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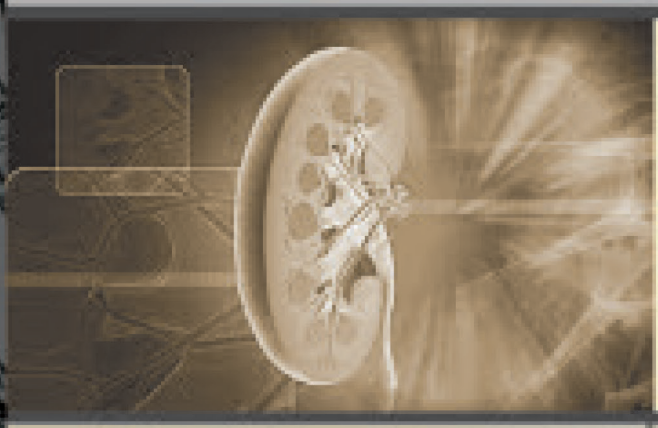

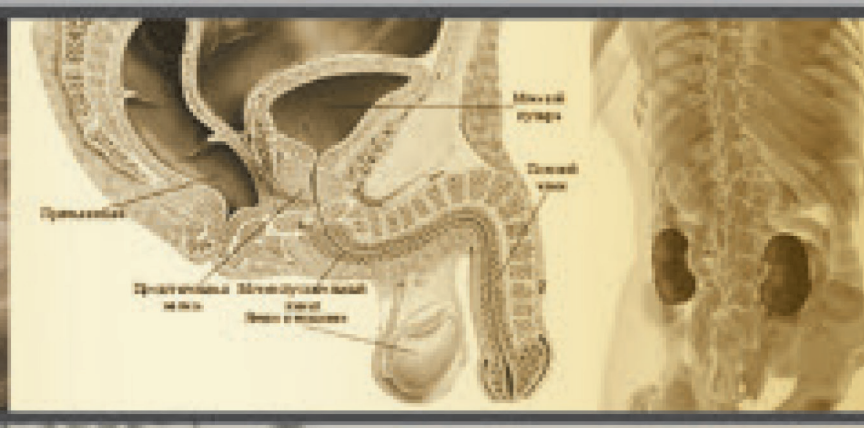

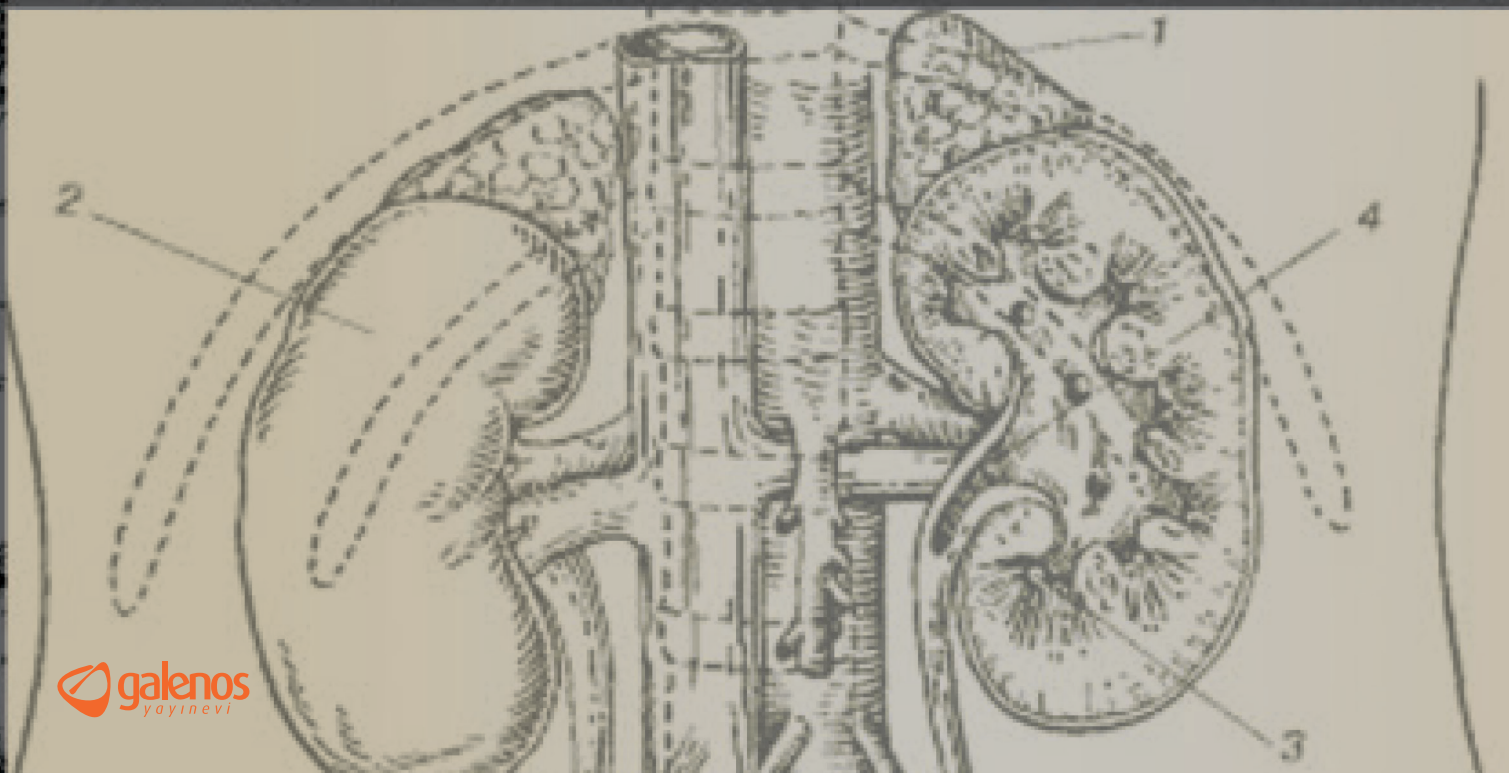

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The Journal of Urological Surgery accepts invited review articles, research articles, brief reports, case reports, letters to the editor, and images that are relevant to the scope of urology, on the condition that they have not been previously published elsewhere. Basic science manuscripts, such as randomized, cohort, cross-sectional, and case control studies, are given preference. All manuscripts are subject to editorial revision to ensure they conform to the style adopted by the journal. There is a single blind kind of reviewing system.

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Manuscripts should be prepared according to ICMJE guidelines (http://www.icmje.org/).

Original manuscripts require a structured abstract. Label each section of the structured abstract with the appropriate subheading (Objective, Materials and Methods, Results, and Conclusion). Case reports require short unstructured abstracts. Letters to the editor do not require an abstract. Research or project support should be acknowledged as a footnote on the title page.

Technical and other assistance should be provided on the title page.

Title Page

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Materials and Methods: Important methods should be written respectively.

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Results: Important findings and results should be provided here.

Conclusion: The study's new and important findings should be highlighted and interpreted.

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After keywords in original research articles there must be a paragraph defining "What is known on the subject and what does the study add".

Original Research

Abstract length: Not to exceed 250 words. "What is known on the subject and what dos the study add" not exceed 100 words.

Article length: Not to exceed 3000 words.

Original researches should have the following sections:

Introduction: The introduction should include an overview of the relevant literature presented in summary form (one page), and whatever remains interesting, unique, problematic, relevant, or unknown about the topic must be specified. The introduction should conclude with the rationale for the study, its design, and its objective(s).

Materials and Methods: Clearly describe the selection of observational or experimental participants, such as patients, laboratory animals, and controls, including inclusion and exclusion criteria and a description of the source population. Identify the methods and procedures in sufficient detail to allow other researchers to reproduce your results. Provide references to established methods (including statistical methods), provide references to brief modified methods, and provide the rationale for using them and an evaluation of their limitations. Identify all drugs and chemicals used, including generic names, doses, and routes of administration. The section should include only information that was available at the time the plan or protocol for the study was devised on STROBE (http://www.strobe-statement.org/).

Statistics: Describe the statistical methods used in enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Statistically important data should be given in the text, tables and figures. Provide details about randomization, describe treatment complications, provide the number of observations, and specify all computer programs used.

Results: Present your results in logical sequence in the text, tables, and figures. Do not present all the data provided in the tables and/or figures in the text; emphasize and/or summarize only important findings, results, and observations in the text. For clinical studies provide the number of samples, cases, and controls included in the study. Discrepancies between the planned number and obtained number of participants should be explained. Comparisons, and statistically important values (i.e. p value and confidence interval) should be provided.

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References

Cite references in the text, tables, and figures with numbers in parentheses. Number references consecutively according to the order in which they first appear in the text. Journal titles should be abbreviated according to the style used in Index Medicus (consult List of Journals Indexed in Index Medicus). Include among the references any paper accepted, but not yet published, designating the journal and followed by, in press. Authors are solely responsible for the accuracy of all references.

Examples of References:

1. List All Authors

Ghoneim IA, Miocinovic R, Stephenson AJ, Garcia JA, Gong MC, Campbell SC, Hansel DE, Fergany AF. Neoadjuvant systemic therapy or early cystectomy? Singlecenter analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. Urology 2011;77:867-870.

2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012, pp 1257-1323.

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5. Abstract

Nguyen CT, Fu AZ, Gilligan TD, Kattan MW, Wells BJ, Klein EA. Decision analysis model for clinical stage I nonseminomatous germ cell testicular cancer. J Urol 2008;179:495a (abstract).

6. Letter to the Editor

Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

Fine MS, Smith KM, Shrivastava D, Cook ME, Shukla AR. Posterior Urethral Valve Treatments and Outcomes in Children Receiving Kidney Transplants. J Urol 2011;185(Suppl):2491-2496.

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Abstract: An unstructured abstract that summarizes the case.

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Authors can submit for consideration an illustration and photos that is interesting, instructive, and visually attractive, along with a few lines of explanatory text and references. Images in Urology can include no more than 500 words of text, 5 references, and 3 figure or table. No abstract, discussion or conclusion are required but please include a brief title.

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Article length: Not to exceed 500 words.

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How I do?

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Article length: Not to exceed 1500 word.

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Can YouTube Video on Urological Problems Be Used As An Additional Resource in Telemedicine During the COVID-19 Pandemic?

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What's known on the subject? and What does the study add?

Although establishing an international consensus about management of diagnosis and treatment of urological diseases during coronavirus disease-2019 (COVID-19) pandemic among urologists has been attempted, another important step is for patients to be informed about what they should do according to these algorithms-which symptoms are urgent versus cases where there is no need to consult a physician. Telemedicine method is not enough to reach and inform all urology patients. In this study, we aimed to evaluate whether the published YouTube videos are compatible with the current literature and whether they may be considered as a reliable additional information source for urological recommendations during COVID-19 period.

Abstract

Objective: Various recommendations are being offered in order of priority in the diagnosis and treatment of urological diseases during the coronavirus disease 2019 (COVID-19) period. Since it may not be possible to provide information to all patients through telemedicine, additional methods are needed to reach all patients. This study aimed to determine the reliability and quality of YouTube videos that provide information on urological disorders during the COVID-19 period. Another aim was to assess the most shared and most viewed videos on urological disorders on YouTube and their usability as an additional resource in telemedicine during the pandemic.

Materials and Methods: From 17 February 2020, to 31 July 2020, the following keywords were used to search videos on YouTube: "covid urology", "covid andrology", "covid fertility", "covid male infertility", "covid prostate", "covid bladder", "covid kidney", "covid renal", "covid testis", "covid cancer", "covid coitus", "covid sex", "covid sperm" and "covid erectile"; "coronavirus" was also used instead of "covid". In total, 232 videos were evaluated by two urologists according to video characteristics. The number of total views, views per day, likes, dislikes, comments, video length, date of video upload and duration on YouTube was recorded. Finally, a total of 136 relevant English videos were included in the study. A 5-point modified DISCERN tool was used to assess reliability, whereas a 5-point Global Quality score (GQS) was used to evaluate quality. Cohen's kappa score was used to determine inter-rater agreement, while the intraclass correlation coefficient was used to evaluate inter-observer reliability.

Results: All videos had a high DISCERN score [4, interquartile range (IQR) (3-5)] and GQS [5, IQR (4-5)] in general. Moreover, 20 (14.7%) videos containing information about "sexual life" and "effects of COVID-19 on sperm" were described as debated. Videos uploaded by "universities/professional organisations/non-profit physician/physician groups" had higher scores ($p<0.001$). However, their rates of "number of views per day" ($p=0.036$) and "likes" ($p<0.001$) were lower. The majority of videos related to urology (63.9%) included conversations about andrological disorders. The median number of total views and number of views per day were also highest for videos related to andrology.

Conclusion: Although andrological disorders are classified as a non-essential issue and andrological consultations are postponed during the COVID-19 period, the results show that the rate of YouTube videos related to andrology is even higher than uro-oncological diseases during this period. Therefore, it is important to share accurate and reliable information in this field. Our analysis shows that informative, easy-to-understand YouTube videos uploaded by "universities/professional organisations/non-profit physicians/physician groups" can be used as an additional method to telemedicine, especially for andrological disorders that do not require follow-up.

Keywords: COVID-19, SARS-CoV-2, telemedicine, urology, YouTube

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Introduction

Coronavirus disease-2019 (COVID-19), which is caused by severe acute respiratory syndrome-coronavirus-2, became evident following an increase in the number of pneumonia cases in China in December 2019 and later announced as a pandemic by the World Health Organization on 11 March 2020, as a result of its global rapid spread (1). All outpatient activities and surgeries except for emergency and oncological cases have been postponed or cancelled. Even oncological cases have been classified as low and high priority. Since the extent and duration of the pandemic are unpredictable, rescheduling is not possible during this period (2).

Urology, like all other fields, has been affected by this pandemic. Various strategies and recommendations are offered in a stepwise approach in order of priority for the diagnosis and treatment of urological diseases (2). Although establishing an international consensus among urologists has been attempted, another important step is to inform patients on what they should do according to these algorithms: which symptoms are urgent versus which cases do not require consultation to a physician. It is often possible to reach and inform patients with urological problems on follow-up by teleconsultation or video-consultation system (3,4). However, it is also important to inform people who are not on a urological follow-up programme about what they should do during the COVID-19 period when they encounter various urological symptoms.

During quarantine, the easiest and most practical source of information on any topic is the Internet. Since YouTube is an open-access video-sharing website, it can disseminate information better than other social media tools (5). We have come across YouTube videos that highlight tasks that should be done during the COVID-19 period regarding urological diseases. Most of the videos are created by specialists in urology and by other healthcare providers. In this study, we aimed to evaluate which urological diseases people are curious about and want to learn during the COVID-19 period. By making a detailed analysis of YouTube videos related to what is needed for urological diseases during the COVID-19 period, we tried to identify the most shared and most viewed videos about urological pathologies on YouTube during the COVID-19 period. Another aim was to evaluate whether contents of YouTube videos are compatible with the current literature and whether they may be considered a reliable information source of urological recommendations during the COVID-19 period.

Materials and Methods

Data Collection

The following keywords were used to search on YouTube (http://www.youtube.com): "covid urology", "covid andrology", "covid fertility", "covid male infertility", "covid prostate", "covid bladder", "covid kidney", "covid renal", "covid testis", "covid cancer", "covid coitus", "covid sex", "covid sperm" and "covid erectile". The same search was performed using the term "coronavirus" instead of "covid". The videos were sorted according to relevance using a YouTube filtering system. We found 232 videos related to "covid" and "urological conditions" between 17 February 2020 and 31 July 2020, and evaluated them for suitability for our study. All videos were saved in a playlist for review on 31 July 2020, since search results can vary every day on YouTube. Two independent urologists with board certification (Fellow of the European Board of Urology) (I.S. and N.B.) viewed and analysed the videos. Both urologists were blinded to each other's scores on video assessments.

Inclusion Criteria for Videos

The main subjects of our study are lay people who are not familiar with medical concepts and terms. These people need videos that provide simple, basic information in an easily understandable language on what they should do when they experience urological symptoms or disease during the COVID-19 period. For this purpose, English videos having accurate, comprehensive and easily understandable information for lay people rather than containing medical terms and scientific data were included in the study.

Exclusion Criteria for Videos

In total, 61 videos mentioned recommendations of the European Urology Association (EAU) guidelines and American Urological Association (AUA) guidelines for urologists using medical concepts and scientific terms. Since they were not suitable for the study purpose, we described them as "irrelevant", and they were excluded from the study. Non-English videos and videos without audio or visuals were also removed from the study. These data collection criteria are similar to previous studies evaluating YouTube videos on different topics (6,7).

Evaluation of Video Characteristics

For each YouTube video, the number of total views, views per day, likes, dislikes, comments, video length, date of video upload and duration on YouTube were recorded. The accuracy of the information in the videos was evaluated according to the EAU and AUA guidelines (8-10). When evaluating videos on infertility, the American Society for Reproductive Medicine guidelines and the European Society of Human Reproduction and Embryology guidelines were considered, in addition to the two aforementioned guidelines (11,12).

Videos containing scientific, accurate and comprehensive information on the diagnosis and treatment of urological diseases during the COVID-19 period that have been agreed upon according to the aforementioned guidelines were

defined as useful information. Since there are some topics with controversial ideas about diagnosis and treatment that have not been agreed on, videos that did not fully convey controversial or uncertain issues and did not make a balanced and neutral assessment were defined as debated information (e.g. How to lead a reliable sexual life during the COVID-19 period?) Many videos mentioned guidelines of the "Centers for Disease Control and Prevention" to inform about whether COVID-19 causes sexually transmitted disease after intercourse (13), but some videos did not. COVID-19 does not cause sexually transmitted disease, but physical contact during intercourse may cause COVID-19 transmission. Therefore, having sex with your spouse or the same partner who is asymptomatic is safer than having sex with a foreign partner. However, no current evidence-based guidelines are available. The classification made according to the source of the video was as follows: universities/professional organisations/non-profit physicians/physicians (source 1), stand-alone health information websites (source 2), medical advertisements/for-profit organisations (source 3) and individual users (source 4). Other classifications were made according to the target audience (female/male/both genders) and the speaker in the video (physician/non-physician health provider/individual in the video/external voice).

Scoring System for Video Evaluation

The original DISCERN tool is a validated tool comprising 16 questions. It evaluates the quality of written health information regarding treatment options (14). It includes questions evaluating the reliability of written documents, such as information leaflets, discussing treatment options. The main items of this tool are useful to evaluate the aims and clarity of written information sources and whether the written documents are sufficient to access support for shared decision-making (15).

Since the DISCERN tool was created long before online YouTube videos became popular, one of the most recent publications stated that the items of the original DISCERN tool are insufficient to evaluate videos (15). By contrast, many studies on identifying educationally useful YouTube videos have pointed out that the modified DISCERN tool and Global Quality score (GQS) provide a more suitable assessment of visual, vocal and verbal information, scientific accuracy of content and clarity of the given massage (6,7,16).

A 5-point modified DISCERN tool was used to evaluate the video reliability and quality of health information available to patients as in previous studies on YouTube videos (Table 1) (6,7). GQS was also used in our study. This 5-point scale is used to evaluate the accessibility, quality and overall flow of information within videos from website resources. A score of "1" indicates "poor quality", and a score of "5" indicates "excellent quality" (Table 1) (6,7). After each urologist evaluated and scored the videos, Cohen's kappa score was used to determine inter-rater agreement, while the intra-class correlation coefficient was used to evaluate inter-observer reliability.

Statistical Analysis

During the analysis of video characteristics and categorisation of video contents, each data related to videos were assessed as independent variables. The normality of these variables was evaluated using Shapiro-Wilk test, Kolmogorov-Smirnov test, histogram and Q-Q plots. Levene's test was used to assess variance homogeneity. Variables not showing normal distribution are expressed as median (25^{th}-75^{th} percentile). Categorical variables are shown as number and per cent (n, %). The Mann-Whitney U test was used to analyse variables with non-normal distribution between the two groups. All analyses were made using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA) software package; $p<0.05$ was considered significant.

Results

General Information on Video Characteristics

After evaluating a total of 232 videos related to "COVID" and various "urological diseases" using the search keywords on YouTube, 136 videos were selected according to the inclusion criteria. The flowchart of the study design is shown in Figure 1. The median duration from the date of upload in YouTube, between 17 February 2020 and 31 July 2020, was 47 (min-max, 3-166) days.

Evaluation of Videos According to the Inter-rater Agreement and Intra-class Correlation

The level of inter-rater agreement in terms of the usefulness assessment of videos was positive (kappa coefficient =0.903). The intra-class correlation coefficient was calculated as 0.941 (95% confidence interval 0.834-0.989) for the DISCERN reliability score and 0.961 (95% confidence interval 0.890-0.991) for GQS. The results show a high inter-rater reliability.

Classification of YouTube Videos According to Their Reliability

Controversial ideas still exist on sexual life during the COVID-19 period. A total of 20 (14.7%) videos that did not talk about contradicting comments on topics described in a balanced and neutral way were evaluated as "debated". Of these videos, four focused on the effects of COVID-19 on sperm and 16 were about sexual intercourse during the COVID-19 period. Content of videos related to all other topics was evaluated as "useful information".

Assessment of Video Characteristics, Sources of Video Upload and Speakers

Table 2 shows the characteristics of the videos evaluated. Although all videos had high DISCERN score and GQS in general,

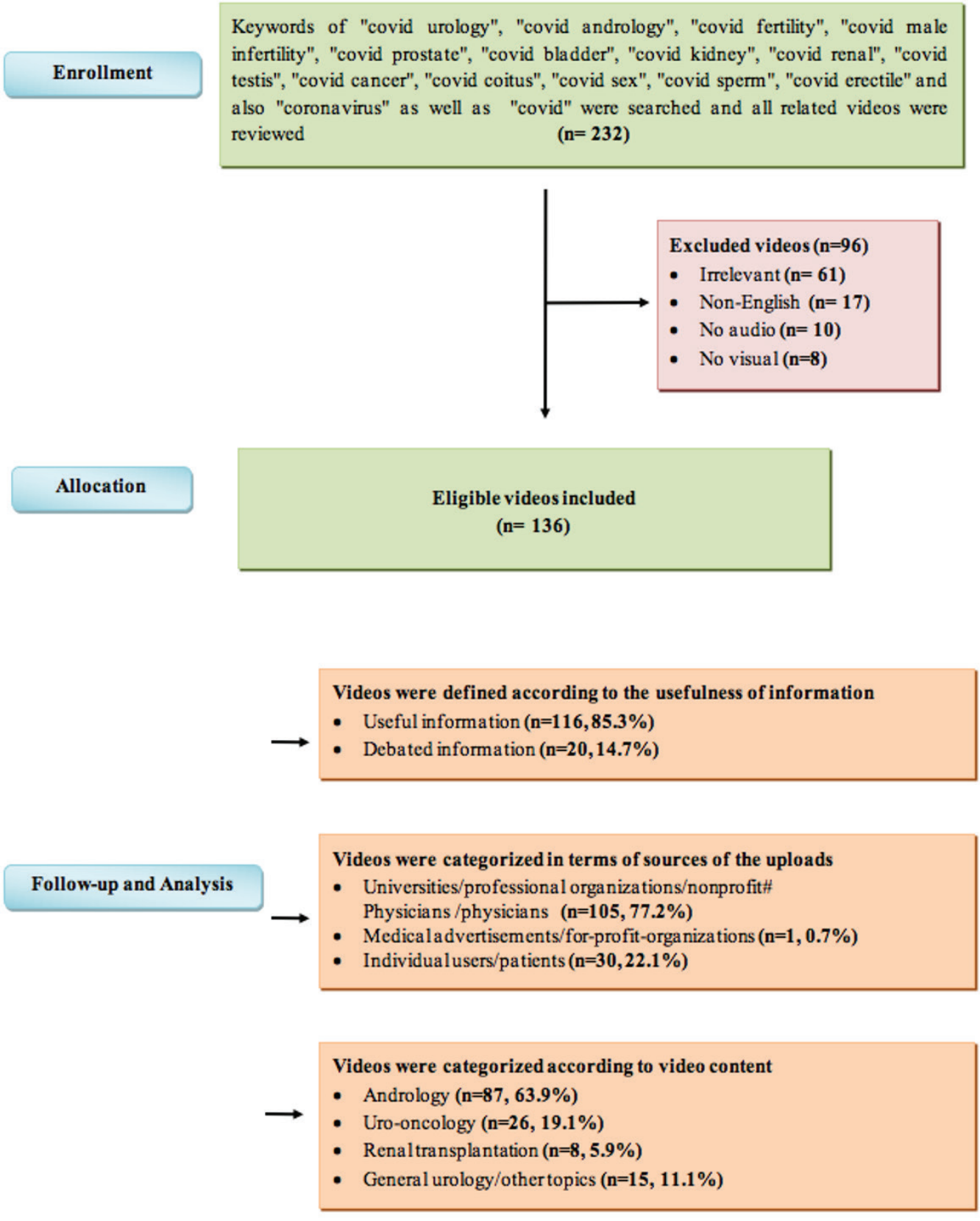

Figure 1. Flowchart of the study design

Table 1. Evaluation tools for reliability and quality of YouTube videos that give information on urological disorders during the COVID-19 period
DISCERN Reliability Tool (1 point per question if answered yes)
1. Are the explanations given in the video clear and understandable?
2. Are useful reference sources given? (publication cited, from valid studies)
3. Is the information in the video balanced and neutral?
4. Are additional sources of information given from which the viewer can benefit?
5. Does the video evaluate areas that are controversial or uncertain?
Global Quality scale
1. Poor quality, poor flow, most information missing and not helpful for patients
2. Generally poor and some information given but of limited use to patients
3. Moderate quality and some important information is adequately discussed
4. Good quality, good flow, most relevant information is covered and useful for patients
5. Excellent quality, excellent flow and very useful for patients
COVID-19: Coronavirus disease-2019

videos uploaded by individual users and medical advertisement/for-profit companies (22.8%) had lower scores. However, the rates of "the number of views per day" and "likes" were higher in the latter group (Table 3). Most of the sources of videos were universities/professional organisations/non-profit physician/physician groups (77.2%), while the physicians and non-physician health providers (83.8%) made up the majority of the speakers (Table 2). Table 4 summarises the characteristics of YouTube videos.

Assessment of Video Contents Related to Different Urological Disorders

When the video content was categorised as andrology, uro-oncology, renal transplantation and general urology/other topics, videos were distributed as 63.9%, 19.1%, 5.9% and 11.1%, respectively. The median number of total views and numbers of views per day were highest for videos related to andrology. The lowest numbers were observed for videos related to uro-oncology (Figure 2).

Discussion

All outpatient activities, except emergency cases, have been suspended and surgical activities, except for emergency and/or oncological interventions, have been limited. How long this unexpected pandemic will continue and its socioeconomic and psychological burden will be alleviated is unknown. In some

Table 2. Analysis of video characteristics according to their usefulness	
Parameters	n=136
Number of total views	286.50 (82-1457.50)
Video length (second)	296.50 (141.50-923)
Duration on YouTube (day)	47 (32-57.75)
Number of views per day	8.20 (2.14-31.56)
Likes	5 (1-25)
Dislikes	0 (0-1)
Comments	1 (0-5)
DISCERN score	4 (3-5)
Global Quality Score	5 (4-5)
Video content, n (%)	
-Infertility	57 (41.9)
-Sexual life	26 (19.1)
-Prostate cancer	15 (11.1)
-Telemedicine in urology and general urology	10 (7.4)
-Bladder cancer	8 (5.9)
-Renal transplantation	8 (5.9)
-Effects of COVID-19 on sperm	4 (2.9)
-Renal cancer	3 (2.2)
-Effects of COVID-19 on testis	2 (1.5)
-Neurogenic bladder	1 (0.7)
-Benign renal diseases	1 (0.7)
-Effects of COVID-19 on kidney physiology	1 (0.7)
Sources of uploads, n (%)	
-Universities/professional organisations/non-profit physician/physician groups	105 (77.2)
-Stand-alone health information websites	0 (0.0)
-Medical advertisement/for-profit companies	1 (0.7)
-Individual users	30 (22.1)
Speakers, n (%)	
-Physician	102 (75.0)
-Non-physician healthcare provider	12 (8.8)
-Individual in the video	15 (11.1)
-External voice	7 (5.1)
Target audience, n (%)	
-Male	5 (3.7)
-Both male and female	131 (96.3)
Usefulness of source, n (%)	
- Useful information	116 (85.3)
- Debated information	20 (14.7)
Non-normally distributed data are expressed as "median (25^{th}–75^{th} percentile)" Categorical data are expressed as "number (percent)", COVID-19: Coronavirus disease -2019	

countries, teams of national experts discuss and try to reorganise possible strategies for patients with urological disorders (3,17).

This pandemic has made "telemedicine" more prominent as a pragmatic approach to reduce the risk of disease transmission. A virtual clinic is formed between physicians and patients so that problems not needing a traditional face-to-face consultation may be evaluated while avoiding a hospital visit (17,18). Various electronic communication devices such as telephone calls, video conferences and online email consultations can be developed for telemedicine (19-21). In this way, telemedicine, which is a very pragmatic option, especially for infectious diseases and public health emergencies, is also on the agenda for urology practice (19).

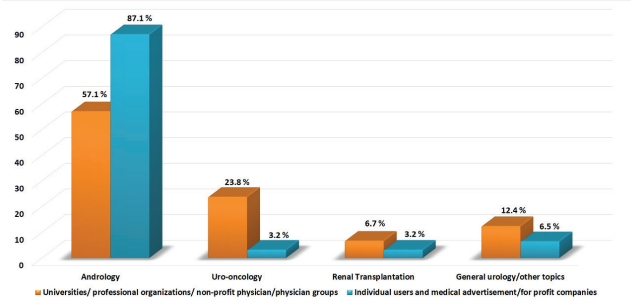

Figure 2. Distribution of video contents according to sources of uploads

During this period, Luciani et al. (19) observed that about half of the patients had to cancel their doctor's appointment. The rate of face-to-face visits dramatically declined from 63% to 9% within the first 4 weeks of the pandemic.

Moreover, the majority (94.5%) of patients with urology diseases are at risk for a severe course of COVID-19 because of their advanced age and comorbidities, so social isolation is

Table 3. Analysis of video characteristics according to sources of uploads

Parameter	Universities/professional organisations/non-profit physician/physician groups n=105 (77.2%)	Individual users and medical advertisement/for-profit companies n=31 (22.8%)	p-value
Number of total views	253 (76-1.022)	705 (107-4.701)	† 0.054
Video length (s)	278 (137-939)	411 (198-731)	† 0.575
Duration on YouTube (day)	46 (30.5-57)	53 (42-58)	† 0.286
Number of views per day	7.19 (1.85-28.08)	15.66 (4.60-100.62)	† 0.036*
Likes	3 (1-15)	20 (5-99)	† <0.001*
Dislikes	0 (0-1)	1 (0-7)	† 0.013*
Comments	0 (0-3)	4 (1-20)	† <0.001*
DISCERN score	4 (3-5)	3 (2-4)	† <0.001*
Global Quality score	5 (4-5)	4 (3-5)	† <0.001*
Video content, n (%)			
- Andrology	60 (57.1)	27 (87.1)	‡ 0.019*
- Uro-oncology	25 (23.8)	1 (3.2)	
- Renal transplantation	7 (6.7)	1 (3.2)	
- General urology/other topics	13 (12.4)	2 (6.5)	
Speakers, n (%)			
-Physician	90 (85.7)	12 (38.7)	‡ <0.001*
-Non-physician healthcare provider	8 (7.6)	4 (12.9)	
-Individual in the video	2 (1.9)	13 (41.9)	
-External voice	5 (4.8)	2 (6.5)	
Target audience, n (%)			
-Male	0 (0.0)	5 (16.1)	¶ <0.001*
-Both male and female	105 (100.0)	26 (83.9)	
Usefulness of source, n (%)			
- Useful information	101 (96.2)	15 (48.4)	¶ <0.001*
- Debated information	4 (3.8)	16 (51.6)	

*p<0.05; asterisk (*) indicates significance
†Mann-Whitney U test data are expressed as "median (25^{th}-75^{th} percentile)"
‡Chi-square test Fisher's exact test Data are expressed as 'number (percent)

Table 4. Appendix summarising the characteristics of YouTube videos

Video no	Video title	URL	Video length (s)	Date of upload	Duration on YouTube (day)	Number of total views	Number of views per day	Number of likes	Number of dislikes	Number of comments	The modified DISCERN scores	Global quality Score
1	How to have safe sex during the quarantine	https://youtu.be/sBXZCZy3E-0	320	24.03.2020	55	341809	6214.7	8200	270	656	3	2
2	Love in the time of coronavirus (washing your hands is sexy now!)	https://youtu.be/6_tsEVOf7r0	133	12.03.2020	67	262425	3916.79	2800	98	118	1	1
3	Stockpiling semen to fight the coronavirus	https://youtu.be/Q7RQ1ZYvCtg	298	13.03.2020	66	68453	1037.16	273	135	173	1	1
4	Sex during coronavirus?|NBCLX	https://youtu.be/cDA9ty2aADQ	244	27.03.2020	52	66222	1273.5	152	21	40	4	4
5	Dr. Oz says regular sex during coronavirus quarantine is good|TMZ TV	https://youtu.be/ClEWmyZFtyk	106	18.03.2020	61	59218	970.78	715	48	167	2	3
6	Trying to get pregnant during coronavirus [TTC MUST WATCH]	https://youtu.be/sZvZK3Bn1zA	1380	17.03.2020	62	37054	597.64	533	13	168	5	5
7		This video is no longer available because the YouTube account associated with this video has been terminated	133	17.03.2020	62	31588	509.48	471	22	125	2	3
8	Coronavirus means some couples may never conceive as COVID-19 puts IVF on hold|ITV News	https://youtu.be/E7KialUwIbE	195	28.03.2020	51	26071	511.19	126	74	0	3	5
9	Coronavirus outbreak: Dating and sex in the time of a pandemic - Wait there's more podcast	https://youtu.be/3VRV3hqsUCM	1420	24.03.2020	55	19416	353.01	149	58	92	3	4
10	Dr. Oz talks possible treatments and drugs for coronavirus, sex during quarantine and more	https://youtu.be/Bz_QEeeAvIw	246	19.03.2020	60	17786	296.43	159	13	26	3	4
11	Couples having sex [DURING THE QUARANTINE SEXY TIMES]!	https://youtu.be/_eA8sr_NdQo	450	26.03.2020	53	13155	248.2	40	7	1	3	4
12		This video is no longer available because the YouTube account associated with this video has been terminated	274	19.03.2020	60	12913	215.21	49	4	8	3	4
13	Your coronavirus questions answered: What about IVF treatments and chemotherapy?|TODAY	https://youtu.be/VsTr6zroLsI	295	19.03.2020	60	12790	213.16	78	5	21	5	5
14	Is coronavirus sexually transmitted? Experts respond	https://youtu.be/Fzwdu-D5BOw	558	22.03.2020	57	12277	215.38	40	1	7	4	5

15	COVID-19: What transplant patients need to know	https://youtu.be/IXMbKt1ZcT4	272	13.03.2020	66	9950	150.75	92	6	0	4	5
16	COVID-19 and kidney disease	https://youtu.be/ELAPITCMF30	191	12.03.2020	67	7369	109.98	61	10	9	3	4
17	COVID 19, what to ask your fertility doctor	https://youtu.be/RuaSYpUPt-Q	1175	25.03.2020	54	6058	112.18	152	11	20	4	5
18	Dr. Oz suggests couples 'have sex' amidst coronavirus chaos	https://youtu.be/ht9LqsB_Nmc	83	20.03.2020	59	5937	100.62	99	8	20	2	3
19	NY Department of health releases COVID-19 sex guide	https://youtu.be/Y35pukvFNJo	152	26.03.2020	53	5519	104.13	30	3	7	5	5
20	Sex cannot transmit virus, but one can be infected because of proximity – Masika	https://youtu.be/KeS6iMGQfFA	1140	20.03.2020	59	5410	91.69	17	1	3	3	4
21		This video is no longer available because the YouTube account associated with this video has been terminated	475	26.03.2020	53	4701	88.69	382	3	89	1	2
22	Coronavirus and getting pregnant|A fertility doctor talks about COVID-19	https://youtu.be/D8jsKnyH0O0	731	13.03.2020	66	3482	52.75	36	1	13	5	5
23		This video is no longer available because the YouTube account associated with this video has been terminated	123	17.02.2020	90	3375	37.5	39	4	28	3	4
24	Practical advice FOR prostate cancer PATIENTS for weathering changes caused by COVID-19	https://youtu.be/v4JyRwNYVZU	1104	27.03.2020	52	2937	56.48	15	0	1	5	5
25	IVF decisions in the time of COVID-19 (Coronavirus): Advice for fertility patients	https://youtu.be/1nD_SVpHHs8	590	23.03.2020	56	2493	44.51	42	2	3	4	5
26	Tips on how to not destroy your relationship while in quarantine for coronavirus|New York Post	https://youtu.be/ysDdWVu6c5A	120	27.03.2020	52	2329	44.78	38	3	10	3	4
27	Male infertility & COVID-19 Infection, what do we know!	https://youtu.be/w9u-N8eGU0k	2545	8.04.2020	44	2185	49.65	110	2	3	5	5
28	Coronavirus: Men infected with COVID-19 may experience testicular damage	https://youtu.be/cun9TJNiOCc	105	14.03.2020	65	2073	31.89	19	5	25	4	4
29	COVID-19: Dr. Michael Braun discusses the virus' impact on patients with renal (kidney) disease	https://youtu.be/j4V95QM87Jw	155	13.03.2020	66	1955	29.62	12	0	3	3	4

30	Sex, sexuality and COVID-19. An open conversation	https://youtu.be/ShH7qn3wx8Y	459	19.03.2020	58	1674	28.86	20	0	3	3	3
31	Telehealth during COVID-19	https://youtu.be/Kx09-tuXUuw	3603	30.03.2020	49	1645	33.57	15	1	6	5	5
32	COVID-19 and the kidney, why are we seeing so much kidney involvement?	https://youtu.be/capCRENmDMc	654	26.03.2020	53	1621	30.58	42	1	35	3	4
33	Coronavirus & fertility expert Q&A	https://youtu.be/ilv_mGDo7xo	509	24.03.2020	55	1574	28.61	19	2	6	5	5
34	Coronavirus causes male infertility: What they are not telling you	https://youtu.be/NjcO_pNedXE	171	29.02.2020	78	1477	18.93	25	0	6	4	4
35	What prostate cancer patients need to know about treatment during the COVID-19 pandemic	https://youtu.be/UkCfLF0tpag	779	16.04.2020	32	1399	43.71	3	0	1	5	5
36	IVF treatments put on hold amid coronavirus concerns	https://youtu.be/ujF9EuGWUwo	96	20.03.2020	59	1328	22.5	8	3	4	5	5
37	COVID-19 - Is it safe to conceive during the outbreak?	https://youtu.be/Z3W03HNE-go	268	4.04.2020	44	1318	29.95	18	0	2	4	5
38	What fertility patients should know about COVID-19 (Coronavirus)	https://youtu.be/svpKGG1Mfjk	356	23.03.2020	56	1299	23.19	17	2	6	4	5
39	How to continue your fertility journey during the COVID-19 crisis: 3 pieces of advice	https://youtu.be/raKGuRQ003Y	607	1.04.2020	47	1179	25.08	32	0	5	4	5
40	COVID-19 & your fertility	https://youtu.be/zqdZssWwkMg	1114	26.03.2020	54	865	16.01	0	0	0	5	5
41	How COVID-19 is affecting transplants	https://youtu.be/yQVEC6hVbkI	119	30.03.2020	49	653	13.32	12	0	2	5	5
42	ZERO update: COVID-19 & prostate cancer	https://youtu.be/RHkkNaxj2zY	167	13.03.2020	66	846	12.81	5	1	0	4	4
43	COVID-19: Impact on kidney disease and dialysis	https://youtu.be/ijqd4sol_IU	242	23.03.2020	56	439	7.83	11	0	0	4	5
44	COVID-19, fertility and pregnancy: Coronavirus updates from a fertility doctor	https://youtu.be/QOE4qScEOSk	948	1.04.2020	47	795	16.91	17	0	6	5	5
45	COVID-19|A urologist's perspective and plan	https://youtu.be/OfveW-0H7LY	374	19.03.2020	60	764	12.73	25	1	2	4	5
46	The responsibilities of an IVF centre during the COVID-19 pandemic: CHR explains the ASRM statement	https://youtu.be/j5rV8f_aLHg	707	1.04.2020	47	738	15.7	9	1	1	5	5
47	Coronavirus & fertility: fact vs fiction with Dr. Cindy Duke	https://youtu.be/oXoaPA9NmcY	2407	23.04.2020	25	732	29.28	27	0	0	5	5
48	Is having sex during COVID-19 outbreak safe? Know from the experts	https://youtu.be/XRY7-aHWkWc	138	4.04.2020	44	677	15.38	5	0	0	2	3
49	COVID-19 CANCELLED OUR IVF FROZEN TRANSFER // Coping with a cancelled IVF cycle due to Corona Virus	https://youtu.be/LPSmBF02DDg	768	3.04.2020	45	705	15.66	26	3	12	3	4

50	Sex + COVID 19	https://youtu.be/Zka6DCPYm1w	2484	31.03.2020	48	650	13.54	5	0	4	2	3
51	A sexual intimacy guide amid COVID-19 outbreak	https://youtu.be/-TF9IqtEeEU	283	20.03.2020	60	668	11.13	22	0	15	5	5
52	Update: fertility treatment during COVID-19 with Dr. William Schoolcraft	https://youtu.be/6bgmaWoGPqg	290	3.04.2020	46	696	15.13	11	0	0	5	5
53	How to SEX with COVID-19 around || Coronavirus can be sexually transmitted	https://youtu.be/CK-6r31XCX8	321	27.03.2020	53	541	10.2	4	0	0	5	5
54	COVID-19 puts fertility treatment, family's dreams on hold	https://youtu.be/LMeI0Ock18g	117	11.04.2020	26	699	26.88	3	0	0	3	4
55	Handling infertility treatments during the coronavirus pandemic	https://youtu.be/PSojdfFcEh4	136	24.03.2020	26	685	26.34	5	0	0	4	5
56	Semen retention|This is your last chance (COVID-19)	https://youtu.be/ePDU0_tfzjo	411	25.03.2020	55	455	8.27	26	3	11	2	2
57	Greater Boston Urology addresses COVID-19 pandemic	https://youtu.be/YBZDhfYI7VU	205	31.03.2020	49	430	8.77	4	0	0	4	4
58	How is COVID-19 affecting people with kidney failure and on the transplant waiting list?	https://youtu.be/_RIUt0hq8pQ	925	28.04.2020	51	417	8.17	5	1	0	4	4
59	Bladder cancer, BCG and COVID-19|Treatment vaccine update for patients and families	https://youtu.be/8R6UQtejVuw?list=PL6k8gHLg nM67FCo xlgRYQsvl E0vmudson	3107	24.04.2020	25	403	7.19	3	0	1	5	5
60	Semen retention|COVID-19 Your immune system NEEDS YOU	https://youtu.be/8KzLnH-bmxE	582	19.03.2020	61	386	6.32	44	0	6	2	2
61	Kidney transplants and COVID-19|National Kidney Foundation	https://youtu.be/HFA-BERo0a0	50	21.04.2020	28	416	14.85	5	0	1	4	4
62	Coronavirus (COVID-19) Impact on IVF and egg freezing process|RSMC	https://youtu.be/QYmXkXAnOvM	183	17.03.2020	63	361	5.73	4	1	3	4	5
63	Are kidney donors at greater risk for COVID-19?|National Kidney Foundation	https://youtu.be/XxADQT7W2yc	63	22.04.2020	27	321	11.88	3	0	1	3	4
64	Infertility & COVID-19 Session 2 /www.gbrclinic.com/+91-9940105555	https://youtu.be/cgJ2Xyo2EeI	2234	23.04.2020	26	293	11.26	3	0	0	3	4
65	Dr. Anindita Singh on fertility treatment plans during COVID-19 pandemic. Teleconsult@1800 313 5677	https://youtu.be/iMW4x8ZKGGQ	172	30.03.2020	50	297	5.94	11	0	0	3	4

66	Fertility treatments halted, delayed during COVID-19	https://youtu.be/OduwM0xttTg	122	15.04.2020	34	280	8.23	0	3	2	3	4
67	CHR's precautions against COVID-19 (coronavirus) infections	https://youtu.be/E4lAvKMAnUI	917	23.03.2020	57	270	4.73	8	0	5	5	5
68	Mark's April 2020 Update - Now COVID-19, too? - Mark's prostate cancer experience	https://youtu.be/IcjI88ja3Ag	391	13.04.2020	36	263	7.3	32	1	4	3	4
69	ICS - COVID 19 and management in neurogenic bladder	https://youtu.be/CbAWK1NRLZY	208	17.04.2020	32	264	8.25	2	0	0	5	5
70	Fertility treatment during COVID-19 with Dr. William Schoolcraft	https://youtu.be/TDX2OfTo4 m0	163	27.03.2020	53	253	4.77	0	0	0	4	4
71	Dr Ritu Hinduja - Advise for patients on fertility treatment during COVID-19 pandemic	https://youtu.be/_KcjkVmFMKg	121	28.03.2020	52	250	4.8	5	0	1	4	5
72	Ovarian stimulation during COVID- 19	https://youtu.be/SdDcDDSB0UY	95	6.04.2020	43	246	5.72	7	1	0	4	5
73	Fertility patients face challenges during COVID-19 pandemic	https://youtu.be/jJDqO_Uhhmw	106	10.04.2020	39	231	5.92	3	0	1	3	4
74	COVID-19 North East United States: What you should know about bladder cancer and COVID-19	https://youtu.be/Bk0TMKOkC1g	3385	9.04.2020	40	227	5.67	1	0	0	5	5
75	Telehealth urology visits and COVID-19 updates ACU	https://youtu.be/xWLN98azf2s	407	26.03.2020	54	214	3.96	12	0	4	5	5
76	Infertility treatment during COVID-19|Dr. Akriti Bharati|Vatsalya Natural IVF|Best IVF Clinic	https://youtu.be/barz3nR2VMg	216	24.04.2020	25	227	9.08	9	0	1	4	4
77	IVF & coronavirus: treatments suspended during pandemic	https://youtu.be/UXkXbl8b4hw	99	7.04.2020	42	201	4.78	3	0	1	4	5
78	COVID 19 and fertility treatment #IVFWEBINARS	https://youtu.be/cIBYFJPparA	3896	7.04.2020	44	222	5.04	1	0	0	5	5
79	How to enjoy sex and to avoid spreading COVID-19??|COVID-19|My Biography	https://youtu.be/uNB2Y4CVwnM	72	24.03.2020	58	196	3.37	1	0	0	3	3
80	Thinking about fertility treatment during COVID-19	https://youtu.be/PUuhfO4f0s4	223	15.04.2020	36	191	5.3	2	0	0	4	5
81	COVID-19 Southeast United States: what you should know about bladder cancer and COVID-19	https://youtu.be/blv7IVqUlVk	3585	10.04.2020	42	173	4.11	4	0	0	5	5
82	Dubai OBGYN explains infertility procedures during COVID-19	https://youtu.be/9NIXgoeQh0o	283	4.05.2020	17	171	10.05	0	0	1	4	5
83	COVID-19 and the West Coast: what you should know about COVID-19 and bladder cancer	https://youtu.be/EqW22OvwcRE	3471	14.04.2020	38	159	4.18	3	0	0	5	5

84	Covid19 could damage male fertility?|Male Sex|Sex Life|Sex Education|Research Associate	https://youtu.be/INszKlxC3vw	121	13.03.2020	70	154	2.2	8	0	3	3	4
85	Can COVID19 (Coronavirus) cause INFERTILITY? Long lasting impacts of COVID-19|Bite-size Science	https://youtu.be/KzUO6gs37ts	202	24.04.2020	28	146	5.21	17	0	19	5	5
86	Safer sex in the time of COVID 19	https://youtu.be/8off_2wtdAw	198	3.04.2020	49	125	2.55	6	0	1	3	4
87	What COVID-19 precautions mean for patients going through fertility treatment|Your Morning	https://youtu.be/-_MwPDTUKVI	205	24.03.2020	59	124	2.1	1	0	1	4	5
88	Fertility Clinic in Orange County response to Coronavirus (COVID-19)	https://youtu.be/qQ8lTJ3 mwbI	77	19.03.2020	64	121	1.89	1	0	0	3	3
89	COVID-19 and Infertility: what the coronavirus pandemic means for patients of CARE Fertility	https://youtu.be/IKDHl9ybAUY	228	23.03.2020	60	109	1.81	3	0	0	4	5
90	REPORT: Coronavirus may damage testicles	https://youtu.be/uf2eMseatYg	332	6.04.2020	46	107	2.32	6	0	0	5	5
91	Utah researchers say COVID-19 unlikely to spread through sexual intercourse	https://youtu.be/IaEuq-AlOqE	474	29.04.2020	23	106	4.6	12	1	4	4	4
92	Facebook Live - bladder cancer and staying grounded in a time of crisis	https://youtu.be/OP3AnQeVB0Y	3204	20.04.2020	32	98	3.06	1	0	0	5	5
93	Doctor: IVF treatments are getting delayed due to COVID-19	https://youtu.be/8XCidyaGXHQ	1402	9.04.2020	43	92	2.13	0	1	0	4	5
94	Coronavirus and sex: does sex transmit COVID-19? How can you protect yourself while having sex?	https://youtu.be/h05RaLbHYQw	1006	10.04.2020	42	89	2.11	1	0	0	4	4
95	Q&A: Prostate Cancer & COVID-19	https://youtu.be/zJhkdf15Rtc	1088	1.05.2020	20	91	4.55	3	0	0	5	5
96	COVID-19: Kidney Cancer Awareness Month Facebook Live Q&A	https://youtu.be/Gc0AyXl4jWs	798	18.03.2020	65	80	1.23	1	0	0	5	5
97	COVID 19 and the Central US: What you should know about bladder cancer and COVID-19	https://youtu.be/6nF0hcnbKr8	3594	22.04.2020	30	82	2.73	0	0	0	5	5
98	Coronavirus-Part 1-Prostate cancer and COVID-19	https://youtu.be/qtt-AvTtS5s	417	24.03.2020	59	82	1.38	1	0	0	4	5
99	Parents struggling with infertility in limbo due to COVID-19 crisis	https://youtu.be/RGa8AxXTyVY	152	1.04.2020	51	75	1.47	0	1	0	4	5
100	How are urologists handling COVID-19?	https://youtu.be/r11IHtakZBQ	88	6.04.2020	46	82	1.78	1	1	0	4	5

101	COVID-19: What the virus means for infertility patients	https://youtu.be/yXRtP_-QnPw	1103	25.03.2020	58	71	1.22	2	0	0	4	5
102	Calming fears about COVID-19 & Your Fertility With Dr. Serena H. Chen & Medanswers	https://youtu.be/Wk1yAxaaH4I	377	16.03.2020	67	69	1.02	2	0	1	4	5
103	Coping with anxiety during infertility and COVID-19	https://youtu.be/t-AzQnq9Izc	278	16.04.2020	36	77	2.13	1	0	0	4	5
104	PCFNZ Webinar|The practicalities of living with prostate cancer during COVID 19	https://youtu.be/exji60pOmxo	3070	23.04.2020	29	69	2.37	1	0	0	5	5
105	Corona and kidney transplant in 2020	https://youtu.be/mtwLs2_4cTU	101	27.03.2020	56	53	0.94	4	0	1	3	5
106	Fertility and the impact of COVID-19	https://youtu.be/ETVbKA5WLQ0	576	30.03.2020	53	49	0.92	1	0	1	4	5
107		This video is no longer available because the YouTube account associated with this video has been terminated	67	17.03.2020	66	48	0.72	0	1	0	3	3
108	What are my prostate cancer treatment options?	https://youtu.be/Ej_mRj226EE	111	10.04.2020	42	48	1.14	0	1	0	3	4
109	What are the benefits of telemedicine?	https://youtu.be/l8Hy48-rnmg	136	7.04.2020	45	49	1.08	1	1	0	3	4
110	STRESS, FERTILITY & COVID-19 WEBINAR #2	https://youtu.be/TtekwwI7SfE	960	7.04.2020	45	48	1.06	0	0	0	4	5
111	COVID-19 and the South West US: What you should know about bladder cancer and COVID-19	https://youtu.be/R8lRF3csu_8	3872	15.04.2020	37	46	1.24	0	0	0	5	5
112	Managing IVF pregnancy during COVID-19 - Dr. Nidhi Jha - Southend Fertility & IVF	https://youtu.be/rFNKVoD2OIU	81	10.04.2020	42	38	0.9	0	0	0	3	4
113	Will COVID 19 affects male infertility?	https://youtu.be/shgNcT95eYM	112	19.04.2020	31	37	1.19	1	0	0	3	4
114	What is telemedicine?	https://youtu.be/clnijuuslNc	55	7.04.2020	45	32	0.71	0	1	0	3	4
115	Does Medicare/insurance cover telemedicine?	https://youtu.be/i68o9V11--c	84	10.04.2020	42	24	0.57	0	1	0	3	4
116	Keeping sex and desire burning during COVID feat Alexa Martinez	https://youtu.be/aLWA-oG4jvI	3407	6.04.2020	46	21	0.45	1	0	2	2	3
117	Do I have to be tech-savvy for a virtual visit?	https://youtu.be/Oj6POx8Qaws	93	10.04.2020	42	12	0.28	0	1	0	3	4
118	Managing urology conditions during COVID-19	https://youtu.be/Uufc16qXuFM	946	29.04.2020	21	14	0.66	0	0	0	4	5
119	COVID-19: infertility consultations during pandemic	https://youtu.be/fs66ySIcoNk	507	22.04.2020	28	15	0.53	0	0	0	4	5

120	Renal medullary carcinoma and COVID-19: Protecting patients with advanced cancers	https://youtu.be/-1GRPtDMDUc	183	19.04.2020	31	6	0.19	0	0	0	4	5
121	COVID-19 and prostate cancer patients	https://youtu.be/YCbOEAuIAQM	115	24.04.2020	26	7	0.26	0	0	0	4	5
122	RCC in the COVID era: immunotherapy for metastatic cancer	https://youtu.be/mypLExMze7A	664	14.04.2020	36	4	0.11	0	0	0	5	5
123	Explaining adapted IVF protocols during COVID-19|CARE Fertility	https://youtu.be/JaItLP22R4o	172	15.05.2020	7	125	17.85	2	0	0	4	5
124	COVID safety protocol at Nova IVF fertility	https://youtu.be/2IU_do4sbQo	327	21.05.2020	1	68	68	2	0	0	4	5
125	How to keep safe from the coronavirus after your IVF treatment resumes	https://youtu.be/kl3MmMu4Xu0	313	14.05.2020	8	819	102.37	37	0	11	5	5
126	The new normal, adjusting to COVID-19 Webinar	https://youtu.be/ZBhkdonqeig	3690	17.05.2020	5	23	4.6	2	0	0	4	5
127	How has COVID-19 affected ongoing IVF treatment|Dr. Shweta Goswami|Zeeva Fertility Clinic	https://youtu.be/vcn7Mwt5i_Y	419	16.05.2020	6	15	2.5	0	0	0	4	5
128	Veterans, Prostate Cancer & COVID-19	https://youtu.be/wSRlJ92Chxg	933	6.05.2020	16	27	1.68	1	0	0	4	5
129	Mark Hagenbuch: Battling prostate cancer during COVID-19 crisis	https://youtu.be/5NjRFbQO9-4	708	7.05.2020	15	14	0.93	0	0	0	4	5
130	Yoga for prostate cancer & COVID-19 relaxation	https://youtu.be/4hnUK6PmDg0	1869	6.05.2020	15	7	0.46	0	0	0	3	4
131	Prostate cancer, COVID-19 & stress: Emotional check-in time	https://youtu.be/PVHAmrjX5I0	1901	7.05.2020	15	10	0.66	0	0	0	3	4
132	ZERO's CEO: 'I have COVID-19'	https://youtu.be/LVYpnhqkY8g	1663	24.04.2020	27	166	6.14	0	2	0	3	4
133	Eckert & Ziegler BEBIG: Prostate brachytherapy in times of COVID-19	https://youtu.be/Qb7Lsv77Tp4	134	13.05.2020	9	317	35.22	5	0	0	3	4
134	What patients with bladder cancer can do When COVID-19 impacts their care	https://youtu.be/ixheM0Fur88	159	14.05.2020	8	27	3.37	0	0	0	3	4
135	Sex and dating in the post COVID World|Q+A	https://youtu.be/_0CvLC3Vszs	198	19.05.2020	3	761	253.66	6	15	3	2	3
136	Sexual health during the COVID era	https://youtu.be/kQiqR0d_NIs	227	19.05.2020	3	18	6	1	0	0	2	3

more important for these patients. Boehm et al. (20) reported that 63.2% of patients with urological conditions were eligible for telemedicine. Among eligible patients, 54.1% stated that they would prefer telemedicine instead of face-to-face consultation. This rate was higher for those aged <68 years (20). Technical limitations were the main cause for refusal. Uro-oncological diseases were the most common reason among patients both eligible and willing to use telemedicine (72.2%). Other diseases were incontinence/bladder dysfunction (6.9%), andrological condition (5.5%), benign prostatic hyperplasia (3.7%), urinary tract infection (3.2%), urolithiasis (2.3%) and other reasons (5.9%) (20). However, interestingly, we observed that uploaded video rates, number of total views and number of views per day were higher for andrology-related YouTube videos. This finding implies that since andrological condition may be the topic that people want to learn most, more andrology-related videos have been uploaded to YouTube. We think that fewer videos on uro-oncology are uploaded since the approach and strategy related to uro-oncology is clearer. By contrast, we think that there are more videos on andrology and sexual life since there are more controversial ideas on this topic. Indeed, among

all urology-related videos during the COVID-19 pandemic, the most viewed videos are related to andrology. We consider that sexual health makes people more curious. For this reason, videos about andrology may be viewed more. We also assume that non-healthcare professionals have uploaded more videos on andrology, considering that they will capture a wider audience.

Sufficient information should be provided to patients under follow-up for urological diseases. However, it appears difficult for patients to determine which of their symptoms can be deferred and for how long. In addition, andrological diseases except for penile fracture, priapism, testicular torsion and scrotal and penile traumas are mostly treated electively and the international guidelines categorise andrological pathologies as a non-essential issue, so consultation with healthcare professionals for this purpose and treatment has to be postponed during the COVID-19 period (8,10). Since patients with andrological pathologies already have a low quality of life, not being able to get treatment during this period may worsen the severity of the disease (17). Because it is not very practical for a urologist to discuss these situations by telemedicine with every patient, we consider that informative, reliable and easy-to-understand YouTube videos may be useful for patients and their relatives.

Despite the ease of access to information, YouTube videos containing medical advertisements and for profit are often listed among the more popular videos (22). For that reason, there is a risk of exposure to misleading and incorrect information (5,23). Although some previous studies have found YouTube to be a source of accurate educational and useful health information (7,16,24,25), there have been opposite views in the literature about the reliability of these videos (16,23,26,27). Studies have recommended using more validated formal assessment tools such as the modified DISCERN tool, GQS or other forms [e.g. instrument that was developed by Azer et al. (24)] (6,7,16). However, it is not possible for lay people to make this evaluation and thereby determine the reliability and quality of the video.

Increasing the awareness of male sexual health and encouraging them to see a physician is important to improve their quality of life. Several studies have stated that the majority of YouTube videos, including videos on andrological topics such as premature ejaculation, are unreliable sources of medical information (7,22,23,28). In the present study, the speaker was a for-profit physician in 7 (35%) of the 20 videos containing debated information, while 65% of the speakers in debated videos were not healthcare providers. We found that 85.3% of all videos contained useful information, and the useful information rate was 96.2% in "universities/professional organisations/non-profit physician/physician groups", which contained 77.2% of all videos. Although most of the YouTube videos contain unreliable information and published by individual users or medical advertisement/for-profit companies (16,23,26,27,29), our findings show that conversations in the COVID-19 period have been made less by individual users, medical advertisements or for-profit companies, unlike YouTube videos on other topics. However, our findings show that videos uploaded by non-healthcare professionals with lower reliability and quality scores garnered higher views and like. We think that this situation is the result of tricks made by such people to increase the discoverability and viewership of such YouTube videos. An extremely interesting headline, cover photo or custom thumbnail, using descriptive tags and writing a concise synopsis of the video content can often trigger the viewers to click on the video. Adding links to other videos that may be relevant by the video creator may be another common trick. In our opinion, these tricks are used more by non-healthcare professionals to make their videos more popular than videos of healthcare professionals.

Although andrological disorders and infertility have to be considered low priority, the number of patients who want to find solutions for their problems is not small, and they are looking for information on what they can do during this period (30). Although it was recommended to postpone appointments related to infertility in the beginning of the COVID-19 period, in the latest version of the EAU guidelines about COVID-19, male fertility surgery is only considered a high priority when women have limited ovarian reserve or have advanced maternal age, provided that a full discussion is held with the couple (8). In our analysis, 41.9% of all YouTube videos focused on infertility during the COVID-19 period. Current developments related to infertility are one of the most looked for topics and these conversations are very popular.

Study Limitations

To the best of our knowledge, this is the first study to assess the content, view rate, reliability and quality of YouTube videos that give information on urological disorders during the COVID-19 period. However, this study has some limitations. Firstly, the search order and number of video views may change every day because of video popularity and newly added videos. Although we recorded the videos on a playlist by snapshot analysis as in previous similar studies, it is a limitation. Secondly, not analysing non-English-language videos prevents commenting on all YouTube videos. Thirdly, we used a 5-point modified DISCERN tool and GQS to analyse videos with reference to previous studies, but their formal validation has not yet been completed. Finally, we used "covid" and "coronavirus" as search keywords with all the main terms or diseases that we considered for urology. However, there is still a possibility of missing some videos using only these terms.

Conclusion

In this study, 85.3% of all videos contained useful information on what should be done for urological disease during the COVID-19 period. This rate was especially higher in videos uploaded by "universities/professional organisations/non-profit physician/physician groups". The international urology committees classify andrological disorders as a non-essential issue, so they recommended that delaying consultation and treatment during the COVID-19 period. However, our results show that the rate of using YouTube as a source of information on andrology is even higher than that of uro-oncological diseases. We think that informative, easy-to-understand YouTube videos uploaded by "universities/professional organisations/non-profit physician/physician groups" can be used as a useful additional method to improve telemedicine, which is not very practical for reaching every patient with andrological disorders that does not require follow-up.

Ethics

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, there is no need for ethical approval.

Informed Consent: This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, there is no need for informed consent.

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Authorship Contributions

Concept: İ.S., N.B., Design: İ.S., N.B., Data Collection or Processing: İ.S., N.B., Analysis or Interpretation: İ.S., N.B., Literature Search: İ.S., N.B., Writing: İ.S.

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Changes That Have Occurred in the Surgical Treatment Preference for Non-emergent Kidney Stones During the COVID-19 Pandemic: Six Months of Clinical Experience in A Tertiary Referral Centre

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What's known on the subject? and What does the study add?

The coronavirus disease 2019 pandemic has affected many of our treatment approaches due to the excessive overload it brings to the health system. Our study found that we operated on much less elective kidney stones during this pandemic process. Besides, the preoperative hydronephrosis rates were higher in patients who underwent retrograde intrarenal surgery. We anticipate that the future reflection of these findings will be a confrontation with more complicated patients and the interruption of residents' surgical training.

Abstract

Objective: Owing to the outbreak of the coronavirus disease-2019 (COVID-19), treatment approaches are reshapened because of the excessive load on the health system. This study aimed to investigate the differences in our surgical approach to kidney stone cases between the COVID-19 period and pre-COVID-19 period.

Materials and Methods: Patients who underwent retrograde intrarenal surgery (RIRS) or percutaneous nephrolithotripsy (PNL) for kidney stones in our clinic between March 11, 2020, and September 11, 2020, and those in the same period 1 year ago were included in the study. Demographic information, laboratory data, stone characteristics, treatment choices and results were evaluated comparatively.

Results: A total of 39 patients in the COVID-19 period (group 1) and 93 patients in the pre- COVID-19 period (group 2) underwent kidney stone surgery. While RIRS was performed to 32 of the patients in group 1, PNL was applied to seven of the patients in group 2. RIRS was performed to 70 patients in group 2, and PNL was applied to 23 of them. While the RIRS/PNL ratio was 4.5 in group 1, it was 3.04 in group 2. During the COVID-19 period, the number of patients who underwent PNL has decreased significantly.

Conclusion: The number of elective surgery cases has significantly decreased during the COVID-19 pandemic. It is predicted that the incidence of organ loss will increase due to complications and delayed treatment. Moreover, interruption of the residents' surgical training secondary to the decreasing number of cases is one of the pandemic's critical drawbacks.

Keywords: COVID-19, RIRS, PNL, kidney stone

Introduction

The prevalence of urinary stones varies between 1% and 20%, and in recent years, this value has increased in many parts of the world. A study reported that it has increased by more than 37% in the last 20 years (1). The European Association of Urology (EAU) guidelines recommended percutaneous nephrolithotripsy (PNL) and retrograde intrarenal surgery (RIRS) as the first choice in the surgical treatment of kidney stones >20 mm and <10 mm, respectively. Both methods are recommended for stone sizes between 10 mm and 20 mm (1). Although the success rate and stone-free rate (SFR) in a single session are lower than that with PNL, the use of RIRS has increased in recent years for stones >20 mm, owing to the growing experience, which results in low complication rates and shorter hospital stay (2,3).

December 2019 was considered the starting time point of the coronavirus disease 2019 (COVID-19) pandemic. In Turkey, the first COVID-19 cases have been identified on March 10, 2020. A

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pandemic was also declared by the World Health Organisation on March 11, 2020 (4). The COVID-19 pandemic has led to radical decisions that affected all aspects of daily practices in many fields, especially in the health system (5).

With the allocation of most of the health resources to patients with COVID-19, changes were necessary in our urology practice, as in all clinical branches, in accordance with the COVID-19 recommendation guide (6). Patients who developed anuria, sepsis due to stone-induced obstruction and renal failure were included in the emergency group. Immediate intervention with nephrostomy or Double-J (DJ) stent placement was recommended to this group. The high priority group included patients who would be clinically impaired if intervention is delayed by >6 weeks. The medium priority group includes cases where a 3-4 week delay in the intervention would cause clinical harm to the patient. The low priority group includes cases in which the patient is unlikely to experience complications even if the intervention was delayed for 6 months. As a result, cases of renal calyx stones were included in the lowest priority group. With these guidelines, the number of surgeries has decreased.

Consequently, it appears possible that we will encounter patients whose treatments were delayed and, therefore, whose disease will become more severe. As an overlooked aspect, we may see the negative indications of this pandemic on the future, as experience with difficult cases, which are a part of the theoretical and practical educations of residents, were disrupted in third-level referral and educational institutions.

With the above background, this study aimed (1) to compare outcomes of RIRS and PNL performed electively on renal stones during the COVID-19 period and 1-year pre-COVID-19 period, (2) to evaluate whether our approaches to similar cases of renal stones have changed and (3) to raise the issue of disruption in the education of the residents. With this study, we hope to draw a future projection with changing approach trends.

Materials and Methods

This retrospective study was approved by the institutional review board (decision number 2020/554), and the study protocol followed ethical standards.

Patients who underwent RIRS or PNL for kidney stones during the 6 months between March 11, 2020, and September 11, 2020, when the COVID-19 pandemic has started, and patients who had undergone the same operations in the same period exactly 1 year ago (between March 11, 2019 and September 11, 2019) were included in the study. Patients who needed urgent decompression with nephrostomy or DJ stent due to obstruction and septic status, with acute kidney damage, were under 18 years of age and were pregnant were excluded. Parameters such as age, gender, preoperative blood creatinine level, blood urea nitrogen level, kidney surgery history, extracorporeal shock wave lithotripsy history, preoperative hydronephrosis (HN) status, stone location and localisation, stone size and volume, presence or absence of accompanying ureteral stones, surgery option and residual stone after treatment were collected from our database and evaluated comparatively between the groups. Before surgery, all patients were assessed with urine analysis, urine culture, serum biochemistry, coagulation test and non-contrast computed tomography of the urinary system as a requirement of routine practice. The stone burden was calculated by the formula according to the EAU guideline (stone volume= length × width × depth × π × 0.167) (7).

Both procedures were performed under general anaesthesia. RIRS was performed in the lithotomy position. A semi-rigid ureteroscope (Olympus Medical Systems, Hamburg, Germany) was routinely performed before flexible ureteroscopy in all patients for dilatation of the ureter and placement of a 0.035-inch sensor guide wire. According to the surgeon's technical preference, all stones were dusted with 272 µm Holmium YAG laser fibre (Dornier Medilas H 20 Laser, Wessling, Germany) until they were deemed small enough to pass spontaneously. A 4.8-Fr DJ stent (Cook Medical, Bloomington, IN, USA) was routinely placed in all patients. PNL was performed in the prone position. Mini PNL (Karl-Storz Medical, Tuttlingen, Baden-Württemberg, Germany) was applied to all patients as a part of routine practice. After 24-Fr dilatation in each patient, an Amplatz sheath (Cook Medical, Bloomington, IN, USA) was placed, and lithotripsy was performed with a pneumatic lithotripter (EMS®, Swiss Lithoclast®Master, Nyon, Switzerland). Stones were extracted with forceps. Malecot catheter was placed in every patient as a routine practice.

Outcome Measures

Primary outcome measures were the differences in treatment selections and stone characteristics between the COVID-19 period and pre-COVID-19 period.

Statistical Analysis

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences version 22 (IBM SPSS Statistics for Windows, Chicago, IL, USA). While quantitative values are given by mean ± standard deviation for parametric data, quantitative values for nonparametric data are provided by the median [minimum-maximum (min-max)]. Data of categorical variables are presented as numbers and percentages. Shapiro-Wilk and Q-Q plots were used to check the normality of the variables. Data were expressed as mean ± standard deviation (range, min-max) or median (interquartile range) for continuous variables and described as counts (n) and percentages (%) for categorical variables. Independent t-test, Mann-Whitney U

test and chi-square test were used to evaluate differences in parameters between the groups. A p-value of less than 0.05 was considered significant.

Results

While 39 patients underwent surgery for kidney stones during the COVID-19 period (group 1), 93 patients underwent surgery during the pre-COVID-19 period (group 2). While 32 of the patients in group 1 had undergone RIRS, 7 of them had received PNL; 70 of the patients in group 2 had undergone RIRS, and 23 had received PNL. The difference was not significant (p=0.396). While the RIRS/PNL ratio was 3.04 in group 1, it was 4.5 in group 2.

Patients' demographic, stone and surgical characteristics are summarised in Table 1. While the median patient age in group 1 was 41 (14-75) years, this value was 49 (21-5) years in group 2, and the difference was not significant (p=0.063). No difference was found in the gender distribution between group 1 and group 2 (p=0.943).

A significant difference was found between the two groups in terms of the presence of HN (p=0.01). While 9 (23%) patients in group 1 did not have HN, 44 (47%) patients in group 2 did not have HN. A significant difference was found between the patients who underwent RIRS in group 1 and group 2 in terms of the presence of HN (p=0.015). Relatively more patients had HN in group 1 (78.1% vs 52.9%) than in group 2.

No difference was found in the preoperative blood urea nitrogen, blood creatinine, stone size and stone volume parameters between group 1 and group 2 (Table 1). Moreover, no difference in stone number was found between group 1 and group 2 (p=0.126). The number of patients with non-lower pole and lower pole localisation in both groups was comparable. No difference was found in terms of residual stones between the two groups (p=0.185).

Table 1. Demographic, stone, and operation characteristics of the patients

Parameter	COVID-19 Period		Pre-COVID-19 Period		p
	RIRS (32)	PNL (7)	RIRS (70)	PNL (23)	
Age (years) median (min-max)	45.34 (14-75)	39.86 (22-62)	49.11 (26-75)	49.61 (21-74)	0.063
Gender					
- Male (n,%) - Female (n,%)	43 (61.4%) 12 (37.5%)	5 (71.4%) 2 (28.6%)	43 (61.4%) 27 (38.6%)	16 (69.6%) 7 (30.4%)	0.943
Urea (mg/dL) Creatinine (mg/dL) Median (min-max)	33.31 (12-51) 0.99 (0.53-1.74)	30.24 (25-40) 0.80 (0.7-1.09)	33.34 (17-80) 0.91(0.5-1.87)	33.13 (18-62) 0.87 (0.51-1.85)	0.602 0.159
Side					
- Right - Left - Bilateral	14 (43.8%) 16 (50.0%) 2 (6.3%)	2 (28.6%) 5 (71.4%)	33 (47.1%) 33 (47.1%) 4 (5.7%)	15 (65.2%) 8 (34.8%)	0.573
Accompanying Ureter Stone					
- Negative - Positive	24 (75%) 8 (25%)	6 (85.7%) 1 (14.3%)	60 (85.7%) 10 (14.3%)	23 (100%) 0	0.100
Hydronephrosis					
- None - Mild - Medium - Severe	7 (21.9%) 9 (28.1%) 10 (31.3%) 6 (18.8%)	2 (28.6%) 4 (57.1%) 1 (14.3%)	33 (47.1%) 18 (25.7%) 14 (20%) 5 (7.1%)	11 (47.8%) 4 (17.4%) 8 (34.8%)	0.01 (No-yes distinction)
Stone size (mm) median (min-max)	13 (5-35)	16 (10-43)	11 (5-38)	23 (14-57)	0.930
Stone volume (mm^3) median (min-max)	284.5 (42-5170)	786 (524-2752)	323.5 (23-4400)	2865 (792-9201)	0.688
Stone Localization					
- Lower calyx stone positive - Lower calyx stone negative	16 (50%) 16 (50%)	5 (71.4%) 2 (28.6%)	35 (50%) 35 (50%)	14 (60.8%) 9 (39.2%)	0.903
Residual Stone					
- None - Minimal crumb - Above 4 mm	16 (50%) 10 (31.2%) 6 (18.8%)	3 (42.9%) 1 (14.3%) 3 (42.9%)	49 (70%) 10 (14.3%) 11 (15.7%)	11 (47.8%) 3 (13%) 9 (39.2%)	0.185 (No-yes distinction)

*RIRS: Retrograde intrarenal surgery, PNL: Percutaneous nephrolithotomy, Min: Minimum, Max: Maximum

When the patients were evaluated separately according to the surgery groups, no significant difference was found between patients in group 1 and group 2 who underwent RIRS. Still, the stone size of patients who underwent RIRS during the COVID period tended to increase slightly (13 mm vs 11 mm).

A significant difference was found between patients in group 1 and group 2 who underwent PNL and between patients with 786 mm^3 versus 2865 mm^3 of stone volume. During the COVID-19 period, the stone volume of patients with PNL decreased ($p=0.048$) and the number of patients with PNL has reduced significantly.

Discussion

The unprecedented COVID-19 pandemic has affected health systems worldwide and revolutionised all medical practices. The number of cases that can be evaluated as elective has decreased significantly (8,9). In this context, many national and international urology associations have published guidelines to clarify clinical and surgical priorities during the COVID-19 pandemic. However, it is still unclear how the priority will be determined in urinary stones. During this process, patients evaluated in the emergency group received interventions according to the EAU recommendation guide. An algorithm for approaching stone diseases was proposed by the EAU stone study group (10). According to this algorithm, nephrostomy or DJ stent intervention was recommended for patients with obstruction (HN) with decreased kidney function and patients with urinary tract infection and severe pain, even if the kidney function was normal. Surgical intervention is not recommended for the vast majority of patients without HN. Surgical drainage is recommended only in patients with urinary tract infection who have the risk of developing sepsis despite antibiotherapy and in patients whose pain persists despite analgesia (10).

No difference was found between the groups in our study regarding accompanying ureteral stones and stone localisation. However, 47% of our patients who underwent surgery during the COVID-19 period had HN. A significant difference was found between the groups in terms of the degree and presence of HN. The increase in the severity of HN in patients who underwent surgery during COVID-19 may indicate that the patients' treatment was delayed. The increased incidence of HN is also considered an indicator that patients with HN are given priority, even if RIRS and PNL were considered.

Lei et al. (11) found that 41% of the patients with COVID-19 required intensive care and 20.5% of the patients who underwent elective surgery died even during the incubation period. For this reason, elective surgeries that may require follow-up in the intensive care unit during the postoperative period have been avoided, and less invasive options have been evaluated instead. Other reasons are as follows: use of hospitals as pandemic hospitals, decrease in the number of service beds, operating rooms and intensive care beds that can be used and patients do not present to the hospital due to the threat of COVID-19 transmission. In our study, when the COVID-19 period and pre-COVID-19 period were compared, the rate of RIRS was significantly increased, and the number of patients who underwent PNL decreased significantly.

Studies have indicated that the trend in kidney stones larger than 2 cm for which PNL is usually recommended has shifted to RIRS as it is less invasive, regardless of the COVID-19 period. The reason is that some PNL surgeries mostly require more than one session because the stones are scattered in different calices, resulting in severe renal damage. In these multiple entry cases, the risk of bleeding complications also increases (12-14). In these patients, RIRS is offered as a treatment option. However, owing to the efficiency of lithotripsy, SFR values are low in RIRS surgeries in stones >2 cm, and more than one surgical application may be required (1). A recent systematic review on renal stones >2 cm showed a cumulative SFR of 91% with 1.45 procedures/patient (15). When the stone volumes and localisation were evaluated in our study, no significant difference was found between the groups. However, the stone size of the patients who underwent RIRS during the COVID period increased slightly. In this case, many studies have demonstrated the possibility of a higher rate of residual stones due to RIRS on larger stones (16,17). In our study, in the intragroup analysis of patients who underwent RIRS, no difference was found between the SFR rates.

With the new normalisation process after the COVID-19 pandemic, elective surgeries have been performed gradually since June 1, 2020. Surgical interventions that were delayed due to the clinics' inability to work at full capacity have accumulated over time. Patients with kidney stone represent a significant proportion of urological surgical cases that were postponed during the pandemic and thus still awaiting surgery. As future reflection, postponement of elective surgery will increase organ losses because of complications and delayed treatment (18). In this study, no difference was found between the blood urea nitrogen and creatinine levels in the renal function evaluation of the patients. However, more detailed examinations are required to evaluate the stone-related damage in the kidneys.

Furthermore, interruption of the residents' surgical training secondary to the decreasing number of cases in hospitals where third-level training is provided is one of the most significant drawbacks. Owing to the decreasing number of cases and quarantine process worldwide, especially in the USA, the surgical training gap has been eliminated by web-based platforms (19). In this process, web-based training programmes were more often organised in Turkey and in our clinic. With this change, there

may be differences in the traditional education programmes of residents because surgery should be learned through practice.

Study Limitations

The retrospective design, postponement of elective cases during the pandemic and low number of patients included in the study because of the decreased patient admissions are the study's limitations. In addition, the 6-month period in which the patients included in the study who underwent surgery, included heterogeneous processes from full restriction to the new normalisation process. However, for prospective research, the pandemic must be over. The increase in COVID-19 cases during the transition to the normalisation process also interrupted elective surgical cases.

Conclusion

During the COVID-19 pandemic, many urological procedures were postponed. The less invasive option was preferred. Although elective surgeries have begun to be performed in a controlled manner with the new normalisation process, it is still uncertain how the accumulated cases will be resolved in the process. As future reflection, organ losses will increase because of complications and delayed treatment. Another critical issue is the delay in the practical training of surgical residents. As the pandemic period gets longer, the variety and number of elective cases performed by residents will decrease significantly.

Ethics

Ethics Committee Approval: This retrospective study was approved by the institutional review board (decision number: 2020/554), and the study protocol followed ethical standards.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.F.B., K.B., Mur.G., M.K., Ö.K., S.G., Concept: A.F.B., Design: A.F.B., Data Collection or Processing: M.G., K.B., Analysis or Interpretation: A.F.B., M.G., Literature Search: A.F.B., Writing: A.F.B., M.G., M.K., Ö.K., S.G.

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Comparing Outcomes of Transurethral Resection of the Prostate in Men with Greater Than or Less Than 100 cc Prostate Volume: A Single-Centre Study

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What's known on the subject? and What does the study add?

Transurethral resection of the prostate (TURP) is the most common surgical treatment method for urinary symptoms secondary to benign prostatic hyperplasia. However, international guidelines suggest using other surgical treatments for larger prostate glands. These other treatments are not universally available and, therefore, TURP may still be the most viable option in some settings. This study assesses the outcomes of TURP in larger glands compared with TURP in smaller glands.

Abstract

Objective: This study describes the peri-operative results, safety, and functional outcomes of transurethral resection of the prostate (TURP) performed in men with benign prostatic hyperplasia [or hypertrophy; (BPH)] and a prostate gland volume ≥100 cc.
Materials and Methods: A retrospective analysis of a cohort of patients undergoing TURP at a single institution over four years was undertaken. Patients with known prostate cancer were excluded. Clinical outcomes were between men with a prostate volume of ≥100 cc and men with a prostate volume <100 cc. Functional outcomes were assessed by defining a series of measurable post-operative "lower urinary tract symptoms (LUTS) events" and comparing the time-to-event profile using a Kaplan-Meier estimator.
Results: Out of a total of 238 men who underwent TURP for BPH during the study period, 72 had a prostate volume ≥100 cc (30%). Baseline demographics were similar to the group of patients with a prostate volume <100 cc. Patients with large prostates had a significantly longer mean operating time (56 vs 98 minutes, p<0.0001). The peri-operative complication profile and post-operative complication rate were similar between the two groups. During a median follow-up period of 27 months (range, 2-54 months), no difference in LUTS events-free survival was observed (p=0.93).
Conclusion: Our results show that TURP can be safely performed in patients with large prostate glands (≥100 cc). Although operating times were longer in the large prostate group, this did not significantly affect the complication rate nor compromise a good functional outcome.
Keywords: Benign prostatic hyperplasia, transurethral resection of the prostate, bladder outlet obstruction

Introduction

Transurethral resection of the prostate (TURP) remains one of the most commonly used methods of surgical management for men with obstructive lower urinary tract symptoms (LUTS) due to benign prostatic hypertrophy [hyperplasia; (BPH)]. The development of numerous, novel surgical techniques has meant the proportion of TURP procedures performed for BPH is decreasing (1). However, TURP remains the operative standard that all current techniques are measured against (2).

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Improvements in medical therapies for LUTS have meant that surgical treatment can often be delayed (3,4). As a result, many patients are presenting with refractory LUTS and large prostate volumes. Although no upper size limit has been documented for TURP resection, current international guidelines suggest using from 80 to 100 cc as the volume at which consideration should be given to TURP alternatives, such as open prostatectomy or endoscopic laser enucleation (5,6). Such recommendations, along with the inherent risks of long transurethral resection times, have partly led to novel techniques to treat large prostate glands endoscopically (7). Despite these developments, newer techniques, such as the holmium laser enucleation of the prostate, are not universally available across all urology departments. These techniques are often unavailable, including their high initial overhead cost and a difficult learning curve for the surgeon (8,9). Furthermore, therapies such as greenlight laser photoselective vaporisation of the prostate (PVP) still entails a risk of conversion to TURP, highlighting the importance of a good TURP technique for urologists. Our study describes the safety and functional outcomes of performing TURP for large prostate glands.

Materials and Methods

Patient Population

Following ethical approval from the Far North Queensland Human Research Ethics Committee (EC00157), we conducted a de-identified retrospective study at our institution of all patients treated with TURP for BPH over four years from March 2014 to July 2018. All patients undergoing TURP were identified; patients with a preoperative prostate cancer diagnosis were excluded from analyses.

Two patient subgroups were established based on the pre-operative prostate volume. Measurements were obtained from imaging studies using ultrasound (transabdominal or transrectal), computerised tomography, or magnetic resonance imaging. The two groups were defined by a prostate volume <100 cc (group 1) versus ≥100 cc (group 2).

Surgical Procedure

All patients underwent TURP using either a bipolar or monopolar energy source. Bipolar TURP was performed using a 26 ch continuous flow Olympus resectoscope sheath (Olympus-Europa SE & Co. Hamburg, Germany) using a Gyrus ACMI PK Superpulse System energy source (Gyrus Medical Inc., Minnesota, USA). Monopolar TURP was performed with a Storz 26 ch continuous flow resectoscope sheath (Karl-Storz - Endoskope, Tuttlingen, Germany) and a Valley Lab Force FX™ energy source (Valley Lab Inc. Boulder, Colorado USA). Bipolar TURP was the preferred modality. Monopolar TURP was used when the bipolar equipment was unavailable. Procedures were performed under general or spinal anaesthesia at the discretion of the anaesthetist. Post-procedure, all patients had a three-way 22 French catheter that was routinely removed on post-operative day 2. All patients were assessed with pre-operative urine culture two weeks before surgery. All infections were treated before surgery. Patients with indwelling urinary catheters were admitted 24 hours before surgery for intravenous antibiotics and a catheter change. Peri-operative antibiotic prophylaxis was administered according to local recommendations.

Variables

A computerised database was created to capture patient demographic, clinical and pathological data regarding their pre-operative, peri-operative and post-operative results using electronic hospital records. Post-discharge complications were captured using local electronic records and electronic records used by all public hospitals in Queensland.

Outcomes

Patients were routinely followed up between six and eight weeks after hospital discharge. Patients who had no residual bothersome LUTS were discharged at this time point. The need for ongoing follow-up was at the discretion of the consulting clinician. Patients who failed to void successfully post-operatively were discharged with a catheter *in situ* and routinely returned for catheter removal after two weeks. Post-operative results regarding functional analysis were collected according to the occurrence of "LUTS events" (Table 1). The timing of occurrence of LUTS events was also documented and plotted on a time-to-event curve.

Statistical Analysis

Statistical analysis of basic demographic, clinical and pathological data and the construction of time-to-event curves

Table 1. Descriptive demographic characteristics of 238 patients treated with transurethral resection of the prostate (TURP) (<100 cc or ≥100 cc)

Demographic	<100 cc Group 1	≥100 cc Group 2
N (total)	166 (70%)	72 (30%)
Mean (median; range) age, years	71.2 (71; 49-89)	73.2 (72; 58-89)
Mean (median; range) prostate volume, cc	54.0 (51; 12-98)	138.4 (130; 100-269)
Preoperative catheter dependence	81 (49%)	40 (55%)
Preoperative combination 5-alpha reductase inhibitor and alpha blocker use	75 (45%)	48 (66%) (p=0.003)
Previous TURP	18 (11%)	8 (11%)

TURP: Transurethral resection of the prostate

were performed using GraphPad Prism 8®. Where reported, a two-sided t-test was used to compare the two groups. LUTS events-free survival curves were compared using the log-rank Mantel-Cox test. A p-value of <0.05 indicated statistical significance.

Results

Baseline Characteristics

A total of 296 patients underwent a TURP procedure during the study period. Overall, 219 patients (74%) had a prostate volume <100 cc (group 1) and 77 patients (26%) had a prostate volume ≥100 cc (group 2). A pre-operative diagnosis of prostate cancer was documented in 58 patients. Therefore, 238 patients were included in the final analysis, with 166 patients (70%) and 72 patients (30%) in groups 1 and 2, respectively. Basic demographic data from our cohort are outlined in Table 1. The only significant demographic difference between the two groups was that a greater proportion of patients in group 2 was prescribed a 5-alpha-reductase inhibitor pre-operatively than group 1 (66% vs 45%). Peri-operative data are shown in Table 2. Group 2 had a significantly longer operating time with a greater volume of tissue resected. The haemoglobin levels measured on the first post-operative day showed a more considerable mean decrease in group 2 (21.8 g/dL) than group 1 (10.5 g/dL). Incidental prostate cancer was detected on histopathology in 28 men (16%) in group 1 compared with six men (8%) in group 2.

Safety

Overall complications were similar in both groups (26.4% vs 25.9%). Figure 1 shows the number of complications described using the Clavien-Dindo classification. Despite a more considerable measured decrease in post-operative haemoglobin for group 2, there was no difference in the transfusion rate between the two patient groups (1% vs 2%) (Table 3). A summary of post-operative complications is shown in Table 3.

Table 2. Peri-operative results of 238 patients treated with transurethral resection of the prostate (TURP) (<100 cc or ≥100 cc)

Peri-operative characteristic	<100 cc Group 1	≥100 cc Group 2
Bipolar TURP	93%	91%
Spinal anaesthesia	38%	54%
Mean operating time (mins)	56	98 (p<0.0001)
Mean (median; range) resection weight (g)	14.8 (13; 0.5-58)	45.3 (43; 3-161)
Mean (median; range) post-operative length of stay (days)	2.8 (2; 1-10)	2.9 (2; 2-14)
Mean drop in post-operative haemoglobin (g/dL)	10.5	21.8

TURP: Transurethral resection of the prostate

Table 3. Summary of post-operative complications

Complication	<100 cc Group 1 n=166	>100 cc Group 2 n=72
Transfusion rate	4 (2%)	1 (1%)
Unexpected ICU admission	2 (1%)	2(3%)
Sepsis	0	0
Cardio-pulmonary complications	2 (1%)	4 (5%)
TUR syndrome	1 (0.5%)	0
Bladder perforation	2 (1%)	0
Re-presentation to ED (no admission required)	17 (10%)	6 (8%)
Re-admission within 28 days	10 (6%)	5 (7%)
Return to theatre	4 (2%)	1 (1%)
Death within 28 days	1 (0.5%)	0

ICU: Intensive care unit, TUR: Transurethral resection, ED: Emergency department

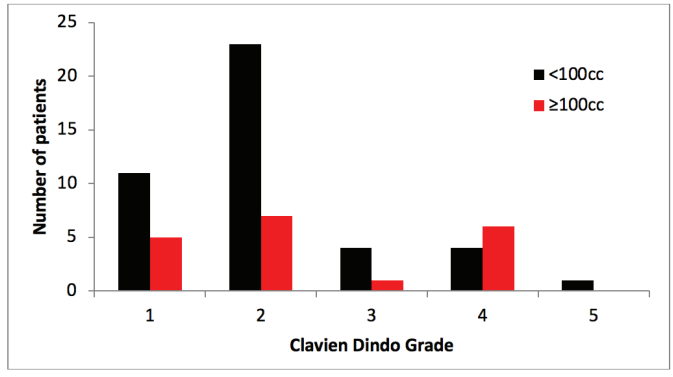

Figure 1. Peri-operative and post-operative complications in 238 men undergoing TURP for BPH

TURP: Transurethral resection of the prostate, BPH: Benign prostatic hyperplasia

Functional Outcomes

All patients underwent an in-patient trial without a catheter during their peri-operative hospital stay. Also, 129 (77%) patients in group 1 (prostate volumes <100 cc) successfully voided and were discharged home without a catheter compared with 61 patients (84%) in group 2. Of the 121 patients who were catheter-dependent pre-operatively, 103 (85%) were voiding spontaneously at the sixth post-operative week with 67 (82%) and 36 (90%) patients in groups 1 and 2, respectively, who were catheter-dependent pre-operatively becoming catheter-free. With a median follow-up time of 27 months (range, 2-54 months), LUTS events as described in Table 1 were observed in 35 (21%) vs 16 (22%) for patient groups 1 and 2. The time to LUTS events is shown in Figure 2. The Kaplan-Meier LUTS events-free survival curves were not different between the two

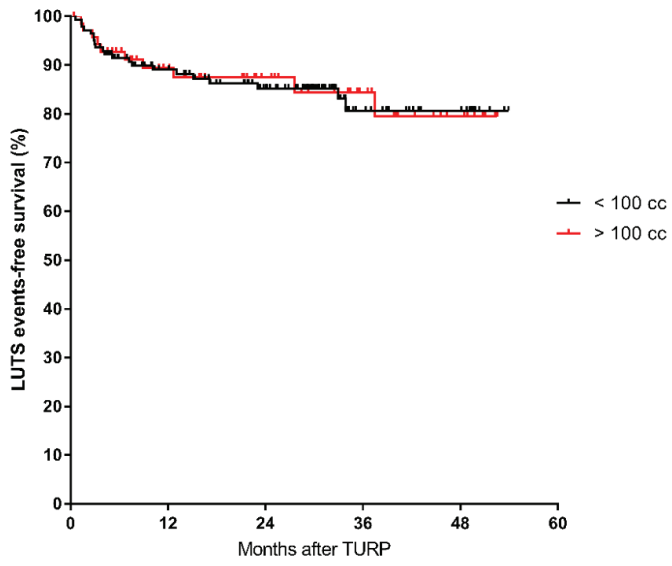

Figure 2. Freedom from LUTS events following TURP in men with prostate volumes <100 cc compared with men with prostate volumes ≥100 cc

TURP: Transurethral resection of the prostate, LUTS: Lower urinary tract symptoms

groups (p=0.93; log-rank Mantel-Cox test). During the follow-up period, a re-do TURP was performed in three (2%) patients of the <100 cc group compared with two (3%) patients of the ≥100 cc group.

Discussion

To our knowledge, our study contains the largest number of patients undergoing TURP for LUTS with a prostate gland ≥100 cc in volume (n=72), comprising 30% of our total cohort of men undergoing TURP for BPH. The selection of 100 cc as the definition of a large prostate was based on the largest volume used to make recommendations from international guidelines. We chose to compare this size directly with the standard "small" gland TURP since, for this latter group TURP remains the current standard of care.

TURP is a well-established surgical treatment for men with symptomatic BPH. Robust long-term data exists supporting the efficacy of TURP that has not yet been replicated for more recently developed techniques (10). Despite this, the support for TURP in large prostate glands is less compelling. Although there is no defined upper limit of prostate size for the use of TURP, urological guidelines recommend considering other forms of surgical treatment in men with large prostate volumes. The European Association of Urology recommends that urologists should offer endoscopic enucleation or open prostatectomy to treat moderate-to-severe LUTS in men with a prostate volume >80 mL (5). This recommendation is supported by available outcome data. However, the higher complication rate of open prostatectomy and the learning curve associated with endoscopic enucleation procedures may be limitations in applying this recommendation. The United Kingdom's National Institute for Health and Care Excellence guidelines on LUTS in men do not set an upper limit for TURP. However, they recommend only offering open prostatectomy as an alternative to endoscopic procedures to men with prostate sizes estimated to be larger than 80 grams. This recommendation is based on expert opinion, and the prostate size cut-off was set from studies that used inclusion criteria from 70 to 100 grammes (11). The 2010 American Association of Urology guidelines (6) on the management of BPH reported a prostate size of >100 grammes as a criterion for considering the use of transurethral enucleation or laser vaporisation procedures. The 2018 AUA guidance recommends that clinicians consider open, laparoscopic or robotic simple prostatectomy for men with very large prostates with no specific size cut-off (12). However, many surgical treatment options, including bipolar TURP, greenlight laser surgery, and prostatic artery embolisation, have all been shown to be safe and efficacious in very large glands with short-to-medium-term follow-up (13-15).

With regard to the safety profile of the TURP procedure, despite the longer operating times (98 vs 56 mins) and a larger decrease in post-operative haemoglobin (21.8 vs 10.5 g/dL), the overall complication rate did not differ between the two groups in our study. This was comparable to the expected complication rate in the literature (16). When distributed across the Clavien-Dindo classification, there was a higher proportion of grade 4 complications in the large prostate group than the <100 cc prostate group (8.3% vs 2.4%; p=0.03). Most of these complications were exacerbations of pre-existing cardio-respiratory medical comorbidities that were not matched between the two groups. Despite the higher incidence of grade 4 complications, overall hospital stays and readmission rates were equivalent between the two groups. Unique complications, such as urinary tract infection, TUR syndrome and transfusion requirement, were evenly matched and similar to those expected from international guidelines (5).

From a functional perspective, the two groups were evenly matched regarding achieving independence from catheterisation irrespective of prior catheterisation status. A substantial proportion of our total patient cohort was catheter-dependent before undergoing TURP (50.8%). Our decision to evaluate "LUTS events" was designed to focus on combined clinically orientated functional outcomes post-TURP. Although IPSS scores may be helpful in objectively determining the improvement in symptoms after BPH treatment, symptom scores may not necessarily drive the need for further investigations and treatments or alter clinicians' decisions to discharge patients back to the care of community practitioners. Our definitions of LUTS events after BPH surgery (Table 1) aimed to represent comprehensive,

measurable clinical outcomes that were highly relevant to BPH surgery and reflect objective functional efficacy and indicate patients' degree of bothersome symptoms that require further investigations or treatments. In addition, given the high proportion of catheter-dependent patients before TURP, the lack of validity of pre-operative IPSS scores in patients with indwelling catheters would eliminate over half of our patients from comparative analysis. The overall shape of the time-to-event curve (Figure 2) showed no statistically significant difference between the two groups, and the incidence of LUTS events as defined in Table 1 was consistent with the accepted event complication rate, such as bladder neck contracture, urethral stricture and re-do TURP in contemporary series (17).

The proportion of patients with incidental prostate cancer demonstrated was double in the <100 cc group compared with the ≥100 cc group, although this finding was not statistically significant (p=0.09). This trend is likely to be due to reduced sampling of the peripheral zone in TURP for the larger glands compared with small glands. The incidental detection rate supports the added benefit of TURP in obtaining histological information compared with vaporisation techniques or prostatic artery embolisation.

Study Limitations

Our study has some important limitations. Given the retrospective design of the study, data collection was dependent on accurate documentation of clinical events. Selection bias is always a limitation of retrospective studies. However, as our two comparative groups were purely based on prostate size, this bias is reduced. In addition, we do not offer any other form of endoscopic outflow surgery in our department (e.g. laser enucleation, laser PVP or UroLift). During the study period, only two patients in our unit underwent simple open prostatectomy (data not shown); both patients had prostate volumes in >350 cc and were deemed unsuitable for endoscopic management after endoscopic assessment. Therefore, except for these two patients, all men requiring outflow surgery for BPH underwent the same treatment modality. The documentation of LUTS events has relied on patients presenting to our institution or regional hospitals and appropriate referrals to our unit from community practitioners. This introduces the potential for under-reporting of such events; however, our institution has the only public urology service in the region.

Conclusion

In the absence of available prospective evidence on this topic, we believe our study supports the use of TURP in large prostate glands when undertaken by an experienced surgical team performing a high caseload. TURP still has a current role in treating LUTS secondary to BPH, even with the variety of minimally invasive techniques available to surgeons. Although international guidelines for the use of TURP in large glands are conservative, we believe that TURP can still be safely offered to such patients with the expectation of a good functional outcome.

Ethics

Ethics Committee Approval: Following ethical approval from the Far North Queensland Human Research Ethics Committee (EC00157), we conducted a de-identified retrospective study at our institution of all patients treated with TURP for BPH over four years from March 2014 to July 2018.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.L., S.A., G.E., P.S., Concept: M.K., A.L.N., S.W.P., Design: A.L., S.A., G.E., P.S., Data Collection or Processing: M.K., A.L.N., S.W.P., Analysis or Interpretation: M.K., A.L.N., S.W.P., Literature Search: A.L., S.A., G.E., P.S., Writing: M.K., A.L.N., S.W.P.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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LUTS events:

Failure to void / need for long term catheterization (urethral or supra pubic)
Need for long term intermittent self-catheterisation
LUTS requiring long term medical therapy eg anticholinergic
LUTS requiring further investigations eg cystoscopy / urodynamics
Re-referral to the department for evaluation of LUTS
Need for repeat TURP
Need for stricture management
Episode of urinary retention
Formation of bladder stones

ORIGINAL RESEARCH
Furctional

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Perceived Stress and Accompanying Low Urine pH Are in Relation to Bladder Pain Syndrome

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What's known on the subject? and What does the study add?

Emotional stress has been demonstrated to be associated with symptom exacerbations in patients with bladder pain syndrome (BPS). Some clinical studies have also revealed that urinary alkalisation therapy improved symptoms in patients with BPS or hypersensitive bladder. This prospective case-control study evaluated the contributions and association of perceived stress accompanied with acidic urine with symptoms of BPS. Perceived stress is independent of urine pH, as they each relate to BPS symptoms in a bidirectional manner. Perceived stress and urine pH should be evaluated in patients with BPS.

Abstract

Objective: The clinical relevance of low urine pH and perceived stress levels in patients with bladder pain syndrome (BPS) has not yet been clarified. In this study, we hypothesised that urine pH and perceived stress levels may differ in patients with BPS and that they may be related to each other.
Materials and Methods: A prospective case-control study was conducted to test the hypothesis. Patients aged >18 years who were newly diagnosed with BPS were included in the patient group. The control group consisted of healthy volunteers aged >18 years. The 10-item Perceived Stress scale (PSS-10), spot urine pH measurements, Interstitial Cystitis Symptom index (ICSI), Interstitial Cystitis Problem index (ICPI), visual analogue scale for pain (VAS-Pain) and quality-of-life (QOL) scores were evaluated. Independent samples t-test and multivariate regression with path analysis were performed.
Results: The study evaluated 84 patients with BPS and 86 healthy participants. The mean spot urine pH, PSS-10, ICSI, ICPI, VAS-Pain and QOL scores were different between the patient group and control group. Spot urine pH level [p=0.01, odds ratio (OR)=0.31] and PSS-10 scores (p=0.01, OR=1.1) remained significant predictors of BPS in the multivariate analysis. Lower urine pH and higher perceived stress levels were associated with worse ICSI, ICPI, VAS-Pain and QOL scores.
Conclusion: Acidic urine pH and high perceived stress levels are associated with the presence of BPS. Perceived stress is independent from low urine pH, as they each relate to BPS symptoms in a bidirectional manner.
Keywords: Acidic urine, bladder pain, interstitial cystitis, perceived stress

Introduction

Since Alexander JC Skene coined the name "interstitial cystitis" in 1887, its definition, estimated prevalence and pathophysiological aspects investigated according to its subtypes have changed considerably over time (1). The phenotypic heterogeneity of the disorder and its associations restrains the physicians when treating patients with persisting symptoms of bladder pain syndrome (BPS). Promising results have been reported in recent studies on the therapeutic effects of urinary alkalisation therapy (2,3). However, incidental findings in these studies such as improving urgency, frequency and pain with medical urine alkalisation barely reveal the aetiological relationships with urine pH. This issue formed the basis for the first hypothesis of this study: Urine pH levels differ between patients with BPS and individuals without BPS. Low urine pH as a marker of renal acid load is also an under-investigated clinical finding. Metabolic acidosis, dietary acid load and renal

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tubular dysfunction are known causes of excessive renal acid load (4). Metabolic acidosis and diet-dependent renal acid load were found to be associated with higher glucocorticoid levels (5). Although data on the association of stress with renal acid load is limited, glucocorticoids are known to be stress response hormones. Emotional stress is known to be a potential trigger of symptom exacerbations in patients with interstitial cystitis/BPS (6-8). At present, clinicians are quantifying the level of stress using valid instruments rating the perceived level of stress in each patient. The relationship between urine acidity level and perceived stress in patients with BPS has not been investigated, and whether perceived stress can be a trigger or mediator of acidic urine is still unclear. This issue provided the basis for our second hypothesis: Perceived stress accompanied by excessive urinary acid load may be associated with the presence and symptom severity of BPS. Therefore, this study aimed to evaluate the accompanying perceived stress levels of patients with BPS in comparison with healthy participants.

Materials and Methods

Study Design and Setting

A prospective case-control study was conducted to test the aforementioned hypotheses. The trial was started in August 2018 and ended in February 2020 after approval from review board (CU-06-07-2018/No: 45). During the recruitment period, potential participants who have given written consent for taking part in the study were evaluated by the researchers in the hospital setting. The patient group consisted of participants aged >18 years who were admitted to the urology clinic with complaints related to BPS and were newly diagnosed with BPS after all appropriate diagnostic tests and consultations were performed. As accepted currently, we used the definition "An unpleasant sensation (pain, pleasure, or discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks in the absence of other identifiable causes" to establish a diagnosis of BPS (9,10). When patients presented with gross or microscopic haematuria, cystoscopy with hydrodistension under general anaesthesia was performed as needed. The control group consisted of volunteers aged >18 years who visited the gynaecology and/or urology outpatient clinic for reasons except as being a patient (relative of a patient, hospital staff, etc.) and who had no complaints related to cystitis or pelvic pain. Spot urine analysis was performed on the control group as a sole laboratory investigation.

Following the written informed consent process, all study participants were asked to rate their complaints using three questionnaires during the interview. In this study, translated forms of the O'Leary-Sant Interstitial Cystitis Symptom index (ICSI) (Appendix A) and O'Leary-Sant Interstitial Cystitis Problem index (ICPI) (Appendix B) were used to measure cystitis symptoms (11,12). Since linguistically validated interstitial cystitis questionnaires were not available, both questionnaires were translated from their original English by an English language teaching professional for the current study. The validated version of the 10-item Perceived Stress scale (PSS-10) was used to measure the perceived stress levels of the participants in the last 4 weeks (13-15). Changes in PSS-10 scores ranged from 0 to 40 points, with higher scores indicating higher levels of perceived stress (13-15). Participants were asked to rate their pain levels using a 10-point (0-10) Likert visual analogue scale (VAS). Quality-of-life (QOL) was rated with a 6-point (0-5) Likert scale, with a higher score indicating better QOL. Patients with central or peripheral nervous system disease and taking antidepressants, antipsychotic, anxiolytic, anticholinergic, alpha blocker, mirabegron, or gabapentinoid medications were excluded from the study. Participants who rated either the ICSI or ICPI questionnaires above 6 points were excluded from the control group. The flowchart of the study is shown in Figure 1.

Study Size and Data Handling

Ninety-two participants for each group have been targeted according to sample size estimation using G*Power software, with 70% power, type 1 error of.05 and type 2 error of.80. Age, body mass index (BMI), current complaints, duration of complaints, comorbidities, medications and abnormal physical examination findings were recorded for each participant. Routine laboratory and radiologic examination findings were also recorded. The main variables investigated between the case and control groups included perceived stress levels (PSS-10) and spot urine pH as independent variables and O'Leary-Sant indexes (ICSI and ICPI), VAS-pain and QOL scores as dependent variables.

Statistical Analysis

At the beginning of the data analysis, Kolmogorov-Smirnov normality test was performed. The independent samples t-test was performed for all normally distributed variables during group comparisons. Non-parametric test was performed on variables that demonstrated a skewed distribution. The reliability of the linguistically translated ICSI and ICPI questionnaires were analysed using Cronbach's alpha test. A multivariate analysis was performed with logistic regression for nominal variables and linear regression for normally distributed dependent variables. In skewed distribution, logarithmic transformation was utilised before rendering the variables into a parametric regression. We used the Hosmer-Lemeshow test during the multivariate analysis with a binary logistic regression model for the final outcome. Hierarchical linear regression and path analysis for the measured dependent variables in the patient group were applied. While this study was planned in a prospective manner,

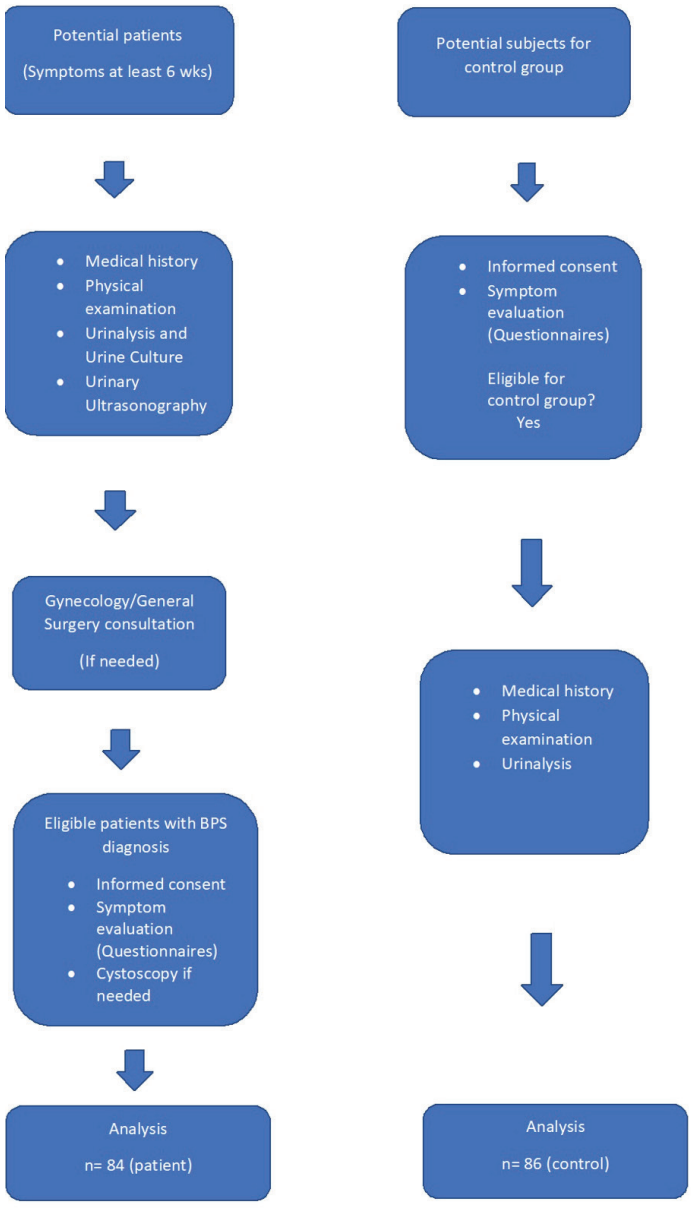

Figure 1. Flowchart of the study

none of the matching techniques were anticipated. All analyses were performed using the PASW Statistics (IBM, Armonk, NY, USA).

Potential Biases

Selection bias was the main confounder of this study. Thus, strict exclusion criteria and previously validated cut-off scores for ICSI and ICPI were used to deal with bias during the recruitment period.

Results

A total of 170 participants were recruited for the study. The patient group included 84 patients with BPS (73 women and 11 men), and 86 healthy participants (70 women and 16 men) were included in the control group. Only the BMI was significantly different between the patient and control groups. Demographic characteristics and comorbidities are shown in Table 1. Among patients with BPS, 42 (50%) patients had pain in the pelvic region, 15 (17.9%) in the pelvic and lumbar regions and 27 (32.1%) in the pelvic and lumbar regions with involvement of other body sites. The mean pain duration was 23.6 (±30.7) months. The mean serum creatinine (mg/dL) and serum C-reactive protein values were 0.83 (±0.19) and 5.7 (±15.6), respectively. Accompanying nephrolithiasis (range, 3-8 mm) was found in 17 (20.2%) patients. Cystoscopy was performed in 19 (22.6%) patients. Ulcerative cystitis was found in 2 (2.4%) patients, non-ulcerative cystitis with glomerulations in 13 (15.5%) patients and normal bladder appearance in the remaining 4 (4.8%) patients.

Among the study variables, only urine pH values demonstrated a skewed distribution in both groups (positive skewness of 0.59±0.26 in the control group and 1.51±0.26 in the BPS group). Therefore, we used the Mann-Whitney U test to compare the urine pH values between the groups. The mean spot urine pH, PSS-10, ICSI, ICPI, VAS-Pain and QOL scores were different between the patient and control groups. Results of comparative analysis within the groups are shown in Table 2. A reliability analysis of the items on the interstitial cystitis questionnaire revealed an intermediate level of internal consistency for the translated versions of the ICSI (Cronbach's alpha value of 0.78) and ICPI (Cronbach's alpha value of 0.84).

Initially, a binary logistic regression model was constructed for the presence of BPS. At the first block of the model, age and BMI were entered. The second block included spot urine pH, spot urine density and PSS-10 scores. Spot urine pH levels [p=0.01, odds ratio (OR)=0.31 (95% confidence interval (CI) 0.12-0.75)] and PSS-10 scores [p=0.01, OR=1.1 (95% CI 1.0-1.2)] were significant predictors in the final model. A hierarchical regression for ICSI, ICPI, VAS-Pain and QOL scores in the patient group revealed that only PSS-10 scores predicted the ICPI [standardised coefficient β=0.34 (p=0.01)] and VAS-Pain [standardised coefficient β=0.35 (p=0.01)] scores and were independent from spot urine pH, age and BMI. The path analysis with the study cohort also revealed significant correlations, as shown in Figure 2. Among the participants, ICSI, ICPI, VAS-Pain and QOL scores were associated with both perceived stress levels and spot urinary pH levels. Lower urine pH and higher perceived stress were associated with worse ICSI, ICPI, VAS-Pain and QOL scores. The perceived stress scores were affected by ICPI and VAS-Pain levels. No predictor of urine pH levels was found among the study variables.

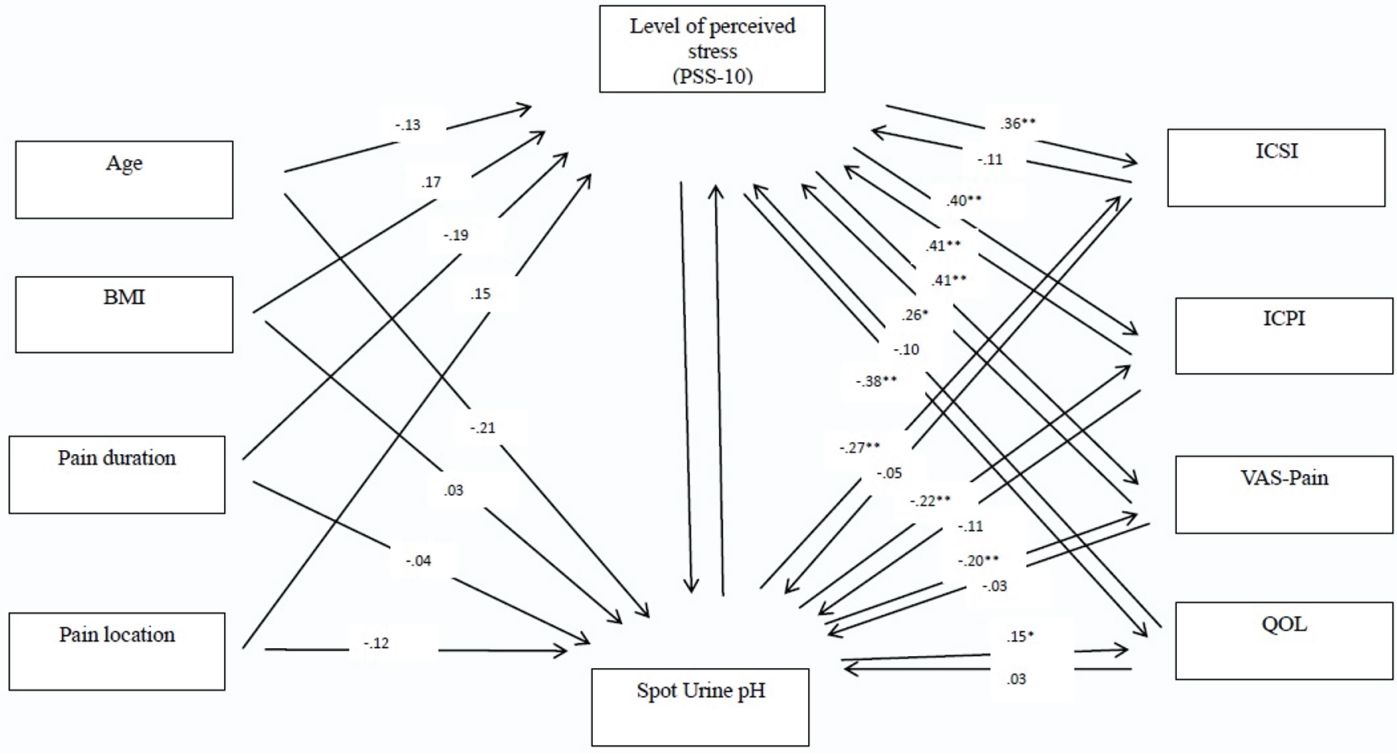

Figure 2. Results of the multivariable path analysis that demonstrates the relations of urine pH, perceived stress and BPS symptoms. Correlation coefficients measured in the multivariable regression analysis are shown in the figure

*indicates p≤0.05 and **indicates p<0.01

Pain duration: Numerically coded as months

Pain location: Categorically ordered as 1 for pelvic region only, 2 for pelvic and lumbar region and 3 for pelvic plus lumbar region and other body parts, BPS: Bladder pain syndrome, BMI: Body mass index, VAS: Visual analogu scale, QOL: Quality-of-life

Table 1. Characteristics of the study participants

	Control group n=86	Patient group (BPS) n=84	p-value
Age (years)	39.7±10.4	42.4±11.4	0.11
Gender (F/M)	70/16	73/11	-
BMI (kg/m^2)	25.8±4.6	27.7±4.7	0.01**
Diabetes mellitus	1 (1.1%)	5 (5.9%)	0.11
Hypertension	7 (6.0%)	11 (13%)	0.32
Asthma (± allergy)	1 (1.1%)	5 (5.9%)	0.11
Thyroid dysfunction	10 (11.6%)	7 (8.3%)	0.61
Other disease	6 (6.9%)	14 (16.6%)	0.059
Smoking history (yes)	20 (23.2%)	14 (16.6%)	0.24
Alcohol consumption (yes)	2 (1.7%)	1 (1.1%)	-

*significant at the level of 0.05 (with two-sided analysis)
**significant at the level of 0.01 (with two-sided analysis), BPS: Bladder pain syndrome, BMI: Body mass index

Table 2. Analysis of measured variables within study groups

	Control group n=86	Patient group (BPS) n=84	p-value
Spot urine pH	6.2±0.5	5.8±0.6	0.0001**
Spot urine density	1.016±0.007	1.015±0.007	0.91
PSS-10 score	18.3±5.7	22.9±6.0	0.0001**
ICSI score	3.2±1.5	10.6±3.7	0.0001**
ICPI score	3.1±1.8	10.6±3.2	0.0001**
VAS-Pain score	2.0±1.7	6.0±2.5	0.0001**
QOL score	2.7±1.4	1.4±1.1	0.0001**

*significant at the level of 0.05 (with two-sided analysis)
**significant at the level of 0.01 (with two-sided analysis), BPS: Bladder pain syndrome, PSS-10: The 10-item Perceived Stress scale, ICSI: Interstitial Cystitis Symptom index, ICPI: Interstitial Cystitis Problem index, VAS-Pain: Visual analogue scale for pain, QOL: Quality-of-life

Discussion

In this case-control study, we investigated the potential interrelations and predictor roles of urine pH and perceived stress level of patients with BPS. We found that low urine pH and increased perceived stress predicted the presence of BPS. The urine pH and perceived stress levels correlated with ICSI, ICPI, VAS-pain and QOL scores independent from each other.

The ICSI, ICPI, VAS-Pain and QOL scores were significantly different between the groups. Although linguistically validated ICSI and ICPI questionnaires are still not available in our country,

the clinical validity of ICSI and ICPI for patients with BPS has already been confirmed (11,12). O'Leary et al. (11) concluded that nearly all patients with BPS have given both ICSI and ICPI questionnaires ratings higher than 6 points. For this reason, we used a cut-off of 6 points while rendering participant to our control group to avoid selection bias. As the ICSI and ICPI questionnaire results showed acceptable internal consistency, we believed that our study groups were constructed appropriately.

We performed cystoscopy with hydrodistension under general anaesthesia as needed. Although recent trials have recommended routine cystoscopic phenotyping of patients with BPS during the initial diagnostic evaluation, our cystoscopic findings, in terms of ulcerative cystitis prevalence, or normal findings do not deviate from those in the literature (16-18). Additionally, we found relatively high rates of nephrolithiasis in our patients with BPS compared with the current known prevalence (19). To the best of our knowledge, no data were available on the prevalence rate of nephrolithiasis in patients with BPS. Further clinical studies are needed on this topic, while we can only speculate that acidic urine pH may increase the risk of kidney stone formation in patients with BPS.

As a novel finding of this study, an increase in the level of urine pH is associated with lower odds for the presence of BPS. Our path analysis also revealed that acidic spot urine pH levels predicted worse symptom scores in the patients. Moreover, the urine pH level is not correlated with any patient characteristics or perceived patient stress. Nguan et al. (20) reported the first investigation of the effect of urine pH changes on pain scores of patients with interstitial cystitis in a double-blind crossover study. They found no difference in the pain scores of patients with intravesical instillation of either an acidic solution (pH 5.0) or a neutral buffered solution (pH 7.5) (20). In 2014, Ueda et al. (3) reported a significant improvement in micturition complaints and ICPI scores of patients with hypersensitive bladder by using urinary alkalisation therapy to increase the urine pH to 6.2. Recently, Sönmez et al. (2) also demonstrated that urine alkalisation therapy improves voiding symptoms and pain scores of women with acidic urine (pH <6) after 4 weeks. Although no physiopathological data exist on the relationship between urine pH level and BPS symptoms, existing preclinical data speculate that the expression of TRPV1 capsaicin and acid-sensing ion channel receptors at the terminals of bladder afferent C fibre terminals might be responsible for symptom improvement through urine alkalisation in women diagnosed with hypersensitive bladder and those with acidic urine (2,3,21-25). Thus, our results may promote current knowledge and might provide a clinical framework for further clinical and preclinical studies to clarify the relationship between acidic urine pH and BPS symptoms.

The higher level of perceived stress in the current study population indicates higher odds for the presence of BPS. In this study, an increase in perceived stress has direct disruptive effects on patients' complaints. The second hypothesis of this study was partially rejected because perceived stress was not associated with urine pH level. However, preclinical studies have demonstrated a relationship between water avoidance stress and severity of cystitis (8,26). Previous clinical studies have also revealed that daily life stress and acute stress are related to increased urgency and pain ratings in patients with interstitial cystitis (6,7,27). Autonomic nervous system hyperactivity and stress-induced hyperalgesia were initially the focus of trials investigating the pathogenetic relationship between stress and interstitial cystitis/BPS (28). Recently, Jhang et al. (29) demonstrated that the dysregulation of bladder corticotrophin-releasing hormone receptor subtypes has improved the pathogenetic theories on stress-induced symptom exacerbations in patients with BPS. In the present study, we measured the perceived stress level of the participants using a valid instrument and demonstrated that, in addition to the predictive value for BPS, the perceived stress of the participants was also influenced by their perception of the cystitis problem and pain level. A previous factor analysis of the PSS-10 revealed that the questionnaire constituted mainly of "inadequate self-efficacy" and "perception of stress discomfort" factors (13). A positive feedback mechanism might underlie the current correlations, i.e. "patients with BPS who have increasing pain and feel that they have problematic bladder complaints are also exposed to higher perceived stress level".

Study Limitations

First, the ICSI and ICPI questionnaires that were used were not linguisticaly validated. Second, we did not perform cystoscopy on all patients during the diagnostic evaluation of the case group.

Conclusion

Acidic urine pH and higher perceived stress levels are associated with the presence of BPS. Perceived stress independent from urine pH is related to BPS symptoms in a bidirectional manner. Physicians should take spot urine pH and perceived stress levels into account during decision making while evaluating patients with BPS. Furthermore, prospective placebo-controlled trials are needed to determine the therapeutic relevance of urinary pH and stress modifiers.

Acknowledgements: We wish to thank Ms. Betül Karamış, (Ph.D) for her support during translation of ICSI and ICPI questionnaires.

Ethics

Ethics Committee Approval: All study participants provided informed consent, and the study design was approved by the appropriate ethics review board (Çukurova University School of Medicine-Adana-CU-06-07-2018/no: 45).

Informed Consent: During the recruitment period, potential participants who have given written consent for taking part in the study were evaluated by the researchers in the hospital setting.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.C., E.C., Concept: A.C., E.C., Design: A.C., E.C., Data Collection or Processing: A.C., E.C., Analysis or Interpretation: A.C., Literature Search: A.C., B.Ç., Writing: A.C., E.C., B.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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Appendix A

Interstitial Cystitis Symptom Index (ICSI)

During the past month:

How often have you felt the strong need to urinate with little or no warning?

0. Not at all
1. Less than 1 time in 5
2. Less than half the time
3. About half the time
4. More than half the time
5. Almost always

Have you had to urinate less than 2 hours after you finished urinating?

0. Not at all
1. Less than 1 time in 5
2. Less than half the time
3. About half the time
4. More than half the time
5. Almost always

How often did you most typically get up at night to urinate?

0. None
1. Once
2. 2 times
3. 3 times
4. 4 times
5. 5 or more times

Have you experienced pain or burning in your bladder?

0. Not at all
1. A few times
2. Almost always
3. Fairly often
4. Usually

Add the numerical values of the checked entries.

Total score

Appendix B

Interstitial Cystitis Problem Index (ICPI)

During the past month, how much has each of the following been a problem for you:

Frequent urination during the day?

0. No problem
1. Very small problem
2. Small problem
3. Medium problem
4. Big problem

Getting up at night to urinate?

0. No problem
1. Very small problem
2. Small problem
3. Medium problem
4. Big problem

Need to urinate with little warning?

0. No problem
1. Very small problem
2. Small problem
3. Medium problem
4. Big problem

Burning, pain, discomfort, or pressure in your bladder?

0. No problem
1. Very small problem
2. Small problem
3. Medium problem
4. Big problem

Add the numerical values of the checked entries.

Total score

ORIGINAL RESEARCH
Furctional

Doi: 10.4274/jus.galenos.2020.0025
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Comparison of the Effect of Continuous Positive Airway Pressure and Surgical Treatment of Obstructive Sleep Apnea Syndrome on Nocturia

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What's known on the subject? and What does the study add?

Obstructive Sleep Apnea syndrome (OSAS) may be one of the aetiological factors of nocturia, and the prevalence of nocturia in patients diagnosed with OSAS ranges from 52% to 76.9%. Continuous positive airway pressure (CPAP) therapy and/or surgical treatment are recommended for the treatment of OSAS. Regardless of treatment modalities (CPAP therapy or surgical treatment), treating OSAS improves nocturia.

Abstract

Objective: This study aimed to compare the effects of continuous positive airway pressure (CPAP) and surgical treatment of Obstructive Sleep Apnoea syndrome (OSAS) on nocturia.

Materials and Methods: Forty-eight patients who received treatment for OSAS and had nocturia between January 2019 and December 2019 were included in the study. Questionnaires of the International Prostate Symptom score, Overactive Bladder Symptoms score, International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms and International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms were administered to all patients. The number of nocturia was evaluated by the mean number of nocturia episodes in the bladder diary.

Results: Thirty-two (66.6%) patients received CPAP therapy, and 16 (33.3%) patients underwent surgical treatment for OSAS. The mean number of nocturia episodes of all patients before and after treatment was 2.3±1.4 and 1.7±2.2, respectively, and the difference was significant (p=0.032). However, surgical treatment and CPAP therapy were not superior to each other in terms of improving nocturia (p=0.901).

Conclusion: Regardless of treatment modalities, i.e., CPAP therapy or surgical treatment, treating OSAS improves nocturia.

Keywords: Obstructive Sleep Apnoea syndrome, nocturia, continuous positive airway pressure

Introduction

Nocturia was defined according to the International Continence Society as the complaint that the individual has to wake at night one or more times to void (1). Nocturia occurs at any age, although it is more common in the older population (2). Although nocturia is generally considered a symptom of benign prostate disease and/or bladder dysfunction, nocturia also occurs as a result of nocturnal polyuria, which is often defined as excessive night-time urine production. The pathophysiology of nocturia is classified into four mechanisms: an overall increase of urine production (24-h polyuria), an increase in urine production only at night (nocturnal polyuria), a permanent or only nocturnal reduced bladder capacity or any primary or secondary sleep disorder (3).

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Obstructive Sleep Apnea syndrome (OSAS), which is a common chronic disorder, is defined as complete or partial obstruction of the upper respiratory tract during sleep, which results in airflow reduction or cessation (4,5). OSAS may be one of the aetiological factors of nocturia, and the prevalence of nocturia in patients with OSAS ranges from 52% to 76.9% (6). Improvement of OSAS is expected to reduce the severity of nocturia. Continuous positive airway pressure (CPAP) therapy is recommended as primary treatment of OSAS (7). Taking into account the results of polysomnography (PSG) and pathologic site, surgical procedures could be performed in some patients. Various surgical procedures are described for these patients, such as septoplasty, uvuloplasty, uvulopalatoplasty, anterior palatoplasty, radiofrequency applications, laser-assisted surgery and maxillary and mandibular advancement (8).

Studies have revealed that CPAP therapy for OSAS also decreases the frequency of nocturia and the associated urine volume (9,10). However, to the best of our knowledge, only one study reported that surgical treatment of OSAS improves nocturia (11). Thus, in this study, we aimed to evaluate the effect of treatment of OSAS on nocturia and the superiority of CPAP therapy and surgical treatment to each other in terms of improving nocturia.

Materials and Methods

Patients who presented to the outpatient clinic with complaints of snoring and apnea were evaluated retrospectively by PSG after routine otorhinolaryngologic examinations between January 2019 and December 2019. Anterior rhinoscopy, oral examination and laryngoscopic examinations were performed to all patients. Patients were examined with the fibre-optic laryngoscope, and a Muller manoeuvre was performed to all patients. All patients were evaluated by the multidisciplinary sleep disorder board. After the evaluation of patients with snoring and apnea complaints who presented to the chest disease and otolaryngology outpatient clinics, pulmonologists and otolaryngologists referred these patients to the urologists.

Patients diagnosed and treated with lower urinary tract disease (benign prostate disease, bladder dysfunction, urinary tract infection, etc.) and previous urogenital operations and neurological disorders patients who did not receive surgical treatment or CPAP therapy due to OSAS were excluded from the study.

PSG tests of patients were performed at the sleep laboratory of Çukurova University, Faculty of Medicine, Department of Chest. The severity of OSAS was determined by the apnea-hypopnea index (AHI; mean number of apnea + hypopnoea per hour of sleep). In this study, AHI was classified as mild (5-15), moderate (16-30) and severe (>30) (12). CPAP or surgical treatment was given to the patients according to their clinical condition, OSAS severity and upper airway pathologies.

All patients filled the three-day bladder diary and questionnaires of the International Prostate Symptom score (IPSS), Overactive Bladder Symptoms score (OABSS), International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms LUTS (ICIQ-MLUTS) and ICIQ-Female LUTS (ICIQ-FLUTS) before PSG was performed and 3 months after CPAP therapy and surgical treatment. The number of nocturia was evaluated by the mean number of nocturia episodes recorded in the bladder diaries.

Ethics

Ethics committee approval for the study was obtained from the ethics committee of the University of Çukurova (approval no: September 4, 2020; 103/5). The study was carried out in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarised as mean and standard deviation and as median and minimum-maximum, where appropriate. Chi-square test was used to compare categorical variables between the groups. For comparison of continuous variables between two groups, Mann-Whitney U test was used. For comparison of two related (paired) continuous variables, paired samples t-test was used. The level of significance for all tests was 0.05.

Results

Forty-eight patients who had nocturia and underwent CPAP therapy or surgical treatment for OSAS were included in the study. The mean patient age was 50.6±11.5 (range, 29-78) years. Of them, 37 (77.1%) were male and 11 (22.9%) were female. Moreover, 5 (10.4%) patients had mild, 13(27.1%) had moderate and 30 (62.5%) had severe OSAS. Furthermore, 32 (66.6%) patients received CPAP therapy, and 16 (33.3%) patients underwent surgical treatment for OSAS. A comparison of demographic and clinical characteristics according to treatment methods are presented in Table 1. The mean AHI of patients who received CPAP therapy was 48.5±27.5 and that of patients who underwent surgical treatment was 41.5±27.7 (p=0.437).

The mean number of nocturia episodes of all patients before and after treatment was 2.3±1.4 and 1.7±2.2, respectively, and the difference was significant (p=0.03). The OAB-SS scores of all patients significantly decreased from 11.6±8.4 to 9.1±8.8 (p=0.004). The total FLUTS scores of all patients significantly decreased from 12.7±7.8 to 10.2±8.4 (p=0.046). Although a significant increase was noted in the total daily urine volume after treatment, there was a significant decrease in the total

Table 1. Demographic data and bladder diary parameters of patients according to treatment methods

	CPAP therapy (n=32)	Surgical treatment (n=16)	p-value
Age (years)[a]	51.5±12.5 52.0 (30.0-78.0)	48.8±9.5 50.0 (29.0-70.0)	0.463
BMI kg/m^2 [a]	32.7±6.0 33.0 (22.0-47.0)	31.8±6.8 30.0 (22.0-47.0)	0.443
Gender[b]			0.999
Male	25 (78.1)	12 (75.0)	
Female	7 (21.9)	4 (25.0)	
AHI value[a]	48.5±27.5 46.0 (7.0-135.0)	41.5±27.7 31.0 (6.0-85.0)	0.437
AHI severity[b]			0.141
Mild	2 (6.2)	3 (18.8)	
Moderate	7 (21.9)	6 (37.5)	
Severe	23 (71.9)	7 (43.8)	
HT[b]	18 (56.2)	7 (43.8)	0.610
DM[b]	9 (28.1)	3 (18.8)	0.725
Smoking[b]	16 (50.0)	10 (62.5)	0.609
Total daily fluid intake (mL)[a]	2303.1±1043.0 2000.0 (1000.0-5000.0)	2393.7±1373.7 1900.0 (1000.0-6000.0)	0.824
Total daily urine volume (mL)[a]	1850.0±830.0 1700.0 (1000.0-5000.0)	1850±783.1 1650.0 (1000.0-3500.0)	0.956
Total night-time urine volume (mL)[a]	532.8±460.9 400.0 (100.0-2000.0)	375.0±179.8 400.0 (100.0-800.0)	0.439

AHI: Apnea-hypopnea index, HT: Hypertension, DM: Diabetes mellitus, BMI: Body mass index, CPAP: Continuous positive airway pressure
[a]Data are expressed as mean ± standard deviation, median (min-max).
[b]Data are expressed as n (%).
Note: Bold values indicate significance (p<0.05)

night-time urine volume (p=0.016 and p=0.024, respectively) (Table 2). No significant difference in terms of IPSS and MLUTS between before and after treatment (p=0.621 and 0.326, respectively). We thought that it was caused by low IPSS score because we excluded patients with benign prostate disease.

Surgical treatment and CPAP therapy were not superior to each other in terms of improving nocturia (p=0.901). Compared with surgical treatment, CPAP therapy was superior only in terms of improving the IPSS score (p=0.017). As regards other parameters, CPAP therapy and surgical treatment were not superior to each other (p>0.005) (Table 3).

Discussion

In this study, we investigated the superiority of CPAP and surgical procedures in nocturia improvement in patients with nocturia due to OSAS. To our knowledge, this topic had never been explored previously. We found that CPAP and surgical

Table 2. Comparison of questionnaire form and bladder diary parameters of patients with OSAS before and after OSAS treatment

	Before treatment (n=48)	After treatment (n=48)	p-value
Nocturia episodesa	2.3±1.4	1.7±2.2	0.032
OABSS[a]	11.6±8.4	9.1±8.8	**0.004**
IPSS[a]	8.1±7.9	7.7±8.3	0.621
MLUTS totala (n=37)	6.7±7.9	5.1±6.2	0.326
FLUTS totala (n=11)	12.7±7.8	10.2±8.4	**0.046**
Total daily urine volume (mL)[a]	1850.0±806.3	2016.2±803.2	**0.016**
Total night-time urine volume (mL)[a]	480.2±395.1	333.7±314.8	**0.024**

[a]Data are expressed as mean ± standard deviation
Note: Bold values indicate statistical significance (p<0.05).
IPSS: International Prostate Symptom score, OABSS: Overactive Bladder Symptoms score, MLUTS: Male lower urinary tract symptoms, FLUTS: Female lower urinary tract symptoms, OSAS: Obstructive Sleep Apnea syndrome

Table 3. Comparison of questionnaire form and bladder diary of patients with OSAS before and after treatment between CPAP therapy and surgical treatment

	CPAP therapy (n=32)	Surgical treatment (n=16)	p-value
Δ-Nocturia Episodes[a]	-0.6±1.9 -1.0 (-6.0 to 6.0)	-0.5±1.9 -0.5 (-3.0 to 5.0)	0.901
Δ-OAV-B8[a]	-2.2±4.2 -1.0 (-14.0 to 6.0)	-1.5±4.3 -1.0 (-10.0 to 5.0)	0.945
Δ-IPSS[a]	-2.2±6.6 -1.0 (-21.0 to 14.0)	3.5±6.7 0.0 (-1.0 to 18.0)	**0.017**
Δ-MLUTS[a]	-1.3±4.8 0.0 (-14 to 11.0)	0.4±3.5 0.0 (-4.0 to 9.0)	0.428
Δ-FLUTS[a]	-1.1±1.8 0.0 (-4.0 to 1.0)	-5.0±6.2 -3.5 (13.0-0.0)	0.412
Δ-Total daily urine volume (mL)[a]	274.2±554.3 200.0 (-1500.0 to 1500)	58.3±556.7 0.0 (-1300.0 to 1000.0)	0.302
Δ-Total night-time urine volume (mL)[a]	-183.5±372.9 -150.0 (-1500.0 to 800.0)	0.0±245.8 -50.0 (-400.0 to 450.0)	0.114

[a]Data are expressed as mean ± standard deviation; median (min-max).
Δ: After treatment-before treatment
Note: Bold values indicate statistical significance (p<0.05).
IPSS: International Prostate Symptom score, OABSS: Overactive Bladder Symptoms score, MLUTS: Male lower urinary tract symptoms, FLUTS: Female lower urinary tract symptoms, CPAP: Continuous positive airway pressure, OSAS: Obstructive Sleep Apnea syndrome

treatment both improved nocturia but were not superior to each other. Thus, it is important to correct the aetiopathogenesis.

OSAS may play a role in the aetiology of nocturia, and a high prevalence of nocturia was reported in patients with OSAS (6). This occurs because of two mechanisms. First, nocturia is a result of airway obstruction caused by OSAS. Airway obstruction causes an increase in the intrathoracic negative pressure and venous blood flow to the heart. This situation stimulated the secretion of atrial natriuretic peptide (ANP) by the cardiac ventricles and right atrium (13). Second, nocturia is related to hypoxia caused by airway obstruction. Hypoxia causes ANP secretion by increasing pulmonary vasoconstriction and right atrial transmural pressure (14). In patients with OSAS, ANP causes nocturia by excessively increasing the production of urine at night. Therefore, we hypothesised that when treating OSAS will improve nocturia. Our study shows that nocturia episodes and night-time overproduction of urine significantly decreased after the treatment of OSAS. However, surgical treatment and CPAP therapy were not superior to each other in terms of improvement of nocturia episodes and night-time overproduction of urine.

A study conducted on 1790 patients reported that nocturia episodes were significantly more common in patients with OSAS. Authors concluded that age, body mass index, hypertension, AHI and respiratory effort index were significantly associated with nocturia (6). In a meta-analysis of 13 studies, with a total of 406 patients and 9518 controls, a significant association was found between OSA and risk of nocturia [RR=1.41, 95% confidence interval (CI) 1.26-1.59] and that patients who had severe OSA were at high risk of nocturia. The authors found that OSA was associated with risk of nocturia in men (RR=1.487, 95% CI 1.087-2.034, p=0.013); however, no significant relationship was found between OSA and nocturia in women (RR=1.537, 95% CI 0.831-2.842, p>0.05) (15). In another study of 1757 men undergoing PSG, nocturia was significantly associated with age and AHI, but OSAS may not be a risk factor for nocturia in the older population (16).

A meta-analysis revealed that the mean number of nocturia episodes decreased by 2.28 and the mean night-time urine volume (mL) decreased by 183.12 mL in patients after CPAP for OSAS (17). Another study reported that CPAP reduced nocturnal urine frequency and improved IPSS, QOL index and OABSS in patients with OSAS. They found that nocturnal urine production was decreased; this might have improved the night-time frequency and hours of undisturbed sleep (18). In another study on 51 patients with OSAS, Miyauchi et al. (10) concluded that 1 month of CPAP therapy significantly improves night-time frequency as well as improves overall IPSS and QOL score.

To our knowledge, only one study investigated the effect of surgical treatment due to OSAS on nocturia and reported that surgical treatment significantly decreased the number of nocturia, IPSS, OABSS, and QOL (11). However, no study has investigated the superiority of CPAP therapy and surgical treatment to each other in terms of improving nocturia in patients with OSAS. Therefore, our study is valuable. In this study, surgical treatment and CPAP therapy were not superior to each other in terms of improving nocturia, OABSS, and FLUTS. Moreover, OSAS treatment did not improve IPSS, and we thought that it was due to the low IPSS score because we excluded patients with benign prostatic hyperplasia. Thus, hypoxia, which is important regardless of the method, should be treated.

Study Limitations

One of the limitations of this study is the low number of patients with OSAS receiving CPAP therapy and surgical treatment. Moreover, we could not perform subgroup analysis according to surgical methods performed.

Conclusion

Regardless of treatment modalities, i.e., CPAP therapy or surgical treatment, treating OSAS improves nocturia. Thus, one of the most important methods of treating nocturia is to eliminate the risk factor.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Ethics Committee of the University of Çukurova (approval no: September 4, 2020; 103/5). The study was carried out in accordance with the principles of the Helsinki Declaration.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D., O.S., I.T., Concept: M.D., S.K., I.A.A., Design: M.D., O.S., S.K., Data Collection or Processing: M.D., O.S., S.K., N.A., M.D., I.T., I.A.A., Analysis or Interpretation: M.D., V.I., N.A., M.D., I.T., Literature Search: M.D., S.K., V.I., N.A., M.D., I.T., I.A.A., Writing: M.D., S.K., V.I., I.T., İ.A.A.

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Effects of Three-dimensional Measurement of the Urinary Stone Size on the Surgical Outcomes of Retrograde Intrarenal Stone Surgery

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What's known on the subject? and What does the study add?

The main objective of this study was to measure stone size by calculating the stone volume owing to its three-dimensional configuration in space, instead of measuring the longest side in a single plane or calculating the stone area. The threshold values that were determined as significant parameters that affect stone-free status were the presence of one stone, stone size of 1.48 cm^2, stone volume of 1.54 cm^3 and 55 min of operation time. If determined by volume calculation, retrograde intrarenal surgery is an effective and reliable method for stones <1.54 cm^3.

Abstract

Objective: This study aimed to investigate peri-/postoperative effects of three-dimensional measurement of stone size in patients who underwent retrograde intrarenal surgery, where preoperative stone size calculations determine the operation decisions and prognosis. Another aim is to determine a limit value in cm^3 for retrograde intrarenal surgery and to predict stone-free status based on this limit value.
Materials and Methods: Data of 184 patients were retrospectively analysed. Patients were divided into two groups according to whether the stone-free status was achieved. Postoperative stone-free status and related effective parameters were analysed statistically.
Results: No significant difference was found between age, gender, Hounsfield unit, length of hospital stay, secondary retrograde intrarenal surgery, renal unit abnormality, stone side, stone opacity, presence of additional ureteral stone, hydronephrosis and preoperative Double-J stent placement with stone-free rate. Subsequent interventions for residual stones, number of stones, stone sizes in cm^2 and cm^3 and operation time were determined as parameters that significantly affected the stone-free rate. As a result of the receiver operating characteristic analysis, the threshold stone size was 1.54 cm^3.
Conclusion: More accurate indications can be determined by calculating the volume of the stone. Retrograde intrarenal surgery success decreases in stones >1.54 cm^3 by volume calculation. A different method such as percutaneous nephrolithotomy should be considered with higher preference for stones above this value.
Keywords: Kidney stone, retrograde intrarenal stone surgery, stone-free rate, stone volume

Introduction

Urinary system stone disease is one of the most important diseases that affect human health and social life. Its prevalence varies according to geographical regions. Stones can be seen in any structure along the urinary tract, but it is most common in the kidney. Current management of kidney stones includes follow-up, medical therapy, extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PNL), retrograde intrarenal surgery (RIRS), laparoscopy/robot and open surgery. At present, open surgery is required only in 1%–2% of the cases, and minimally invasive methods are preferred in most of the patients with stones, because of the new developments in medical technology and advances in endoscopic approaches (1,2).

RIRS was defined by Fuchs in the early 1990s, and following publications of the first experiences with RIRS, flexible

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ureterorenoscopes were improved further in the last 15 years and used extensively with increasing success and decreasing complication rates (3). Along with the new developments in technology, flexible ureterorenoscopes are used in the treatment of kidney stones <2 cm, having higher mobility with increased deflection ability and providing higher image quality with fibre optic lighting, which are also smaller and relatively more durable. The use of holmium laser technology and nickel-titanium alloy baskets in endourology is the most important factor in the development of RIRS.

In the latest stone guides, stone size measurement that guides the treatment procedure is evaluated in a single plane, even if the kidney stones have three-dimensional (3D) configuration, and the treatment indication is determined according to this single plane measurement. We are concerned on whether the measurement of the longest axis is adequate or whether calculating the surface area in a single plane may give false results for each parameter that can affect success in kidney stone treatment modalities. Thus, in this study of patients who underwent RIRS for stone disease, we aimed to calculate stone volume considering the 3D configuration in space, compare results with those of patient who underwent RIRS with preoperative measurement of maximum stone size in one plane, and investigate the effects of that choice on the operation and patient, in the light of the literature and stone guide. In addition, we aimed to determine a limit value in cm^3 for RIRS, based on volume calculations, and to predict stone-free status based on this limit value.

Materials and Methods

This study was carried out by reviewing data of patients who underwent RIRS for kidney stones in the urology clinic of our hospital between May 2013 and September 2017. Patients with horseshoe kidneys and ectopic/pelvic kidneys, patients aged <18 years, and those with missing preoperative and postoperative data were excluded from the study. Finally, 184 patients were included in the analysis.

The retrospective analysis of data was performed after obtaining the approval of the local ethics committee of our hospital (September 21, 2017; session no: 13 and decision no: 17). Verbal and written informed consent forms were obtained from all patients before the procedure.

The longest measurements in the axial, coronal and sagittal planes were used in calculating the stone size in computed tomography (CT) images. Area calculation was noted in cm^2 by multiplying the lengths in the axial and coronal planes. The volume calculation in cm^3 was performed using an ellipsoid formula as recommended by the European Association of Urology (EAU) guideline by multiplying the lengths in the three aforementioned planes and 3.14*0.167 (stone volume = 3.14 × width × length × height × 0.167). In case of multiple stones, the dimensions of each stone were measured separately and then added. Postoperative stone-free status was evaluated by CT performed at the first month after RIRS. Absence of stones or stone fragments ≤4 mm was considered a stone-free status or clinically insignificant fragments, respectively (4).

General anaesthesia was administered in the supine position. A guidewire was placed into the target ureter, under the control of a C-arm fluoroscopy unit. The ureteral access sheath (9.5/11.5 Fr or 12/14 Fr and 35 cm or 45 cm hydrophilic-coated sheath) was inserted over the guidewire placed in the ureter to the ureteropelvic junction under fluoroscopic control. After entering through the ureteral access sheath with a flexible ureterorenoscope (Flex-X2, Karl Storz, Tuttlingen, Germany) with a 7.5-Fr outer diameter and upon observing the stone, lithotripsy was performed by Litho brand laser system, using 272- or 365-µm holmium laser probe with a frequency of 8-12 Hz and a power of 1.2-1.5 Joules. During the procedure, isotonic sodium chloride irrigation was performed to ensure imaging. Fluoroscopy control was initiated when the stones were completely fragmented. The time elapsed from insertion of the guidewire to the placement of the Double-J stent (DJS) was recognised as the operation time. DJS was placed in all patients after the procedure. DJSs were removed under local anaesthesia within 4 weeks after the surgery.

Statistical Analysis

Shapiro-Wilk test was used to test the normality of data distribution, and Levene's test was performed to assess the homogeneity of variance. Independent samples t-test, Mann-Whitney U test, Pearson's chi-square test and Fisher's exact test results were used in the comparison of factors that affect stone-free status. The cut-off values calculated for the stone number, stone size (cm^2), stone volume (cm^3) and operation time (min), which show significant relations with stone-free status, were analysed and expressed by receiver operating characteristic (ROC) analysis. The stone number, stone size (cm^2), stone volume (cm^3), operation time (min) and presence of additional interventions were analysed according to the Naive Bayes classification in predicting stone-free status. Quantitative variables were shown as mean ± standard deviation (minimum/maximum) and median (minimum/maximum), and categorical variables as n (%). Variables were analysed at a 95% confidence level, and p-value less than 0.05 was considered significant. SPSS 25.0 (IBM Corp., Armonk, NY, USA) package programme was used in the data analysis.

Results

A total of 184 patients were included in the study; 68 were female (37%) and 116 were male (63%). Stone sizes ranged from 1 cm to 4 cm. Demographic data, stone characteristics and peri-/postoperative data are shown in Table 1. Total renal abnormality was determined in 25 (13.7%) patients (renal malrotation in 12 (6.6%) patients, solitary kidney in 10 (5.5%) and bifid renal pelvis in 3 (1.6%).

The median American Society of Anesthesiologists score was 2.

As regards the distribution of stones, 85 (46.7%) patients had pelvic stones, 55 (30.2%) had lower calyceal stones, 10 (5.5%) had middle calyceal stones and 8 (4.4%) had upper calyceal stones, while other cases had stones distributed to multiple sites, including the proximal ureter.

Clinically significant residual fragments remained in 64 (34.8%) patients. Moreover, 49 (76.6%) patients with residual stones were followed up, while the remaining 15 (23.4%) underwent re-operation [in these patients, 3 underwent ESWL and subsequent PNL due to failure, 3 underwent PNL alone, 3 underwent ESWL alone, 4 underwent RIRC and 2 underwent ureterorenoscopy (URS)].

No significant relationship was found between the stone-free rate and factors that affect stone-free status, including age, gender, Hounsfield unit value of the stone, length of hospital stay, preoperative ESWL, preoperative PNL, renal unit abnormality, stone side, stone opacity, accompanying ureter stone, hydronephrosis and preoperative DJS insertion. However, additional intervention to postoperative residual stones (p<0.001), number of stone (p=0.018), stone size in cm^2 (p=0.003), stone volume in cm^3 (p=0.005) and operation time (p=0.036) were significant parameters that affect stone-free status after RIRS (Table 2).

The threshold values determined as a result of the ROC analysis of the significant parameters that affect the stone-free status were as follows: presence of one stone, stone size of 1.48 cm^2,

Table 1. Demographic data, stone characteristics and peri-/postoperative data

	Mean ± SD	Median (min/max)
Age	46.38±14.72	47 (18/83)
Number of stones	1.23±0.54	1 (1/4)
HU value of stones	1.043,70±354.65	1100 (300/1700)
Stone size (cm^2)	1.50±1.02	1.3 (0.25/8)
Stone volume (cm^3)	2.46±2.82	1.68 (0.24/25.02)
Operation time (min)	53.63±19.44	50 (25/145)
Length of hospital stay (day)	2.11±0.40	2 (1/4)

HU: Hounsfield unit, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Factor affecting stone-free status

	Stone-free status		p-value
	No	Yes	
	(n=64)	(n=120)	
	Mean ± SD (min/max)	Mean ± SD (min/max)	
Age (years)	46.08±13.79 (18/81)	46.54±15.25 (18/83)	0.804
	n (%)	n (%)	
Gender			
Female	22 (34.4)	46 (38.3)	0.633
Male	42 (65.6)	74 (61.7)	
Preoperative ESWL			
No	28 (43.8)	66 (55.0)	0.165
Yes	36 (56.3)	54 (45.0)	
Preoperative PNL			
No	55 (85.9)	111 (92.5)	0.193
Yes	9 (14.1)	9 (7.5)	
Abnormality in renal unit			
No	51 (81.0)	106 (89.1)	0.174
Yes	12 (19.0)	13 (10.9)	
Stone side			
Left	36 (56.3)	64 (53.3)	0.757
Right	28 (43.8)	56 (46.7)	
Stone opacity			
Opaque	6 (9.4)	13 (10.8)	0.806
Non-opaque	58 (90.6)	107 (89.2)	
Accompanying ureter stone			
No	59 (92.2)	111 (92.5)	1.000
Yes	5 (7.8)	9 (7.5)	
Hydronephrosis			
No	23 (35.9)	56 (46.7)	0.211
Yes	41 (64.1)	64 (53.3)	
Preoperative DJS			
No	52 (81.3)	90 (75.6)	0.459
Yes	12 (18.8)	29 (24.4)	
Additional intervention for residual stone			
No	49 (76.6)	120 (100.0)	<0.001
Yes	15 (23.4)	0 (0.0)	75.5 (4.4-1285.9)*
Need for intensive care			
No	63 (98.4)	119 (99.2)	-
Yes	1 (1.6)	1 (0.8)	
	Median (min/max)	Median (min/max)	
Stone number	1.3 (1/4)	1 (1/2)	0.018
HU value	1200 (300/1650)	1000 (300/1700)	0.244

Stone size (cm^2)	1.53 (0.45/8)	1.24 (0.25/4)	0.003
Stone volume (cm^3)	2.37 (0.45/25.02)	1.52 (0.24/8.64)	0.005
Operation time (min)	50 (30/125)	45 (25/145)	0.036
Length of hospital stay (day)	2 (1/4)	2 (2/4)	0.783

ESWL: Extracorporeal shock wave lithotripsy, PNL: Percutaneous nephrolithotomy, DJS: Double J-stent, HU: Hounsfield unit, SD: Standard deviation, Min: Minimum, Max: Maximum; *Odss Ratio (95% confidence interval)

Table 3. ROC analysis of parameters affecting stone-free status

	Stone-free status		AUC (sh)	p-value	Odss ratio (95% CI)
	No	Yes			
	n (%)	n (%)			
Number of stones					
>1	18 (28.1)**	17 (14.2)	0.574 (0.033)	0.024	2.4 (1.1-5.0)
≤1	46 (71.9)	103 (85.8)*			
Stone size (cm^2)					
>1.48	38 (59.4)**	44 (36.7)	0.635 (0.042)	0.001	2.5 (1.4-4.7)
≤1.48	26 (40.6)	76 (63.3)*			
Stone volume (cm^3)					
>1.54	47 (73.4)**	59 (49.2)	0.634 (0.042)	0.001	2.9 (1.5-5.5)
≤1.54	17 (26.6)	61 (50.8)*			
Operation time (min)					
>55	28 (43.8)**	33 (27.5)	0.596 (0.043)	0.027	2.1 (1.1-3.9)
≤55	36 (56.3)	87 (72.5)*			

ROC: Receiver operating characteristic, AUC: Area under the ROC curve, SE: Standard error, CI: Confidence Interval, Sensitivity* Specificity**

stone volume of 1.54 cm^3 and 55 min of operation time. The stone-free rate decreased significantly as these values increased. The main objective of this study was to measure the stone size by calculating the stone volume owing to its 3D configuration in space, instead of measuring the longest side in a single plane or calculating the stone area. In our opinion, the true stone size can only be determined by volume calculation. In accordance with this objective, the results of the ROC analysis and the area under the ROC curve (AUC) supported our hypothesis. The parameter that determines the stone-free rate with the highest AUC value and odds ratio was the stone volume (cm^3) (Table 3).

According to the multiple logistic regression model, a stone-free status can be estimated significantly ($p<0.001$) with an overall accuracy rate of 74.5%, based on the threshold values calculated by the ROC analysis. Stone-free status can be predicted with an odds ratio of 2.5 if the stone volume (cm^3) is below the specified threshold value and with an odds ratio of 2.9 if the operation time is shorter than the specified threshold value (Table 4).

The parameters that significantly affect stone-free status were examined according to the Naive Bayes classification model, and these parameters had general accuracy of 78.8% to predict stone-free status. According to these results, the parameter of "additional intervention needed for postoperative residual stones" displayed the highest power to predict stone-free status, with respect to the Bayesian Information Criterion (BIC) and Rank score. However, this is a highly predictable situation that would not require any statistical analysis. "Stone volume calculation in cm^3" is another parameter having the highest predictive power according to the BIC and Rank score. This is followed by the parameters of "stone size measurement in cm^2", "operation time" and "number of stones" (Table 5).

Table 4. Prediction rate of stone-free status according to the multiple logistic regression model

	b	SE	p-value	Odss ratio	95% Confidence interval for odds	
					Lower limit	Upper limit
Stone size cm^3 (≤1.54)	-0.933	0.381	0.014	2.5	1.2	5.4
Operation time (min) (≤55)	-1.067	0.366	0.004	2.9	1.4	6.0
Prediction rate; Stone-free status (Yes) = 98.3% (No) = 29.7% Overall accuracy = 74.5% P-model <0.001						

Method: Backward stepwise (Wald), b: Regression coefficient, SE: Standard error

Table 5. Predictive power of stone-free status according to the naive bayes classification model

Predicting Parameter	Rank	BIC	Average log-likelihood
Additional intervention for residual stones	5	0.567	-0.553
Operation time (min)	2	0.520	-0.492
Stone number	1	0.509	-0.466
Stone size (cm^2)	3	0.521	-0.464
Stone volume (cm^3)	4	0.540	-0.469
Prediction rate; Stone-free status (Yes) = 100% (No) = 39.1% Overall accuracy 78.8%, BIC: Bayes information criterion			

Discussion

The main aim of kidney stone management is to achieve complete stone-free status with minimal damage to the patient. Stone fragments remaining in the kidney after treatment may be a source of new stones causing new symptoms once again as well as provide a basis for infection. In the era where open stone

surgery was performed, complete stone-free status was usually attained, and in those days, no difference was found in the definitions of surgical success. However, at present, minimally invasive techniques are developed, and some disagreements are observed in the definition of success (5-7).

In the literature, the average success rate of RIRS for lower pole stones in a single session is 86% (8). In a study of 185 patients with kidney stones ≥2 cm, Sari et al. (9) reported a success rate of 73.5% after the first RIRS and 85.4% in a multistaged approach. Preminger (10) reported a stone-free rate of 85% after the third month in patients who underwent RIRS for lower calyceal stones <2 cm. In another study, the early postoperative stone-free rate and success rate of RIRS in all localisations were 69.7% and 80.3%, respectively, and high stone-free rates were reported, especially for small stones (11). Palmero et al. (12) reported a success rate of 73.6% after RIRS. The total success rate after additional procedures was 93.5% in the same study. In our study, early stone-free status rate was approximately 65%, which is close to literature data. This result was achieved by a single procedure and determined by CT within one month after surgery, and it is obvious that even higher rates of stone-free status would be expected with additional treatments and in control films within three months after surgery. Thus, our success rate increased to 74% when the secondary procedures were performed on 15 patients in whom a stone-free status could not be achieved. When the literature and our study data were evaluated, we can speculate that the most important reason for these variations in success rates is the measurement and consequent indication errors owing to the failure of calculating the stone volume.

The properties of post-RIRS residual stones were examined by Fabrizio et al. (13) in a study of 100 patients, and they observed that the proportion of patients with residual stones increased as the stone size increased. Among parameters that affect the success of RIRS, stone size was significant. To the best of our knowledge, this is the first study to have calculated the stone volume in evaluating RIRS success and where a threshold value is given, considering the whole literature or the EAU guideline and advising the longest measurement of stone size in a single plane or area calculation. The success rate of RIRS decreased in stones larger than 1.54 cm^3, with a highly predictive power and prediction rate of stone-free status, according to our study that centred on the hypothesis that stone measurement should be made by volume calculation owing to its 3D structure in space, namely, width, length and height. Based on this data, more accurate indications can be determined in patients with urinary stone as a result of measuring the stone size and volume to increase the surgical success.

Lim et al. (11) categorised RIRS indications into primary and secondary RIRS. Patients who had unsuccessful ESWL and PNL treatments constituted the secondary RIRS group, and the vast majority of them were patients who underwent ESWL (32 ESWL/4 PNL). They found significant difference in the stone-free rates between the secondary RIRS group and primary RIRS group, in favour of patients who underwent primary RIRS. Other studies have reported that RIRS was an effective and reliable method in ESWL-resistant stones (14,15). In our study, preoperative unsuccessful ESWL and PNL treatments did not affect the success in the secondary RIRS group.

Elbir et al. (16) concluded that the number of stones was an important parameter that affects the success of RIRS. According to their findings, RIRS success decreased statistically when the number of stones exceeded 1. In another study, the initial and final stone-free rates decreased significantly as the number of stones increased. Residual stones were significantly higher in the first day and first month after surgery in cases with multiple stones (17). Our results were similar to those of the literature, and we found that the number of stones was a parameter that effectively affects RIRS success. According to the ROC analysis, the surgical success decreased significantly as the number of stones exceeded 1. Stone number is a robust parameter in predicting stone-free status according to BIC and Rank score.

Kirac et al. (18) reported that the mean operation time was 66.4±15.8 min and the duration of hospitalisation was 24.5±4.6 hours in patients who underwent RIRS. In our study, the average operation time was 45 min in the stone-free group and 50 min in the non-stone-free group. The mean operation time was shorter than the values reported in the literature for both groups, suggesting a significant difference in determining stone-free status. Moreover, the stone-free status significantly decreased in procedures longer than 55 min based on the ROC analysis. This result can explain the shorter operation time achieved in the stone-free group. A decrease in stone-free rates along with the increase in the operation time may be attributed to the lack of surgical experience, increased complication rates in cases with prolonged operation time and difficult localisation of the stones, such as the lower calyx, that may cause decreased manoeuvrability of the flexible URS and consequent fatigue and attention problem experienced by the surgeon. Moreover, our results revealed that operation time <55 min was an important parameter that can predict stone-free status with a high predictive power and rate. The length of hospital stay was 48 hours in the groups with and without stone-free status, which was a longer period when compared with literature data and had no significance in determining stone-free status.

Preoperative DJS placement was reported to increase stone-free rate by dilating the ureter, in a retrospective study that evaluated preoperative DJS placement for passive dilatation purposes due to reasons such as anuria or pyelonephritis (9). Another study pointed out the absence of no consensus on preoperative DJS

placement for additional operation and the lower occurrence of urinary system complications of DJS (19). However, in our study, preoperative DJS had no effect on the success of RIRS. These data suggest that preoperative DJS placement for passive dilatation in patients undergoing RIRS was not effective in providing stone-free status, contrary to various reports. Thus, there will be less additional procedures, less cost, less morbidity and less emergency room admissions.

Study Limitations

This study has some limitations. Apart from the retrospective design, which is the main limitation, a standard volume calculation could not be performed (the lack of a software that can calculate the stone volume) because of the specific configuration of each stone, and procedures were performed by several surgeons with varying skills and experiences.

Conclusion

RIRS, one of the minimally invasive endourological techniques, is increasingly performed in the treatment of kidney stones. Our findings suggest that a more accurate indication can be determined by calculating stone volume instead of measuring stone size on a single plane. If determined by volume calculation, RIRS is an effective and reliable method for stones <1.54 cm^3. Regardless of the measurements in a single plane, another minimally invasive endourological method such as PNL should be prioritised in stones with a volume >1.54 cm^3. We believe that our results, supported by the data of other studies, will provide a new milestone in stone surgery and shed light on guidelines.

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Ethics

Ethics Committee Approval: The retrospective analysis of data was performed after obtaining the approval of the local ethics committee of our hospital (September 21, 2017; session no: 13 and decision no: 17).

Informed Consent: Verbal and written informed consent forms were obtained from all patients before the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.E., Z.K., Concept: Z.K., Design: B.E., Data Collection or Processing: B.E., Analysis or Interpretation: B.E., Z.K., Literature Search: B.E., Z.K., Writing: B.E.

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A Technique Which We Should Consider More: Temporary Cutaneous Ureterostomy

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What's known on the subject? and What does the study add?

Cutaneous ureterostomy (CU) is an easy method of decompressing the upper urinary system. Although the techniques and methods have changed over the years, CU still protect the patients from possible damages.

Abstract

Objective: To evaluate the feasibility, efficacy and complications of cutaneous ureterostomy (CU) in different indications.
Materials and Methods: Data from 83 patients who underwent CU between 1991 and 2019 were reviewed retrospectively. Patients with neurogenic bladder, posterior urethral valves, solitary kidney and bilateral kidney involvement were excluded. A total of 53 patients aged <2 years were included in the analysis. Indications to perform CU were ureterovesical junction obstruction (UVJO) and high-grade vesicoureteral reflux (VUR) with dilatation. Ureteroureterostomy or ureteroneocystostomy methods were preferred for undiversion according to the dilatation status of the ureter.
Results: The mean patient age was 4.47±3.6 months, 40 (75.5%) were male and 13 (24.5%) were female. The mean follow-up time was 57.4±41.4 (6-150) months. Loop and end CU were performed in 18 (34%) and 35 (66%) patients, respectively. The indications for CU were UVJO in 26 (49%) and high-grade VUR in 27 patients. Two (3.7%) patients needed dilatation because of stenosis that occurred after CU. Within the follow-up time, 39 patients underwent undiversion. The clinical improvement rate was 94.3%.
Conclusion: CU is a simple method with satisfactory results when performed in patients with megaureter and massive dilatation. Despite the less frequent use, it is still an important alternative to the increasingly used conservative methods.
Keywords: Cutaneous ureterostomy, urinary diversion, hydronephrosis, megaureter, vesicoureteral reflux, ureterovesical junction obstruction

Introduction

Megaureter arises from a functional or anatomical abnormality of the ureterovesical junction and is classified according to the presence of reflux or obstruction (1). Smith classified megaureters into four categories, namely, obstructed, refluxing, refluxing with obstruction and non-refluxing/non-obstructing. Later, King subdivided megaureters into primary and secondary (1,2). Ureteric diameter >7 mm was defined as abnormal (3), and it is often diagnosed in the infantile period and regresses is most cases. In the vast majority of patients, a megaureter does not lead to clinical problems and loss of renal function (4,5). However, surgical intervention may be necessary when progressive massive dilation and loss of renal function occur. Cutaneous ureterostomy (CU) is a simple method of decompressing the upper urinary system (6). Although the techniques and methods have changed over the years, CU still protects the patients from possible kidney damage. Thus, this study aimed to evaluate the feasibility, efficacy and complications of CU in patients with vesicoureteral reflux (VUR) and ureterovesical junction obstruction (UVJO) and extremely dilated ureters.

Materials and Methods

Data from 83 patients who underwent CU between 1991 and 2019 were reviewed retrospectively. Patients with neurogenic bladder (n=10), posterior urethral valves (n=12), solitary kidney (n=2) and bilateral CU cases (n=4) were excluded from this study.

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In total, 53 patients aged <2 years were included in the analysis. After diagnosis, all patients were started antibiotic prophylaxis. Surgery was performed in two groups of patients: primary high-grade VUR group and UVJO group. Indications for surgery were refractory urinary tract infection (UTI) in patients with VUR and increasing severity of hydronephrosis (HN) in patients with UVJO who were unsuitable for reimplantation into a small bladder. Ultrasonography (US) is the primary imaging modality in the prenatal period and initial study in the symptomatic group. Voiding cystourethrography (VCUG) was performed to assess for the presence of VUR and to further delineate the anatomy of the bladder and outlet. Mercaptoacetyltriglycine-3 scintigraphy was used to evaluate and follow the obstruction status. After the loop or end CU, the patients who have shown resolution of the dilatation in the renal unit and completed their bladder development underwent undiversion procedures. The choice of the UC type mostly depends on the underlying pathology. In patients with primary UVJO, we tried to perform end UC as the standard approach. However, at the beginning of this series, some patients with VUR underwent end CU. As the experience improved over time, we started to perform loop CU to understand whether it may be a good alternative that keeps the chance of further ureteroureterostomy without bladder surgery in some patients whose VUR was resolved. In every patient, diagnostic cystoscopy is performed, the ureter is catheterised with a 3-Fr or 4-Fr catheter, a retrograde pyelography is performed to visualise the renoureteral unit and the catheter is left in the ureter. The surgery is performed through a 2 cm incision at the lateral border of Pfannenstiel incision at the lower quadrant with a muscle splitting technique. The peritoneum is deviated medially, and the ureter is found in the retroperitoneal area, turned with a tape and brought outside to the incision. The tortuosity of the ureter is straightened. In end CU, the ureter is ligated at the most distal part, the proximal ureteral end is brought to the incision with the proper length to prevent kinking and a 10-Fr feeding catheter is indwelled into the ureter for 7 days. In loop CU, the ureter is incised by a no.15 scalpel, and the ureter is anastomosed to the skin. Both the proximal and distal parts of ureterostomy are catheterised by an 8-Fr or 10-Fr feeding catheter for 7 days. In both techniques, the ureter is fixed to the fascia with four stitches to prevent the inside retraction of the ureter. The timing of undiversion was decided by evaluating the resolution of HN using US and assessing the bladder volume and shape by VCUG. Ureteroureterostomy and ureteroneocystostomy (UNC) with remodelling methods were preferred for undiversion according to the dilatation status of the ureter. In patients with bilateral kidney involvement, the more affected side in the dimercaptosuccinic acid (DMSA) scan and the side with a higher HN grade on US were chosen for surgical intervention.

Patient demographics, complaints and underlying diseases were recorded preoperatively. After preoperative evaluation using US, VCUG and DMSA or mercaptoacetyltriglycine scan, postoperative follow-up was performed using US at regular intervals. Patients with serum creatinine levels higher than the age-specific reference values were considered to have chronic renal disease. Status of improvement was assessed by the radiological and clinical course of the patient.

Complications were assessed according to the Clavien-Dindo classification. Evaluation of HN grades on US was based on the Society of Fetal Urology (SFU) criteria, whereas the evaluation of VCUG was based on the criteria of the International Reflux Study Committee. This study was approved by the local ethical committee (GO-18/267).

Statistical Analysis

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Mann-Whitney, chi-square, Fisher's exact test and t-tests were used where appropriate. P-value <0.05 indicated significance.

Results

The mean patient age at the time of surgery was 4.47±3.6 (1-15) months. The median age was 3 months, 40 (75.5%) were male and 13 (24.5%) were female. The mean follow-up time was 57.4±41.4 (6-150) months.

Indications for CU were primary UVJO and high-grade VUR in 26 and 27 patients, respectively. Moreover, 41 (77.4%) patients had SFU grade 4 HN, while 10 patients had grade 3 HN. HN was also detected in the contralateral kidney in 18 patients. Scarring was detected on preoperative DMSA scan in 52.8% (28/53) of the patients. The clinical improvement rate was 94.3%.

CU was performed in 27 patients with primary VUR (with high-grade reflux causing recurrent febrile UTI), while the clinical or radiological improvement rate was 92.6% (25/27). The mean patient age was 4.81±4.3 months, and loop CU was performed in 59.3% (16/27) of the patients. The mean follow-up time was 68.2±44.4 months. Two patients underwent nephrectomy due to loss of renal function.

Furthermore, 26 patients underwent CU for primary UVJO, and the clinical or radiological improvement rate was 96.2% (25/26). The mean patient age was 4.12±2.8 months, and 92.3% (24/26) of the patients underwent end CU. The mean follow-up time was 46.1±35.3 months. When patients with primary VUR and primary UVJO were compared, the difference in the type of CU (loop vs end) and presence of a renal scar on DMSA were found significant (p=0.009, p<0.001) (Table 1).

Table 1. Comparison of patients with primary VUR and primary UVJO

Patient characteristics	Primary VUR	Primary UVJO	p
No. of patients	27 (51%)	26 (49%)	
Mean age (months)	4.81±4.3	4.12±2.8	0.767
Gender (M/F)	20/7	20/6	0.810
Renal scar on DMSA (%)	70.4%	34.6%	**0.009**
Indication for surgery (HN/infection)	17/10	21/5	0.150
Type of cutaneostomy (end/loop)	11/16	24/2	**<0.001**
Type of undiversion (UNC/ureteroureterostomy)	16/2	21/0	0.206
Interval between CU and undiversion (months)	15.4±10.4	11.9±6.57	0.460
Mean age at undiversion	18.5±8.5	15.9±7.5	0.269
Mean follow-up (months)	68.2±44.4	46.1±35.3	0.081
Follow-up (radiological/clinical)	20/7	24/2	0.142
Complication (yes/no)	0/27	3/26	0.069
Clinical or radiologic improvement (%)	92.6%	96.2%	0.575
Postoperative UTI	7/27	8/26	0.696

CU: Cutaneous ureterostomy, VUR: Vesicoureteral reflux, UVJO: Ureterovesical junction obstruction, UTI: Urinary tract infection, DMSA: Dimercaptosuccinic acid, HN: Hydronephrosis, UNC: Ureteroneocystostomy

In this study, loop and end CU were performed in 18 (34%) and 35 patients, respectively. None of the patients who underwent loop CU and two patients who underwent end CU required revision due to stomal stenosis. In addition, 15 (28.3%) patients developed postoperative UTI, of which six developed two or more. Postoperative UTI was found in 22.2% (4/18) of the patients in the loop CU group and in 31.4% (11/35) of the patients in the end CU group. Postoperative UTI was found in 25.9% (7/27) of the patients in the primary VUR group and in 30.8% (8/26) of the patients in the primary UVJO group (Table 2).

Of the 53 patients who underwent CU, four had follow-up shorter than 6 months. Of the 39 patients (39/53, 73.6%) who underwent undiversion, 37 underwent UNC (Cohen UNC in 30, Lich-Gregoir UNC in 1, Politano-Leadbetter UNC in 3 and extravesical UNC in 3), and ureteroureterostomy was performed in two patients. Ureteroureterostomy was performed in patients with VUR after confirming the complete resolution of VUR by preoperative VCUG and intraoperative positioned instillation of contrast cystography. The mean patient age at undiversion was 17.1±7.9 (7-44) months, and the average time between CU and undiversion was 12.7±7.7 (5-42) months. After undiversion, the clinical or radiological improvement rate and complication rates were 100% (39/39) and 10.2% (4/39), respectively. One patient developed postoperative urinoma, and one patient had persistent asymptomatic VUR. Percutaneous nephrostomy was performed in one patient for worsening HN that was resolved during follow-up. One patient underwent reoperation because of Double-J stent (DJS) displacement.

Table 2. Comparison of loop and end CU

Patient characteristics	Loop CU	End CU	p
No. of patients	18 (34%)	35 (66%)	
Mean age (months)	4.2±3.8	4.6±3.6	0.554
Indication for surgery (HN/infection)	11/7	27/8	0.220
Type of undiversion (UNC/ureteroureterostomy)	10/2	27/0	0.089
Interval between CU and undiversion (months)	13.3±10.5	12.5±6.3	0.360
Mean follow-up (months)	59.6±44.8	56.3±40.2	0.506
Complication (yes/no)	18/0	32/3	0.201
Clinical or radiologic improvement	94.4%	94.3%	0.556
Postoperative UTI	4/18	11/35	0.481

CU: Cutaneous ureterostomy, UTI: Urinary tract infection, DMSA: Dimercaptosuccinic acid, UNC: Ureteroneocystostomy, HN: Hydronephrosis

Undiversion was not performed in 14 patients because four patients had follow-up <6 months, four patients had kidney function <10%, two patients had chronic failure and four patients had inadequate bladder volume for undiversion.

Discussion

CU is known as an old-fashioned method of decompressing massive dilatation in the ureter presented early in infancy with a high risk of loss of renal function and recurrent febrile UTI. In addition to from CU, various urinary diversions and methods, such as vesicostomy, pyelostomy, DJS insertion, nephrostomy and balloon dilatation, have also been shown to be applicable in megaureters (7-10). However, these methods will not remove the anatomical/functional problem and have lower clinical or radiological improvement rates than CU. CU lowers the pressure of the urinary system without disturbing the bladder function, and under certain conditions, CU is even successful even when closed only by ureteroureterostomy without reimplantation. In our series, we performed ureteroureterostomy without an additional UNC after CU in two patients, and all patients achieved clinical improvement. This possibly supports the opinion that the anatomical and physiological development of UVJ continues after birth and that CU provides time for this development.

In patients with bilateral high-grade reflux causing recurrent febrile UTI, unilateral loop CU has been a very good temporising diversion by creating a refluxing stoma. The refluxing stoma helps not only the resolution of dilatation in the diverted renal unit but also in the non-diverted contralateral side by reducing the bladder pressures.

CU aims to relieve obstruction and to prevent the deleterious effect of VUR by avoiding possible side effects of bladder surgery and gain time, specifically in small babies, until definitive ureterovesical junction surgery. The repair can be performed with or without remodelling. Particularly, undiversion is not recommended in children aged <1 year because of the unwanted effects on the development of bladder functions (3,11). Massively dilated ureters mostly require tapering surgeries during reimplantation, and temporary CU has the potential to decrease this necessity. Indeed, our experience revealed that only 25.6% (10/39) of the patients required tapering during reimplantation.

The choice of the CU type mostly depends on the underlying pathology. End CU may be preferred for patients with UVJO. However, loop CU may be a good alternative, which keeps the chance of further ureteroureterostomy in some patients. For bilateral VUR cases, we often prefer the less functioning kidney for loop CU. This approach enables the cessation of VUR on the worse side and provides effective cycling of the bladder by the urine of the better functioning side and gives the option of performing clean intermittent catheterisation in patients requiring it.

Some studies have reported up to 91% of clinical or radiological improvement rate in CU with permanent repair (6,12-14). In our series, the overall clinical or radiological improvement rate was 94.3%, while the clinical or radiological improvement rate in 39 patients who underwent undiversion was 100%.

Some authors have presented balloon dilatation and stent placement both as temporary and definitive treatments for UVJO. Stent placement is not easy as expected in these patients and as described in some series of open stent placement (15). In some cases, stent placement may worsen the patients' condition, cause UTİ and will not provide improvement of dilatation. The CU is advantageous in these aspects over stent placement (9,10). Ortiz et al. (16) reported 87.3% success rate of endoscopic balloon dilatation in patients with obstructive megaureter. The postoperative VUR rate was 21.5% in this series. However, only a few studies have reported about balloon dilatation; thus, further studies are needed. Placement of percutaneous nephrostomy can be preferred to provide drainage and evaluate renal function. However, prolonged use of a nephrostomy tube during the waiting period to decrease the ureter calibre may lead to complications, such as infection or tube dislodgement. Lee et al. (17) proposed an alternative temporary solution for infants with UVJO. They created a refluxing ureteral implant by an extravesical approach through a Pfannenstiel incision. It may appear advantageous, as it prevents the anxiety of parents about caring for a CU. However, this approach has associated risk for ureter kinking during bladder filling and emptying. Moreover, it still places the upper tract at risk of VUR. CU enables improvement of ureter calibre for future reimplantation and accurate evaluation of renal function without misinterpretation due to persisting VUR.

Study Limitations

The main limitation is the retrospective nature of this study and the lack of prospective randomisation or stratification. Another limitation is the lack of data on renal scans and glomerular filtration rate values in each patient, which help in assessing renal function. However, to the best of our knowledge, this is one of the largest series from a single centre. Although CU is a technique that has been described a long time ago, it is an easy and reliable method and helps decrease the pressure of the upper urinary system. Our experience showed that it is a feasible method and can be utilised in patients with certain indications.

Conclusion

CU is a simple method with satisfactory results when performed in patients with megaureter and massive dilatation. Despite the less frequent use, it is still an important alternative to the increasingly used conservative and minimally invasive methods. CU can be performed with high success rates in patients with primary megaureter with VUR or UVJO.

Ethics

Ethics Committee Approval: This study was approved by the local ethical committee (GO-18/267).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ç., H.S.D., T.C., M.A., S.T., Concept: B.Ç., H.S.D., S.T., Design: B.Ç., H.S.D., S.T., Data Collection or Processing: B.Ç., T.C., M.A., Analysis or Interpretation: B.Ç., H.S.D., Literature Search: B.Ç., H.S.D., S.T., Writing: B.Ç., H.S.D., S.T.

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Endoscopic Treatment of Vesicoureteral Reflux: Changing Trends Over the Years

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What's known on the subject? and What does the study add?

Endoscopic subureteral injection (ESI) is an easy and minimally invasive procedure and may be an alternative to open surgery and continuous antibiotic prophylaxis by offering some advantages in patients with vesicoureteral reflux (VUR). In our study, we detected that the rate of patients with history of failed ESI, high grade reflux and renal scarring have increased significantly in our patient population over time. ESI is increasingly preferred with our increasing surgical experience over the years in patients who failed after the first ESI and especially in those with high grade VUR and appropriate ureter configuration on cystoscopy.

Abstract

Objective: To investigate factors affecting the success rate of endoscopic subureteral injection (ESI) in patients with vesicoureteral reflux (VUR) and to evaluate the changes in years.
Materials and Methods: A total of 439 patients with primary VUR who underwent ESI were included. We used dextranomer hyaluronic acid co-polymer (Dx-HA) as bulking agent. Statistical analyzes were performed by SPSS 20.0 programme.
Results: Overall patient-based and renal unit-based success rates of ESI were 75.6% and 78.2%, respectively. Operational age of 82 months and lower grades of VUR were found to be the factors increasing success rate (p=0.023, p=0.005). Success rates were as 83.6%, 77.9% and 64.5% for grades of reflux 1-2, 3 and 4-5, respectively (p=0.002). When patients were seperated into four equal chronological groups, we observed that the ratio of patients who had previous failed ESI, high-grade reflux and renal scarring and volume of injected material has increased over the years.
Conclusion: ESI has higher success rates in older children and lower grades (grades 1-3) of VUR. It is performed also in high-grade patients with acceptable success rates which tended to increase over the years.
Keywords: Vesicoureteral reflux, endoscopic subureteral injection, STING procedure, dextranomer hyaluronic acid co-polymer

Introduction

Vesicoureteral reflux (VUR) is one of the most common urological abnormalities in children with an incidence of approximately 1% (1). Appropriate management, either via conservative or surgical means, is crucial to prevent complications of VUR, such as hypertension, pyelonephritis, renal scarring and renal failure (2,3). Treatment options include close observation, continuous antibiotic prophylaxis (CAP), endoscopic subureteric injection (ESI) and open/laparoscopic/robotic ureteric reimplantation. Some indications for surgical intervention are breakthrough urinary tract infection (BTI) despite antibiotic prophylaxis, progression (reflux grade, symptoms and parenchymal damage) and parental preference (2).

ESI, an easy and minimally invasive procedure, may be an alternative to open surgery. It offers excellent advantages over other methods, such as low morbidity, short post-operative recovery time and low cost (3).

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We hypothesised that ESI treatment of VUR is effective even in high-grade cases. Thus, in this study, we aimed to investigate the factors affecting the success rate of ESI in patients with VUR and evaluate changes in our patient profiles and surgical outcomes over time.

Materials and Methods

Data from a total of 439 patients younger than 18 years old who underwent ESI between 2000 and 2020 were retrospectively collected. Informed consent was obtained from the patients' parents prior to the operation. The higher grade in patients with bilateral VUR was recorded as "the reflux grade". Reflux grades were classified as "low" for grades 1-2 reflux, "moderate" for grade 3 reflux and "high" for grades 4-5 reflux. Forty-four patients with incomplete data, neurogenic bladder, ureterocele and duplex system were excluded from the study.

Lower urinary tract dysfunction (LUTD) is defined as the presence of lower urinary tract symptoms in children older than 5 years; these symptoms may include urgency, incontinence, poor voiding flow rate, intermittent voiding and pollacuria, all of which may be detected by questionnaires and/or urodynamic studies. Prior to any surgery, behavioural arrangements (urotherapy) and/or medications were first recommended and administered to all patients with LUTD.

In our study, the indications for surgery were recurrent or symptomatic urinary tract infection (UTI) despite CAP, increasing reflux grade and renal scarring and, sometimes, parental preference. All patients underwent the classical STING technique under the supervision of two paediatric urology board-certified clinicians (H.S.D. and S.T.). Positioned instillation of contrast cystography (PIC-C) on the contralateral ureter was performed in some patients with unilateral reflux in case an incompetent appearance and presence or suspicion of scarring on DMSA were noted. ESI of the contralateral ureter was performed if reflux was detected by PIC-C. We used dextranomer–hyaluronic acid co-polymer (Dx/HA) as the injection material. Ureteral orifices with a golf-hole appearance were not injected. Bladders were drained for 24 hours with a Foley catheter, and patients were hospitalised for approximately 1 day (range, 0–2 days) after surgery.

We performed early ultrasonography 1 month after operation, every 3 months in year 1, every 6 months in year 2 and then every year thereafter up to year 5. All patients were given antibiotic prophylaxis until follow-up voiding cystourethrography (VCUG), which was performed once between 3 and 6 months after operation. Our definition of success was based on the patient, not the renoureteral unit; thus, a procedure was considered "successful" if no reflux in any side of the organ was observed during follow-up VCUG.

We constructed four chronological groups including nearly equal numbers of patients to evaluate changes in patient characteristics and treatment outcomes as follows: group 1 (n=109; those operated on between 2000 and 2009), group 2 (n=110; those operated on between 2010 and 2012), group 3 (n=110; those operated on between 2013 and 2016) and group 4 (n=110; those operated on between 2016 and 2020).

Statistical Analysis

Statistical Package for the Social Sciences version 20 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The Mann-Whitney U, Kruskal-Wallis, chi-squared and t-tests were used where appropriate, and logistic regression analysis was used for multivariate analysis. A p-value of <0.05 was considered to be significant. The area under the curve (AUC) calculated from the receiver operating characteristic (ROC) curve was used to assess the predictive ability of age.

Results

The male-to-female ratio was 108/331 (24.6%/75.4%). The mean age at diagnosis and mean operation age were as 64.9 ± 50.5 and 82.4 ± 51.9 months, respectively. The mean follow-up period was 17.3 ± 24.9 months. Unilateral VUR was present in 244 patients (55.6%), whilst bilateral VUR was noted in 195 (44.4%). The VUR grade of 116 patients was low, that of 199 patients was moderate and that of 124 patients was high (26.5%, 45.3% and 28.2%, respectively). Of the patients with bilateral reflux (n=195), 131 had low-grade VUR on both sides (67.2%), 33 had high-grade VUR on both sides (16.9%) and 31 had low-grade VUR on one side and high-grade VUR on the other (15.9%). Contralateral VUR was detected intraoperatively by PIC-C in 46 of 244 unilateral reflux patients. Therefore, ESI was performed unilaterally and bilaterally in 198 and 241 patients, respectively. Our overall radiological patient-based success rate was 75.6%. Success rates according to pre-operative VUR grades 1-2, 3 and 4-5 were 83.6%, 77.9% and 64.5%, respectively (p=0.002 in univariate analyses; p=0.005 in multivariate analyses). We detected radiological patient-based success rates in patients with bilateral low, low/high and bilateral high grades as 77.1%, 71% and 63.6%, respectively; differences noted amongst groups were not statistically significant (p=0.268). Of 151 patients whose unilateral reflux completely disappeared on control VCUG, two had post-operative contralateral reflux (1.3%).

The mean age of patients with post-operative success was older. When the effect of age on overall success rate was examined, 82 months appeared to be the cut-off with the best predictive value (p=0.002, 51.6% sensitivity on the ROC curve, AUC=0.586 with 66.3% specificity). Success rates of 70.7% and

83.5% were obtained in patients younger and older than 82 months, respectively, and the difference noted between groups was significant (p=0.002 in univariate analyses; p=0.023 in multivariate analyses).

We obtained the pre-operative data of renal scarring status in 407 patients (M/F ratio=100/307) and renal scarring was detected in 221 individuals (54.3%). The rates of renal scarring in patients with high- and low-grade reflux were 71.8% (84/117) and 47.2% (137/290), respectively (p<0.001). The presence of renal scarring was not affected by gender (male: 59% vs female: 52.8%, p=0.277) or LUTD status (with LUTD: 59.5% vs without LUTD: 60.3%, p=0.900).

We also obtained data on the volume of injected material 481 RU (307 patients), and the mean injected volume was 1.05±0.43 mL (range, 0.3-2 mL). Analysis of overall groups revealed no statistical difference in injected volume or its effect on outcomes. The mean volumes for patients with successful and failed operations were 1.06 and 1.01 cc, respectively (p=0.109, Mann-Whitney U test). However, when we analysed the data by grade, we found that injected volumes were higher in groups with low (1.03 mL vs 0.83 mL, p=0.019) and high (1.19 mL vs 1.02 mL, p=0.045) grades than in that with a moderate grate. The difference observed was not significant in moderate-grade patients (1.01 mL vs 1.05 mL, p=0.721). We learned that 0.75 mL is the best possible cut-off point (82% sensitivity, 31% specificity, AUC=0.545, p=0.148). Higher volumes were associated with higher success rates (Table 1). Chronological evaluation showed that the volume of the injected material increased with time (Table 2).

Multivariate analysis revealed that age less than 82 months, high reflux grade and volume of the injected material of less than 0.75 mL were associated with failure.

We examined the four chronological groups and found that the number of patients with a history of failed endoscopic procedure, high-grade reflux, renal scarring and volume of injected material increased significantly over time (Table 2).

An indication for intervention was pre-operative symptomatic UTI, which was detected in 39% of the patients and significantly decreased to 18.5% within the post-operative follow-up period (McNemar test, p<0.001). Univariate and multivariate analyses revealed that post-operative UTI occurred significantly more frequently in females than in males and in those with pre-operative BTI than in those without (p=0.001, p=0.049 and p<0.001, respectively). Post-operative success and UTI rates according to various factors are shown in Table 1.

Table 1. ESI success and post-operative UTI rates according to the indicated factors

		Success % (n)	p*	p**	Post-op. UTI % (n)	p*	p**
Gender	Male	73.1 (79)	0.490		7.4 (8)	0.001*	0.006*
	Female	76.4 (253)			22.1 (73)		
Age (month)	<82	70.7 (152)	0.002*	0.023**	18.2 (41)	0.899	
	≥82	83.5 (162)			18.7 (40)		
Side of VUR	Unilateral	77.0 (188)	0.437		19.7 (48)	0.461	
	Bilateral	73.8 (144)			16.9 (33)		
Preop. grade of VUR	1-2	83.6 (97)	0.002*	0.005**	18.1 (21)	0.501	
	3	77.9 (155)			16.6 (33)		
	4-5	64.5 (80)			21.8 (27)		
History of LUTD (>5 y.o)	No	81.2 (112)	0.342		14.5 (20)	0.105	
	Yes	76.5 (104)			22.1 (30)		
Preop. BTI	No	77 (188)	0.368		13.5 (33)	<0.001*	<0.001**
	Yes	73.1 (114)			28.8 (45)		
History of failed STING	No	77 (264)	0.254		17.8 (61)	0.590	
	Yes	71.3 (67)			20.2 (19)		
Renal scar	No	75.8 (141)	0.995		18.8 (35)	0.760	
	Yes	75.6 (167)			17.6 (39)		
Injected volume (mL)	≤0.75	64.9	0.004	0.014**	18.6	0.846	
	>0.75	78.9			17.7		

*Univariate analysis: Chi-squared test **Multivariate analysis: Logistic regression
n: Number of patients, mL: Millilitres, Pre-op. BTI: Pre-operative breakthrough infection, LUTD: Lower urinary tract dysfunction, VUR: Vesicoureteral reflux, Post-op. UTI: Post-operative urinary tract infection, >5 y.o.: >5 years old, ESI: Endoscopic subureteral injection

Table 2. Pre- and post-operative features of patients in the different chronological groups

Features	Group 1 2000-2009	Group 2 2010-2012	Group 3 2013-2016	Group 4 2016-2020	p
No. of patients	109	110	110	110	-
Gender (F/M)	91/18	79/31	82/28	79/31	0.145
Mean age at diagnosis (months)	62.99	67.07	65.03	64.22	0.967
Mean operation age (months)	80.32	80.38	79.74	82.91	0.920
Side (unilateral/bilateral)	61/48	61/49	62/48	60/50	0.994
LUTD +/– (patients >5 y.o)	35/37 (72)	32/36 (68)	36/34 (70)	37/32 (69)	0.872
History of failed STING	15.6%	16.4%	20.9%	32.7%	**0.007**
VUR grades 4 and 5	14.7%	23.6%	32.7%	41.8%	**<0.001**
Success rate in grades 4 and 5	62.5%	65.4%	63.9%	65.2%	0.997
Overall success rate	73.4%	70.9%	77.3%	80.9%	0.328
Renal scar	45.9%	47.6%	58.3%	65.3%	**0.017**
Injected volume (cc)	0.84	0.90	1.16	1.21	**<0.001**

No: Number, F/M: Female/male, LUTD: Lower urinary tract dysfunction, >5 y.o.: >5 years old, VUR: Vesicoureteral reflux, mL: Millilitre

We detected post-operative ureteral obstruction in two patients (0.4%) 6 and 9 months post operation, and both patients underwent open ureteral reimplantation. None of the patients revealed signs of obstructive reflux (e.g. breaking signs or sustained contrast material in the ureter after bladder emptying) during pre-operative VCUG. Patient 1 was a 4-year-old boy who underwent ESI with 1 mL of material for unilateral left-sided grade 4 VUR. Post-operative VCUG was normal on the third month. He interestingly developed bilateral worsening hydroureteronephrosis on the ninth month post operation. We suspected overlooked LUTD, which we evaluated by questioning and videourodynamic study. However, no abnormal functions were found. Thus, we performed bilateral open reimplantation to correct the issue. Patient 2 was an 18-month-old girl with unilateral left-sided grade 4 VUR, which was treated by 1 mL of material. We detected worsening hydroureteronephrosis 6 months post operation with symptomatic pain prior to the control VCUG. We performed cystoscopy under anaesthesia, which revealed no reflux in cystography but obstruction in retrograde pyelography; thus, we placed a Double J stent. However, the patient's issue did not resolve during follow-up, and unilateral open reimplantation was performed. No difficulty was encountered during ureteral dissection in these 2 patients, and neither of showed obstructive refluxing ureter preoperatively.

Discussion

One of the main objectives of this study is to evaluate the factors affecting the success of ESI in children. The overall success rate of ESI with Dx/HA has been reported to be between 68% and 92%, which is comparable with open surgery (4,5). In our study, the overall patient-based success rate of ESI was 75.6%, which is comparable with the rates reported in the literature. In previous studies, pre-operative reflux grade, renal scarring, age, gender, anatomical anomalies, injection technique, injection volume, surgical experience and accompanying LUTD were reported as factors affecting the success rate of ESI (5,6). In our study, the effects of age and VUR grade on the success rate were found to be statistically significant.

In a meta-analysis, Elder et al. (5) reviewed 63 studies including 5,527 patients and reported that the success rate of ESI decreased as the VUR grade increased and that the success rates of single-session ESI were as high as 78.5%, 72%, 63% and 51% for VUR grades 1-2, 3, 4 and 5, respectively. In our study, the success rates of the STING procedure in patients with VUR grades 1-2, 3 and 4-5 were calculated as 83.6%, 77.9% and 64.5%, respectively (p=0.005). The relatively high success rate in high-grade cases in our series may be attributed to the fact that we did not perform ESI in orifices with a clear golf-hole appearance. Therefore, we also selected the patients according to their anatomic deficiency at the time of cystoscopy.

The effect of LUTD in children >5 years old on the success of ESI with Dx/HA remains unclear. Capozza et al. (7) detected concomitant LUTD in nearly all patients who had failure of ESI and displacement of the Dx/HA mound and supposed that high voiding pressures secondary to LUTD may have caused the observed displacement. Lavelle et al. (8) reported that the success of ESI in patients with LUTD is not significantly different compared with those without and that ESI with Dx/HA is not contraindicated in these patients. Of the 274 patients older than 5 years of age in our study, 136 (49.6%) had LUTD. The success rates of ESI were calculated to be 76.5% and 81.2% in patients with and without LUTD, respectively; however, the difference between groups was not statistically significant (p=0.342).

Our main aim is to investigate LUTD in patients with VUR, especially those who are >5 years old, by using questionnaires and urodynamic studies, if necessary. We believe that that insignificant effect of LUTD on the success rate of ESI in our study may be due to our provision of standard urotherapy and/or medical treatment to all patients with LUTD prior to surgery and excluding the patients with neurogenic bladder from the study. American Urological Association guidelines recommend that concomitant LUTD should be investigated and treated in all patients with VUR regardless whether surgery is planned (2). In this sense, age could be a factor, as shown by a previous study (9). In our study, we found the success rates of ESI in patients younger and older than 82 months to be 70.7% and 83.5%, respectively (p=0.023). We feel that relatively higher voiding pressures and unstable bladder dynamics in younger children who are not fully toilet-trained may have resulted in lower success rates.

The presence of renal scarring is an indication for intervention, and our patients with high-grade VUR had significantly higher rates of renal scarring compared with those with low-grade VUR (71.8% vs 47.2%, p<0.001), as expected (10). Pre-operative renal scarring status did not significantly affect our post-operative success and UTI rates (p=0.995 and p=0.760, respectively).

An important aim of ESI in VUR is to prevent episodes of UTI. However, post-operative UTI may also be observed after successful surgery; this issue has been reported to occur more frequently in patients with persistent reflux, LUTD, history of BTI and female gender (4). In our series, the post-operative UTI rate was found to be 18.5%, and UTI was detected more frequently in females and patients with pre-operative BTI.

We detected contralateral reflux by control VCUG in two of 151 patients whose unilateral reflux completely disappeared (1.3%). The rate of contralateral reflux is reported to be between 7.9% and 12.5% in the literature (8,10,11). Our very low rate of contralateral reflux in unilateral ESI patients may be due to our use of intra-operative PIC-C for the contralateral side. We performed ESI in the same session in case contralateral reflux was detected. This approach seems to decrease the rate of post-operative contralateral reflux. We were also aware of the extremely low chance of detecting VUR by conventional post-operative VCUG on the contralateral side detected by PIC-C. This can only be evaluated by means of clinical observation as post-operative febrile UTI with symptoms of pain on the relevant ureteral unit.

The effect of the volume of injected material on the surgical outcome is controversial (3,12). Although subgroup analysis revealed that higher material volumes are associated with success in low- and high-grade reflux cases, evaluation of overall groups did not yield a difference between successful and failed cases. This insignificance may be due to the fact that 45% of the sample population comprised cases with moderate-grade reflux. Our finding of an increase in injection volume over the years is similar to that reported in a previous study (13). This result can be attributed to increases in the number of the patients with high-grade reflux during the time period. The frequent use of PIC-C and application of injection to the contralateral side in some patients may also explain this interesting result.

The injection technique may be another point of interest in the interpretation of surgical outcomes. The hydrodistention implantation technique (HIT) and double HIT methods were popularised by Kirsch and Arlen (14) and showed higher success rates than the STING method; thus, these methods gained wide acceptance amongst clinicians (4). We also perform these modified techniques in our daily practice, especially in high-grade reflux cases. However, we do not have a sufficient number of cases with adequate follow-up to compare these techniques with the standard STING method. Therefore, we are unable to comment on this topic at this time.

Another main objective of the present study is to observe changes in patient characteristics and surgical outcomes. Amongst the four chronological groups, we determined that ESI had become increasingly preferred in the last 10 years. We believe that this finding may be attributed to the increased availability of and developments in ESI procedures for VUR over the years. We also found that the rate of patients with a history of failed ESI, high-grade reflux and renal scarring increased significantly over time. Although statistically insignificant, our overall success rate slightly increased over time despite the increased number of patients with high reflux grades. This finding may be due to the frequent preference of ESI for patients with high-grade VUR if the ureter configuration seems normal and the submucosal tunnel is found to be relatively long during cystoscopy. In other words, when the status of the ureter orifice and submucosal tunnel in cystoscopy is considered rather than the pre-operative degree of reflux, higher success rates can be obtained through ESI even in patients with high-grade reflux.

We believe that the increase in history of failed ESI over the time may be attributed to our institution becoming a referral centre; our surgical knowledge and experience in dealing with patients with a history of failed ESI, especially those with the appropriate ureter configuration, has led to ESI becoming the preferred treatment of choice. Indeed, we observed that a history of previous failed ESI history did not affect our surgical outcomes.

In the literature, the most significant complication after ESI was reported to be ureterovesical (UV) obstruction (15). If recognised in the early post-operative period, most obstructions resolve with close follow-up or after placement of a temporary ureteral

stent. However, ureteral obstruction can develop without any symptoms. Therefore, post-operative follow-up for 3-5 years is recommended. However, according to the recent systematic review of Friedmacher and Puri (16), the incidence of ureteral obstruction is less than 1% and the issue can develop regardless of the material type, volume of injected material, injection technique or ESI history. We performed early ultrasonography 1 month post operation, every 3 months for year 1, every 6 months for year 2 and every year thereafter up to year 5. Here we experienced 2 (0.4%) cases of delayed UV obstruction within the first year post operation, which was addressed by open re-implantation.

Although several studies on the efficacy of ESI in children are available, the present study is unique in that it includes a large number of patients and a long follow-up period. These features provide excellent opportunities to observe changes in patient characteristics and analyse the factors affecting treatment outcomes.

Study Limitations

This study presents some limitations that may affect the generalisability of the results. First, this study is retrospective in nature, and we were unable to obtain data on the injected volumes of Dx/HA and pre-operative renal scarring for each patient. Moreover, post-operative USG in the follow-up period was investigated only if ureterohydronephrosis was present, and the height of the mound was not measured in all patients. Finally, routine annual VCUG was not performed for delayed recurrences. However, delayed VCUG was performed in patients with symptomatic infection or sustained hydroureteronephrosis.

Conclusion

The surgical outcomes of ESI are better in older children and those with low-grade VUR. Post-operative UTI develops more frequently in girls than boys and in patients with pre-operative BTI than in those without. The presence of LUTD does not change the outcome if properly treated before ESI. Given the extensive knowledge obtained over years of experience, endoscopic methods are generally preferred even in children with high-grade VUR and a history of failed STING.

Ethics

Ethics Committee Approval: Data from a total of 439 patients younger than 18 years old who underwent ESI between 2000 and 2020 were retrospectively collected.

Informed Consent: Informed consent was obtained from the patients' parents prior to the operation.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.S.D., S.T., Concept: T.C., B.Ç., H.S.D., Design: T.C., H.S.D., S.T., Data Collection or Processing: T.C., A.C.B., M.A., K.G., T.A. Analysis or Interpretation: T.C., A.C.B., M.A., H.S.D., Literature Search: T.C., B.Ç., Writing: T.C., H.S.D.

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The Current Approach to Male Patients with Lower Urinary Tract Symptoms

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What's known on the subject? and What does the study add?

Lower urinary tract symptoms in older men should be considered a remarkable public health issue, with significant urology outpatient clinic admissions. This study will determine the current approach of urologists to these men and will aid in the provision of a standard cost-effective clinical assessment policy.

Abstract

Objective: The goal of this study was to investigate the current daily approach of urologists for the initial evaluation of men with lower urinary tract symptoms (LUTS) in accordance with the European Association of Urology (EAU) guidelines.
Materials and Methods: An online survey was used to identify the daily practices of urologists for men over the age of 45 with LUTS. Based on the EAU guidelines, an 11-item questionnaire was created. A link to the SurveyMonkey questionnaire was sent to members of a national urology association along with an e-mail message. Moreover, the data were analysed after collecting all of the responses.
Results: Out of 1.182 urologists who received an invitation message, 166 (14.04%) responded and completed the questionnaire. The mean age of the urologists who responded was 42.24+10.11. More than half of the participants (56.6%) work at centres that have a urology residency programme. Furthermore, the most commonly performed laboratory test in men with LUTS was urinalysis. Approximately 90% of urologists performed urinalysis. In addition, 84% of participants routinely measured prostate-specific antigen in every man between the ages of 45 and 75. In all men with LUTS, approximately half of the urologists routinely used renal function tests, urinary ultrasonography, post-void residual urine measurement, uroflowmetry, and symptom score assessment. For men with nocturia and/or storage phase symptoms, the majority of participants (69.9%) used a bladder diary. Moreover, urologists who worked at university hospitals were found to use bladder diaries significantly more frequently in their clinical practice (p=0.037).
Conclusion: We discovered that there was no clinical approach standard among urologists for men with LUTS.
Keywords: Lower urinary tract symptoms, benign prostatic hyperplasia, prostate

Introduction

Lower urinary tract symptoms (LUTS) in older men account for the majority of the urologists' work, and the presence of LUTS has a negative impact on these patients' quality of life (1,2). Although benign prostatic hyperplasia (BPH) is the primary cause of LUTS in older men, a wide range of disorders, including systemic metabolic pathologies, are associated with LUTS (3). Furthermore, it is a well-known fact that aging is closely related to a higher prevalence of LUTS (2). As a result of the aging population, the cost of managing men with LUTS is constantly increasing (4). Consequently, urology associations and health authorities recommend standardized simple algorithms for evaluating these men with LUTS in order to provide a cost-effective clinical approach. One of the most well-known clinical guidelines belongs to the European Association of Urology (EAU). The EAU guideline titled "Management of Non-neurogenic Male LUTS" provides a comprehensive clinical guideline for these

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patients, including a stepwise clinical policy (5). This guideline outlines a straightforward standard clinical approach for men with LUTS.

According to the EAU guidelines, the initial assessment of men with LUTS includes a medical history, sexual function evaluation and a straightforward physical examination. Administration of a symptom score, urinalysis, measurement of post-void residual (PVR) urine and prostate-specific antigen (PSA) in patients if a diagnosis of prostate cancer will change the management policy are the diagnostic tools that should be performed at the initial presentation. If the initial evaluation reveals several risk factors, such as haematuria and a high PVR, all other tests, including renal function assessment and ultrasonography, are recommended.

Data on the primary approach pattern of urologists for BPH in daily practice, as well as the comparison with guidelines, are scarce and not investigated in the literature. The goal of this prospective trial was to investigate the current practices of urologists for male patients with LUTS. The concordance with the EAU guidelines was also assessed to see if there were any notable differences in the evaluation of these patients.

Materials and Methods

The current national cross-sectional study used an online self-administered survey to identify the daily practices of urologists for men over 45 years old with LUTS in outpatient urology clinics in Turkey in 2019. Based on the EAU guidelines, a questionnaire was created. The questionnaire had 11 questions about the clinical approach and diagnostic tests for men with LUTS. A link to the SurveyMonkey questionnaire was sent to members of a national urology association (The Society of Urological Surgery) along with an e-mail message. The e-mail message made it clear that participation in the study was entirely voluntary, and consent forms were obtained electronically. Respondent urologists could skip any question or opt out at any time. At 2-week intervals, all members of the association received three e-mail reminders with the survey link. Those who responded to and completed the questionnaire were not permitted to fill another online form. The study only included a survey of urologists about their clinical attitudes, with no personal information other than age, place of employment and working duration.

Statistical Analysis

All responses were obtained using the online SurveyMonkey platform, and the data were imported into Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the normality of the data. Categorical variables in contingency tables were created to assess variable independence using the chi-square test or Fisher's exact test. The threshold for statistical significance was set at $p \leq 0.05$.

Results

The online survey was distributed via e-mail to all the members of the Society of Urological Surgery. In terms of participation in the study, 1.182 urologists were contacted via e-mail. In the end, 166 urologists (14.04%) responded and completed the questionnaire (Table 1).

The urologists who completed the online survey had a mean age of 42.24+10.11. The majority of the participants (36.1%) worked at urology departments of the university hospitals (Table 1). In addition, 20.5% of urologists worked at urology departments of the ministry of health education and research hospitals.

Table 1. Demographic characteristics of the participants

	N	%
Response rate (Participant urologists/whole group receiving invitation mail)	166/1182	14.04
Mean age (± SD)	**42.24±10.11**	
Working institution	**N**	**%**
University hospital	60	36.1
Education and research hospital	34	20.5
State hospital	31	18.7
Private hospital	33	19.9
Private office or small outpatient clinics	8	4.8

SD: Standard deviation

Table 2. The utilization of laboratory tests in men with LUTS

	N	%
Urinalysis		
Every man	153	92.2
When there is an indication based on the medical history and physical examination	13	7.8
Prostate-specific antigen (PSA)		
Every man between the ages of 45 and 70	139	83.7
Every man, regardless of the patient's age	5	3
When there is a family history of prostate cancer and/or suspicious rectal examination	7	4.2
When the patients accept PSA measurement after discussing the possible consequences of PSA screening	15	9
Serum renal function tests		
Every man	77	46.4
Never	3	1.8
When there is a risk (high post-voiding residual urine, history of stone disease, haematuria, etc.) detected after initial assessment	86	51.8

LUTS: Lower urinary tract symptoms

Consequently, 56.6% of urologists work in centres that have a urology residency programme.

Urinalysis was the most commonly performed laboratory test in men with LUTS. A total of 153 urologists (92.2%) reported routine urinalysis for every man with LUTS. Similarly, the majority of urologists (83.7%) routinely measured PSA levels in all men aged 45-70. In addition, 77 urologists (46.4%) stated that they routinely measured renal function tests in all male LUTS patients. Table 2 summarizes the urologists' clinical proclivity for performing laboratory tests.

According to an assessment of current policy regarding radiological imaging techniques for men with LUTS, 84 urologists (50.6%) performed routine urinary ultrasonography (Table 3). Only 2.4% (4/166) of urologists requested routine transrectal ultrasonography for all men with LUTS. On the other hand, according to the EAU guidelines, approximately half of the urologists (90/166, 54.2%) used PVR assessment, which is a routine initial test (Table 3).

Uroflowmetry, as a non-invasive test, was reported to be a routine part of the initial assessment for men with LUTS by nearly half of the urologists (84/166, 50.6%). The remaining urologists (82/166, 49.4%) preferred uroflowmetry in severe symptomatic cases or prior to treatment (surgery or medical) (Table 4). Almost half of the urologists (81/166, 48.8%) used validated questionnaires to assess symptom scores as an initial test of the EAU guidelines in men with LUTS (Table 4). On the other hand, a bladder diary was never obtained by any of the 44 urologists (26.5%). For men with nocturia and/or storage phase symptoms, the majority of participants (69.9%) used a bladder diary (Table 4).

Table 3. The utilization of radiological techniques in men with LUTS

	N	%
PVR (post-void residual) urine		
Every man	90	54.20
Never	4	2.40
When there is an indication based on the medical history and physical examination	72	43.40
Urinary ultrasonography		
Every man	84	50.60
Never	0	0
When there is a risk (high post-voiding residual urine, history of stone disease, haematuria, etc.) detected after initial assessment	78	47.00
Transrectal ultrasonography		
Every man	4	2.40
Never	162	77.60

LUTS: Lower urinary tract symptoms

Table 4. The utilization of specific diagnostic tools in men with LUTS

	N	%
Uroflowmetry		
Every man	84	50.6
In severely symptomatic cases or before initiation of the treatment (surgery or medical)	82	49.4
Never	0	0
Symptom score		
Every man	81	48.8
Never	85	51.2
Bladder diary		
Ever man	6	3.6
Never	44	26.5
In men with nocturia and/or storage phase symptoms	116	69.9

LUTS: Lower urinary tract symptoms

Table 5. The impact of the urologists' institution on the use of the bladder diary in men with LUTS

	University hospital (N=60) n, (%)	Others (N=106) n, (%)	p-value
Every man	3 (5)	3 (3.8)	0.037
Never	9 (15)	35 (33)	
In men with nocturia and/or storage phase symptoms	48 (80)	68 (64.2)	

LUTS: Lower urinary tract symptoms

Except for the bladder diary, there is no difference in the use of clinical diagnostic tools for men with LUTS among urologists based on their working environment (university hospitals vs other centres). Moreover, urologists at university hospitals were found to use bladder diaries more frequently (80% vs 64.2%) in their clinical practice (p=0.037, Table 5).

Discussion

Older men with LUTS are a significant burden on urologists' daily clinical practice of urologists. These male LUTS patients are also putting a strain on urology outpatient clinics. The ever-increasing aging of the population raises the cost of evaluating men with LUTS for healthcare systems (4,6). Therefore, there is certainly a need for a cost-effective standard clinical evaluation policy that employs the bare minimum of diagnostic tools.

One of the topics of discussion on men with LUTS is the routine use of PSA (7). PSA may be used as a screening tool by urologists and primary care physicians for all men. It was even proposed that primary care physicians preferred routine PSA screening over urologists (8). Currently, it is generally recommended that the physician and the patient reach an agreement on PSA

measurement after discussing the potential consequences of prostate cancer screening for men with LUTS (9). Similarly, the EAU guidelines recommend PSA measurement for men with LUTS if a prostate cancer diagnosis changes management or if it aids in the treatment and/or decision-making process (5). In contrast, the current study found that the majority of urologists (about 84%) routinely measured PSA in every man between the ages of 45 and 70. Moreover, 3% of the urologists obtained PSA without taking age into account.

For men with LUTS, symptom score assessment using validated questionnaires is strongly advised (5,10-12). However, our results revealed that roughly half of the urologists did not use any kind of symptom score for these men. Similarly, according to the EAU guidelines, PVR measurement is a critical diagnostic tool in the evaluation of men with LUTS (5). It is incorporated into the management algorithm and serves as an indication for additional diagnostic tools such as renal function tests and pressure flow studies. It is a simple non-invasive test that provides important information about bladder function. It was also reported that a PVR threshold of 50 mL has a positive predictive value of 63% and a negative predictive value of 52% for predicting bladder outlet obstruction (13). Furthermore, in these men with LUTS, a high PVR is found to be associated with symptom progression (14,15). Only about half of the urologists obtained PVR on a regular basis in their daily practice.

On the other hand, the EAU guidelines do not recommend routine urinary ultrasonography for men with LUTS (5). A radiological examination is recommended for men with a high PVR, haematuria, or a history of urolithiasis. The current study found that half of the urologists routinely performed ultrasonography.

The assessment of serum renal functions in the current trial also revealed a policy that differed from the EAU guidelines. According to some authors, men with LUTS are more likely to have hydronephrosis, renal failure and urinary retentions (15). However, the exact relation between these complications and LUTS caused by BPH is unknown (16). Therefore, the EAU recommends measuring renal function if renal impairment is suspected based on history and clinical examination, or if hydronephrosis is present, or when considering surgical treatment for male with LUTS (5). In this study, 46.4% of urologists stated that they performed renal function tests on all men with LUTS.

Uroflowmetry is a simple non-invasive diagnostic tool used to evaluate voiding function (17). The EAU does not recommend routine uroflowmetry in all men with LUTS (5). Moreover, it can be used to track treatment progress. Then, according to the EAU guidelines, uroflowmetry can be used prior to medical or invasive treatment. According to our findings, half of the urologists performed uroflowmetry on every patient, while the other used this test prior to medical or surgical treatment.

A bladder diary is an extremely useful diagnostic tool, particularly for patients suffering from nocturia (18,19). In addition, a bladder diary is the only way to diagnose nocturnal polyuria. The EAU guidelines suggest using a bladder diary to assess male with LUTS with a prominent storage component or nocturia (5). In this study, approximately 70% of the urologists used a bladder diary, as recommended by the EAU guidelines. In addition, according to the EAU guidelines, 80% of urologists working in university hospitals used bladder diaries appropriately. This rate was significantly lower for other urologists, which was around 64%.

Urinalysis was the most commonly used test, and it is also strongly recommended by the EAU guidelines. Approximately 92% of all urologists used this test on every man with LUTS on a regular basis. However, when there is an indication based on the medical history and physical examination, approximately 8% of urologists obtained this test.

Conclusively, our results of the current study showed that urologists continue to prefer laboratory tests such as PSA and renal function assessment during the evaluation of men with LUTS. One possible reason for regularly obtaining these tests is the "time constraint" at outpatient clinics. The online central system of the ministry of health is set to take 5-10 minutes for each patient. Due to time constraints, a thorough history and physical examination may be impossible. Therefore, to avoid medicolegal problems, urologists prefer to obtain routine tests such as PSA and renal function. Similarly, ultrasonography may be overused for the same reasons. The lack of a national guideline approved by the ministry of health is another possible explanation for the discrepancy between current evaluation for men with LUTS and the EAU guidelines. Another reason is that there are no regular postgraduate courses available on this issue.

Study Limitations

One of the limitations of the study was the small sample size. Despite receiving multiple invitation e-mails, only 14% of urologists completed the online survey. The second issue is that the online survey may differ from actual clinical practice. To avoid any potential bias, personal information, including names, were withheld.

Conclusion

The results of the study clearly demonstrated that there was no standard clinical approach among urologists for men with LUTS. Furthermore, the current attitude differed from the EAU guidelines. Only half of the urologists routinely used the

EAU-recommended symptom score and PVR assessment in the initial evaluation of men with LUTS. In contrast to the EAU recommendations, PSA, serum renal function tests and urinary ultrasonography were overused. More studies and educational models are needed to develop a standardized approach to LUTS in everyday practice.

Ethics

Ethics Committee Approval: The current national cross-sectional study used an online self-administered survey to identify the daily practices of urologists for men over 45 years old with LUTS in outpatient urology clinics in Turkey in 2019.

Informed Consent: Informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.K.Ç., Design: H.K.Ç., B.Ş., Data Collection or Processing: B.Ş., Analysis or Interpretation: B.Ş., H.K.Ç., Literature Search: B.Ş., Writing: B.Ş., H.K.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Trends and Risk Factors for Ciprofloxacin Resistance and Extended-spectrum Beta-lactamase Production in Uropathogens from Urology and Non-urology Outpatients

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What's known on the subject? and What does the study add?

The increased rates of antibiotic resistance of urinary pathogens influence the empirical medical management of urological infections in the outpatient setting. In this study, increased ciprofloxacin resistance and extended-spectrum beta-lactamase production were associated with being adult, male and old and isolates of *E. coli* and *Klebsiella* spp.

Abstract

Objective: This study aimed to identify the patterns and temporal changes of ciprofloxacin resistance and extended-spectrum beta-lactamase (ESBL) production in uropathogenic isolates obtained from urology and non-urology outpatients.

Materials and Methods: In this cross-sectional study, electronic data of urine culture and antimicrobial susceptibility test results of samples collected in urology and non-urology outpatient departments from 2008 to 2016 were retrospectively analysed to identify correlations between basic demographic features and clinical settings.

Results: *Escherichia coli* (*E. coli*) was the most prevalent (70%) uropathogenic isolate in a cohort of 7.973 patients consisting of 82.8% women, 70.7% adults and 15.7% urology outpatients. Overall, resistance to ciprofloxacin was found in 16.3% of the patients. Ciprofloxacin resistance was associated with being male and old, observed more frequently in urology outpatients, detected in 19.2% of *E. coli* isolates and increased to 54.5% among ESBL-producing bacterial strains ($p<0.05$). ESBL production was observed in 12% of all isolates. Increased ESBL production was associated with old age and isolates of *E. coli* and *Klebsiella* spp. ($p<0.05$). Statistical analysis using multivariate generalised linear mixed models (mGLMMs) to assess the relationship between the outcomes predicted a significantly higher ESBL production in *E. coli* and *Klebsiella* spp. isolates and in geriatric patients. Furthermore, mGLMM analysis predicted a significantly increased likelihood of ciprofloxacin resistance in older adult male patients, especially in *E. coli* and *Enterococcus* spp. isolates. Moreover, a high rate of ESBL production was observed, reaching over 15% in 2015 ($p<0.05$). The rates of ciprofloxacin resistance remained >10% and peaked in 2015 (20.2%, $p<0.001$). However, in 2016, the rate of ESBL production and ciprofloxacin resistance started to decline, displaying significance only regarding the latter ($p<0.05$).

Conclusion: Empirical ciprofloxacin treatment of community-acquired urinary tract infections carries a higher risk of an unsuccessful outcome in male, geriatric and urology outpatients. Empirical antibacterial therapy for urological infections in the outpatient setting should be conducted based on patient risk profiles and contemporary local resistance data.

Keywords: Urinary tract infections, antibiotic resistance, ciprofloxacin, extended-spectrum beta-lactamases, uropathogens

Introduction

The increasing prevalence of antibiotic-resistant bacteria restricts the utility of empirical treatment of community-acquired urinary tract infections (CAUTIs). Current monitoring of the regional pattern of bacterial resistance is essential in managing appropriate treatments of urological infections. The European Association of Urology guidelines strongly recommend against using fluoroquinolones to treat uncomplicated cystitis, but stated fluoroquinolones as the first-line regimen (empiric

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or sensitivity-directed) of complicated UTIs, pyelonephritis, prostatitis and epididymitis/orchitis (1). If there is a lack of a coordinated strategy for judicious use of antimicrobials, quinolones may often be prescribed for the empirical treatment of CAUTIs in various clinical settings, contrary to the guidelines (2).

Remarkably high rates of fluoroquinolone resistance have been observed globally in *Escherichia coli* (*E. coli*) and *Klebsiella pneumonia* strains, which are common causes of healthcare-associated and community-acquired UTIs (3,4). Although incidences vary by geography, multinational studies have reported fluoroquinolone-resistant *E. coli* isolates in 20% of uncomplicated and more than 50% of complicated CAUTIs (4,5).

Extended-spectrum beta-lactamases (ESBLs) are a heterogeneous group of enzymes responsible for resistance against beta-lactam antibiotics, which are among the most frequently used antibiotics in outpatient settings worldwide (6). ESBL-producing *Enterobacteriaceae* spp. commonly show cross-resistance to other groups of antibiotics, such as fluoroquinolones. The close relationship between ESBL production and ciprofloxacin (CIP) resistance is particularly troublesome because it narrows the range of alternative therapies for isolates harbouring both mechanisms at the same time (7).

In this study, the primary aim was to determine the current regional situation and temporal changes in antimicrobial resistance in common uropathogens. This study set out to explore the rates of CIP resistance and ESBL production in urinary isolates obtained from outpatients and examine the relationship between patterns of resistance with demographic features and clinical settings.

Materials and Methods

In this cross-sectional study, the electronic database of urine culture and antimicrobial susceptibility test results of samples collected in outpatient departments of Acibadem Kadiköy Hospital affiliated to Acibadem Mehmet Ali Aydinlar University (Istanbul, Turkiye) from 2008 to 2016 was analysed retrospectively. Outpatients were defined as paediatric (<18 years old), adult and geriatric (>65 years old) individuals who visited hospital-based outpatient clinics. Urine samples were sent to the in-hospital laboratory for culture and sensitivity tests.

The inclusion criteria were as follows: any age, presentation of a urine sample to the in-hospital laboratory as an outpatient who has positive cultures for common urinary pathogens during the study period, CIP susceptibility and available ESBL activity data. All cultures were collected from outpatients with medical requests from the urology department and all other outpatient clinics from midstream urine samples, except for children aged <2 years old who had collections by sterile collector vials or urethral catheterisation.

This study analysed CIP susceptibility and ESBL activity data exclusively for uropathogens, namely, *E. coli*, *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., *Enterobacter* spp., *Staphylococcus saprophyticus* and "other" rare isolates. Data collected during the study period were analysed to determine the prevalence, tendency of uropathogens to CIP resistance and ESBL production and to examine risk factors among outpatient groups.

Patients were excluded from the study if they had more than one culture collected <30 days apart (to eliminate contamination caused by recurrent or resistant UTIs, and multiple samples were sent on a patient during treatment), urinary growth of non-uropathogenic bacterial strains and >2 strains simultaneously or any bacterial growth with a density $<10^5$ CFU/mL in adults and $<10^3$ CFU/mL in children whose sample was taken by urinary catheterisation.

Bacterial growth was expressed as the number of CFUs/mL. Identification of bacteria, antibiotic susceptibility tests and detection of ESBL production was performed by Phoenix (Becton Dickinson, USA) automated system, following the standard procedures defined by the Clinical and Laboratory Standards Institute (8).

Statistical Analysis

Statistical analyses were performed using the R Statistical Software. Descriptive statistics were used to summarise data. Binary logistic regression analyses were used for univariable comparisons. Multivariate generalised linear mixed models (mGLMMs) with logit link function were used to assess the relationship between outcomes (presence of ESBL production and CIP resistance as dependent variables) and exploratory variables (gender, age, uropathogen, outpatients and year as independent variables). The reference categories for statistical (mGLMM) analysis were "female" for gender, "<18 years old" for age, "others" for uropathogens, "non-urology" for outpatients and "2008" for years. A p-value <0.05 was considered significant.

Ethics Approval

This is a non-interventional research based on a retrospective chart review of electronic data. Approval for the study protocol was obtained from the Acibadem MAA University İnstitutional Ethics Committee (no: 2020-12/4). The study was conducted according to the criteria set by the Declaration of Helsinki. Waiver of patient consent was approved by local institutional ethics committee. All data were analysed anonymously, and the waiver of informed consent did not and will not have adverse effect on the rights and health of the patients.

Results

Among 7973 urinary isolates, 82.8% belonged to female patients and 70.7% belonged to adult and geriatric patients. Isolates from the urology outpatients comprised 15.7% of the cohort. *E. coli* was the most prevalent (70%) uropathogen isolated, followed by *Klebsiella* spp. (10.8%), *Enterococcus* spp. (7.5%), *Proteus* spp. (3.7%), *Enterobacter* spp. (2%), *Staphylococcus saprophyticus* (1.2%) and others (4.9%). Table 1 displays the summary statistics of the cohort and uropathogens.

Overall, ESBL production was observed in 12% and CIP resistance was found in 16.3% of the isolates. The rate of CIP resistance was 54.5% among all ESBL-positive uropathogens and 58.4% in ESBL-positive *E. coli* isolates, whereas it remained at 11.1% among ESBL-negative isolates.

Patterns of ESBL Activity

ESBL production was markedly higher in the geriatric group (p<0.001). No difference was found in the rate of ESBL activity related to gender or between isolates from urology and non-urology outpatient clinics (p>0.05). ESBL production was significantly increased (15%) in *E. coli* and *Klebsiella* spp. isolates (p<0.05) (Table 2). The rates of ESBL production among isolated uropathogens throughout the study period are given in Table 2, where a high rate of ESBL production reaching >15% in 2014 and 2015 stands out (p<0.05) (Figure 1).

The mGLMM analysis was performed to assess a range of factors on ESBL production, and the final model was found significant for prediction (F=19.236, p<0.001) (Table 3). The statistical analysis revealed that the risk of ESBL production of isolates was significantly higher in patients aged >65 years [odds ratio (OR) (95% confidence interval (CI) 2.095 (1.702, 2.580), p<0.001]. The risk of ESBL positivity was lower in 2012 [OR (95% CI) 0.624 (0.428, 0.909), p=0.014] (Table 3). Among uropathogens, *E. coli* and *Klebsiella* spp. were associated with higher prevalence of ESBL production (p<0.001). Further analysis showed that the probability of ESBL production remained significantly high from 2014 through 2016.

Table 1. Patient demography and distribution of microorganisms of interest isolated from urine samples

		n (%)
Gender	Female	6604 (82.8)
	Male	1369 (17.2)
Age	Paediatric (0-17)	2337 (29.3)
	Adult (18-65)	4654 (58.4)
	Geriatric (>65)	982 (12.3)
Outpatients	Urology	1252 (15.7)
	Non-urology	6721 (84.3)
Uropathogens	*Escherichia coli*	5580 (70)
	Klebsiella spp.	864 (10.8)
	Proteus spp.	292 (3.7)
	Enterococcus spp.	599 (7.5)
	Enterobacter spp.	156 (2)
	Staphylococcus saprophyticus	95 (1.2)
	Others*	387 (4.9)

*Rare isolates referred as "others" include *Pseudomonas aeruginosa, Morganella morganii, Serratia marcescens* and *Streptococcus agalactiae*

Patterns of CIP Resistance

Male sex and old age among patient groups were significant factors for CIP resistance (p<0.05). CIP resistance was more often observed in isolates from urology than those delivered from non-urology outpatient clinics (19.6% vs 15.7%, p<0.05). The statistical analysis also detected a remarkably high (19.2%) level of CIP resistance in *E. coli* isolates (p<0.001) (Table 2).

During the study period, the rates of CIP resistance constantly remained >10%. From 2012 to 2015, a continual rise was noted, reaching the highest rate in 2015 (20.2%, p<0.001). However, in 2016, the rate of CIP resistance significantly decreased to 12.7% (p<0.05) (Figure 1).

The mGLMM analysis was performed to assess the effects of numerous factors on CIP resistance, and the obtained model was significant (F=30.810, p<0.001). The results established a relationship of elevated risk of CIP resistance with male sex [OR (95% CI) 1.357 (1.140, 1.616), p=0.001] and increased age. The probability of CIP resistance was higher in adults (18-65 years) [OR (95% CI) 2.013 (1.685, 2.405), p<0.001] and the highest in the geriatric group [OR (95% CI) 7.544 (6.151, 9.254), p<0.001].

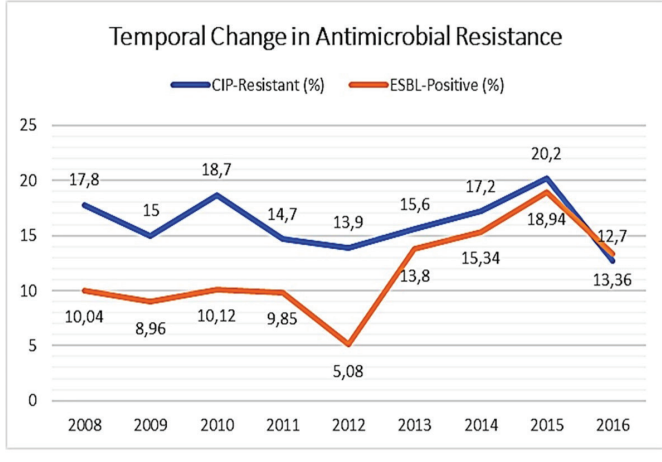

Figure 1. Frequency of ciprofloxacin resistance and extended-spectrum beta-lactamase production of uropathogens isolated from urine samples of outpatients evaluated from 2008 to 2016 For ciprofloxacin resistance: p<0.05 in 2015 and 2016

For extended-spectrum beta-lactamase production: p<0.05 in 2008, 2009, 2011, 2012, 2014 and 2015

The likelihood of CIP resistance was significantly increased in isolates of *E. coli* and *Enterobacter* spp. (p<0.001). The relative declines in the risk of CIP resistance in 2013 [OR (95% CI) 0.766 (0.597, 0.983), p=0.036] and 2016 [OR (95% CI) 0.631 (0.488, 0.815), p<0.001] were significant (Table 3).

Discussion

This study was carried out to determine the recent local prevalence of uropathogens and antimicrobial susceptibility patterns by assessing CIP resistance and ESBL activity in isolates. Data collected from urology and non-urology outpatients in

Table 2. ESBL production and CIP resistance status of urinary isolates according to patient features, bacterial strains and years

	ESBL (-)	ESBL (+)	p	CIP-resist. (-)	CIP-resist. (+)	p
	n (%)	n (%)		n (%)	n (%)	
Gender						
Female	5805 (87.9)	799 (12.1)	0.564	5563 (84.2)	1041 (15.8)	0.003**
Male	1211 (88.5)	158 (11.5)		1109 (81)	260 (19)	
Age						
Paediatric (0-17)	2091 (89.5)	246 (10.5)	<0.001**	2166 (92.7)	171 (7.3)	<0.001**
Adult (18-65)	4148 (89.1)	506 (10.9)		3906 (83.9)	748 (16.1)	
Geriatric (>65)	777 (79.1)	205 (20.9)		600 (61.1)	382 (38.9)	
Clinics						
Urology	1087 (86.8)	165 (13.2)	0.163	1006 (80.4)	246 (19.6)	<0.001**
Non-urology	5929 (88.2)	792 (11.8)		5666 (84.3)	1055 (15.7)	
Uropathogens						
Escherichia coli	4755 (85.2)	825 (14.8)	<0.001**	4509 (80.8)	1071 (19.2)	<0.001**
Klebsiella spp.	734 (85)	130 (15)	0.004 **	798 (92.4)	66 (7.6)	<0.001**
Proteus spp.	291 (99.7)	1 (0.3)	<0.001**	275 (94.2)	17 (5.8)	<0.001**
†*Enterococcus* spp.	599 (100)	0 (0)	0.991	492 (82.1)	107 (17.9)	0.287
Enterobacter spp.	155 (99.4)	1 (0.6)	0.002**	148 (94.9)	8 (5.1)	<0.001**
†*Staphylococcus saprophyticus*	95 (100)	0 (0)	0.996	93 (97.9)	2 (2.1)	0.002**
†Others	387 (100)	0 (0)	0.992	357 (92.2)	30 (7.8)	<0.001**

*p<0.05, **p<0.01
†Excluded from the analysis because of insufficient ESBL (+) observation, i.e. OR values could not be computed. ESBL: Extended-spectrum beta-lactamase, CIP: Ciprofloxacin

Table 3. Multivariate generalised linear mixed model analysis of the relationship between the outcomes (presence of ESBL production and CIP resistance) and exploratory variables (gender, age, uropathogen, outpatient clinic and year)

	ESBL (+)			CIP Resistance (+)		
	Beta	OR (95% CI)	p	Beta	OR (95% CI)	p
Gender (Male)	0.163	1.177 (0.970, 1.427)	0.098	0.305	1.357 (1.140, 1.616)	0.001**
Age (18-65)	-0.151	0.860 (0.726, 1.019)	0.081	0.700	2.013 (1.685, 2.405)	<0.001**
Age (>65)	0.740	2.095 (1.702, 2.580)	<0.001**	2.021	7.544 (6.151, 9.254)	<0.001**
Services (urology)	0.112	1.119 (0.928, 1.349)	0.240	0.102	1.107 (0.940, 1.304)	0.223
Uropathogens						
E. coli	1.974	7.200 (5.006, 10.357)	<0.001**	1.335	3.799 (2.591, 5.571)	<0.001**
Klebsiella spp.	1.901	6.690 (4.487, 9.975)	<0.001**	0.286	1.332 (0.854, 2.077)	0.207
Proteus spp.	0.241	1.273 (0.602, 2.690)	0.528	0.328	1.388 (0.767, 2.513)	0.278
Enterococcus spp.	ǂ-	ǂ-	ǂ-	1.014	2.756 (1.795, 4.230)	<0.001**
Enterobacter spp.	0.199	1.220 (0.475, 3.133)	0.679	0.074	1.076 (0.509, 2.275)	0.847
Staphylococcus saprophyticus	ǂ-	ǂ-	ǂ-	-0.370	0.691 (0.234, 2.039)	0.503

GLMM (with logit link function), OR: Odds ratio, CI: Confidence interval, ESBL: Extended-spectrum beta-lactamase, CIP: Ciprofloxacin
*p<0.05, **p<0.01
ǂExcluded from the analysis because of insufficient ESBL (+) observation, i.e. OR values could not be computed

a 9-year interval were retrospectively examined. This study confirms that *E. coli* is the predominant uropathogen isolated in CAUTIs. The frequency rate (70%) was similar to the rate observed in other prevalence studies that examined data from patients clinically diagnosed with UTI.

Recent multinational, prospective surveillance studies in Europe established an *E. coli* prevalence of 74%-76.7% in women with acute uncomplicated UTI (9,10). International studies that are methodologically comparable to the present study have reported *E. coli* prevalence of 56.8%-70.4% (11,12). A previous study conducted in Turkey reported that *E. coli* is the causative agent in 90% of the uncomplicated CAUTIs and 78% of the complicated CAUTIs (13). Differences regarding prevalence could be attributed to a broader selection of outpatients with uncomplicated and complicated UTIs in the current cohort. The microbiology of complicated UTI is characterised by a greater spectrum of bacterial strains and an increased likelihood of antimicrobial resistance compared with acute uncomplicated UTI (14).

Resistance Patterns

The pattern of CIP resistance was the main focus in this study owing to its key role in the management of complicated urological infections. We identified an overall CIP resistance rate of 16.3% among common uropathogens, which increased to 19.2% among *E. coli* isolates and 54.5% among ESBL-producing bacterial strains. Surveillance studies have demonstrated widely fluctuating rates of CIP resistance in different geographical areas (4). A large multicentre surveillance study, with a similar methodology to this study, reported a 5.5% of CIP resistance rate in North America (15). A meta-analysis of observational studies revealed an estimated pooled CIP resistance of 27% in CAUTIs caused by *E. coli* (5). For uncomplicated CAUTIs, rates of CIP resistance ranged from 0% to 14.7% in Europe, with the lowest in Nordic countries and Austria and highest in Portugal and Spain (9). In Turkey, results from earlier studies demonstrated a 25%-38% frequency of CIP resistance among urinary pathogens (13,16). Overuse or misuse of antibiotics is known to propagate bacterial multidrug resistance. A positive correlation was found between widespread prescription of quinolones and antibiotic resistance, limiting their effectiveness in the treatment of UTIs. Moreover, in communities, frequent use of prescription drugs without medical advice may contribute to increasing bacterial resistance (2).

ESBLs frequently carry resistance genes for additional antibiotic classes including fluoroquinolones (17). Hence, ESBL activity of Gram-negative bacteria may be viewed as a surrogate to multidrug resistance. ESBL production ranges widely from 2.6% to 100% in various geographical areas, highest in the Asia-Pacific region and moderate to low in Europe and North America (4). A study from Turkey reported a 17.4% rate of ESBL-producing *E. coli* in adults with CAUTI (15). In the present study, the level of ESBL production in *E. coli* isolates observed was 14.8%. As one of the significant findings emerging from our data, among ESBL-positive isolates, the CIP resistance coexisted in 54.5%, in contrast to 11.1% among ESBL-negative isolates. Studies have demonstrated that CIP resistance is more common in ESBL-positive uropathogenic *E. coli* isolates in CAUTIs (7,16). ESBL production is also higher in *E. coli* isolates in complicated CAUTIs than in uncomplicated cases (15,18). Taken together, these data suggest a close correlation between ESBL production and fluoroquinolone resistance in uropathogenic bacteria. In regions where ESBL-producing Gram-negative community-acquired uropathogens are common, enhanced efforts for accurate determination of ESBL activity in combination with antibiotic sensitivity is warranted, along with restriction of fluoroquinolones in empirical treatments.

In the present study, isolates from older (geriatric > adult), male, adult urology outpatients were related to higher CIP resistance. Additionally, isolates of *E. coli*, leading pathogen in community-onset urological infections, were more likely to exhibit CIP resistance and ESBL production. A higher risk of ESBL production was further related to the older age (>65 years) of outpatients, which is known as one of the common risk factors for community-onset ESBL-producing *E. coli* or *Klebsiella* spp. infections (3,18-22). The incidence of UTI is increased in elderly patients owing to their immune status and aging-related physiological and anatomical changes. Elderly patients are more likely to be immunocompromised, have co-morbidities and are hospitalised more often than younger patients. Such conditions expose them to frequent or high consumption of antimicrobial drugs, which brings about an increment of resistance to antimicrobial agents (20-23).

Assessment of regional, population-based resistance patterns data and patient-specific risk factors data is key to establishing country-specific guidelines on empirical antibiotic treatment recommendations (24).

In the present study, the 19.2% CIP resistance rate in *E. coli* isolates raises a concern regarding the clinically meaningful susceptibility threshold for fluoroquinolones in CAUTIs. Statistical modelling of our results can infer that an empirical CIP treatment of CAUTI carries a higher risk of an unsuccessful outcome in a male, geriatric, urology outpatient.

Temporal Changes in Antimicrobial Resistance

We observed an increasing level of CIP resistance among uropathogens during the study period with a peak (20.2%) in 2015. Surprisingly, a significant decrease was noted in CIP resistance in 2016. Likewise, ESBL production remained stable at approximately 10% until 2013 and thereafter increased to

20% in 2015. A brief decrease in ESBL production occurred in 2016, albeit without significance. The present results provided additional and contemporary evidence regarding the persistent problem of antimicrobial resistance in CAUTIs, which represents a challenge to urology practice. Comprehensive reviews indicate a continuous, worldwide increase of antimicrobial resistance. In southern European countries as well as in the USA, a gradual increase in the resistance of *E. coli* to fluoroquinolones has been reported (24). In Switzerland, an analysis of urinary *E. coli* specimens obtained from 1997 to 2007 found an increasing trend in CIP resistance from 1.8% to 15.9% (25). A gradual rise in resistance of *E. coli* strains to CIP from 8% to 11% in 2009-2011 is noted in Australia (26). Studies on antimicrobial resistance have revealed that irrational prescription habits and high consumption of fluoroquinolones lead to the dissemination of quinolone resistance in the community (22,24). The high quinolone resistance in our region may be due to increased fluoroquinolone consumption over the years. In 2013, a "Rational Drug Use National Action Plan" was issued by the Turkish Ministry of Health, implementing several integrated interventions to survey, contain and prevent antimicrobial resistance emergence and spread. It could be argued that the significant decrease in CIP resistance in the last year of the study period may be attributed to the positive result of the plan; however, further research should be undertaken to investigate the consequences of this initiative.

Study Limitations

This study has some limitations. First, hospital and laboratory-based surveillance data obtained from a single centre may overestimate the rates of antibiotic resistance. Uncomplicated UTIs in the outpatient setting may be treated empirically without sending a urine culture sample to the laboratory. Cultures are usually performed if the patient fails to respond to treatment, has recurrent episodes of UTI or has complicated UTI. Second, data are retrospectively analysed, and the investigation is limited by the lack of uniform clinical information on previous antibiotic treatment, previous hospitalisations and interventions, whether urine samples came from patients with asymptomatic bacteriuria, uncomplicated or complicated UTIs. Since our data lacked information on symptomatology or clinical history of patients, we excluded uncommon urinary isolates to omit cases that may not have represented CAUTIs. The analysis of in vitro microbiological data alone may have altered uropathogen prevalence.

The strengths of our study are the large sample size, use of only common community-acquired uropathogenic isolates to avoid selection bias and the very stringent classification of electronic surveillance data.

Conclusion

It is essential to know the current, local bacteriological environment and resistance patterns as well as risk factors to guide the physicians in choosing the appropriate antibiotic treatment for infections. The increased rates of CIP resistance and ESBL production of urinary pathogens undeniably influence the medical management of urological infections in the outpatient setting. Determined efforts regarding a comprehensive policy and detailed action plans on prudent use of all antibiotics, including CIP should be developed and enforced by regional multidisciplinary teams.

Ethics

Ethics Committee Approval: Approval for the study protocol was obtained from the Acibadem MAA University İnstitutional Ethics Committee (no: 2020-12/4).

Informed Consent: Waiver of patient consent was approved by local institutional ethics committee. All data were analysed anonymously, and the waiver of informed consent did not and will not have adverse effect on the rights and health of the patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ö., K.F.N., L.T., A.Ş., Concept: B.Ö., K.F.N., L.T., A.Ş., Design: B.Ö., K.F.N., L.T., A.Ş., Data Collection or Processing: B.Ö., K.F.N., Analysis or Interpretation: B.Ö., K.F.N., L.T., A.Ş., Literature Search: B.Ö., Writing: B.Ö.

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CASE REPORT
Urooncology

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Localised Mass-forming Amyloidosis of the Genitourinary Tract Mimics Urothelial Carcinoma: Two Cases of Mistaken Identity

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Abstract

Amyloidosis of the lower genitourinary tract is an extremely rare condition and often mimics urothelial malignancy. In this paper, we report two cases of ureteral and urethral amyloidosis that initially presented as urothelial carcinoma and were successfully treated with laparoscopic nephroureterectomy and trans-urethral resection, respectively. This disease, with its various atypical presentations, presents a diagnostic challenge to urologists. Awareness is important as excision can be curative, and presence of systemic disease must be excluded.
Keywords: Amyloidosis, ureter, urethra

Introduction

Amyloidosis is a pathological process involving extracellular deposition of abnormal protein fibrils within the body. Localised amyloidosis of the genitourinary tract is a rare entity and may masquerade as urothelial carcinoma clinically, radiologically and endoscopically. In this report, we describe our experience with isolated mass-forming amyloidosis of the ureter and urethra.

Case 1

A 57-year-old woman presented with left-sided flank pain of 2 months duration. She denied visible haematuria and other lower urinary tract symptoms. She was a non-smoker and had no history of urolithiasis. Her estimated glomerular filtration rate was >90 mL/min/1.73 m^2 with a serum creatinine of 53 mg/dL. Urine culture was sterile.

An initial computed tomography intravenous pyelogram demonstrated a 17×8 mm^2 contrast-enhancing lesion of the distal left ureter, raising suspicion for a urothelial tumour (Figure 1). Urine cytology, however, was negative for high-grade urothelial cancer.

An attempt at endoscopic biopsy of the lesion was unsuccessful because of a dense distal ureteric stricture. The patient therefore underwent laparoscopic left nephroureterectomy on the basis of a clinical and radiological suspicion for a primary urothelial malignancy. Histopathology confirmed mass-forming amyloidosis in the ureter without evidence of neoplasia. There was no amyloid deposition in the kidney. Immunohistochemistry for light chains and amyloid A did not contribute in the typing of ureteric amyloid.

This patient was followed up 12 months later with a negative result for systemic amyloidosis. Her kidney function is stable, and she remains disease-free with no recurrence.

Case 2

A 23-year-old man presented with intermittent urethral bleeding and haematospermia. He described obstructive voiding symptoms, including a poor stream and spraying on voiding. On examination, he had a palpable urethral mass at the level of the coronal sulcus, presumed to be a urethral malignancy. He was a non-smoker with a history of treated chlamydial urethritis.

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A papillary lesion was visualised in the anterior urethra with a 22-Fr rigid cystoscope. The mass was completely avulsed with passage of the scope, followed by completion cold-cup biopsy and Bugbee diathermy haemostasis. Histopathology showed mass-forming amyloidosis containing a mixed infiltrate of plasma cells and lymphocytes, in keeping with localised amyloidosis (Figure 2).

The patient was examined 12 months later, with no symptoms suggestive of recurrence and a negative result for systemic amyloidosis. Written and verbal informed consent was obtained from both patients to report their case and publish related clinical images.

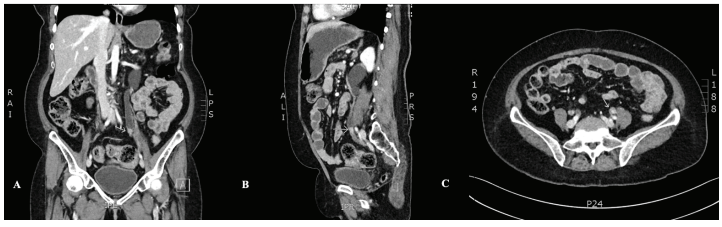

Figure 1. Coronal (A), sagittal (B) and axial (C) views on abdominal computed tomography demonstrating a contrast-enhancing soft tissue mass within the distal left ureter with upstream hydroureteronephrosis

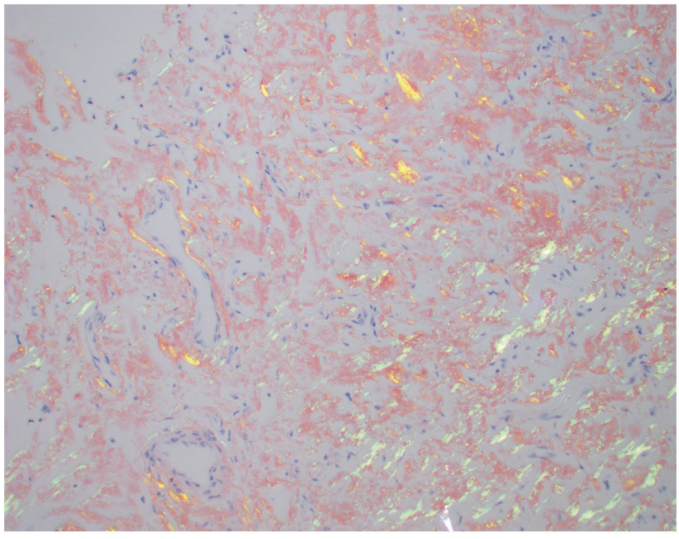

Figure 2. Histopathology slide of the urethral mass with Congo red stain displaying an apple-green birefringence (bottom right of image)

Discussion

Amyloidosis can be systemic (multiorgan involvement) or localised (limited to one organ). Within the genitourinary tract, amyloidosis more commonly involves the bladder and rarely the ureter, renal pelvis or urethra (1). Herein, we presented two rare cases of ureteral and urethral amyloidosis masquerading as urothelial malignancy. Management included nephroureterectomy and trans-urethral resection, respectively, with no disease recurrence at 12 months.

Amyloidosis results from extracellular deposition of abnormal proteins in healthy tissue. These mis-folded fibrils aggregate into beta-pleated sheets that disrupt normal function. Primary amyloidosis (AL) arises from abnormal plasma cells producing excessive light chains that eventually deposit into tissues. Secondary amyloidosis (AA) is typically seen in inflammatory and autoimmune conditions such as Chron's disease, in which serum amyloid A protein (SAA), an acute phase reactant, is persistently elevated. SAA is amyloidogenic at chronically high levels, and up to 10% of patients eventually develop AA-type amyloidosis (2).

Diagnosis is made with biopsy. Staining with Congo red dye, which displays an apple-green birefringence under polarised light, confirms the diagnosis (3). Electron microscopy shows non-branching rigid 8-12 mm fibrils (3). Immunohistochemistry can be used for typing (e.g. kappa or lambda light chains).

1. Ureter

The deposition of amyloid in the ureter is uncommon and usually unifocal, often involving the distal ureter (4). Patients usually present with haematuria and symptoms of ureteric obstruction such as flank pain. There is predilection in women (female-to-male ratio of 3:2), and the left ureter is more commonly affected than the right (5). Synchronous or metachronous bilateral involvement is seen in up to 12.7% of cases and may present with obstructive uropathy and renal failure (5).

Radiological findings include diffuse or focal wall thickening, intra-ureteral filling defects and irregular narrowing and stricturing with subsequent upstream hydronephrosis (4,6). These imaging findings are indistinguishable from urothelial neoplasia; thus, biopsy is recommended. Amyloidosis, along with tuberculosis and schistosomiasis, should be considered in the non-neoplastic differential diagnosis (7).

Historically, amyloidosis of the ureter has been treated with nephroureterectomy (6). However, if amyloidosis can be diagnosed preoperatively with biopsy, one of two nephron-sparing conservative approaches can be used. One is segmental resection of the ureter including resection with end-to-end anastomosis (uretero-ureterostomy), ureteral reimplantation (ureteroneocystostomy), auto-transplantation and ileal ureter replacement after confirming the pathology by frozen section (6). Another treatment includes ureteric stenting with occlusive dressing using dimethyl sulfoxide for 6 months, leading to complete resolution of the lesion (4,6).

A radical approach was taken in Case 1, as the surgeons were unable to obtain an endoscopic biopsy safely. The suspicion was that it was an urothelial malignancy, until proven otherwise;

therefore, a nephroureterectomy was performed. Over-treatment would have been avoided if confirmatory biopsy was feasible.

2. Urethra

The urethra is a rare site for amyloidosis and has mainly been reported in men (5). Patients with urethral amyloidosis usually present with urethral bleeding, dysuria or obstructive voiding symptoms. Lesions are most commonly unifocal, and any portion of the urethra may be affected. Imaging findings include areas of hypointense urethral and periurethral mucosa on T2-weighted magnetic resonance imaging (MRI) and urethral foci of increased echogenicity with posterior shadowing on penile ultrasonography (4).

Because the differential diagnosis includes urothelial cancer, urethroscopy with trans-urethral resection is recommended. Clinically, a mass, mucosal friability and/or stricturing are seen with urethroscopy. Differential diagnosis includes structural abnormalities such as urethral valves, urethral cysts or fibroepithelial polyps, which can present as stricture or mass (2). Other benign conditions in the differential diagnosis include nephrogenic adenoma, malakoplakia, condyloma and ectopic prostatic tissue. In women, urethral caruncles and urethral diverticula can present as a urethral mass (2,4).

In almost all published cases, the condition appear to be self-limiting and no specific treatment is required, other than excision of the lesion and appropriate management of any stricture formation (8).

3. Systemic Workup

The most common site for systemic amyloidosis includes the kidneys, heart, nerves and liver (9). In our institute, we routinely perform kidney and liver function tests as well as serum and urine protein electrophoresis, urine Bence-Jones proteins and serum free light chains to exclude systemic disease. Cardiac biomarkers such as troponin and B-type natriuretic peptide are also measured, and a baseline electrocardiogram is obtained. If cardiac amyloid is suspected, a thoracic echocardiography and cardiac MRI is suggested. Nerve conduction studies are performed if peripheral neuropathy is present. A bone marrow biopsy may also be required to confirm the presence of abnormal plasma cells.

Treatment of systemic disease may require a combination of chemotherapy, corticosteroids and autologous stem cell transplant (9).

Conclusion

We presented two rare cases of ureteral and urethral mass-forming amyloidosis that presented as urothelial malignancy. Preoperative biopsy is recommended for ureteral lesions to avoid radical surgery and to spare the kidneys. Urethral amyloidosis can be managed with trans-urethral resection with good outcomes. Referral to a haematologist should be made for evaluation of systemic disease.

Ethics

Informed Consent: Written and verbal informed consent was obtained from both patients to report their case and publish related clinical images.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and medical practices: H.R., M.J.R., E.C., Concept: E.C., Design: P.S., Data Collection or Processing: P.S., Analysis or Interpretation: P.S., Literature Search: P.S., Writing: P.S., A.A.A., H.R., D.A., M.J.R., E.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
Urooncology

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Epididymal Leiomyoadenomatoid Tumour: A Rare Case Report and Literature Review

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Abstract

Adenomatoid tumours are benign neoplasms of mesothelial origin that most often occur in the epididymis in men and the uterus or fallopian tubes in women. When the stromal smooth muscle component is prominent, the term leiomyoadenomatoid tumour is recommended. To date, only 10 cases of epididymal leiomyoadenomatoid tumour have been reported. In some cases, coagulation necrosis associated with worrisome regenerative changes can occur and leads to an increase in diagnostic pitfalls such as malignant neoplastic processes. Pathologists should be aware of this entity to avoid misdiagnosis. Herein, we present the eleventh case of epididymal leiomyoadenomatoid tumour in a 59-year-old man.
Keywords: Adenomatoid tumour, smooth muscle, leiomyoadenomatoid tumour, epididymis

Introduction

Adenomatoid tumours (ATs) are benign neoplasms of mesothelial origin that predominantly occur in the genital tract of men and women (1). They most often occur in the epididymis in men and the uterus or fallopian tubes in women (1). ATs are characterised by a minimally infiltrative proliferation consisting of tubular and gland-like spaces lined by flattened layer of neoplastic cells. Their collagenous stroma is often hyalinised, but admixed smooth muscle may also be present. The term leiomyoadenomatoid tumour (LAT) is recommended when the smooth muscle component is prominent (2). Our literature review revealed 27 cases of LAT located in the epididymis and uterus or adnexa. Only ten of them were located in the epididymis (3-11). Herein, we present a rare case of epididymal LAT in a 59-year-old man and review the literature.

Case Report

A 59-year-old man presented to our clinic for testicular pain of 2 weeks duration. On physical examination, a mass of approximately 2 cm was found in his right scrotum. Doppler ultrasonography showed an intrascrotal solid lesion 19×18 mm in size within the right scrotal cavity, which had parenchymal microcalcifications. The lesion was compressing the nearby parenchyma of the testis and exhibited peripheral vascularity. Ultrasonographic examination showed that the mass was extratesticular and intrascrotal. Tumour markers were normal (alpha-fetoprotein, 2.2 IU/mL; human chorionic gonadotropin, <0.200 MIU/mL; lactate dehydrogenase, 220 U/L). Thoracal and abdominopelvic computed tomography did not detect metastatic lesion preoperatively. The patient had hypertension and had undergone aortic surgery for aortic aneurysm, transurethral resection of the prostate and total thyroidectomy. Inguinal orchiectomy was performed since mass margins could not be clearly distinguished from the normal testicular tissue.

On macroscopic examination, a solid mass arising from the tail of the epididymis was found. The size of the mass was 1.7×1.5×1.3 cm. It was pushing toward the testicular tissue. The cut surface showed a greyish white whorled pattern. Other parenchymal areas were normal.

Microscopically, the lesion was well-circumscribed and had two components. The first component consisted of bundles of uniform, fusiform smooth muscle cells in a fascicular arrangement. Smooth muscle bundles were separated by the second component composed of cords, small nests or tubular-like structures lined by plump epithelioid cells with round

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nuclei, evident nucleoli and scanty, pale, eosinophilic cytoplasm (Figure 1). Mitotic figures were not observed. Additionally, there were scattered lymphoid aggregates in the stroma. Coagulation necrosis was seen at the centre of the lesion, and there was a hyalinised smooth muscle zone around the necrosis (Figure 2).

On immunohistochemical analysis, the cells in the smooth muscle component were positive for smooth muscle actin and desmin (Figure 3A). Epithelioid cells were positive for cytokeratin AE1/AE3, calretinin (Figure 3B) and Wilms tumour 1 (WT1) and negative for MOC-31, carcinoembryonic antigen, epithelial membrane antigen, prostate-specific antigen, NKX3.1, factor VIII, CD34 and BerEP4. The Ki-67 proliferation index was 3%. Informed consent was obtained from the patient.

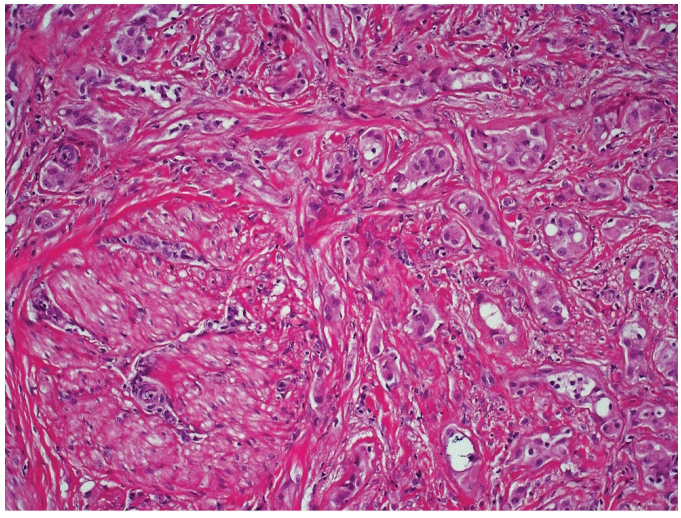

Figure 1. Smooth muscle bundles were separated by tubular structures lined by epithelioid cells with round nuclei and pale eosinophilic cytoplasm (haematoxylin and eosin staining, ×200)

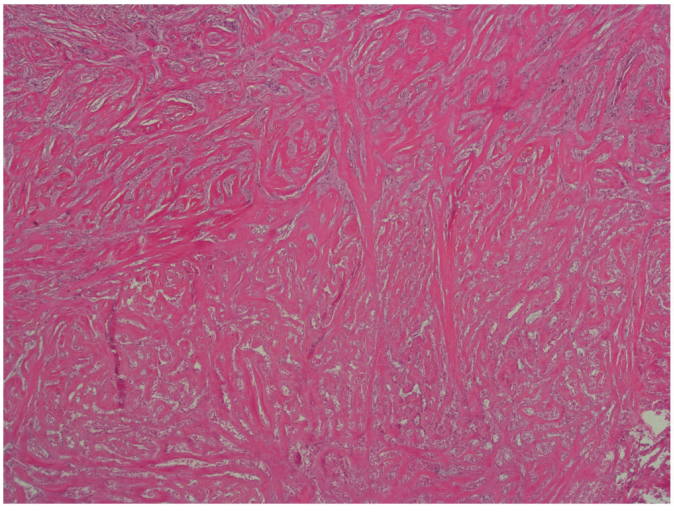

Figure 2. In the lower right corner of the field there was a necrotic region and a hyalinized smooth muscles around it (haematoxylin and eosin staining x100)

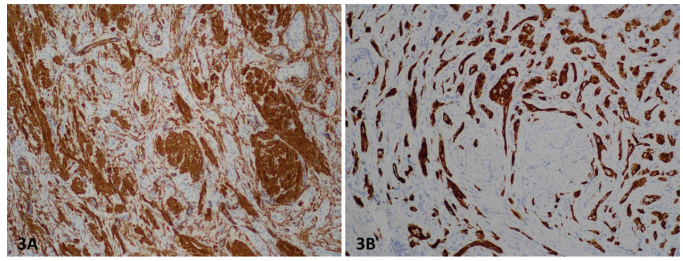

Figure 3A. Smooth muscle component showed expression for smooth muscle actin (×100), **3B**. The cells lining the tubular structures were positive for calretinin (x100)

Discussion

ATs are the second most common paratesticular neoplasia after lipoma, accounting for approximately 30% of all paratesticular neoplasms (12,13). They are the most common epididymal tumour and constitute 70% of all benign tumours (followed by leiomyoma and papillary cystadenoma, 11% and 9%, respectively) and 55% of all epididymal tumours (14). Most patients with AT present with a mass, but some cases are discovered incidentally on imaging studies indicated for other purposes. Epididymal ATs are between 0.4 and 5 cm in diameter, and most of them arise adjacent to the tail or head of the epididymis. Microscopically, ATs consist of irregular tubules lined with flat and cuboidal epithelioid cells. The stroma is often hyalinised and contains variable amounts of smooth muscle and elastic fibres. Lesions in which the smooth muscle component is prominent are called LAT, which was first used by Epstein in 1992 (2). These lesions have also been reported under different names such as adenomatoid leiomyoma, and adenomatoid tumor with leiomyomatous component (3,9).

To the best of our knowledge, 27 cases of LAT have been reported in the literature. Seventeen of them were located in the uterus or adnexa, and 10 were found in the epididymis. We report an additional case of LAT located in the epididymis. The clinicopathologic features of the cases of epididymal LAT are listed in Table 1.

The lesion diameter of the reported epididymal cases of LAT varied between 1 and 3.5 cm (mean, 2.25 cm), and the ages of the patients ranged from 28 to 76 (mean, 50.9) years. While most of the patients had painless mass (6 cases), some patients complained of pain (3 cases). In 6 of 10 patients, the tumour occurred in the tail of the epididymis. No recurrence was observed in any patient. One case exhibited coagulation necrosis, and three cases contained lenfoid aggregates (3,4,8,9). Lesional cells may exhibit mild to moderate cytological atypia (15). In our case, there was coagulation necrosis at the centre of the lesion. The cause of the necrosis was not fully clear. Larger tumour size may be related with necrosis (16), but in

Table 1. Clinicopathologic features of cases of epididymal leiomyoadenomatoid tumour

Authors	Patient age (year)	Symptoms	Lesion diameter (cm)	Laterality	Localisation	Lenfoid aggregates	Necrosis	Radiological features
Wilson (3)	46	Painless lump	2	Left	Lower pole of the epididymis	+	NM*	NM
Romanelli and Sanna (4)	60	Painless swelling	2	Left	Body of the epididymis	+	NM	NM
Hoffmann et al. (5)	57	Painless lump	2	Left	Tail of the epididymis	NM	NM	US*: Sharply delimited mass that is more echo-rich than the testicular parenchyma
Kausch et al. (6)	63	Painful mass	3	Right	Tail of the epididymis	NM	NM	US: Combined hypodense and hyperdense mass Doppler US: Enhanced signals of the right rete testis when compared with the contralateral testis
Canpolat (7)	76	Painful swelling	3.5	Right	Tail of the epididymis	NM	-	US: Lobular mass showing echogenic areas
Cazorla et al. (8)	57	Painless mass	2.5	Right	Tail of the epididymis	NM	+	US: Solid, extra testicular, well-limited, heterogeneous and mainly hypoechogenic mass
Khan et al. (9)	39	Mass	2.2	Left	Tail of the epididymis	+	NM	US: Extratesticular swelling, with heterogenous echo pattern, no fluid and calcification
Wazwaz et al. (10)	33	Painless scrotal swelling	1.3	Left	Tail of the epididymis	NM	-	US: Well-defined heterogeneous, predominantly hypoechoic lesion with internal vascularity Scrotal MRI: Extra testicular solid mass with very low T2 signal intensity
Shehabeldin et al. (11)	28 50	Painless swelling Scrotal swelling, with acute onset scrotal pain	1 3	Right Right	Epididymis and rete testis Epididymis, rete testis and testicular parenchyma	NM NM	- -	US: 1-cm hypoechoic mass US: 3-cm heterogeneous, exophytic mass situated at the superior pole of the testis
Present case	59	Testicular pain	1.7	Right	Tail of the epididymis	+	+	Doppler US: Intrascrotal solid lesion with microcalcifications US: Extratesticular and intrascrotal mass

US*: Ultrasonography, NM: Not mentioned, MRI: Magnetic resonance imaging

our case, the lesion was not large (1.7 cm in diameter). Lymphoid aggregates are commonly present in ATs of the male genital tract. Immunohistochemically, epithelioid cells of LATs are positive for pancytokeratin, CK7 and markers typical of mesothelial origin such as calretinin, podoplanin, WT1 and HBME1. The smooth muscle cell component is positive for smooth muscle actin and desmin.

Microscopic differential diagnoses primarily include leiomyoma, epithelioid haemangioendothelioma, malignant mesothelioma and malignant tumour infiltrating smooth muscle bundles. In some cases, the smooth muscle component may obscure the epithelioid (adenomatoid) component and results in the misdiagnosis of leiomyoma. However, this can be easily

resolved by detecting the adenomatoid component by careful microscopic examination. For the differential diagnosis with epithelioid haemangioendothelioma, the use of vascular markers such as CD34 and CD31 may lead to correct diagnosis; hence, ATs show negative staining for vascular markers. The presence of coagulation necrosis with associated worrisome regenerative changes can increase diagnostic pitfalls such as malignant neoplastic processes (mesothelioma and invasive carcinomas). In contrast to malignant neoplasms, LATs are usually small and well-circumscribed lesions. Furthermore, the relatively bland cytological features of LATs and the lack of definitive invasion into the adjacent tissues are helpful in this respect. When invasive carcinomas are suspected, immunohistochemical markers could point to the correct interpretation. Other entities to consider in the differential diagnoses include lymphangioma, Sertoli cell tumour, haemangioma and angiosarcoma.

The pathogenesis of LAT remains poorly understood. To date, several hypotheses have been considered on the pathogenesis of these tumours. First, LAT may be a variant of AT. Cazorla et al. (8) suggested that LAT should be considered a variant of AT that originated in precursor cells with dual differentiation, mesothelial and muscle cells. Second, LAT may represent a collision neoplasia consisting of leiomyoma and AT. Third, LAT may be the result of a common AT associated with reactive smooth muscle hyperplasia (17).

To date, none of the reported cases of LAT have shown recurrence or malignant degeneration. Therefore, the surgical removal of the tumour, without orchiectomy, is recommended in cases of epididymal LATs. Orchiectomy is performed only in cases with suspected malignancy. In the present case, inguinal orchiectomy was performed since the mass borders could not be clearly distinguished from the normal testicular tissue.

Conclusion

LATs are rare benign tumours reported in the epididymis in men and uterus and adnexa in women. Pathologists should be aware of this entity to avoid the undesirable results of the misdiagnosis.

Ethics

Informed Consent: Written informed consent was obtained from the patient to report this case study and publication of images.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.Y., B.B.C., A.Ö., İ.Ü., M.F.A., Design: F.Y., B.B.C., A.Ö., İ.Ü., M.F.A., Data Collection or Processing: F.Y., A.Ö., M.F.A., Analysis or Interpretation: F.Y., A.Ö., İ.Ü., M.F.A., Literature Search: F.Y., B.B.C., M.F.A., Writing: F.Y., M.F.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Urooncology

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Journal of Urological Surgery, 2021;8(2):149-150

Inguinal Bladder Hernia with Bladder Carcinoma: An Unusual Manifestation

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Abstract

It is extremely uncommon for bladder carcinoma to manifest in an inguinal hernia. Only 1-3% of inguinal hernias involve the bladder, and very few of these hernias are associated with bladder carcinoma. Furthermore, the tumour is removed, and the hernia is repaired as part of the treatment. We present the case of an 89-year-old man who came to our clinic complaining of haematuria and was diagnosed with an inguinal bladder hernia filled with tumours.
Keywords: Inguinal hernia, bladder carcinoma, an unusual manifestation, case report, haematuria

Introduction

Inguinal hernias affect 3%-8% of the population (1). Inguinal bladder hernias are extremely rare, accounting for only 1%-3% of all inguinal hernias (1). The presence of carcinoma within the herniated portion of the bladder is an exceedingly rare entity that has only been anecdotally reported in the literature (2).

Here, we present a case of an 89-year-old man who had macroscopic haematuria and was later diagnosed with an inguinal bladder hernia filled with a tumour.

Case Report

An 89-year-old male patient arrived at our clinic complaining of haematuria. The results of the blood tests and kidney functions were both normal. Moreover, urine analysis and physical examination both supported macroscopic haematuria. The patient had no symptoms of the lower urinary tract, and digital rectal examination was normal. The urine culture was sterile, and the prostate-specific antigen level (0.8 ng/mL) was within the normal range. An abdominopelvic computed tomography with intravenous contrast substance revealed a tumour-filled inguinoscrotal bladder hernia (Figure 1). During the examination, it was discovered that the hernia could be manually reduced. Cystoscopy was performed, and papillary tumoural structures in the hernia sac were noted (Figure 2).

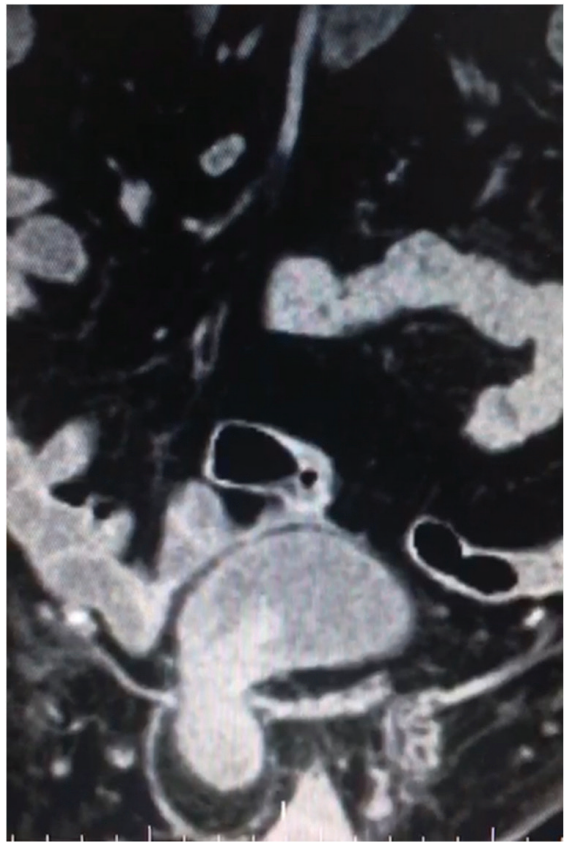

Figure 1. Abdominopelvic computed tomography showed a tumour-filled inguinoscrotal bladder hernia

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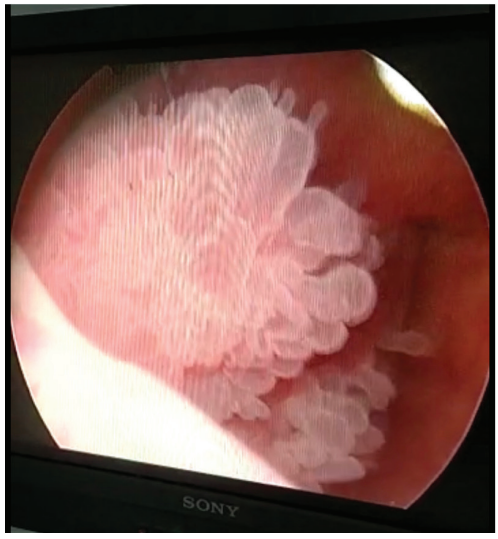

Figure 2. Hernia sac filled with papillary tumoural structures

Transurethral resection was used to remove the tumour. The pathology report revealed that the tumour was a low grade, non-invasive urothelial carcinoma. The patient was followed up in the urology department.

Discussion

Bladder herniation is a rare condition that accounts for only 1%-3% of all inguinal hernias (2). Bladder cancer in an inguinal hernia is an even more uncommon phenomenon (2). Levine first described scrotal cystocele as a hernia of the bladder to the scrotum in 1951 (3). Age, chronic bladder distension, loss of bladder tone, and factors that increase intraabdominal pressure, such as obesity, urinary tract obstruction, protrusion of perivesical fat, pelvic mass, or previous hernia surgery, are all known etiological factors (4).

Bladder herniation is usually asymptomatic and found incidentally, but it may present with urinary tract obstruction on rare occasions. It can also cause life-threatening complications such as bladder rupture, sepsis, cystolithiasis, hydronephrosis, vesicourethral reflux, kidney failure, and ischaemia-induced bladder infarction (5). During hernia surgery, the diagnosis is usually made. To avoid complications during surgical repair, it is critical to make an early diagnosis using adequate and detailed medical anamnesis and radiological imaging. According to Gomella et al. (6), approximately 38% of inguinal hernia surgeries resulted in unrecognised bladder injury. Moreover, postoperative complications such as gross haematuria, sepsis, or fistula formation occurred in these patients. In our case, the patient was admitted to the hospital with a complaint of macroscopic haematuria caused by a bladder tumour.

In the differential diagnosis, mesenteric cyst hernia, hydrocoele, bladder diverticulum, and spermatic cord cyst was considered (7). The primary course of action is an endoscopic diagnosis, followed by tumour resection and bladder hernia repair (7). Alternatively, an inguinal hernia can also be repaired prior to tumour resection. In our case, since the hernia sac could be manually reduced, the resection of the bladder tumour was prioritised. Following a consultation with the general surgery clinic, it was determined that the patient's hernia did not require repair.

Conclusion

Inguinal bladder hernia is an uncommon condition, and the presence of tumours in an inguinal bladder hernia is even rarer (Medline/PubMed). The absence of findings specific to inguinal bladder tumours in the examination causes some difficulties during diagnosis. This could result in bladder injury during surgery. Therefore, radiological imaging is critical in the treatment of bladder tumours and the repair of inguinal hernias.

Ethics

Informed Consent: Patient's approval was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.M., Ö.Ç., Concept: U.M., Ö.Ç., Design: U.M., Data Collection or Processing: U.M., Analysis or Interpretation: U.M., Ö.Ç., Literature Search: U.M., Writing: U.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Endourology

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A Urological Twist: Literature Review, An Australian Experience and Management Algorithm for Knotted Ureteric Stents

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Abstract

Knotted ureteric stents remain a rare complication, with only 34 cases reported to date. They require prompt recognition and skilful management to avoid ureteric injury. Knots more often occur at the proximal end of stents, have a male preponderance, are associated with multi-length stents and relate to the J-coil configuration, which is affected by the renal pelvis anatomy, hydroureter and presence of urolithiasis. We present our experience of a knotted stent managed using holmium:yttrium aluminium garnet laser and traction. We also provide an updated literature review and recommend a treatment algorithm for this rare but important complication.

Keywords: Knotted ureteric stent, holmium:YAG laser, stent removal, multi-length stent, percutaneous nephrostomy, treatment algorithm

Introduction

Ureteric stents are an indispensable component of modern urological practice. Knot formation is a rare complication but must be recognised to prevent ureteric injury. To date, 34 cases (26 papers) of knotted ureteric stents have been reported since its first description in 1989 (Supplementary Table 1)(1). Herein, we report an illustrative case where holmium:yttrium aluminium garnet Ho:YAG laser was utilised to remove stent encrustation and enabled stent removal using gentle traction. The optimal management for the retrieval of a knotted ureteric stent is contextual, but we provide a recommended treatment algorithm using a graded approach.

Case Presentation

A 31-year-old man presented with sudden-onset left flank pain, rigours, anorexia and vomiting. He had left nephrolithiasis that was managed conservatively, but he had no past medical history. He was haemodynamically stable and had an unremarkable abdominal examination with no evidence of peritonism or renal angle tenderness. Microscopic haematuria was noted on urinalysis. The provisional diagnosis was renal colic, and a computed tomography kidney, ureter and bladder scan demonstrated a left 8×6×6 mm^3 proximal ureteric calculus with mild hydroureteronephrosis. Emergency ureteric stenting was undertaken due to intractable pain despite use of non-steroidal anti-inflammatory and opioid analgesia. An intraoperative retrograde pyelogram (RGP) demonstrated a thin distal left ureter with a proximal filing defect corresponding with the location of the ureteric calculus. Moderate difficulty was encountered traversing the obstruction during stent insertion. A 5-Fr multi-length Double-J stent was eventually deployed successfully. Completion intraoperative X-ray imaging demonstrated satisfactory stent placement.

During the definitive stone procedure, performed 6 weeks later, there was significant difficulty in retrieving the ureteric stent. Intraoperative fluoroscopy revealed a knot at the proximal J-coil of the ureteric stent (Figure 1). Gentle traction under fluoroscopic guidance was used to tease the knotted stent into the distal ureter; however, further traction was met with resistance, and the knot could not be moved beyond the vesicoureteric junction. Ureteroscopy demonstrated significant debris and heavy encrustation around a tight knot, resulting in a widened diameter that impeded stent extraction (Figure

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Table 1. Recommended algorithm for knotted ureteric stent treatment

Removal technique	Indication	Anaesthetic required
Traction	1. First-line 2. Should be completed with real-time fluoroscopic guidance	Local or general/ spinal
Guidewire	1. When traction encounters significant resistance or if further knot tightening visualised	General/spinal
Endoscopic guided	1. If traction and/or guidewire unsuccessful 2. To provide visualisation of the knot	General/spinal
Holmium YAG laser	1. Significant stent encrustation 2. Knot diameter prevents removal 3. To fragment the knot or severe the stent below the knot	General/spinal
Percutaneous removal	1. Unable to advance ureteroscope to level of knot 2. Patient unable to undergo general or spinal 3.Fragments in renal pelvis unable to be removed endoscopically	Local or general/ spinal
Open ureterotomy or surgery	1. Failure of all less invasive options 2. Ureteric avulsion	General

YAG: Yttrium aluminium garnet

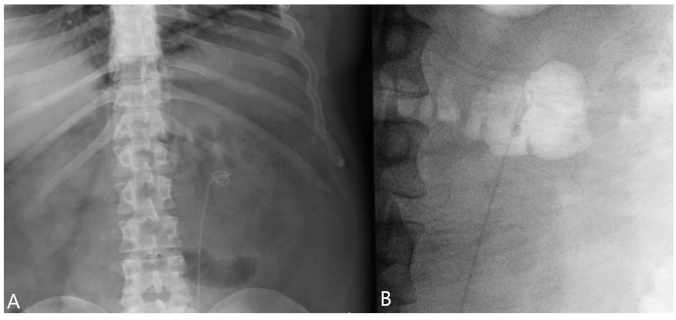

Figure 1. At the second-stage procedure, 6 weeks after initial left ureteric stent insertion, a preoperative X-ray kidney, ureter and bladder taken 24 hours earlier demonstrated an abnormal configuration in the proximal J-coil that may have formed during stent insertion and/or predisposed to knot formation during stent retrieval (A). Intraoperative fluoroscopy demonstrated knot formation at the proximal J-coil of the ureteric stent after significant difficulty was met during traction retrieval (B)

2). Careful laser lithotripsy of the encrustation/debris reduced the diameter, increased the mobility of the distal knot and facilitated stent extraction with gentle traction. No contrast extravasation was identified on completion RGP to suggest ureteric injury. No residual collecting system calculi were identified on completion ureteropyeloscopy. The patient had an uncomplicated postoperative course, with no issues at the 6-month follow-up period. The patient provided informed written consent for the publication of the case.

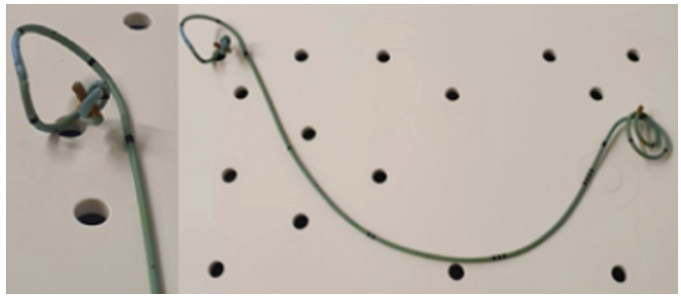

Figure 2. Left ureteric stent demonstrating knot formation in the proximal J-coil with residual encrustation following lithotripsy and extraction. Significantly more encrustations were observed during ureteroscopy around the knot, which increased its diameter and prevented extraction and passage at the vesicoureteric junction

Discussion

The mechanism of knot formation remains unclear. However, studies have demonstrated higher occurrence at the proximal end (only three cases reported at the middle or distal end), male preponderance (4:1) and association with excessive stent length and coil formation (2,3).

Multi-length stents are preferred because they are easier to use, reduce stent migration risk and cost-effective (4). However, they appear to knot more often with 18 of the 24 previous cases, that reported stent length, being multi-length stents. Studies have proposed that the increased length leads to excessive proximal coiling, which occurs after the stent abuts the wall of the renal pelvis (4,5). Subsequently, a knot forms when the stent passes through this open coil (6,7). Fixed-length stents may decrease knot occurrence, but have their own issues (4). By contrast, stent diameter does not appear to affect knot formation, as diameters ranging from 4.7 to 7 Fr have been observed (3).

Yamamoto et al. (8) suggested that knotting occurs during insertion, possibly due to excessive guidewire coiling within the renal pelvis, rather than during retrieval. Patient factors like the renal pelvis anatomy and presence of hydronephrosis or urolithiasis may further alter the configuration of the proximal J-coil during insertion, thereby predisposing to knot formation (3). Interestingly, an analysis of previous cases demonstrated that knot formation occurred more often in cases without hydronephrosis than with hydronephrosis (9).

Stent encrustation on knotted stents can add difficulty during stent retrieval, as it increases the knot diameter and prevents passage of a guidewire through the stent lumen (10). We

postulate that encrustation increases the friction during retrieval, which impedes the uncoiling process and possibly precipitates knot formation. However, knots have occurred in stents without significant encrustation (10,11).

No clinical practice guidelines exist for the management of knotted stents. We present a recommended treatment algorithm for knotted ureteric stents based on the literature and our experience, summarised in Table 1. For instance, we recommend simple traction with real-time fluoroscopic guidance, which is successful in most cases. Traction can lead to tightening of the knot or ureteric avulsion, although no studies have reported avulsion (5).

If significant resistance is met during traction or the knot is tightened, attempts at straightening the knot should be pursued using a guidewire. This has been successfully completed using an Amplatz super stiff guidewire and straight tip guidewire (7,11).

If this is unsuccessful, possibly due to confounding stent encrustation that occludes the stent lumen, endoscopic extraction should be pursued, as it allows for visualisation of the knot and facilitates more precise traction, knot manipulation and/or application of the holmium:YAG laser (3,6,12,13). This requires general or spinal anaesthesia and adequate advancement of the ureteroscope to the level of the knot, which can be restricted by urethral strictures, obstructing urolithiasis or the stent itself in a narrow calibre ureter (10).

Holmium:YAG laser was first utilised to remove a knotted stent in 2011 (12). The laser can be used to fragment/sever the stent below the knot, fracture the knot itself or remove stent encrustation/debris (4,10,12,13). This technique is minimally invasive and reproducible and allows for direct visualisation, which reduces the occurrence of inadvertent ureteric damage (3,12). Excessive fragmentation of the ureteric stent should be avoided, as this requires removal using basket, graspers or percutaneous nephrostomy if endoscopic techniques fail (10,13).

Percutaneous nephrostomy is useful in patients who cannot undergo a general or spinal anaesthesia or if endoscopic removal is unsuccessful (2,3,9,10,14,15). The first case was performed in Australia after failure of traction and endoscopic retrieval (15). Other techniques have utilised a Terumo guidewire in a patient with steinstrasse, Amplatz guidewire through a dilated nephrostomy tract, and the use of a 26-Fr nephroscope via a superior caliceal puncture into the renal pelvis and upper ureter (2,3). Open removal procedures can be considered, if all other methods fail.

Ethics

Informed Consent: The patient provided informed written consent for the publication of the case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.W.H.L A.J.N., D.R.A., A.J.M., Concept: A.J.N., D.R.A., A.J.M., Design: B.W.H.L, D.R.A., A.J.M., Data Collection or Processing: B.W.H.L, A.J.N., D.R.A., A.J.M., Analysis or Interpretation: B.W.H.L, A.J.N., D.R.A., A.J.M., Literature Search: B.W.H.L, A.J.N., D.R.A., Writing: B.W.H.L, A.J.N., D.R.A., A.J.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Supplementary Table 1. Updated review of knotted ureteric stent literature

Author	Year	Patient	Stent model	Stent length	Indication for stent	Knot location	Removal method
Groeneveld	1989	N/A	N/A	N/A	N/A	Proximal	Traction distally during cystoscopy
Das and Wickham	1990	45 M	Single J	N/A	Nephrolithiasis	Distal	Traction distally during cystoscopy
Braslis and Joyce	1992	37 F	4.7 Fr double J	Multilength	Nephrolithiasis	Proximal	Percutaneous
Kundargi	1994	53 M	6 Fr double J	26 cm	Nephrolithiasis	Proximal	Percutaneous
Flam et al.	1995	86 M	6 Fr double J	26 cm	Ureterolithiasis	Proximal	Alligator forceps to untie knot *in situ* and traction during ureteroscopy
Baldwin et al.	1998	73 M	7 Fr double J	Multilength	Transitional cell carcinoma	Proximal	Amplatz super stiff guidewire inserted through stent to untie knot *in situ*
Quek and Dunn	2002	66 F	7 Fr double J	24 cm	Nephrolithiasis	Mid	Traction distally during cystoscopy
Sighinolfi et al.	2005	48 M	5 Fr double J	Multilength	Nephrolithiasis	Proximal	Extracorporeal shock wave lithotripsy followed by continuous traction with the stent attached to patient's leg for 3 days
Corbett and Dickson	2005	4 M	4.7 Fr double J	Multilength	Reimplantation of an obstructed megaureter	Proximal	Traction distally during cystoscopy
Kondo et al.	2005	37 M	6 Fr double J	Multilength	Nephrolithiasis	Proximal	Open ureterotomy
Eisner et al.	2006	82 F	6 Fr Cook Kwart Retro-Inject stent	Multilength	Nephrolithiasis	Proximal	2x extracorporeal shock wave lithotripsy and laser lithotripsy during ureteroscopy
Eisner et al.	2006	82 F	6 Fr Cook Kwart Retro-Inject stent	Multilength	Excessive manipulation during stent removal	Proximal	Traction after forceful coughs that induced valsalva and caused knot to come undone
Basavaraj et al.	2007	70 F	6 Fr double J	Multilength	Nephrolithiasis and ureterolithiasis	Proximal	Rigid conduitoscopy
Rivalta et al.	2009	83 M	7 Fr	N/A	Bladder and prostate cancer	Proximal	Traction with sterile petroleum jelly within a ureterocutaneostomy
Picozzi and Carmignani	2010	41 F	7 Fr double J	26 cm	Ureteral injury following surgery	Proximal	Traction distally during cystoscopy
Richards et al.	2011	67 M	N/A	N/A	Ureterolithiasis	Proximal	Holmium YAG laser during ureterorenoscopy
Tempest et al.	2011	68 M	6 Fr stent	Multilength	Nephrolithiasis	Proximal	Holmium YAG laser and removal using tri-radiate graspers
Moufid et al.	2012	32 M	Double J	N/A	Ureterolithiasis	Proximal	Traction proximally during ureteroscopy with fluoroscopic guidance
Karaguzel et al.	2012	53 M	4.7 Fr double J	28 cm	Ureterolithiasis	Proximal	Foreign body forceps during ureterorenoscopy
Nettle et al.	2012	43 M	6 Fr double J	N/A	N/A	Proximal	Holmium YAG laser during ureteroscopy
Bhirud et al.	2012	41 M	Double J	N/A	Nephrolithiasis	Mid	Percutaneous using 26 Fr nephroscope
Manohar et al.	2014	65 M	4.8 Fr stent	Multilength	Ureterolithiasis	Proximal	Percutaneous, antegrade
Manohar et al.	2014	68 F	4.8 Fr stent	Multilength	Ureteric injury following surgery	Proximal	Holmium YAG laser
Manohar et al.	2014	55 F	6 Fr double J	Multilength	Nephrolithiasis	Proximal	Holmium YAG laser during rigid ureteroscopy

Manohar et al.	2014	59M	4.8 Fr stent	Multilength	Nephrolithiasis	Proximal	Traction of stent on wire
Ahmadi et al.	2015	45 M	6 Fr double J soft	Multilength	Nephrolithiasis	Proximal	Holmium YAG laser and basket to retrieve fragments under ureteroscopy
Ahmadi et al.	2015	43 M	6 Fr double J stiff	Multilength	Ureterolithiasis	Proximal	Holmium YAG laser and basket to retrieve fragments
Ahmadi et al.	2015	71 M	7 Fr double J stiff	Multilength	Retroperitoneal fibrosis secondary to treated lymphoma	Proximal	Percutaneous after unsuccessful holmium YAG laser
Ahmadi et al.	2015	71 M	7 Fr double J stiff	Multilength	Retroperitoneal fibrosis secondary to treated lymphoma	Proximal	Percutaneous
Ahmadi et al.	2015	52 M	6 Fr double J soft	Multilength	Ureterolithiasis	Proximal	Holmium YAG laser to remove encrustation during rigid and flexible pyeloscopy with retrieval over a wire
Kim et al.	2015	53 M	Double J	N/A	Nephrolithiasis and Ureterolithiasis	Proximal	Percutaneous, antegrade
Zhou et al.	2018	33 M	6 Fr double J	26 cm	Postoperative ureterovesical anastomotic stricture	Proximal	Holmium YAG laser and basket to retrieve fragments
Bradshaw et al.	2019	57 F	N/A	N/A	Bilateral vesicoureteric junction radiation-induced strictures	Proximal	Percutaneous, antegrade removal using Amplatz guidewire and dilation of nephrostomy tract using serial metal dilators
Cho	2020	62 M	6 Fr double J	Multilength	Ureterolithiasis	Proximal	Straight tip guidewire to untie knot under fluoroscopic guidance

YAG: Yttrium aluminium garnet

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