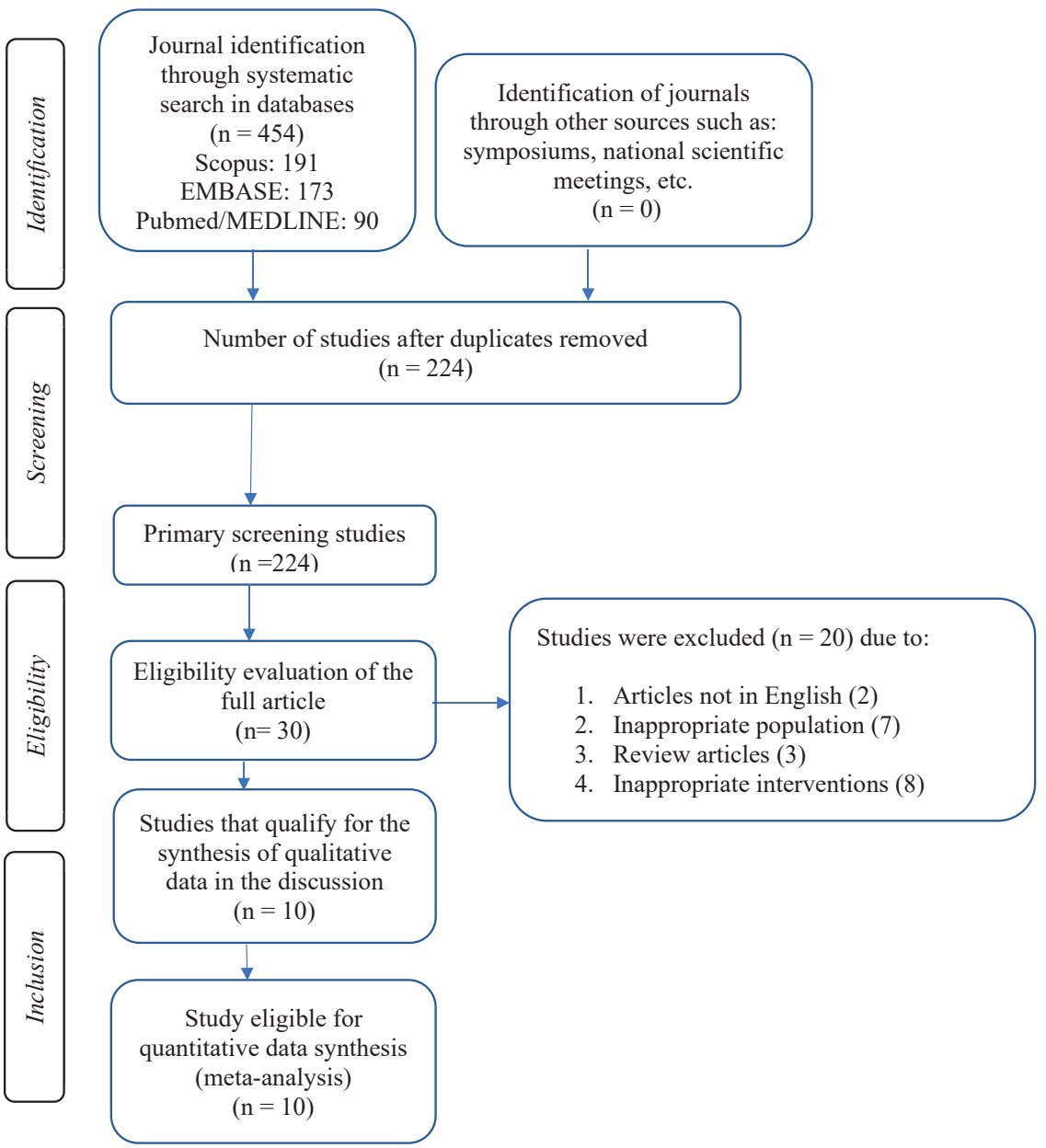
Meta-analysis results on mortality

Based on the analysis of ten included studies (7, 10-18), patients with HBOT have a significantly lower mortality rate than patients without HBOT (OR 0.29; 95%CI 0.12, 0.69; p=0.005) (Figure-2). The random-effects model was used due to high heterogeneity between studies (P = 0.03; I^2 = 51%). Of the ten studies, Creta et al. and Feres et al. have notable significance in the analysis due to the larger number of samples compared to other studies (7, 10). Only two studies reported an increase in mortality in patients treated with HBOT (13, 18).

Meta-analysis result on the length of stay

The forest plot analysis in this study also evaluated the difference in length of stay between HBOT and non-HBOT groups. The analysis results of two included studies (11, 13) did not reveal any significant difference regarding the mean length of stay between the HBOT and non-HBOT groups in FG patients (MD -0.18; 95%CI: -7.68 – 7.33; p=0.96) (Figure-3a). The fixed-effects model was used due to low heterogeneity between studies (p = 0.94; I^2 = 0%).

Figure 1 - Study selection based on the PRISMA 2020 flowchart.



Meta-analysis results on the number of debridement

This meta-analysis also compared the number of debridement procedures performed in HBOT and non-HBOT groups. Three included studies (11, 13, 14) in the analysis of this outcome revealed no significant difference in the mean number of debridement procedures between HBOT and non-HBOT in FG patients (MD 1.33; 95% CI -0.58-3.23; p=0.17) (Figure-3b). The random-effects model was used due to the heterogeneity between studies was high at 95% (<0.00001; I^2 95%)

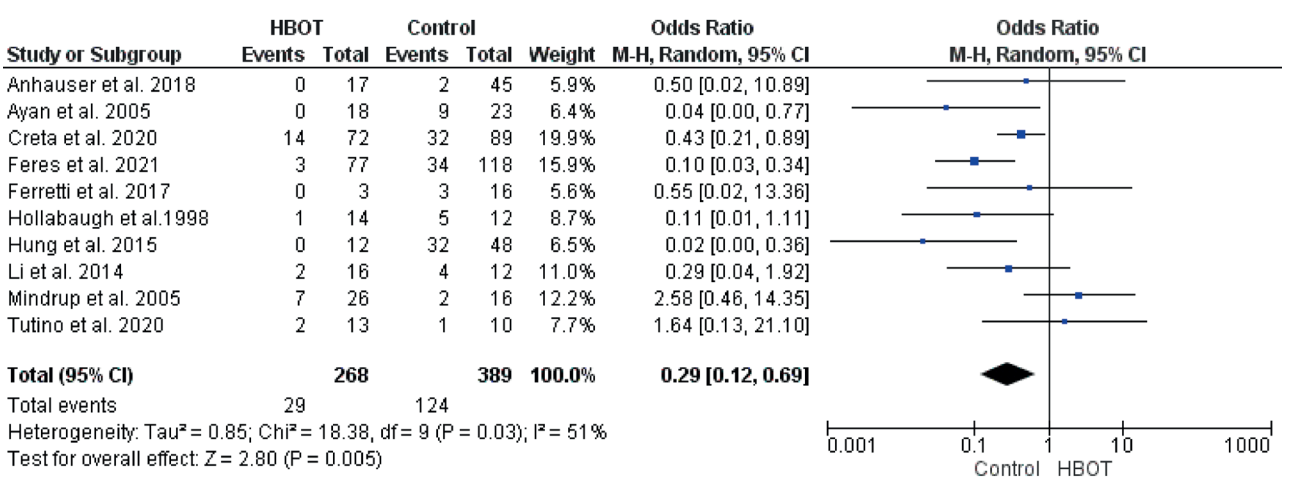
Table 2 - Evaluated Parameters in the assessment of the outcome.

Study (Years)	Study Type	Intervention	Sample Number	Outcome		
				Mortality (event/total)	Number of debridement (mean ± SD)	Length of stay (mean ± SD)
Feres et al., 2021 (7)	Retrospective	With Hyperbaric Oxygen Therapy	79	3 / 77	NR	NR
		Without Hyperbaric Oxygen Therapy	118	34 / 118	NR	NR
Creta et al., 2020 (10)	Retrospective	With Hyperbaric Oxygen Therapy	72	14 / 72	NR	NR
		Without Hyperbaric Oxygen Therapy	89	32 / 89	NR	NR
Tutino et al., 2020 (18)	Retrospective	With Hyperbaric Oxygen Therapy	13	2/13	NR	NR
		Without Hyperbaric Oxygen Therapy	10	1/10	NR	NR
Anheuser et al., 2018 (14)	Retrospective	With Hyperbaric Oxygen Therapy	17	0 / 17	13.3 ± 6.3	NR
		Without Hyperbaric Oxygen Therapy	45	2 / 45	4.8 ± 2.9	NR
Ferretti et al., 2017 (12)	Retrospective	With Hyperbaric Oxygen Therapy	3	0/3	NR	NR
		Without Hyperbaric Oxygen Therapy	16	3/16	NR	NR
Hung et al., 2016 (17)	Retrospective	With Hyperbaric Oxygen Therapy	12	0/12	NR	NR
		Without Hyperbaric Oxygen Therapy	48	32/48	NR	NR
Li et al., 2015 (11)	Retrospective	With Hyperbaric Oxygen Therapy	16	2 / 16	1.32 ± 0.48	31.4 ± 12.51
		Without Hyperbaric Oxygen Therapy	12	4 / 12	2.17 ± 0.72	31.3 ± 14.47
Mindrup et al., 2005 (13)	Retrospective	With Hyperbaric Oxygen Therapy	26	7 / 26	1.75 ± 0.878	30.8 ± 17
		Without Hyperbaric Oxygen Therapy	16	2 / 16	1.75 ±0.878	31.3 ± 18.2
Ayan et al., 2005 (15)	Retrospective	With Hyperbaric Oxygen Therapy	18	0/18	NR	NR
		Without Hyperbaric Oxygen Therapy	23	9/23	NR	NR
Hollabaugh et al., 1998 (16)	Retrospective	With Hyperbaric Oxygen Therapy	14	1/14	NR	NR
		Without Hyperbaric Oxygen Therapy	12	5/12	NR	NR

Table 3 - NOS instrument to assess the risk of bias of the study.

No.	Author	Year	Type of Studies	Quality Score			
				Selection	Comparability	Exposure	Total
1	Feres et al., (7)	2021	Retrospective study	3	1	3	7
2	Creta et al., (10)	2020	Retrospective study	3	2	3	8
3	Tutino et al., (18)	2020	Retrospective study	3	1	2	6
4	Anheuser et al., (14)	2018	Retrospective study	3	0	3	6
5	Ferretti et al., (12)	2017	Retrospective study	3	1	3	7
6	Hung et al., (17)	2016	Retrospective study	3	2	2	7
7	Li et al., (11)	2015	Retrospective study	4	0	2	6
8	Mindrup et al., (13)	2005	Retrospective study	3	0	3	6
9	Ayan et al., (15)	2005	Retrospective study	3	1	2	6
10	Hollabaugh et al., (16)	1998	Retrospective study	3	1	2	6

Figure 2 - Forest plot for the mortality rate of FG patients in HBOT and non-HBOT groups.



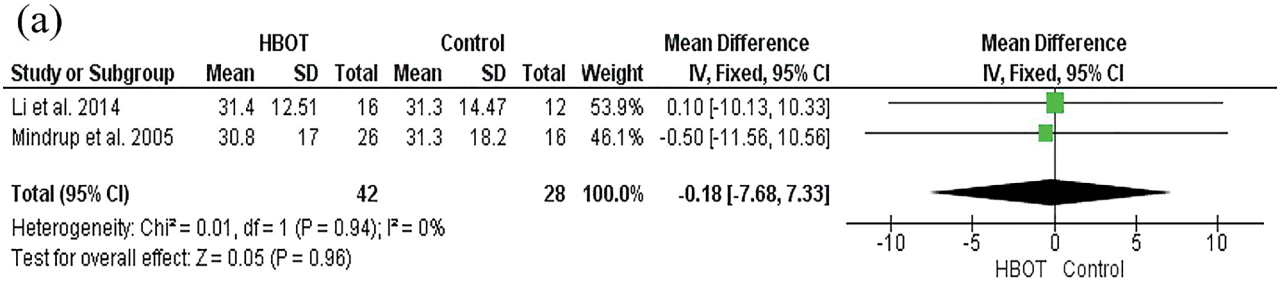
DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis study on the evaluation of HBOT in Fournier Gangrene patients. Oxygen therapy (HBOT) is an adjunctive treatment to the primary surgical debridement in the cases of soft tissue infection. This treatment involves inhaling 100% fraction of Oxygen in a pressurized environment. However, the benefit of HBOT for Fournier Gangrene (FG) is still controversial (19). Further investigation is needed before HBOT can be recommended for routine use in cases of FG. Our study demonstrated a significant result that HBOT might reduce the mortality rate in FG patients. However, the effect of HBOT on the length of stay and number of debridement was not proven in this study.

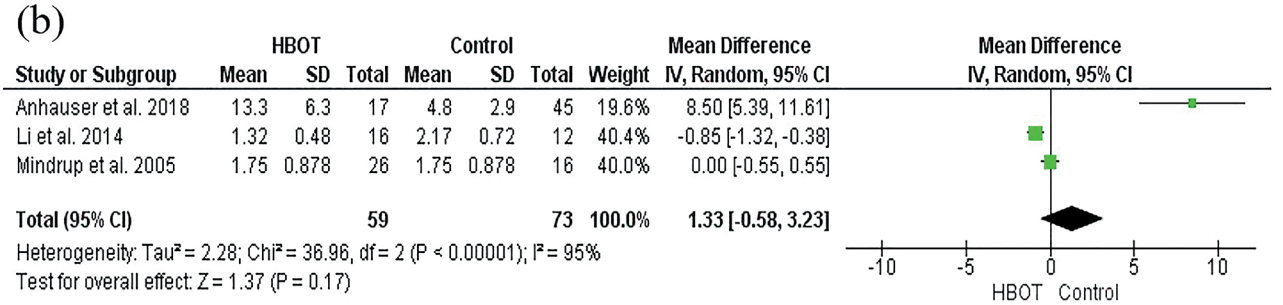
Several previous studies have proven that the most important intervention to control the progressivity of the rapidly infectious process of FG involves repeated surgical debridement, broad-spectrum antibiotics, and intensive care. However, FG patients still posses a high risk of mortality

Figure 3 - a) Forest plot for the length of stay of FG patients in HBOT and non-HBOT groups, b) Forest plot for the number of debridement of FG patients in HBOT and non-HBOT groups.

(a)



(b)



and morbidity. Finding an adjunctive treatment to the standard treatment was crucial and may significantly benefit survival and prevent higher mortality of FG patients. This meta-analysis revealed a significantly lower mortality rate in FG patients who received adjuvant HBOT than conventional therapy (OR 0.29; 95% CI 0.12, 0.69; p = 0.005), consistent with findings in several studies (10, 11, 20, 21). A study by Anheuser et al. (2018) reported that this promising result in the HBOT group was also influenced by the well availability of hyperbaric oxygen therapy and safe patient transfer despite the patient's poor physical condition because delaying the patient transfer to surgical debridement may significantly increase mortality rate (14). However, HBOT alone cannot replace the initial treatment of FG, which includes aggressive resuscitation, broad-spectrum antibiotic therapy, early colostomy, and adequate debridement (17). Another study suggested that HBOT became an independent predictor for decreased mortality rate due to Fournier Gangrene (12). A study by Mindrup et al. (2005) has contradictory results regarding the HBOT group's mortality rate. It revealed that patients who underwent HBOT have a higher mortality rate, 12.5% in the non-HBOT group and 26.9% in the HBOT group (13). On the other hand, a study by Pizzorno et al. (1997) showed 0% mortality rate in patients that did not undergo HBOT (22), while other studies only reported a 3 and 9% mortality rate (23, 24). Differences may occur due to several factors which may affect mortality in the treatment of Fournier Gangrene patients, such as surgeon experience, early administration of antibiotic therapy, intensive care, and early surgical therapy (22, 25-27). Another study also reported that the surface area of the infected body is also a factor that affects survival and mortality (28). Hyperbaric oxygen therapy was considered to be safe because it did not cause a delay in surgical debridement or interrupt the standard therapy.

The length of stay between the two studies did not reveal a significant difference (MD -0.18; 95%CI: -7.68 – 7.33). Only one study reported a reduction in length of stay among patients with FG receiving HBOT (29). However, the sample of this study was consisted of HBOT and NPWT treatment thus it was difficult to confirm specifically

the adjunctive effect of HBOT treatment in FG patients. According to a study by Anheuser et al., there was no difference in patients with FG receiving HBOT in terms of length of stay (14). Other study also reported a shorter length of stay along and decreased mortality rates (10). In relation to the length of stay, physical disability is a significant predictor of longer hospitalization (13). It could be due to community issues, as approximately 30% of FG patients require treatment at rehabilitation centres, long-term care facilities, or local hospitals (13). The length of stay was also influenced by the need to perform concurrent surgeries such as colostomy. Regarding Fournier Gangrene Severity Index score, sepsis significantly influences the length of stay in FG patients. Understanding the importance of predicting length of stay may provide strategy in patient-based treatment and aid in decision-making in treatment choice.

Pooled analysis of the number of debridement procedures suggested no significant difference between HBOT and conventional therapy (MD 1.33; 95% CI: -0.58 – 3.23). A previous study reported that the average number of surgical debridement procedures was similar between HBOT and conventional therapy leading to the interpretation that HBOT had no advantage in decreasing the number of debridement procedures when used as an adjuvant treatment of FG (30). A lower number of debridement procedures among control that did not receive HBOT has also been reported. The number of required debridement was an important parameter because complete recovery in FG patients may be determined with a lower number of repeated debridement (11).

Based on a study reported by Mindrup et al., the cost of HBOT was not negligible, as hospital charges were significantly higher among HBOT group (13). A study conducted in Germany stated that the availability of HBOT was relatively low. In addition, the expense of a patient treated with the HBOT ranges from 8,000 to 25,000 EUR and is not covered by health insurance (14). Therefore, the recommendations of HBOT as adjunctive therapy requires more cost analysis studies before it can be implemented for routine use in FG cases.

Several limitations existed in this study. Firstly, other factors that may affect the outcome cannot be entirely analysed, leaving the possibility of influence on the outcome results. Secondly, cost analysis could not yet be performed as only a few included studies mentioned this aspect in relation to the given intervention. Thirdly, the high heterogeneity of the included studies occurred due to various characteristics among study population, including patient comorbidities in both arms, the manner of the intervention, and the endpoint for analysis. Therefore, it is necessary to conduct research with a uniform design setting and population. Lastly, all included studies were retrospective observational studies. The nature of this design may raise several biases. More studies on this topic should be done, especially randomized-control trial studies, to create an adequate analysis of the usage of Hyperbaric Oxygen for Fournier's Gangrene Patients.

CONCLUSION

The adjunctive therapy of Hyperbaric Oxygen possessed a significantly lower mortality rate compared to conventional therapy. However, the effect of HBOT on the length of stay and number of debridement was not proven in this study. The influence of multiple factors warrants the need for future randomized controlled trials.

ABBREVIATIONS

HBOT = Hyperbaric Oxygen Therapy
FG = Fournier's Gangrene
PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analyses
PICO = Population-Intervention-Comparison-Outcome
MD = Mean Difference
OR = Odds Ratio
CI = Confidence Interval
NOS = Newcastle-Ottawa Scale
WMD = Weighted Mean Difference
FGSI = Fournier's Gangrene Severity Index

CONFLICT OF INTEREST

None declared.

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APPENDIX:

Supplementary Table 1 - Baseline characteristics of the included studies.

Study (Years)	Study Type	Group	Age (mean)	Type of Intervention	Comorbidity				FGSI Score (mean ± SD)
					Diabetes Mellitus (n, %)	Alcoholism (n, %)	Hypertension (n, %)	Smoking (n, %)	
Feres et al., 2021 (7)	Retrospective	With Hyperbaric Oxygen Therapy	48.2 (10 – 81)	HBOT was administered once daily for a total of 15 sessions (2.4 atmospheric oxygen, for 2 hours)	29 (36.7)	28 (35.4)	27 (34.1)	24 (30.3)	NR
		Without Hyperbaric Oxygen Therapy	46.6 (1 – 82)		33 (27.9)	35 (29.6)	33 (27.9)	30 (25.4)	NR
Creta et al., 2020 (10)	Retrospective	With Hyperbaric Oxygen Therapy	64.3 (16.1)	HBOT given twice a day for 4-7 days (2.4 – 2.8 atmospheric oxygen, for 50 – 90 minutes)	NR	NR	NR	NR	9.0 ± 4.8
		Without Hyperbaric Oxygen Therapy	68.3 (14.2)		NR	NR	NR	NR	8.0 ± 4.0
Tutino et al., 2020 (18)	Retrospective	With Hyperbaric Oxygen Therapy	NR	HBOT was offered to 13 (56.5%) patients using a scheduled session of 60 minutes daily.	11 (55)	4 (15)	NR	11 (50)	NR
		Without Hyperbaric Oxygen Therapy							
Anheuser et al., 2018 (14)	Retrospective	With Hyperbaric Oxygen Therapy	58	NR	9 (52.9)	5 (29.4)	NR	NR	NR
		Without Hyperbaric Oxygen Therapy	60		23 (50)	14 (31.1)	NR	NR	NR
Ferretti et al., 2017 (12)	Retrospective	With Hyperbaric Oxygen Therapy	56 (19-74)	NR	3(16)	NR	NR	0 (0)	4.3 (3-6)
		Without Hyperbaric Oxygen Therapy			10 (53)			3(16)	8.3 (2-19)
Hung et al., 2016 (17)	Retrospective	With Hyperbaric Oxygen Therapy	59.6 ± 14.5	NR	44(73)	NR	25 (41)	NR	NR
		Without Hyperbaric Oxygen Therapy							
Li et al., 2015 (11)	Retrospective	With Hyperbaric Oxygen Therapy	46.13± 13.11	HBOT given twice daily for 5-7 days (2.5 units of atmospheric oxygen, 90-120 minutes per session at 10 hours intervals)	NR	NR	NR	NR	7.38±3.20
		Without Hyperbaric Oxygen Therapy	48.42± 15.31		NR	NR	NR	NR	7.42±3.20
Mindrup et al., 2005 (13)	Retrospective	With Hyperbaric Oxygen Therapy	57 ±14	HBOT given 1-3 times (2.4-3 units of atmospheric oxygen, 30-90 minutes)	19 (73)	6 (23)	4 (15)	19 (73)	NR
		Without Hyperbaric Oxygen Therapy	57 ±15		10 (63)	5 (31)	2 (13)	10 (63)	NR
Ayan et al., 2005 (15)	Retrospective	With Hyperbaric Oxygen Therapy	57.3 (35-74)	Hyperbaric Oxygen (HBO) using 2.5 atmospheric pressure for 90 min/day was applied to 18 patients (43.9%) for three to 10 days.	17 (41.4)	5 (12.1)	NR	NR	NR
		Without Hyperbaric Oxygen Therapy							
Hollabaugh et al., 1998 (16)	Retrospective	With Hyperbaric Oxygen Therapy	57 (26-87)	HBOT was offered to 14 (54%) patients, The dive parameters were 90 min at 2.4 atmospheres absolute/45 feet sea water. Duration of therapy averaged 12 days.	10 (38)	9 (35)	NR	NR	NR
		Without Hyperbaric Oxygen Therapy							

EDITORIAL COMMENT

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Hyperbaric oxygen therapy in Fournier's gangrene

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COMMENT

Fournier's gangrene (FG) is a devastating condition with a high mortality rate. The incidence increases with age and comorbidities, especially Diabetes Mellitus.

Standard treatment consists of aggressive broad-spectrum antibiotics, debridement, and intensive care, with long hospitalization periods and almost always significant sequelae in the eventual survivors.

Adjuvant measures such as Hyperbaric Oxygen Therapy (HBOT) have been offered and used in the treatment of FG, with apparently promising results.

Despite the in vitro biological plausibility and the beneficial effect demonstrated in dogs, the absence of RCTs allows for more appropriate evidence. It limits the recommendations and validity of these findings.

Aware of this limitation, the authors, in a well-conducted paper, summarized the findings of observational studies carried out in the last 25 years on the theme. They demonstrated a significant reduction in the mortality rate in FG patients but could not confirm a reduction in the length of stay and number of debridements (1).

These findings agree with a retrospective review of a large nationwide database of cases of necrotizing soft tissue infection database (45913 subjects) that reported a significant reduction in mortality among those treated after controlling for possible confounders with HBOT (2).

On the other hand, the heterogeneity of the population evaluated; the studies' observational and retrospective character of the included studies is the main limitation of this metanalysis. These aspects suggest that the described benefits can not have the magnitude observed but signal a scenario of use and cost-effectiveness with HBOT.

Despite some criticism and inspiration by Voltaire: "All is for the best in the best of all worlds."

CONFLICT OF INTEREST

None declared.

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A novel nomogram can predict pathological T3a upstaged from clinical T1a in localized renal cell carcinoma

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ABSTRACT

Hypothesis: Nomogram can be built to predict the pathological T3a upstaging from clinical T1a in patients with localized renal cell carcinoma before surgery.

Purpose: Renal cell carcinoma (RCC) patients with clinical T1a (cT1a) disease who are upstaged to pathological T3a (pT3a) have reduced survivals after partial nephrectomy. We aimed to develop a nomogram-based model predicting pT3a upstaging in RCC patients with preoperative cT1a based on multiple preoperative blood indexes and oncological characteristics.

Materials and Methods: Between 2010 and 2019, 510 patients with cT1a RCC were individually matched according to pT3a upstaging and pathological T1a (pT1a) at a 1:4 ratio using clinicopathologic features. Least absolute shrinkage and selection operator regression analysis was used to identify the most important risk factor from 40 peripheral blood indicators, and a predictive model was established. Multivariate logistic regression analysis was performed with the screened blood parameters and clinical data to identify significant variables. Harrell's concordance index (C-index) was applied to evaluate the accuracy of the model for predicting pT3a upstaging in patients with cT1a RCC.

Results: Out of 40 blood indexes, the top ranked predictor was fibrinogen (FIB). Age, the ratio of the tumor maximum and minimum diameter (ROD), FIB, and tumor size were all independent risk factors for pT3a upstaging in multivariate analysis. A predictive ARFS model (Age, ROD, FIB, tumor Size) was established, and the C-index was 0.756 (95% CI, 0.681-0.831) and 0.712 (95% CI, 0.638-0.785) in the training and validation cohorts, respectively.

Conclusions: Older age, higher ROD, increased FIB level, and larger tumor size were independent risk factors for upstaging. The ARFS model has a high prediction efficiency for pT3a upstaging in patients with cT1a RCC.

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INTRODUCTION

Renal cell carcinoma (RCC) is the third most common urological tumor. Approximately 403,262 new cases of renal cell carcinoma were diagnosed and 175,098 patients died worldwide in 2018, and the incidence rate and mortality continue to increase (1). According to the American Joint Committee on Cancer stage (the 8th AJCC stage), localized T1 RCC (stage I) is classified only according to tumor size (T1a ≤ 4 cm, and 4cm < T1b ≤ 7 cm), while T3a (stage III) is classified according to the presence of peripheral fat invasion, renal sinus fat infiltration, pelvicalyceal system invasion or renal vein extension regardless of the tumor size. The five-year survival rate for stage to stage RCC is reduced from 95% to 60% (2).

For clinical T1 (cT1) tumors, partial nephrectomy (PN) is the preferred treatment, especially for clinical T1a (cT1a) (3). PN can better protect kidney function, reduce the occurrence of chronic kidney disease, and decrease cardiovascular risk (4, 5). Meanwhile, radical nephrectomy (RN) is recommended for clinical T3a disease, excluding patients with a solitary kidney, inadequate contralateral renal function, and bilateral synchronous RCC (6). However, there is a risk of upstaging to pathological T3a (pT3a) when performing PN for cT1a as identifying fat invasion by preoperative imaging can be challenging. Existing studies have reported that 4.4% - 13.3% of cT1 tumors were upstaged to pT3a after surgery (7-10). Non-clear cell RCC had a much higher likelihood of pseudocapsule or fat invasion (11). Upstaging to pT3a could jeopardize oncological outcomes, probably due to positive surgical margins or other factors (9, 12, 13). Although RN is recommended for patients with T3, whether RN is better than PN in these upstaging cases remains debated (14). Preoperative prediction of cT1 upstaging could assist urologists in determining the surgical strategy. Previous studies have suggested that preoperative risk factors such as age, tumor size, hilar location, mean platelet volume (MPV), and serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio may be related to cT1 upstaging to pT3a (15-18), but there is a lack of prediction indicators or models. Our work aims to establish a nomogram that can predict pathological T3a upstaging from clinical T1a disease in patients with localized renal cell carcinoma before surgery.

In this study, we reviewed RCC patients with cT1a upstaging to pT3a and screened four risk factors: age, the ratio of the tumor maximum and minimum diameter (ROD), fibrinogen (FIB) and tumor size. Among them, ROD is a unique tumor morphology indicator that we introduced in previous research (19). We established and validated the predictive ARFS model based on the four above risk factors, which is beneficial to guide the choice of surgical methods for patients with cT1a.

MATERIALS AND METHODS

Patients

The study protocol was approved by the Ethics Committee of the Cancer Institute and Hospital of the CAMS (approval number: 20/245-2441). Localized RCC patients with pT3a upstaging from cT1a between January 2010 and December 2019 at the Cancer Institute and Hospital of the Chinese Academy of Medical Sciences (CAMS) were reviewed. The inclusion criteria of the study were as follows: (1) no primary cancer of any other organs before RN or PN; (2) no chronic inflammatory allergic disease (avoiding interfering blood indexes, such as CRP and immunoglobulin, during screening peripheral blood indicators); (3) no history of anticoagulants use, such as for cardiovascular or cerebrovascular thrombosis; (4) exact pathological diagnosis of RCC; (5) complete resection of the tumor, which was defined as a negative surgical margin; (6) complete clinicopathological characteristics; (7) preoperative assessment of the diameter of the renal tumor by contrast-enhanced computer tomography (CT) or magnetic resonance (MR); and (8) no evidence of extrarenal metastasis. Additional RCC patients with a final pathological diagnosis of T1a (pT1a) were individually matched at a 1:4 ratio. The clinical T stage was assessed with contrast--enhanced CT or MRI. All patients signed informed consents in each medical record.

Clinicopathological data

Clinicopathologic parameters such as age, sex, clinical and histopathological characteristics,

and preoperative peripheral blood indexes were investigated retrospectively. The dimensions of the primary tumor were measured in three planes (coronal, sagittal, and axial), and the maximum diameters of these planes were measured separately by two radiologists. The three maximum diameters in the three planes were named the maximum diameter, submaximum diameter, and minimum diameter according to the value. The ROD was determined as the ratio of the maximum diameter to the minimum diameter. Pathological staging was evaluated according to the 8th AJCC stage. Additionally, peripheral blood samples were obtained 10 days (range, 7-14) before the operation in our center.

Statistical Analysis

The dataset was split into training and validation cohorts with repeated random sampling until there was no significant difference between the two cohorts with respect to all variables. The tumor and blood indexes out of 40 blood indexes were selected by least absolute shrinkage and selection operator (LASSO) regression (R software and 'glmnet' package). Then, multivariate logistic regression analysis was performed with the screened blood parameters and clinical data to identify significant variables. We evaluated the prognostic accuracy of the risk model using Harrell's concordance index (C-index), which is appropriate for censored data. Both the multivariable logistic regression model and the C-index were completed with R version 3.6.2, and the mean C-index was calculated using Stata 14.0 (Stata Corp. Texas, USA). The P value was calculated using Welch's t test for continuous variables and $\chi 2$ test or Fisher's exact test for categorical variables. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 2712 RCC patients had cT1a disease, and 121 (4.5%) had pT3a upstaging. After screening, 510 patients with cT1a were finally enrolled in our study including 102 patients in the pT3a upstaging subgroup and 408 patients in the consistent pT1a subgroup. The median age was 53 years (range, 22-83), the median tumor size was 3 cm (range, 0.6-4.0), the median ROD was 1.29 (range, 1.0-3.18), and the median FIB was 2.89 g/L (range, 1.44-6.59). In the pT3a upstaging subgroup, 50 (49.0%) patients had perinephric adipose invasion, 51 (50.0%) patients had sinus fat invasion, 27 (26.5%) patients had segmental renal vein invasion, and 4 patients had pelvicalyceal system invasion. There were 27 patients who had more than two types of pathological invasion (Table-1). The whole population was split into a training cohort (255 patients) and a validation cohort (255 patients) (Table-2).

Risk factors screened from preoperative blood indexes and independent diagnostic factors in the training cohort

Using LASSO regression analysis, the most important risk factor from 40 peripheral blood indicators before surgery was FIB (Supplementary Figure-S1).

The multivariate logistic regression analysis showed that a larger tumor size (odds ratio: 1.76, 95% CI: 1.13-2.88, P<0.001) was an independent risk factor for upstaging, as well as older age (OR: 1.06, 95% CI: 1.02-1.1, P = 0.004), larger ROD (OR: 3.93, 95% CI: 1.4-11.35, P=0.03) and high levels of FIB (OR: 1.74, 95% CI: 1.01-3.01, P = 0.01). Neither the MPV (OR: 1.0, 95% CI: 0.99-1.02, P = 0.29) nor the AST/ALT ratio (OR: 1.02, 95% CI: 0.33-3.05, P = 0.33) were independent risk factors (Figure-1).

Development of a nomogram of a diagnostic ARFS model for pathological T3a upstaging

As shown in Figure-2, a diagnostic ARFS model nomogram that included age, ROD, FIB, and tumor size for pT3a upstaging was established. The C-index for the prediction of RCC pathological upstaging from cT1a to pT3a in the training cohort was 0.756 (95% CI, 0.681-0.831).

Validation of the predictive accuracy of the ARFS model for pathological T3a upstaging

In the validation cohort, the C-index of the nomogram for predicting pT3a upstaging was 0.712 (95% CI, 0.638-0.785), which was also con-

Table 1 - Baseline characteristics of pT3a upstaged patients and pT1a patients.

	Overall (n=510)	pT3a (n=102)	pT1a (n=408)	P-value
Age (years)				0.009
Mean (SD)	53.4 (11.3)	57.9 (11.0)	52.3 (11.1)	
Median [Min, Max]	53 (22, 83)	57 (30, 80)	52 (22, 83)	
Sex				0.901
Male	323 (63.3%)	64 (62.7%)	259 (63.4%)	
Female	187 (36.7%)	38 (37.3%)	149 (36.6%)	
BMI (kg/m2)				0.886
< 25	214(42.0%)	42 (41.2%)	172 (42.2%)	
> 25	296 (58.0%)	60 (58.8%)	236 (57.8%)	
Size (cm)				< 0.001
Mean (SD)	2.83 (0.83)	3.19 (0.68)	2.75 (0.85)	
Median [Min, Max]	3.00 [0.60, 4.00]	3.35 [1.30, 4.00]	2.90 [0.60, 4.00]	
Location				0.368
Upper	125 (24.5%)	21 (20.6%)	104 (25.5%)	
Middle	245 (48.0%)	58 (56.9%)	187 (45.8%)	
Lower	140 (27.5%)	23 (22.5%)	117 (28.7%)	
R.E.N.A.L Score				0.263
Low	168 (32.9%)	29 (28.4%)	139 (34.1%)	
Moderate	285 (55.9%)	57 (55.9%)	228 (55.9%)	
High	57 (11.2%)	16 (15.7%)	41 (10.0%)	
ROD				0.007
Mean (SD)	1.37 (0.31)	1.46 (0.31)	1.34 (0.30)	
Median [Min, Max]	1.29 [1.00, 3.18]	1.40 [1.04, 2.50]	1.25 [1.00, 3.18]	
Type of nephrectomy				
Partial	136 (26.7%)	27 (26.5%)	109 (26.7%)	1
Radical	374 (73.3%)	75 (73.5%)	299 (73.3%)	
Pathology				1
Clear cell carcinoma	420 (82.4%)	84 (82.4%)	336 (82.4%)	
Non-clear cell carcinoma	90 (17.6%)	18 (17.6%)	72 (17.6%)	
Etiology of pT3a Upstaging				
Perinephric Adipose		50 (49.0%)	NA	
Renal Sinus Fat Invasion		51 (50.0%)	NA	
Pelvicalyceal system		4 (3.9%)	NA	
Segmental Renal Vein		27 (26.5%)	NA	
FIB (g/L)				0.001
Mean (SD)	2.91 (0.64)	3.12 (0.70)	2.86 (0.62)	
Median [Min, Max]	2.89 [1.44, 6.59]	3.04 [1.44, 4.78]	2.85 [1.50, 6.59]	
MPV				0.52
Mean (SD)	25.3 (34.6)	23.5 (33.0)	25.7 (35.0)	
Median [Min, Max]	10.7 [1.03, 142]	10.5 [8.39, 131]	10.8 [1.03, 142]	
AST/ALT				0.799
Mean (SD)	1.01 (0.371)	1.01 (0.319)	1.01 (0.384)	
Median [Min, Max]	0.94 [0.10, 2.80]	0.95 [0.34, 2.00]	0.94 [0.10, 2.80]	

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **BMI** = body mass index; **FIB** = fibrinogen; **PV** = mean platelet volume; **ROD** = the ratio of the tumor maximum and minimum diameter

Table 2 - Characteristics of the training and validation cohorts.

	Training (n=255)	Validation (n=255)	P-value
Age (years)			0.697
Mean (SD)	53.3 (11.1)	53.5 (11.5)	
Median [Min, Max]	53 (22, 80)	53 (25, 83)	
Sex			0.849
Male	172 (67.5%)	175 (68.6%)	
Female	83 (32.5%)	80 (31.4%)	
Size (cm)			0.534
Mean (SD)	2.83 (0.835)	2.84 (0.834)	
Median [Min, Max]	3.00 [0.60, 4.00]	3.00 [1.00, 4.00]	
Location			0.217
Upper	56 (22.0%)	69 (27.1%)	
Middle	134 (52.5%)	111 (43.5%)	
Lower	65 (25.5%)	75 (29.4%)	
R.E.N.A.L Score			1.000
Low	84 (32.9%)	84 (32.9%)	
Moderate	143 (56.1%)	142 (55.7%)	
High	28 (11.0%)	29 (11.4%)	
ROD			0.360
Mean (SD)	1.37 (0.31)	1.36 (0.30)	
Median [Min, Max]	1.32 [1.00, 3.18]	1.27 [1.00, 2.67]	
FIB (g/L)			0.262
Mean (SD)	2.91 (0.64)	2.92 (0.65)	
Median [Min, Max]	2.88 [1.44, 4.90]	2.89 [1.50, 6.59]	
MPV			0.451
Mean (SD)	23.5 (32.8)	27.1 (36.3)	
Median [Min, Max]	10.7 [1.03, 131]	10.8 [7.98, 142]	
AST/ALT			0.564
Mean (SD)	1.01 (0.348)	1.01 (0.394)	
Median [Min, Max]	0.950 [0.38, 2.22]	0.931 [0.10, 2.80]	
pT3a			0.319
No	209 (82.0%)	199 (78.0%)	
Yes	46 (18.0%)	56 (22.0%)	

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **FIB** = fibrinogen; **MPV** = mean platelet volume; **ROD** = the ratio of the tumor maximum and minimum diameter

Figure 1 - Forest plots of multivariate logistic analysis in the training cohort.

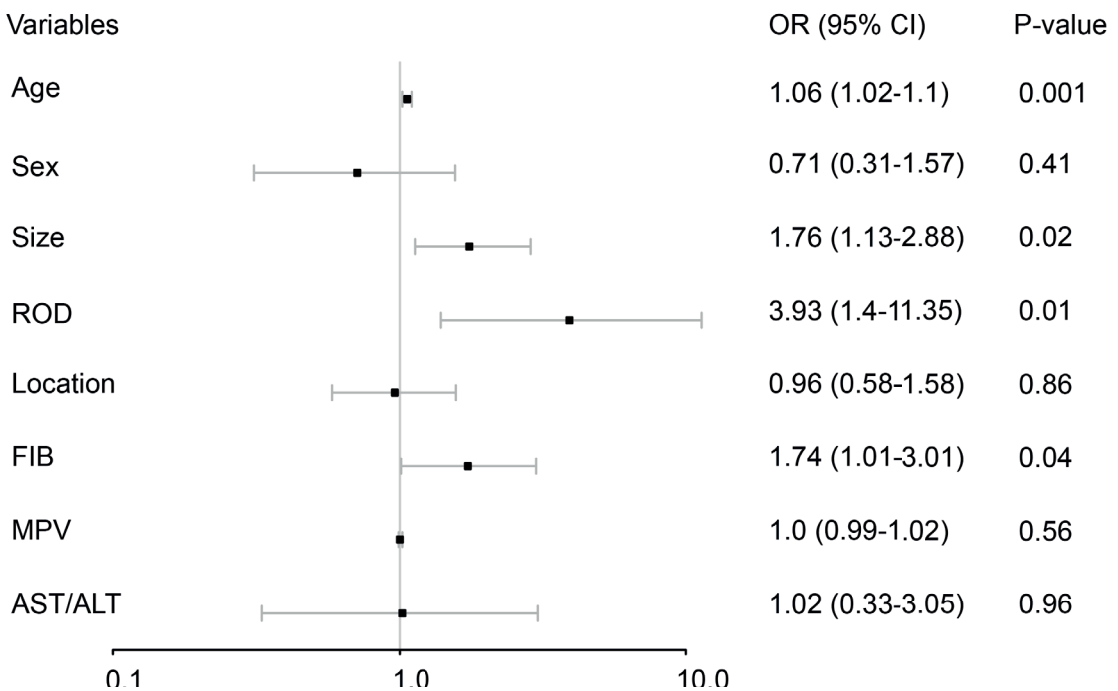
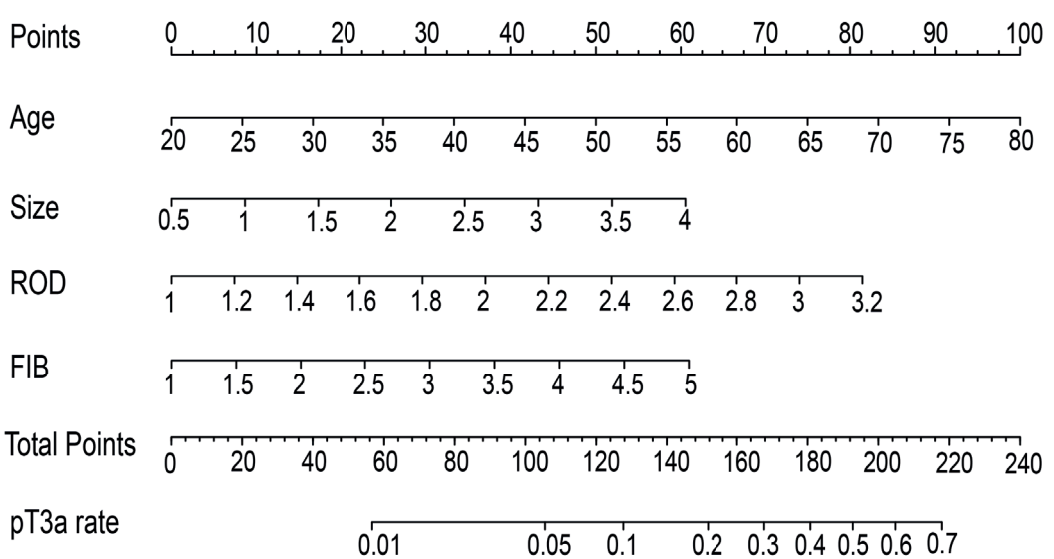


Figure 2 - Construction of the nomogram for the ARFS model combining age, the ratio of the tumor maximum and minimum diameter (ROD), fibrinogen (FIB), and tumor size.



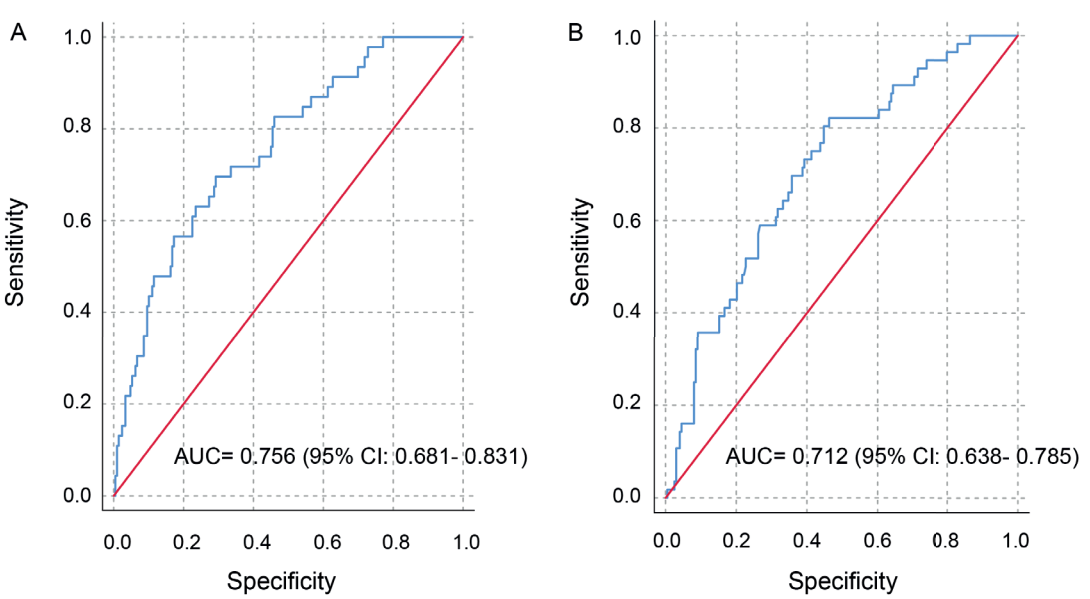
firmed in receiver operating curve analysis (Figure-3). This was consistent with the results obtained from the training cohort. This result again suggested that the nomogram model was useful for predicting pT3a upstaging from cT1a in patients with renal cell carcinoma.

DISCUSSION

In this study, we sought to determine predictors for RCC upstaging from cT1a to pT3a and built a predictive model that could guide surgeons to perform PN or RN in patients with clinical T1a RCC. With regard to the individual variables, age, ROD, FIB, and tumor size appeared to be associated with upstaging risk. The C-index for the nomogram was 0.712 (95% CI, 0.638-0.785). Compared with other studies (20, 21), the advantage of our study was that the ARFS nomogram was more objective and could be easily calculated with 4 preoperative quantitative risk factors.

The clinical benefits of PN and RN in pT3a RCC remain highly debated. Several previous retrospective studies have indicated that PN had worse oncological outcomes in upstaging patients (9, 12). Alvim et al. did not find a significant difference in complication rate or oncological survival between planned PN and RN for pT3a RCC (22). Veccia et al. conducted a systematic review and meta-analysis on upstaging to pT3a RCC patients and demonstrated that five-year recurrence-free survival was worse in the upstaged group (p = 0.02) perhaps due to positive surgical margins. However, there is very limited evidence regarding whether RN would be better than PN in these cases (13). Recently, a newly published meta-analysis involving 12 studies on pT3a RCC indicated that there were no significant differences between PN and RN in terms of the operative time, surgical complications, or oncological survival (14). In summary, PN might be a suitable choice for upstaging patients, but close attention should be given to avoid positive surgical margins. On the other hand, predicting pT3a RCC by a nomogram can assist urologists in screening localized cT1 RCC patients as perinephric fat, sinus fat or segmental renal vein invasion might weaken the local control efficacy of ablation therapies (23, 24).Our ARFS nomogram may benefit therapeutic decisions regarding ablation therapy, especially for cT1a patients.

Figure 3 - Receiver operating characteristic curves for the predictive ARFS model in the training cohort (A) and in the validation cohort (B).



Some reports have demonstrated that older age and increased tumor size are independently associated with renal cell carcinoma upstaging from cT1 to pT3a (15, 17, 25). The findings from these reports are consistent with the results of our research in which larger tumor size (OR: 1.76) and increasing age (OR: 1.06) were independently associated with pT3a upstaging.

On the three-dimensional plane of the tumor, the longest and shortest maximum diameters could be calculated, and we defined a parameter factor as the ROD in previous research (19). As an innovative predictor, the ROD contained the morphological characteristics of the tumor and may reflect the polycentric developmental characteristics and aggressive proliferation of RCC. Recently, Teishima et al reported the impact of the radiological morphology of RCC cT1 on the prediction of pT3 upstaging. They classified the tumor into 3 types: round, lobular or irregular, and their results suggested that an irregular radiological morphology could predict the pathological upstaging to T3a (26). We depicted the morphology as a quantitative value that was more objective and easily calculated.

In a previous study, we found that the preoperative FIB level was positively correlated with the circulating tumor cell (CTC) count and that FIB was an independent prognostic marker of RCC (27, 28). Another meta-analysis demonstrated that elevated pretreatment plasma fibrinogen is associated with poorer survival in renal cell carcinoma (OS: HR=2.13, CSS: HR=2.99) (29).

In contrast to other studies, our study focused on cT1a upstaging. According to the ARFS model, we should pay attention to the resection of perirenal fat and renal parenchyma during PN for patients with a higher risk of upstaging. Although the relationships between positive surgical margins and the recurrence rate and survival are controversial (9, 30-32), it is better to perform RN or complete resection of tumor by RN for possible T3 RCC patients. If PN is the absolute indication and the AFRS nomogram indicates a higher upstaging risk for some RCC patients, intraoperative ultrasound might be necessary to decrease the risk of positive surgical margins (33).

The limitations of this study are as follows: first, there is inherent bias associated with its retrospective design, and it was a study with a large time span. Second, this is a single-institutional analysis. In the future, we hope to carry out multicenter and prospective studies to further verify the predictive performance of the model.

CONCLUSIONS

In summary, age, the ratio of the tumor maximum and minimum diameter, fibrinogen, and tumor size were independent risk factors for upstaging. The novel model that combines these four factors could aid in predicting pT3a upstaging in patients with cT1a RCC. Large--scale multicenter studies may be needed to confirm this model in the future.

ABBREVIATIONS

ALT = alanine aminotransferase
AST = aspartate aminotransferase
CAMS = Chinese Academy of Medical Sciences
C-index = concordance index
CT = computer tomography
cT1a = clinical T1a
FIB = fibrinogen
LASSO = least absolute shrinkage and selection operator
MR = magnetic resonance
MVP = mean platelet volume
OR = odds ratio
PN = partial nephrectomy
pT1a = pathological T1a
pT3a = pathological T3a
RCC = Renal cell carcinoma
RN = radical nephrectomy
ROD = the ratio of the tumor maximum and minimum diameter

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Chuanzhen Cao and Xiangpeng Kang, these authors have contributed equally to this work

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethics Committee of the Cancer Institute and Hospital of the Chinese Academy of Medical Sciences (approval number: 20/245-2441, approval date: 2020-9-30). Patient written informed consent and follow-up was included in each medical record.

CONFLICT OF INTEREST

None declared.

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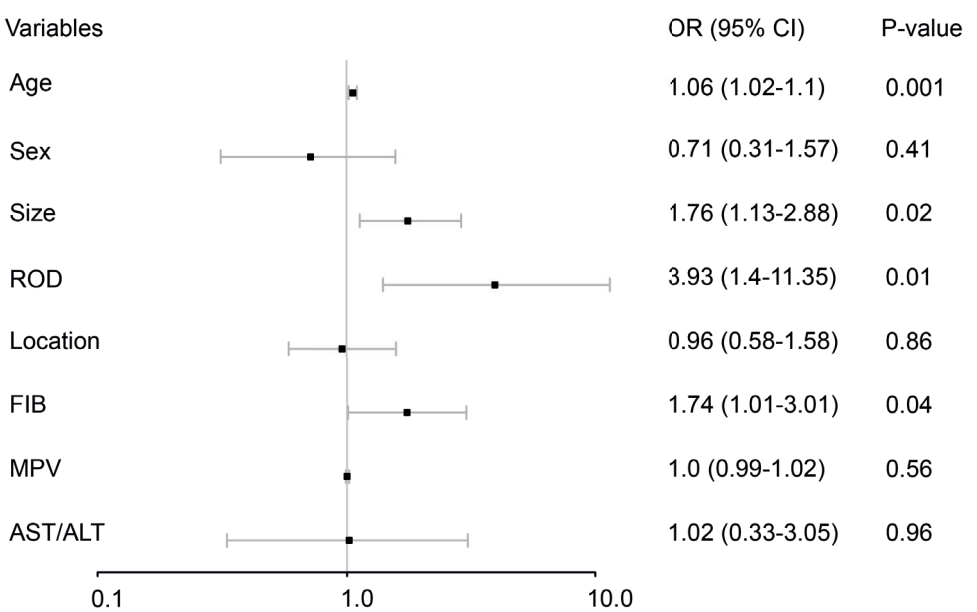
APPENDIX

The 40 blood indexes

WBC, white blood cell count; Hb, haemoglobin; PLT, platelet count; PDW, platelet distribution width; PCT, platelet haematocrit, HCT, haematocrit; NEUT, neutrophil count; NETU%, neutrophil percentage; LYMPH, lymphocyte count; MONO, monocyte count; MONO%, monocyte percentage; NLR, neutrophil-lymphocyte ratio; EOS, eosinophils count; BAS, basophils count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MPV, mean platelet volume; ALP, alkaline phosphatase; GGT, glutamyl transferase; LDH, lactate dehydrogenase; TBIL, total bilirubin; DBIL;TP, total protein; Alb, albumin; URIC, uric acid; BUN, blood urea nitrogen; CRE, creatinine; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; CRP, C-reactive protein; APTT, activated partial thromboplastin time; FIB, fibrinogen; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; potassium kalium; sodium; chlorine; calcium.

Supplementary Figure S1 - Least absolute shrinkage and selection operator regression analysis was used to identify the top risk factor, fibrinogen (FIB), which was screened from 40 peripheral blood indicators.



EDITORIAL COMMENT

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The dilemma of partial nephrectomy and surgical upstaging

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COMMENT

Malignant kidney neoplasms are increasingly on the rise. The National Cancer Institute expects, in 2022, in the United States, 79.000 new cases and 13.920 deaths. Precise clinical staging at diagnosis impacts therapy, prognosis, and oncologic outcomes.

The TNM (Tumor-Node-Metastasis) staging system was initially proposed by the French surgeon Pierre Denoix, between 1943 and 1952, at Institute Gustave-Roussy. To this day is considered a tool to estimate solid tumor prognosis (1, 2).

TNM is rooted in the Halstedian principle of temporal determinism that solid tumors spread sequentially from the primary site to lymphatics, then to distant organs. TNM clinical staging is based on the anatomic spread of the disease. However, the TNM system has several drawbacks:

1. It is limited by the need for a correlation between the anatomic progression of the disease and the progression to more advanced stages. Furthermore, in patients with equivalent anatomic spread, heterogeneity is induced when variable outcomes (recurrence or survival) are forced into the same stage.
2. It fails to incorporate the variables: tumor, nodules, and metastases as continuous variables. This fact creates a system with a finite number of stages, limiting the determination of an individual prognosis.
3. It relates a clinical outcome (prognosis) to descriptive, not determinant, variables. It states that if the disease is anatomically more advanced the prognosis will be worse, without considering other variables, such as biomarkers, genetic scores, histology, and behavioral factors.

Nomograms are visual graphical representations of equations that allow clinicians to estimate the probability of a final medical outcome. It uses a points-based system whereby patients accumulate points based on levels of the selected variables.

Nomograms are widely used in different clinical scenarios and have become an epidemic in the recent medical literature. The search of articles in PubMed using the term “cancer nomogram” retrieved 8344 articles between 2012 and 2022. In oncology, they are commonly used to estimate the risk of recurrence and death. Nomograms incorporate anatomic and non-anatomic variables from a

specific patient, resulting in a personalized and more precise tool to risk assessment (3).

In recent years we observed the development of new nomograms incorporating old and new prognostic and risk factors (genetic, biomarkers, histology). Although, the vast majority are not validated in different populations (4-7).

The inclusion of the TNM classification as a variable in the majority of the new nomograms corroborates its importance. TNM is an anatomic classification, and the accuracy of imaging methods is crucial to reduce it as low as possible surgical upstaging.

Imaging is typically performed using contrast-enhanced CT, although there is a risk of missing renal sinus fat invasion, perirenal fat invasion, or renal vein thrombosis, which can lead to pT3a upstaging (8-10). In 2020, Veccia A. et al. published a systematic review and meta-analysis of the outcomes and predictive factors for upstaging to pT3a in 21869 patients who underwent partial or radical nephrectomy for cT1 renal tumors. The authors concluded that upstaging is not common, but was correlated with worse oncologic outcomes. Upstaging was correlated to age, tumor size and complexity, and histology. (11, 12) de la Barra CC et al. reported a preoperative model to predict pT3 upstaging in renal cancer. The authors developed a nomogram that included age, contact with the main vessels, and size. The nomogram presented an AUC (area under the curve) of 0.864 in the ROC curve (13).

The study by Cao et al. published in the International Brazilian Journal of Urology (14), addressed the need for a tool to help urologists predict upstaging for localized cT1 renal cancer. The authors evaluated retrospectively 2712 patients with Renal Cell Carcinoma and cT1a disease, 121 (4.5%) were upstaging to pT3a on the final pathology report. Based on the findings, they constructed a nomogram with the variables, age, tumor size, maximum and minimum diameter ratio, and fibrinogen level. They split the whole population in two, one for validation purposes.They reported the C-index for predicting upstaging (cT1 - pT3a) of 0.756 (95% CI, 0, 6081-0.831), in the validation cohort, the C-index was 0.712 (95% CI, 0.638-0.785). They concluded that their nomogram is a tool for predicting upstaging, cT1 - pT3a, in patients with RCC. They also pointed out the need for multicenter studies to confirm their findings. I congratulate the authors for their work and methodology. Should be highlighted the inclusion of fibrinogen level as a variable. I also agree that the nomogram should be tested in a larger population to confirm or not the findings. Furthermore, adding new variables to the described nomogram may increase its accurancy (C-index).

CONFLICT OF INTEREST

None declared.

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Ventral onlay glanuloplasty for treatment of fossa navicularis strictures

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ABSTRACT

Purpose: Management of fossa navicularis (FN) strictures balances restoring urethral patency with adequate cosmesis. Historically, FN strictures are managed via glans cap or glans wings, and in severe cases, multi-stage procedures. Ventral onlay glanuloplasty (VOG) is an easily reproducible technique that involves a single-stage augmentation with buccal mucosal graft. We have been applying this technique for several years and present early promising outcomes of this novel approach.
Materials and Methods: We retrospectively reviewed all patients with FN strictures who underwent VOG at our institution. Treatment success was designated by the absence of extravasation on voiding cystourethrogram and no need for further urethral instrumentation on follow up. Glans cosmesis was assessed by patients providing binary (yes/no) response to the satisfaction in their appearance. We also noted stricture length, stricture etiology, demographic characteristics and any post-operative complications and reported median, interquartile range (IQR) and count, frequency (%), accordingly.
Results: Ten patients underwent VOG and fit our inclusion criteria. Median stricture length was 2.0 cm (IQR 1.6 -2). Success rate was 90% (9/10) with a median follow up of 30 months (IQR 24.3 – 36.8). The one recurrence was treated by dilation combined with triamcinolone injection at 419 days post-op. Stricture etiology included primarily iatrogenic causes such as transurethral prostate resection (4/10), greenlight laser vaporization (2/10), cystolitholapaxy (1/10), and traumatic catheterization (3/10). All patients were satisfied with penile cosmesis.
Conclusion: VOG is a simple technique for treating FN strictures. Based on our preliminary series, VOG provides sustained distal urethral patency and patients are pleased with the appearance.

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INTRODUCTION

Fossa navicularis (FN) strictures comprise 18% of all anterior urethral strictures (1). The most described etiology of FN stricture is lichen sclerosis (LS), a chronic inflammatory dermatosis affecting the glans, prepuce and urethra (2-4). Other common causes include idiopathic, iatrogenic, trauma, or prior hypospadias repair (2-4). Despite being a relatively common occurrence, the precise management of FN strictures remains unclear. The inherent difficulty of repair lies in restoring urethral patency while maintaining adequate penile cosmesis (5-7). Ultimately, the chosen approach tai-

lors to patient-specific factors such as the length of stricture, extent of surrounding spongiofibrosis, quality of distal penile skin and presence of LS (6, 8). Approaches to management range from less invasive options such as endoscopic dilation, direct vision internal urethrotomy and extended meatotomy to more extensive reconstructions such as flap and graft urethroplasty. Ventral onlay graft placement, or ventral onlay glanuloplasty (VOG), for FN strictures is a straightforward approach with limited available studies in the literature. We hypothesize that the outcomes of VOG have success rates similar to other surgical techniques in repairing the FN. The aim of this study is to describe our early experience with VOG using buccal mucosa, and to contextualize this technique in the broader literature on FN urethral reconstruction.

MATERIALS AND METHODS

Data Collection and Analysis

All urethroplasty cases at our institution performed by a single reconstructive urologist from January 2018 to June 2021 were compiled in an institutional IRB approved database which we used to obtain patient data for this study. This study was approved by our institution's IRB (FWA00000176).

Inclusion/Exclusion Criteria

Only single stage FN repairs with VOG were included. Our inclusion criteria consisted of patients with isolated FN strictures that did not extend continuously to more proximal segments of the urethral. We did however include patients with skip lesions in the bulbar or membranous urethra, but focused on their FN repair for the purpose of this study. We excluded patients with lichen sclerosis and excluded FN repairs that were not performed as a VOG as well as any multi-stage repairs. Additionally, for the purposes of this study, VOG repair with adjunctive maneuvers, ie an additional dorsal inlay, were excluded to maintain a homogenous treatment group.

Outcome Measures

We defined treatment success as (1) the absence of extravasation on VCUG at 3 weeks and (2) no need for urethral dilation or other instrumentation. We also noted any 30-day complications. Stricture etiology, stricture length (cm), prior instrumentation and prior urethroplasty were also noted as well as background patient data such as age, ethnicity, BMI, hypertension, diabetes, and smoking history. We routinely assess penile cosmesis by asking patients whether they were satisfied subjectively with the appearance of their penis (binary: yes/no response) during subsequent follow up visits. This was recorded and reported. Follow up time was reported in months. Measures were reported as count, frequency (%) or median (interquartile range (IQR)), accordingly.

SURGICAL TECHNIQUE

Ventral Onlay Glanuloplasty

With the patient in supine position, a 2-0 silk suture is placed on the glans for traction and a sensor wire is advanced through the lumen of the strictured urethra, if possible. A ventral incision is made directly through the glans in the midline starting at the meatus, extending proximally while incising urethra until healthy mucosa is identified. Stay sutures with 4-0 vicryl are placed on the edges of the urethral mucosa for traction, and a cystoscopy is performed to rule out any additional areas of narrowing. A BMG is then harvested and defatted in the standard fashion. (At this time, if the narrowing is particularly severe, a dorsal "Asopa" inlay may be used for further augmentation). For the ventral onlay, the BMG is anastomosed in a longitudinal fashion with interrupted sutures at the apex and a running 5-0 PDS suture is used for the lateral edges over a 20Fr red rubber catheter. After BMG anastomosis is complete, a flap of Dartos fascia is approximated over the repair and the glans is reapproximated for further support of the graft. Of note, we do not undermine the glans in order to create glans wings for closure, but rather reapproximate the edges of the glans with an initial deep horizontal mattress suture, followed by interrupted sutures. We create the neomeatus by suturing the distal edge of the graft to the glans itself, calibrating over a 20Fr red rubber catheter. Patients are discharged with a Foley catheter that is removed during the first follow up visit at 3 weeks where

urethral patency is assessed with VCUG. Routine follow up then continues at 1 month, 3 months and annually thereafter. Surgical technique and follow up images can be found in Figures 1 and 2.

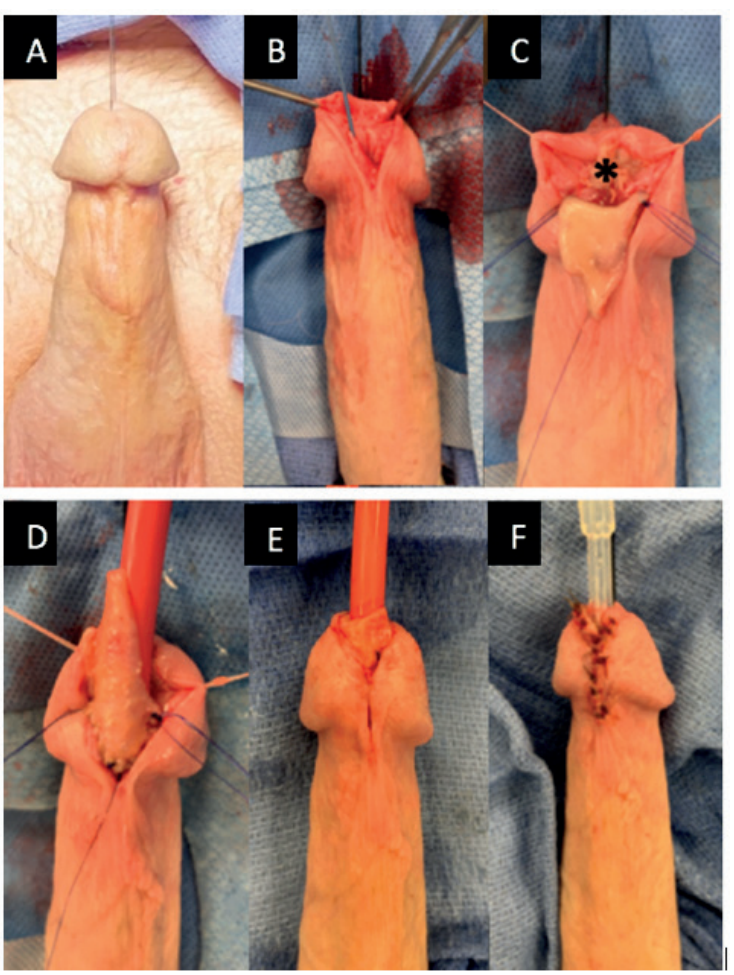
RESULTS

We reviewed our institutional database which consisted of 151 urethroplasties performed by a single surgeon. We identified 17 urethroplasties involving FN stricture repair, 11 of which used the VOG surgical technique. One patient was excluded due to lichen sclerosis stricture etiology. Thus, 10 patients were included in total.

Median age was 65.5 years (IQR: 60-69.8) and median body mass index was 25.2 (IQR: 23.1-29.4). Ethnicity breakdown included 40% white Hispanic, 40% white non-Hispanic and 20% Asian. 50% of patients were diabetic, 90% had hypertension and 40% had a smoking history.

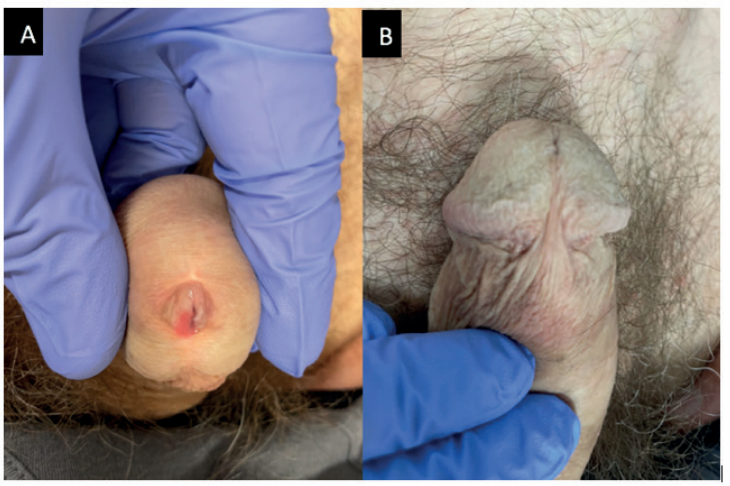
Eighty percent of patients had a stricture etiology related to a prior surgery for BPH: 1/7 had cystolitholapaxy, 2/7 underwent greenlight laser vaporization and 5/7 underwent bipolar

Figure 1 – Ventral Onlay Glanuloplasty Technique.



A) In this figure, 2-0 silk suture is placed on the glans for traction; **B)** In this figure, the sensor wire is advanced into strictured urethra, and the glans is divided in the midline, incising the urethral mucosa until healthy tissue encountered; **C)** In this figure, a small piece of BMG is placed as a dorsal inlay. An additional, larger piece is sutured longitudinally as a ventral onlay; **D)** In this figure, the ventral onlay graft is sutured in place by first placing three interrupted sutures at the apex and then running two 5-0 PDS sutures on each side over a 20Fr red rubber catheter; **E)** In this figure, the glanuloplasty is performed with one horizontal mattress suture in the midline; **F)** In this figure, interrupted sutures are used to re-approximate skin edges.

Figure 2 - One-year follow up after VOG.



A) In this figure, the BMG can be seen in ventral aspect of meatus; **B)** In this figure, the normal appearance of ventral penile skin.

transurethral resection of the prostate (TURP). The remaining 2 patients had a stricture secondary to traumatic catheterization. Four patients had a prior urethral dilation and one patient had a direct vision internal urethrotomy (DVIU).

Median measured fossa stricture length was 2 cm (IQR: 1.6 – 2.0). The overall success rate was 90% with a median follow up to date of 30 months (IQR: 24.3 – 36.8). One patient developed a recurrence at 14.0 months and was managed by urethral dilation with triamcinolone injection. Since re-intervention, this patient reports strong urinary stream without spray and complete emptying. There were no complications in the study (Table-1).

Table 1 - Patient background and outcomes.

ID	Age	BMI	Race	DM	HTN	Smoker	Stricture Etiology	Prior Dilation Or DVIU	Defect Length (cm)	Success	Time to Failure (days)
1	71	20	WNH	N	Y	Never	TURP	Dilation	1.5	yes	-
2	71	23	WH	Y	Y	Former	TURP	None	2	yes	-
3	66	24	WNH	N	Y	Never	Greenlight	None	2	yes	-
4	59	26	WNH	N	Y	Former	Catheter	Dilation	3	no*	419
5	66	25	WH	N	N	Never	Other‡	Dilation	2	yes	-
6	54	31	WH	N	Y	Never	TURP	None	2	yes	-
7	31	31	A	Y	Y	Former	Catheter	DVIU	1.5	yes	-
8	63	25	WH	Y	Y	Current	TURP	None	2	yes	-
9	65	31	WNH	Y	Y	Never	Greenlight	None	2.5	yes	-
10	73	22	A	Y	Y	Never	Catheter	Dilation	1.5	yes	-

Abbreviations: BMI = Body Mass Index, DM = diabetes mellitus, HTN = hypertension, DVIU = direct vision internal urethrotomy, WNH = White non-Hispanic, WH = White Hispanic, A = Asian, TURP = Transurethral resection of prostate, Greenlight = greenlight laser vaporization, Catheter = catheterization, Other‡ = cystolitholapaxy
*patient had decreased flow on follow up and was treated by dilation with triamcinolone injection

On routine follow up visits, patients were asked about their satisfaction regarding penile cosmesis. All patients reported satisfaction with the appearance of their reconstruction.

DISCUSSION

The challenge in treatment of FN strictures lies in the dichotomy of maintaining a cosmetically appealing glans and achieving satisfactory functional outcomes. Patient-specific factors and surgeon preference play a role in choosing between the range of available repairs. Patients with LS, hypospadias and those with completely obliterated strictures pose an even greater challenge and traditionally require a complex multi-stage approach, which albeit successful, can be psychologically and physically taxing to the patient. Single-stage repairs have been popularized as they offer high rates of success in one anesthetic session with good aesthetic outcomes. Some still employ ventral flap repairs, first described by Orandi, with either closure with glans wings or utilizing the more labor-intensive glans cap to avoid dividing the glans. Single-stage BMG urethroplasty is particularly promising in treatment of FN strictures of any etiology as the glans provides a robust vascular bed for graft take. However, much of the literature thus far has described dorsal placement of the BMG partly due to concern for fistula formation. Many series have described techniques to prevent fistula formation in anterior urethroplasties such as overlying repair with a tunica vaginalis flap as described by Favorito and colleagues. (9). However, we believe that for isolated FN strictures, particularly in the setting of iatrogenic etiologies, there is a good graft take and low rate of urethrocutaneous fistula without need for interposition flaps.

Our preliminary series of 10 patients provides evidence in favor of VOG as a surgical technique for FN strictures. Surgically, we feel that the procedure has a short learning curve, with short operative time and favorable long-term outcomes. Despite our results being limited to a small sample size, they echo similar series in the literature and attest to the efficacy of VOG in the glans urethra. Although the majority of FN strictures in our series resulted from an iatrogenic cause, we believe there is a role for single-stage repair with VOG in strictures of any etiology, including milder cases of LS. However, in those with severe disease with completely obliterated lumen, a two-stage repair would still be the treatment of choice.

Early approaches to FN reconstruction focused on using vascularized skin flaps to minimize graft-take issues. In 1987, Jordan first described transposing a ventral skin island flap with a vascularized dartos pedicle onto a distal urethrotomy defect and closing with glans wings (6). The surgeon went on to report an 83% success rate with this technique over a mean follow-up of 10.2 years (N= 35). They found success in 23/23 patients without LS and recurrence in 6/12 patients with LS (10). Like Jordan, Armenakas et al. used a ventral transverse island flap but approached and closed the glans differently. Through a subcoronal incision, they dissected under the glans to create a glans cap to access the FN. This method precluded closing with glans wings, which may reduce scarring and fistulization as well as improve cosmesis. In their study, 1 recurrence occurred in 15 patients that received glans cap over a mean follow up of 42 months (11). The cosmetic advantage of performing a glans cap has not been established, since Fiala et al. reported 100% satisfaction with appearance following FN repair that utilized glans wings (N=21) (12).

Moreover, grafted FN repairs offer advantages, especially in inflammatory strictures where the use of diseased genital skin increases failure rate (2, 10). In 28 patients with lichen sclerosis, Venn and Mundy compared genital skin flaps to two-staged grafted repairs utilizing non-genital skin (either full-thickness postauricular skin or buccal mucosa). One of 16 patients in the non-genital skin group had recurrence while 12 of 12 patients in the genital skin flap group had a recurrence, concluding that penile skin flaps should not be used to repair urethral stricture caused by LS (13). In this vein, Gelman et al. combined Jordan's preputial flap with a dorsal inlay of buccal mucosa to repair FN strictures in one stage. All 12 patients were stricture-free with a mean follow up of 39 months; however, 2 patients developed a urethral fistula (14).

To our knowledge, only two studies have described ventral onlay of BMG for FN strictures (14). In their series, Chowdhury et al. reported 5

out of 6 patients (83%) to have durable functional and cosmetic outcomes at median follow up of 37 months (20). However, we believe our approach has key differences that make it simpler. For example, we do not raise glans wings, which decreases dissection and bleeding. We also do not take anchoring bites on the graft during glans apposition. After graft placement and closure of dartos, we approximate the glans to relieve tension with a deep horizontal mattress suture using 2-0 monocryl, bringing the edges together in a natural position without overly compressing the graft. We then re-approximate the skin edges in an interrupted fashion and suture the distal edge of BMG to the glans itself to create the neomeatus. Conversely, Chowdhury describes suturing the distal edge of the BMG to the margins of the initial ventral slit made on the meatus. Goel et al. expanded use of BMG to both a dorsal inlay and ventral onlay, reporting 'satisfactory clinical outcomes' in 10 of 10 patients at a mean follow up of 13.5 months (15).

Given the heterogeneity in effective treatment approaches, one group recently proposed an algorithm based on stricture etiology and functional anatomy (16). They demonstrated that single--stage repair with dorsal inlay BMG is suitable for most FN strictures but recommend a multistage approach for hypospadias and those with severe LS (1). They use ventral fasciocutaneous flap as an adjunct if urethra cannot be calibrated to 20Fr after dorsal inlay. Although much of the literature describes dorsal placement of BMG, our series supports that ventral BMG onlay (± dorsal inlay) can be a valuable addition to the FN reconstruction armamentarium.

Recent innovations explore the use of minimally invasive modalities of FN stricture repair without skin incision. Nikolavsky et al. first described a transurethral placement of BMG as an inlay following wedge resection of the narrowed segment. They reported no recurrences, no fistula formations, and improved flow in 3 out of 3 patients with at least 1 year follow up (range 12-24 months) (17). The procedure was studied again but at a multi-institutional level (15 sites total), finding 3 recurrences in 57 patients with a median follow up of 17 months (IQR 13-22) (17). Others have even successfully adapted transurethral circular graft placement through a circum-meatal incision and careful dissection of the urethra from the glans. Notably, 9 out of 19 patients required proximal ventral urethrotomy due to inadequate urethral exposure (19). These approaches may offer a feasible single-stage option for distal FN stricture repair with avoidance of skin incision or urethral mobilization. However, they may prove more surgically challenging, particularly in longer and more proximal FN strictures.

Our study had a small sample size of 10 patients, however, it was larger than the only other study presenting VOG for FN strictures, which included 6 patients in total (20). Furthermore, the majority of patients in that analysis had lichen sclerosis stricture etiology whereas the vast majority of strictures in our study were iatrogenic. Thus, our findings show the feasibility of VOG for iatrogenic FN strictures. Another limitation involved our definition of treatment success with no further need for urethral instrumentation. While objective measures are limited by patient follow up, this was the only practice measure from our database that has been used as an outcome measure in prior published series (10, 15, 18). In addition, cosmetic satisfaction as a binary question is limited, however, this measure has been used in other series as well (12, 15, 16). Due to the retrospective nature of the study, we were unable to provide validated patient reported outcomes on penile or glans cosmesis. Despite this, our preliminary data provides evidence for the feasibility of ventral onlay for fossa navicularis strictures and adds to the armamentarium of urethral reconstructive techniques.

CONCLUSION

A variety of techniques are available for addressing glans urethral strictures. This study has the potential to further change clinical practice as ventral grafts have long been used in the bulbar urethra but not as commonly in the distal urethra. VOG shows promise to treat various stricture etiologies providing patency and pleasing cosmesis. Given the short learning curve of this technique and the promising early results, we feel that VOG belongs in most reconstructive urologists' toolkits for addressing the often-challenging case of the FN stricture.

ABBREVIATIONS

FN = Fossa Navicularis
VOG = Ventral Onlay Glanuloplasty
BMG = Buccal Mucosal Graft
LS = Lichen Sclerosis
VCUG = Voiding Cystourethrogram

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George Wayne and Alejandra Perez, contributed similarly as first author

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Treatment of fossa navicularis strictures

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COMMENT

The article describes the authors' experience with their technique to treat fossa navicularis strictures with ventral buccal mucosa grafts (1). They analyzed complications and outcomes in a retrospective case series of ten patients, selected from their institution's 151-patient strong database. The series included those with synchronous proximal strictures discontinuous with the distal one, i.e. skip strictures; and excluded those with Lichen Sclerosus et Atrophicus (LSA). In all but one patient the stricture resulted from either transurethral surgery or urinary catheterization. The authors achieved a high success rate (by the customary criterion of no further urethral instrumentation): Nine out of ten patients had a favorable functional and aesthetic outcome, and no complications such as urinary fistulae were reported.

Their technique is rather straightforward, with few modifications from the original description by Chowdhury at al (2). After cystoscopically ensuring that the distal stricture was limited to the fossa navicularis, a buccal mucosal graft was sutured (with 5-0 polydioxanone) to the mucosal edges of the ventrally incised urethra, with vascular support being provided by both a dartos flap and a glans spongiosum 2-layered closure. In narrower strictures, a dorsal Asopa-like (3) graft was used to augment the urethral lumen.

This paper timely addresses one of our most vexing complications: A fossa navicularis stricture after transurethral surgery or urethral instrumentation, which the practicing urologist will inevitably encounter many times during his or her career. Thus, knowledge of treatment options other than dilatation or simple ventral meatotomy/distal urethrotomy looks like sound individual policy. The latter procedures, however simple, effective and widely taught as they are, often lead to aesthetically unfavorable outcomes, which may compromise the patient-physician relationship.

Yet, the question whether the procedure should be performed by any urologist or by a specialist, that is, an experienced reconstructive urologist, has a less clear-cut answer. Although the authors claim that the operation has a short learning curve, it does require buccal mucosal harvesting and exquisite technique to handle both graft and graft bed, which may fall outside the scope of many urologists trained during the bygone "direct visual urethrotomy era". Perhaps the new generation of urologists, trained in the ongoing "reconstructive era", may judge themselves more apt to adopt this technique (or any of its variations that will surely follow). For those lacking proper reconstructive urology training, either during their residency or by going through a reconstructive urology fellowship, it may be wise to address the knowledge gap by referencing these patients to more experienced colleagues, and to involve oneself in these operations until acquiring familiarity with the procedure and with its postoperative care.

A subtler point of this procedure is that it may act to preserve some of the hydrodynamic features of the fossa navicularis, lost in simple ventral meatotomy/distal urethrotomy and ventrally placed penile

skin flap (that are not an option in LSA patients) procedures. The fossa owes its transversal elliptical shape from the combination of the higher tissue compliance of the glans spongiosum and Henle's septum glandis (4,5), which tethers the urethra at its 6 and 12 o'clock positions, and seems to function as a urinary "flow control" chamber (6). Indeed, one may conjecture that with time the graft should accommodate to its relatively capacious glanular bed, and acquire a geometric configuration capable of producing a coherent, wave-like, normal voiding stream.

CONFLICT OF INTEREST

None declared.

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Association of physical therapy techniques can improve pain and urinary symptoms outcomes in women with bladder pain syndrome. A randomized controlled trial

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ABSTRACT

Purpose: to verify the effects of biofeedback (BF) and manual therapy (MT) associated with transcutaneous electrical nerve stimulation (TENS) or postural exercises (PE) in the treatment of bladder pain syndrome (BPS) in women regarding pain and urinary symptoms.

Materials and Methods: a parallel-randomized controlled trial was conducted in BPS patients diagnosed according to NIH clinical criteria. Two specialized physiotherapists applied demographic and validated questionnaires of perineal and suprapubic pain (VAS), urinary symptoms and problems (ICSI and ICPI) and sexual function (FSFI) and a physical assessment was made to identify myofascial trigger points. Thirty-one women, mean age 51.8 ± 10.9 were randomized in three groups of treatment consisting of ten weekly sessions of BF and MT (Conventional group); BF, MT, and TENS (TENS group); and BF, MT, and PE (Postural group).

Results: Postural group improved perineal and suprapubic pain after treatment ($p<0.001$ and $p=0.001$, respectively), and the suprapubic pain improvement remained persistent at 3 months of follow up ($p=0.001$). Postural group improved urinary symptoms and problems after treatment ($p<0.001$ and $p=0.005$, respectively) and during follow up ($p<0.001$ and $p=0.001$).

Conclusions: Biofeedback and manual therapy associated with postural exercises showed a significant improvement in perineal and suprapubic pain and urinary symptoms after treatment and during follow-up. Both results suggest a possible role for the use of this physiotherapy technique to treat BPS patients. Longer follow-up and a larger number of patients are necessary to confirm these conclusions.

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INTRODUCTION

Bladder pain syndrome (BPS) is defined as the presence of pain, pressure and discomfort in the pelvis, perineum, and genitalia for more than 6 months with at least one lower urinary tract symptom, such as frequency, urgency, or nocturia, in the absence of urinary infection or other pathology. This condition can be associated with pelvic floor disorders and gynecological and gastrointestinal symptoms and has a significant impact on sexual activity and overall quality of life (1, 2).

Considerable variability in treatment recommendations is noted in the main BPS guidelines. Based on phenotype classification, the treatment should be multidisciplinary and include behavioral, physical and psychological approaches (1, 3). Referring to the tenderness phenotype, women with BPS can present pelvic floor myofascial pain characterized by sensitivity during palpation and local or referred pain during the physical assessment (4, 5). An increase in muscle tension due to difficulties in relaxation that can generate myofascial trigger points has also been observed (5, 6). Trigger points can lead to pelvic floor dysfunction and consequently perineal pain and dyspareunia associated with urgency, frequency and nocturia (7, 8). Pelvic floor dysfunction can generate an increase in pelvic asymmetry and changes in diaphragmatic excursion, compromising respiratory and postural stability. Some evidence indicates that pelvic floor muscles contribute to respiratory and postural function (9).

The main guidelines (1-3) consider manual therapy and biofeedback valuable tools for the conservative treatment of BPS.

Manual therapy provides muscle fiber stretching, a decrease in muscle tension and trigger point release, restoring the normal movement amplitude and increasing body consciousness (10). Several studies show the efficacy of manual therapy to improve pain in women with BPS (11). The use of biofeedback with surface electrodes provides an indication of myoelectrical activity to modify the neuromuscular response and to acquire motor control improvement (12).

Despite the lack of recommendations in current guidelines, other noninvasive techniques, such as transcutaneous electro nerve stimulation (TENS) and postural exercises, may be associated with pain and urinary symptom treatment in women with BPS (13, 14).

TENS is used for acute and chronic pain through the placement of transcutaneous electrodes on the pain sites (15). The application is based on the gate control theory of pain, which suggests that a counter stimulation of the nervous system can modify the perception of pain. In the literature, women treated with high frequency, i.e., between 75-100 Hz, presented better pain effects and tolerability (13).

Postural exercises are used to improve musculoskeletal system function that can be compromised in the presence of visceral dysfunction in women with BPS. Musculoskeletal dysfunction is commonly demonstrated in women with self-reported chronic pelvic pain with the presence of iliac crest asymmetry and an increase in sensitivity in abdominal and pelvic floor muscles (14, 16-18). Long-lasting pain in the pelvic area generates neuroplasticity and contributes to disturbances in motor control and consequent changes in the activation performance of synergistic muscles, causing balance and gait disturbance, lack of coordination, a decrease in diaphragmatic excursion and an increase in tension in the pelvic area (19).

In this study, our hypothesis was that women with BPS presented musculoskeletal dysfunction, and we tested a different physiotherapy approach that has not being used. The reason for that understanding was the presence of refractory urinary and pain symptoms notwithstanding the physiotherapy conventional treatment, such as manual therapy and biofeedback. To test our hypothesis, we decided to add either TENS or postural exercises to the conventional treatment.

The objective of this study was to verify the effects of biofeedback (BF) and manual therapy (MT) associated with transcutaneous electrical nerve stimulation (TENS) or postural exercises (PE) in the treatment of bladder pain syndrome (BPS) in women regarding pain and urinary symptoms.

MATERIALS AND METHODS

A parallel randomized controlled trial was conducted after approval from our Ethics Review Board (61595016.0.0000.0068) and registered at ClinicalTrials.gov (NCT03755375). Women with a diagnosis of BPS according to NIH clinical criteria (20) ≥ 18 years old were evaluated by the medical team of the Urology Clinic at the "Hospital das Clinicas of the University of Sao Paulo School of Medicine" and referred to a physical therapy outpatient clinic from February 2018 to December 2019. Women who presented symptoms of perineal and suprapubic pain, using painkillers, anticholinergics, antidepressants, and anticonvulsants for at least 6 months, and exhibited absence of urinary infection for at least 3 months for the initial assessment were included.

Women with positive urine culture, under actual or previous oncologic treatment, with systemic or neurological diseases that could compromise pelvic structures, with cognitive deficiency that compromised the understanding of the provided instructions and those who refused to participate in the study were excluded.

In the initial assessment, two specialized and trained physiotherapists applied a demographic questionnaire to identify the characteristics of the sample and validated questionnaires of perineal and suprapubic pain (Visual Analog Scale of Pain [VAS]) (21) to quantify the pain; urinary symptoms and problems (O'Leary-Sant - The Interstitial Cystitis Symptom and Problem Index) (22) to evaluate the presence of urgency, frequency, nocturia and to quantify how much these symptoms represent a problem to the patients, and the Female Sexual Function Index (FSFI) (23) to evaluate the impact on sexual life. Then, a physical assessment by the inspection and palpation of pelvic and perineal areas was made to identify myofascial trigger points.

After the assessment, participants were blinded randomized by a mask researcher using random.org and allocated into three groups of treatment (TENS, Postural and Conventional) held over 10 sessions once a week. All participants needed to attend the whole treatment to be included with a maximum delay of 2 weeks to start treatment.

Conventional group was treated with biofeedback for pelvic floor relaxation and manual therapy to release the tension in the suprapubic, pelvic, and intravaginal areas. The manual therapy consisted of a myofascial trigger point release maneuver using digital pressure and muscle fiber stretching in pain areas. Biofeedback consisted of pelvic floor muscle coordination and relaxation exercises using intravaginal probes. The training program was initiated with 10 fast contractions with 5 seconds of relaxation between them followed by 10 sustained contractions of 5 seconds with 10 seconds of relaxation between them. Finally, one minute of pelvic floor relaxation was performed.

TENS group was treated with biofeedback, manual therapy, and transcutaneous electrostimulation (TENS), a peripheral neuromodulation to promote analgesia in pain areas, using two transcutaneous self-adhesive electrodes Axelgaard 5 cm x 5 cm with 2 cm of distance between them. The parameters used were frequency = 100 Hz, pulse width = 50-100 μs, and current intensity according to the patient's sensitivity.

Postural group was treated with biofeedback, manual therapy, and postural exercises, which promoted pelvic mobility and functional training associated with respiratory exercises increasing the diaphragmatic excursion. Postural exercises consisted of 10 repetitions of breathing exercises in the lay-down position, 10 repetitions of hip anteversion and retroversion in the sitting position, and 10 repetitions of hip anteversion, retroversion, and lateral movement in the stand-up position.

The biofeedback and TENS device used was a Myotrac Infiniti T9800 (Thought Technology Ltda., Montreal, Canada, ISO 13485:2016ISO 13485:2016), a 2-channel system of surface electromyography and electrostimulation using the Biograph Infiniti platform. For biofeedback training, we used intravaginal electrodes St-Cloud/Femelex 6.9 cm.

All participants were evaluated post treatment and at 3 months of follow-up using the same procedures of the initial assessment.

All participants were instructed to perform home training daily 3 times/day during treatment and completed an exercise diary to demonstrate

adherence to treatment. TENS and Conventional groups were instructed to perform pelvic floor relaxation exercises, and Postural group was instructed to perform pelvic floor relaxation exercises plus postural exercises.

Sample calculation and statistical analysis

The sample size analysis was calculated in a pilot study based on previous nonpublished data of our participants (n=15). The variables considered in the sample size calculation included "Perineal and Suprapubic Pain VAS Score" and "O'Leary-Sant – Symptoms and Problems Index". The "O'Leary-Sant – Problems Index" was chosen to estimate the sample size of this study because it reached the largest number of patients. The estimated sample was 27. Considering 20% loss, the calculated sample size was 22 volunteers. The sample sizes calculated for other variables were 12 for perineal pain and 18 for suprapubic pain and urinary symptoms. G Power software, version 3.1, was used with the following parameters: MANOVA Test for repetitive measures to compare the three groups, α=0.005, power (1-β) =0.80 and effect size (f): 0.55

Statistical analysis was performed using the SPSS program (IBM, SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). To assess the normality of continuous variables, the Kolmogorov–Smirnov test was used. The Z score was used to standardize data that did not follow the normality curve.

Descriptive analysis was used (mean ± standard deviations) for the characterization of the groups. For the analysis of continuous variables, the univariate general linear model (GLM) test was used to compare the groups. The analysis of categorical variables was performed using the chi-square test and, when necessary, Fisher's test.

The GLM for repeated measures was performed for the treatment. The significance level was $\alpha \leq 0.05$ (24).

RESULTS

Of 41 women with BPS initially assessed by eligibility, 9 were excluded. Thus, 32 women were randomized into three groups of treatment: TENS Group, Postural Group and Conventional Group. The study flowchart is shown in Figure-1. The socio-demographic characteristics of 23 women (mean age = 51.95 ± 11.55 and BMI= 26.57 ± 4.23) who completed the 3 months of follow-up are shown in Table-1.

Perineal and Suprapubic Pain

Postural group had a significantly longer time of symptoms than the other two groups (p=0.028) (Table-1).

After treatment, Postural group exhibited significantly improved perineal and suprapubic pain compared to pretreatment assessment (p<0.001 and p=0<0.001, respectively) and the suprapubic improvement persisted during follow--up (p=0.001).

The comparison between groups showed that Postural group exhibited significantly improved perineal and suprapubic pain after treatment (p=0.002 and p=0.026, respectively) and during follow-up compared to Conventional group (p=0.008 and p=0.011, respectively).

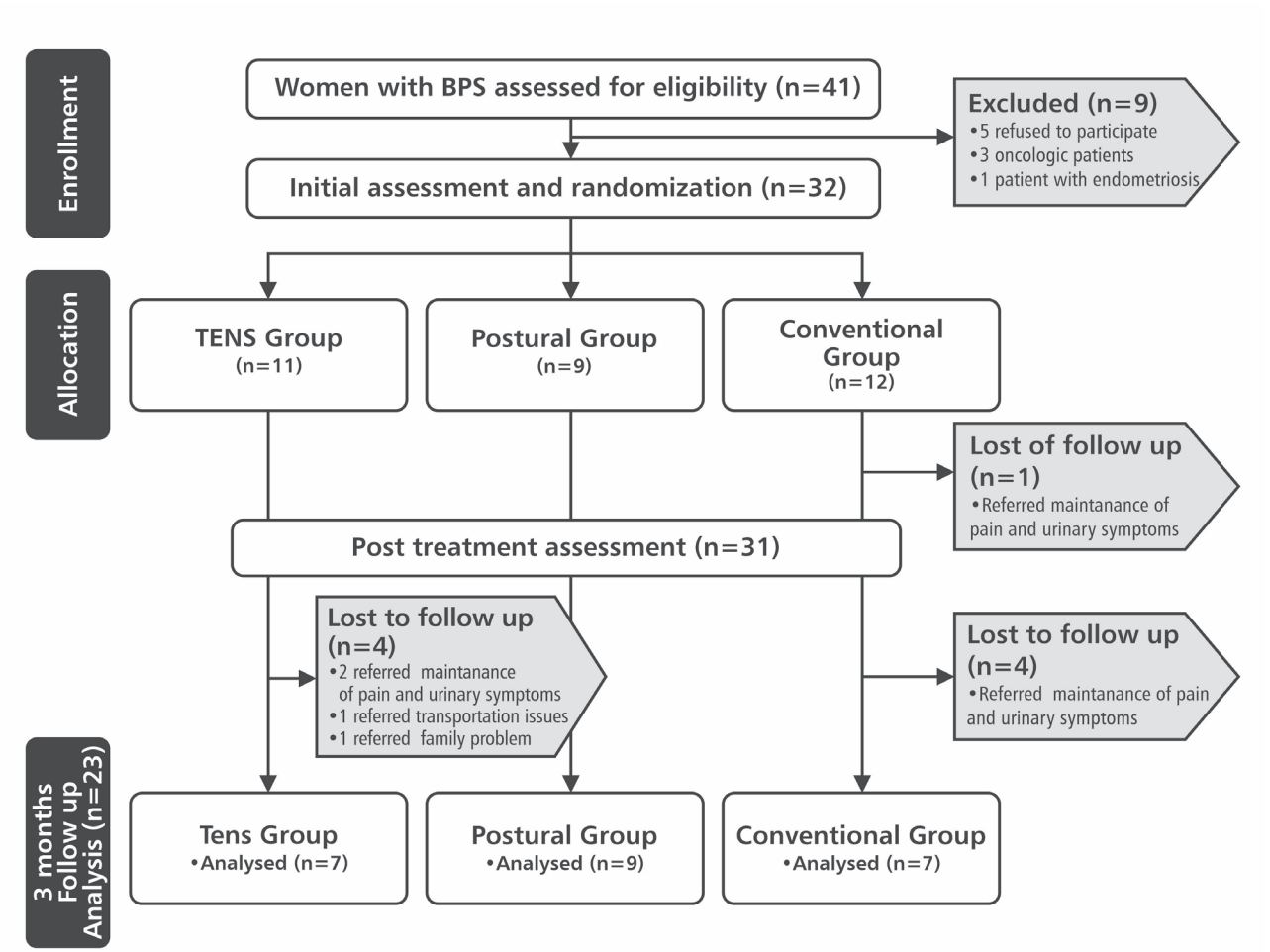
Urinary Symptoms (ICSI) and Urinary Problems (ICPI)

Postural group showed significant improvement in urinary symptoms and problems after treatment compared to pretreatment (p<0.001 and p=0.005, respectively) and a persistence of improvement during follow-up (p<0.001 and p=0.001, respectively).

The comparison between groups showed that TENS group exhibited significantly improved urinary symptoms problems after treatment compared to Conventional group (p=0.043 and p=0.048, respectively). During the follow-up, Postural group showed a significant improvement in urinary symptoms and problems compared to Conventional group (p=0.017 and p=0.025, respectively). Table-2 shows the intragroup and between-group comparisons of perineal and suprapubic pain, urinary symptoms, and problems (ICSI and ICPI, respectively) at pretreatment and posttreatment as well as during follow-up. We observed that conventional treatment alone did not achieve satisfactory results.

Related to the presence of perineal and suprapubic trigger points, we observed that

Figure 1 - Flowchart of the study.



Postural group showed a significant decrease after treatment and during follow-up (Table-3).

Related to medications, we did not observe a decrease in anticholinergic, antidepressant, or anticonvulsant intake after treatment. However, we observed a significant decrease in painkiller intake in Postural Group after treatment. Regarding sexual function, none of the groups presented any improvement after treatment (Table-4).

In each session, the physiotherapists asked the participants about possible side effects caused by the treatment, such as burning sensation, pain, and discomfort. We noticed that no women from the whole sample reported any complaints during or after sessions during the entire treatment period.

DISCUSSION

Biofeedback and manual therapy are recommended in the main urology guidelines as conventional treatment for patients with BPS; however, a common protocol is not available. We considered these techniques as conventional treatment for research purposes.

In this randomized controlled trial, we compared conventional treatment alone with the combination of TENS or postural exercises to verify whether the combination would be beneficial.

Our study showed significant improvement of perineal and suprapubic pain by the association of postural exercises with conventional treatment. In a randomized control trial with 81 women with BPS, Fitzgerald et al. (11) showed that 59% of

Table 1 - Sociodemographic data of the sample (n=23).

	TENS (n=7)	Postural (n=9)	Conventional (n=7)	p value
Age (years ± SD)	54±13	48±11	54±9	0.43
BMI (Kg/cm2 ± SD)	24.0 ± 4.0	28.8 ± 3.9	26.3 ± 3.7	0.068
Education level N (%)				
Illiterate	1 (14.3%)	3 (33.3%)	1 (14.3%)	0.452
Elementary school	1 (14.3%)	1 (11.1%)	2 (28.6%)	
High school	2 (28.6%)	4 (44.4%)	4 (57.1%)	
University	1 (14.3%)	1 (11.1%)	0 (0%)	
Postgraduate	2 (28.6%)	0 (0%)	0 (0%)	
Marital status N (%)				
Single	2 (28.6%)	4 (44.4%)	3 (42.9%)	0.664
Married	2 (28.6%)	4 (44.4%)	1 (14.3%)	
Divorced	2 (28.6%)	0 (0%)	2 (28.6%)	
Widow	1 (14.3%)	1 (11.1%)	1 (14.3%)	
Menopause N (%)	5 (71.4%)	4 (44.4%)	6 (85.7%)	0.209
Time of symptoms (years)	6.60 ±5.20	21.70±15.90	9.40±6.50	**0.028**
Use of painkillers N (%)	6 (85.7%)	9 (100%)	6 (85.7%)	0.531
VAS Perineal pain score (0-10)	7.28±3.86	7.88±1.16	6.14±3.13	0.479
VAS Suprapubic pain score (0-10)	7.57±3.55	6.11±3.58	6.00±2.88	0.621
Urinary Symptoms (ICSI) (0-20)	12.00±6.83	16.66±3.28	15.14±2.73	0.146
Urinary Problems (ICPI) (0-16)	9.43±6.05	13.44±4.47	14.43±2.76	0.121
Sexual function (FSFI) (2-36)	7.48 ± 8.15	12.58 ± 9.54	10.47± 10.55	0.34

SD = standard deviation; **BMI** = Body Mass Index; **VAS** = Visual Analogue Scale; **ICSI** = Interstitial Cystitis Symptom Index; **ICPI** = Interstitial Cystitis Problem Index; **FSFI** = Female Sexual Function Index.

women treated with manual therapy reported a subjective improvement of pain and pelvic floor tension. However, in our study, we did not observe that this conventional treatment improved perineal and suprapubic pain in women with BPS.

In this study, Postural group showed a significant improvement in urinary symptoms and problems after treatment and during follow-up. Haugstad et al. (19) evaluated 60 women with chronic pelvic pain to study the clinical characteristics of posture, movement, gait, sitting posture, and respiration and demonstrated a nonfunctional motor pattern and a lack of coordination and irregular high costal respiration. The association of postural exercises, which included pelvic mobility, functional training and diaphragmatic exercises, was applied in participants in the postural group to improve global movements, coordination, and balance due to a protective blockage of movement to avoid pain. This blockage decreases diaphragm

Table 2 - Pain and urinary symptoms' ratings pretreatment, post treatment and during follow-up.

Variable	Pre treatment	Post treatment	Follow-up	p value intra groups			p value inter groups		
				Pre x Post	Post x Follow-up		Pre treatment	Post treatment	Follow-up
Perineal Pain VAS Score (0-10)									
TENS	7.30±3.90	3.30±3.40	3.45±4.40	<0.001 ↑	0.002 ↓	TENS X Postural	0.676	0.179	0.214
Postural	7.90±1.20	1.35± 2.00	1.44±1.74	<0.001 ↑	<0.001 ↓	TENS X Conventional	0.457	0.057	0.132
Conventional	6.15±3.15	6.30±3.00	6.00±2.80	0.853	0.898	Postural X Conventional	0.234	0.002	0.008
Suprapubic Pain VAS Score (0-10)									
TENS	7.60±3.55	2.60±3.35	3.30±3.70	<0.001 ↑	0.001 ↓	TENS X Postural	0.402	0.826	0.398
Postural	6.11±3.60	2.22±2.90	1.90±3.00	0.001 ↑	0.001 ↑	TENS X Conventional	0.395	0.052	0.082
Conventional	6.00±2.90	6.00±3.10	6.42±2.93	1.00	0.71	Postural X Conventional	0.949	0.026	0.011
Urinary Symptoms (ICSI) (0-20)									
TENS	12.00±6.85	9.14±8.00	10.00±7.80	0.07	0.28	TENS X Postural	0.054	0.734	0.492
Postural	16.70±3.30	10.10±5.00	8.10±4.80	<0.001 ↑	<0.001 ↑	TENS X Conventional	0.209	0.043	0.088
Conventional	15.15±2.75	15.60±2.60	15.15±2.05	0.77	1.00	Postural X Conventional	0.512	0.066	0.017
Urinary Problems (ICPI) (0-16)									
TENS	9.50±6.05	8.00±7.10	9.00±7.45	0.286	0.805	TENS X Postural	0.100	0.506	0.524
Postural	13.45±4.50	9.80±5.20	7.20±5.60	0.005 ↑	0.001 ↑	TENS X Conventional	0.056	0.048	0.111
Conventional	14.45±2.80	13.85±2.00	13.85±1.35	0.666	0.742	Postural X Conventional	0.677	0.136	0.025

VAS = Visual Analogue Scale; **ICSI** = Interstitial Cystitis Symptom Index; **ICPI** = Interstitial Cystitis Problem Index; ↑ = improved; ↓ = worsened

excursion and pelvic mobility and leads to an increase in pelvic floor and lumbopelvic tension, stiffening of the core and consequently increased pain intensity. Nickel et al. (25) observed in 93 women with BPS that approximately 50% of patients experienced clinically significant improvement using an individualized phenotype-directed therapeutic approach. Our approach focusing on postural exercises helped us confirm that technique as a valuable tool for BPS patients with urinary symptoms.

Table 3 - Comparison between the presence of perineal and suprapubic trigger points between groups at pretreatment, post treatment and during follow-up.

Trigger points	Groups	Pretreatment n (%)	Post treatment n (%)	Follow-up n (%)	p value
Perineal area	TENS (n=7)	6 (85.7%)	4 (57.1%)	3 (42.8%)	0.087
	Postural (n=9)	9 (100%)	4 (44.4%)	4 (44.4%)	**0.009***
	Conventional (n=7)	6 (85.7%)	6 (85.7%)	6 (85.7%)	1.0
Suprapubic area	TENS (n=7)	6 (85.7%)	3 (42.8%)	4 (57.1%)	0.088
	Postural (n=9)	7 (77.8%)	5 (55.5%)	3 (33.3%)	**0.039***
	Conventional (n=7)	6 (85.7%)	6 (85.7%)	6 (85.7%)	1.0

*p value was significant in comparison between pretreatment versus post treatment assessment.

Table 4 - Comparison of painkiller's intake and sexual function score (FSFI) between groups at pretreatment and post treatment.

Painkiller's intake	Pretreatment	Post treatment	P value
TENS n (%)	6 (85.7%)	6(85.7%)	1.0
Postural n (%)	9 (100%)	5 (55.5%)	0.035
Conventional n (%)	6(85.7%)	6(85.7%)	1.0
FSFI			
TENS (mean ± SD)	7.48 ± 8.15	7.60 ± 7.85	0.85
Postural (mean ± SD)	12.58 ± 9.54	14.74 ± 13.82	0.26
Conventional (mean ± SD)	10.47± 10.55	13.57 ± 14.92	0.87

FSFI = Female Sexual Function Index (2-36); SD = standard deviation.

Our study did not show a significant improvement in sexual function. In total, 69.6% of the participants reported menopause symptoms and dysfunctional or absence of sexual activity (65.2%); of these, 52.2% reported dyspareunia and history of sexual abuse (21.7%). In a retrospective study, Seth et al. (26) observed that women with BPS with sexual abuse presented more pain and pelvic tension and fewer urinary symptoms. In our study, we did not observe a significant difference in pain, pelvic tension, or urinary symptoms in women with and without sexual abuse.

The strengths of this study were that it was a randomized prospective controlled trial that used conventional treatment associated with postural exercises with a significant improvement in perineal and suprapubic pain and urinary symptoms. The treatment consisted of 10 sessions once weekly with no side effects reported by the participants. Postural group showed increased adherence during the treatment and during follow-up (100%) compared to TENS and Conventional groups (63.6% each group). We concluded that postural exercises were easily understood by the participants, promoting their adherence.

This study had a few limitations. In total, 32 women were randomized and initiated the treatment, and 31 finished it. During follow-up, 23 (74.19%) remained in the study. We calculated a loss of approximately 20% out of 23 and not out of 32. If so, our study had an approximately 30% attrition rate. Although the sample size was small for a randomized controlled trial, the results showed a positive and impactful improvement.

CONCLUSIONS

Biofeedback and manual therapy associated with postural exercises showed a significant improvement in perineal and suprapubic pain and urinary symptoms after treatment and during follow-up. Both results suggest a possible role for the use of this physiotherapy technique to treat BPS patients. Longer follow-up and a larger number of patients are necessary to confirm these conclusions.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A novel nomogram and a simple scoring system for urinary leakage after percutaneous nephrolithotomy

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ABSTRACT

Introduction: The present study aimed to investigate the factors of prolonged urinary leakage (PUL) after percutaneous nephrolithotomy (PCNL) and develop a new and simple scoring system to predict it.

Patients and Methods: We retrospectively reviewed patients with renal stones who underwent PCNL at the University of Health Sciences Izmir Bozyaka Training and Research Hospital between April 2011 and January 2020. The patients were divided into two groups according to the presence of PUL, and their preoperative and perioperative data were compared. A multivariate regression analysis was applied to examine the relationship between perioperative descriptors and PUL, and a nomogram was developed using significant predictors. Then, the individual components of the nomogram were assigned points to form a scoring system.

Results: There were 92 and 840 patients in the groups with and without PUL, respectively. The results of the univariate logistic regression analysis showed that hydronephrosis grade, parenchymal thickness, duration of nephroscopy, and duration of nephrostomy catheter were significantly associated with PUL. Subsequently, a multivariate regression analysis was carried out with these four factors as possible independent risk factors of PUL after PCNL. Based on the results of this analysis, a nomogram prediction model was developed with an area under the curve value of 0.811, which was consequently used to develop a new simple score system consisting of three characteristics: parenchymal thickness (1–5 points), duration of nephroscopy (1–3 points), and hydronephrosis grade (1–3 points).

Conclusion: A novel scoring system is a useful tool for predicting PUL in patients who have undergone percutaneous nephrolithotomy.

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INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the standard treatment for renal stones of >2 cm (1). High stone-free rates reaching 96.1% can occur in PCNL (2). Despite the high efficacy of PCNL, complications of up to 20-83% are described in the literature. The most common of these complications are postoperative fever (4-32.1%), bleeding requiring transfusion (10.9-17.5%), and urine extravasation (7.2%) (3-5). However, when complications are classified according to the Clavien scoring system, the most common grade-3 complication is urine leakage persisting for >24 h (4%) treated by a double-J (DJ) ureteral stent (3).

After PCNL, a percutaneous nephrostomy (PCN) is placed in most cases for one to two days to provide both hemostasis and improvement in the access area (6). However, when the nephrostomy tube is removed at the end of this period, urine extravasation from the nephrostomy tract may sometimes continue. Nevertheless, a recent review by Xun Y et al. reported that patients who underwent tubeless PCNL, rather than standard PCNL, were associated with a lower risk of postoperative urine leakage (7). This is a disturbing event for both the patient and the physician. Although this returns to normal after the placement of a retrograde DJ stent, it requires re-anesthesia and an additional invasive procedure.

Many scoring systems have been developed to predict the results of PCNL (8-11). A previous meta-analysis also showed that complications could be predicted with scoring systems for PCNL (12). However, such scoring systems were not effective in showing prolonged urinary leakage (PUL). Although risk factors, such as hydronephrosis grade, duration of PCN catheter, type of dilator, PCN catheter diameter, renal parenchymal thickness in access line, residual stones, and mean stone burden have been identified for the development of PUL after PCNL, no scoring system is available to separately predict PUL (13, 14).

In this study, factors related to PUL were evaluated to predict which cases should receive a DJ catheter intraoperatively to shorten the length of hospital stay caused by PUL and decrease the exposure to additional anesthesia due to postoperative DJ catheter requirement, and a novel scoring system was developed to predict PUL after PCNL.

PATIENTS AND METHODS

Patients who underwent PCNL were analyzed at the Izmir Bozyaka Training and Research Hospital between April 2011 and January 2020, retrospectively. The study was approved by Ethical Board (Meeting/Decision No.2021/145). Patients with chronic renal failure, ureteropelvic junction obstruction, concurrent ureteral stones, lower urinary system symptoms, residual stones causing obstruction, those requiring an intraoperative DJ stent implantation, and those that underwent tubeless PCNL were excluded from the study.

The patients who did not develop PUL were defined as Group 1, and those that developed PUL as Group 2. The patients who were immediately dry or experienced urinary leakage for less than 24h after nephrostomy removal were evaluated in Group 1. Retrograde DJ stents were placed in all patients with urinary leakage that lasted for >24h, and these patients constituted Group 2. Of the patients with >24 hours of urinary leakage or /and who were symptomatic, those with opaque stones were evaluated with ultrasonography and those with non-opaque stones were evaluated with non-contrast computed tomography (CT). The patients with residual stones causing obstruction were excluded from the study. The presence of urine leakage was determined by patient-reported wet dressings and/or hourly checks by the physician associate.

All the patients were preoperatively evaluated with a multi-slice plain CT. The degree of hydronephrosis was calculated according to the Society for Fetal Urology Hydronephrosis Grading System (15). We defined the renal parenchymal thickness as the access line distance from the renal capsule to the apex of the pyramid in the coronal plane CT images. The skin-to-parenchyma distance was defined based on the distance indicators on the needle, which was accessed using an 18-G initial puncture needle during the operation. Perioperative and postoperative data included operative time, duration of nephroscopy, duration of fluoroscopy, length of hospital stay,

calyx of puncture, puncture site, access number, duration of PCN catheter, and presence of residual stones. The nephroscopy time was recorded from the access to the collecting system of the kidney to antegrade pyelography. The presence of residual stones was evaluated with fluoroscopy image and visual evaluation at the end of surgery. Sterile urine culture was detected in all patients before the operation.

The stone burden was calculated in square millimeters in all patients: length x width x ϖ x 0.25, where ϖ is a mathematical constantequalto 3.14 (16). In multiple intrarenal stones, the stone burden was calculated individually, and then the sum of all values were taken.

Surgical procedure

After general anesthesia, a 5- or 6-F ureteral catheter was inserted into the collecting system of the kidney with stones and fixed to a Foley catheter. Then the patient was placed in the prone position, access was performed with an 18-G needle, and the tract was dilated with Amplatz dilatators to the 30 F caliber under fluoroscopy. A 26-F rigid nephroscope was used in the operation. Stones were fragmented with pneumatic lithotripter (Vibrolith; Elmed, Ankara, Turkey). At the end of the procedure, routinely, a 14-F nephrostomy tube was inserted. On the postoperative first day, the Foley catheter and the ureteral catheter were removed. The nephrostomy tube was removed on the postoperative first or second day in the absence of fever or significant hematuria after antegrade nephrostography showing ureteral drainage down to the bladder. After the nephrostomy tube was removed, the presence of a leak was defined by wet dressings either reported by the patient or determined by hourly checking in the ward by a resident. The decision for a dry patient was based on patient-reported comfort and doctor-determined dry dressing. Urinary leakage that persisted for more than 24 h was considered as PUL, and a retrograde DJ stent was placed in these patients. These procedures were routinely applied to all patients. Success was defined as the presence of asymptomatic residual stones of less than 4 mm or no evidence of stones on the postoperative first-month CT.

Statistical Analysis

Categorical data were given as numbers and percentages. The conformance of continuous variables to normal distribution was evaluated using the Shapiro-Wilk test. Normally distributed variables were presented as mean and standard deviation, and those that did not show a normal distribution were presented as median and interquartile range. The independent-samples t-test was used to compare two independent normally distributed data, while the Mann-Whitney U test was used for the comparison of non-normally data. Pearson's chi-square and Fisher's exact tests were used in the comparison of categorical variables. Possible predictive variables associated with urine leakage were evaluated using multivariate logistic regression analysis, and the Backward elimination (Wald) method was used to create a model. The exclusion criterion for the model was set at $p < 0.1$. A prognostic nomogram was constructed using the regression coefficients of independent predictive variables.

The predictive ability of the nomogram and scoring system was evaluated with the receiver operating characteristic (ROC) analysis. The nomogram was validated using the Bootstrap method (1,000 resamples). The scoring system was developed based on the score weights of the variables in the nomogram. The internal validation of the new scoring system was performed by calculating the score for each patient. Prediction ability was evaluated with the ROC analysis, and sensitivity and specificity values were calculated by determining the optimal cut-off value based on the Youden index. SPSS software (version 23.0; IBM Corporation, Armonk, NY, USA) was used for statistical analysis, and R-project statistical software and the 'rms' package included in this software were used for the nomogram.

RESULTS

There were 932 patients in the study. There were 840 and 92 patients in Group 1 and Group 2, respectively. PUL was detected in 9.9% of the patients. The median age of the patients was 48 (38-57) years, and the median BMI was 26.1 (23.0-

29.3). There was a history of extracorporeal shockwave lithotripsy (ESWL) in 169 (18.1) patients, history of ipsilateral surgery in 279 (29.9), and metabolic syndrome in 71 (7.6). The relationship between the demographic and preoperative characteristics of the patients and PUL are presented in Table-1. The two groups were similar in terms of renal pelvis anteroposterior diameter, stone location, stone density, and stone burden (p>0.005). The presence of hydronephrosis, a high hydronephrosis grade, and a decreased renal parenchyma thickness were found to be associated with PUL (p=0.014, p<0.001, and p<0.001, respectively). Residual Stone rates were similar between the groups (p=0,210). The relationship between the perioperative and postoperative outcomes of the patients and PUL is given in Table-1. Duration of nephroscopy, length of hospital stay, and length of PCN catheterization were significantly longer in Group 2 (p<0.001, p<0.001, and p=0.002, respectively).

Nomogram and simple scoring system development

In the univariate analysis, hydronephrosis grade, parenchymal thickness, duration of nephroscopy, and duration of nephrostomy catheter were found to be associated with PUL (Table-1). The multivariate analysis conducted with these four variables revealed that hydronephrosis grade, parenchyma thickness, and duration of nephroscopy were independent risk factors for PUL (Table-2). Based on the results of the multiple regression analysis, a prognostic nomogram containing these three independent variables was developed (Figure-1). The area under the curve (AUC) value of the nomogram was 0.811 (95% CI: 0.767-0.855) with an optimal cut-off value of 14.96%, at which the model showed a sensitivity of 77.2% and specificity of 74.2% (Figure-2). The optimized corrected mean AUC value was determined as 0.800. Then, to be used in daily practice, a scoring system with a total score of 3 to 11 was created based on the effect sizes of a parenchymal thickness (1-5 points), duration of nephroscopy (1-3 points), and hydronephrosis grade (1-3 points) in the nomogram (Figure-1).

The novel scoring system was applied to each patient and internal validation was performed. While the median score was 7 (7-8) in the patients with PUL, it was 6 (5-7) in those without PUL (p <0.001). The AUC value of the scoring system to predict PUL was 0.793 (0.745-0.841) (Figure-2). This value was comparable with the AUC value of the nomogram (0.800). The optimal cut-off value of the scoring system was 6.5, at which it had 76.1% sensitivity and specificity of 71.0% in predicting PUL. Based on novel scores, the patients were divided into the risk groups of low (3-6), moderate (7-9), and high (10-11) (Figure-3), which were found to have the PUL rates of 3.6%, 19.4%, and 80%, respectively.

DISCUSSION

Despite its high stone-free rates and efficacy, large-scale complications can occur after PCNL (3, 4). The prolongation of urinary leakage from the nephrostomy tract after nephrostomy requires the insertion of a DJ catheter, which is classified as a grade 3 complication according to the Clavien scoring system (3). Residual stones migrate to the ureter and cause edema and blood clot obstruction, leading to PUL. The way to resolve this is the placement of a ureteral DJ catheter. In a study conducted by Binbay et al., 57 (4.3%) of 1,326 patients who underwent PCNL required a DJ catheter due to PUL, and this increased the length of hospital stay (13). Tefekli et al. supported the idea that PUL was the most common type of grade 3A complication that increased the duration of hospital stay (3). Similarly, in a recent study, the length of hospital stay was significantly longer in patients with PUL.

Although there are accepted scoring systems that predict success in renal stone treatment, these scoring are insufficient to predict the risk of complications. Thomas et al. proposed a scoring system (Guy's stone score, GSS) to preoperatively predict stone-free status by grading the complexity of PCNL. However, they found that although the score was associated with the stone-free rate, it was not associated with complications (8). Okhunov et al. indicated the necessity of additional studies to determine the role of the S.T.O.N.E. scoring system in predicting complications (9). In a single study of Ansari et al., GSS III and IV were

Table 1 - Comparison of demographic and preoperative characteristics of the patients according to the presence of urinary leakage.

Variables	Urinary Leakage		*p* value
	Absent (n=840)	Present (n=92)	
Age (years)	48 (38-57)	50.5 (37-60)	0.327
Gender, n (%)			0.273*
Female	272 (32.4)	35 (38.0)	
Male	568 (67.6)	57 (62.0)	
Laterality, n (%)			0.337*
Right	394 (46.9)	48 (52.2)	
Left	446 (53.1)	44 (47.8)	
BMI, kg/m^2, median (25th-75th percentile)	26.1 (22.9-29.4)	26.7 (24.2-29.4)	0.111
Metabolic syndrome, n (%)	61 (7.3)	10 (10.9)	0.216*
Previous history of ESWL, n (%)	155 (18.5)	14 (15.2)	0.534*
Ipsilateral surgery, n (%)	248 (29.5)	31 (33.7)	0.407*
Renal pelvis AP diameter	28.2 (19.7-60.0)	28.1 (19.3-47.2)	0.298
Hydronephrosis, n (%)			**0.014***
Absent	259 (30.8)	17 (18.5)	
Present	581 (69.2)	75 (81.5)	
Hydronephrosis, n (%)			**<0.001***
Grade 0	259 (30.8)[a]	17 (18.5)[b]	
Grade I	315 (37.5)[a]	21 (22.8)[b]	
Grade II	154 (18.3)[a]	25 (27.2)[b]	
Grade III	94 (11.2)[a]	24 (26.1)[b]	
Grade IV	18 (2.1)[a]	5 (5.4)[a]	
Stone location, n (%)			
Pelvis	220 (26.2)	30 (32.6)	0.164*
Partial Staghorn	360 (42.8)	32 (34.8)	
Staghorn	108 (12.8)	17 (18.5)	
Multiple calyces	152 (18.1)	13 (14.1)	
Stone density, HU	1,100 (800-1,300)	1,100 (800-1,252)	0.828
Stone burden, mm^2	314 (204-510)	282 (206-618)	0.831
Renal parenchymal thickness in access line, (mm)	15.4 (13.0-17.7)	11.8 (9.3-14.0)	**<0.001**
Skin-to-parenchyma distance, (mm)	80.0 (65-95)	79.2 (65-97.4)	0.942
Calyx of puncture, n (%)			0.210*
Upper	34 (4.0)	8 (8.7)	
Middle	285 (33.9)	29 (31.5)	
Lower	468 (55.7)	48 (52.2)	
Multiple	53 (6.3)	7 (7.6)	
Puncture site, n (%)			0.918*
Supracostal	288 (34.3)	33 (35.9)	
Subcostal	519 (61.8)	56 (60.9)	
Multiple	33 (3.9)	3 (3.3)	
Number of access, n (%)			0.264*
1	761 (90.6)	80 (86.9)	
≥2	79 (9.4)	12 (13.0)	
Duration of operation, min.	90 (70-120)	100 (71.25-120)	0.850
Duration of nephroscopy, min.	40 (30-50)	50 (40-70)	**<0.001**
Duration of fluoroscopy, sec.	66 (42-102)	63 (46-97)	0.944
Length of hospital stay, days	3 (2-4)	4 (3-6)	**<0.001**
Duration of PCN catheter, days	2 (2)	2 (2-3)	**0.002**
Blood transfusion requirement, n (%)	70 (8.3)	6 (6.5)	0.547*
Residual stone, n (%)	216 (25.7)	34 (37.0)	0. 210*

BMI: Body massindex, **AP**: Anterior-posterior; *Pearson'schi-square test

[a, b] = No significant difference between the same superscripts.

Table 2 - Multivariate logistic regression analysis of possible factors in predicting urinary leakage.

	Multivariate analysis		Reduced multivariate analysis	
	OR 95% CI	p value	OR 95% CI	p value
Hydronephrosis grade				
Grade 0	Ref		Ref	
Grade I	1.317 (0.650-2.666)	0.445	1.270 (0.633-2.548)	0.502
Grade II	2.658 (1.328-5.321)	**0.006**	2.624 (1.317-5.228)	**0.006**
Grade III	3.548 (1.698-7.411)	**0.001**	3.536 (1.696-7.371)	**0.001**
Grade IV	4.017 (1.199-13.457)	**0.024**	4.319 (1.270-14.689)	**0.019**
Parenchymal thickness	0.761 (0.710-0.816)	**<0.001**	0.765 (0.714-0.820)	**<0.001**
Duration of nephroscopy	1.017 (1.009-1.025)	**<0.001**	1.018 (1.010-1.026)	**<0.001**
Duration of PCN catheter	1.219 (0.936-1.588)	0.141		

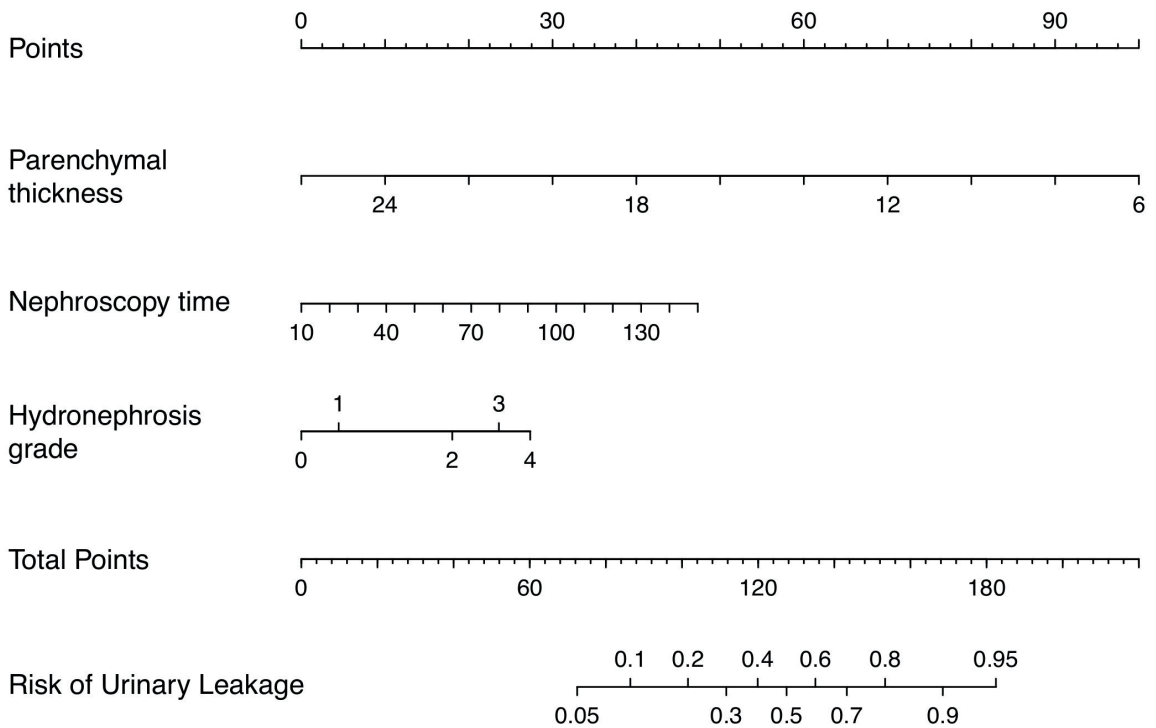
OR = odds ratio

reported to be associated with PUL (18). In the current study, we developed a new scoring system to prevent additional surgical interventions and reduce the length of hospital stay.

Previous studies have also evaluated the effect of hydronephrosis on urinary leakage from the nephrostomy tract after PCNL and shown that both the presence and degree of hydronephrosis are significantly associated with urinary leakage. Dirim et al. reported that the presence of hydronephrosis increased the incidence of urinary leakage, and a one-unit increase in the degree of hydronephrosis caused urinary leakage at the access site to prolong three times (14). The degree of hydronephrosis and the duration of urinary leakage have also been correlated in studies evaluating the relationship between the degree of renal hydronephrosis and long-term urinary leakage (13,17,18). Similarly, in our study, we showed that as the degree of hydronephrosis increased, the rate of PUL increased. It was also previously stated that a decreased parenchymal thickness caused less blood loss during PCNL (19). This may cause PUL due to delayed healing resulting from decreased blood supply to this area and the loss of the compressive properties of the thin parenchyma. Uyeturk et al. reported that the renal parenchymal thickness in the access line showed a more significant correlation with the duration of urinary leakage compared to the degree of hydronephrosis (20), which was also supported by Ansari et al. (18). In our study, we showed that renal parenchymal thickness in the access line was a factor predicting PUL.

Since residual stones may cause urinary obstruction after PCNL, operation success has been shown to be the strongest predictor of DJ catheter placement after PCNL due to PUL (21). Recent studies have stated that stone burden was associated with stone-free rates. So, increasing the stone burden affects the success rates negatively (22). Considering this information, it has been shown that both increased stone size and the presence of complex stones can predict the development of PUL after PCNL (13). Thomas et al. showed that most of the patients with GSS 3 and 4 required a second-look procedure due to multiple punctures and residual stones, and these patients developed more complications (8). Ansari et al. demonstrated that PUL was associated with GSS 3 and 4, multiple access attempts, and the presence of residual stones, but not with the stone burden (18). Dirim et al. found no significant relationship between stone burden and access number and urinary leakage (14). In our study, a significant relationship was not observed between PUL and the presence of residual stones, in addition, this complication was not related to access number and stone burden. In previous studies, it was not clearly stated

Figure 1 - Nomogram and scoring system predicting urinary leakage after PCNL. The scoring system is based on radiological (parenchymal thickness, hydronephrosis grade) and surgical parameters (nephroscopy time). Parenchymal thickness (1–5 points), nephroscopy time (1–3 points), and hydronephrosis grade (1–3 points) are summed to provide a total score ranging from 3 to 11 points.



	1 pt	2 pts	3 pts	4 pts	5 pts
Parenchymal thickness, mm	>22	18-22	14-18	10-14	≤10
Nephroscopy time, min	≤50	50.1-100	≥100		
Hydronephrosis grade	0-1	2	3-4		

whether residual stones caused obstruction (13, 18). Gucuk et al. reported that routine flexible nephroscopy during percutaneous nephrolithotomy was associated with a higher stone-free rate (23). However, in present study, flexible nephroscopy was not performed in any of the patients at the end of the procedure, so we could not evaluate its effectiveness. The feature that makes our study different from other studies is that patients with residual stones causing obstruction were not included in our sample. Although a previous study reported in a significant relationship between the skin-stone distance and PUL, the same authors did not reveal a similar relationship between this complication and the skin-calyx distance, which is a confusing finding (18). In our study, we found that skin-parenchyma distance was not associated with PUL.

Recently, the routine placement of a nephrostomy tube after an uncomplicated PCNL and

Figure 2 - Receiving operator characteristic curve for predicting urinary leakage based on the nomogram and the scoring system. (a) The area under the curve (AUC) value of the nomogram was 0.811 (95% CI: 0.767-0.855) with an optimal cut-off value of 14.96%, at which it had a sensitivity of 77.2% and specificity of 74.2%. (b) The AUC value of the scoring system was 0.793 (0.745-0.841) with an optimal cut-off value of 6.5, at which it had 76.1% sensitivity and 71.0% specificity.

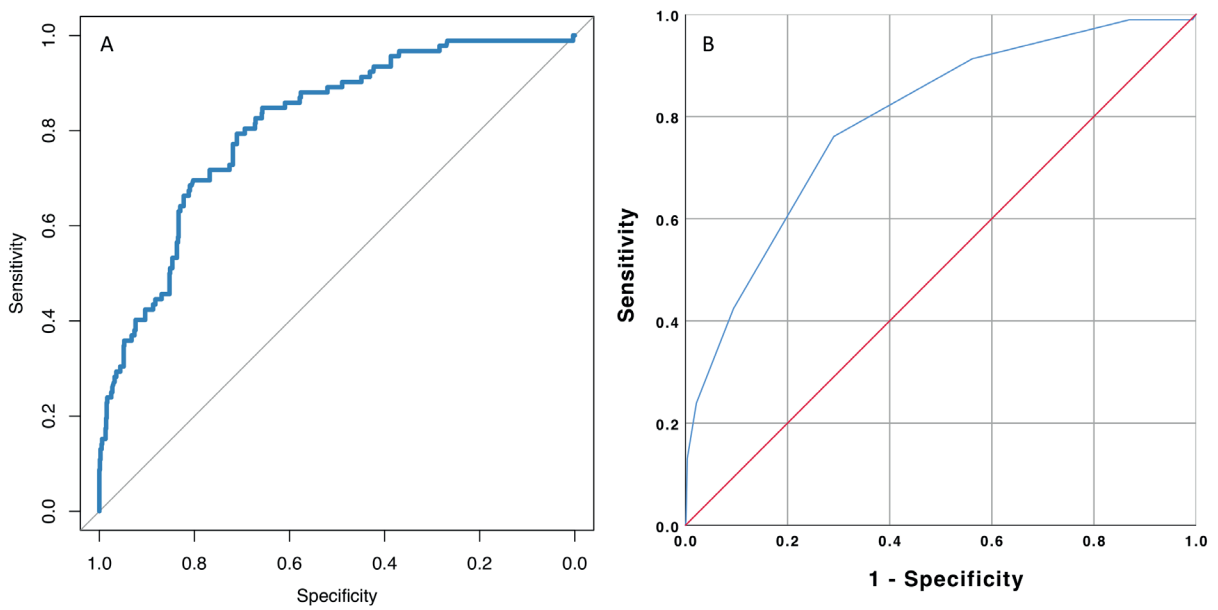
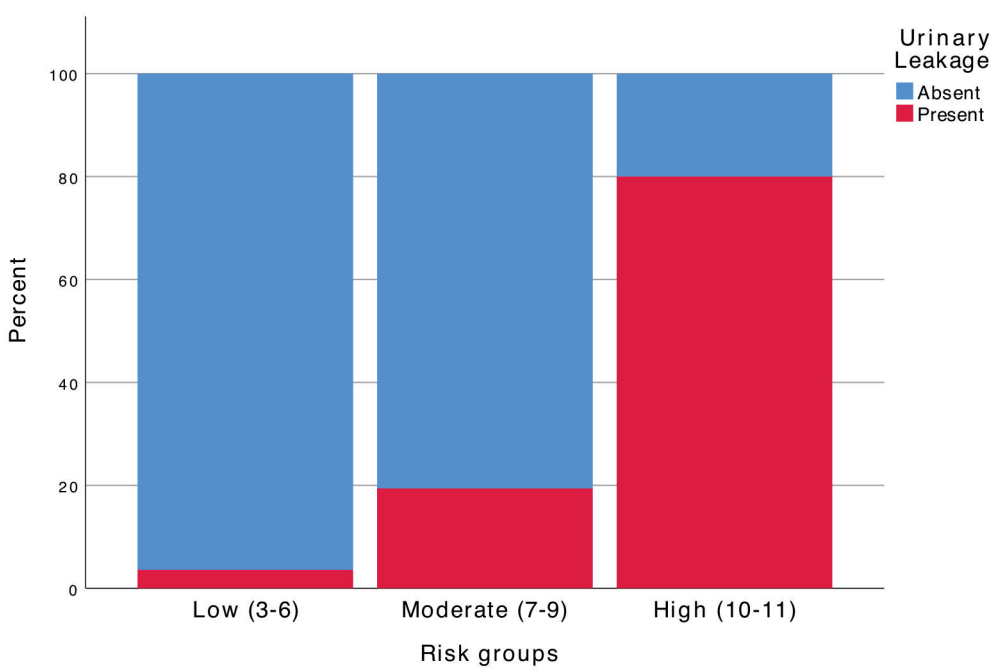


Figure 3 - Stacked bar graph of the classification of urinary leakage risk as low, moderate, and high based on our score. Based on novel scores, the patients were divided into the risk groups of low (3-6), moderate (7-9), and high (10-11), which were found to have the PUL rates of 3.6%, 19.4%, and 80%, respectively.



complete stone cleaning have been questioned, except in required cases, such as those with residual stones, the possibility of a second-look procedure, significant intraoperative blood loss, and urine extravasation. It has been suggested that nephrostomy tubes cause postoperative discomfort and morbidities, such as urinary leakage and bleeding (24, 25). Therefore, there are studies supporting tubeless PCNL in the literature (25-27). In a study examining DJ catheter requirement due to urinary leakage after PCNL, Binbay et al. recommended using the tubeless approach in the treatment of small renal stones that are not complex (13). In another study conducted by Dirim et al., the prolongation of urinary leakage was determined to be in parallel with the time elapsed until the removal of the nephrostomy tube (14). In our study, a significant relationship was detected between the duration of nephrostomy tube use and PUL. To our knowledge, the effect of the duration of nephroscopy on urinary leakage from the nephrostomy tract after PCNL has not been previously evaluated. In the current study, the longer nephroscopy duration in the group with PUL can be explained by the greater stone burden and the higher number of staghorn stones in this group. We, therefore, determined that a longer duration of nephroscopy was a factor predicting PUL.

In previous studies, it has been shown that PCNL can be safely applied to patients with a history of ESWL or open nephrolithotomy with similar success and complication rates to those with no previous history of intervention (28, 29). Dirim et al. reported that a history of previous surgery or ESWL had no effect on urinary leakage following PCNL (14). Ansari et al. determined that a history of open surgery was not associated with PUL (18). Similarly, in our study, there was no relationship between previous surgery or ESWL history and PUL.

We thought that excessive bleeding requiring blood transfusion might influence the development of PUL with the mechanism of small blood clot formation causing pelvicalyceal system obstruction. Usually, small blood clots cannot be detected easily using the currently available radiological imaging tools. A previous study reported that there was no statistical correlation between bleeding and PUL development necessitating Double-J stent placement (13). Similarly, in our study, bleeding requiring blood transfusion was similar between the groups.

The novel scoring system created in our study had 76.1% sensitivity and 71.0% specificity in predicting PUL after PCNL. In the risk classification for a novel scoring system to be easily applicable in daily practice, the rate of PUL was found to be 80% in the patients in the high-risk group and 19.4% and 3.6% in the moderate- and low-risk groups, respectively. Considering this information, we recommend that intraoperative DJ stents should be placed in patients determined to have a high risk according to this classification.

Although the factors predicting PUL in our study were those that were previously proven to affect this complication and the results did not cause any confusion, our study has certain limitations. First, it had a retrospective and single--center design. Second, PCNL was performed on all patients with the same tract size, operation position, and lithotripsy technique, and the same--size nephrostomy tube and nephroscope were used. Third, since patients with intraoperative DJ stenting could not be included in the study, this may have possibly caused a bias in patient selection. Lastly, there was a relatively small number of patients with PUL. There is a need for prospective studies with larger series.

CONCLUSION

The novel scoring system presented in this study is easy to use and repeatable. The efficacy of the factors predicting urinary leakage in the scoring system was demonstrated to be in agreement with the literature. In addition, this scoring system can be used as a predictive method to determine which patients should receive a DJ catheter intraoperatively to shorten the length of hospital stay by estimating the risk of urinary leakage and to decrease additional anesthesia exposure due to postoperative DJ catheter requirement.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordan-

ce with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ethics Committee of the Turkish Ministry of Health Izmir Bozyaka Training and Research Hospital (Meeting/Decision No.2021/71).

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Both the nomogram and the score system can represent an useful tool especially in those cases where the complication is foreseen by the surgeon

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COMMENT

Urinary Leakage represents in the modern endourology a relatively non-frequent complication after PCNL (3-8.3%). It is generally related to obstructive residual fragments in the ureter, blood clots or simply to pyelo-ureteric junction or ureteral edema. Urinary leakages can be managed conservatively but frequently obligates the surgeon to take the patient back to the operating room to insert a double-J stent or even to remove a ureteral residual fragment (1, 2). Many factors have been implicated in the occurrence of urinary leakage after PCNL including stone burden, high grade hydronephrosis, multiple accesses, a decreased renal parenchyma thickness at the access line, a longer duration of surgery and a prolonged drainage by a nephrostomy tube, among others.

Currently, with the improvement of techniques in PCNL like reducing the caliper of nephroscopes, ultrasound guided punction, flexible nephroscopy at the end of the procedure and tubeless PCNL, the occurrence of leakages tends to reduce. Anyway, to have in mind predictive factors for its occurrence is important once the surgeon can prevent its occurrence inserting a double J stent at the end of the procedure at at particular case for instance. In this retrospective article, the authors identified, in a multivariate analysis, the occurrence of hydronephrosis Grade 2 or more, a renal parenchyma thickness in the access line less than 11.8 mm and the duration of nephroscopy longer than 50 minutes as predictive factors for the development of urinary leakage after PCNL. Based on this they developed a nomogram and proposed an internally validated scoring system with a total score ranging from 3 to 11 where 3-6 represents a low risk, 7-9 moderate risk and 10-11 a high risk for developing urinary leakage after PCNL (3). Both the nomogram and the score system can represent an useful tool especially in those cases where the complication is foreseen by the surgeon. On the other hand, the study was based only in 932 patients (92 patients with urinary leakage and 840 without) studied retrospectively in a single center. Certainly, other series with a bigger number of prospectively studied patients and including other centers is needed for surgeons to adopt it in daily practice.

CONFLICT OF INTEREST

None declared.

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Deep learning model-assisted detection of kidney stones on computed tomography

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ABSTRACT

Introduction: The aim of this study was to investigate the success of a deep learning model in detecting kidney stones in different planes according to stone size on unenhanced computed tomography (CT) images.

Materials and Methods: This retrospective study included 455 patients who underwent CT scanning for kidney stones between January 2016 and January 2020; of them, 405 were diagnosed with kidney stones and 50 were not. Patients with renal stones of 0–1 cm, 1–2 cm, and >2 cm in size were classified into groups 1, 2, and 3, respectively. Two radiologists reviewed 2,959 CT images of 455 patients in three planes. Subsequently, these CT images were evaluated using a deep learning model. The accuracy rate, sensitivity, specificity, and positive and negative predictive values of the deep learning model were determined.

Results: The training group accuracy rates of the deep learning model were 98.2%, 99.1%, and 97.3% in the axial plane; 99.1%, 98.2%, and 97.3% in the coronal plane; and 98.2%, 98.2%, and 98.2% in the sagittal plane, respectively. The testing group accuracy rates of the deep learning model were 78%, 68% and 70% in the axial plane; 63%, 72%, and 64% in the coronal plane; and 85%, 89%, and 93% in the sagittal plane, respectively.

Conclusions: The use of deep learning algorithms for the detection of kidney stones is reliable and effective. Additionally, these algorithms can reduce the reporting time and cost of CT-dependent urolithiasis detection, leading to early diagnosis and management.

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INTRODUCTION

Urolithiasis is a common health problem, with a worldwide prevalence of 1.7-14.8% (1). Multiple factors contribute to the increase in its prevalence, including lifestyle changes, nutritional habits, obesity, diabetes mellitus, metabolic syndrome, and hypertension. In the United States, more than 2 million people with renal colic are admitted to the emergency departments each year, and approximately half of these patients undergo unenhanced computed tomography (CT). From 1992 to 2009, the use of CT was estimated to triple

in the United States, with a corresponding increase in its cost of use (2, 3). The cost of nephrolithiasis management is high for both individuals and the society. The choice of the most appropriate treatment for kidney stones is challenging because it depends on several factors such as the type, shape, size, and location of the stones (4).

Deep learning is a type of machine learning termed artificial neural networks and is inspired by the structure and function of the brain (5). Nowadays, with the successful use of computer vision with deep learning algorithms, deploying these algorithms to study medical images has become popular (6). Artificial intelligence (AI)-based systems for the evaluation of unenhanced CT images may be used to develop reliable and accurate anatomical models for operational support, as well as for predicting the success rate and outcomes of the treatment (7, 8). These systems assist medical decision-making and minimize iatrogenic errors in clinical practice. AI models employ synergistic working methods where learning abilities and performance are developed rather than a priori coded. Therefore, these models can fulfil their tasks with high speed, functionality, and efficiency (9). We hypothesized that AI can be efficiently used to diagnose and detect kidney stones. In the present study, we aimed to investigate the success of a deep learning model for the diagnosis of kidney stones.

MATERIALS AND METHODS

Study population

This study was approved by the ethics committee of our institution (permission number: 378/358; dated: 10/11/2021). For this retrospective study, we selected 455 patients, between January 2016 and January 2020, of whom 405 bore kidney stones diagnosed via CT while the remaining 50 did not. A total of 2,959 unenhanced CT images, including 2,709 with kidney stones and 250 without, were evaluated by two experienced abdominal radiologists (X.X. with 12 years of experience and Y.Y. with 8 years of experience) based on consensus and using a dedicated workstation. Kidney stone diagnoses were based on their observation in the renal collecting system and on the measurement of Hounsfield units on unenhanced CT images. The final diagnosis of kidney stones was made by a radiologist. The patients were divided into three groups as follows: group 1 contained patients with renal stone sizes of 0–1 cm, group 2 had sizes of 1-2 cm, and group 3 had sizes greater than 2 cm. When multiple kidney stones were present, the largest stone size was included in the study. The results of the AI algorithm for the detection of kidney stones were compared with the radiologists' diagnoses to determine the efficiency of the AI model.

Patients with solitary kidneys, atrophic kidneys, renal anomalies, calcified renal masses, renovascular calcifications, regional lymph node calcifications, metallic implants, pigtail ureteral catheters, percutaneous nephrostomy catheters, and CT images with artefacts were excluded from the study.

CT image acquisition

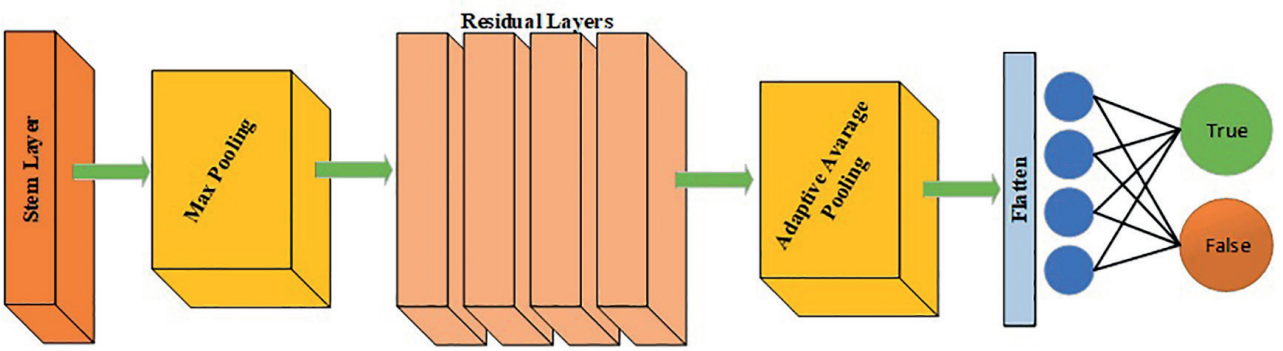
The anatomical area between the diaphragm and the symphysis pubis was scanned using a CT scanner (Optima CT 660, GE Healthcare System, Milwaukee, USA). During the scan, the gantry angle was set to 0°; the matrix size, 512×512 pixels; the voltage, 120 kV; the tube current; 100-200 mAs; the collimation, 64×0.5; and the slice thickness, ≤1.25 mm on a 128-slice CT device. All images were reconstructed in the axial, coronal, and sagittal planes with a 2-mm section thickness using the medical imaging program, AW Server 3.2 Ext. 1.2 by GE Healthcare.

Artificial Intelligence Algorithm

ResNet is a convolution-based deep residual network architecture. ResNet consists of several residual blocks (composed of a convolutional layer), a batch normalization layer, and a shortcut that connects the original input to the output of the residual block (8). We used the xResNet50 convolutional neural network architecture in our study. The xResNet architecture was derived from the convolution-based deep residual network architecture ResNet with a few minor changes (7). The layer organization of the model is shown in Figure-1.

The number of patients and CT images with and without kidney stones in the three groups ac-

Figure 1 - Layer organization of the xResNet50 deep learning model. xResNet50 architecture consists of an input stem, four xResNet50 blocks, and an output stem. Images are put in from the input stem, then processed in the model, and classified in the output stem; finally, they are returned as a percentage of kidney stone presence or absence.



cording to the sizes of kidney stones evaluated using the deep learning algorithm are presented in Table-1.

First, training of the CT images of patients with and without kidney stones was performed using the AI model, followed by model testing. Training and testing were performed in the three planes and among the three study groups using the Fastai (v2) library and the Google Collaboratory platform. We used the Adam algorithm as the optimization algorithm (10). Cross-entropy loss was utilized as the loss function. During model training, we selected the learning rate to be 0.01 and achieved the best validation scores after an average of the 35th epoch. The images used for training the model were not preprocessed or augmented in any way (7-10).

Table 1 - Number of patients and CT images with and without kidney stones of 3 groups evaluated with the deep learning algorithm and the training group accuracy rates of the deep learning model of the CT images.

		Group 1 (0-1 cm)		Group 2 (1-2 cm)		Group 3 (>2 cm)	
		Patient n, %	Image n, %	Patient n, %	Image n, %	Patient n, %	Image n, %
	Normal	40 (30.5%)	200 (21%)	40 (26.8%)	200 (21%)	40 (24.1%)	200 (21%)
	Stone	91 (69.5%)	753 (79%)	109 (73.2%)	753 (79%)	126 (75.9%)	753 (79%)
AI training		**Accuracy**					
	Axial	98.2%		99.1%		97.3%	
	Coronal	99.1%		98.2%		97.3%	
	Sagittal	98.2%		98.2%		98.2%	
	Normal	10 (18.5%)	50 (25%)	10 (27.7%)	50 (25%)	10 (52.6%)	50 (25%)
	Stone	44 (81.5%)	150 (75%)	26 (72.3%)	150 (75%)	9 (47.4%)	150 (75%)
AI testing		**Accuracy**					
	Axial	78.0%		68.0%		70.0%	
	Coronal	63.0%		72.0%		64.0%	
	Sagittal	85.0%		89.0%		93.0%	

AI = Artificial Intelligence

Statistical Analysis

All statistical analyses were conducted using SPSS Statistics version 26.0 (IBM Inc., Chicago, IL, USA). The demographic characteristics of the patients are presented as mean±standard deviation for continuous variables and as median and percentage for categorical variables. The sensitivity, specificity, and positive and negative predictive values of the results for all planes were calculated using receiver operating characteristic (ROC) curve analysis for each group.

RESULTS

The mean age of patients in our study was 42.54±14.76 (range: 23-77) years. Two hundred ninety-two (65.2%) patients were male and 163 (35.8%) were female. We used the Grad-CAM technique, which is deployed to produce "visual explanations" for convolutional neural networks, to identify the areas where our models were concentrated (11). CT images of the patients in the three study groups visualized with the Grad-CAM technique are demonstrated in Figures 2, 3, and 4.

The accuracy rates of the deep learning model in the training group are presented in Table-1. The success rates were as follows: 98.2% in the axial section, 99.1% in the coronal section, and 98.2% in the sagittal section in group 1; 99.1% in the axial section, 98.2% in the coronal section, and 98.2% in sagittal section in group 2; 97.3% in the axial section, 97.3% in the coronal section, and 98.2% in the sagittal section in group 3.

The AI accuracy rates for the three planes in the three groups are presented in Table-2. The success rates obtained by verifying the trained deep learning model in the test group were: 78% in the axial section, 63% in the coronal section, and 85% in the sagittal section in group 1; 68% in the axial section, 72% in coronal section and 89% in sagittal section in group 2; and 70% in the axial section, 64% in the coronal section, and 93% in the sagittal section in group 3.

The sensitivity, specificity, and positive and negative predictive values of the AI algorithm for the planes in the three groups are presented in Table-2.

DISCUSSION

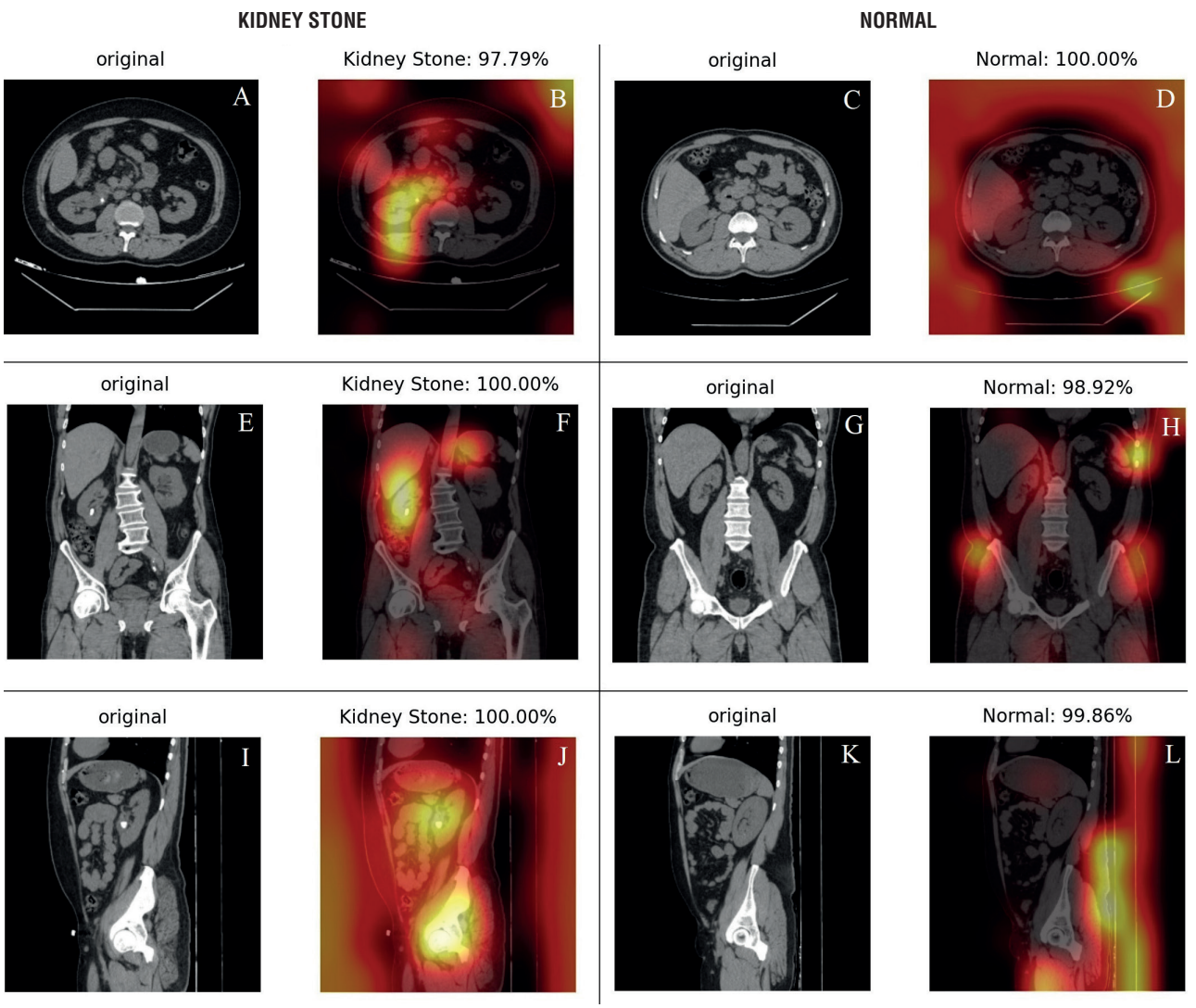
In our study, we investigated the success rate of AI methodologies in the diagnosis of kidney stones and found that the AI-based system we used provided accurate results. The sensitivity and specificity of diagnosis based on sagittal plane images were found to be higher than those of the other planes. This study is the first study in the literature to use an artificial intelligence model in the diagnosis of urinary system stone disease by classifying both in 3 different imaging axes and according to different stone sizes.

In a study by Imamura et al., choosing an appropriate imaging modality for the diagnosis of stones resulted in a high stone-free rate, low morbidity, high probability of survival, fast recovery, and low treatment cost (12). The guidelines provided by the American College of Radiology, the American Urological Association, and the European Association of Urology differ in the optimal initial imaging modality being used for evaluating patients with suspected obstructive nephrolithiasis. Although CTs of the abdomen and pelvis provide the most accurate diagnosis, they expose patients to harmful ionizing radiations. Ultrasonography has lower sensitivity and specificity than CT but does not require the use of radiation. Radiography of the kidney, ureter, and bladder is very helpful in the periodic evaluation of stone growth in patients with known stone disease but has limited utility in the diagnosis of acute stones. Of all the imaging modalities available currently, CT is the most sensitive technique for detecting kidney stones with a sensitivity of approximately 95% (13).

Cost and reimbursement issues among CT stakeholders, including hospitals, insurance companies, and patients, often complicate the choice of CT as an imaging modality. A review of Medicare data revealed that the cost of performing a CT scan is approximately double that of a renal ultrasound scan and approximately one third that of an MRI. This has caused AI models to come to the forefront in terms of cost, efficiency, and imaging preference (14, 15).

Recently, artificial neural network-based AI has attracted significant attention in medical

Figure 2 - Axial, sagittal, and coronal CT images of patients bearing 0–1-cm-sized kidney stones and without kidney stones, demonstrated with the Grad-CAM technique. Percentages refer to the estimates of the AI model.

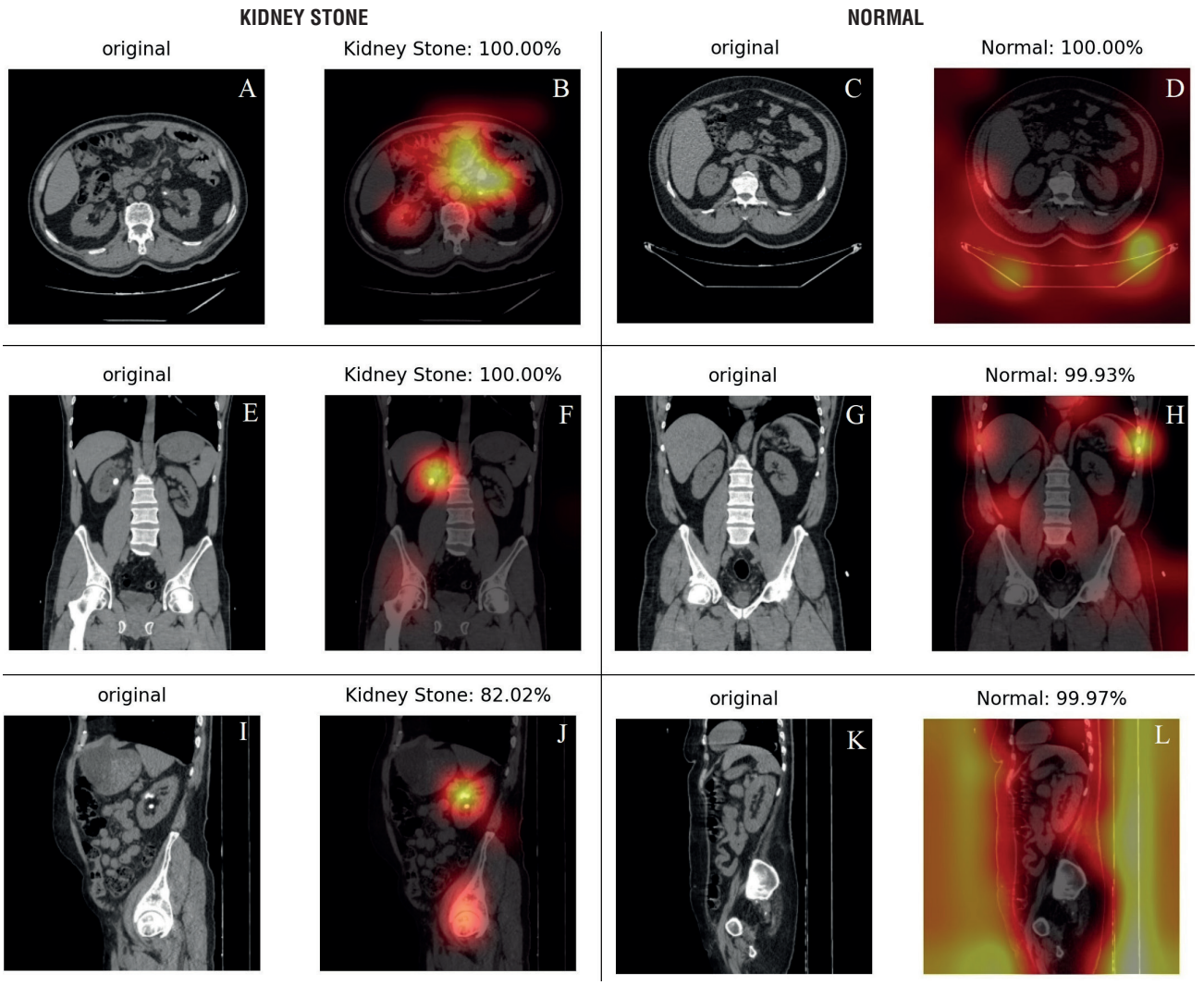


A) Kidney stone original axial CT image; B) Kidney stone axial CT image with GRAD-CAM technique; C) Normal kidney original axial CT image; D) Normal kidney axial CT image with GRAD-CAM technique; E) Kidney stone original coronal CT image; F) Kidney stone coronal CT image with GRAD-CAM technique; G) Normal kidney original coronal CT image; H) Normal kidney coronal CT image with GRAD-CAM technique; I) Kidney stone original sagittal CT image; J) Kidney stone sagittal CT image with GRAD-CAM technique; K) Normal kidney original sagittal CT image; L) Normal kidney sagittal CT image with GRAD-CAM technique.

imaging. An artificial neural network (ANN) calculates the output value from multiple input values using a simple mathematical neuron model. ANN systems are composed of a large number of neurons arranged in interconnected layers that can be trained to predict results based on the input of the first layer. In contrast, conventional neural networks have convolutional layers that are suitable for image analysis. Conventional neural networks can be fed with annotated images and can learn classification with automatic iterative adjustments of weighted neural functions (16, 17).

Computer-aided detection/diagnosis (CADe/CADx) is a successful research area in medical image processing. Recent developments have revealed the importance of applying conventional neural network-based deep learning algorithm approaches, although they require a large amount of

Figure 3 - Axial, sagittal, and coronal CT images of the patients bearing 1–2 cm-sized kidney stones and without kidney stones, demonstrated with the Grad-CAM technique. Percentages refer to the estimates of the AI model.

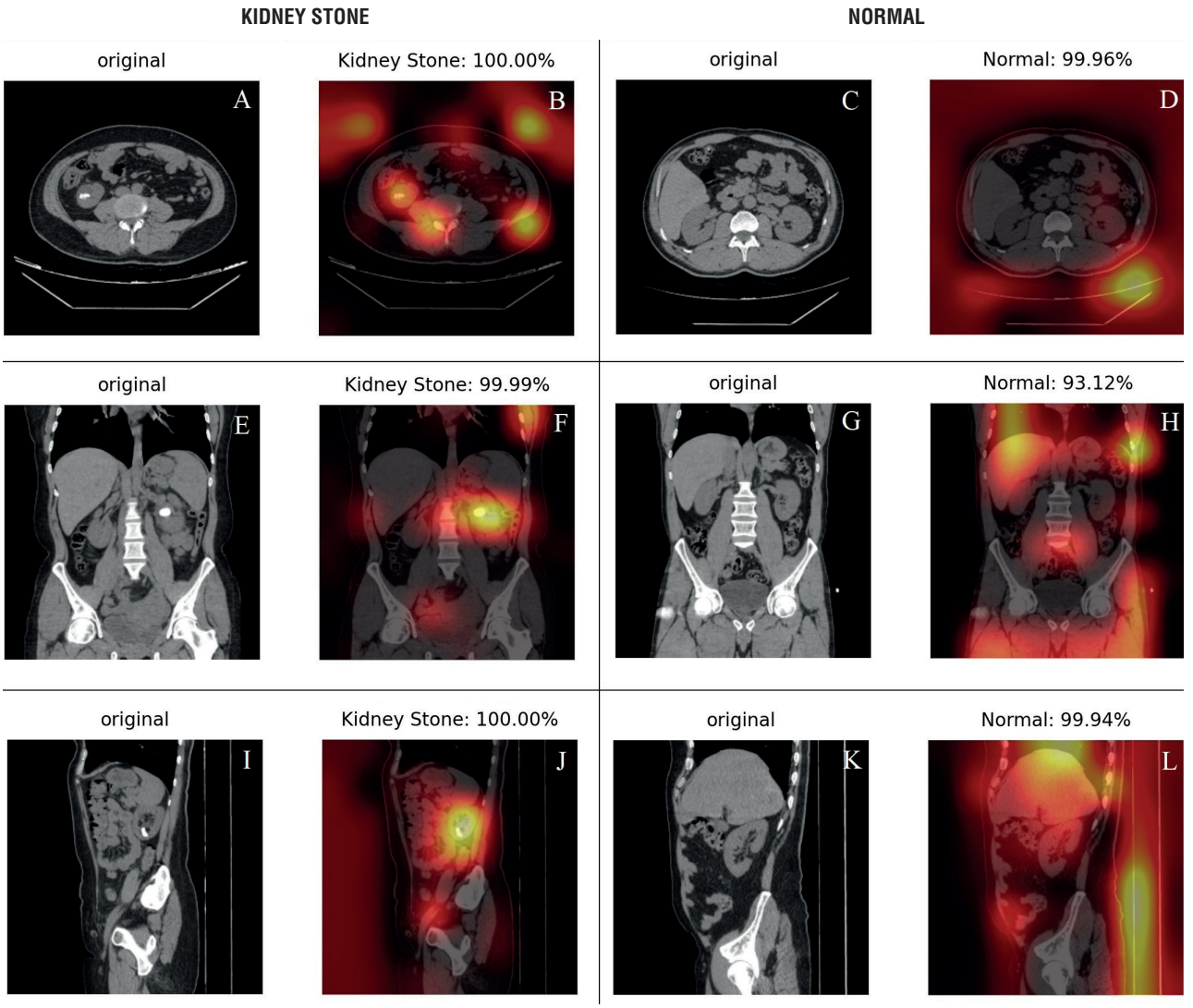


A) Kidney stone original axial CT image; B) Kidney stone axial CT image with GRAD-CAM technique; C) Normal kidney original axial CT image; D) Normal kidney axial CT image with GRAD-CAM technique; E. Kidney stone original coronal CT image; F) Kidney stone coronal CT image with GRAD-CAM technique; G) Normal kidney original coronal CT image; H) Normal kidney coronal CT image with GRAD-CAM technique; I) Kidney stone original sagittal CT image; J) Kidney stone sagittal CT image with GRAD-CAM technique; K) Normal kidney original sagittal CT image; L) Normal kidney sagittal CT image with GRAD-CAM technique.

training data (16, 18). Yan et al. developed a universal lesion detector (DeepLesion) that can detect any lesion with a single unified frame (19).

The use of AI in urology has considerably increased in recent years. In particular, studies comparing AI models with imaging methods in diagnosis and patient selection have been reported. Recently, there has been an increase in the demand for CT in the diagnosis of kidney stones due to an increase in the number of patients suffering from this condition. This has led to a prolongation of the radiological evaluation period owing to the relatively less number of radiologists available to evaluate the images (20). Furthermore, during the coronavirus disease pandemic, reporting processes have become even more problematic due to the increased workload of radiologists. This workload also resulted in reducing surgery volumes and

Figure 4 - Axial, sagittal, and coronal CT images of the patients bearing kidney stones greater than 2 cm in size and without kidney stones, demonstrated with the Grad-CAM technique. Percentages refer to the estimates of the AI model.



A) Kidney stone original axial CT image; B) Kidney stone axial CT image with GRAD-CAM technique; C) Normal kidney original axial CT image; D) Normal kidney axial CT image with GRAD-CAM technique; E) Kidney stone original coronal CT image; F) Kidney stone coronal CT image with GRAD-CAM technique; G) Normal kidney original coronal CT image; H) Normal kidney coronal CT image with GRAD-CAM technique; I) Kidney stone original sagittal CT image; J) Kidney stone sagittal CT image with GRAD-CAM technique; K) Normal kidney original sagittal CT image; L) Normal kidney sagittal CT image with GRAD-CAM technique.

urology residency programs (21, 22). In such a scenario, using computer-assisted AI methods to diagnose urolithiasis can ensure a fast and accurate diagnosis, leading to early management in urological clinical practice.

Längkvist et al. developed a conventional neural-network method to detect ureteral stones in thin-section CT scans and showed that CT images can be read primarily with an automated detection algorithm (23). Sokolovskaya et al. found a significant positive relationship between the fast--reading speed of tomography and the number of interpretation errors. Furthermore, several studies reported that diagnostic errors due to radiological diagnosis maybe due to perceptual and cognitive interpretation errors of radiologists and that stra-

Table 2 - Accuracy rates, sensitivity, specificity, positive predictive, and negative predictive values of the deep learning model for the planes among 3 groups of kidney stones.

Classification Reports (Test Set)		Axial		Coronal		Sagittal	
		normal	stone	normal	stone	normal	stone
Group 1 (0-1 cm)	Precision	76.0 %	80.0 %	69.0 %	60.0 %	**83.0 %**	**87.0 %**
	Recall	82.0 %	74.0 %	48.0 %	78.0 %	**88.0 %**	**82.0 %**
	f1-score	79.0 %	77.0 %	56.0 %	68.0 %	**85.0 %**	**85.0 %**
	Accuracy	78.0 %		63.0 %		**85.0 %**	
	Positive Predictive Value	75.0 %		78.0 %		**82.0 %**	
	Negative Predictive Value	82.0 %		48.0 %		**88.0 %**	
	Sensivity	80.4 %		60.0 %		**87.2 %**	
	Specificity	75.9 %		68.5 %		**80.0 %**	
Group 2 (1-2 cm)	Precision	70.0 %	66.0 %	76.0 %	69.0 %	**91.0 %**	**87.0 %**
	Recall	62.0 %	74.0 %	64.0 %	80.0 %	**86.0 %**	**92.0 %**
	f1-score	66.0 %	70.0 %	70.0 %	74.0 %	**89.0 %**	**89.0 %**
	Accuracy	68.0 %		72.0 %		**89.0 %**	
	Positive Predictive Value	74.0 %		80.0 %		**92.0 %**	
	Negative Predictive Value	62.0 %		64.0 %		**86.0 %**	
	Sensivity	66.1 %		68.9 %		**86.7 %**	
	Specificity	70.4 %		76.1 %		**91.4 %**	
Group 3 (>2 cm)	Precision	73.0 %	68.0 %	85.0 %	59.0 %	**94.0 %**	**92.0 %**
	Recall	64.0 %	76.0 %	34.0 %	94.0 %	**92.0 %**	**94.0 %**
	f1-Score	68.0 %	72.0 %	49.0 %	72.0 %	**93.0 %**	**93.0 %**
	Accuracy	70.0 %		64.0 %		**93.0 %**	
	Positive Predictive Value	76.0 %		94.0 %		**94.0 %**	
	Negative Predictive Value	64.0 %		34.0 %		**92.0 %**	
	Sensivity	67.8 %		58.7 %		**92.1 %**	
	Specificity	72.7 %		85.0 %		**93.8 %**	

tegies to improve the performance of radiologists should be developed (12, 24, 25). Another study revealed that developing a machine learning-based system can assist urologists in managing large kidney stones (26). Recent technological advances have demonstrated high sensitivity, specificity, and positive predictive value in detecting urinary tract stones ≥3 mm with an average radiation dose of 1-1.5 mSv, allowing for dose reduction with the advent of low-dose CT techniques (27).

Our study bears several limitations. The major limitation of this study was the lack of consideration of the stone composition, which is one of the most important parameters in the management of kidney stones. Another limitation was the lack of testing of the effect of the AI algorithm in predicting the success of the treatment.

CONCLUSIONS

Deep learning models are reliable and effective for the detection of kidney stones. The sagittal-plane images on CT had higher diagnostic accuracy rates than those of other planes. Using these methods, the waiting time for results and cost of diagnosis can be reduced, and early diagnosis can be achieved, resulting in prompt management.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Deep learning is a promising technology and seems to be the future of the CT stone evaluation

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COMMENT

Computed tomography (CT) is the current gold standard diagnostic imaging exam for urolithiasis (1). However, making a CT report is a time-consuming process and requires a specialist. Therefore, an automated model of kidney stones detection would help saving health resources.

The authors of "Deep learning model-assisted detection of kidney stones on computed tomography" showed that a convolution-based algorithm, xResNet50, detected kidney stones with accuracy up to 85.0% for 0-1 cm stones, 89.0% for 1-2 cm stones and 93.0% for > 2 cm stones in CT sagittal section compared to experienced radiologists. Not surprisingly, larger stones are easier to detect (1). However, the accuracy of this automated model to detect kidney stones seems to be not sufficient to dismiss the specialist analysis. Although detection of stones is a good primary objective for an automated model, the mere detection of a kidney stone is not enough for clinical application. A complete report of the stone features is necessary for the best clinical decision. Also, the automated model algorithm should take in consideration CT settings as tube current and window as it impacts measurements of clinically relevant stone features such as size and density (2, 3).

However, artificial intelligence is advancing fast. Other authors were able to show good agreement of other automated model algorithm with radiologist results for stone size, volume, location, number and density (4, 5). Deep learning is a promising technology and seems to be the future of the CT stone evaluation.

CONFLICT OF INTEREST

None declared.

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Transurethral flexible ureteroscopic incision and drainage with holmium laser in the treatment of parapelvic renal cysts: A retrospective study

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ABSTRACT

Background: We aimed to investigate the clinical efficacy and safety of transurethral flexible ureteroscopic incision and drainage with holmium laser in the treatment of parapelvic renal cysts.

Materials and Methods: Between October 2017 and April 2021, the clinical data of 65 patients with parapelvic renal cysts were evaluated retrospectively. Thirty-one patients with parapelvic cysts (Group 1) underwent a transurethral flexible ureteroscopic incision and drainage with a holmium laser, whereas the other 34 patients (Group 2) underwent retroperitoneal laparoscopic unroofing. The patients' clinical features were documented. The surgery time, intraoperative blood loss, hospitalization time, complications and cyst size were recorded and statistically assessed one year following the procedure.

Results: All of the patients were successfully treated with flexible ureteroscopic incision and drainage or retroperitoneal laparoscopic unroofing. In terms of clinical parameters, such as age, gender, BMI, location, cyst size, and Bosniak classification of renal cysts, no statistically significant difference was detected between Groups 1 and 2. Compared to the control group (Group 2), Group 1 demonstrated a shorter surgery duration, less intraoperative blood loss, and a shorter hospital stay ($p < 0.001$). However, no significant differences in complications and cyst size were observed between the two groups one year after the surgery ($p > 0.05$).

Conclusions: Transurethral flexible ureteroscopic incision and drainage with holmium laser in the treatment of parapelvic renal cysts has obvious advantages over traditional surgery, and is worthy of advancement and application, but its long-term effect needs further follow-up studies.

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INTRODUCTION

Renal cysts are quite prevalent in the urinary system. Renal cysts affect 50% of adults over the age of 50, and 66 percent of adults will have developed renal cysts by the age of 80, according to studies (1). Parapelvic renal cysts are associated with a special type of renal cystic disease (2), and non-hereditary cysts that develop adjacent to the renal pelvis are especially serious. Renal cysts originate from the renal sinus, around the renal pelvis or renal

sinus as parapelvic cysts, according to Kiryluk and Gupta (3).

The clinical symptoms of parapelvic cysts are usually atypical. Parapelvic cysts can be diagnosed by ultrasonography, enhanced computed tomography (CT), magnetic resonance imaging and other imaging examinations. Parapelvic cysts are usually benign lesions with slow progression. If the cyst is tiny, the patient has no symptoms, no complications are observed, and imaging examination reveals no evident renal pelvic compressions, conservative surveillance and regular follow-up are recommended. Parapelvic cysts may compress the renal arteries or renal pelvis due to their unique location, resulting in hypertension, hydronephrosis, and other symptoms. When symptoms appear as a result of compression, aggressive therapy should be initiated.

Laparoscopic renal cyst unroofing is the preferred treatment for parapelvic cysts (4). With the development of minimally invasive technology, Yu et al. (5) reported that incision and drainage under ureteroscopy were performed to treat parapelvic cysts. However, just a few studies compared the procedure to laparoscopic renal cyst unroofing. In the treatment of parapelvic cysts, we believe that transurethral flexible ureteroscopic incision and drainage offers greater advantages than laparoscopic renal cyst unroofing. Therefore, this study aims to report the clinical efficacy and safety of transurethral flexible ureteroscopic incision and drainage, compared with retroperitoneal laparoscopic unroofing in the treatment of parapelvic renal cysts.

MATERIALS AND METHODS

The study was authorized by the Ethics Committee of Dongguan People's Hospital (Dongguan, China) (Ethics approval no.: XJS2018-009). Individual participants agreed to publish informed consent forms with detailed information and provided signed informed consent.

Between October 2017 and April 2021, 65 patients with parapelvic renal cysts treated by transurethral flexible ureteroscopic incision and drainage or retroperitoneal laparoscopic unroofing were retrospectively enrolled in this study. Among them, 31 patients with parapelvic cysts (Group 1) underwent a transurethral flexible ureteroscopic incision and drainage with holmium laser, and the other 34 (Group 2) underwent retroperitoneal laparoscopic unroofing. Surgeries were performed according to normal methods by a surgeon with ten years of experience. The patients' clinical characteristics are reported in Table-1. Preoperative intravenous urography, ultrasonography and CT were performed to diagnose parapelvic cysts. As needed, retrograde pyelography was performed. Patients with parapelvic cysts >3 cm were included in this study. Patients with parapelvic cysts that were suspected to be malignant according to CT, were excluded. In addition, those with an uncontrolled urinary tract infection, urethral or ureteral stricture, hemorrhagic diseases and cardiopulmonary insufficiency were excluded.

Preoperatively, urine analysis, urine culture, and serum biochemical tests were performed in all patients. Patients with infection were not submitted to the procedures until the infection was controlled. All patients were administered a dose of prophylactic antibiotics 30 min preoperatively. In an outpatient department, all patients were followed up at 1, 3, and 12 months postoperatively. Ultrasonography and CT scans were used in the follow-up assessment.

Surgical protocol

A total of 31 patients (Group 1) underwent a transurethral flexible ureteroscopic incision and drainage with holmium laser. A ureteral double J tube was routinely indwelled to dilate the ureter 2 weeks preoperatively. The procedure was performed under general anesthesia in the lithotomy position. To examine the ureter, a rigid ureteroscope (F8.0/9.8 Wolf) was retrogradely inserted into the renal pelvis, and a ureteral access sheath (Flexor 12/14F, Cook) was placed along the guide wire. The flexible ureteroscope (URF-V, OLYMPUS) was then inserted into the renal pelvis through the ureteral access sheath. A translucent blue area was observed on the mucosa of the renal pelvis and calyx, which was considered the area of renal cysts adjacent to the renal pelvis. The incision and drainage of the parapelvic cysts were performed

Table 1 - Comparison of clinical and perioperative factors between flexible ureteroscope incision (Group 1) and retroperitoneal laparoscopic unroofing (Group 2).

Variable	Group 1	Group 2	P value
Patients (n)	31	34	NA
Age (years)	47.6 ±8.7	46.8 ±7.8	0.701
Gender (n)			0.73
Male	15 (48.4)	15 (51.6)	
Female	16 (44.1)	19 (55.9)	
*BMI (kg/m^2)	23.8 ±2.2	24.1 ±2.0	0.551
Location			0.271
Right	14 (46.2)	20 (58.8)	
Left	17 (54.8)	14 (41.2)	
※Cyst size (cm)	5.3 ±0.9	5.1 ±0.9	0.333
Bosniak classification of renal cysts			0.336
Bosniak I	31 (100)	33 (97.1)	
Bosniak II	0 (0)	1 (2.9)	
Surgery duration (min)	30.1 ±4.3	54.4 ±6.4	<0.001
Blood loss (mL)	5.5 ±1.7	59 ± 9.9	<0.001
Length of hospitalization (days)	4.5 ± 0.8	5.6 ±0.9	<0.001
Cyst size at 1 year, postoperatively (cm)	1.0 ±0.9	0.6 ±0.6	0.106
Complications (n)	1	1	0.947

Data are presented as the mean ± SD or number (percent);
NA indicates not applicable;
*BMI indicates body mass index;
※Cyst size = the diameter of the stone based on preoperative CT scanning.

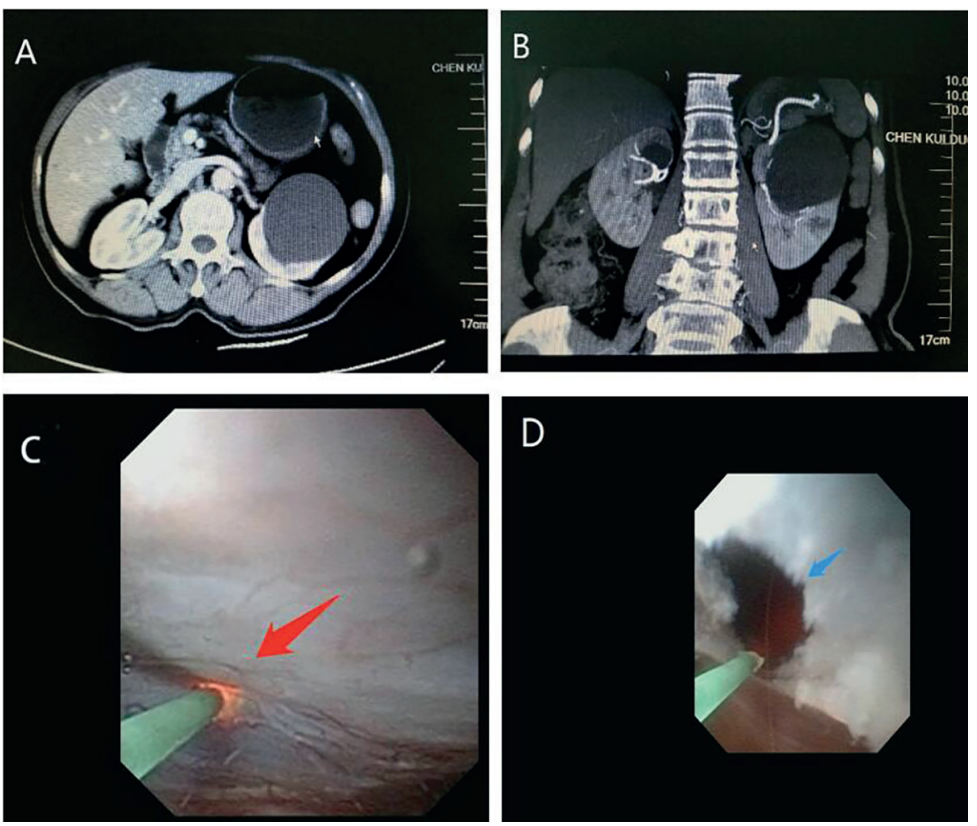
using a holmium laser device (LUMENIS Versa Pulse Power Suite). The laser setting was 0.8 J with a frequency of 30 Hz (Figure-1). Percutaneous renal puncture was conducted by ultrasonography localization if the surgeon had difficulty identifying cysts. Methylene blue was injected into the cyst, which caused the cyst wall to turn blue, allowing the surgeon to properly identify the cyst wall (Figure-2). Finally, ureteral stenting (JJ stent) was routinely indwelled with proximal end inside the cyst for 4 weeks. There were five procedures (16%) in which the surgeon required methylene blue injection to locate cysts in this study.

In Group 2, 34 patients underwent retroperitoneal laparoscopic unroofing by the retroperitoneal approach. The procedure was performed in the standard left/right lateral decubitus position under general anesthesia. First, three functioning ports were installed (0.5, 0.5, and 1.0 cm, respectively). The kidneys were then isolated, especially the area adjacent to the cyst's location. The cyst was unroofed 0.5 cm adjacent to the renal parenchyma. The cystic wall was delivered to a pathologist for examination. A drainage tube (22 French) was inserted into the retroperitoneum.

Statistical Analysis

Data are presented as the mean ± standard deviation (SD) or number. Age, BMI, cyst size, surgery duration, blood loss, length of hospitalization and cyst size at 1 year after the procedure were normally distributed. Student's t-test was used to compare continuous variables between groups,

Figure 1 - A 67-year-old woman underwent a transurethral flexible ureteroscope incision and drainage. The maximum intensity projection image showed parapelvic cyst in left kidney (A and B). The typical wall (red arrow) of parapelvic cyst looked transparent (C). The image of parapelvic renal cyst after the flexible ureteroscope incision (blue arrow) and drainage (D).



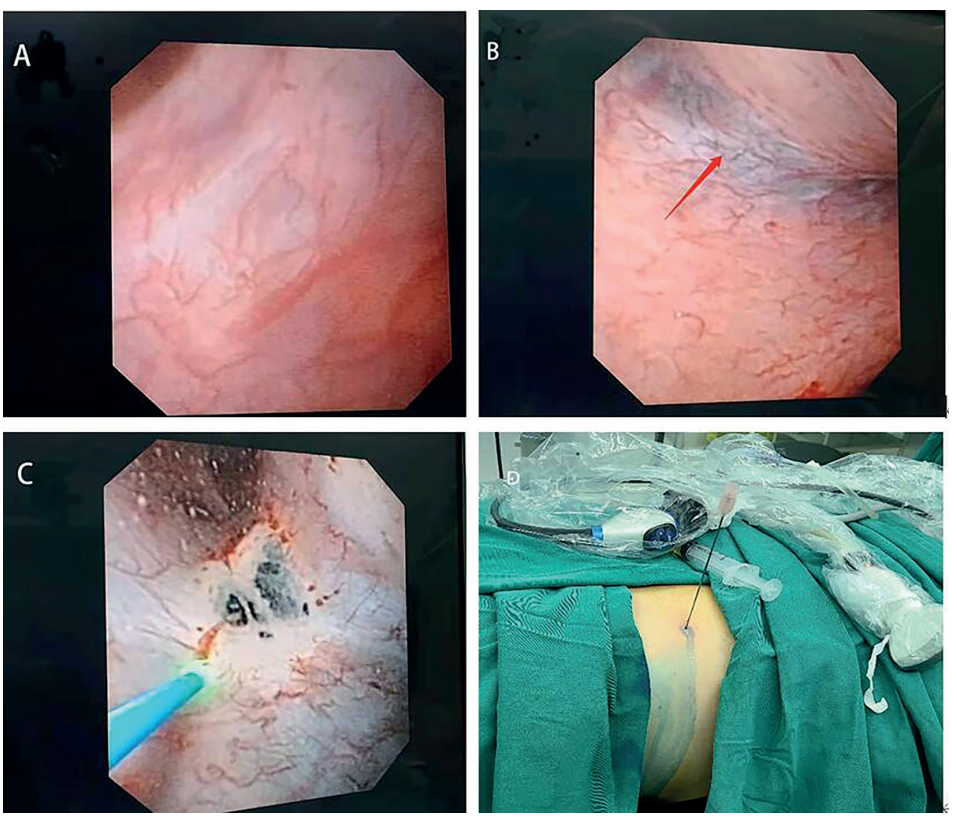
and the Chi-square test was used to compare categorical variables. SPSS 17.0 (SPSS, Chicago, IL, USA) was utilized for statistical analysis. Significance was established at $P < 0.05$.

RESULTS

A total of 65 patients were successfully treated with transurethral flexible ureteroscopic incision and drainage or retroperitoneal laparoscopic unroofing. Among them, 31 with parapelvic cysts (Group 1) underwent a transurethral flexible ureteroscopic incision and drainage with holmium laser, while the remaining 34 patients (Group 2) underwent the retroperitoneal laparoscopic unroofing. When the surgeon could not locate the cyst wall during the transurethral flexible ureteroscopic incision and drainage technique in Group 2, retroperitoneal laparoscopic unroofing was performed instead. A comparison of clinical and perioperative factors between the transurethral flexible ureteroscopic incision and retroperitoneal laparoscopic unroofing is shown in Table-1.

The mean ages were 47.6±8.7 and 46.8±7.8 years in Groups 1 and 2, respectively, without a significant difference between the two groups (p = 0.701). No significant difference in gender was observed between Group 1 and Group 2 (p = 0.73). In terms of BMI, no significant difference was found between two groups (23.8±2.2 vs. 24.1±2.0 kg/m^2, p=0.551). No significant difference regarding the location of renal cyst was observed between the two groups (p=0.271). Ultrasonography and CT were preoperatively performed to measure the size of renal cyst. The size of the renal cysts was 5.3±0.9 min in Group 1 and 5.1±0.9 min in Group

Figure 2 - The left parapelvic cyst was identified by injecting methylene blue. The cyst wall before the injection of methylene blue is shown(A). Methylene blue was injected into the cyst to identify the parapelvic cyst, and the cyst wall (red arrow) became blue (B). The parapelvic cyst was incised by a holmium laser (C). Percutaneous renal puncture (D).



1, with no significant difference between the two groups (p=0.333). According to CT diagnosis, there were 31 patients with Bosniak category I renal cysts in Group 1, 33 with Bosniak category I renal cysts and 1 with a Bosniak category II renal cyst in Group 2, without a significant difference between Group 1 and Group 2 (p=0.336).

Group 1 had a shorter surgery duration than Group 2, and the difference between the two groups was statistically significant (30.1±4.3 vs. 54.4±6.4 min, p<0.001). Blood loss was 5.5±1.7 mL and 59±9.9 mL in Groups 1 and 2, respectively, with a significant difference between the two groups (p<0.001). The length of hospitalization in Group 1 was shorter than that in Group 2, with statistically significant difference between the two groups (4.5±0.8 vs. 5.6±0.9 days, p<0.001). The follow-up examination was postoperatively performed to measure the size of the renal cyst. At one year following the procedure, there was no significant difference in cyst size between the two groups (1.0±0.9 vs. 0.6±0.6 cm, p=0.106). No severe complications were observed in the two groups. In Group 1, significant hemorrhage was noted in 1 patient, which lasted for 2 days after the procedure. One patient had transient fever (38.7 °C temperature) in Group 2, but no significant difference was found between the two groups (p=0.947).

DISCUSSION

The kidney is prone to cystic lesions. A parapelvic cyst is a cyst that occurs near the renal pelvis or pedicle, and its occurrence incidence increases with age. Parapelvic renal cysts manifest as a result of a special type of renal cystic disease (2), are nonhereditary, and cysts that develop ad-

jacent to the renal pelvis are especially serious. Kiryluk (3) describes renal cysts that originate from the renal sinus, around the renal pelvis or renal sinus as parapelvic cysts. Chronic inflammation, according to Kutcher et al. (6), created parapelvic cysts by causing localized growth of pelvic lymphatic vessels.

Parapelvic cysts are frequently asymptomatic because they grow slowly. Parapelvic cysts cause symptoms by compressing the renal collecting system and renal vessels. The common symptoms include lumbar pain, hypertension, hematuria, recurrent urinary tract infection, and urinary tract obstruction (7, 8). Parapelvic cysts need surgical intervention when larger cysts cause symptoms.

To date, various methods have been used for the treatment of renal cysts, including percutaneous sclerotherapy, unroofing by open surgery, laparoscopic unroofing, and ureteroscopic drainage. Compared with simple renal cysts, the treatment of parapelvic cysts is relatively difficult due to the cyst's adjacent location to renal pelvis and vessels (9, 10). Percutaneous sclerotherapy is simple and economical. However, the recurrence rate for cysts is high due to the existence of a cyst wall. In addition, because the parapelvic cyst is adjacent to the renal hilum and pelvis, sclerotherapy could cause severe pyelonephritis or secondary ureteropelvic junction obstruction (11-13). In the past, laparoscopic unroofing was the preferred treatment for parapelvic cysts. Most surgeons, however, considered laparoscopic unroofing challenging. Because of the deep position of parapelvic cyst, the renal pelvis and vessels are easily injured intraoperatively (14, 15). The study reported that the incidence of pelvic injury was 9.5% during laparoscopic unroofing (8).

With the development of minimally invasive technology, Basiri et al. (15-18) reported that ureteroscopic incision and internal drainage were used to treat parapelvic cysts. In 1991, Kavoussi et al. (19) reported that they successfully performed ureteroscopic incision and internal drainage by ureteroscopy. They considered that this method has the advantages of minimal invasiveness, less postoperative pain, and rapid recovery. In this study, 31 patients successfully underwent a transurethral flexible ureteroscopic incision and drainage with holmium laser. Under the flexible ureteroscope, the visual field was not limited, the pelvis and all calyces were observed. The flexible ureteroscope can reach the target calyces and incise parapelvic cysts. Compared with the method of retroperitoneal laparoscopic unroofing, no significant difference was observed in terms of cyst size at one year postoperatively.

The key to ureteroscopic incision and drainage is to locate and identify renal cysts under a flexible ureteroscope. To avoid renal parenchyma or renal vessel injury, the incision should be located in the thin wall of the parapelvic cyst. The typical wall of a parapelvic cyst looks transparent. However, the surface of some parapelvic cysts is the same as that of the renal pelvis; therefore, it is difficult to identify the parapelvic cysts under the flexible ureteroscope (20). When methylene blue is injected into the cyst, the cyst wall turns blue, which can aid surgeons accurately identify the cyst wall (21). For parapelvic cysts in the posterior part of the kidney, percutaneous renal puncture was performed under B-ultrasound, the puncture needle was inserted into the renal pelvis through the cyst, and then an incision was performed along the puncture. Ulisses L G Pereira Sobrinho (22) reported that surgeon can train before proposing the appropriate surgical schedule to the patient using the 3D printed kidney. In this study, only one patient failed to undergo transurethral flexible ureteroscopic incision and drainage because the surgeon could not identify the cyst wall.

Some limitations exist in this study. First, selection bias occurred in our study due to its retrospective nature. Second, because this was a single center study, the number of patients was rather small, and further prospective randomized research is needed. Third, the transurethral flexible ureteroscopic incision and drainage has a number of drawbacks, such as higher costs and the need for two hospitalizations. Despite the limitations described above, the results of our study suggest potential avenues for future research and possible practice changes.

CONCLUSIONS

In summary, transurethral flexible ureteroscopic incision and drainage with holmium laser in the treatment of parapelvic renal cysts has obvious advantages over traditional surgery, and is worthy of advancement and application, but its long-term effect needs further follow-up studies.

ABBREVIATIONS

CT = enhanced computed tomography
SD = standard deviation
BMI = indicates Body Mass Index

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval and consent to participate

The Ethics Committee of Dongguan People's Hospital (Dongguan, China) approved the study, which adhered to the International Conference on Harmonization Good Clinical Practice standards. Ethics approval no.: XJS2018-009. In this study, all patients signed a preoperative informed consent form and agreed to participate in the accompanying scientific research and all procedures were performed in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the patient for publication of the case.

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CONFLICT OF INTEREST

None declared.

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The role of clomiphene citrate in late onset male hypogonadism

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COMMENT

The World is getting old. Aging is associated with degenerative changes in multiple organ and systems. Yet, overall, men's life expectancy increased from 63.2 years in the 1990s to 70.5 years in 2017, what represents an increase of 7.3 years in this period (1). Men's life expectancy has always been lower than women´s, as several biological, ethnic and sociocultural factors weighed in, but lifestyle modifications, such as decreasing smoking and alcoholism, controlling weight and adopting physical activity, has helped to minimize this difference (2). In addition to the desire to live longer, people value more and more quality of life, and among health issues that involve quality of life, we have what concerns cognition, reasoning, libido and the feeling of well-being. These aspects are all tightly related to testosterone, which is the main male hormone, responsible for all of this and, still, for strength and muscle mass, maintenance of bone structure, penile erections, etc. Greater attention has been given to health in this group of older male patients, not least because there is a high prevalence of metabolic and psychological alterations related to aging among them (3).

Symptomatic late-onset hypogonadism (LOH) is a clinical and laboratory syndrome that accompanies male aging and is associated with hormonal profile changes, which negatively affect libido, sexual function, mood, behavior, lean body mass, and bone density, that is, it affects not only the homeostasis of the organism but also its psychological function (3-5). Currently, the most common treatment of symptomatic LOH is testosterone therapy with various options of administration: transcutaneous, buccal, oral or intramuscular. Once the indications are observed, i.e., a clinical picture associated with laboratory confirmation, there are safe and efficient replacement alternatives (6, 7). In recent years, the prescription of testosterone has increased greatly, however men who wish to maintain their reproductive potential are not completely warned of the risks of using exogenous testosterone (8). But as life expectancy is increasing, it is perceived that the first marriage occurs later in life, consequently the intention of having the first child is postponed, so men also tend to be parents later nowadays. If a man who desires later paternity is hypogonadal, testosterone replacement can bring an unwanted damage to spermatogenesis (8, 9).

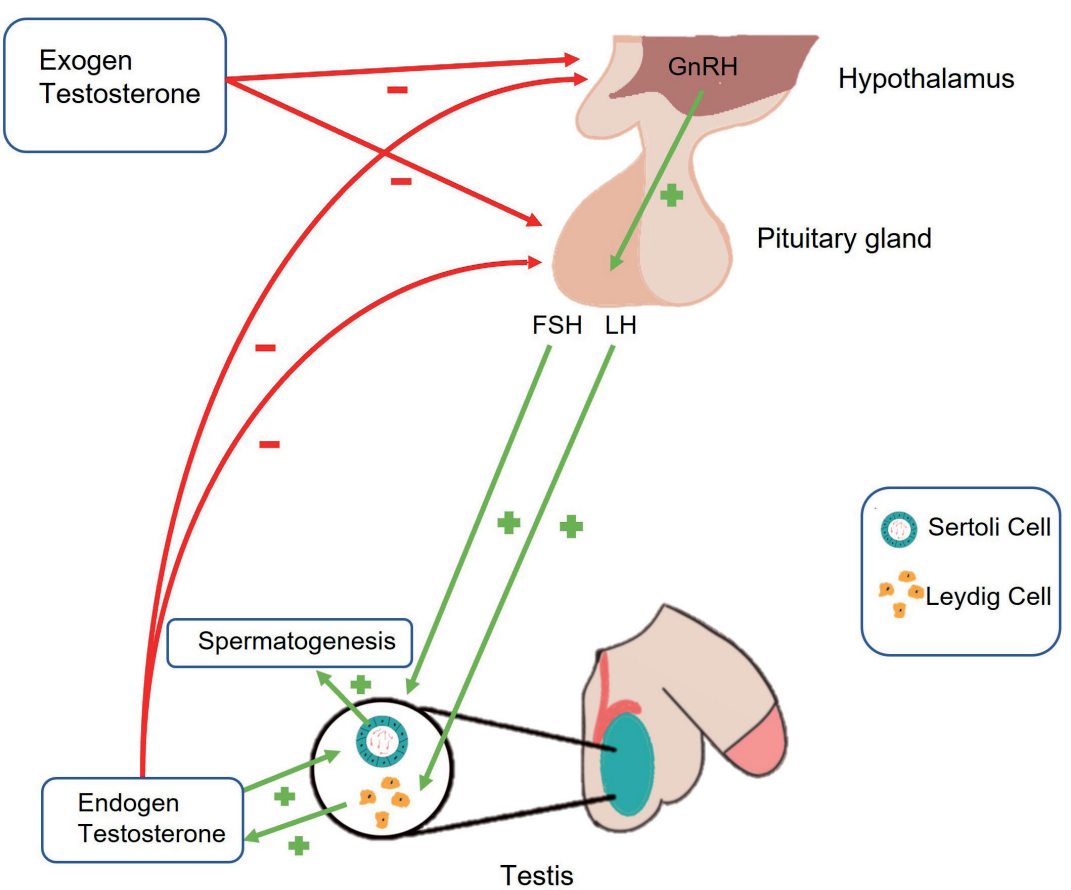
Testosterone replacement has been used as a treatment for symptomatic hypogonadal men and the administration of exogenous testosterone is the pillar of this therapy. The goal of replacement is to maintain physiological hormone levels. But there are some contraindications to its use, such as in those individuals who still desire offspring. So, we need alternatives to raise testosterone levels in these cases, without providing replacement and rather stimulate endogenous production of the hormone, and among them is clomiphene citrate, the theme of this current review.

Late onset male hypogonadism

Testosterone production is controlled by the hypothalamic-pituitary-testicular axis, where the gonadotropin-releasing hypothalamic hormone (GnRH) stimulates the pituitary gland to produce gonadotropins (luteinizing hormone (LH) and follicle stimulating hormone (FSH)). LH acts on testicular Leydig cells, stimulating testosterone production, while FSH, along with testosterone, stimulates spermatogenesis (8) (Figure-1). Unlike women, men do not show a cessation of hormone production, but rather a gradual decrease of 40 years of age. This leads to a deficiency of androgens (10-12), which can compromise both the quality of life and the functioning of certain organs (3-5). It is already well established that this decrease in testosterone (TT) can cause sarcopenia, muscle weakness, increased adipose tissue, fatigue, lack of motivation, depression, irritability, anemia, lower memory, and reasoning capacity. This late-onset hypogonadism is also related to diabetes mellitus, metabolic syndrome, coronary artery disease, and cardiovascular disease in general. In addition to the reduced serum TT levels and the signs and symptoms listed above, individuals report decreased in libido, less erotic thoughts, fewer nocturnal and morning erections, and they also present erectile dysfunction (3).

The decrease in total testosterone occurs in a rate of 1% per year and free testosterone, 2% per year, from the age of 40. This decrease is due to a smaller number and minor function of Leydig cells, changes in the hypothalamus-pituitary-gonadal axis and increased sex hormone binding globulin (SHBG) (3, 4, 10). Hypogonadism in aging is also associated with increased body weight and adipose tissue, resulting from peripheral conversion of testosterone into estradiol, and the negative feedback from estradiol in the pituitary gland results in a low LH secretion

Figure 1 - Sites where endogenous and exogenous testosterone can act on the hypothalamic pituitary gonadal axis.



despite a low testosterone level. Clinical syndrome is directly related to some risk factors including metabolic syndrome, diabetes mellitus, sleep apnea and chronic obstructive pulmonary disease, rheumatoid arthritis, hemochromatosis and other chronic diseases, and also is related to a higher risk of death in general (3, 8).

The prevalence of hypogonadism is not yet completely determined because there are still no longitudinal studies with large enough casuistry to obtain this data. Morley et al., in the Study of Baltimore (13), found a higher prevalence of hypogonadism in patients over 50 years of age. The literature shows a prevalence of hypogonadism ranging from 2 to 38% of the adult male population (5, 14).

Testosterone Replacement Therapy

Once hypogonadism (clinical and biochemical) has been diagnosed, hormone replacement should be initiated, provided that there are no contraindications. The treatment for hypogonadism most used is the administration of exogenous testosterone, which can be administered in oral, buccal, intramuscular or transdermal form (gel or patch) (4, 10).

In symptomatic patients, recovery of sexual desire is one of the first responses of TT replacement (4). Testosterone also exerts an important effect on body composition, increasing lean mass and decreasing fat mass (4, 10). In the wake of the recovery of physiological hormone levels, we can see response in the most different areas: decrease in negative thoughts, improvement in bone mineral density, increases in lean mass and in muscle strength (4, 15, 16). Overall, the recovery of normal hormone levels improves the quality of life of patients (3, 11).

Testosterone replacement can cause suppression of the hypothalamic-pituitary-gonadal axis via negative feedback mechanism and the clinical manifestations of the axis malfunction comprise reduction of both testicular size and sperm count. So, patients who still have an interest in offspring, should not receive any form of exogenous testosterone (3, 10, 12).

When the use of exogenous testosterone is contraindicated, the patient has an interest in offspring, or there are side effects related to gel or intramuscular applications, we can use dopaminergic agonists, gonadotropins, aromatase inhibitors or selective inhibitors of androgenic receptors (SERM), which are all effective in treating hypogonadism (12).

Exogenous gonadotropins (human chorionic gonadotropin - hCG, human menopausal gonadotropin - hMG, highly purified FSH - hpFSH, human recombinant FSH - rhFSH, long-lasting analogue FSH - alpha coryfolitropin) can be used to replace endogenous testosterone production by stimulation of Leydig cells due to their similarity with LH, and their use is quite common in cases of oligospermia or even azoospermia (17). There are several treatment regimens, and these drugs can be used intramuscularly or subcutaneously. Data are limited in the treatment of late-onset hypogonadism, but it is a feasible option that preserves fertility because it does not suppress the hypothalamus-pituitary-gonadal axis, however it has an elevated cost (8, 12).

Aromatase inhibitors (anastrozol and letrozole) inhibit the conversion of androgens into estrogens, preserving TT levels and limiting estrogen production. By doing so, they will prevent negative estradiol feedback on the production and release of gonadotrophins at the hypothalamic level. As a result, there will be a greater stimulation towards testosterone production (8, 11, 12). Unlike selective estrogen receptor modulators (SERM), aromatase inhibitors reduce estrogen levels (12). Its use in male infertility, to stimulate spermatogenesis, and in hypogonadism, to increase TT, is off label, like any other estrogen modulator. The dose of anastrozol usually used is 1mg 1x/day (8). Studies show increased testosterone levels, but the analysis of clinical response related to sexuality, body composition or muscle strength is still small. In addition, there is an association with a lower bone mineral density in patients when compared to testosterone replacement, since estrogens participate in various physiological functions, including bone metabolism, cardiovascular health, spermatogenesis, and cognition (4, 12).

Clomiphene citrate (CC)

Clomiphene Citrate (CC) is a weak selective estrogen receptor modulator (SERM) antagonist at the hypothalamus level. It attaches to the receiver for an extended period, reducing the availability of these receptors. As estradiol exerts negative feedback

on the hypothalamus, down-regulating the production and the release of gonadotropic-releasing hormone (GnRH), CC will increase hormone levels and consequently increase the stimulus on the pituitary gland. CC has the ability to compete with estradiol for the estrogen receptors at the level of the hypothalamus, so this drug blocks the normal negative feedback of circulating estradiol on the hypothalamus, preventing estrogen from lowering the output of GnRH. During clomiphene therapy, the frequency and amplitude of GnRH pulses increase, stimulating the pituitary gland to release more FSH and LH. Consequently, sperm and testicular testosterone productions are stimulated (18, 19).

This drug was developed for the treatment of female infertility in the 1960s, but it has also been used for treating male hypogonadism and infertility since then (20). The usual dose is 25-50mg per day, and testosterone elevation takes place after 4 weeks of treatment (12, 21). CC is effective in increasing TT levels as well as improving symptomatology caused by hypogonadism (22). But unlike the testosterone formulations employed to correct hormone levels, this drug preserves the patients' fertility. However, it is not effective in those cases where LH and FSH are elevated, characterizing primary hypogonadism (8, 12).

Tenover et al. used CC in 5 young patients (between 26 and 33 years) and 5 over 65 years of age, at a dose of 100mg/day for 8 weeks. They noticed that testosterone levels rose in both groups, more significantly in the youth group. These findings show that the alternative is effective regardless of age group (21).

Katz et al. used CC to treat hypogonadism of 86 young and infertile patients (mean age of 29 years) for an average period of 19 months. The dose used ranged from 25 to 50mg every other day and the aim of the study was to reach a testosterone value of approximately 550ng/dL. This was achieved in all patients and an important improvement in libido, in the feeling of well-being, the mood and in physical performance were also observed (22). No side effects were observed during the study. The same authors observed a group of 76 hypogonadal patients (testosterone levels <300ng/dL), with a mean age of 46 years, who were treated with CC. The treatment of all of these patients was successful, but they realized that those who had normal volume testicles (>14mL) and those with LH levels lower than 6 IU/mL had a better response to treatment (23).

Guay et al. observed an increase in testosterone and an improvement in erections in 173 hypogonadal men who complained of erectile dysfunction. Patients used CC 50mg 3x/week for 4 months (24).

In a comparison between exogenous testosterone and CC, a group of 52 patients received injections or TT gel, while 23 patients were instructed to use CC. The authors observed a similar increase in TT levels in both treated groups, as well as improvement of clinical parameters (25).

Taylor and Levine found elevation of TT levels in 104 patients treated with testosterone gel or CC. In this study, 65 of the patients used CC 50mg 2/2 days and were followed for up to 23 months. TT increased from mean pre-treatment value of 277ng/dL to a mean value of 573ng/dL after. The result showed that CC serves as an alternative to the use of exogenous testosterone (gel), with few side effects and a much lower cost (15).

In a group of 36 young hypogonadal patients (mean age 39 years), Shabsigh et al. observed an important increase in TT levels (247.6ng/dL, mean pre-treatment; 610ng/dL, mean post-treatment) after the use of CC at a dose of 25mg/day for 4 to 6 weeks (26).

In a comparison between CC (25mg/day) and anastrozol (1mg/day), Helo et al. treated 26 hypogonadal and infertile men for 12 weeks, observed an increase in TT levels in both groups, but more significant with CC (27).

In a study involving young patients (mean age of 36.5 years), who were both obese and hypogonadal, the use of CC 50mg/day for 12 weeks brought benefit on sexual function, lean mass and muscle mass, demonstrating improvement in the hormonal profile of patients, as well as body composition (28). Lim and Fang also observed improved in libido, in the erections and in the feeling of well-being in a group of 5 hypogonadal patients with chronic renal failure who received CC 100mg/day for a period of up to 12 months. They also showed that these patients remained eugonadic for up to 5 months after discontinuation of treatment (29). On the other hand, Marconi et al. used CC 50mg/day

for 50 days in 27 patients with hypogonadism; there was a significant increase in hormone levels, which decreased again after discontinuation of the drug (30). Hormone replacement, in general, is of continuous use. The use of testosterone replacement is uninterrupted, because when it is suspended, the patient becomes hypogonadic again, and experiences the recurrence of the clinical picture that motivated the initial consultation. This is probably the case for the therapeutic alternatives to hormone replacement, such as CC, which should also be continuous as was showed by this study by Marconi et al. (30).

There are also long-term publications, such as the study by Moskovic et al. who treated 46 hypogonadal patients with CC and had a follow-up period of up to 3 years. Patients had a mean age of 44 years in the baseline and used 25 to 50mg of CC every other day. In the end of follow-up, a TT elevation was shown, as expected (228ng/dL in baseline, 582ng/dL in the third year of treatment) and virtually no side effects occurred (31).

Da Ros and Averbeck (32) observed an improvement in TT levels and in libido in a group of 125 hypogonadal patients, with a mean age of 62 years, who were treated with 25mg/day of CC for 3 months. There was an average increase in TT levels from 309ng/dL to 642ng/dL. And they had virtually no notable side effects.

Studies show good tolerability and only a few mild side effects, such as hot flashes, headache, gynecomastia, dizziness and fatigue (11, 20, 25). CC is a good alternative for the treatment of symptomatic hypogonadal patients and has as advantages the absence of hypothalamus-pituitary-testicular axis block, the fact that it does not suppress spermatogenesis and does not cause polycythemia and its low cost (18, 31, 32).

CONCLUSION

In our modern World, the desire for later paternity has been frequent, mainly due to socio--economic-cultural issues, which include longer life expectancy, greater use of contraceptives and the large female presence in the labor market. Men are thus, more frequently experiencing fatherhood in late adulthood. The average age of paternity increased, in the last 40 years, from 27.4 to 30.9 years, and in the 1970s, 6.1% of men became a father over 40 years; between 2011 and 2015, this percentage rose to 12.7% (9). However, the late pregnancy, besides being more difficult due to changes in the hypothalamus-pituitary-gonadal axis (hypogonadism) and spermatogenesis, is related to harmful DNA damage accompanied by congenital mutations, autism and schizophrenia (33). Despite the risks, the trend of later paternity shows us the importance of maintaining good health and also of tending to the men's fertility.

Along with the well-established non-pharmacological interventions, such as lifestyle changes, that can be made in this population, testosterone replacement remains the standard treatment for those men with androgenic deficiency of male aging. It is not an option for those who desire offspring, since testosterone replacement decreases sperm production, or for those who have a difficult-to-control polycythemia. For these hypogonadal patients, there are other alternatives such as CC.

CONFLICT OF INTEREST

None declared.

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Is it safe to resume large scale in-person medical meetings?

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INTRODUCTION

Participating in medical meetings is important for medical and other healthcare professionals with different backgrounds. The brightest minds share their expertise and present cutting-edge advancements in their field of knowledge [1]. The COVID-19 pandemic has had broad consequences for medical meetings worldwide. In support of public authorities in their effort to slow the spread of the disease, in-person medical meetings have been cancelled throughout the World since March/2020, or transformed in a virtual-only format, where the audience used online access. Most lectures, panel discussions and point-counter-point sessions are usually recorded in advance, through an online chat service, with no in-person interactions between speakers.

Although online meetings have served as a strong tool for medical education since the beginning of the pandemics, people are getting exhausted with this format. Being on a video call or teleconference requires more focus than face-to-face chat and lectures because it is harder to process non-verbal cues like facial expressions, the tone and pitch of the voice, and body language. Paying more attention to this drains a lot of energy. In addition, many of us are using video calls at work, family celebrations and interaction with friends. Everything seems to be happening in the same place, which further contributes to negative feelings for online meetings. Moreover, the online meeting is a reminder of the people, opportunities, and lifestyle that we have lost temporarily (2).

In-person meetings have been the most common and preferred format of medical conferences. They allow participants to interact with leaders and novices in the field, providing a unique networking experience that can foster future collaborations, help build a reputation, and create funding and career opportunities. In addition, browsing through the booths or presentations from vendors allows access to the latest technologies and tools in the field. However, social distancing is still effective throughout the World as we prepare this manuscript, and one cannot predict when in-person meetings will be safe again. Recent attempts to resume in-person medical meetings have been frustrated by the resurgence of COVID-19 due to the omicron variant. The Annual Congress of the European Association of Urology is one of the most important scientific meetings in the specialty and has been postponed from March/2022 to July/2022 due to the COVID-19

resurgence. Many other large meetings initially scheduled for the first semester of 2022 have been postponed, including the 52nd World Economic Forum Annual Meeting which was deferred from January to late May 2022.

In this study, we report our experience with a large medical meeting that took place in Brasilia, Brazil, in December/2021. We hypothesized that with most in-person participants being fully vaccinated and using proper precautions the number of new COVID-19 cases would be very low and not different from online participants.

MATERIALS AND METHODS

Meeting characteristics

The Brazilian Meeting of Urology is organized every other year by the Brazilian Society of Urology. It is considered the third-largest urological meeting globally, with a historical audience of approximately 4,000 attendees per event. The organization committee of the 38th meeting edition faced many challenges due to the global COVID pandemics. Initially scheduled for August 2021, it was postponed to October and eventually was held from 12 to 15 of December 2021. A hybrid format was employed with real-time broadcasting of all face-to-face activities to those who opted not to attend in person. The meeting had a duration of four days, with 10 daily hours of educational activities including plenary sessions with a total of 28 hours, 8 subspecialty workshops (10 hours duration each) and 44 educational courses (each with 2 to 4 hours duration).

Characteristics of the venue

The meeting was held at the Brasilia International Convention Center (CCIB), a venue with 65,000 m2 of built area with closed air conditioning system. Only two of the three floors of the venue were used, including the 3rd floor with an area of 12,000 m2 that includes lobby entrance, main plenary, exhibition area, VIP room, restaurant and living rooms and the 1st floor with the same area, containing the rooms where the courses were held.

Safety protocols

Participants were not required to present proof of vaccination status nor test for SARS-CoV-2 before the event. The use of facemasks was mandatory in the venue except for the eating areas. Measures were used to restrict participants per room, aiming to reach no more than 50% of the maximum room capacity (Figures 1 A-F). On the first day of the meeting, every participant received a bottle of 70% alcohol gel and facemask in the meeting kit.

Online survey

This study was conducted as an electronic cross-sectional survey sent by e-mail to all registered urologists who provided their e-mail address. There were no incentives for completion. The first e-mail inviting to participate was sent on January 10th/2022; four additional invitations were sent on January 12, 14, 17 and 21/2022. Data collection was closed on January 22/2022. A total of 1077 urologists who attended the meeting in-person were invited to participate in the study. Online participants (n= 781) served as a control group and were invited to complete the online survey at the same date, with the main purpose of identifying new cases of COVID-19. Since most online participants are urologists with similar lifestyle as the in-person participants we felt this would be an appropriate control group.

The invitation e-mail contained a link to a 10-question web-based survey. All questions were closed-ended, multiple choice. The survey included an assessment of previous COVID disease and vaccination status (Table-1).

Risk of COVID-19 after the Meeting

Both in-person and online participants were asked whether they had been diagnosed with COVID-19 during the first 15 days after the end of the meeting.

The in-person participants were evaluated in terms of behaviors regarding the use of facemasks while at the meeting venue, time spent in the convention center during the meeting and concern regarding getting infected with SARS-CoV-2 during the meeting.

Informed consent was obtained from all participants.

Data collection and Statistical analyses

Data were initially elaborated using Survey Monkey® software online. Data were expressed as

Figures 1 (A-F) - Measures were used to restrict participants per room, aiming to reach no more than 50% of the maximum room capacity.

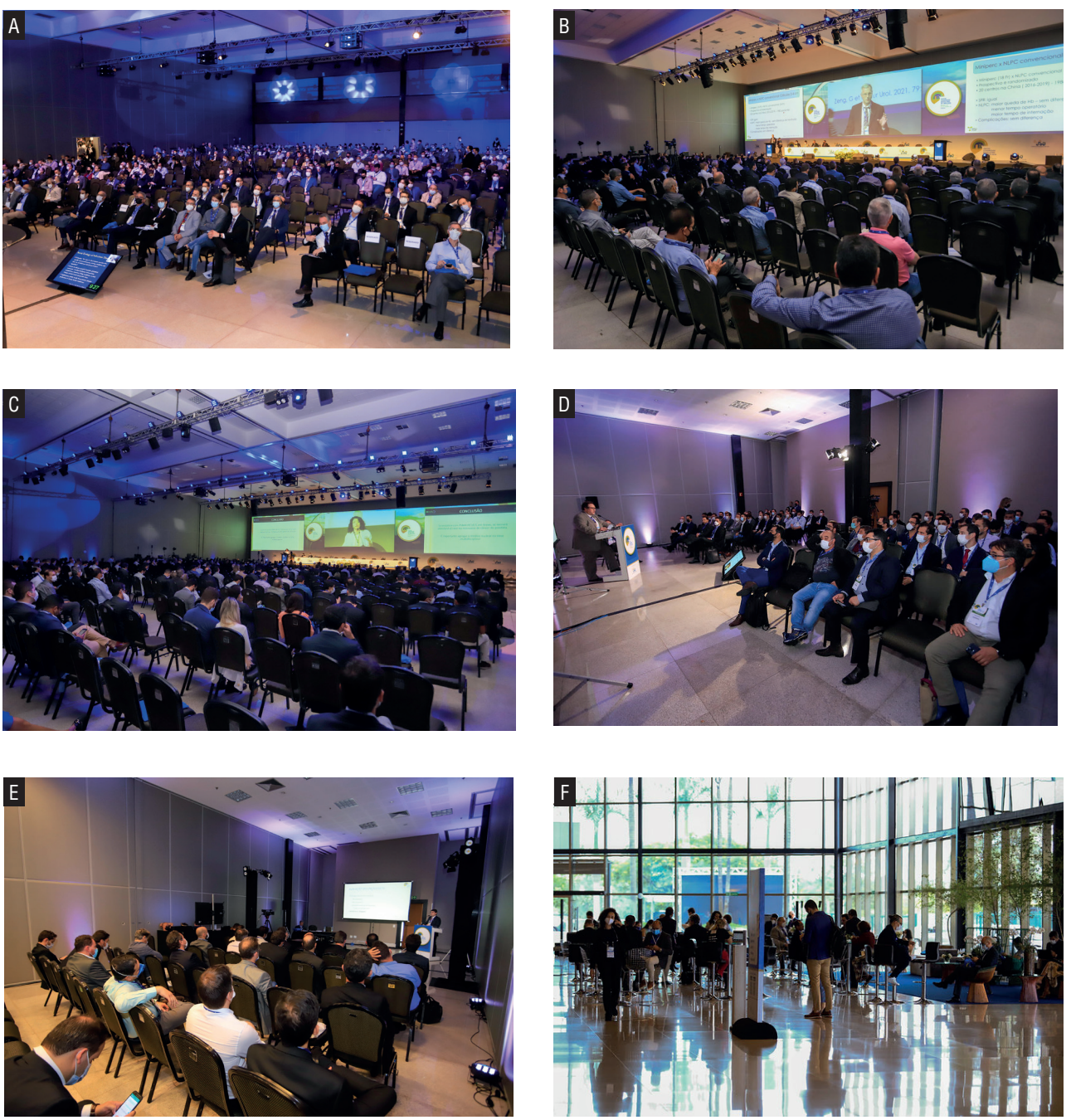

Table 1 - Baseline characteristics and new cases of COVID-19 after the meeting: Comparison between in-person and online participants.

	In-person participants (n = 309)	Online participants (n = 138)	P value
Age	42.0 (35.00-53.00)	43.5 (32.00-56.25)	0.634
Previous COVID-19	111 (35.92%)	39 (28.26%)	0.114
Vaccination status		**	0.989
No vaccination	2 (0.65%)	1 (0.72%)	
Incomplete	1 (0.32%)	1 (0.72%)	
Complete	55 (17.80%)	22 (15.94%)	
Complete + boost	251 (81.23%)	108 (78.26%)	
New onset COVID*	4 (1.29%)	6 (4.35%)	0.070

*Diagnosed within 15 days after the meeting; ** 6 participants did not complete

medians and interquartile ranges, or absolute values and fractions. The Student t test was used to compare continuous variables while categorical variables were compared using the chi-square or Fisher's exact tests. All tests were 2-sided with $p < 0.05$ considered statistically significant and were performed using GraphPad Prism® version 9.03 for Windows.

RESULTS

A total of 2608 subjects registered for the meeting including 1494 who participated in-person and 1114 who participated exclusively online. At the peak, 356 participants were online simultaneously. Respondents of the online survey included 309 (28.69%) of the in-person urologists and 138 (17.67%) of the online participants. The median age of onsite participants was 42 and the median age of the online participants was 43. The complete survey response rate was > 99% for both groups.

Onsite and online participants were comparable in terms of vaccination status against coronavirus. The vast majority in the two groups had received the complete vaccination scheme (99.03% vs 94.20%, in-person vs online participants, respectively; p= 0.989) and less than 1% in each group had not been vaccinated (Table-1). The groups were comparable in terms of age (p= 0.634), previous COVID-19 (p= 0.114) and vaccination status (p= 0.989). Participant's characteristics (age, vaccination status, previous and new COVID diagnosis) are summarized in Table-1.

Risk of COVID-19 after the Meeting

Four (1.29%) of the 309 in-person participants and six (4.35%) of the 138 online subjects reported being diagnosed with COVID within the fifteen days after the end of the meeting (p= 0.070).

Among the onsite attendants, 7 (2.2%) participants were at the meeting for one day, 33 (10.5%) for two days, 100 (31.8%) for three days and 174 (55.4%) for all four days. Regarding the use of facemasks, 217 (68.67%) onsite participants stated they wore a mask the whole time and briefly removed it during meals; 82 (25.95%) stated they wore a mask most of the time, but removed it for relatively long periods of time, on multiple occasions, for eating and other activities while 17 (5.38%) stated they removed their masks as much as they could.

Due to the small number of in-person participants who had COVID after the meeting, we could not evaluate whether vaccination status, mask-related behaviours or time spent at

the convention center were associated with an increased risk of getting the disease.

As for the preoccupation of getting COVID-19 while attending the meeting, most participants (56.37%) stated they felt a little concerned, 39.17% were not concerned at all and 4.46% felt very concerned. Most (94.27%) considered the safety protocols at the convention center as adequate, while 4.78% found them deficient and 0.96% found them excessive. Only 33 (10.51%) onsite participants had attended other in-person medical event of similar or larger size during the pandemics.

DISCUSSION

We have shown that participation in a large, indoor, medical meeting with nearly 1500 onsite participants and with four days duration held in December 2021 in Brasilia, Brazil, was not associated with increased SARS-CoV-2-infection risk. Four (1.29%) of the 309 in-person respondents became infected within 15 days of the meeting, compared with six (4.55%) of the138 online respondents, thereby confirming the absence of transmission risk. The groups were comparable in terms of history of previous COVID-19 and immunization status for the disease. Most onsite participants felt concerned about the risk of getting COVID-19 during the meeting, including 14 (4.46%) who were highly concerned and 177 (56.37%) who felt a little concerned.

Our finding of similar SARS-CoV-2--infection rates among in-person and online meeting attendees indicates that, in the context of high rates of immunization coverage against COVID-19 and low to medium circulation of SARS-CoV-2, the resumption of large medical meetings seems to be safe, as long as safety protocols are followed. Urologists in our control group have the same exposition risks in their daily activities as the in-person participants. In fact, it is reasonable to suppose that they are even more cautious and less exposed, since many may have opted not to attend in--person to minimize exposition.

From 12 to 15 of December 2021, when the meeting was held, the seven-day moving average of new daily cases in Brazil was 3,452 cases, which was close to the lowest rate of new cases in Brazil in 2021 (3). It was just before the outbreak of the omicron variant in Brazil, which was first detected in late November/2021 and increased the number of infections in the country to 8,000 cases/day and 100,000 cases/day 15 days and 30 days after the meeting, respectively. At the time of the meeting, 66% of Brazilians were fully vaccinated (4). Since urologists are healthcare workers and were prioritized by the government to receive vaccination, over 98% of both in-person and online meeting participants had been fully vaccinated, which was probably instrumental for the meeting to gather almost 1500 in-person attendants.

Few studies have evaluated the impact of participating in a major gathering since the outbreak of the COVID-19 pandemics. The SPRING study was the only randomized control trial where researchers evaluated the risk of attending a live indoor four-hour duration concert on May 29/2021, in Paris (5). Participants were healthy young men and women (18-45 years) that were evaluated for COVID-19 symptoms, recent case contact and had had a negative rapid antigen diagnostic test within 3 days before the concert. They were randomized to an experimental group (4451 attendees) or a control group (2227 non-attendees) and were tested for SARS-CoV-2 by RT-PCR on self-collected saliva 7 days post-gathering. Authors found no differences between the two groups in terms of positivity for SARS-CoV-2 seven days post--gathering (0.20% vs 0.15%, respectively for attendees and non-attendees). Less than 10% of the study population was fully vaccinated. They concluded that participation in a large, indoor, live gathering without physical distancing was not associated with increased SARS-CoV-2–transmission risk, provided a comprehensive preventive intervention was implemented. Other observational or small randomized controlled trials found similar results (6, 7). In common, these studies evaluated short duration events - of 3 to 5 hours duration - and all had stringent pre-event precautions. Our study, on the other hand, had no

pre-event precaution and had a much longer duration, of 10 daily hours for up to 4 days.

To our knowledge, this is the first study reporting on the outcome of COVID-19 infections following attendance of a large medical meeting since the beginning of the pandemics. The event brought together around 1500 in-person participants for a meeting with four days of duration and showed a low risk of acquiring COVID-19 15 days after the meeting. The use of a control group composed of urologists that participated online gave us the opportunity to compare the rate of new cases among the onsite participants with that of a population of similar age and lifestyle that was not exposed to the risk of contagious associated with attending a large medical meeting.

Large indoor gatherings are considered high risk situations for Sars-CoV-2 transmission (8, 9), which justifies many people's fear of attending such events. Among the meeting attendees, most were at least a little concerned about getting COVID, and for almost 90% this was the first large gathering they took part in since the beginning of the pandemic. Although the attendees were not required to present a negative COVID test, many other measures were taken as part of the preventive strategy, and the vast majority of participants found the implemented safety protocols to be adequate. Also, most reported adequate use of face masks. Combined with the high vaccination rate among participants, all these factors may have contributed to the safety of the meeting.

Our study does have significant limitations. First, the percentage of meeting attendants that participated in the survey was small and may not fully represent the whole population. Second, the diagnosis of COVID-19 was based on self-report, with no laboratory confirmation. In addition, it may not be appropriate to extrapolate our findings to other medical meetings in Brazil or other countries, since a number of conditions may vary, including the transmissibility of the circulating COVID-19 variants, the population's vaccination status, the number and behavior of meeting participants and the size and characteristics of the venue where the meeting is held.

CONCLUSIONS

In conclusion, our study showed that participation in a large, indoor, medical meeting with four days duration was not associated with increased SARS-CoV-2 infection risk, provided usual preventive measures were implemented. In the context of high rates of immunization coverage against COVID-19 and low to medium circulation of SARS-CoV-2, the resumption of large medical meetings seems to be safe. Our results may not be applied to the case of highly transmissible variants with shorter incubation period.

CONFLICT OF INTEREST

None declared.

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EXPERT OPINION

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Robotic-assisted radical prostatectomy with a single port platform: current and future perspectives of a referral center

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COMMENT

Several authors have described the robotic surgery benefits and outcomes in urological procedures, and numerous generations of multiport consoles have been created since the first robotic surgery was approved by the FDA (Food and Drug Administration) in 2000. In this context, all platforms had something in common: the multiport design with several independent arms responsible for controlling the instruments individually.

The minimally invasive surgical concept is always evolving and looking for alternatives to further reduce surgical trauma while improving outcomes. In this scenario, an innovative Single Port (SP) robotic platform was recently cleared by the FDA in urologic procedures. The da Vinci SP is different from the previous robotic generations because instead of independent arms working through multiple abdominal incisions, the SP has only one trocar that houses three biarticulated arms and one flexible scope, allowing the same surgical procedure to be realized with a single access and fewer abdominal incisions (1).

We previously compared the short-term outcomes of da Vinci Xi and SP platforms in patients who underwent radical prostatectomy (2). Despite the increased operative time for the SP group, mainly due to the delicate instruments and learning curve, we could describe less blood loss with minimal intraoperative complications. In our experience, having a less invasive robotic technology facilitated the surgery in patients with renal transplants, inflatable penile prosthesis (IPP), ileostomies, and colostomies. These patients usually have extensive adhesions, increasing the challenges to place multiple trocars. In addition, these cases have intraabdominal obstacles (ileostomy, colostomy, prosthesis reservoir, and pelvic transplanted kidney), which blocks the optimal triangulation and working space of multiport consoles. Therefore, placing the SP trocar on the midline facilitates the appropriate instrument deployment without limiting the movements on the sides, decreasing the chances of clashing, and damaging these internal structures.

Furthermore, in our experience, the SP platform is a less invasive option for lymphocele drainage in symptomatic patients with previous Interventional Radiology (IR) drainage attempts (3). Instead of six conventional incisions done with the multiport robot, the same surgical drainage is performed with only one or two

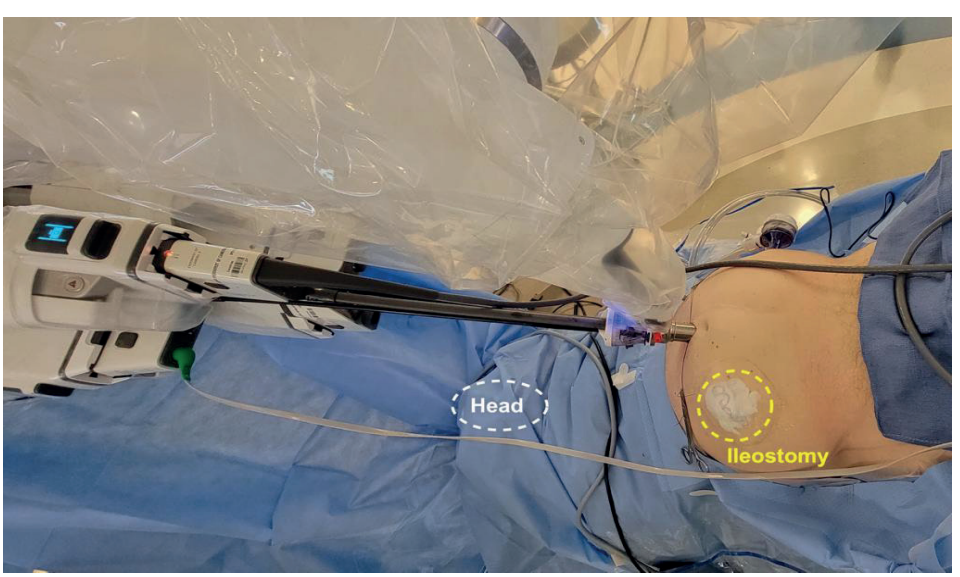
abdominal accesses, which enables definitive treatment of the lymphocele sac and fewer days with abdominal drain.

As an oncological referral center, we believe that treatment delays affect the outcomes of each patient, and the appropriate therapy must be provided as soon as possible to optimize results. Patients with the abovementioned circumstances usually have their surgical treatment deferred or even canceled (sent to radiation) due to potential challenges faced during surgery, such as bowel injury, prolonged operative time, and even aborted procedures when the multiport trocar placement is not feasible. Therefore, we believe that the current SP generation is not a replacement of the multiport but an option for these patients to avoid treatment delays, providing appropriate oncological management through only one or two abdominal incisions (SP plus the assistant trocar).

We recently described our experience in patients undergoing radical prostatectomy with the SP robot, and we found that by maintaining selection criteria, using only two ports (instead of six), the trends of positive surgical margins have minimal variations during the learning curve, with rates compatible with our multiport approach (4). In addition, our experience performing lymphocele drainage is positive due to the less invasive procedure on these patients, allowing for definitive treatment with a single incision (3). Finally, the SP robot benefits patients with ileostomy, colostomy, prosthesis reservoir, and transplanted kidney with satisfactory intraoperative outcomes, minimizing delays and complications on the definitive treatment. Figure-1 illustrates the SP docked in a patient with rectal amputation and ileostomy (SP trocar supraumbilical and midline, and 12mm assistant trocar on the left lower quadrant). The right side was totally blocked by the ileostomy and bowel adhesions, which impeded the multiport trocar placement.

The initial barrier to the SP implementation is the increased price of the robotic platform, instruments, and disposables compared to the multiport (5). However, by adopting same-day discharge protocols in selected cases and minimizing the hospitalization time, some centers could reduce the final surgical cost. The second barrier is that this platform is available only in a few centers (USA, Korea, and Hong Kong), and only some specialties are cleared by the FDA to use it in clinical settings. Finally, this platform demands a new

Figure 1 - Da Vinci SP radical prostatectomy in a patient with ileostomy and rectal amputation.



learning curve and training requirements for the whole team, which may not motivate expert surgeons established for years with the multiport robot.

Single Port surgery, as previously described, provides a less invasive robotic approach with potential benefits to some patients that are not candidates for the multiport. However, the current literature is based on retrospective studies with its inherent risks of bias. Most studies have less than 150 patients with short-term outcomes (6). We believe that the SP technology diffusion depends on well-designed comparative studies performed by referral centers, reporting long-term outcomes. In this scenario, considering the higher costs and the new learning process associated with this robot, some institutions maintain the multiport console while waiting for mature data to justify the SP investment.

Since the SP clearance by the FDA, we observed an expansion of this technology in academic centers, which may benefit the diffusion of this robot in the following years due to the early exposure of residents, fellows, and surgeons training robotics. In addition, the experience of these centers in terms of reducing costs, optimizing outcomes, and describing their experience with the technological implementation, enables smaller centers to minimize initial mistakes and complications during the learning curve, which are also factors to influence the diffusion of this technology.

Finally, considering that the current SP robot is the first version of this technology, we believe that Single Port surgery will be the standard approach with succeeding generations and its expansion will gain traction with long-term outcomes reports, decreased costs, and instruments improvements.

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CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

PEDIATRIC UROLOGY

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Editorial Comment: Anterior component separation technique for abdominal closure in bladder exstrophy repair: Primary results

Francisco Nicanor Araruna Macedo [1], Eduardo Corrêa Costa [2], Jovelino Quintino de Souza Leão [3], Antônio Carlos Amarante [4], Fernanda Ghilardi Leão [5], Hélio Buson Filho [6], et al.

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COMMENT

Kelly´s Together Project (KTP) is a great initiative. The results of this work may bring very important information to the Pediatric Urologists community.

The opportunity to treat a relatively high number of OIES cases, including complex patients with a single and standardized technique is unique. The number of patients tends to be high because of Brazilian´s territorial scope and big population, where legal abortion is prohibited. The availability of the National Brazilian Health Service facilitates logistics.

KTP is similar to other programs to treat bladder exstrophy going on in India and North America, using other techniques. In due time it may be possible to compare results between big cohorts treated with different techniques at the same time frame.

The idea of professional consortia is a great development in what concerns rare surgical diseases, and the recent availability of online transmission of surgeries in real-time time and of planning online meetings adds to its implementation. Financial support from the government, in the case of countries counting on public health systems, is needed for travel expenses and to allow paid licenses for the professionals to participate in the initiative.

The present paper (1) is the first to be presented by KTP group and deals with one of the most difficult aspects of exstrophy treated without pelvic osteotomy: the closure of the abdomen, especially after the first days of life and in cases exhibiting large pubic diastasis. The authors ingeniously associate techniques of rectus muscle releasing and myofascial compartment mobilization. We wonder whether associating intramuscular pre-operative botox injections would also help (2). This would be easy to accomplish, as surgeries are usually programmed electively after 3 months of age.

The results described by the authors are great but must be evaluated with a grain of salt, as long-term results are as yet unknown, especially in what concerns genital prolapse in females, late sexual results, and the possibility of dyspareunia and/or penile fracture attaining the released penises, that are fixed on myofascial structures and will not count on the physiologically normal long osseous anchorage of the corpora during coitus in adulthood. To the best of our knowledge, those data are not yet available, either concerning the "classical" Kelly technique (that used radical tissue mobilization to treat the penis and bladder neck AFTER neonatal bladder closure (3)) or the new adaptations being used now, that propose radical tissue mobilization to close the bladder and bladder neck and penile reconstruction simultaneously.

Mr. Justin Kelly has recently suggested that the right term to describe the surgical treatment of bladder exstrophy is to construct, not to reconstruct, as to reconstruct means to put up something together again, while to construct means creating something new (4). In OIES cases the surgeon does not "recover" tissues. He/she build something new from scratch, using abnormal tissues. This applies to all techniques described at the moment and probably reflects on the results of any technique.

The authors are to be congratulated for their persistence, resilience, and personal investment in making clinical research. Their effort is at the same time valuable, stimulating and beautiful. This paper is the first from their group, but, for sure, many more will follow.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

PEDIATRIC UROLOGY

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Editorial Comment: Open Versus Laparoscopic Gubernaculum-Sparing Second-Stage Fowler-Stephens Orchiopexy for Intra-Abdominal Testis: A Long-Term Study

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COMMENT

The high abdominal undescended testis is a challenging situation in pediatric urology. The surgery to put the testicle in the scrotal region without harming its vascularization is very important for the treatment of these cases. Fowler-Stephens surgery performed in two times is the best strategy to preservation of vascular supply to the testis. In this important paper the authors shows the benefits of performing open versus laparoscopic gubernaculum-sparing second-stage Fowler-Stephens orchiopexy (FSO). The gubernaculum is the most important structure in the inguinoscrotal stage of testicular migration (1, 2). The knowledge of testicular and gubernaculum vascular anatomy is a key point in this procedure (3). In this paper the authors retrospectively studied a cohort of patients who underwent laparoscopic first-stage FSO and open versus laparoscopic gubernaculum-sparing second-stage FSO and concluded that the second-stage gubernaculum-sparing FSO achieved high testicular survival rates and satisfactory testicular positions. Neither the open nor laparoscopic approach appeared superior, because the overall testicular survival rates and incidence of testicular ascent and other complications were equivalent between both groups.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

UROANATOMY

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Editorial Comment: Identification of Recurrent Anatomical Clusters Using Three-dimensional Virtual Models for Complex Renal Tumors with an Imperative Indication for Nephron-sparing Surgery: New Technological Tools for Driving Decision-making

Daniele Amparore [1, 2], Federico Piramide [1], Angela Pecoraro [1, 2], Paolo Verri [1], Enrico Checcucci [3, 4], Sabrina De Cillis [1], Alberto Piana [1], Giovanni Busacca [1], Matteo Manfredi [1], Cristian Fiori [1], Francesco Porpiglia [1]

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COMMENT

In this interesting paper the authors shows the importance of the 3-D virtual models (3DVMs) to the study of kidney anatomy and the renal tumors before the nephron-sparing surgery (NSS). The robotic surgery provided important advances for the realization of the NSS, but the tumor anatomy is the key point of this procedure. Recently several papers shows the importance of the study of renal and ureteral anatomy with 3D printing models and CT-reconstruction models for surgical training for urological procedures (1-3). In the present paper the authors studied three patients with high-complexity renal masses with unusual anatomy and an imperative indication for NSS underwent contrast-enhanced computed tomography from which a 3DVM was obtained. The paper has amazing pictures of the kidney tumors anatomy. The authors concluded that three-dimensional models help in defining the best surgical strategy for kidney tumors, especially for complex tumors that require surgery to spare as much of the kidney as possible.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Ultrasound guided endoscopic combined Intrarenal surgery – 10 steps for the success

Fabio C. Vicentini [1], Kayann Kaled Reda El Hayek [1], Marcelo Szwarc [1], Rodrigo Perrella [1], Priscila Kuriki [1], David Cohen [1], Daniel Beltrame [1], Carlos Alfredo Batagello [1], Claudio Murta [1], Joaquim Francisco de Almeida Claro [1]

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ABSTRACT

Background: Endoscopic combined intrarenal surgery (ECIRS) has been used to treat complex kidney stones (1). The combined use of ultrasound (US) has the potential to improve safety and reduce radiation exposure, however, it is still underutilized (2).
Objectives: Our objective is to describe, in a step-by-step manner, the ultrasound-guided ECIRS (USG ECIRS) technique, in order to facilitate learning by urologists.
Materials and Methods: We describe the 10 standardized steps that we recommend to achieve a good outcome, based on our previous experience on a high-volume kidney stone center. We recorded a case of a 37-year-old female patient with complex bilateral kidney stones that underwent a left simultaneous combined retrograde and antegrade approach. The 10 described steps are: 1 - case evaluation with CT scan (3); 2 - preoperative care with antibiotics and tranexamic acid; 3 - warm-up and training with phantoms; 4 - patient positioning in Barts flank free position; 5 - retrograde nephroscopy with flexible ureteroscope; 6 - US and endoscopic guided puncture; 7 - tract dilation under endoscopic view; 8 - stone fragmentation; 9 - status free checking and 10, kidney drainage. Images were captured by external and internal cameras, promoting a complete understanding of the procedure. The patient has signed a written informed consent form.
Results: Puncture was achieved under US guidance with one attempt. Another puncture was necessary in the lower pole, parallel to the initial puncture, due to a large fragment. Surgical time was 140 min. Stone-free status was verified by retrograde and antegrade view. Kidney drainage was done with ureteral stent on string, removed after 7 days. Hb drop was 1.1 Hb/dL. The first postoperative day CT scan showed no residual stones and no complications. The patient was discharged after the CT and urethral catheter removal.
Conclusion: The USG ECIRS seems to be a very efficient and reproducible technique for the treatment of complex kidney stones. Its use should be widespread.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Distal ureter and bladder cuff excision using the "Keyhole Technique" during Robotic Radical Nephroureterectomy

Luis G. Medina [1], Muhannad Alsyouf [1], Alireza Ghoreifi [1], Aref S. Sayegh [1], Kailyn Koh [1], Wenhao Yu [1], Sina Sobhani [1], Antoin Douglawi [1], Hooman Djaladat [1]

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ABSTRACT

Introduction: Upper tract urothelial carcinoma (UTUC) accounts for 5-10% of all urothelial tumors (1). Radical nephroureterectomy (RNU) remains the standard treatment for high, and low-grade UTUC (2). Although the open approach has been considered the gold standard, robotic techniques have shown comparable oncological outcomes with potential advantages in terms of peri-operative morbidity (3).
Materials and Methods: We present a novel "Keyhole" technique for management of distal ureter and bladder cuff during robotic RNU. This technique allows the surgeon to directly visualize the ureteric orifices, delineate resection borders, and maintain oncologic principles of en-bloc excision without necessitating secondary cystotomy incision or concomitant endoscopic procedure. Descriptive demographic characteristics, surgical, pathological, and oncological outcomes were analyzed. Complications were reported using the Clavien-Dindo classification system.
Results: Between 2015 and 2020, ten patients underwent robotic RNU with bladder cuff excision using the Keyhole technique (single-dock, single-position). Median age was 75 years. Eight patients underwent surgery for right-sided tumors. Median operative time, estimated blood loss, and length of hospital stay were 287 min, 100 mL, and 3 days, respectively. No intraoperative complications occurred, and one grade II complication occurred during the 90-day postoperative period. All patients had high-grade UTUC, being 90% pure urothelial. Bladder recurrences occurred in 30% of patients with an overall median follow-up of 11.2 months.
Conclusions: Keyhole technique for the management of distal ureter and bladder cuff during RNU represents a feasible approach with minimal 90-day complications and low bladder recurrence rate at centers of experience.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Total corpora mobilization for penile reconstruction

Ubirajara Barroso Jr. [1, 2], Bruna Venturini [1, 2], Eliakim Massuqueto [1, 2], Filip Prado [1], Ana Castro [2], Herbert Santos [2]

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ABSTRACT

Purpose: Total corpora mobilization (TCM) is a novel technique that is used for penile reconstruction in cases of micropenis and penile amputation. Its principle is based on Kelly's procedure for bladder exstrophy (1). In contrast to the Kelly procedure, TCM is performed entirely through the perineum with the patient in the lithotomy position.
Materials and Methods: TCM was performed on three patients. The first was a boy who suffered trauma from a dog bite at an age of eight months. At 23 years old he underwent TCM. The second patient had genital self-amputation induced by psychiatric disorder. After treatment, at 27 years old, he desired surgery for penile reconstruction. The third patient had partial androgen insensitivity syndrome (PAIS) with a micropenis and at 23 years old had TCM procedure.
The patients were placed in the lithotomy position with a perineal incision in the midline. A subperiosteal incision was made and the corpora cavernosa were detached from the pubic arch and the ischial rami. The periosteum and the neurovascular bundles were preserved. Subsequently the corpora cavernosa was mobilized upward and the periosteum that was left attached to them was sutured to the pubis.
Results: At twenty-four, nine, and six months, respectively, in the follow-up process, all patients expressed satisfaction with the final cosmetic appearance, penile length, and erectile function.
Conclusion: TCM may prove to be an alternative for patients with a functional disturbance because of small penile length, though a higher number of cases and a more extended follow-up are needed to draw a more definitive conclusion.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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The paradox of erectile dysfunction data after radical prostatectomy

Tomás Bernardo Costa Moretti [1, 2], Leonardo Oliveira Reis [1, 2]

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To the editor,

Who have never been approached in peer-reviewed journals or conference panel discussions on post-prostatectomy erectile dysfunction (PPED) with following questions: "Which assessment to apply? Has it been validated for a specific language? Self-applied or performed by another professional? Does it involve quality of life assessment and partner satisfaction?".

These heterogeneities might limit more accurate comparisons of PPED rates among the three main techniques: open (ORP), laparoscopic (LRP) and robot-assisted radical prostatectomies (RARP) (1). Knowing the existence of a multifactorial influence on PPED and the great discrepancy among the studies, systematic reviews (SR) on this subject are still criticized for not being able to eliminate such allocation biases (2).

Although 14 types of review studies are described, all are monitored by a concept of sample homogeneity and evidence hyperfiltration to avoid spurious comparisons. However, the era of large databases and infinite amount of information has brought the need to analyze heterogeneous population data from the real world (3).

From this concept, a methodology developed by our study group, called Reverse Systematic Review (RSR) was born. In short, we started with the greatest evidence on a subject, the SR, and collected all the data found in the primary studies in order to generate a heterogeneous enough population-based database to bring together different scenarios where a surgical technique evidence was developed; in this case, radical prostatectomy (RP) (3, 4).

Thus, we applied RSR to understand how the main ED criteria were used throughout the natural history of RP techniques in order to allow a critical analysis of the literature. Through a systematic search carried out in December 2020, in 8 databases (PubMed, Web of Science, Cochrane Library, Embase, ProQuest, CINAHL, BVS/Bireme and Scopus), we selected 80 SR studies on radical prostatectomy (ORP, LRP and RARP) in a period between 2000/01/01 and 2020/12/05. When analyzing all the primary studies used in these SR, we found a total of 406 cohorts (nc= number of cohorts) that evaluated PPED using two most cited criteria: "Erection Sufficient for Intercourse" (ESI) and "Sexual Health Inventory for Men" (SHIM).

Among 406 cohorts corresponding to 118,994 patients (np= number of patients), 305 (75.1%) used the ESI and 101 (24.9%) used the SHIM. Among the group that used SHIM score, we subdivided it into categories regarding the degree of erectile dysfunction: moderate ED [SHIM 8-11] (nc=4; 1.0%); mild to moderate ED [SHIM 12-16] (nc=28; 6.9%); mild ED [SHIM 17-21] (nc=59; 14.5%) and no ED [SHIM 22-25] (nc=10; 2.5%).

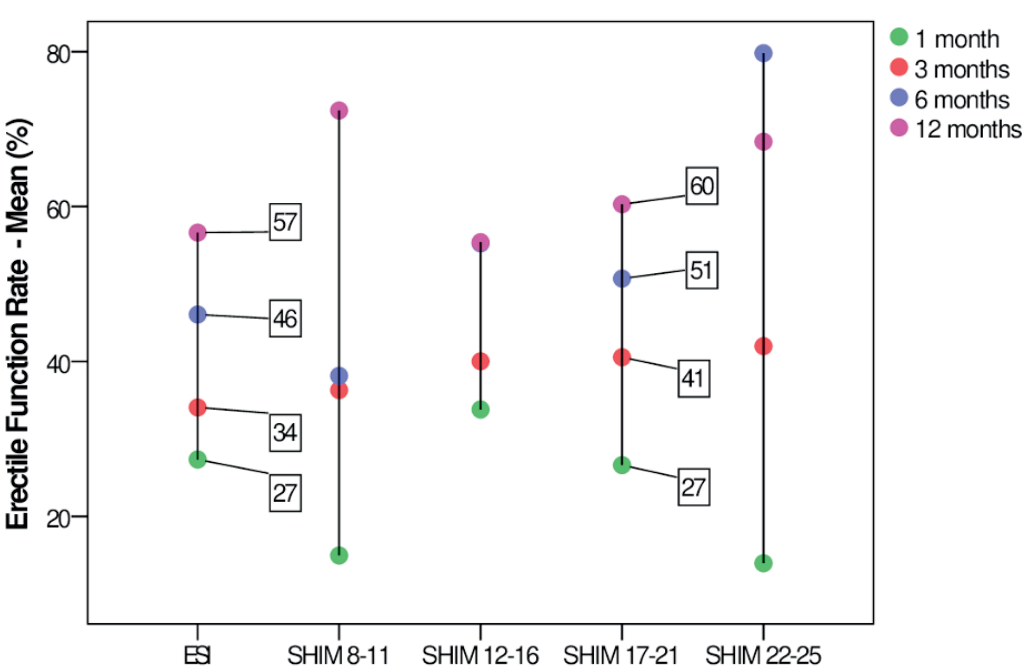
The overall rate of sexual potency regardless of the criterion used was 25.5% (np=14,238; SE= 0.12) at 1 month, 33.6% (np =33,416; SE=0.09) at 3 months, 46.6% (np=41,936; SE= 0.09) at 6 months and 53.3% (np =78,089; SE=0.07) at 12 months.

A graphical representation of the mean values found in these studies was performed for each analysis period after surgery (1, 3, 6 and 12 months) according to the classification criteria listed above (Figure-1). In the graph, it is noted that the two lines that present a proportional distribution of the points are from the ESI and the SHIM 17-21, demonstrating that the results of these two assessments are closer and corresponding. The two most commonly used criteria reflect the same assessment intent to measure an "acceptable" degree of PPED.

Despite the ESI criterion having presented worse results when compared to the other criteria, it was the most used by the authors in 20 years of analysis. This demonstrates how the difficulty of application, validation and reproducibility of scores at an international level can influence scientists' choices throughout RP natural history. Obviously, a field is not just influenced by science, but by the lack of it, and the acceptance of less rigorous and non-standard criteria by leading researchers might determine the available evidence, which creates a precedent for the scientific community, endorsing the use of a much-criticized evaluation criteria of sexual function.

This is the capacity that scientific influencers as a small group of prolific researchers on the issue have in the rest of the scientific community, which uses Cartesian arguments to criticize the works on erectile dysfunction and the lack of standardization of studies, but in practice applies the most comfortable and simple ED criterion. Interestingly, according to our methodology, different criteria might overlap.

Figure 1 - Erectile function recovery rates over time (colored dots) stratified by different definition criteria



After 20 years of coexistence between the three radical prostatectomy techniques (ORP, LRP and RARP) and much discussion, including among others (5) the best ED criteria to use, one sentence can summarize the state of art: "In practice, the theory is different".

The Author

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Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
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a) **DO NOT** embed the images in the text; save them as a separate file
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Papers published in periodicals:

▪ Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

▪ Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

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

Chapters in Books:

▪ Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

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The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

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- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
- A corresponding author with complete address, telephone, Fax, and E-mail are provided.
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- A list of abbreviations is provided.