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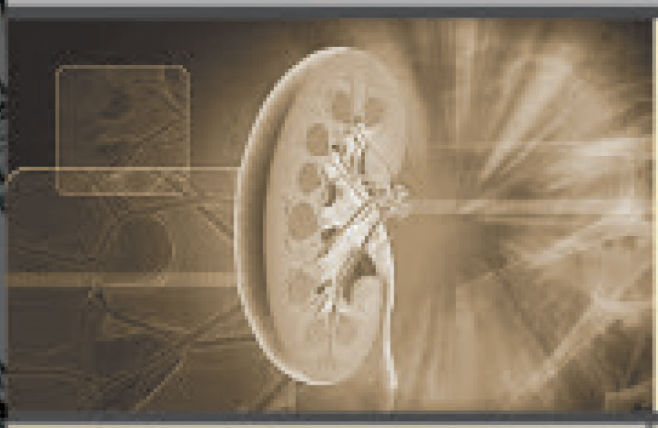

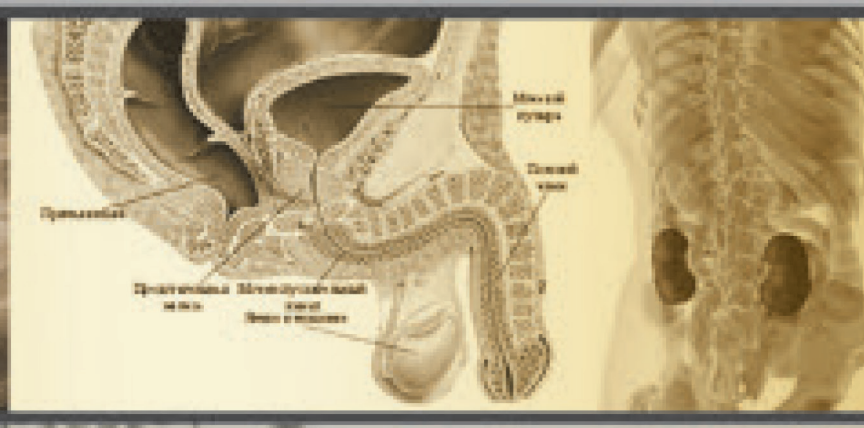

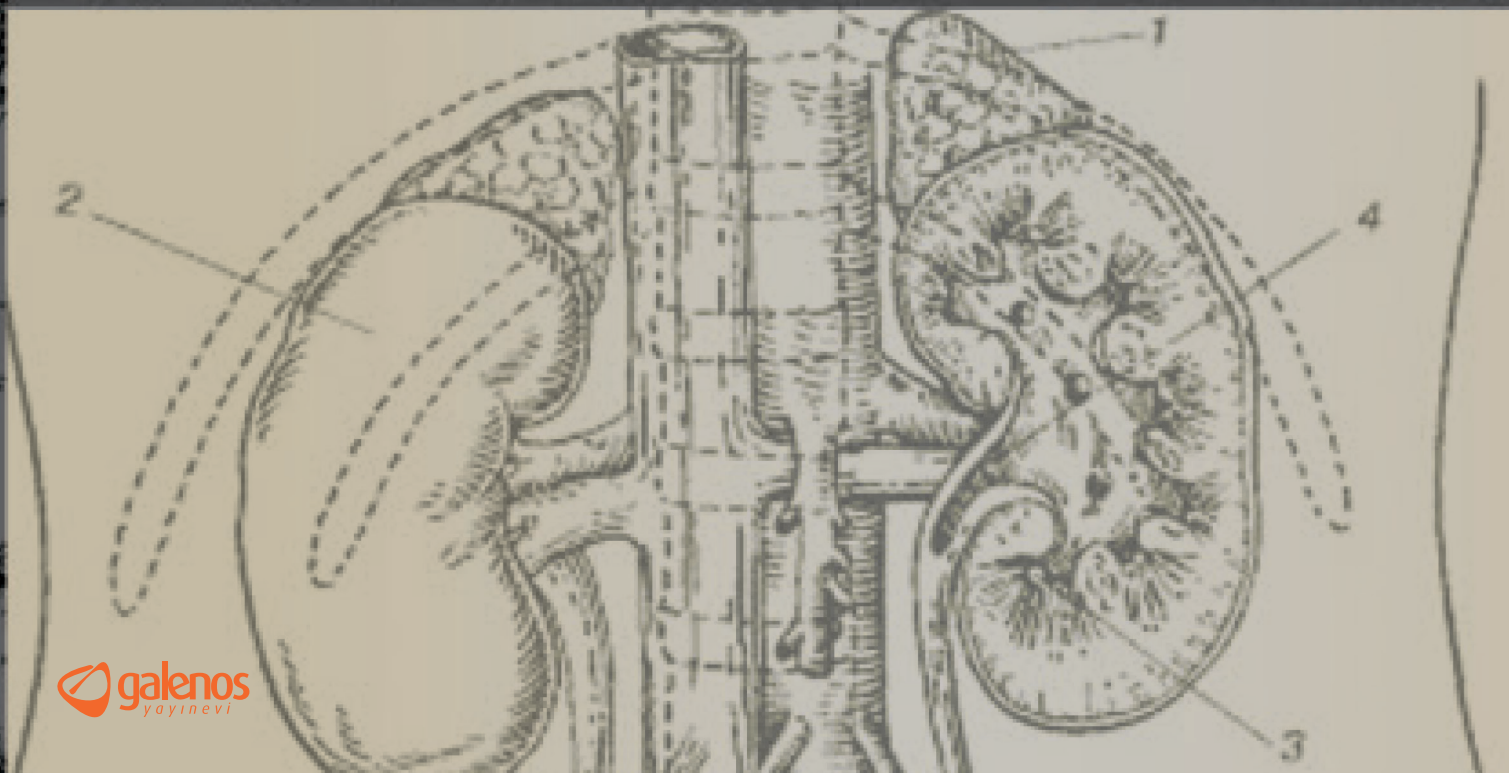

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ABOUT US

Journal of Urological Surgery is the official open access scientific publication organ of the Society of Urological Surgery. Journal of Urologic Surgery is being published in İstanbul, Turkiye. It is a double peer-reviewed journal published quarterly in March, June, September and December.

Journal of Urological Surgery is indexed in Web of Science-Emerging Sources Citation Index (ESCI), DOAJ, EBSCO, CINAHL, Research Bib-Academic Resource Index, Root Indexing, TUBITAK/ULAKBIM Turkish Medical Database, TurkMedline, Turkiye Citation Index.

The target audience of the journal includes physicians working in the fields of urology and all other health professionals who are interested in these topics.

The editorial processes of the journal are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE) (http://www.icmje.org) and the Committee on Publication Ethics (COPE) (http://publicationethics.org).

All manuscripts should be submitted through the journal's web page at www.jurolsurgery.org. Instructions for authors, technical information, and other necessary forms can be accessed over this web page. Authors are responsible for all content of the manuscripts.

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Urooncology,

Andrology,

Functional urology,

Endourology,

Transplantation,

Reconstructive surgery,

Urologic pathology,

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Journal of Urological Surgery does not charge any fee for article submission or processing. Also manuscript writers are not paid by any means for their manuscripts.

The journal should be abbreviated as "J Urol Surg" when referenced.

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.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (201, archived at http://www.icmje.org/).

Editorial Process

Following receiving of each manuscript, a checklist is completed by the Editorial Assistant. The Editorial Assistant checks that each manuscript contains all required components and adheres to the author guidelines, after which time it will be forwarded to the Editor in Chief. Following the Editor in Chief's evaluation, each manuscript is forwarded to the Associate Editor, who in turn assigns reviewers. Generally, all manuscripts will be reviewed by at least three reviewers selected by the Associate Editor, based on their relevant expertise. Associate editor could be assigned as a reviewer along with the reviewers. After the reviewing process, all manuscripts are evaluated in the Editorial Board Meeting.

The Journal of Urological Surgery's editor and Editorial Board members are active researchers. It is possible that they would desire to submit their manuscript to the Journal of Urological Surgery. This may be creating a conflict of interest. These manuscripts will not be evaluated by the submitting editor(s). The review process will be managed and decisions made by editor-in-chief who will act independently. In some situation, this process will be overseen by an outside independent expert in reviewing submissions from editors.

Preparation of Manuscript

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

Title: The title should provide important information regarding the manuscript's content.

The title page should include the authors' names, degrees, and institutional/professional affiliations, a short title, abbreviations, keywords, financial disclosure statement, and conflict of interest statement. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number that corresponds to their institution, which is listed separately. Please provide contact information for the corresponding author, including name, e-mail address, and telephone and fax numbers.

Running Head: The running head should not be more than 40 characters, including spaces, and should be located at the bottom of the title page.

Word Count: A word count for the manuscript, excluding abstract, acknowledgments, figure and table legends, and references, should be provided not exceed 3000 words. The word count for an abstract should be not exceed 250 words.

Conflict of Interest Statement: To prevent potential conflicts of interest from being overlooked, this statement must be included in each manuscript. In case there are conflicts of interest, every author should complete the ICMJE general declaration form, which can be obtained at: http://www.icmje.org/coi_disclosure.pdf

Abstract and Keywords: The second page should include an abstract that does not exceed 250 words. For manuscripts sent by authors in Turkiye, a title and abstract in Turkish are also required. As most readers read the abstract first, it is critically important. Moreover, as various electronic databases integrate only abstracts into their index, important findings should be presented in the abstract.

Turkish abstract texts should be written in accordance with the Turkish Dictionary and Writing Guide of the Turkish Language Association.

Abstract

Objective: The abstract should state the objective (the purpose of the study and hypothesis) and summarize the rationale for the study.

Materials and Methods: Important methods should be written respectively.

2010 Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

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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.

Other types of manuscripts, such as case reports, reviews and others will be published according to uniform requirements. Provide at least 3 keywords below the abstract to assist indexers. Use terms from the Index Medicus Medical Subject Headings List (for randomized studies a CONSORT abstract should be provided (http://www.consort-statement.org).

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.

Discussion: This section should include a discussion of the data. New and important findings/results, and the conclusions they lead to should be emphasized. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by the data. Do not repeat the findings/results in detail; important findings/results should be compared with those of similar studies in the literature, along with a summarization. In other words, similarities or differences in the obtained findings/results with those previously reported should be discussed.

Study Limitations: Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

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, 201, pp 1257-1323.

Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

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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.

Case Reports

Abstract length: Not to exceed 100 words.

Article length: Not to exceed 1000 words.

Case Reports can include maximum 1 figure and 1 table or 2 figures or 2 tables.

Case reports should be structured as follows:

Abstract: An unstructured abstract that summarizes the case.

Introduction: A brief introduction (recommended length: 1-2 paragraphs).

Case Presentation: This section describes the case in detail, including the initial diagnosis and outcome.

Discussion: This section should include a brief review of the relevant literature and how the presented case furthers our understanding to the disease process.

Review Articles

Abstract length: Not to exceed 250 words.

Article length: Not to exceed 4000 words.

Review articles should not include more than 100 references. Reviews should include a conclusion, in which a new hypothesis or study about the subject may be posited. Do not publish methods for literature search or level of evidence. Authors who will prepare review articles should already have published research articles on the relevant subject. There should be a maximum of two authors for review articles.

Preparation of Manuscripts

The " Journal of Urological Surgery'' follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (International Committee of Medical Journal Editors - http://www.icmje.org /). Upon submission of the manuscript, authors are to indicate the type of trial/research and provide the checklist of the following guidelines when appropriate:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org /),

PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org /),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org /),

STROBE statement-checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org /),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

CARE guidelines are designed to increase the accuracy, transparency, and usefulness of case reports. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; the CARE Group. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.) (http://www.care-statement.org /

Images in Urological Surgery

Article length: Not to exceed 500 words.

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.

Urological Pathology

Article length: Not to exceed 500 words.

Urological pathology 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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Letters to the Editor

Article length: Not to exceed 500 words.

Letters can include no more than 500 words of text, 5-10 references, and 1 figure or table. No abstract is required, but please include a brief title.

How I do?

Unstructured abstract: Not to exceed 50 words.

Article length: Not to exceed 1500 word.

Urologic Survey

Article length: Not to exceed 250 words.

Tables, Graphics, Figures, and Images

Tables: Supply each table on a separate file. Number tables according to the order in which they appear in the text, and supply a brief caption for each. Give each column a short or abbreviated heading. Write explanatory statistical measures of variation, such as standard deviation or standard error of mean. Be sure that each table is cited in the text.

Figures: Figures should be professionally drawn and/or photographed. Authors should number figures according to the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure should be accompanied by a legend that does not exceed 50 words. Use abbreviations only if they have been introduced in the text. Authors are also required to provide the level of magnification for histological slides. Explain the internal scale and identify the staining method used. Figures should be submitted as separate files, not in the text file. High-resolution image files are not preferred for initial submission as the file sizes may be too large. The total file size of the PDF for peer review should not exceed 5 MB.

Authorship

Each author should have participated sufficiently in the work to assume public responsibility for the content. Any portion of a manuscript that is critical to its main conclusions must be the responsibility of at least 1 author.

Contributor's Statement

All submissions should contain a contributor's statement page. Each manuscript should contain substantial contributions to idea and design, acquisition of data, or analysis and interpretation of findings. All persons designated as an author should qualify for authorship, and all those that qualify should be listed. Each author should have participated sufficiently in the work to take responsibility for appropriate portions of the text.

Acknowledgments

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Authors are expected to disclose on the title page any commercial or other associations that might pose a conflict of interest in connection with the submitted manuscript. All funding sources that supported the work and the institutional and/or corporate affiliations of the authors should be acknowledged on the title page.

Ethics

When reporting experiments conducted with humans indicate that the procedures were in accordance with ethical standards set forth by the committee that oversees human experimentation. Approval of research protocols by the relevant ethics committee, in accordance with international agreements (Helsinki Declaration of 197, revised 2013 available at http://www.wma.net/e/policy/b3.htm, "Guide for the Care and use of Laboratory Animals" www.nap.edu/catalog/5140.html/), is required for all experimental, clinical, and drug studies. Studies performed on human require ethics committee certificate including approval number. It also should be indicated in the "Materials and Methods" section. Patient names, initials, and hospital identification numbers should not be used. Manuscripts reporting the results of experimental investigations conducted with humans must state that the study protocol received institutional review board approval and that the participants provided informed consent.

Non-compliance with scientific accuracy is not in accord with scientific ethics.

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On the other hand, short abstracts published in congress books that do not exceed 400 words and present data of preliminary research, and those that are presented in an electronic environment are not accepted pre-published work. Authors in such situation must declare this status on the first page of the manuscript and in the cover letter. (The COPE flowchart is available at: http://publicationethics.org).

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4. All authors are responsible for the manuscript's content

5. All authors participated in the study concept and design, analysis and interpretation of the data, drafting or revising of the manuscript, and have approved the manuscript as submitted. In addition, all authors are required to disclose any professional affiliation, financial agreement, or other involvement with any company whose product figures prominently in the submitted manuscript.

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Online Article Submission Process

The Journal of Urological Surgery uses submission software powered by Online Article Submission articles the website for submissions to the Journal of Urological Surgery is http://submitjurolsurgery.org. This system is quick and convenient, both for authors and reviewers.

The Review Process

Each manuscript submitted to the Journal of Urological Surgery is subject to an initial review by the editorial office in order to determine if it is aligned with the journal's aims and scope, and complies with essential requirements. Manuscripts sent for peer review will be assigned to one of the journal's associate editors that has expertise relevant to the manuscript's content. All manuscripts are single-blind peer reviewed. All accepted manuscripts are sent to a statistical and English language editor before publishing. Once papers have been reviewed, the reviewers' comments are sent to the Editor, who will then make a preliminary decision on the paper. At this stage, based on the feedback from reviewers, manuscripts can be accepted, rejected, or revisions can be recommended. Following initial peer-review, articles judged worthy of further consideration often require revision. Revised manuscripts generally must be received within 3 months of the date of the initial decision. Extensions must be requested from the Associate Editor at least 2 weeks before the 3-month revision deadline expires; the Journal of Urological Surgery will reject manuscripts that are not received within the 3-month revision deadline. Manuscripts with extensive revision recommendations will be sent for further review (usually by the same reviewers) upon their re-submission. When a manuscript is finally accepted for publication, the Technical Editor undertakes a final edit and a marked-up copy will be e-mailed to the corresponding author for review and to make any final adjustments.

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English Language Editing

All manuscripts are professionally edited by an English language editor prior to publication.

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The video articles are prepared on urological surgeries by experts who have extensive experience and knowledge of certain advanced surgical techniques. Video article should introduce the clinical problem, describe the surgical solution, and present brief outcome of the technique or produce details in the video. This section is also intended to enable urologists to learn, evaluate, and apply new or complex surgical principles in their surgical practice.

All video article submissions should include all of the elements of original article (please label each section of the structured abstract with the appropriate subheading as objective, materials and methods, results and conclusion) or case report (please submit with a short unstructured abstract), and be presented with a video that demonstrates a novel or established surgical technique, or focuses on tips and tricks, and troubleshooting of common technical challenges. There is no minimum number of cases required, but priority is given to series with at least 8 cases. Videos are peer reviewed for relevance and overall scientific quality.

Video Presentation:

Authors who have a video that they wish to submit with their article are strongly encouraged to refer to the video within the body of the article, in the same way as a figure or table. All submitted files should properly labeled so that they directly relate to the video file's content. All names and institutions should be removed from all video materials. Please provide the file in one of recommended file formats with a preferred maximum size of 1 GB total and a maximum duration of 10 minutes. The resolution of the video should be at least 960 x 720 for 4:3 aspect ratio videos, and 1280x720 for 16:9 videos.. Videos can be larger than these dimensions, but not smaller. For larger video documents, please contact info@galenos.com.tr.

Video Format	
MP4	MP4 Preferred video format; H.264+AAC, max target 720p
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The video should include audio narration explaining the procedure. All text and audio in the video must be in English. Audio must include narration in clear, grammatically correct English. Videos must be clear, in focus, and without excessive camera movement. Radiographs and other material must not contain any patient-identifiable information. A limited number of slides incorporated into the video may be included to provide details about the patient's history, clinical and laboratory findings.

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CONTENTS

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The Effect of the MAYO Adhesive Probability Score on Intraoperative Parameters in Laparoscopic Live Donor Nephrectomy and Bench Surgery

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

In the literature, there are different scoring systems defined to predict the degree of difficulty of nephrectomy surgery. PADUA, RENAL and centrality-index scoring systems are some of them. Mayo Adhesive Probability score (MAP score) is also one of these nephrometry systems developed by Davidiuk et al. in 2014 to predict surgical difficulty using radiologic image-based measurements and interpretations. Published studies associate parameters such as intraoperative difficulty, conversion to open surgery, operation time, and estimated blood loss in laparoscopic donor nephrectomy with a high MAP score. Bench surgery is an important step in kidney transplantation. Since it is a dissection-based procedure and its complications can directly affect the success of kidney transplantation, it is important to predict the degree of difficulty in advance. This is the first study in the literature investigating the effect of MAP score on bench surgery parameters in kidney transplantation. In this respect, it contributes to the existing knowledge on laparoscopic donor nephrectomy and presents new point of view on bench surgery.

Abstract

Objective: Mayo Adhesive Probability score (MAP score) is a nephrometry system to predict surgical difficulty using radiologic image-based measurements and interpretations. MAP score is based on two main factors: Perinephric fat thickness at the level of the renal vein and perinephric fat stranding, which was defined as a linear area of soft tissue attenuation in the perinephric space. This study evaluated the efficacy of the MAP score on intraoperative parameters of laparoscopic donor nefrectomy and bench surgery.

Materials and Methods: Four hundred twenty-one laparoscopic live-donor nephrectomies (LDN) and subsequent bench surgeries carried out between 2016 and 2022 have been included in this study. Preoperative computerized tomography images of donors were blindly scored for determination of MAP scores. Sex, age, hypertension, cigarette smoking, dyslipidemia, and body mass index (BMI) were evaluated as risk factors for high MAPS.

Results: In females and males, the percentage of donors in the high MAPS group was 11.79% and 25.32%, respectively, and the difference between the two groups is statistically significant. Similarly, the percentage of donors in the high MAPS group is higher in smokers (42.57%) compared to non-smokers (8.75%) ($p<0.05$).

Conclusion: Although a high MAP score can lead to longer operative time both in LDN and bench surgery, complications in LDN and bench surgery do not seem to be affected by a high MAP score.

Keywords: Kidney, transplantation, live donor nephrectomy, bench surgery, MAP score

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Introduction

The most common technique used for organ retrieval in kidney transplantation is laparoscopic live-donor nephrectomy (LDN) (1). It has succeeded over open donor nephrectomy with decreased morbidity, less postoperative pain, shorter hospital stay, and a shorter time to return to social and professional life while achieving similar outcomes in terms of graft function and survival rates (2,3). Kidneys retrieved laparoscopically from live donors also have shown better results compared to kidneys from deceased donors (4). On the other hand, LDN is a technically challenging operation that may require training and experience in laparoscopic surgery (5). A factor that may contribute to these difficulties is the presence of thick and sticky inflammatory fat tissue surrounding the kidneys, which is defined as adherent perinephric fat (APF). In previous studies evaluating difficulty in partial nephrectomies, a positive correlation was found between the presence of APF and operative time, a higher risk for conversion to open surgery, surgical difficulty, and blood loss during surgery (6,7).

Different renal morphometry systems have been developed to predict surgical difficulty in partial nephrectomy, including Preoperative Aspects and Dimensions Used for Anatomical classification (PADUA) score, Radius Endophytic/exophytic Nearness Anterior posterior Location (RENAL) score and Centrality-index score (8-10). Mayo Adhesive Probability score (MAP score) was also one of these nephrometry systems developed by Davidiuk et al. (11) in 2014 to predict surgical difficulty using radiologic image-based measurements and interpretations. MAP score (MAPS) is based on two main factors: Perinephric fat thickness at the level of renal vein and perinephric fat stranding, which was defined as a linear area of soft tissue attenuation in the perinephric space (Figure 1). Stranding is speculated to be indicative of underlying metabolic and inflammatory processes

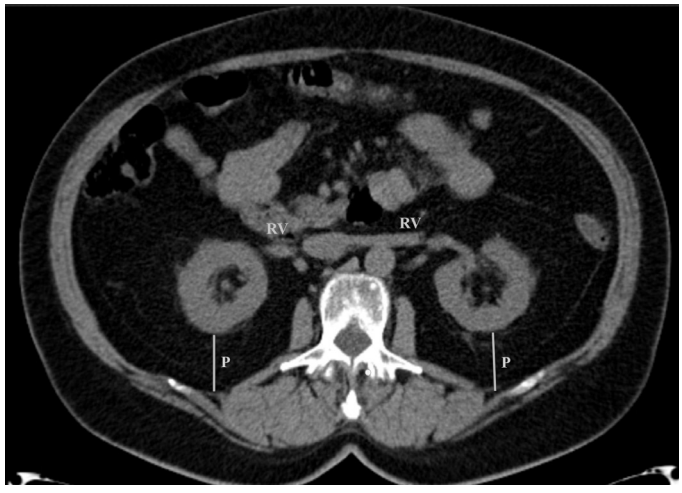

Figure 1. Perinephric stranding and fat measurements at the level of the renal vein

(12). The sum of points taken from these two factors forms the MAP score ranging from 0 to 5. Previous studies have revealed the effectiveness of MAP score in predicting the presence of APF and a high MAP score is associated with longer operative time and increased complications in laparoscopic and robot-assisted partial nephrectomy series (13-16). Intraoperative difficulty, conversion to open surgery, operative time, and estimated blood loss have also been associated with high MAP scores in laparoscopic donor nephrectomy (17-19).

To minimizing ischemia time in live-donor kidney transplantation, coordination of donor and recipient operations is of paramount importance. Thus, the prediction of operative time for donor and bench surgery helps in determining when the recipient operation should be initiated. As the presence and severity of APF is a factor that can affect operative times, its prediction using MAP score may aid efforts to minimize warm ischemia time.

To our knowledge, this study is novel in evaluating the efficacy of MAP score on bench surgery operative time and complications, which was facilitated by recording of operative data during bench surgery. In this study, we retrospectively analyzed the effect of MAP score on intraoperative parameters in LDN and bench surgery.

Materials and Methods

This study complies with the Declaration of Helsinki and was performed by institutional approval from İstanbul Gelişim University Ethics Committee (approval no: 2023-01-32). Four hundred twenty-one laparoscopic live-donor nephrectomies and subsequent bench surgeries that have been carried out between 2016 and 2022 have been included in this study. All of the laparoscopic donor nephrectomies were performed by one senior surgeon (MA) and all bench surgeries were performed by one senior transplant surgeon (SA). Laparoscopic donor nephrectomies were performed transperitoneally with three 5 mm trocars and a 12 mm trochar placed in the Pfannenstiel incision, which is prepared at the beginning of surgery and temporarily sutured until organ extraction. LDN is performed using the dissection plane outside Gerota's fascia as in radical nephrectomy. The renal artery and vein are controlled by separate Endo-GIA staplers (Covidien, Medtronic Inc., USA) and ureter using Hem-O-Lok polymer clips (Weck Surgical Instruments, Teleflex Medical, Durham, NC, USA). At the end of the surgery, no surgical drains were placed in any patient. Intraoperative complication data were extracted from operation notes in the patient charts. After extraction, the kidneys were perfused by Custodiol (histidine-tryptophan ketoglutarate) solution. Kidneys were then skeletonized over the capsule, all of perinephric fat and lymphatics were dissected, and all perihilar lymphatics

were ligated to avoid lymphoceles. Bench surgery data were collected and recorded by a kidney transplantation coordinator. Preoperative computerized tomography images of donors were blindly scored for determination of MAP scores (Table 1). Zero-two MAPS are accepted as low and ≥3 MAPS are accepted as high. Sex, age, hypertension, cigarette smoking, dyslipidemia and body mass index (BMI) were evaluated as risk factors for high MAPS. Diabetes mellitus was excluded due to the low number of donors. Laparoscopic donor nephrectomy complications were classified according to Clavien-Dindo system.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 25.0 (IBM Corporation, Armonk, NY, USA). Formalities of distributions for continuous variables were checked by histogram graphics and Kolmogorov-Smirnov test. In the presentation of descriptive analyses, mean, standard deviation, median, minimum, and maximum values have been used. In normally distributed variables, results were presented as mean ± standard deviation. For categorical variables, results were presented as count and percentage. Categorical variables were compared with the chi-square test. Mann-Whitney U test was used for mean univariate differences in ordinal variables and for continuous variables that were not normally distributed. Metric data were compared using Spearman's correlation test. Multivariate analyses for factors affecting MAP scores were performed by binary logistic regression analysis. Factors affecting operative time and bench time were evaluated by linear regression analysis. P values less than 0.05 were considered statistically significant.

Results

A total of 421 donors who had laparoscopic donor nephrectomy and whose grafts subsequently underwent bench surgery were enrolled in this retrospective study. The mean age of the donors was 48.92±13.31. Two hundred and sixty-three (62.47%) donors were female and 158 (37.53%) of the donor were male. The mean BMI of the donors was 27.46±5.35 kg/m^2. Forty-one (9.74%) donors were operated on the right side, and the remaining 380 (90.26%) donors were operated on the left side. One hundred and one (23.99%) donors were cigarette smokers and 320 (76.00%) of them were non-smokers. The number of donors who had dyslipidemia and hypertension was 109 (25.89%) and 45 (10.68%), respectively (Table 2).

Table 1. Mayo Adhesive Probability score algorithm

		Points
Posterior perinephric fat thickness (cm)	<1 cm	0
	1.0-1.9	1
	≥2.0	2
Stranding	None	0
	Type 1	2
	Type 2	3

Mean MAP scores in relation to sex, cigarette smoking, laterality, presence of hypertension, dyslipidemia, and multiple arteries are given in Table 3. Mean MAPS in female and male donors were 0.78±1.28 and 1.3±1.56, respectively and the difference was statistically significant ($p<0.05$). Mean MAPS in smokers were 1.37±1.73 whereas mean MAPS in non-smokers were calculated as 0.73±1.2 and the difference was statistically significant ($p<0.05$). There were no significant differences in mean MAPS in relation to laterality, presence of hypertension, and multiple arteries ($p>0.05$).

Patients who had a MAP score of 0-2 were accepted as the Low MAPS group, whereas donors with MAP score of 3-5 were accepted as the High MAPS group. Three hundred and fifty (83.13%) donors had a MAP score <2 and 71 (16.86%) had a MAP score ≥3. In females and males, the percentage of donors in the high MAPS group is 11.79% and 25.32%, respectively and the difference between two groups is statistically significant. Similarly, the percentage of donors in the high MAPS group is higher in smokers (42.57%) compared to non-smokers (8.75%) ($p<0.05$). The percentage of patients in the high MAPS group in relation to laterality, presence of dyslipidemia, hypertension, and multiple arteries is given in Table 4.

Mean age in the low and high MAPS groups were 49.1±16.8 and 56.2±18.1 respectively and the difference between the groups were statistically significant. Mean BMI in the low MAPS group was 26.3±5.3 and mean BMI in high MAPS group was 28.28±5.6. The difference was statistically significant ($p<0.05$) (Table 5). Correlation of MAPS with age and BMI was evaluated with Spearman's correlation test and a correlation in the same

Table 2. Descriptive data

Age (Mean ± SD)		48.92±13.31
Sex (n, %)	Female	263(62.47)
	Male	158 (37.53)
Body mass index (Mean ± SD)		27.46±5.35
Laterality (n, %)	Right	41 (9.74)
	Left	380 (90.26)
Smoking (n, %)	No	320 (76.00)
	Yes	101 (23.99)
Dyslipidemia (n, %)	No	312 (74.10)
	Yes	109 (25.89)
Hypertension (n, %)	No	376 (89.31)
	Yes	45 (10.68)

SD: Standard deviation

direction was found between MAPS and age, as well as BMI (r=0.155 and 0.118, respectively).

Mean operative time in the low MAPS and high MAPS groups was 72.53±10.52 min and 80.72±12.21 min, respectively and the difference was statistically significant. Mean bench time in the low MAPS group was 42.02±6.81 and mean bench time in the high MAPS group was 48.27±8.18. The difference between the groups was statistically significant (p<0.001) (Table 6).

Binary logistic regression analysis was performed to evaluate risk factors for the high MAPS group. Each year increase in

Table 3. MAP score by parameters

Mean ± SD		MAP score		p-value
		Median (Min-Max)		
Sex	Male	1.3±1.56	1 (0-5)	**<0.05**
	Female	0.78±1.28	0 (0-5)	
Cigarette smoking	No	0.73±1.2	0 (0-5)	**<0.05**
	Yes	1.37±1.73	1 (0-5)	
Laterality	Right	0.73±1.36	0 (0-5)	0.158
	Left	1±1.42	0 (0-5)	
Hypertension	No	1±1.44	0 (0-5)	0.455
	Yes	0.78±1.15	0 (0-3)	
Dyslipidemia	No	0.95±1.37	0 (0-5)	0.581
	Yes	1.05±1.53	0 (0-5)	
Multiple arteries	No	0.94±1.41	0 (0-5)	0.271
	Yes	1.08±1.44	0 (0-5)	

SD: Standard deviation, Mann-Whitney U test, MAP score: Mayo Adhesive Probability score, Min: Minimum, Max: Maximum

Table 4. Number of patients in MAPS groups

		MAPS				p-value
		Low (0-2)		High (3-5)		
		n	%	n	%	
Sex	Male	118	(74.68)	40	(25.32)	**<0.05**
	Female	232	(88.21)	31	(11.79)	
Cigarette smoking	No	292	(91.25)	28	(8.75)	**<0.05**
	Yes	58	(57.43)	43	(42.57)	
Laterality	Right	35	(85.37)	6	(14.63)	0.688
	Left	315	(82.89)	65	(17.11)	
Hypertension	No	312	(82.98)	64	(17.02)	0.804
	Yes	38	(84.44)	7	(15.56)	
Dyslipidemia	No	261	(83.60)	51	(16.40)	0.668
	Yes	89	(81.82)	20	(18.18)	
Multiple arteries	No	269	(83.85)	52	(16.15)	0.479
	Yes	81	(80.81)	19	(19.19)	

chi-square test, MAPS: Mayo Adhesive Probability score

Table 5. Age and BMI in MAPS groups

	MAPS				p-value
	Low (0-2)		High (3-5)		
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
Age	47.78±13	48 (15-81)	54.56±13.48	55 (25-83)	**<0.001**
BMI	26.3±5.3	27 (17-42)	28.28±5.6	28 (18-40)	**<0.05**

Mann-Whitney U test, BMI: Body mass index, Min: Minimum, Max: Maximum, MAPS: Mayo Adhesive Probability score, BMI: Body mass index, SD: Standard deviation

age increases the risk of having a high MAPS score by 1.051 and male sex increases the risk of having a high MAPS by 2.69 compared to female sex. The risk increase by BMI and cigarette smoking is presented in Table 7.

Five (1.18%) Clavien-Dindo classification grade 2 or above complications included blood transfusion, paralytic ileus, chylous ascites treated medically, chylous ascites treated surgically, and splenectomy with pancreatic leak. The MAP scores of donors whom encountered these complications are given in Table 8. In bench surgery there were 2 complications, both of which were injury to segmental arteries and they were reconstructed meticulously. One of these donors had a MAP score of 2, whereas the other had a score of 3, which was statistically insignificant (p>0.05).

Discussion

MAPS is a score that allows numerical expression of the presence and adhesion severity of perinephric fat by measurements and interpretations made on radiological imaging. It was first defined by Davidiuk et al. (11) in robotic partial nephrectomy operations to evaluate the adhesion severity of perinephric adipose tissue and thus to predict intraoperative parameters and surgical difficulty. It has been shown that as this score ranging between 0 and 5 increases, the perinephric adipose tissue is thicker and has a more adhesive structure. Using this score, the presence of APF can be predicted in the preoperative period (11). There are other studies in the literature confirming the efficacy of MAP score in predicting intraoperative parameters (operation time, specifically) in laparoscopic and robot -assisted partial nephrectomy series (20). In one of these studies conducted with 311 Robot Assisted Partial Nephrectomy (RAPN) patients by Ishiyama et al. (14), RAPN surgery was evaluated in 2 parts: Dissection and resection. It was shown that the dissection time was significantly prolonged in patients when MAPS was higher than 3.

After the definition of the MAP score, the predictive capacity of this score was evaluated not only in robotic partial nephrectomy operations but also in other renal surgery modalities. In their study of 215 patients who underwent laparoscopic partial nephrectomy (LPN), Fang et al. (21) stated that the presence of APF was associated with longer operation and warm ischemia time and more estimated blood loss, and emphasized that the only independent variable indicating APF was MAPS. Similarly,

Table 6. Operative and bench time in MAPS groups

	MAPS				p
	Low (0-2)		High (3-5)		
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
Operative time	72.53±10.52	71 (45-110)	80.72±12.21	80 (60-120)	**<0.001**
Bench time	42.02±6.81	40 (25-70)	48.27±8.18	45 (30-70)	**<0.001**

Mann-Whitney U test, MAPS: Mayo Adhesive Probability score, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 7. Regression analysis of risk factors

MAPS	B	S.E.	p	Exp (B)	95% CI for Exp (B)	
					Lower	Upper
Age	0.050	0.012	**<0.001**	1.051	1.027	1.075
BMI	0.296	0.132	**0.001**	1.171	1.018	1.216
Male sex	0.985	0.300	**0.001**	2.679	1.488	4.823
Cigarette smoking	2.100	0.402	**<0.001**	6.164	4.517	14.753

Binary Logistic Regression Analysis, BMI: Body mass index, MAPS: Mayo Adhesive Probability score, CI: Confidence interval

Table 8. LDN complications by MAPS groups

Clavien-Dindo classification	Number of complications	Complication	Low MAPS (n=350)	High MAPS (n=71)	p-value
Grade 2	3	Blood transfusion	1 (0.28%)	0	0.216
		Paralytic ileus	1 (0.28%)	0	0.216
		Chylous ascites - Medical	0	1 (1.40%)	0.067
Grade 3	2	Chylous ascites - Surgery	1 (0.28%)		0.216
		Splenectomy and pancreatic leak	1 (0.28%)		0.216

LDN: Laparosacopic donor nephrectomy, MAPS: Mayo Adhesive Probability score

Yao et al. (13) reported that patients with MAPS ≥3 had longer dissection time and higher estimated blood loss in their LPN series of 318 patients. In another study, Sempels et al. (20) evaluated the PADUA, RENAL, arterial-based complexity (ABC) score, and MAP scoring systems in partial nephrectomy patients and stated that among these scoring systems, MAPS was the only scoring system that predicted serious surgical complications as well as longer operation time. After a review by Lee et al. (22), usage of MAP score has gained wider acceptance due to its ability to predict the presence of APF and to give information that can guide preoperative planning and patient assessment.

The efficacy of the MAP score in predicting APF in the partial nephrectomy series has led to the interest of using this score in the prediction of surgical parameters in laparoscopic donor nephrectomy operations. With the fact that donors are selected from healthy individuals for living kidney donation, being able to predict intraoperative parameters was more of concern to increasing patient safety. In their study evaluating the effect of the MAP score on LDN parameters, Sato et al. (18) evaluated renal transplantation results from 782 living donors. Although no significant effect was observed on surgical complications and postoperative graft functions, a higher MAP score resulted in a longer operation time and increased estimated blood loss. In the same study, age, male gender, high BMI and presence of hypertension, hyperlipidemia and diabetes mellitus were determined as predisposing factors for a high MAP score. Similarly, Özçelik et al. (19) stated that LDN operative time was longer in patients with a MAP score ≥1 and found age, male gender and high BMI to be predictive for high MAP scores. In another study, Franquet et al. (17) stated that conversion to open surgery and Clavien-Dindo grade 3-4 complication rates were significantly higher in LDN patients with a MAP score of 3 and higher. In this study, the LDN operation time was found to be significantly longer in the group with high MAP scores. However, there was no difference in perioperative complication rates of LDN. In this sense, the presence of APF seems to complicate dissection during donor nephrectomy resulting in longer operative time, which is consistent with previous studies (17-19,23). As the dissection was performed outside Gerota's fascia in this series, increased lymphatics at the kidney hilum might have resulted in longer operative time. The overall Clavien-Dindo Grade 2 or above complication rate in this study was 1.1%, which is low compared to similar studies. Franquet et al. (17) reported 16% intraoperative difficulties, which lead to 4.2% conversion to open surgery, and Sato et al. (18) reported 2.4% complications according to the classification proposed by Kocak et al. (24). The low number of complications in this study can be attributed to the experience of the team in a high -volume center and it mighy be postulated that few number and percentage of complications might have affected the statistical analysis. With the current increased bleeding control capacity of endoscopic surgical instruments and sealing devices used for dissection, and possibly with surgical experience, the difficulty associated with the presence of APF appears to be eliminated without a significant increase in complication rates. Blood loss is another parameter commonly used in describing operative difficulty. At our center, due to very low blood loss, which is usually less than 50 cc, it has not been recorded as an operative parameter since 2015 and has not been mentioned in this retrospective analysis.

When the determining risk factors for a high MAP score in this study, age, high BMI, male gender and smoking were significant predisposing factors in multivariate analysis, but the presence of hypertension and dyslipidemia was not found to be significant for high MAPS and similar results can be seen in the literature. As a general rule, uncontrolled hypertension and diabetes mellitus are a contraindication for kidney donation, and willing candidates can only be accepted under certain conditions (25). This makes a great impact on study groups evaluating MAPS. Studies involving patients with kidney tumors undergoing LPN will be incomparable to studies involving kidney donors in terms of hypertension and diabetes, and no data is available about diabetes in most previous studies evaluating the MAP score in patients with LDN patients (17,19,23). When the previous studies are evaluated in general, it would not be wrong to interpret that the parameters with the strongest emphasis for high MAPS are age, male gender, and high BMI. In our study, in addition to these factors, smoking is also related to high MAPS. In a study including 46 donor nephrectomies, Yanishi et al. (23) reported 44% of smokers in the high MAP score group, whereas 18.9% of the low MAP score group were smokers, but the difference was insignificant. In the literature, smoking is a widely accepted risk factor that causes inflammation by smoking-related oxidative stress (26). Also, in our clinical experience, smokers are a group of patients where hilar lymphatics are abundant and lymphatic dissection during LDN and bench surgery is harder and takes longer to perform.

In our study, the effect of the MAP score on surgical parameters was also evaluated for bench surgery. Bench surgery time was also significantly longer in the group with a high MAP score, but there was no difference in complications that required reconstruction. To our knowledge, this is the first data in the literature about how MAP score can affect bench surgery parameters. As there are no previous studies, it was impossible to evaluate the current results of bench surgery considering the literature. However, considering that bench surgery is essentially based on the complete removal of perinephric adipose tissue from the renal parenchyma, it is understandable that the presence of APF shown by high MAPS makes this dissection difficult and prolongs the operation time. Avoiding vascular complications that may require reconstruction may partially

depend on the experience of the surgeon, which might have resulted in the current results.

Considering this data, when the MAP score is over 3, a difficulty in LDN and bench surgery should be expected. The Surgical teams must be psychologically and technically well prepared when evaluating such donors and performing surgery. It can be recommended that donor and recipient operations may be synchronized according to the surgical team's evaluation of the MAP score.

Study Limitations

The main limitation of this stuy is its retrospective design. The data has been collected in more than 5 years, and it is possible that surgical practices might have changed in this time period and this might have affected the results. The second limitation may be in interpreting and scoring perirenal fat in terms of stranding. This is a subjective evaluation and carries the risk of interobserver differences.

Conclusion

A high MAP score has been linked to age, male gender, BMI, and cigarette smoking. While a high MAP score can lead to longer operative time both in LDN and bench surgery, complications in LDN and bench surgery do not seem to be affected by a high MAP score.

Ethics

Ethics Committee Approval: This study complies with the Declaration of Helsinki and was performed by institutional approval from İstanbul Gelişim University Ethics Committee (approval no: 2023-01-32).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., M.A., Concept: S.A., M.A., Design: S.A., O.A., Data Collection or Processing: S.A., O.A., Analysis or Interpretation: S.A., O.A., Literature Search: S.A., O.A., M.A., Writing: S.A., O.A.

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References

1. Rodríguez Faba O, Boissier R, Budde K, Figueiredo A, Taylor CF, Hevia V, Lledó García E, Regele H, Zakri RH, Olsburgh J, Breda A. European Association of Urology Guidelines on Renal Transplantation: Update 2018. Eur Urol Focus 2018;4:208-215.
2. Andersen MH, Mathisen L, Oyen O, Edwin B, Digernes R, Kvarstein G, Tønnessen TI, Wahl AK, Hanestad BR, Fosse E. Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant 2006;6:1438-1443.
3. Altinel M, Akinci S, Gunes ZE, Olcucuoglu E, Gonenc F, Yazicioglu AH. Open versus laparoscopic donor nephrectomy: perioperative parameters and graft functions. Transplant Proc 2011;43:781-786.
4. Yohanna S, Naylor KL, McArthur E, Lam NN, Austin PC, Habbous S, McCallum MK, Ordon M, Knoll GA, Kim JS, Garg AX. A Propensity Score-weighted Comparison of Outcomes Between Living and Standard Criteria Deceased Donor Kidney Transplant Recipients. Transplantation 2020;104:e317-e327.
5. Raque J, Billeter AT, Lucich E, Marvin MM, Sutton E. Training techniques in laparoscopic donor nephrectomy: a systematic review. Clin Transplant 2015;29:893-903.
6. Kocher NJ, Kunchala S, Reynolds C, Lehman E, Nie S, Raman JD. Adherent perinephric fat at minimally invasive partial nephrectomy is associated with adverse peri-operative outcomes and malignant renal histology. BJU Int 2016;117:636-641.
7. Khene ZE, Peyronnet B, Mathieu R, Fardoun T, Verhoest G, Bensalah K. Analysis of the impact of adherent perirenal fat on peri-operative outcomes of robotic partial nephrectomy. World J Urol 2015;33:1801-1806.
8. Ficarra V, Novara G, Secco S, Macchi V, Porzionato A, De Caro R, Artibani W. Preoperative aspects and dimensions used for an anatomical (PADUA) classification of renal tumours in patients who are candidates for nephron-sparing surgery. Eur Urol 2009;56:786-793.
9. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol 2009;182:844-853.
10. Simmons MN, Ching CB, Samplaski MK, Park CH, Gill IS. Kidney tumor location measurement using the C index method. J Urol 2010;183:1708-1713.
11. Davidiuk AJ, Parker AS, Thomas CS, Leibovich BC, Castle EP, Heckman MG, Custer K, Thiel DD. Mayo adhesive probability score: an accurate image-based scoring system to predict adherent perinephric fat in partial nephrectomy. Eur Urol 2014;66:1165-1171.
12. Cockerill KJ, Kahn AE, Young SM, Ball CT, Mai ML, Taner CB, Perry DK, Thiel DD. Mayo Adhesive Probability (MAP) score of non-donated kidney aids in predicting post-operative renal function following donor nephrectomy. BMC Urol 2020;20:124.
13. Yao Y, Xu Y, Gu L, Liu K, Li P, Xuan Y, Gao Y, Zhang X. The Mayo Adhesive Probability Score Predicts Longer Dissection Time During Laparoscopic Partial Nephrectomy. J Endourol 2020;34:594-599.
14. Ishiyama R, Kondo T, Takagi T, Iizuka J, Kobayashi H, Omae K, Fukuda H, Ishihara H, Tanabe K. Impact of the Mayo Adhesive Probability Score on the Complexity of Robot-Assisted Partial Nephrectomy. J Endourol 2018;32:928-933.
15. Kim H, Kim M, Byun SS, Hong SK, Lee S. Clinical Implication of Adherent Perinephric Fat in Robot-Assisted Partial Nephrectomy: Validation With Video Review. Front Surg 2022;9:840664.
16. Egen L, Kowalewski KF, Riffel P, Honeck P, Kriegmair MC. Nephrometry Scores: Can Preoperative Assessment of Sectional Imaging Really Mirror Intraoperative Renal Tumor Anatomy? Urol Int 2021;105:108-117.
17. Franquet Q, Matillon X, Terrier N, Rambeaud JJ, Crouzet S, Long JA, Fassi-Fehri H, Codas-Duarte R, Poncet D, Jouve T, Noble J, Malvezzi P, Rostaing L, Descotes JL, Badet L, Fiard G. The Mayo Adhesive Probability score can help predict intra- and postoperative complications in patients undergoing laparoscopic donor nephrectomy. World J Urol 2021;39:2775-2781.
18. Sato Y, Noguchi H, Mei T, Kaku K, Okabe Y, Nakamura M. Impact of the Mayo Adhesive Probability Score on Donor and Recipient Outcomes After Living-

donor Kidney Transplantation: A Retrospective, Single-center Study of 782 Transplants. Transplant Direct 2021;7:e728.

19. Özçelik Ü, Eren E, Urut DU, Talih T, Tokaç M, Dinçkan A. Correlation Between the Mayo Adhesive Probability Score and the Operative Time in Laparoscopic Donor Nephrectomy. Transplant Proc 2021;53:793-798.
20. Sempels M, Ben Chehida MA, Meunier P, Waltregny D. Open and Laparoscopic Partial Nephrectomy: Comparison and Validation of Preoperative Scoring Systems, Including PADUA, RENAL, ABC Nephrometric Scores and Perinephric Fat Evaluation with Mayo Adhesive Probability Score. Res Rep Urol 2021;13:509-517.
21. Fang L, Li H, Zhang T, Liu R, Zhang T, Bi L, Xie D, Wang Y, Yu D. Analysis of predictors of adherent perinephric fat and its impact on perioperative outcomes in laparoscopic partial nephrectomy: a retrospective case-control study. World J Surg Oncol 2021;19:319.
22. Lee SM, Robertson I, Stonier T, Simson N, Amer T, Aboumarzouk OM. Contemporary outcomes and prediction of adherent perinephric fat at partial nephrectomy: a systematic review. Scand J Urol 2017;51:429-434.
23. Yanishi M, Kinoshita H, Koito Y, Taniguchi H, Mishima T, Sugi M, Matsuda T. Adherent Perinephric Fat Is a Surgical Risk Factor in Laparoscopic Single-Site Donor Nephrectomy: Analysis Using Mayo Adhesive Probability Score. Transplant Proc 2020;52:84-88.
24. Kocak B, Koffron AJ, Baker TB, Salvalaggio PR, Kaufman DB, Fryer JP, Abecassis MM, Stuart FP, Leventhal JR. Proposed classification of complications after live donor nephrectomy. Urology 2006;67:927-931.
25. Yoshinaga K, Araki M, Wada K, Sekito T, Watari S, Maruyama Y, Mitsui Y, Sadahira T, Kubota R, Nishimura S, Edamura K, Kobayashi Y, Tanabe K, Takeuchi H, Kitagawa M, Kitamura S, Wada J, Watanabe M, Watanabe T, Nasu Y. Feasible kidney donation with living marginal donors, including diabetes mellitus. Immun Inflamm Dis 2021;9:1061-1068.
26. Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutat Res Rev Mutat Res 2021;787:108365.

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Importance of Malignant Core Length in the Detection of Clinically Significant Prostate Cancer in Transrectal Prostate Biopsies

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

The main factors in the evaluation of the adequacy of biopsy specimens include the absence of non-prostatic tissues in the biopsy specimen, the presence of glandular prostate tissue, fragmentation of specimens, total core length, and length of each core according to the biopsy localization. In published studies, the biopsy samples were compared between the patients with and without a diagnosis of prostate cancer (PCa). In addition to the biopsy cores of the patients with PCa, we analyzed PCa subgroups, and to our knowledge, this is the first study in the literature to evaluate the core samples of PCa subgroups (CsPCa vs. non-CsPCa). In this study, although there was no statistically significant difference between the PCa and non-Ca groups or between the PCa subgroups in terms of the mean final core length, when the malignant cores were separately examined, their mean length was found to be statistically significantly greater in the CsPCa group. This raises the probability of underestimation due to shorter core length, resulting in overlooking high Gleason grading that would have led to the diagnosis of CsPCa.

Abstract

Objective: To examine cores obtained using prostate biopsy under transrectal ultrasound guidance and determine the ideal total malignant core length for the diagnosis of clinically significant prostate cancer (PCa).

Materials and Methods: From the beginning of 2017 to the end of 2021, 1.611 transrectal ultrasonography-guided prostate biopsy procedures were retrospectively analyzed. The data were divided into two groups as PCa and non-cancer (non-Ca) according to the pathology reports. The PCa group was further divided into two subgroups as clinically significant and non-significant. After comparing the core numbers and lengths between the groups, a statistical analysis was undertaken to determine the optimal cut-off value of the total malignant core length in predicting the diagnosis of clinically significant PCa.

Results: A total of 1.181 biopsy procedures were included in the evaluation. The mean malignant core lengths of the clinically significant and non-significant PCa groups were 6.7±5.1 and 3.6±2.9, respectively, indicating a statistically significant difference between these subgroups. In the presence of PCa, the mean length of malignant cores was found to have an area under the curve value of 0.708 (95% confidence interval: 0.654-0.759) in the prediction of clinically significant PCa, and it had 56.44% sensitivity and 78.05% specificity at a cut-off value of >4.7 cm.

Conclusion: Taking the cut-off value of the mean length of malignant cores as 4.7 cm, if the total length of malignant cores is above this value according to the pathology report following transrectal prostate biopsy, the probability of detecting clinically significant PCa increases.

Keywords: Clinically significant prostate cancer, core length, gleason underestimation, prostate cancer, transrectal biopsy

Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020 (1). A systematic review of autopsy studies reported a PCa prevalence of 5% in patients aged <30 years, increasing to 59% (48-71%) by >79 years, with an odds ratio (OR) of 1.7 per decade (2).

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Since defined by Hodge et al. (3) in 1989, prostate biopsy has become the gold standard for diagnosis, and it has been shown that the length of the biopsy tissue significantly correlates with the PCa detection rate (4). A core length greater than 11.9 mm has been associated with an increased detection rate of PCa [OR: 2.57, 95% confidence interval (CI): 1.46-4.52] (5). Some researchers have suggest that the lower ideal limit of the mean core length is 12 mm. When values are below this number, it is necessary to repeat the sampling of the prostate (6). In another study conducted to evaluate whether the core length taken during the biopsy affected the accuracy of the procedure and the underestimation of the Gleason score by comparing biopsy samples with radical prostatectomy (RP) samples, each unit increase in core length in millimeters was shown to reduce the risk of Gleason upgrading by 89.9% (OR: 0.10, 95% CI: 0.01-0.99) (7).

The definition of clinically significant PCa (CsPCa) is widely used to distinguish PCa that can cause morbidity or mortality associated with other types of PCa. This differentiation is particularly important since clinically non-significant PCa (non-CsPCa) is very common and does not cause any harm (2). In the literature, the lengths of biopsy cores reported as malignant and benign have been previously compared (5-8). To contribute to the literature, in the current study, we evaluated patients diagnosed with PCa in more detail and further examined biopsy core lengths in PCa subgroups. We also tried determining a cut-off value for core length that could increase the detection of CsPCa.

Materials and Methods

Transrectal ultrasonography (TRUS)-guided procedures performed at a tertiary education and research hospital between January 01, 2017, and December 31, 2021, and routine examinations undertaken before these procedures were retrospectively evaluated from the hospital information management system. The patients' age, pre-biopsy -free prostate-specific antigen (PSA) and total PSA values, and parameters included in the pathology reports of the procedure (diagnosis, number of cores, and core length) were recorded.

Patients with suspected PCa according to the physical examination and/or high PSA values were included in the study. Excluded from the sample were patients whose pathology results or pre-biopsy PSA values could not be obtained, those referred from an external center for consultation, and those with a PSA value above 20 ng/mL to ensure the homogenization of the sample.

Systematic biopsy procedures were performed in the lateral decubitus position following the rectal application of an anesthetic agent using an automatic biopsy gun with a 30-cm 18-gauge side-notch cutting needle (cutting length of 17 mm). Biopsy samples were taken in the sagittal plane using the same ultrasound device. The quality of the cores was evaluated macroscopically, and if the sample was of insufficient quality, a new sample was immediately obtained from the same site. For histopathological analysis, each sample taken was transferred to the laboratory in separate tubes containing 10% formol, with the necessary information's being noted on the tubes. If a second core was obtained from the same site, it was placed in the tube reserved for that site with the previously obtained suboptimal core.

In the pathology report, the length of each core was defined in cm. In cases where multiple fragments were obtained from a single site due to the fragmentation of tissues or a second core was obtained due to the poor quality of the first, the pathologist recorded the length of each tissue in the report. The sum of the lengths of all fragmented cores taken from the same site was recorded and analyzed. The cores with a pathology result of atypical small acinar proliferation (ASAP) or non-prostatic tissue (i.e., containing only rectal mucosa, periprostatic tissue, or blood) were excluded from the evaluation. Patients diagnosed with high-grade prostatic intraepithelial neoplasia were categorized into the same group as those with benign outcomes while patients with basal cell carcinoma were evaluated in the CsPCa group.

The data were divided into two groups as PCa and non-Ca according to the pathology reports. The PCa group was further divided into two subgroups. The data of the procedures with a Gleason score of 3+4 and above in the pathology report were included in the CsPCa group, and those of the procedures with a Gleason score below 3+4 were included in the non-CsPCa group. The number and length of cores were compared between the PCa and non-Ca groups, as well as between the CsPCa and non-CsPCa groups. The final number and length of cores were obtained by subtracting the number and lengths of the excluded cores from those of all biopsy cores obtained. Statistical analyses were performed to determine the minimum acceptable cut-off value of the mean biopsy core length in the prediction of a CsPCa diagnosis.

Statistical Analysis

The data were examined using the Shapiro-Wilk test to determine whether they had a normal distribution. The results are presented as mean ± standard deviation (minimum-maximum) or frequency and percentage values. Continuous variables were compared using Student's t-test when the data were normally distributed and the Mann-Whitney U test otherwise. The receiver operating curve (ROC) at the optimal cut-off value for malignant core lengths was constructed using MedCalc Statistical Software version 19.1.5 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020). Sensitivity

and specificity at the optimal cut-off value were also derived from the ROC analysis. The univariate logistic regression analysis was performed, and ORs were reported along with their 95% CIs. The statistical significance level was accepted as α=0.05. Statistical analyses were performed using IBM SPSS ver. 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

Results

The data of 1.611 TRUS-biopsy procedures performed in 1.077 patients between January 01, 2017, and December 31, 2021, were analyzed retrospectively. Figure 1 presents the flowchart of the study. After applying the exclusion criteria, the final sample consisted of 980 patients, of whom 97 had repeated biopsy procedures (four times in one patient, three times in five, and twice in 91).

There was more than one diagnosis in the pathology reports of 46% of the 1.181 biopsy procedures included in the study. Figure 2 summarizes the diagnoses included in the final pathology reports of the samples taken during the biopsy procedures.

Table 1 summarizes the data on age, free and total PSA values, and free/total PSA ratios, as well as statistical differences between the groups.

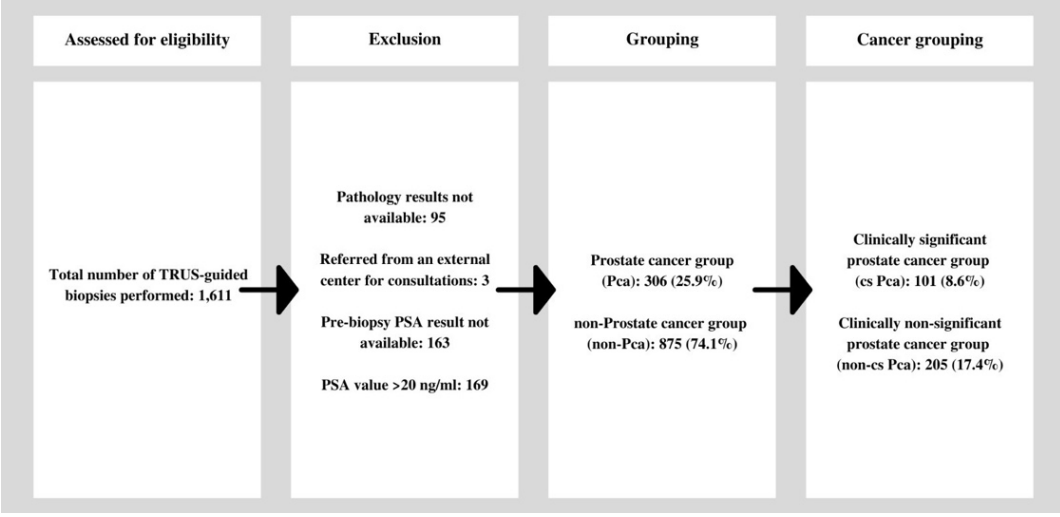

Figure 1. Flowchart of the study

TRUS: Transrectal ultrasonography, PSA: Prostate-specific antigen

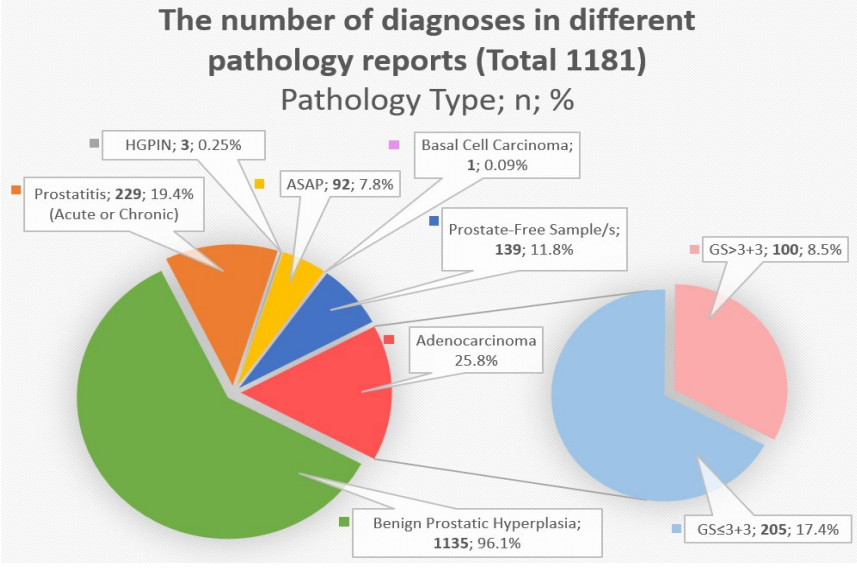

Figure 2. Distribution of diagnoses in the pathology reports of biopsy procedures*

*More than one diagnosis can be found to be related to any procedure due to the differences in the pathology results of the biopsy cores

ASAP: Atypical Small Acinar Proliferation, HGPIN: High Grade Prostatic Intraepithelial Neoplasia, GS: Gleason score

In this study, first the number of cores taken from the prostate lobes and then the number of excluded cores were calculated. Subsequently, the number of excluded cores was subtracted from the number of cores taken to obtain the final core number. When the number of cores taken per prostate was examined, it was determined that the mean number of cores in the PCa group was statistically significantly higher than in the non-Ca group (p<0.05) (Table 2).

After calculating the length of cores taken from the prostate, the length of excluded cores was subtracted from the length of all cores taken, and the final core length was obtained. When the mean final length of cores per prostate was examined, no statistically significant difference was observed between the groups (p>0.05) (Table 3).

Since the mean final length of cores taken per prostate did not statistically significantly differ between the non-Ca and

Table 1. Age, free and total PSA values, and free/total PSA ratios according to the groups

	Non-Ca and PCa Groups			Non-CsPCa and CsPCa Groups		
	Non-Ca	PCa	p	Non-CsPCa	CsPCa	p
Age[α]	63.1±6.6 (41.0-80.0)	65.8±7.1 (44.0-84.0)	<0.001*	66.6±7.4 (44.0-84.0)	68.3±7.7 (48.0-84.0)	0.006*
Free PSA[α]	1.7±1.0 (0.2-7.5)	1.5±1.0 (0.2-6.2)	0.034	1.4±0.9 (0.2-6.2)	1.6±1.1 (0.2-5.7)	0.124
Total PSA[α]	7.6±3.5 (0.8-19.7)	8.9±4.2 (1.3-19.8)	<0.001*	8.3±4.0 (1.3-19.5)	10.2±4.3 (2.1-19.8)	<0.001*
Free/total PSA[α]	0.2±0.1 (0.0-0.7)	0.2±0.1 (0.0-0.8)	<0.001*	0.2±0.1 (0.0-0.8)	0.2±0.1 (0.0-0.6)	0.287

[α]Data are presented as mean ± standard deviation (min-max)
*statistically significant at p<0.05

Table 2. Data on the number of cores taken from the prostate according to the groups

	Non-Ca and PCa Groups			Non-CsPCa and CsPCa Groups		
	Non-Ca	PCa	p	Non-CsPCa	CsPCa	p
Total number of cores taken from the left lobe[α]	5.280, 6.0±0.5 (0.0-12.0)	1.846, 6.0±0.4 (1.0-9.0)	0.329	1.238, 6.0±0.5 (1.0-9.0)	608, 6.0±0.2 (6.0-8.0)	0.453
Total number of cores taken from the right lobe[α]	5.271, 6.0±0.4 (0.0-12.0)	1.845, 6.0±0.3 (5.0-9.0)	0.691	1.235, 6.0±0.3 (5.0-9.0)	610, 6.0±0.4 (5.0-9.0)	0.987
Total number of cores taken from the prostate[α]	1.0551, 12.1±0.8 (4.0-24.0)	3.691, 12.1±0.6 (6.0-16.0)	0.173	2.473, 12.1±0.6 (6.0-15.0)	1.218, 12.1±0.5 (11.0-16.0)	0.325
Number of excluded cores taken from the left lobe[α]	224, 0.3±0.6 (0.0-5.0)	55, 0.2±0.6 (0.0-6.0)	0.019*	43, 0.2±0.7 (0.0-6.0)	12, 0.1±0.4 (0.0-2.0)	0.202
Number of excluded cores taken from the right lobe[α]	267, 0.3±0.8 (0.0-6.0)	86, 0.3±0.8 (0.0-6.0)	0.345	68, 0.3±0.9 (0.0-6.0)	18, 0.2±0.5 (0.0-3.0)	0.290
Total number of excluded cores[α]	491, 0.6±1.2 (0.0-11.0)	141, 0.5±1.2 (0.0-10.0)	0.015*	111, 0.5±1.4 (0.0-10.0)	30, 0.3±0.8 (0.0-5.0)	0.254
Total final number of cores for the left lobe[α]	5056, 5.8±0.8 (0.0-12.0)	1791, 5.9±0.8 (0.0-9.0)	0.009*	1.195, 5.8±0.9 (0.0-9.0)	596, 5.9±0.5 (4.0-8.0)	0.498
Total final number of cores for the right lobe[α]	5.004, 5.7±0.9 (0.0-12.0)	1.759, 5.7±0.9 (0.0-9.0)	0.169	1.167, 5.7±1.0 (0.0-8.0)	592, 5.9±0.6 (3.0-9.0)	0.472
Total final core number[α]	10.060, 11.5±1.4 (1.0-24.0)	3.550, 11.6±1.4 (2.0-16.0)	0.007*	2.362, 11.5±1.6 (2.0-15.0)	1.188, 11.8±0.9 (7.0-16.0)	0.593

[α]Data are presented as n, mean ± standard deviation (min-max)
*statistically significant at p<0.05

PCa groups, the cores were separately evaluated as benign and malignant. There was a statistically significant difference between the PCa subgroups in terms of the mean length of malignant cores (p<0.05) (Table 4).

The ROC analysis revealed that the mean length of malignant cores provided a maximum Youden index at >4.7 cm. Therefore, the cut-off value of the mean length of the malignant cores was determined as 4.7 cm. In the presence of PCa, the mean

Table 3. Data on the lengths of cores taken from the prostate according to the groups

	Non-Ca and PCa Groups			Non-CsPCa and CsPCa Groups		
	Non-Ca	PCa	p	Non-CsPCa	CsPCa	p
Total length of the cores taken from the left lobe[α]	5,756.7, 6.6±2.1 (0.0-16.1)	2,010.9, 6.6±2.0 (0.5-15.7)	0.957	1,358.9, 6.6±2.0 (0.5-13.0)	652.0, 6.5±2.1 (2.7-15.7)	0.483
Total length of the cores taken from the right lobe[α]	5,581.2, 6.4±2.3 (0.0-15.8)	1,940.4, 6.3±2.0 (1.7-13.2)	0.784	1,293.6, 6.3±2.0 (1.7-12.2)	646.8, 6.4±2.0 (3.1-13.2)	0.697
Total length of cores taken from the prostate[α]	11,337.9, 13.0±4.1 (4.0-31.4)	3,951.3, 12.9±3.6 (4.8-28.0)	0.858	2,652.5, 12.9±3.7 (4.8-23.1)	1,298.8, 12.9±3.6 (6.7-28.0)	0.858
Total length of the excluded cores taken from the left lobe[α]	152.1, 0.2±0.6 (0.0-5.7)	44.1, 0.1±0.7 (0.0-8.2)	0.496	39.5, 0.2±0.9 (0.0-8.2)	4.6, 0.0±0.2 (0.0-1.5)	0.024*
Total length of the excluded cores taken from the right lobe[α]	155.4, 0.2±0.6 (0.0-6.8)	61.4, 0.2±0.8 (0.0-7.5)	0.611	50.8, 0.2±0.9 (0.0-7.5)	10.6, 0.1±0.3 (0.0-1.7)	0.047*
Total length of the excluded cores[α]	307.5, 0.4±1.0 (0.0-10.2)	105.5, 0.3±1.4 (0.0-13.9)	0.929	90.3, 0.4±1.7 (0.0-13.9)	15.2, 0.2±0.4 (0.0-1.8)	0.019*
Total final length of the cores for the left lobe[α]	5,604.6, 6.4±2.1 (0.0-15.6)	1,966.8, 6.4±2.1 (0.0-15.7)	0.874	1,319.4, 6.4±2.1 (0.0-13.0)	647.4, 6.4±2.1 (2.7-15.7)	0.917
Total final length of the cores for the right lobe[α]	5,425.8, 6.2±2.3 (0.0-15.8)	1,879.0, 6.1±2.1 (0.0-13.2)	0.685	1,242.8, 6.1±2.1 (0.0-12.2)	636.2, 6.3±2.0 (2.0-13.2)	0.352
Total final core length[α]	11,030.4, 12.6±4.1 (1.1-31.4)	3,845.8, 12.6±3.8 (2.2-28.0)	0.886	2,562.2, 12.5±3.8 (2.2-23.1)	1,283.6, 12.7±3.6 (5.9-28.0)	0.646

[α]Data are presented in centimeter as mean ± standard deviation (min-max)
*statistically significant at p<0.05

Table 4. Characteristics of the malignant and non-malignant (benign) cores

	Non-Ca and PCa Groups			Non-CsPCa and CsPCa Groups		
	Non-Ca	PCa	p	Non-CsPCa	CsPCa	p
Number of benign cores[α]	10,060, 11.5±1.4 (1.0-24.0)	2,353, 7.7±3.2 (0.0-13.0)	<0.001*	1,747, 8.5±2.6 (0.0-13.0)	606, 6.0±3.6 (0.0-11.0)	<0.001*
Length of benign cores[β]	11,030.4, 12.6±4.1 (1.1-31.4)	2,439.6, 8.0±4.1 (0.0-19.3)	<0.001*	1,828.7, 8.9±3.8 (0.0-19.3)	610.9, 6.0±4.0 (0.0-16.7)	<0.001*
Number of malignant cores[α]	-	1,197, 3.9±3.0 (1.0-16.0)	-	615, 3.0±2.2 (1.0-12.0)	582, 5.8±3.6 (1.0-16.0)	<0.001*
Length of malignant cores[β]	-	1,406.2, 4.6±4.1 (0.5-28.0)	-	733.5, 3.6±2.9 (0.5-16.6)	672.7, 6.7±5.1 (0.8-28.0)	<0.001*

[α]Presented as n, mean ± standard deviation (min-max)
[β]Presented in centimeter as mean ± standard deviation (min-max)
*statistically significant at p<0.05

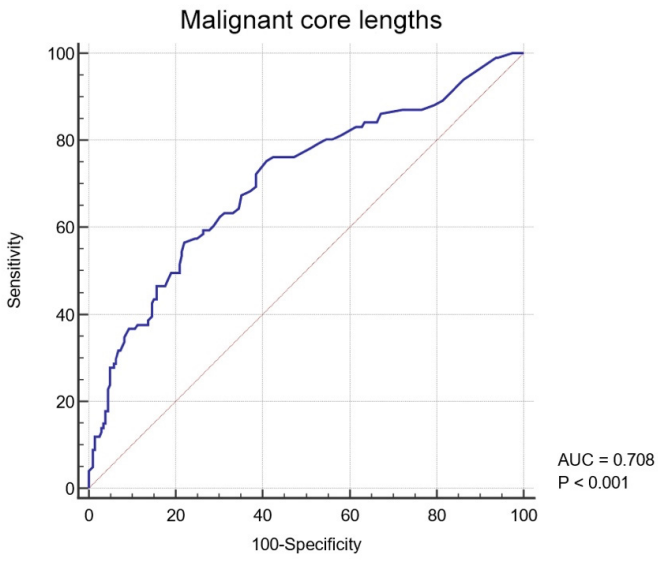

Figure 3. ROC curve of the mean length of malignant cores

ROC: Receiver operating curve

length of malignant cores had an area under the curve value of 0.708 in the prediction of CsPCa (95% CI: 0.654-0.759), and it had 56.44% sensitivity and 78.05% specificity (OR: 1.23, 95% CI: 1.14-1.32) at a cut-off value of >4.7 cm (Figure 3).

Discussion

The role of the urologist in prostate biopsy procedures is to provide adequate tissue samples to assist the pathologist to identify and map cancer in the prostate, in addition to obtaining clinical history, including data on the patient's identity, PSA level, and/or reason for the biopsy, and, if relevant, previous diseases of the genitourinary tract (9).

Currently, there are no defined definitive criteria for evaluating the adequacy of prostate needle biopsies for a histopathological examination. The main factors in the evaluation of the adequacy of biopsy specimens include the absence of non-prostatic tissues in the biopsy specimen, the presence of glandular prostate tissue, fragmentation of specimens, total core length, and length of each core according to the biopsy localization (4,10,11). However, there are only few studies on this issue, which is one of the important parameters to determine biopsy quality (4-6,12). In published studies, the biopsy samples were compared between the patients with and without a diagnosis of PCa. In addition to the biopsy cores of the patients with PCa, we analyzed PCa subgroups, and to our knowledge, this is the first study in the literature to evaluate the core samples of PCa subgroups (CsPCa vs. non-CsPCa).

In almost all studies, the effect of core length on cancer detection was evaluated by comparing the samples of patients with PCa and those with other (benign) pathologies, and cores with cancer were found to be longer. This suggests the possibility that cancer may be overlooked because of shorter core lengths in patients with benign pathology (6). In our study, there was no statistically significant difference in the mean total core length between the PCa and non-Ca groups and between the PCa subgroups. However, when the mean total length of malignant cores was examined in the PCa subgroups, a statistically significant difference was observed between the CsPCa and non-CsPCa groups (6.7±5.1 vs. 3.6±2.9). This raises the possibility that CsPCa may have been overlooked because of shorter core lengths in patients whose pathology result was reported as non-CsPCa. For this reason, we evaluated the samples of the patients with cancer in more detail and determined a cut-off value for the mean length of malignant cores that can be accepted in the literature.

In a retrospective study by Öbek et al. (5) evaluating the data of 245 patients, the mean length of whole biopsy cores was reported as 11.4 mm. The mean length of cores containing cancer was found to be statistically longer (12.3 mm) than those without cancer (11.4 mm). In the same study, there was a linear increase in the cancer detection rate in cases of long biopsy cores. Biopsy core being longer than 11.9 mm was associated with a 2.5-fold higher probability of detecting PCa.

Although Ergün et al. (6) determined the cut-off value of the core length to be 12 mm in the detection of cancer in biopsy, they also noted that a core length of at least 10 mm had diagnostic value, while the cancer detection rate was significantly reduced when the core length was below this limit. Similarly, Boccon-Gibod et al. (9) suggested that taking 10 mm tissue as the shortest acceptable length, the mean needle biopsy length should be a quality control measure.

In a study by Fiset et al. (12), evaluating 197 Canadian patients with an average of 11 cores taken during biopsy, it was found that the cancer-positive cores were significantly longer (mean length: 14.1 mm) than the benign cores (13.2 mm) ($p<0.001$). Additionally, 13-mm cores had optimal sensitivity (42.8%) and specificity (76.5%) in the detection of carcinoma (OR: 2.43) (12).

Van der Kwast et al. (11) evaluated cores from different centers and reported that the rate of cancer detection increased in direct proportion to the total sample length obtained. In another study, Berber et al. (8) showed that the total core length greatly affected the rate of cancer detection in the 12-core biopsy method. There was a 65.3% difference in the rate of cancer detection between the patients with a total core length of <10 cm and those with a total core length of ≥10 cm, indicating that no significant portion of cancers in patients with a core

length of <10 cm could be diagnosed. In the same study, it was reported that the rate of cancer detection increased as the total core length value increased from 10 cm to 15 cm, but there was no additional increase in the rate of cancer detection at the total core length values of 15 cm and above (8). In our study, the mean final total core length was found to be 12.6 cm in the non-Ca and PCa groups, and it was determined to be of ideal size for a diagnosis.

Dogan et al. (10) stated that the rate of cancer detection in glandular cores decreased in patients with serum PSA levels between 4-10 ng/mL. In the current study, we examined the effect of the total core length by excluding patients with non-prostate cores and those whose pathology result was ASAP; therefore, we did not evaluate the effect of glandular cores on the rate of PCa detection.

In this study, although there was no statistically significant difference between the PCa and non-Ca groups or between the PCa subgroups in terms of the mean final core length, when the malignant cores were separately examined, their mean length was found to be statistically significantly greater in the CsPCa group. This raises the probability of underestimation due to shorter core length, resulting in overlooking high Gleason grading that would have led to the diagnosis of CsPCa. In the literature, a high Gleason grading discrepancy of approximately 32-73% has been reported between the rates of biopsy and radical prostatectomy samples (7,13,14). This may be related to the insufficiencies in the length of malignant cores.

In this study, the mean final core length in the PCa group was 12.6 cm, and the cut-off value of the mean length of malignant cores was 4.7 cm. In other words, if the length of malignant cores exceeds 37% of the final core length (4.7/12.6x100), the pathology report is more likely to result in CsPCa. Additionally, the mean final number of cores was calculated as 11.6 in the PCa group, suggesting that the pathology report is more likely to result in CsPCa if 4.4 cores (11.6x0.37) and above are found to be malignant in a biopsy procedure. Based on our results, if malignancy is seen in more than 4.4 (~5) cores according to the pathology report of a biopsy procedure, but the Gleason score is reported to be 3+3 (non-CsPCa) in the same report despite the expectation of a CsPCa result, we would suspect the possibility of Gleason underestimation. To evaluate this new hypothesis, a separate study must examine the pathology reports obtained after the final RP.

Biopsy core length may vary according to different factors, such as trans-rectal versus trans-perineal route, urologist performing the biopsy, needle used, biopsy tissue retrieval and handling methods, and pathological analysis (7).

Study Limitations

In the current study, although all biopsies were performed transrectally using the same ultrasound device and biopsy gun and needle, there are still certain limitations. First, the study was a retrospective design. Second, the transrectal biopsy procedures were performed by different urologists. Finally, the pathology results were evaluated by different pathologists.

Conclusion

Taking the cut-off value of the mean length of malignant cores as 4.7 cm, if the total length of malignant cores is above this value according to the pathology report following transrectal prostate biopsy, the probability of detecting CsPCa increases. Conversely, if the total length of the malignant cores is greater than 4.7 cm and the pathology result is non-CsPCa, the possibility of Gleason underestimated should be considered.

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Ethics

Ethics Committee Approval: For this study, permission was obtained from the Clinical Research Ethics Committee of Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital with the protocol number 2011-KAEK-25 2021/06-01.

Informed Consent: Retrospective study.

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References

1. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol 2020;77:38-52.
2. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer 2015;137:1749-1757.

3. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound -guided transrectal core biopsies of the prostate. J Urol 1989;142:71-74; discussion 4-5.
4. Iczkowski KA, Casella G, Seppala RJ, Jones GL, Mishler BA, Qian J, Bostwick DG. Needle core length in sextant biopsy influences prostate cancer detection rate. Urology 2002;59:698-703.
5. Öbek C, Doğanca T, Erdal S, Erdoğan S, Durak H. Core length in prostate biopsy: size matters. J Urol 2012;187:2051-2055.
6. Ergün M, İslamoğlu E, Yalçınkaya S, Tokgöz H, Savaş M. Does the length of prostate biopsy cores impact the diagnosis of prostate cancer? Turk J Urol 2016;42:130-133.
7. Reis LO, Sanches BC, de Mendonça GB, Silva DM, Aguiar T, Menezes OP, Billis A. Gleason underestimation is predicted by prostate biopsy core length. World J Urol 2015;33:821-826.
8. Berber U, Haholu A, Küçükodacı Z, Yılmaz. 12 Kadran prostat biyopsi protokolünde toplam kor uzunluğunun kanser saptanma oranına etkisi. Gülhane Tıp Dergisi 2013;55:203-206. (Turkish)
9. Boccon-Gibod L, van der Kwast TH, Montironi R, Boccon-Gibod L, Bono A; European Society of Uropathology; European Society of Pathology Uropathology Working Group. Handling and pathology reporting of prostate biopsies. Eur Urol 2004;46:177-181.
10. Dogan HS, Aytac B, Kordan Y, Gasanov F, Yavascaoglu İ. What is the adequacy of biopsies for prostate sampling? Urol Oncol 2011;29:280-283.
11. van der Kwast TH, Lopes C, Santonja C, Pihl CG, Neetens I, Martikainen P, Di Lollo S, Bubendorf L, Hoedemaeker RF; Members of the pathology committee of the European Randomised Study of Screening for Prostate Cancer. Guidelines for processing and reporting of prostatic needle biopsies. J Clin Pathol 2003;56:336-340.
12. Fiset PO, Aprikian A, Brimo F. Length of prostate biopsy cores: does it impact cancer detection? Can J Urol 2013;20:6848-6853.
13. Colleselli D, Pelzer AE, Steiner E, Ongarello S, Schaefer G, Bartsch G, Schwentner C. Upgrading of Gleason score 6 prostate cancers on biopsy after prostatectomy in the low and intermediate tPSA range. Prostate Cancer Prostatic Dis 2010;13:182-185.
14. Reis LO, Zani EL, Freitas LL, Denardi F, Billis A. Higher prostate weight is inversely associated with Gleason score upgrading in radical prostatectomy specimens. Adv Urol 2013;2013:710421.

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Safety and Efficacy of Holmium Laser Enucleation of the Prostate (HoLEP) in Patients Requiring Anticoagulants/Antiplatelets: A Retrospective Study

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

Anticoagulant/antiaggregant (AC/AP) treatments in elder patients may be a concern for the safe surgical application, when any operation is necessary. It is important to choose a surgical method that can be applied to these patients with satisfactory functional outcomes and low perioperative complication rates. In the present study, we found that there was no operation-related disadvantage in the group with patients requiring AC/AP in terms of intraoperative and postoperative complications, with the improvement of functional outcomes. HoLEP is a safe and effective surgery that improves functional parameters in benign prostatic obstruction patients requiring AC/AP, with low bleeding complications and transfusion rates.

Abstract

Objective: We evaluated Holmium Laser Enucleation of the Prostate (HoLEP) surgery performed in patients with benign prostatic obstruction (BPO) requiring anticoagulant/antiplatelet (AC/AP) therapy in terms of safety and efficacy.

Materials and Methods: The retrospective data of 250 patients who underwent HoLEP between January 2020-May 2022 were included in the study. AC/AP treatment status' of patients was recorded. The patients were divided into two groups as those requiring AC/AP (group 1, n=129) and those not using (group 2, n=121). Basic characteristics, preoperative and postoperative IPSS scores, Q_{max} and continence status' at 1st and 6th month follow-up were recorded. Intra- and postoperative complications were recorded according to Clavien-Dindo classification.

Results: No significant difference was observed between the groups in terms of preoeprative characteristics including prostate-specific antigen, hemoglobin (Hb), prostate volume, IPSS, Quality of Life score, Q_{max}, Qave and postvoiding residuel volume (p>0.05). There was no significant difference between the two groups in terms of postoperative functional parameters and urinary continence (p>0.05) and in Hb drop (0.13±0.1 g/dL vs. 0.08±0.15 g/dL, respectively; p=0.21). The blood transfusion rate was 2.3% in group 1 and 0.8% in group 2, and there was no significant difference between the groups (p=0.62). Additionally, there was no significant difference between the groups regarding complications.

Conclusion: HoLEP is a safe and effective, minimally invasive surgical method that improves functional parameters in BPO patients requiring AC/AP.

Keywords: Anticoagulant, bleeding, HoLEP, safety

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Introduction

Holmium Laser Enucleation of the Prostate (HoLEP), one of the alternative to benign prostatic obstruction (BPO) surgical treatment, is being applied with increasing frequency worldwide as the most popular prostate surgery (1). Recently, interest in HoLEP surgery has been increasing due to its success in functional results and low complication rates. The fact that it can be applied even as a daily surgical procedure shows that the method has acceptable complication rates (2).

BPO is usually seen in older men and there is an increase in the incidence of BPO with age (3,4). Similarly to BPO, the incidence of cardiovascular diseases also increases with age (5,6). Since elderly patients are more likely to receive anticoagulant/antiaggregant (AC/AP) treatment, AC/AP treatments in patients with BPO age group may be a concern for the safe surgical application, when BPO surgery is desired. The increase in bleeding and perioperative complications is one of the most important concerns (7-9). Therefore, it is important to choose a surgical method that can be applied to patients requiring AC/AP therapy with satisfactory functional outcomes and low perioperative complication rates.

Although laser enucleation of the prostate has become the most popular prostate surgery of recent years in Turkiye as well as worldwide, studies on the efficacy and safety of laser enucleation in patients requiring AC/AP are lacking in the Turkish literature. In this retrospective study, we evaluated the HoLEP surgery performed in patients with BPO requiring AC/AP therapy in terms of safety and efficacy considering our own experience.

Materials and Methods

Patients Selection and Study Design

After ethics committee approval was obtained [Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) - date/approval number: 2021/21-38], informed consent was obtained from all patients. This study was conducted following the Helsinki Declaration. The data of 405 patients who underwent HoLEP between January 2020-May 2022 were reviewed retrospectively. All patients received alpha-blocker medication and/or 5-alpha reductase inhibitor for at least 6 months before the surgery. The status of patients receiving AC/AP therapy (warfarin, aspirin, apixaban, rivaroxaban, clopidogrel or dabigatran) was recorded. Inclusion criteria for HoLEP surgery were as follows: Failure of BPO medical treatment, discontinuation of medical therapy due to side effects, maximal urinary flow rate (Q_{max}) ≤15 mL/s, International Prostate Symptom Score (IPSS) ≥8, postvoiding residual volume (PVR) ≥50 mL, a history of refractory urinary retention and bladder stones. Exclusion criteria for HoLEP surgery were as follows: Patients with a history of BPO surgery, bladder, prostate, urethra or rectum surgery (n=27), history of a pelvic radiation therapy (n=9), neurogenic bladder (n=5), with a history of prostate or bladder cancer (n=11), urethral strictures (n=15) and with less than 6-month follow-up (n=88).

Age, preoperative serum prostate-specific antigen (PSA) levels, IPSS, Quality of Life score (QoL), mean Qmax and average urinary flow rate (Qave), PVR, prostate volume measured by transabdominal ultrasonography, hemoglobin (Hb) levels were recorded. Postoperative functional parameters, stress urinary incontinence (SUI) and urge urinary incontinence (UUI) status' at 1st and 6th month follow-up were recorded. Postoperative urinary continence status was assessed according to the standards presented by the International Continence Society (ICS) (10). All patients were questioned in terms of any leak due to coughing, exertion, sneezing, or effort. Any urine leaks were considered positive regarding SUI. Total control in urin was evaluated in favor of continence. UUI was determined as involuntary leakage preceded immediately by urgency. Complete dryness was considered in favor of continence.

Enucleated tissue weight (ETW, g), enucleation time (ET, min), enucleation efficiency (ETW/ET, g/min), morcellation time (MT, min), morcellation efficiency (ETW/MT, g/min), total operation time (OT, min) were recorded. Catheterization time (CT) (hours), hospitalization time (HT) (hours) and Hb drop levels were also recorded. Intraoperative and postoperative complications were recorded according to the modified Clavien-Dindo classification (11).

A total of 250 patients who underwent HoLEP were included in the study. The patients were divided into two groups as those requiring AC/AP (group 1, n=129) and those not receiving (group 2, n=121). Group 1 and 2 were compared in terms of perioperative and postoperative parameters. We preferred to consult the patient's cardiologist or hematologist to assess the risk/benefit of continuing AC/AP perioperatively. According to the recommendations, AC/AP therapy was discontinued 5-10 days before surgery in these patients. To prevent cardiac adverse events, bridging therapy was applied to selected patients once a day with low-molecular-weight heparin (LMWH) according to the patient's body weight (twice a day for the patients with artificial heart valves). LMWH was discontinued at least 12 h before surgery to normalize coagulation parameters. If the patient reports a significant postoperative hematuria, the AC/AP continuation plan for the postoperative period was changed according to cardiologist/hematologist recommendations.

Surgical Method and Equipments

All patients were operated by the same surgeon performing the previously described Omega Sign HoLEP technique (12). A 26-

Fr continuous flow laser resectoscope, a laser-fiber stabilizing bridge, a 120-W holmium laser (VersaPulse; Lumenis Ltd., Yokneam, Israel), and a 550-µm end-firing laser fiber (SlimLine; Lumenis Ltd.) were used. A 26-Fr nephroscope and a tissue morcellator (Versacut; Lumenis Ltd.) were used to morcellate and remove the enucleated prostate tissue.

Statistical Analysis

The Statistical Package for Social Sciences 23.0 software (SPSS 23.0, Chicago, USA) was used for the statistical analysis. The Kolmogorov-Smirnov, Kurtosis, and Skewness tests were used to assess the data normality. The clinical characteristics of the two groups were compared with Mann-Whitney U or Student t-test for continuous variables and with the Fisher's Exactor Pearson chi-square test for categorical variables. All statistical tests were two-sided, and the $p<0.05$ value was considered statistically significant.

Results

A total of 250 patients who underwent HoLEP were included in the study. The patients were divided into two groups as those requiring AC/AP (group 1, n=129) and those not receiving (group 2, n=121). In terms of preoperative characteristics, no significant difference was observed between the groups in terms of age, preoperative PSA level, Hb level, preoperative prostate volume, IPSS, QoL, Qmax, Qave and PVR ($p>0.05$) (Table 1). Table 2 shows the perioperative parameters of the groups. There was no statistically significant difference between the two groups in terms of ETW, ET, EE, MT, ME, OT, HT, CT and Hb-level drop (Table 2). The operative functional parameters are presented in Table 3. A significant improvement was observed in IPSS, QoL, Qmax, Qave, PVR, PSA values in both groups at the 1st and 6th months postoperatively ($p<0.001$). However, there was no significant difference between the two groups in postoperative follow-

Table 1. Baseline characteristics and preoperative data of the patients

	Group 1 (n=129)		Group 2 (n=121)		p-value
	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	
Age (y)	63.93±7.04	64 [8]	65.17±7.23	66 [9]	0.09
PSA (ng/mL)	2.21±1.64	1.6 [1.89]	2.26±1.81	1.7 [2]	0.93
Prostate volume (mL)	100.76±47.61	94 [58.5]	97.31±46.71	90 [57.89]	0.56
Hb level (ng/mL)	13.63±1.27	13.66 [1.41]	13.54±1.06	13.4 [1.23]	0.83
IPSS	30.17±3.67	31 [5]	29.41±4.74	30 [6]	0.29
QoL	5±0.74	5 [1]	5±0.75	5 [1]	0.4
Qmax (mL/s)	12.33±3.23	12.4 [3.35]	13±2.9	13 [3.33]	0.19
Qave (mL/s)	5.46±1.92	5.3 [1.65]	5.64±1.72	5.3 [1.95]	0.57
PVR (mL)	230.35±185.82	184.5 [92.25]	214.17±195.4	168.5 [81.75]	0.15

PSA: Prostate specific antigen, Hb: Hemoglobin, IPSS: International prostate symptom score, QoL: Quality of life score, Qmax: Maximum flow rate, Qave: Average flow rate, PVR: Postvoiding residuel volume, SD: Standard deviation, IQR: Interquartile range, Statistically analyzed with Mann-Whitney U test

Table 2. Perioperative data of the patients

	Group 1 (n=129)		Group 2 (n=121)		p-value
	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	
ETW (g)	56.02±35.55	50 [43.5]	54.3±40.1	43 [53]	0.37
ET (min)	72.84±32.61	66 [43]	67.85±32.3	60 [34]	0.22
EE (g/min)	1.51±0.61	1.4 [0.76]	1.49±0.56	1.39 [0.84]	0.96
MT (min)	10.82±2.06	10 [7]	10.19±7.16	8.5 [7.75]	0.46
ME (g/min)	12.25±8.3	10.71 [7.48]	13.25±10.62	10.62 [7.69]	0.8
Laser Energy (joule)	84.81±37.91	76.5 [52.87]	99.41±104.66	76 [56.3]	0.77
Laser Efficiency (g/min)	1±0.73	0.84 [0.53]	1.24±108	0.88 [0.79]	0.31
Operation Time (min)	82.73±37.61	78 [52]	78.56±36.23	71 [41]	0.33
Hospital Time (hour)	30.04±5.85	29 [6]	29.79±6.63	28 [6]	0.47
Catheter Time (hour)	27.23±7.43	26 [6]	26.66±6.17	25 [6]	0.19
Hemoglobin Drop (g/dL)	0.13±0.1	0.1 [0.1]	0.08±0.15	0.1 [0.09]	0.21

ETW: Enucleated tissue weight, ET: Enucleation time, EE: Enucleation efficiency, MT: Morcellation time, ME: Morcellation efficiency, SD: Standard deviation, IQR: Interquartile range, Statistically analyzed with Mann-Whitney U test

ups in terms of these parameters and postoperative UI (p>0.05) (Table 3).

Intra and postoperative complications and management methods according to the modified Clavien-Dindo classification are presented in Table 4. There was no significant difference between the groups regarding complications. When the complications related to bleeding were examined more closely, hematuria requiring prolonged irrigation and following blood transfusion rate was 2.3% in the group receiving AC/AP and 0.8% in the group not receiving AC/AP, and there was no significant difference between the groups in terms of blood transfusion (p=0.62). The clot formation, which refers to patients who develop glob vesicale postoperatively and was detected after bladder irrigation with a urethral catheter, was observed in 2 patients in group 1 and in 1 patient in group 2, but there was no significant difference between the groups (p=1). No clot formation was observed in any patient, which required evacuation by cystoscopic intervention (Table 4).

Discussion

Although it has not yet taken its place in the guidelines as the gold standard, the use of laser in the surgical treatment of BPO is now accepted as an alternative minimally invasive approach to transurethral resection of the prostate (TURP) (13,14). HoLEP has low morbidity, short hospital stay, and can be applied to a wide variety of prostate sizes (15). In this study, we observed improvement in functional outcomes after HoLEP in all patients, and there was no significant difference in functional outcomes between groups requiring AC/AP and not receiving. Moreover,

Table 3. Postoperative parameters of the groups

	IPSS	QoL	Qmax	Qave	PVR	PSA	SUI	UUI
Preoperative								
Group 1	30.17±3.67	5±0.74	12.33±3.23	5.46±1.92	230.35±185.82	2.21±1.64		
Group 2	29.41±4.74	5±0.75	13±2.9	5.64±1.72	214.17±195.4	2.26±1.81		
p-value	0.29	0.4	0.19	0.57	0.15	0.93		
Postop. 1st month								
Group 1	2.41±2.51+	0.63±0.63+	28.1±5.73+	13.75±2.83+	22±19.52+	1.16±0.77+	2 (1.6%)	2 (1.6%)
Group 2	2.32±2.7+	0.59±0.69+	28.22±5.23+	13.6±2.68+	20.52±19.93+	1.08±0.81+	2 (1.7%)	1 (0.8%)
p-value	0.39	0.45	0.82	0.7	0.84	0.35	1	1
Postop. 6th month								
Group 1	1.55±1.81+	0.38±0.5+	35.43±3.66+	18.1±3.23+	7.06±12.7+	0.91±0.52+	0 (0%)	0 (0%)
Group 2	1.32±1.71+	0.36±0.5+	35.07±3.74+	17.77±2.33+	7.13±13.92+	0.86±0.51+	0 (0%)	0 (0%)
p-value	0.3	0.69	0.56	0.33	1	0.44	N/A	N/A

IPSS: International Prostate Symptom Score, QoL: Quality of Life, Qmax: Maximum urinary flow rate (mL/s), Qave: Average urinary flow rate (mL/s), PVR: Postvoiding residual volume (mL), PSA: Prostate specific antigen(ng/mL), SUI: Stress urinary incontinence, UUI: Urge urinary incontinence, Statistically analyzed with Wilcoxon and Mann-Whitney U test; *Others analyzed with Fisher's Exact test, + p<0.001 compared to baseline

Table 4. Intra- and postoperative complications according to the modified Clavien-Dindo classification and managements

	Group 1	Group 2	p	Management
Intraoperative complications				
Hematuria required prolonged irrigation	3	1	0.62	Blood transfusion and irrigation (G3a)
Capsular perforation	1	1	1	Longer catheterization (G1)
Superficial bladder mucosal injury	1	0	1	Longer catheterization (G1)
Postoperative complications				
UTI*	3	2	0.7	Intravenous antibiotic (G2)
Clot evacuation using urethral catheter	2	1	1	Irrigation (G3a)
Clot evacuation with cystoscopy	0	0	NA	
Re-catheterization	1	0	1	3 days with antiinflamatory drug (G3a)
Bladder neck contracture	1	1	1	Bladder neck laser incision (G3b)
Urethal stricture	1	1	1	Internal urethrotomy (G3b)
Meatal stenosis	1	0	1	Meatoplasty (G3b)

*Statistically analyzed with Pearson chi-square test; others analyzed with Fisher's Exact test

we found that there was no operation-related disadvantage in the patient group requiring AC/AP in terms of intraoperative and postoperative complications. There was no significant difference in complications between the two groups. In terms of bleeding complications, although the rate of blood transfusion and clot formation was higher in the group requiring AC/AP, there was no significant difference between the groups.

HoLEP has less perioperative blood loss and lower transfusion rates compared with TURP and open prostatectomy (OP) (8,15,16). This can be explained by the nature of the Ho:YAG laser: The holmium laser has a penetration depth of 0.4 mm in the prostate tissue, and the heat dissipation allows simultaneous coagulation of small and medium vessels up to 2-3 mm deep, resulting in excellent hemostasis (16). This allows the surgeon to control bleeding during this procedure (17). Furthermore, Holmium laser has a unique wavelength and energy density to achieve hemostasis. This effect can be adjusted by reducing the energy pulse or increasing the distance from the tip of the laser to the target tissue (8). Additionally, Holmium laser has a wavelength of 2140 nm, it is strongly absorbed by water and cell fluids (1,13,14). The high water content of the prostatic tissue, resulting in excellent thermal conductivity, enables the Holmium laser to coagulate and ablate the tissue (13).

Although hemostasis is achieved with a Holmium laser, bleeding may occur during the operation and in the postoperative period of HoLEP surgery. In previous studies, the hemoglobin drop after HoLEP was found in the range of 0.8-1.67 g/dL (18-21). El Tayeb et al. (22) compared 116 patients requiring AC/AP and 1558 patients non-recieving AC/AP who underwent HoLEP for BPO. In the study, no significant difference was observed between the two groups in terms of postoperative lowest hemoglobin levels and transfusion rates (3.5% vs. 1.6%, p=0.128). Similarly, in our study, there was no significant difference in Hb drop between patients who received and did not receive AC/AP (0.13±0.1 g/dL vs. 0.08±0.15 g/dL, respectively; p=0.21).

Adverse reactions to blood product transfusions are rare and often associated with significant morbidity and mortality (23,24). Transfusion also has metabolic complications such as citrate toxicity, hyperkalemia, and hypothermia (23). Low blood transfusion rates after HoLEP surgery can be considered one of the most important advantages of HoLEP surgery. Elzayat et al. (25) compared patients who received HoLEP while anticoagulating with warfarin or low-molecular-weight heparin, and those who received HoLEP after stopping anticoagulant therapy. Perioperative transfusion rates of 14.2% and 14.7% were found in patients on continued anticoagulant and low-molecular-weight heparin therapy. The transfusion rate was reported as 3% in patients whose treatment was stopped. In another study, Tyson and Lerner (26) reported no transfusions in the first 76 patients who underwent HoLEP and continued anticoagulation therapy with a mean INR of 1.5. In a meta-analysis, it was found that patients who received HoLEP had a lower blood transfusion rate (OR 0.21, 95% CI 0.10-0.45, p<0.0001) in those who did not receive antithrombotic therapy (27). Consistent with the literature, in our study, blood transfusion rate was 2.3% in the group requiring AC/AP and 0.8% in the group not receiving AC/AP, and there was no significant difference between the groups in terms of blood transfusion (p=0.62).

Study Limitations

This study has some limitations. Firstly, its design is retrospective and the follow-up period was short and the number of patients included in the study is relatively small. Secondly, we stopped AC/AP treatment before surgery, there was no continuous use. As is known, AC/AP drugs significantly increase the tendency to bleed. In this respect, the use of these drugs causes concern in surgeons in clinical practice, even if they are discontinued. we stopped these drugs 5-10 days before surgery in accordance with consultation with cardiologists/hematologists and heparinized patients up to 12 h before surgery if necessary. Of course, the discontinuation of these drugs reduces the bleeding tendency during and after surgery. However, we believe that they do not have the same bleeding profile as patients who have never used these drugs. Furthermore, the discontinuation of these drugs (if possible) before any kind of surgery is essential for both patient safety and surgeon comfort. Thirdly, we evaluated the urinary continence status only in the postoperative period and urinary incontinence was not quantified; we assessed urinary continence according to the ICS definition of incontinence. Lastly, we also did not stratify patients according to the types of AC/AP they were treated with.

Conclusion

HoLEP is a safe and effective, minimally invasive surgical method that improves functional parameters in BPO patients requiring AC/AP, with low bleeding complications and transfusion rates.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained. [Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) - date/approval number: 2021/21-38].

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Authorship Contributions

Surgical and Medical Practices: E.G., L.T., Concept: M.Y., O.A., K.Y.Y., E.G., L.T., Design: M.Y., O.A., H.Ç.A., E.G., L.T., Data Collection

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References

1. Vincent MW, Gilling PJ. HoLEP has come of age. World J Urol 2015;33:487-493.
2. Larner TR, Agarwal D, Costello AJ. Day-case holmium laser enucleation of the prostate for gland volumes of < 60 mL: early experience. BJU Int 2003;91:61-64.
3. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984;132:474-479.
4. Egan KB. The Epidemiology of Benign Prostatic Hyperplasia Associated with Lower Urinary Tract Symptoms: Prevalence and Incident Rates. Urol Clin North Am 2016;43:289-297.
5. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-2375.
6. Gacci M, Corona G, Sebastianelli A, Serni S, De Nunzio C, Maggi M, Vignozzi L, Novara G, McVary KT, Kaplan SA, Gravas S, Chapple C. Male Lower Urinary Tract Symptoms and Cardiovascular Events: A Systematic Review and Meta-analysis. Eur Urol 2016;70:788-796.
7. Jin S, Liu Z, Liu Y, Wu J, Yu Q. Analysis of Risk Factors and Nursing Strategies for Postoperative Hemorrhage of Benign Prostatic Hyperplasia. Evid Based Complement Alternat Med 2022;2022:4205015.
8. Martin AD, Nunez RN, Humphreys MR. Bleeding after holmium laser enucleation of the prostate: lessons learned the hard way. BJU Int 2011;107:433-437.
9. Bozzini G, Maltagliati M, Besana U, Berti L, Calori A, Sighinolfi MC, Micali S, Roche JB, Gozen A, Mueller A, Pushkar D, Liatsikos E, Boldini M, Buizza C, Rocco B. Holmium laser enucleation of the prostate with Virtual Basket mode: faster and better control on bleeding. BMC Urol 2021;21:28.
10. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37-49.
11. Mamoulakis C, Efthimiou I, Kazoulis S, Christoulakis I, Sofras F. The modified Clavien classification system: a standardized platform for reporting complications in transurethral resection of the prostate. World J Urol 2011;29:205-210.
12. Tunc L, Yalcin S, Kaya E, Gazel E, Yılmaz S, Aybal HC, Yılmaz M, Tokas T. The "Omega Sign": a novel HoLEP technique that improves continence outcomes after enucleation. World J Urol 2021;39:135-141.
13. Nair SM, Pimentel MA, Gilling PJ. A Review of Laser Treatment for Symptomatic BPH (Benign Prostatic Hyperplasia). Curr Urol Rep 2016;17:45.
14. Rieken M, Ebinger Mundorff N, Bonkat G, Wyler S, Bachmann A. Complications of laser prostatectomy: a review of recent data. World J Urol 2010;28:53-62.
15. Jhanwar A, Sinha RJ, Bansal A, Prakash G, Singh K, Singh V. Outcomes of transurethral resection and holmium laser enucleation in more than 60 g of prostate: A prospective randomized study. Urol Ann 2017;9:45-50.
16. Yin L, Teng J, Huang CJ, Zhang X, Xu D. Holmium laser enucleation of the prostate versus transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. J Endourol 2013;27:604-611.
17. Selim A, Nottingham CU, York NE, Dauw CA, Borofsky MS, Boris RS, Lingeman JE. Holmium laser enucleation of the prostate in Jehovah's Witness patients. Int Urol Nephrol 2020;52:455-460.
18. Elmansy HM, Kotb A, Elhilali MM. Holmium laser enucleation of the prostate: long-term durability of clinical outcomes and complication rates during 10 years of followup. J Urol 2011;186:1972-1976.
19. Elzayat EA, Habib EI, Elhilali MM. Holmium laser enucleation of the prostate: a size-independent new "gold standard". Urology 2005;66:108-113.
20. Placer J, Gelabert-Mas A, Vallmanya F, Manresa JM, Menéndez V, Cortadellas R, Arango O. Holmium laser enucleation of prostate: outcome and complications of self-taught learning curve. Urology 2009;73:1042-1048.
21. Shah HN, Mahajan AP, Hegde SS, Bansal MB. Peri-operative complications of holmium laser enucleation of the prostate: experience in the first 280 patients, and a review of literature. BJU Int 2007;100:94-101.
22. El Tayeb MM, Jacob JM, Bhojani N, Bammerlin E, Lingeman JE. Holmium Laser Enucleation of the Prostate in Patients Requiring Anticoagulation. J Endourol 2016;30:805-809.
23. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. Anesth Analg 2009;108:759-769.
24. Osterman JL, Arora S. Blood Product Transfusions and Reactions. Emerg Med Clin North Am 2017;31:1159-1170.
25. Elzayat E, Habib E, Elhilali M. Holmium laser enucleation of the prostate in patients on anticoagulant therapy or with bleeding disorders. J Urol 2006;175:1428-1432.
26. Tyson MD, Lerner LB. Safety of holmium laser enucleation of the prostate in anticoagulated patients. J Endourol 2009;23:1343-1346.
27. Zheng X, Peng L, Cao D, Han X, Xu H, Yang L, Ai J, Wei Q. Holmium laser enucleation of the prostate in benign prostate hyperplasia patients with or without oral antithrombotic drugs: a meta-analysis. Int Urol Nephrol 2019;51:2127-2136.

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Correlation of the Proximal Urethra Diameter in Voiding Cystourethrography with the Severity of the Disease, Vesicoureteral Reflux and the Uroflowmetry Parameters in Children with Voiding Dysfunction

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

The voiding dysfunction is a commonly encountered problem in children. If the patient has a history of urinary tract infection presenting with fever, a voiding cystourethrography is frequently utilized. Bladder wall irregularity, elongated bladder, widened bladder neck, and dilatation of proximal urethra can be detected in voiding cystourethrography scans of the children with voiding dysfunction. There are studies in the literature that have assessed the correlation between the dilatation of proximal urethra and voiding dysfunction. In our study, in addition to the existing literature, we analyzed the relationship between proximal urethra diameter determined in voiding cystourethrography of children with voiding dysfunction, the severity of the disease, the presence of reflux, and uroflowmetry parameters. We found that in the group with the high proximal urethra diameter, dysfunctional voiding incontinence scoring was observed to be high. However, a negative correlation was determined between high proximal urethra diameter and vesicoureteral reflux. There was no correlation between the uroflowmetry parameters, post-voiding residual urine volume and proximal urethra diameter.

Abstract

Objective: Voiding dysfunction is a commonly encountered problem in children. If a patient has a history of urinary tract infection (UTI) and presents with fever, voiding cystourethrography (VCUG) is frequently used. Proximal urethra dilatation in VCUG was determined to be an indication of voiding dysfunction. Studies in literature have been the ones assessing the correlation between the presence of proximal urethra dilatation and voiding dysfunction. In our study, however, we analyzed the relationship between the proximal urethra diameter determined in VCUG of children with voiding dysfunction, the severity of the disease, the presence of reflux, and uroflowmetry parameters.

Materials and Methods: Of the 522 VCUG-received patients 96 between the ages of 6-8 with voiding dysfunction concomitant with febrile UTI were evaluated. Dysfunctional voiding incontinence scoring (DVIS), uroflowmetry parameters, post-void residual measurements (PVR), proximal urethra diameter noted in VCUG, and presence of reflux in the patients were analysed.

Results: The mean age was 7.2±0.66. The average proximal urethra diameter was 7.6±1.8 mm. Regarding the diameter, the patients were divided into two groups: Group 1 (7.6 mm and below) and group 2 (above 7.6 mm). DVIS was higher but vesicoureteral reflux (VUR) was lower in group 2 (p=0.017, p=0.008; respectively). For uroflowmetry parameters and PVR, no significant differences were noted.

Conclusion: In the group with the high-proximal urethra diameter, DVIS was observed to be high. However, a negative correlation was determined between high-proximal urethra diameter and VUR.

Keywords: Proximal urethra diameter, VUR, uroflowmetry, dysfunctional voiding, VCUG

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Introduction

In children, voiding dysfunction (VD) is also called bladder dysfunction, and it indicates the anomalies in the filling or emptying functions of the urinary bladder (1). The International Children's Continence Society (ICCS) stated that VD should be considered in neurologically normal children aged five and above (2). VD is a frequently encountered clinical entity and is more common in girls (3).

The main symptoms of VD can be listed as urgency, frequency, daytime, and nighttime urinary incontinence. It can be diagnosed by detailed history, physical examination, voiding diary, and non-invasive methods, including urinalysis, urinary bladder ultrasound (US), and uroflowmetry (3,4).

However, voiding cystourethrography (VCUG) is performed if US findings suggest a urinary system anomaly or there is a history of recurrent urinary tract infection (UTI) (4). Bladder wall irregularity, elongated bladder, widened the bladder neck, and dilatation of proximal urethra can be detected in the VCUG scans of the children with VD (5).

Before the 1990s, proximal urethra dilatation was not considered a finding consistent with VD, especially in males without a posterior urethral valve, Prune Belly syndrome, urethral stricture, or a tumor. However, in 1992, Hausegger et al. (6) defined proximal urethral dilatation determined by VCUG as an essential finding of lower urinary tract dysfunction.

In subsequent studies, overt dilatation of the proximal urethra during voiding was termed as spinning top urethra (7). Spinning top urethra is caused by the discoordination between the external urethral sphincter and detrusor muscle, and this condition is associated with vesicoureteral reflux (VUR), UTI, and VD.

In the literature, several studies have assessed the relationship between proximal urethral dilatation and VD (6,7). Our study evaluated the relationship between proximal urethral diameter (PUD) determined in VCUG, uroflowmetry findings, the severity of VD, and the presence of VUR in children with VD.

Materials and Methods

This study was approved by the Ethical Review Committee of Muğla Sıtkı Koçman University (approval number: 180079). Data of the pediatric patients diagnosed with VD and who underwent VCUG during diagnostic management at our center between January 2016 and December 2020 were retrospectively reviewed. Patients with complete data without a congenital urinary tract anomaly or neurological disorder and those without occult spinal dysraphism or a history of urological surgery were included. Since patient age can affect the PUD, only patients aged between 6 and 8 were selected. Patients without urine culture, urinary US, post-voiding residual (PVR) urine volume assessment, uroflowmetry results, and a filled dysfunctional voiding and incontinence scoring system (DVIS) form were excluded. Children with monosymptomatic nocturnal enuresis were also omitted.

Data including demographic characteristics, DVIS scores, uroflowmetry results, flow pattern, PVR measured by the US, PUD measured during VCUG, and presence or absence of VUR was recorded to a database. The study population was divided into two groups based on PUD: Patients who had PUD of ≤7.6 mm were assigned to group 1, while those with PUD of >7.6 mm were included in group 2.

The DVIS scores were determined by reviewing the DVIS form completed by the children's parents or caregivers. In patients who underwent uroflowmetry testing twice or three times, mean values were calculated for each parameter. The uroflowmetry flow patterns (bell, staccato, tower, interrupted, or plateau) were identified on the basis of ICCS guidelines (2). The PVR measurements were performed by the US immediately after uroflowmetry. The mean PVR value was calculated for patients whose PVR was measured multiple times.

The same pediatric urologist performed the VCUG tests without sedation or anesthesia. Firstly, a spot X-ray was taken before the administration of the contrast medium. Subsequently, X-rays were taken during the filling and the voiding phases. The images were stored in the picture archiving and communication system (PACS). The largest PUD was measured on these anterior-posterior images in both genders, and the VUR grade was determined in patients with VUR (Figure 1).

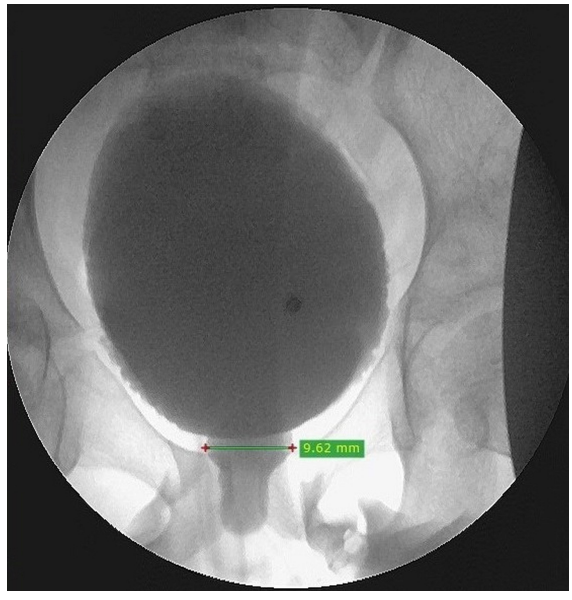

Figure 1. The measurement of proximal urethral dilatation in the voiding cystourethrography image

Statistical Analysis

The Statistical Package for Social Sciences software (SPSS for Windows, v22, IBM Corp., Armonk, NY, US) was used for all statistical analyses. Descriptive statistics were used to assess the basic characteristics. Continuous variables were expressed as mean ± standard deviations. The Student's t-test was used for comparing the groups. Categorical variables were expressed as numbers and percentages, and the chi-square test was used for comparisons between groups. Univariate and multivariate logistic regression analyses were performed to determine the predictive factors for VUR. All tests were two-sided, and the p-value was considered significant when it was less than 0.05.

Results

Our review revealed that 522 children underwent VCUG during diagnostic management of VD at our center during the study period. Among these patients, 96 were aged between 6 and 8. Six of these patients were excluded because of incomplete data, three were omitted due to monosymptomatic nocturnal enuresis, two were not included due to congenital urinary tract anomaly, and one was excluded due to the presence of a neurological disorder. Eighty-four patients who met the inclusion criteria were included.

The mean age of the patients (n=84) was 7.2±0.66 [minimum (min): 6-maximum (max): 8] years. Among these patients, 48 (57.1%) were girls, while 36 (42.9%) were boys. The mean PUD was 7.6±1.8 (min: 4-max: 12) mm. There were 40 (47.6%) patients in group 1, while group 2 consisted of 44 (52.4%) patients. There was no significant difference between the groups regarding gender distribution (p=0.705). There were more female patients than male patients in both groups. The mean DVIS score was significantly higher in group 2 than in group 1 (17.4±5.9 vs. 13.9±7.19; p=0.017). The overall rate of VUR was 31% in the entire cohort (n=26). Our comparative analysis revealed that the rate of VUR was significantly higher in group 1 than in group 2 (45% vs. 18.2%; p=0.008). The mean voided urine volume, max flow rate, and PVR was similar between the two groups (p=0.236, p=0.381, p=0.460, respectively). No significant difference between the groups was noted regarding the flow pattern (p=0.09). However, staccato and tower type flow patterns were encountered at higher rates in group 2 without reaching the level of significance (Table 1).

The univariate analysis elucidated that the VUR rate was negatively correlated with PUD; the rate of VUR was higher in patients with relatively shorter PUDs with an adjusted odds ratio (AOR) of 0.61 [AOR 95% confidence interval (CI): 0.61 (0.43-0.86), p=0.005]. Multivariate analysis confirmed the negative correlation between these two parameters (i.e., PUD and VUR) [AOR (95% CI): 0.36 (0.21-0.59), p=0.001]. These analyses also showed that female gender and DVIS scores were associated with the presence of VUR [AOR (95% CI): 4.33 (1.09-17.2), p=0.03, and AOR (95% CI): 1.46 (1.12-1.65), p=0.002)] (Table 2).

Discussion

The VD is widely ascribed to poor voiding habits, the etiology of proximal urethral dilatation -a common finding in these patients- has not been fully clarified yet. However, it was

Table 1. Comparison of the parameters between the two groups

	Group 1* n=40 (47.6%)	**Group 2* n=44 (52.4%)**	**p-value**
Gender			
Boy (n, %)	18 (45%)	18 (40%)	0.705
Girl (n, %)	22 (55%)	26 (60%)	
DVIS	13.9±7.19	17.4±5.9	**0.017**
VUR+ (n, %)	18 (45%)	8 (18.2%)	**0.008**
Mean Q_{max} (mL/sec ± SD)	16.1±6.34	17.3±6.02	0.381
Mean voided volume (mL ± SD)	192±80.3	213±80.3	0.236
Flow pattern			
Staccato (n, %)	9 (22.5%)	14 (31.8%)	0.090
Tower (n, %)	9 (22.5%)	15 (36.1%)	
Interrupted (n, %)	6 (15%)	8 (18.2%)	
Bell (n, %)	15 (37.5%)	5 (11.4%)	
Plateau (n, %)	1 (2.5%)	3 (4.5%)	
Mean PVR (mL ± SD)	16.4±14.5	17.3±12.8	0.460

*Group 1: Proximal urethral diameter ≤7.6 mm, Group 2: Proximal urethral diameter >7.6 mm, SD: Standard deviation, PVR: Post-void residual measurements, DVIS: Dysfunctional voiding incontinence scoring, VUR: Vesicoureteral reflux

Table 2. Univariate and multivariate analyses of potential prognostic factors for vesicoureteral reflux

Parameters OR (95% CI)		Univariate		Multivariate	
		p-value	OR (95% CI)	p-value	
Proximal urethral diameter (mm)	≤**7.6** >**7.6**	Ref. 0.61 (0.43-0.86)	**0.005**	Ref. 0.36 (0.21-0.59)	**0.001**
Gender	**Male** **Female**	Ref. 4.33 (1.09-17.2)	**0.03**	Ref. 1.35 (0.82-8.3)	0.12
Dysfunctional voiding score		1.46 (1.12-1.65)	**0.002**	1.12 (0.94-1.36)	0.08

OR: Odds ratio, CI: Confidence interval

postulated that, in these children, the voluntary contractions during voiding led to the contraction of the distal urethral sphincter and a subsequent pressure increase in the proximal urethra. The increased pressure, which persists until the relaxation of the external urethral sphincter relaxes, also affects the proximal urethra. At this stage, the proximal urethra starts to dilate for compliance. This dilatation appears as an infundibular-shaped tube in VCUG (Figure 1) (7-9).

It was reported that PUD is more common in girls than in boys (7,9). Urethral sphincters are looser in girls than in boys. Besides, the bladder neck's anatomical features in males also contribute to the difference in the proximal urethral dilatation rates between male and female children (9). In line with these data, among the patients with VD who underwent VCUG, proximal urethral dilatation was encountered 6-fold more frequently in girls than in boys (7,9). As such, in our study, there were more girls than boys in both groups. This finding was more prominent in group 2 than group 1. However, no significant difference was detected between the groups concerning gender distribution (p=0.705). These findings may be due to the small patient number in our study.

It was previously reported that urgency (87.3%), frequency (81.8%), daytime incontinence (76.3%), and enuresis (47.2%) were the most frequently encountered symptoms in patients with VD, and there was a significant correlation between the presence of these symptoms, VD and proximal urethra dilatation (4). In some other studies, it was noted that the most common symptom was urgency, and it was present in 52-87% patients with VD (3,10). These studies also reported that daytime and nighttime incontinence could be detected in up to 77% of these patients. We use the DVIS system defined by Akbal et al. (11) for scoring the VD. Our comparative analysis revealed that the mean DVIS score was significantly higher in group 2 (i.e., patients with relatively higher PUD) than in group 1 (i.e., patients with relatively lower PUD) (p=0.0017). We also found that PUD and DVIS scores (i.e., the severity of disease) were correlated with each other.

UTI and VUR can accompany VD (11). High intravesical pressure in patients with VD leads to ischemia in the bladder mucosa. Both ischemia and the urine returning to the bladder from the urethral meatus and transferring bacteria to the bladder increase UTI risk (12). It has been demonstrated that high intravesical pressures in patients with VD amplify the risk of VUR and its severity (6). It was reported that in patients with VUR and overactive bladder, gradually increasing pressure resulting from the resistance of the pelvic floor and external urethral sphincter to the involuntary contractions increases the risk of renal damage (6). In a study including 121 patients, Kibar et al. (7) determined that the rate of VUR was 81% in patients diagnosed with spinning top urethra. In another study, it was reported that 12.7% of the patients with VD had VUR by VCUG (4). However, the rate of VUR in patients with proximal urethral dilatation was not analyzed.

Our study found a negative correlation between the PUD and VUR by univariate and multivariate analyses. These analyses also showed that VUR was more frequently encountered in girls with high DVIS. We postulate that an increase in the PUD and urethral compliance reduces both the intravesical pressure and intramural pressure in the urinary bladder. Besides, an insufficient increase in PUD can lead to a rise in bladder pressure and the risk of VUR.

Staccato and tower type flow patterns detected in uroflowmetry tests are considered to be diagnostic of VD (3). In our study, there was no association between PUD and voiding patterns. However, staccato and tower patterns were detected more frequently in group 2.

It was reported that the mean PVR was significantly higher in patients with VD and proximal urethral dilatation than in healthy persons (13). In our study, there was no difference between the two groups regarding mean PVR (p=0.46). The difference between the PUDs did not lead to a significant difference between the groups regarding flow patterns and PVR.

The ideal method for diagnosing VD is urodynamic testing (5). However, some parameters obtained by VCUG can reduce the number of patients undergoing this invasive procedure. Kakizaki et al. (5) reported that an inner external urethral sphincter diameter of less than 3 mm measured during the voiding phase of VCUG indicated detrusor-sphincter incoordination. They stated that urodynamic testing was necessary for these patients.

This study has set a cut-off value using the data obtained from VCUGs performed in children without VD. They also showed that in 96% children with normal voiding, the external urethral sphincter's inner diameter was determined to be 3 mm and above in VCUG (5).

In our study, we did not determine a cut-off value for PUD to indicate VD. This limitation was because it was a retrospective study, and it was not appropriate from an ethical perspective to perform VCUG in healthy children to measure PUD. Besides, only children aged between 6 and 8 were included in our study.

Some studies showed that the possibility of urodynamically diagnosed overactive bladder was relatively high in children who had symptoms of VD and VCUG findings were consistent with trabeculation, spinning top urethra, and the low bladder capacity in the urinary US (4,14). These studies reached an actual diagnosis without performing invasive urodynamic tests.

Conclusion

The determination of age-specific cut-off values for PUD in VCUG by prospective studies can open up new perspectives for assessing children with VD. We suggest that the utilization of parameters including PUD, bladder wall thickness, bladder capacity, symptom scores, and uroflowmetric parameters can reduce the need for performing invasive urodynamic procedures to diagnose VD.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Ethical Committee of Muğla Sıtkı Koçman University (approval number: 180079).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: H.T., İ.A., S.C.K., N.C., H.Ş., Concept: H.T., İ.A., Design: H.T., İ.A., Data Collection or Processing: S.C.K., N.C., H.Ş., Analysis or Interpretation: H.T., İ.A., Literature Search: S.C.K., N.C., H.Ş., Writing: H.T., İ.A.

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References

1. Farhat W, Bägli DJ, Capolicchio G, O'Reilly S, Merguerian PA, Khoury A, McLorie GA. The dysfunctional voiding scoring system: Quantitative standardization of dysfunctional voiding symptoms in children. J Urol 2000;164:1011-1105.
2. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, Rittig S, Walle JV, von Gontard A, Wright A, Yang SS, Nevéus T. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn 2016;35:471-481.
3. Feldman AS, Bauer SB. Diagnosis and management of dysfunctional voiding. Curr Opin Pediatr 2006;18:139-147.
4. Ichim G, Fufezan O, Farcău M, Asăvoaie C, Pop D, Staticescu S, Nanulescu MV. Clinical, imaging and cystometric findings of voiding dysfunction in children. Med Ultrason 2011;13:277-82.
5. Kakizaki H, Moriya K, Ameda K, Shibata T, Tanaka H, Koyanagi T. Diameter of the external urethral sphincter as a predictor of detrusor-sphincter incoordination in children: comparative study of voiding cystourethrography. J Urol 2003;169:655-658.
6. Hausegger KA, Fotter R, Sorantin E, Schmidt P. Urethral morphology and bladder instability. Pediatr Radiol 1991;21:278-280.
7. Kibar Y, Demir E, Irkilata C, Ors O, Gok F, Dayanc M. Effect of Biofeedback Treatment on Spinning Top Urethra in Children with Voiding Dysfunction. Urology 2007;70:781-784.
8. Tanıdır Y, Şekerci ÇA, Top T, Talibzade F, Şahan A, Şener TE, Tarcan T, Şimşek F, Akbal C. Utility of Voiding Dysfunction Symptom Score in Diagnosis and Treatment of Enuresis Nocturna. J Urol Surg 2017;4:8-12.
9. Saxton HM, Borzyskowski M, Robinson LB. Nonobstructive posterior urethral widening (spinning top urethra) in boys with bladder instability. Radiology 1992;182:81-85.
10. Hellerstein S, Linebarger JS. Voiding dysfunction in pediatric patients. Clin Pediatr (Phila) 2003;42:43-49.
11. Akbal C, Genc Y, Burgu B, Ozden E, Tekgul S. Dysfunctional voiding and incontinence scoring system: Quantitative evaluation of incontinence symptoms in pediatric population. J Urol 2005;173:969-973.
12. De Paepe H, Hoebeke P, Renson C, Van Laecke E, Raes A, Van Hoecke E, Daele JV. Pelvic-floor therapy in girls with recurrent urinary tract infections and dysfunctional voiding. Br J Urol 1998;81:109-113.
13. Kutlu O, Koksal IT, Guntekin E, Kukul E. Role of spinning top urethra in dysfunctional voiding. Scand J Urol Nephrol 2010;44:32-37.
14. Ramamurthy HR, Kanitkar M. Non invasive urodynamic assessment in children-are they reliable? validation of non-invasive urodynamics in children with functional voiding disorders. Indian J Pediatr 2010;77:1400-1404.

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Assessment of Cardiac Functions and Subclinical Cardiovascular Risk in Children with Urolithiasis: A Pilot Study

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

The incidence of urolithiasis is increasing globally. Chronic inflammation is associated with subclinical atherosclerosis. Subclinical atherosclerosis, in addition to early systolic and diastolic dysfunction, is observed in children with urolithiasis.

Abstract

Objective: Information on cardiovascular problems related to childhood urinary stone disease is limited. The aim of this study was to assess the ventricular functions and subclinical cardiovascular risk in children with urolithiasis using echocardiographic measurements.

Materials and Methods: Children diagnosed with urolithiasis were prospectively enrolled in the study as well as children with no urinary stone disease were confirmed via urinary ultrasonography. Body mass index and blood pressures were noted, as well as basic serum parameters. Carotid intima media thickness (cIMT), epicardial fat tissue (EFT) thickness and periaortic fat tissue (PFT) thickness were measured via transthoracic echocardiography in addition to pulsed and tissue Doppler imaging. Myocardial performance indexes were also calculated and correlation analyses were conducted.

Results: A total of 17 patients (10 boys) with a mean age of 8.57±2.62 years were included in this study. There were 17 children (12 boys) in the control group and their mean age was 9.53±1.72 years. There was no statistically significant difference between the two groups in terms of demographic and laboratory variables. Tissue Doppler echocardiography revealed that Tei indexes of the left ventricle, right ventricle and septum were significantly higher in the study group than in the controls ($p<0.001$ for all). The cIMT (0.041±0.012 vs. 0.025±0.002), EFT (0.432±0.083 vs. 0.325±0.032) and PFT thicknesses (0.138±0.029 vs. 0.113±0.008) of the study group was statistically higher than the control group ($p<0.001$, $p<0.001$ and $p=0.002$, respectively) indicating a higher CVD risk.

Conclusion: Children with urolithiasis had not only biventricular early systolic and diastolic dysfunction but also subclinical atherosclerosis at early ages. Cardiovascular complications should be considered in the follow-up and treatment of children with urolithiasis.

Keywords: Urolithiasis, subclinical atherosclerosis, cardiovascular risk, children

Introduction

Urolithiasis is a global disease with increasing prevalence recently and it causes significant morbidity for all ages. In the USA, 11% of men and 7% of women are diagnosed with urinary stone disease throughout their lives (1). Further, recurrences may be observed in 30% to 50% of the cases in 5-10 years after the first stone incidence (2). On the other hand, chronic inflammation is an independent factor for subclinical atherosclerosis and thus, cardiovascular complications. It was shown that inflammatory cytokines play a role in the progression of atherosclerosis (3). Studies in the adult population indicated that urolithiasis is related to chronic systemic inflammation such as hypertension, diabetes and metabolic syndrome. Also, it has been demonstrated

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that myocardial infarction, stroke and coronary artery disease are more commonly found in patients with urinary stone disease (4). A recent study that looked into adolescents with urolithiasis reported increased levels of urinary cytokines that mention the presence of chronic inflammation (5).

Furthermore, studies showed oxidative stress and inflammation induces Randall's plaque, which is the initial step in stone formation (6). In CARDIA study, researchers revealed a positive correlation between urolithiasis and subclinical atherosclerosis in young adults (7). To date, a single study investigated atherosclerosis and cardiovascular complications in children which showed Carotid intima media thickness (cIMT) that is a sign of subclinical atherosclerosis was increased in children with nephrolithiasis this study (8).

In current practice, cIMT is used as a marker to identify subclinical atherosclerosis and epicardial fat tissue (EFT) thickness and periaortic fat tissue (PFT) thickness. Several researchers demonstrated the use of these markers of subclinical atherosclerosis in different chronic diseases in the pediatric population (9,10). The aim of this initial prospective case-control study was to assess the risk of subclinical cardiovascular risk in children with urolithiasis using cIMT, EFT and PFT thickness in addition to tissue Doppler imaging (TDI) echocardiographic evaluation of cardiac functions. Our hypothesis was children with urolithiasis would show signs of systemic inflammation in terms of echocardiographic assessments.

Materials and Methods

Patients

After obtaining by the Institutional Reviewer Board of Konya Chamber of Commerce University (number: 419011325-050.99), patients were prospectively included for this study between December 2019 and May 2020. Patients >5 years of age and had kidney stones (>3 mm) that were confirmed by two consecutive ultrasonographic images or computed tomography and those had normal serum chemistry were included in the study. Those with congenital heart disease, chronic kidney disease, inflammatory bowel disease, monogenic stone phenotypes, urogenital malformations (vesicoureteral reflux, posterior urethral valves, neuropathic bladder etc.), obesity, hypertension, chronic diseases (i.e., diabetes mellitus) and patients who were passive smokers were excluded. The control group consisted of health children who have normal BMI and blood pressure (adjusted for age) with no known history of urolithiasis (confirmed by urinary ultrasonography). All parents gave informed consent for inclusion.

Blood pressures were measured from the left arm using age-appropriate manual sphygmomanometer cuffs after 5 min of resting and a mean of 3 measurements were noted. All blood samples including urea, creatinine, glucose, uric acid, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) were obtained a.m. after 8 h of fasting. Glomerular Filtration Rate (GFR) was calculated by Schwartz formula (11). Echocardiographic measurements were performed as previously described (12).

Statistical Analysis

The compatibility of numerical variables to normal distribution was examined using the Shapiro-Wilk test. Descriptive findings were presented as number, percentage mean and standard deviation. Comparisons between groups were made using chi-square test for categorical variables, and t-test for independent groups if assumptions were met for numerical variables, otherwise by Mann-Whitney U test. Statistical significance level was set as $p<0.05$.

Results

A total of 17 patients, 10 boys and 7 girls (41% and 59%), were enrolled in the study. Mean age of the study group was 8.57±2.62 years (range years). Eleven (64.7%) of the patients in the study group had a positive family history for urolithiasis, 10 (58.8%) had multiple stones, 6 (35.3%) had bilateral stones. Mean stone size was 8.6±4.3 mm and mean follow-up period was 16.2±9.3 months. In terms of metabolic abnormality, 7 (41.2%) had hypocitraturia, 4 (23.5%) had hypercalciuria, 2 (11.8%) had hyperoxaluria, while no abnormalities were detected in 4 (23.5%). At the time of enrollment, 8 (47.1%) children were on medical treatment (in the form of oral potassium citrate), 4 (23.5%) and 5 (29.4%) have undergone Extracorporeal Shock Wave Lithotripsy and surgical treatment (3 ureterorenoscopic intervention, 2 percutaneous nephrolithotomy), respectively. There were 12 boys and 5 girls (71% and 29%) in the control group with a mean age of 9.53±1.72 years. There was no significant difference between the two groups in terms of age, gender, blood pressure, BMI, serum lipids, hemoglobin and GFR (Table 1).

There was no statistical difference between the M-mode echocardiography, LVM and LVMI results of the study and control groups (Table 2). Pulsed Doppler echocardiographic evaluation revealed that; LV ejection time (261.71±21.09 vs. 279.59±28.51, p=0.046) was significantly shorter in the study group. Additionally, while LV MPI (0.283±0.27 vs. 0.166±0.07, p=0.013) was significantly higher in the study group, the tricuspid valve E/A ratio (1.13±0.24 vs. 1.29±0.19, p=0.026) was statistically lower for the same group (Table 3).

Tissue Doppler echocardiography measurements revealed that; mitral valve lateral annulus e' (11.34±2.08 vs. 16.23±3.16,

Table 1. Demographic and laboratory data of study population			
	Patients (n=17)	Controls (n=17)	p
Age (years)	8.57±2.62	9.53±1.72	0.214
Gender (male/female)	10/7	12/5	0.473
BMI (kg/m²)	16.09±2.83	16.50±2.01	0.592
BMI Z-score	0.09±1.43	-0.28±0.81	0.391
SBP (mmHg)	98.82±8.58	98.24±8.09	0.865
DBP (mmHg)	63.37±6.17	64.71±6.29	0.423
Glucose (mg/dL)	93.94±12.94	95.41±7.99	0.693
eGFR (mL/min/1.73 m²)	91.03±10.82	92.94±9.06	0.586
Uric acid (mg/dL)	3.98±0.78	3.89±0.62	0.702
Total cholesterol (mg/dL)	160.55±44.82	152.71±24.98	0.539
Triglyceride (mg/dL)	102.17±74.95	81.35±24.47	0.287
LDL-C (mg/dL)	93.03±37.56	83.75±26.96	0.596
HDL-C (mg/dL)	52.61±13.61	47.53±9.72	0.249
Hemoglobin (g/dL)	13.04±0.74	13.19±0.78	0.562
CRP (mg/dL)	2.46±1.31	2.31±1.53	0.436

Data are expressed mean ± standard deviation. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, eGFR: Estimated glomerular filtration rate, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, CRP: C-reactive protein

Table 2. M-mode echocardiographic measurements in patients with urolithiasis and control groups			
	Patients (n=17)	Controls (n=17)	p
	Mean ± SD	Mean ± SD	
IVSd (cm)	0.69±0.18	0.67±0.14	0.838
IVSs (cm)	1.09±0.22	1.10±0.20	0.876
LVPWd (cm)	0.71±0.10	0.64±0.18	0.180
LVPWs (cm)	1.12±0.21	1.17±0.21	0.342
LVEdD (cm)	3.79±0.39	3.82±0.36	0.121
LVEsD (cm)	2.21±0.26	2.28±0.27	0.350
EF (%)	72.98±3.44	72.86±10.54	0.23
FS (%)	41.26±3.19	39.45±3.59	0.130
LVM (gr)	66.18±29.26	70.57±24.44	0.322
LVMI (g/m$^{2.7}$)	32.59±12.14	29.85±4.95	0.433

IVSd: Interventricular septum diastolic thickness, IVSs: Interventricular septum systolic thickness, LVPWd: Left ventricular posterior wall diastolic thickness, LVPWs: Left ventricular posterior wall systolic thickness, LVEdD: Left ventricular end-diastolic dimension, LVEsD: Left ventricular end-systolic dimension, EF: Ejection fraction, FS: Fractional shortening, LVM: Left ventricular mass, LVMI: Left ventricular mass index

p<0.001), a' (7.07±1.11 vs. 8.49±2.14, p=0.021), tricuspid valve lateral annulus e' (11.67±1.66 vs. 13.56±1.94, p=0.005), interventricular septum e' (9.26±1.69 vs. 13.46±2.34, p<0.001) and a' velocities (5.39±0.89 vs. 6.43±1.17, p=0.007) were significantly decreased in the study group than in controls (Table 4). However, time intervals including IVCT (isovolumic contraction time) measured from tricuspid valve lateral annulus (53.12±8.43 vs. 47.06±6.49, p=0.025) and interventricular septum (53.53±6.86 vs. 47.41±7.63, p=0.020), IVRT (isovolumic relaxation time) measured from tricuspid lateral annulus (58.41±8.91 vs. 51.88±8.40, p=0.035) and interventricular septum (55.47±6.77 vs. 47.41±8.64, p=0.005) were statistically increased in children with urolithiasis. Additionally, mitral valve lateral annulus contraction time (CT) (184.94±43.09 vs. 259.53±16.46, p<0.001), tricuspid valve lateral annulus CT (199.53±37.22 vs. 254.82±11.63, p<0.001) and interventricular septum CT (187.29±54.56 vs. 259.88±16.77, p<0.001) were significantly lower in the urolithiasis group. Also, e'/a' ratios measured from mitral valve lateral annulus and interventricular septum were statistically lower in patients with urolithiasis (p=0.018 and 0.005, respectively). E/e' ratios measured from

Table 3. Pulsed Doppler echocardiographic measurements in patients with urolithiasis and control groups			
	Patients (n=17)	Controls (n=17)	p
	Mean ± SD	Mean ± SD	
Mitral valve blood flow			
Peak E (cm/s)	89.56±16.12	84.84±12.86	0.352
Peak A (cm/s)	60.51±15.95	59.52±10.94	0.834
E/A ratio	1.56±0.49	1.45±0.23	0.838
Tricuspid valve blood flow			
Peak E (cm/s)	61.21±10.41	62.29±7.45	0.322
Peak A (cm/s)	55.62±12.22	48.56±6.82	0.140
E/A ratio	1.13±0.24	1.29±0.19	**0.026**
LV ejection time (ms)	261.71±21.09	279.59±28.51	**0.046**
RV ejection time (ms)	263.76±24.89	271.29±19.66	0.341
LV MPI	0.283±0.27	0.166±0.07	0.013
RV MPI	0.231±0.24	0.166±0.08	0.658

Early (E) and late (A) mitral/tricuspid diastolic velocities, LV: Left ventricle, RV: Right ventricle, MPI: Myocardial performance index, SD: Standard deviation

LV was increased in the study group (p<0.001). Furthermore, Tei indexes of LV, RV and septum were significantly higher in urolithiasis patients than in controls (Table 4).

The cIMT (0.041±0.012 vs. 0.025±0.002), EFT (0.432±0.083 vs. 0.325±0.032) and PFT thickness (0.138±0.029 vs. 0.113±0.008) of the study group was statistically higher than the control group (p<0.001, p<0.001 and p=0.002, respectively) (Table 5). Post hoc power analysis for each variable was determined by taking at least 80% and Type-I error as 5%.

Discussion

Besides urinary tract obstruction and related renal damage, urolithiasis may also release inflammatory cytokines due to crystal storage and this has been associated with cardiovascular complications (13,14). Clinical and experimental studies have shown that there is a strong relationship between crystal adhesion and crystal formation in renal tubular cells and inflammation and oxidative stress (6,15). Taguchi et al. (16) demonstrated genes related to oxidative stress and stated that proinflammatory conditions were highly expressed in calcium oxalate stone formers than normal renal papillary tissue (16). Same group further demonstrated that M1 macrophages (inflammatory) stimulated renal calcium oxalate crystal deposition and M2 macrophages (anti-inflammatory) limited such crystal formation in a murine model of hyperoxaluria (14).

Clinically, cIMT is used as a reliable marker in the evaluation of atherosclerotic change in the early period. In some studies that evaluated the progression of atherosclerosis, a strong relationship has been reported between cIMT and IL-6 (17). cIMT was reported to show subclinical atherosclerosis in different chronic diseases of childhood (9). The only study in the literature in which cIMT was evaluated in children with urolithiasis, Kusumi et al. (5) found that cIMT was significantly higher in children aged 12-17 years and reported that urine osteopontin and fibronectin-1could predict elevated cIMT. Similarly, in our study, cIMT was significantly higher in children with urolithiasis than in the control group, and this shows subclinical atherosclerosis in patients with pediatric urolithiasis. However, mean age of our study group was lower than those included in their study. Thus, it can be suggested that subclinical atherosclerosis begins at an even earlier age in children with urolithiasis.

Body fat distribution is an important cardiovascular risk factor, and fat depositions are associated with all-cause deaths. One component of the abnormal body fat depot, called ectopic fat, is the accumulation of adipose tissue around organs and vessels. Ectopic adipose tissue, unlike subcutaneous adipose tissue, is not an ordinary place for lipid storage (18). Epicardial and periaortic adipose tissue, like other adipose tissues, has endocrine functions that can produce inflammatory cytokines and secrete hormones. Moreover, they have been recently identified as strong risk factors for cardiovascular disease due to their role in the inflammatory process in atherosclerosis (18,19). It was reported that EFT is a reliable parameter for cardiovascular risk in adult chronic kidney disease and EFT thickness can predict coronary artery disease (20). In obese children, an increase in EFT thickness was associated with coronary artery disease, magnified cIMT and arterial stiffness (21). Studies also showed that in non-obese children with neurological disabilities, EFT thickness was significantly higher and correlated with clinical and metabolic risk factors (22). Akyurek et al. (10) evaluated the relationship between PFT thickness and cardiovascular risk in 135 children with type-1 DM and they showed a positive

correlation between PFT thickness and cIMT and metabolic risk factors (10). In our study, EFT and PFT thicknesses were significantly higher in children with urolithiasis.

It is known that E/e' ratio shows the strongest correlation with LV/RV diastolic filling pressure and LV/RV compliance (23), whereas E/A and e'/a' ratio correlates with relaxation type dysfunction (24). Limited data from the children with chronic kidney diseases revealed that left ventricular E/A and e'/a' ratio decreases and E/e' ratio increases along with the worsening of renal functions from mild-moderate to severe renal failure (25).

Table 4. Tissue Doppler echocardiographic measurements in patients with urolithiasis and control groups

	Patients (n=17)	Controls (n=17)	p
	Mean ± SD	Mean ± SD	
Mitral valve lateral annulus			
e' (cm/s)	11.34±2.08	16.23±3.16	**<0.001**
a' (cm/s)	7.07±1.11	8.49±2.14	**0.021**
s' (cm/s)	11.04±3.48	9.55±3.07	0.205
IVCT (ms)	55.64±8.87	50.35±11.94	0.152
IVRT (ms)	57.00±12.91	50.18±7.80	0.071
CT (ms)	184.94±43.09	259.53±16.46	**<0.001**
e'/a' ratio	1.62±0.29	1.99±0.54	**0.018**
E/e' ratio	8.22±2.47	5.38±1.14	**<0.001**
Tricuspid valve lateral annulus			
e' (cm/s)	11.67±1.66	13.56±1.94	**0.005**
a' (cm/s)	9.18±2.19	9.43±1.37	0.690
s' (cm/s)	11.56±2.79	13.09±1.95	0.074
IVCT (ms)	53.12±8.43	47.06±6.49	**0.025**
IVRT (ms)	58.41±8.91	51.88±8.40	**0.035**
CT (ms)	199.53±37.22	254.82±11.63	**<0.001**
e'/a' ratio	1.32±0.26	1.46±0.26	0.136
E/e' ratio	5.14±1.59	4.68±0.91	0.314
Interventricular septum			
e' (cm/s)	9.26±1.69	13.46±2.34	**<0.001**
a' (cm/s)	5.39±0.89	6.43±1.17	**0.007**
s' (cm/s)	8.19±2.44	8.29±1.22	0.866
IVCT (ms)	53.53±6.86	47.41±7.63	**0.020**
IVRT (ms)	55.47±6.77	47.41±8.64	**0.005**
CT (ms)	187.29±54.56	259.88±16.77	**<0.001**
e'/a' ratio	1.74±0.36	2.13±0.39	**0.005**
LV Tei index	0.642±0.195	0.362±0.102	**<0.001**
RV Tei index	0.581±0.144	0.393±0.047	**<0.001**
Septum Tei index	0.639±0.229	0.366±0.049	**<0.001**

e': Peak early diastolic myocardial velocities, a': Peak atrial systolic myocardial velocities.
s': Peak systolic myocardial velocities, IVCT: Isovolumetric contraction time, IVRT: Isovolumetric relaxation time, CT: Contraction time, LV: Left ventricle, RV: Right ventricle

Table 5. cIMT, EFT and PFT thickness measurements in patients with urolithiasis and control groups

	Patients (n=17)	Controls (n=17)	p
	Mean ± SD	Mean ± SD	
cIMT (cm)	0.041±0.012	0.025±0.002	**<0.001**
EFT thickness (cm)	0.432±0.083	0.325± 0.032	**<0.001**
PFT thickness (cm)	0.138±0.029	0.113± 0.008	**0.002**

cIMT: Carotid intima-media thickness, EFT: Epicardial fat tissue, PFT: Periaortic fat tissue

However, Celik et al. (26) reported decreased E/A and increased e'/a' ratio in non-obese-treated hypertensive patients. These studies revealed the dysfunction of LV relaxation and diastolic filling pressures, however, right ventricular functions were not studied and possibly RV dysfunction was underestimated. In this context, our study revealed that the E/A ratio measured from RV and e'/a' ratio measured from LV were significantly lower in children with urolithiasis compared with healthy controls (p=0.026 and p=0.018, respectively). Additionally, E/e' ratio measured from LV was detected to be increased in the patient group. This finding suggests that LV function and diastolic filling pressures are worsened in children with urolithiasis.

Subsequently, MPI or Tei index is a good predictor of ventricular systolic functions in children and adults (27). MPI measured by PWD, M-mode and TDI methods are valuable parameters indicating systolic and parameters show worsening of these functions. The results from Celik et al. (26) showed that left ventricular MPI was higher in non-obese-treated hypertensive children, but no significance was achieved. However, in our study MPI values of LV was significantly higher in patients (p=0.013) while no statistical significance was shown in right ventricular MPI. Besides, both Tei index values of LV, RV and septum were significantly increased in the study group than in the controls (in all p<0.001). By this way, we demonstrated a significant reduction of systolic and diastolic functions of LV and RV in children with urolithiasis compared to healthy children.

Study Limitations

The main limitation of our study was the limited number of patients. Also, inflammatory cytokines have not been studied in patients, which is unfortunately, beyond the scope of our facility. However, extensive echocardiographic investigation was performed for both the study and the control group performed in this prospective study.

Conclusion

LV and RV early systolic and diastolic dysfunction, with subclinical atherosclerosis, were detected in children with urolithiasis in early ages. Cardiovascular complications should be considered in the follow-up and treatment of these patients, and the pediatric urolithiasis patients deserve further studies in terms of cardiovascular risks. Longitudinal studies with long-term follow-up will enlighten the adulthood consequences of these findings.

Ethics

Ethics Committee Approval: The approval of the research protocol by the Institutional Reviewer Board of Konya Chamber of Commerce University (number: 419011325-050.99).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.M.E., H.A., M.İ.D., Concept: A.M.E., H.A., M.İ.D., Design: A.M.E., H.A., M.İ.D., Data Collection or Processing: A.M.E., H.A., M.İ.D., Analysis or Interpretation: A.M.E., H.A., M.İ.D., Literature Search: A.M.E., H.A., M.İ.D., Writing: A.M.E., H.A., M.İ.D.

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References

1. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol 2012;62:160-165.
2. Johnson CM, Wilson DM, O'Fallon WM, Malek RS, Kurland LT. Renal stone epidemiology: a 25-year study in Rochester, Minnesota. Kidney Int 1979;16:624-631.
3. Moreira DM, da Silva RL, Vieira JL, Fattah T, Lueneberg ME, Gottschall CA. Role of vascular inflammation in coronary artery disease: potential of anti-inflammatory drugs in the prevention of atherothrombosis. Inflammation and anti-inflammatory drugs in coronary artery disease. Am J Cardiovasc Drugs 2015;15:1-11.
4. Hsi RS, Spieker AJ, Stoller ML, Jacobs DR Jr, Reiner AP, McClelland RL, Kahn AJ, Chi T, Szklo M, Sorensen MD. Coronary Artery Calcium Score and Association with Recurrent Nephrolithiasis: The Multi-Ethnic Study of Atherosclerosis. J Urol 2016;195:971-976.
5. Kusumi K, Ketz J, Saxena V, Spencer JD, Safadi F, Schwaderer A. Adolescents with urinary stones have elevated urine levels of inflammatory mediators. Urolithiasis 2019;47:461-466.
6. Khan SR. Reactive oxygen species as the molecular modulators of calcium oxalate kidney stone formation: evidence from clinical and experimental investigations. J Urol 2013;189:803-811.
7. Reiner AP, Kahn A, Eisner BH, Pletcher MJ, Sadetsky N, Williams OD, Polak JF, Jacobs DR Jr, Stoller ML. Kidney stones and subclinical atherosclerosis in young adults: the CARDIA study. J Urol 2011;185:920-925.
8. Kusumi K, Smith S, Barr-Beare E, Saxena V, Schober MS, Moore-Clingenpeel M, Schwaderer AL. Pediatric Origins of Nephrolithiasis-Associated Atherosclerosis. J Pediatr 2015;167:1074-1080.e2.
9. Bakkaloglu SA, Saygili A, Sever L, Noyan A, Akman S, Ekim M, Aksu N, Doganay B, Yildiz N, Duzova A, Soylu A, Alpay H, Sonmez F, Civilibal M, Erdem S, Kardelen F. Assessment of cardiovascular risk in paediatric peritoneal dialysis patients: a Turkish Pediatric Peritoneal Dialysis Study Group (TUPEPD) report. Nephrol Dial Transplant 2009;24:3525-3532.
10. Akyurek N, Atabek ME, Eklioglu BS, Alp H. Evaluation of the relationship between cardiovascular risk factors and periaortic fat thickness in children with type 1 diabetes mellitus. Diabetes & Metabolism 2015;41:338-341.
11. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629-637.

12. Elmacı AM, Alp H, Dönmez Mİ. Evaluation of subclinical cardiovascular risk and cardiac function in children with vesicoureteral reflux: a prospective study. Cardiol Young 2022;32:1222-1228.
13. Kim SY, Bang WJ, Min C, Choi HG. Association of nephrolithiasis with the risk of cardiovascular diseases: a longitudinal follow-up study using a national health screening cohort. BMJ Open 2020;10:e040034.
14. Taguchi K, Okada A, Hamamoto S, Unno R, Moritoki Y, Ando R, Mizuno K, Tozawa K, Kohri K, Yasui T. M1/M2-macrophage phenotypes regulate renal calcium oxalate crystal development. Scientific Reports 2016;6:35167.
15. Kovacevic L, Lu H, Caruso JA, Kovacevic N, Lakshmanan Y. Urinary proteomics reveals association between pediatric nephrolithiasis and cardiovascular disease. Int Urol Nephrol 2018;50:1949-1954.
16. Taguchi K, Hamamoto S, Okada A, Unno R, Kamisawa H, Naiki T, Ando R, Mizuno K, Kawai N, Tozawa K, Kohri K, Yasui T. Genome-Wide Gene Expression Profiling of Randall's Plaques in Calcium Oxalate Stone Formers. J Am Soc Nephrol 2017;28:333-347.
17. Okazaki S, Sakaguchi M, Miwa K, Furukado S, Yamagami H, Yagita Y, Mochizuki H, Kitagawa K. Association of interleukin-6 with the progression of carotid atherosclerosis: a 9-year follow-up study. Stroke 2014;45:2924-2929.
18. Djaberi R, Schuijf JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. Am J Cardiol 2008;102:1602-1607.
19. Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends Endocrinol Metab 2011;22:450-457.
20. Aeddula NR, Cheungpasitporn W, Thongprayoon C, Pathireddy S. Epicardial Adipose Tissue and Renal Disease. J Clin Med 2019;8:299.
21. Manco M, Morandi A, Marigliano M, Rigotti F, Manfredi R, Maffeis C. Epicardial fat, abdominal adiposity and insulin resistance in obese pre-pubertal and early pubertal children. Atherosclerosis 2013;226:490-495.
22. Calcaterra V, Cena H, Casali PM, Iacobellis G, Albertini R, De Amici M, de Silvestri A, Comparato C, Pelizzo G. Epicardial Fat Thickness in Non-Obese Neurologically Impaired Children: Association with Unfavorable Cardiometabolic Risk Profile. Ann Nutr Metab 2018;72:96-103.
23. Harada K, Tamura M, Yasuoka K, Toyono M. A comparison of tissue Doppler imaging and velocities of transmitral flow in children with elevated left ventricular preload. Cardiol Young 2001;11:261-268.
24. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, Lai WW, Geva T. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010;23:465-495; quiz 576-7.
25. Doyon A, Haas P, Erdem S, Ranchin B, Kassai B, Mencarelli F, Lugani F, Harambat J, Matteucci MC, Chinali M, Habbig S, Zaloszyc A, Testa S, Vidal E, Gimpel C, Azukaitis K, Kovacevic A, Querfeld U, Schaefer F. Impaired Systolic and Diastolic Left Ventricular Function in Children with Chronic Kidney Disease - Results from the 4C Study. Sci Rep 2019;9:11462.
26. Celik SF, Karakurt C, Tabel Y, Elmas T, Yologlu S. Blood pressure is normal, but is the heart? Pediatr Nephrol 2018;33:1585-1591.
27. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol 1995;26:135-6.

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The Efficacy and Safety of Retrograde Intrarenal Surgery: A Multi-Center Experience of the RIRSearch Group Study

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

Retrograde intrarenal surgery (RIRS) is a reliable surgical method for the treatment of urinary system stone disease. This study evaluated the effectiveness and safety of RIRS considering more than 1000 cases based on multi-center experience. The size of the stone, stone location and surgical experience could affect the success rate. Although most consequences are mild and rare, there could nevertheless be serious, life-threatening complications.

Abstract

Objective: We reported the results of retrograde intrarenal surgeries (RIRS) according to multi-center experience and to assess the efficacy and safety of this procedure.

Materials and Methods: A total of 1067 patients to whom RIRS operations were performed between 2016 and 2021 were included in the study. The demographic and clinical features of patients, stone properties, per-operative, and post-operative results were analyzed retrospectively. Additionally, the success and complication rates of RIRS according to the clinical and demographic properties of the patients were analyzed.

Results: The mean age, stone volume, operation time, and hospitalization time were 46.8±15.4, 1011 mm^3 (min 19 mm^3- max 12.483 mm^3), 67.4±30.8 min, and 1.83±2.3 days, respectively. The stone-free (success) rate after RIRS was 74.5%. In multivariate analysis, pre-op pyuria, number of stones, and stone volume had a significant effect on success. There were 251 (23.5%) patients with post-operative complications. The most common complications were hematuria, fever, and urinary tract infections; they comprised 86.8% of all complications. The number of stones, pre-op ESL, and absence of pre-operative DJ stent had a significant effect on complications in multivariate analysis.

Conclusion: Retrograde intrarenal surgery is an efficient minimal invasive procedure for treating urinary system stone disease with low morbidity and high success rates. Although the complication rates are mostly insignificant, there may also be severe vital complications.

Keywords: Urinary system stone disease, retrograde intrarenal surgery, success rates, complication

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Introduction

Urinary system stone disease (USSD) is one of the most common urological diseases with a worldwide prevalence ranging between 2% and 20% (1-3). It is also a prevalent disease in our country with a reported prevalence rate of 11.1% (4). Extracorporeal shock wave lithotripsy (ESL), percutaneous nephrolithotomy (PNL), mini percutaneous nephrolithotomy, micropercutaneous nephrolithotomy, retrograde intrarenal surgery (RIRS), laparoscopic stone surgery, and open stone surgery are the treatment opportunities for USSD (5,6). With the technological advancements in endoscopic systems, minimally invasive procedures replaced open surgical procedures. A flexible ureteroscope was one of these innovations that enabled the clinician to reach the intrarenal system through the ureters in a retrograde fashion.

During the last 2 decades, RIRS had a significant role for treating USSD with its high efficiency and safety. The urologic guidelines recommended this technique as an alternative to the first-line treatment option for upper urinary tract stones smaller than 2 cm (7,8). Even some studies have showed that this technique might be used effectively in USSD larger than 2 cm (9). Retrograde intrarenal surgery was also shown to be effective and safe in patients with a solitary kidney, pregnant patients, obese patients, and patients with renal anomalies (10,11). However, RIRS is not a complication-free surgery and may also have some significant complications. For this reason, it is important to evaluate the efficiency and safety of RIRS by the data obtained from high-volume centers.

In this study, we aimed to report the multi-center experience of RIRS and evaluate the efficiency and safety of this surgery.

Materials and Methods

The study was designed according to the Declaration of Helsinki principles and was approved by the Tekirdağ Namık Kemal University Ethics Committee (no: 2020.114.05.15). The patients who underwent RIRS for treating USSD between 2017-2021 in 7 referral centers were retrospectively included in the study. Patients younger than 18 years old were excluded from the study. The demographic and clinical characteristics of the patients, including age, gender, body mass index, presence of preoperative DJ stent, anatomic abnormalities, age-adjusted Charlson Comorbidity index (CCI), preoperative serum creatinine level, presence of preoperative hematuria - pyuria, preoperative urine culture, the usage of anticoagulants, preoperative hydronephrosis, operation time, surgical side, stone volume, stone density, stone location, perioperative and postoperative complications, hospitalization time, and stone-free status were noted. All patients had the evaluation of urinalysis, urine culture, serum creatinine level, and non-contrast abdominopelvic tomography before the surgery. The 3-dimensional sizes of the stones were used to determine the stone volume by using the formula: AxBxCx0.524 (12). The sum of each stone volume was used to calculate the total stone volume for the patients with multiple stones. Pre-operative hematuria is defined as the presence of 3 or more erythrocytes (≥3 RBC) per high power field and pre-operative pyuria is defined as >10 white blood cell per high-power field on a urine microscopy evaluation. The patients who had positive urine cultures were treated according to the antibiogram, and the surgery was performed under sterile urine. All patients received second-generation cephalosporins for antibiotic prophylaxis before the surgery. To evaluate the stone-free status of the patients, non-contrast abdominal pelvic tomography was performed in the post-operative 4th week of the surgery. The success of the surgery was defined as the presence of stone-free patients after the surgery, and the patients with residual stone <4 mm were defined as stone-free patients.

The surgical procedure was performed by an experienced surgeon (>50 cases). The surgery started with standard cystoscopy and retrograde pyelography evaluation. Under direct vision and fluoroscopy guidance, a 0.035-inch safety guidewire (Sensor®, Boston Scientific, Marlborough, MA, USA) was introduced to the system. To visualize the ureter and perform active dilatation, a semirigid ureteroscopy was performed. After the semirigid ureteroscopy, a 10-12 Fr. ureteral access sheath (Bi-Flex™, Rocamed, Monaco) was inserted over the guidewire and placed just 1 cm below the ureteropelvic junction or just distal to the upper ureteral stone. For the patients in whom the insertion of the ureteral access sheath (UAS) was impossible, the back-loading technique was used. In this approach, a flexible ureteroscope was directly inserted into the system via the glide wire without UAS. If this was also impossible, the surgery was finished by the insertion of a Double J (DJ) stent and was postponed for 2 weeks. On the other hand, DJ stent insertion was also applied for patients, especially those with colic pain and urinary tract infection in whom diversion was required pre-operatively. In our study design, there is no stone burden limit for the back-loading approach. The bladder was drained by a 10 Fr. feeding tube during the procedure. The flexible ureteroscope (Storz Flex X^2, Germany) was inserted through the UAS and a holmium: YAG laser with a 272 µm laser fiber was used to fragment the stones. Constant gravity-based irrigation was used with a height of 50 cm above the patient, and a hand pumping system was used if necessary. The laser energy and pulse frequency were varied based on the stone burden, stone density, and the surgeon's preference. Stone fragments >2 mm were extracted using a nitinol basket catheter (Dakota®, Boston Scientific, Marlborough, MA, USA). A 4.7Fr DJ stent was inserted into the urinary system and left in place for 2-4 weeks according to the surgeon's preference.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages (%). Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). The Shapiro-Wilk test was used to assess the normality assumption for the continuous variables. The differences in proportions between the groups were compared using chi-square or Fisher Exact tests as appropriate. The Student's t-test was used to compare continuous variables in two independent groups. Odds ratios [95% confidence intervals (CI)] of the independent clinical parameters were calculated using univariate and multiple logistic regression models to predict the outcome variables: Success and total complications. A multivariate logistic regression analysis was built by performing a stepwise variable selection on those variables with a univariate p-value <0.25. The Hosmer and Lemeshow test was computed to detect the goodness of fit in the multiple logistic regression models, and a nonsignificant p-value indicated a good fit. All statistical analyses were conducted using SPSS 19.0 for Windows Version 19.0 software (IBM Corp., Armonk, NY, USA). All p-values of less than 0.05 were considered to indicate statistical significance.

Results

A total of 1.067 patients were included in the study. The mean age of the patients was 46.8±15.4 years. There were 429 (40.2%) female and 638 (59.8%) male patients with a female: male ratio of 1:1.48. The clinical and demographic properties of the patients are given in Table 1. There were 509 (47.7%) patients with right-sided, 500 (46.9%) patients with left-sided and 58

Table 1. Demographic and clinical properties of study population

Parameter	Value
Age (years)	46.8±15.4
Gender	
Male (%)	638 (59.8%)
Female (%)	429 (40.2%)
Surgical side	
Right (%)	509 (47.7%)
Left (%)	500 (46.9%)
Bilateral (%)	58 (5.4%)
Body mass index (kg/m^2)	26.9±3.5
Preoperative ESL	
No (%)	737 (69.1%)
Yes (%)	330 (30.9%)
Preoperative DJ stent	
No (%)	729 (68.3%)
Yes (%)	338 (31.7%)
Age adjusted CCI	1.57±1.62
Preoperative creatinine (mg/dL)	0.95±0.37
Preoperative pyuria	
No (%)	449 (42.1%)
Yes (%)	618 (57.9%)
Preoperative hematuria	
No (%)	299 (28.0%)
Yes (%)	768 (72.0%)
Anticoagulant usage	
No (%)	953 (89.3%)
Yes (%)	114 (10.7%)
Preoperative urine culture	
Negative (%)	981 (91.9%)
Positive (%)	86 (8.1%)
Stone location	
Upper calyx	37 (3.5%)
Middle calyx	56 (5.2%)
Lower calyx	120 (11.2%)
Pelvis	237 (22.2%)
Upper ureter	243 (22.8%)
Multicalyx	374 (35.1%)
Stone density (HU)	956±326
Number of stones	1.63±1.20
Stone volume (mm^3)	1011.2±1977.7
Multiple stone	
No (%)	624 (58.5%)
Yes (%)	443 (41.5%)
Preoperative hydronephrosis	
No (%)	618 (57.9%)
Yes (%)	449 (42.1%)
Operation time (min)	67.4±30.8
Hospitalisation time (day)	1.83±2.30
Peroperative complication	
No (%)	972 (91.1%)
Yes (%)	95 (8.9%)
Postoperative complication	
No (%)	816 (76.5%)
Yes (%)	252 (23.5%)
Postoperative creatinine (mg/dL)	0.93±0.68
Stone-free status	
No (%)	272 (25.5%)
Yes (%)	795 (74.5%)

ESL: Extracorporeal shock wave lithotripsy, CCI: Charlson Comorbidity index, DJ: Double J, HU: Hounsfield unit

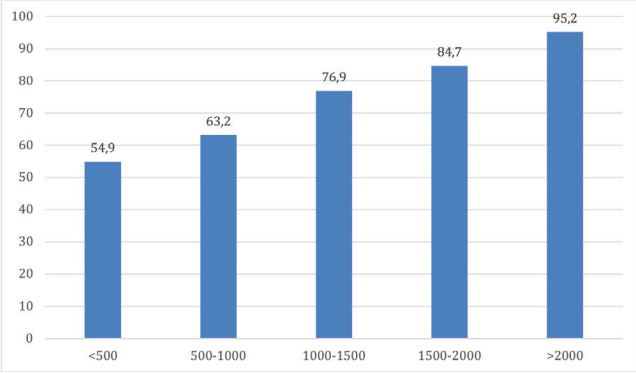

Figure 1. Retrograde intrarenal surgery operation time (minute) according to the stone volume (mm^3)

(5.4%) patients with bilateral RIRS. According to the presence of a kidney anomaly, there were 61(5.7%) patients with a solitary kidney, 25 (2.3%) patients with horseshoe kidney, 7 (0.7%) patients with a double collecting system, and 7 (0.7%) patients with malrotated kidney. In the preoperative evaluation, 981 (91.9%) patients had sterile urine, whereas 86 (8.1%) patients had positive cultures and the most common microorganisms were *E. coli* and *Enterococci*. The mean hospitalization time was 1.83±2.30 days. The mean operation time was 67.4±30.8 min ranging between 20-180 min. The operation times according to the stone volumes are shown in Figure 1. It was observed that the operation time increased significantly as the stone volume increased (p<0.001).

The stone-free rate of the study population was 74.5%. When we evaluated the patients according to surgical succes, the surgical side, age-adjusted CCI, the presence of preoperative pyuria, presence of preoperative hematuria, stone location, Modified Seoul National University Renal Stone Complexity (RESC) score, stone density, the number of stones, stone volume, presence of multiple stones, and operation time were significantly different between the groups (Table 2). The mean age-adjusted CCI was 1.75±1.53 in patients with unsuccessful surgery whereas it was 1.47±1.61 at patients with successful surgery (p=0.003). The presence of preoperative pyuria and hematuria was significantly higher in patients with unsuccessful surgery. The odd's ratios for preoperative pyuria and hematuria were 0.348 (95% CI: 0.252-0.481) and 0.607 (95% CI: 0.422-0.873) respectively. The rate of lower calyx location and the presence of multicalyx stone were significantly higher in patients with unsuccessful surgery (p<0.001). The mean stone density and the mean stone volume were 1067.4±287.5 HU and 1922.4±2781.6 mm^3 in patients with unsuccessful surgery, which were significantly higher than the patients with successful surgery. A total of 338 (31.7%) patients had a DJ stent preoperatively. In this group, the ureteral access sheath was successfully inserted in all cases, except 11 (3.3%). On the other hand, the ureteral access sheath could not be inserted in 55 (7.5%) of 729 patients who did not have a DJ stent preoperatively (p=0.007).

There were 251 (23.5%) patients with postoperative complications. When we compared the study group according to the presence of complications, the surgical side, the presence of preoperative ESL, presence of DJ stent, age-adjusted CCI, preoperative culture, stone location, number of stones, presence of multiple stones, and the presence of preoperative hydronephrosis were significantly different between the groups (Table 3). The rate of the presence of preoperative DJ stent was 17.5% in patients with complications, whereas it was 36.1% in patients without complications (p<0.001). The odd's ratio for the preoperative DJ stent was 0,403 (95% CI: 0.281-0.578). The mean age-adjusted CCI was significantly higher in patients with postoperative complications (p=0.006). The preoperative urine culture was positive at 11.2% and 7.1% of patients with and without postoperative complications, respectively (p=0.039). The odd's ratio for preoperative urine culture was 1.742 (95% CI: 1.056-2.876). The rate of multicalyx stone location and the mean number of stones were significantly higher in patients with postoperative complications (p<0.001 for each). The presence of preoperative hydronephrosis was 47.8% in patients with postoperative complications, whereas it was 40.3% in patients without a complication (p=0.036). The odd's ratio for preoperative hydronephrosis was 1.152 (%95 CI: 0.859-1.546).

The most common complications were hematuria, fever, and urinary tract infection. These three complications compromised 86.8% of all complications (Table 4). When we classified the complications according to Clavien-Dindo classification, 96 (38.2%) patients had Clavien I, 125 (49.8%) patients had Clavien II, 17 (6.8%) patients had Clavien IIIb, 12 (4.8%) patients had Clavien IVa, and 1 (0.4%) patient had Clavien V complications (Table 4). The patient who had a Clavien V complication had a significantly rare complication. This patient had persistent fever, pancytopenia, and hepatosplenomegaly who was diagnosed with hemophagocytic syndrome. The patient died from multiorgan failure during the postoperative third week of the RIRS. The rate of Clavien < III complications was 88.0% and the rate of Clavien ≥ III complication was 12.0%. The main complications in Clavien ≥ III were stent migration and sepsis.

The univariate and multivariate analyzes for the success and complications of RIRS are shown in Table 5. In univariate analysis, bilaterality, age-adjusted CCI, pre-op pyuria, pre-op hematuria, stone location, RESC score, stone density, number of stones, and stone volume had a significant effect on success. In multivariate analysis, pre-op pyuria, number of stones, and stone volume had a significant effect on success. When we examined the univariate and multivariate analyzes for complications; bilaterality, pre-op ESL, absence of pre-op DJ stent, age-adjusted CCI, pre-op pyuria, stone location, RESC score, number of stone and stone

Table 2. Success rates of retrograde intrarenal surgery according to clinical and demographic properties of the patients				
	Success (+) (n=795)	**Success (-) (n=272)**	**Odd's ratio**	**p-value**
Age (years)	46.1±14.8	47.1±13.6		0.348
Gender				
Male (%)	465 (58.4%)	173 (66.6%)		0.078
Female (%)	330 (41.6%)	99 (33.4%)		
Surgical side				
Right (%)	382 (48.0%)	127 (46.7%)		**0.002**
Left (%)	359 (45.2%)	141 (51.8%)		
Bilateral (%)	54 (6.8%)	4 (1.5%)		
Body mass index (kg/m^2)	25.8±3.18	27.5±4.38		0.597
Preoperative ESL				
No (%)	548 (68.9%)	189 (69.5%)	1.126 (95% CI: 0.823-1.541)	0.864
Yes (%)	247 (31.1%)	83 (30.5%)		
Preoperative DJ stent				
No (%)	545 (68.6%)	184 (67.6%)	0.948 (95% CI: 0.697-1.288)	0.782
Yes (%)	250 (31.4%)	88 (32.4%)		
Age adjusted CCI	1.47±1.61	1.75±1.53		**0.003**
Preoperative creatinine (mg/dL)	0.94±0.32	0.99±0.51		0.187
Preoperative pyuria				
No (%)	380 (47.8%)	69 (25.4%)	0.348 (95% CI: 0.252-0.481)	**<0.001**
Yes (%)	415 (52.2%)	203 (74.6%)		
Preoperative hematuria				
No (%)	244 (30.7%)	55 (20.2%)	0.607 (95% CI: 0.422-0.873)	**0.007**
Yes (%)	551 (69.3%)	217 (79.8%)		
Anticoagulant usage				
No (%)	715 (89.9%)	238 (87.5%)	0.763 (95% CI: 0.487-1.196)	0.261
Yes (%)	80 (10.1%)	34 (12.5%)		
Preoperative urine culture				
Negative (%)	737 (92.7%)	244 (89.7%)	0.541 (95% CI: 0.316-0.926)	0.117
Positive (%)	58 (7.3%)	28 (10.3%)		
Stone location				
Upper calyx	21 (2.6%)	16 (5.9%)		**<0.001**
Middle calyx	47 (5.9%)	9 (3.3%)		
Lower calyx	76 (9.6%)	44 (16.2%)		
Pelvis	186 (23.9%)	51 (18.8%)		
Upper ureter	212 (26.7%)	31 (11.4%)		
Multicalyx	253 (31.8%)	121 (44.4%)		
RESC score	1.99±1.66	2.32±1.53		**<0.001**
Stone density (HU)	929.2±293.6	1067.4±287.5		**<0.001**
Number of stones	1.51±1.10	1.99±1.36		**<0.001**
Stone volume (mm^3)	727.5±1557.8	1922.4±2781.6		**0.011**
Multiple stone				
No (%)	500 (62.9%)	124 (45.6%)	0.423 (95% CI: 0.312-0.524)	**<0.001**
Yes (%)	295 (37.1%)	148 (54.4%)		
Preoperative hydronephrosis				
No (%)	464 (58.4%)	154 (56.6%)	0.993 (95% CI: 0.743-1.328)	0.614
Yes (%)	331 (41.6%)	118 (43.4%)		
Operation time	61.56±27.36	83.68±34.36		**0.001**

ESL: Extracorporeal shock wave lithotripsy, CCI: Charlson Comorbidity index, DJ: Double J, HU: Hounsfield unit, CI: Confidence interval

Table 3. Complication rates of retrograde intrarenal surgery according to clinical and demographic properties of the patients				
	Complication (+) (n=251)	**Complication (-) (n=816)**	**Odd's ratio**	**p-value**
Age (years)	45.5±14.7	47.3±15.7		0.043
Gender				
Male (%)	147 (58.6%)	491 (60.2%)	1.074 (95% CI: 0.801-1.440)	0.633
Female (%)	104 (41.4%)	325 (39.8%)		
Surgical side				
Right (%)	114 (45.4%)	395 (48.4%)		**<0.001**
Left (%)	111 (44.2%)	389 (47.7%)		
Bilateral (%)	26 (10.4%)	32 (3.9%)		
Body mass index (kg/m^2)	27.2±5.2	26.9±4.1		0.818
Preoperative ESL				
No (%)	200 (79.7%)	537 (65.8%)	0.507 (95% CI: 0.359-0.716)	**<0.001**
Yes (%)	51 (20.3%)	279 (34.2%)		
Preoperative DJ stent				
No (%)	207 (82.5%)	522 (63.9%)	0.403 (95% CI: 0.281-0.578)	**<0.001**
Yes (%)	44 (17.5%)	294 (36.1%)		
Age adjusted CCI	1.65±1.61	1.37±1.61		**0.006**
Preoperative creatinine (mg/dL)	0.95±0.3	0.95±0.4		0.930
Preoperative pyuria				
No (%)	112 (44.6%)	337 (41.3%)	0.628 (95% CI: 0.464-0.848)	0.351
Yes (%)	139 (55.4%)	479 (58.7%)		
Preoperative hematuria				
No (%)	67 (26.7%)	232 (28.4%)	1.021 (95% CI: 0.731-1.426)	0.592
Yes (%)	184 (73.3%)	584 (71.6%)		
Anticoagulant usage				
No (%)	227 (90.4%)	726 (89.0%)	0.828 (95% CI: 0.506-1.356)	0.453
Yes (%)	24 (9.6%)	90 (11.0%)		
Preoperative urine culture				
Negative (%)	223 (88.8%)	758 (92.9%)	1.742 (95% CI: 1.056-2.876)	**0.039**
Positive (%)	28 (11.2%)	58 (7.1%)		
Stone location				
Upper calyx	10 (4.0%)	27 (3.3%)		**<0.001**
Middle calyx	16 (6.4%)	40 (4.9%)		
Lower calyx	40 (15.9%)	80 (9.8%)		
Pelvis	41 (16.3%)	196 (24.0%)		
Upper ureter	36 (14.3%)	207 (25.4%)		
Multicalyx	108 (43.1%)	266 (32.6%)		
Stone density (HU)	1008.1±316.3	953.7±343.7		0.203
Number of stones	2.07±1.42	1.57±1.15		**<0.001**
Stone volume (mm^3)	1154.0±1840.7	838.6±1402.6		0.352
Multiple stone				
No (%)	109 (43.4%)	515 (63.1%)	2.118 (95% CI: 1.578-2.842)	**<0.001**
Yes (%)	142 (56.6%)	301 (36.9%)		
Preoperative hydronephrosis				
No (%)	131 (52.2%)	487 (59.7%)	1.152 (95% CI: 0.859-1.546)	**0.036**
Yes (%)	120 (47.8%)	329 (40.3%)		
Operation Time	70.94±36.78	69.22±29.67		0.815

ESL: Extracorporeal shock wave lithotripsy, CCI: Charlson Comorbidity index, DJ: Double J, HU: Hounsfield unit, CI: Confidence interval

Table 4. Complications after retrograde intrarenal surgery according to Clavien-Dindo classification								
	Clavien I	Clavien II	Clavien IIIa	Clavien IIIb	Clavien IVa	Clavien IVb	Clavien V	Total (%)
Hematuria (%)	72 (28.7)	20 (8.0)	-		-		-	92 (36.7)
Fever (%)	15 (5.9)	39 (15.5)						54 (21.4)
Urinary tract infection (%)	9 (3.6)	63 (25.1)						72 (28.7)
Stent migration (%)				12 (4.8)				12 (4.8)
Sepsis (%)		3 (1.2)			12 (4.8)			15 (6.0)
Ureteral perforation (%)				3 (1.2)				3 (1.2)
Bladder perforation (%)				2 (0.8)				2 (0.8)
Hemophagocyte syndrome (%)							1 (0.4)	1 (0.4)
Total (%)	96 (38.2)	125 (49.8)	-	17 (6.8)	12 (4.8)	-	1 (0.4)	251 (100)

volume had a significant effect on complications in univariate analysis. Pre-op ESL, absence of pre-op DJ stent, and number of stones had a significant effects on complications in multivariate analysis. When the surgical side was right as a reference side at univariate analysis, there was no difference between the right and left sides on success and complication rates. However, there was a statistical difference between bilateral RIRS both in success and complications (p=0.005 and p=0.003) (Table 5).

Discussion

Urinary System Stone Disease (USSD) is one of the most common diseases in the world. The prevalence rates ranged between 2% and 20% in different parts of the world. It has a significantly high rate of recurrence that has been reported to be 50% (13,14). In terms of prevalence and recurrence rates, USSD is a general health system problem. The success rate of stone surgery depends on many factors; such as stone size, stone localization, stone type, presence of kidney anomaly, presence of obesity, and presence of a skeletal anomaly. For this reason, it may not be easy to choose the most suitable option for treating USSD. In the last three decades, the treatment strategy of USSD significantly changed. With the evolution of new technologic materials, minimally invasive surgical techniques became the pioneer of the USSD treatment. In a recent study, Heers and Turney (15) evaluated the types of procedures that were performed for treating USSD in the United Kingdom between 2009 and 2015. In this study, they documented a decrease in the number of ESLs, while they observed a significant increase in the number of RIRS.

With the worldwide acceptance of RIRS, several studies have evaluated the efficacy and safety of this surgery. Although there are several studies with a high number of patients in the international literature, there are not so many high-volume studies in our country. This kind of study is important for our national data and might be a significant source for international literature. In a national study, Firdolaş et al. (16) reported the result of 598 RIRS and reported a 78% stone-free rate in their series. In another national study, Akcay et al. (17) reported the results of their 290 patients series and reported a stone-free rate as 80%. In our study, the stone-free rate was found to be 74.5%. The stone-free rate of our series was lower than the literature. This difference might be due to the high rate of patients in our series with multicalyx location (35.1%) and lower calyx (11.2%) localization. Additionally, it might be due to the different definitions of "stone-free" status. Another possible reason for this difference may be related to the timing of the control evaluation. The small size of stones may persist just after the surgery that may expulse spontaneously over time. This might lead to lower stone-free rates for the studies, which evaluate their patients just after the surgery. Another factor may be the way of radiological control evaluation. Some studies have evaluated their patients' stone-free status with ultrasonography (USG) or kidney ureter bladder (KUB) X-ray that had lower sensitivity and specificity for evaluating renal stones. Small stones might not be noticed by USG or KUB X-ray and the stone-free rates might be overestimated. The size and localization of the stones could also affect the stone-free rates. Evaluating different high-volume series and performing standardized meta-analyses may overcome these possible biases.

In our study, a multivariate analysis of the demographic and clinical characteristics of the patients documented that the number of stones, preoperative pyuria, and stone volume were the main indicators of RIRS success. In the literature, stone volume was found to be one of the main predictors that may affect the success of the stone-free situation similar to our findings (18-20). Sari et al. (18) observed that stone volume, opacity, and operation time were the main factors that could change considerably the success status of RIRS according to multivariate analysis. Another study showed that (≥15 mm stones), increasing age, presence of a concomitant ureteral stone, and the presence of intraoperative complications were the main predictor factors that may affect the stone-free status (19). We found that preoperative stenting did not affect the

Table 5. Success and complication of retrograde intrarenal surgery according to univariate and multivariate analysis

	Success								Complication							
	Univariate analysis				Multivariate analysis				Univariate analysis				Multivariate analysis			
	p-value	OR	95% CI for OR		p-value	OR	95% CI for OR		p-value	OR	95% CI for OR		p-value	OR	95% CI for OR	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Age	0.368	0.995	0.986	1.005					0.119	0.993	0.983	1.002				
Gender (male reference)	0.205	1.210	0.901	1.627					0.633	1.074	0.801	1.440				
Surgical side (right reference)																
Left	0.232	0.837	0.626	1.120					0.757	0.953	0.705	1.290				
Bilateral	0.005	4.487	1.591	12.657					0.003	2.338	1.336	4.091				
Body mass index	0.790	1.016	0.906	1.138					0.576	1.027	0.935	1.128				
Preop ESL	0.458	1.126	0.823	1.541					<0.001	0.507	0.359	0.716	0.001	0.526	0.365	0.756
Preop DJ stent	0.731	0.948	0.697	1.288					<0.001	0.403	0.281	0.578	<0.001	0.417	0.285	0.609
Age adjusted CCI	0.024	0.901	0.822	0.987					0.022	0.895	0.814	0.984				
Preop creatinine	0.063	0.707	0.491	1.019					0.883	0.971	0.660	1.430				
Preop pyuria	<0.001	0.348	0.252	0.481	0.001	0.454	0.290	0.713	0.002	0.628	0.464	0.848				
Preop hematuria	0.007	0.607	0.422	0.873					0.903	1.021	0.731	1.426				
Anticoagulan usage	0.238	0.763	0.487	1.196					0.453	0.828	0.506	1.356				
Stone location (upper calyx reference)																
Middle calyx	0.001	6.576	2.249	19.227					0.113	0.420	0.144	1.228				
Lower calyx	0.012	2.705	1.249	5.858					0.119	0.470	0.182	1.214				
Pelvis	0.014	2.579	1.208	5.505					0.106	0.460	0.179	1.181				
Upper ureter	0.003	3.201	1.490	6.874					0.071	0.420	0.164	1.077				
Multicalyx	<0.001	0.423	0.312	0.574					<0.001	2.118	1.578	2.842				
RESC score	0.010	0.891	0.816	0.973					<0.001	1.222	1.118	1.336				
Stone density (HU)	<0.001	0.998	0.998	0.999					0.124	1.000	1.000	1.001				
Number of stone (1 reference)																
Number of stone (2)	<0.001	0.429	0.297	0.620	0.002	5.925	1.962	17.889	<0.001	2.216	1.531	3.208	<0.001	2.097	1.437	3.060
Number of stone (3)	<0.001	0.240	0.144	0.401	0.016	2.724	1.208	6.142	<0.001	3.264	1.963	5.429	<0.001	3.215	1.906	5.424
Number of stone (4)	0.001	0.324	0.172	0.613	0.002	3.691	1.644	8.287	<0.001	3.726	1.991	6.972	<0.001	3.238	1.704	6.154
Number of stone (≥5)	0.010	0.409	0.196	0.853	0.008	2.940	1.319	6.557	0.012	2.526	1.227	5.199	0.076	1.943	0.932	4.051
Stone volume	<0.001	0.999	0.999	0.999	<0.001	0.999	0.999	1.000	0.045	1.001	1.000	1.000				
Multiple stone	<0.001	0.423	0.312	0.574					<0.001	2.118	1.578	2.842				
Preop hydronephrosis	0.964	0.993	0.743	1.328					0.346	1.152	0.859	1.546				

success rate (p=0.782). The effect of pre-operative stenting on success is controversial in the literature (21). Yuk et al. (22) found that preoperative ureteral stenting did not affect the success rate but it increased the success rate of access sheath placement. Bai et al. (23) also stated that preoperative stenting might not benefit the stone-free rate of the first month after surgery. However, there are also lots of studies in the literature that discuss the positive effect of preoperative stenting in RIRS (24,25). On the other hand, we found that preoperative stenting affects positively on complications.

Clavien and Dindo described a classification to standardize the complications of different surgeries (26). We also used this scale to evaluate the complications of our RIRS. The overall complication rate in our study group was 23.5%, which ranged between 8.3% and 37.5% in the literature (27,28). In a study, Cakici et al. (29) reported that the most frequent complications were fever, urinary system infection, and bleeding in their series. A similar relationship was also observed in our study. The most frequent complications were; bleeding, fever, and urinary tract infection. According to the Clavien classification, 88% of the complications were in the Clavien 1-2 category. These data documented that RIRS is a safe surgical technique. On the other hand, there were 12% of patients who had Clavien-3 or more complications, which documented that RIRS might also have life-threatening complications. We believe that this data also verify the importance of studies with high volume patients. Studies with a limited number of patients may underestimate the rates of Clavien 4 and 5 category complications.

In our study, a multivariate analysis of demographic and clinical characteristics showed that the number of stones, presence of preoperative ESL, and absence of preoperative DJ stent were predictors of postoperative complications. It was shown that different reasons might be related to complications in the literature according to the multivariate analysis (30,31). The study 602 RIRS cases determined that stone size and the mean operation time were the main indicators to predict complication status based on their multivariate analysis results (30). Another study found that urinary tract infections within six months, being female gender, mean operation time, and preoperative urine culture were the main determiners for RIRS related to complications (31).

Retrograde intrarenal surgery may also have mortal complications. The first case of mortality was reported in 1997 with septic shock (32). In the CROES study, it was reported that 5 patients (0.04%) died from various factors such as sepsis, cardiac, and pulmonary embolism (33). We did not have any mortality with sepsis, but one of our patients died due to "hemophagocytic syndrome". This complication was unexpected, but we could diagnose and start the appropriate treatment. Despite the early diagnosis and appropriate treatment, "hemophagocytic syndrome" has high mortality rates. We also observed the progressive deterioration of our patient with a mortal result (34).

Study Limitations

Our study has some limitations. The retrospective nature of our study is a limitation. On the other hand, the data that were used in the study were collected during the surgeries and postoperative time of the patients instantaneously. This may reduce the possible limitation of the retrospective design. The surgeries in this multi-center study were performed by different surgeons, which might lead to interpersonal bias. On the other hand, the surgeons used the same surgical procedures, which might also reduce the multi-surgeon bias.

Conclusion

Retrograde intrarenal surgery is an effective and safe surgical technique for treating USSD. RIRS is on its way to becoming the gold standard for USSD with advances in technology. The success rate of the RIRS depends on the stone size, stone location, and surgical experience. Although the complication rates are mostly low and mostly minor, there may also be severe life-threatening complications.

Ethics

Ethics Committee Approval: The Local Institutional Ethics Committee Tekirdağ Namık Kemal University (no: 2020.114.05.15) approved this study, and all steps were planned and conducted following the Declaration of Helsinki and its later amendments.

Informed Consent: Written informed consent on admittance to the hospital was obtained from all individuals, which permitted the use of respective medical information in clinical studies.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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References

1. Smith LH. The medical aspects of urolithiasis: an overview. J Urol 1989;141:707-710.
2. Trinchieri A. Epidemiology of urolithiasis. Arch It Urol Androl 1996;68:203-249.
3. Curhan GC. Epidemiology of stone disease. Urol Clin N Am 2007;34:287-293.
4. Muslumanoglu AY, Binbay M, Yuruk E, Akman T, Tepeler A, Esen T, Tefekli AH. Updated epidemiologic study of urolithiasis in Turkey. I: Changing characteristics of urolithiasis. Urol Res 2011;39:309-314.
5. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, Pace KT, Pais VM, Pearle MS, Preminger GM, Razvi H, Shah O, Matlaga BR. Surgical management of stones: American Urological Association / Endourological Society Guideline, Part I. J Urol 2016;196:1153-1160.
6. Yazıcı C, Akgül M, Arda E, Akpınar H. Can the Urologists Perform Stone Analysis, Metabolic Evaluation and Metaphylaxis at UrinaryTract Stone Disease in Tekirdağ? Dicle Med J 2019;46:405-410.
7. Parikh KP, Jain RJ, Kandarp AP. Is retrograde intrarenal surgery the game changer in the management of upper tract calculi? A single-center single-surgeon experience of 131 cases. Urol Ann 2018;10:29-34.
8. Turk C, Petrik A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T. EAU guidelines on interventional treatment for urolithiasis. Eur Urol 2016;69:475-482.
9. Al Busaidy SS, Kurukkal SN, Al Hooti QM, Alsaraf MS, Al Mamari SA, Al Saeedi AK. Is RIRS emerging as the preferred option for the management of 2 cm-4 cm renal stones: our experience. Can J Urol 2016;23:8364-8367.
10. Lavan L, Herrmann T, Netsch C, Becker B, Somani BK. Outcomes of ureteroscopy for stone disease in anomalous kidneys: a systematic review. World J Urol 2020;38:1135-1146.
11. Sanguedolce F, Bozzini G, Chew B, Kallidonis P, de la Rosette J. The Evolving Role of Retrograde Intrarenal Surgery in the Treatment of Urolithiasis. Eur Urol Focus 2017;3:46-55.
12. Sorokin I, Cardona-Grau DK, Rehfuss A, Birney A, Stavrakis C, Leinwand G, Herr A, Feustel PJ, White MD. White. Stone volume is best predictor of operative time required in retrograde intrarenal surgery for renal calculi: implications for surgical planning and quality improvement. Urolithiasis 2016;44:545-550.
13. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int 2003;63:1817-1823.
14. Amato M, Lusini ML, Nelli F. Epidemiology of nephrolithiasis today. Urol Int 2004;72:1-5.
15. Heers H, Turney BW. Trends in urological stone disease: a 5-year update of hospital episode statistics. BJU Int 2016;118:785-789.
16. Firdolaş F, Pirinççi N, Ozan T, Karakeçi A, Orhan I. Retrograde intrarenal surgery technique without using fluoroscopy and access sheet in the treatment of kidney Stones. Turk J Med Sci 2019;49:821-825.
17. Akcay M, Tepeler A, Tosun M, Basibüyük İ, Elbir F, Kardaş S, Akman T, Armağan A, Taşçı Aİ. Current Minimal Invasive Surgery Treatment for Kidney Stones: Bezmialem Experience. Bezmialem Science 2016;2:38-42.
18. Sari S, Caniklioglu M, Oztekin Ü, Selmi V, Taspinar MS, Isikay L. Factors Affecting Retrograde Intrarenal Surgery Success: 6 Years Experience of a Clinic in Central Anatolia. Journal of Laparoendoscopic & Advanced Surgical Techniques 2020;30:1340-1343.
19. Goldberg H, Golomb D, Shtabholtz Y, Tapiero S, Creiderman G, Shariv A, Baniel J, Lifhshitz D. The "old" 15 mm renal stone size limit for RIRS remains a clinically significant threshold size. World J Urol 2017;35:1947-1954.
20. Ozbek R, Senocak C, Haberal HB, Damar E, Sadioglu FE, Bozkurt OF. Comparison of scoring systems for predicting stone-free status and complications after retrograde intrarenal surgery. World J Urol 2020;1-6.
21. Law YXT, Teoh JYC, Castellani D, Lim EJ, Chan EOT, Wroclawski M, Pirola GM, Giulioni C, Rubilotta E, Gubbioti M, Scarcella S, Chew BH, Traxer O, Somani BK, Gauhar V. Role of pre-operative ureteral stent on outcomes of retrograde intra-renal surgery (RIRS): systematic review and meta-analysis of 3831 patients and comparison of Asian and non-Asian cohorts. World J Urol 2022;1-13.
22. Yuk HD, Park J, Cho SY, Sung LH, Jeong CW. The effect of preoperative ureteral stenting in retrograde Intrarenal surgery: a multicenter, propensity score-matched study. BMC Urol 2020;20:1-7.
23. Bai PD, Wang T, Huang HC, Wu Z, Wang XG, Qin JX, Wang HQ, Chen B, Hu MB, Xing JC. Effect of Preoperative Double-J Ureteral Stenting before Flexible Ureterorenoscopy on Stone-free Rates and Complications. Curr Med Sci 2021;41:140-144.
24. Assimos D, Crisci A, Culkin D, Xue W, Roelofs A, Duvdevani M, Desai M, de la Rosetta J. Preoperative JJ stent placement in ureteric and renal stone treatment: results from the Clinical Research Office of Endourological Society (CROES) ureteroscopy (URS) Global Study. BJU Int 2016;117:648-654.
25. Chen H, Chen G, Zhu Y, Yang Z, Xiong C, Pan Y. Analysis of Prestenting on Outcomes of Flexible Ureteroscopy for Upper Urinary Urolithiasis: A Historical Control Study. Urol Int 2019;102:175-180.
26. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.
27. Fayad AS, Elsheikh MG, Ghoneima W. Tubeless mini-percutaneous nephrolithotomy versus retrograde intrarenal surgery for lower calyceal stones of 2 cm: a prospective randomised controlled study. Arab J Urol 2017;15:36-41.
28. Vilches RM, Aliaga A, Reyes D, Sepulveda F, Mercado A, Moya F, Ledezma R, Hidalgo JP, Olmedo T, Marchan F. Comparison between retrograde intrarenal surgery and extracorporeal shock wave lithotripsy in the treatment of lower pole kidney stones up to 15 mm. Prospective, randomized study. Actas Urol Esp 2015;39:236-242.
29. Cakici M, Sari S, Selmi V, Sandıkçı F, Karakoyunlu N, Ozok U. Is the Efficacy and Safety of Retrograde Flexible Ureteroscopy in the Elderly Population Different from Non-elderly Adults? Cureus 2019;11:e4852.
30. Zhang H, Jiang T, Gao R, Chen Q, Chen W, Liu C, Mao H. Risk factors of infectious complications after retrograde intrarenal surgery: a retrospective clinical analysis. J Int Med Res 2020;48:300060520956833.
31. Baboudjian M, Gondran-Tellier B, Abdallah R, Sichez PC, Akiki A, Gaillet S, Delaporte V, Karsenty G, Lechevallier E, Boissier R. Predictive risk factors of urinary tract infection following flexible ureteroscopy despite preoperative precautions to avoid infectious complications. World J Urol 2020;38:1253-1259.
32. Robert M, Drianno N, Marotta J, Delbos O, Guiter J, Grasset D. The value of retrograde ureterorenoscopy in the treatment of bulky kidney calculi. Prog Urol 1997;7:35-41.
33. Somani BK, Giusti G, Sun Y, Osther PJ, Frank M, Sio MD, Turna B, Rosette JDL. Complications associated with ureterorenoscopy (URS) related to treatment of urolithiasis: the Clinical Research Office of Endourological Society URS Global study. World J Urol 2017;35:675-681.
34. Akgül M, Yazıcı C, Ateş H, Altın E, Turgut B. A Rare Retrograde Intrarenal Surgery Complication: Hemophagocytic Syndrome. J Endourol Case Rep 2020;6:339-342.

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Evolution of the Percutaneous Nephrolithotomy: A Holistic Investigation of Global Outputs with Bibliometric Analysis

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

Percutaneous nephrolithotomy (PCNL) is important because it involves invasive procedures for the treatment of large and complex nephrolithiasis. Nowadays, as the number of PCNL operations increases, clinicians are focused on increasing the success rate of surgical treatments and reducing complication rates. Bibliometrics is a statistical method used to analyze scientific research. It enables us to analyze the most cited studies and trending issues in a specific subject, as well as explore new ideas by examining new trends from the past to the present. Over time, we have observed an increase in the number of papers related to PCNL in our analyses. Incidentally, we have noticed that these studies primarily focus on the success and reliability of PCNL. In this context, we have observed a significant increase in research on surgical approaches, such as the use of the Guy's scoring system to select appropriate patients pre-operatively, mini PCNL, and the prone position.

Abstract

Objective: This bibliometric study identifies the studies, institutions and journals with the highest impact by analyzing the articles published about percutaneous nephrolithotomy (PCNL) and further to establish trend topics and to holistically summarize and interpret collaboration among countries.

Materials and Methods: Studies published about PCNL between 1975-2020 were downloaded from the Web of Science (WoS) database. They were analyzed using bibliometric and statistical methods. Spearman's correlation coefficient was used for correlation analysis. Non-linear regression analysis was used to estimate the number of publications in the coming years.

Results: A total of 4170 publications were found and 1936 (46.4%) of these publications were articles. We observed that the articles on PCNL have gradually increased in an exponential trend. Top 5 countries having contributed most to the literature ranked as Turkiye (n=376), USA (n=332), China (n=323), India (n=210) and Iran (n=123). Top 3 most active institutions were ranked as Guangzhou Medical University (n=63), University of Health Sciences Turkiye, İstanbul Haseki Training and Research Hospital (n=52) and Başkent University (n=32).

Conclusion: In our study, we observed that there has been an increase in the number of PCNL-related publications over the course of time. Besides, we determined that recent publications, mainly focused on the success and reliability of PCNL. In this context, there has been a steady increase in the number of studies on the use of Guy's scoring system for preoperative selection of eligible patients and surgical approaches such as mini PCNL, prone position.

Keywords: Percutaneous nephrolithotomy, trend topics, bibliometric analysis

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Introduction

Urinary stone diseases date back to 4000 B.C. and have played a crucial role in the practice of urology. There has been a significant increase in its prevalence in particular given the changing lifestyles of the societies during time. urolithiasis affects almost 12% of the world population (1). In parallel to the technological advancements in the field of medicine, the main approaches used for treating urolithiasis are the minimally invasive methods. Among these methods, percutaneous nephrolithotomy (PCNL) plays a major role (2). This treatment modality, firstly described in 1976 by Fernström and Johansson, has started to be used in a wide geography in particular as from the beginning of the 20th century for the treatment of urinary stone diseases, mainly complex renal stones (3). Today, it is intensely focused on increasing the success rate of PCNL and obtaining lower complication rates. In this respect, several different strategies have been developed, mainly to produce more minimal surgical equipment and to make modifications in the surgical techniques (4).

Bibliometrics is the use of statistical methods to analyze scientific research as mainly the articles (5). It has been observed that there is an increasing interest in studies based on bibliometric analyses in parallel to the increasing number of publications in the literature, particularly in the recent years on major topics in the field of medicine (6). Bibliometric analyses allow researchers to identify the most cited studies on a certain topic; most researched trend topics; the impact of the countries, institutions, journals and authors and international collaborations (5,6). Besides, this type of article, which provides a summary of the literature, also enables researchers to explore new ideas by analyzing the past and present trends (5).

An evolving interest in global medical research is emerging. Nevertheless, there is still no bibliometric study in the literature on PCNL, which is a minimally invasive approach used widely for treating urinary stone diseases, despite the changing surgical techniques and advances in surgical equipment technology. This study analyzes the articles published about PCNL between 1975 and 2020 by using bibliometric and statistical methods and thus to holistically summarize and interpret PCNL by identifying the studies, institutions and journals with the highest impact, establishing trend topics and international collaboration among countries.

Materials and Methods

The Web of Science (WoS) database by Clarivate Analytics was used for literature review. "Percutaneous nephrolithotomy" and "PCNL" were used as search keywords in WoS. Publications were searched only in the "title" section of the studies. With this search method, all publications containing PCNL or PCNL in their title were obtained and downloaded from the WoS database. The search period was between the years 1975-2020 (access date: 15.01.2021, search findings may vary according to different access dates). Repeatability codes for researchers to access similar documents: [title: ("percutaneous nephrolithotomy") or title: ("PCNL") Timespan: 1975-2020. Indexes: SCI-Expanded, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI]. For bibliometric network visualizations, VOSviewer (Version 1.6.15, Leiden University's Center for Science and Technology Studies) package program was used (7). The website (https://app.datawrapper.de) was used to draw the world map.

Statistical Analysis

Statistical analysis was performed with SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA, License: Hitit University) package program. The normal distribution of the data was tested with the Shapiro-Wilk test. The Spearman's correlation coefficient was used in accordance with the data distribution to calculate the correlations between the number of articles produced by the world countries and some economic development indicators of the world countries Gross Domestic Product (GDP), gross domestic product per capita (GDP per capita), gross domestic product at purchasing power parity (GDP PPP), Gross Domestic Product per capita at purchasing power parity (GDP per capita PPP) whose data were obtained from the world bank (https://data.worldbank.org/indicator/NY.GDP.MKTP.CD) to identify the effective indicators of academic productivity on PCNL. Nonlinear regression analysis was used to estimate the number of publications in the coming years. The R^2 value was used to evaluate the success of the model in regression analysis. A statistically significant difference was accepted as $p<0.05$.

Results

Because of the literature review, no publication was found on PCNL in the WoS database between the years 1975-1980. A total of 4170 publications were found between 1981-2020. The breakdown of the types of these publications was identified as follows; 1936 (46.4%) articles, 1594 (38.2%) meeting abstracts, 248 (5.9%) editorial materials, 191 (4.58%) letters, 160 (3.8%) reviews, 41 (0.9%) proceedings papers, and other types of publications (namely; early access, correction, note, book chapter, news item, reprint). Of these 4170 publications, bibliometric analyses were performed on 1936 articles. A total of 1856 (95.9%) articles were written in the English language and the rest in French (n=35), Spanish (n=26), German (n=13) and Turkish (n=6) languages. H-index, average citations per article and sum of times cited for 1936 articles were 74, 15.36 and 29730 (without self-citations: 15174), respectively.

Research Areas

The top research areas in PCNL are as follows: Urology nephrology (n=1564, 80.8%), medicine general internal (n=141, 7.3%), surgery (n=74, 3.8%), medicine research experimental (n=62, 3.2%), pediatrics (n=26, 1.3%), anesthesiology (n=25, 1.3%), radiology nuclear medicine medical imaging (n=22, 1.1%), multidisciplinary sciences (n=20, 1%), pharmacology pharmacy (n=11, 0.6%), public environmental occupational health (n=10, 0.5%).

Evolution of Publications and Future Trends

The distribution of the articles over the years is given in Figure 1. The results of the nonlinear (exponential model) regression analysis, used to estimate the number of articles in 2020 and beyond, are also shown in Figure 1. Based on the regression analysis results, it is estimated that 207 [confidence interval (CI)%: 181-233] articles will be published in 2021 and 251 (CI%: 218-283) articles in 2025.

Active Countries

The distribution of the articles over the countries in the world is given in Figure 2. Most productive countries (those producing 20 articles and more) over the number of articles ranked as Turkiye (n=376), the USA (n=332), China (n=323), India (n=210), Iran (n=123), the UK (n=118), Egypt (n=81), Canada (n=76), Germany (n=61), Italy (n=58), France (n=48), Spain (n=47), Taiwan (n=41), Netherlands (n=38), Pakistan (n=35), Israel (n=32), Greece (n=29), South Korea (n=24), Brazil (n=20), Thailand (n=20). The international collaboration network visualization map, demonstrating the collaboration between 38 countries, which produced minimum 5 articles out of the 60 countries producing publications on PCNL, is given in Figure 3a and the density map in Figure 3b.

Correlation Analysis

A moderate level of statistically significant positive correlation was found between the number of articles on PCNL produced by the countries and the GDP, GDP per capita, GDP PPP and GDP per capita PPP ($r=0.653$, $p<0.001$; $r=0.548$, $p<0.001$; $r=0.607$, $p<0.001$; $r=0.512$, $p<0.001$, respectively).

Active Authors

Most active authors producing 25 articles, and on PCNL were ranked as Zeng GH (n=53), Tepeler A (n=36), Binbay M (n=32), Unsal A (n=29), Zhao ZJ (n=29), Muslumanoglu AY (n=27), Wu WQ (n=25).

Active Institutions

The top 15 most actively publishing universities (those producing 20 articles and more) in this area ranked as; Guangzhou Medical University (n=63), University of Health Sciences Turkiye, İstanbul Haseki Training and Research Hospital (n=52), Başkent University (n=32), Bezmialem Foundation University (n=29), AMC Hospital (n=28), Huazhong University of Science and Technology (n=26), Duke University (n=25), All India Institute of Medical Sciences (n=24), Hacettepe University (n=24), Mansoura University (n=24), Muljibhai Patel Urological Hospital (n=24),

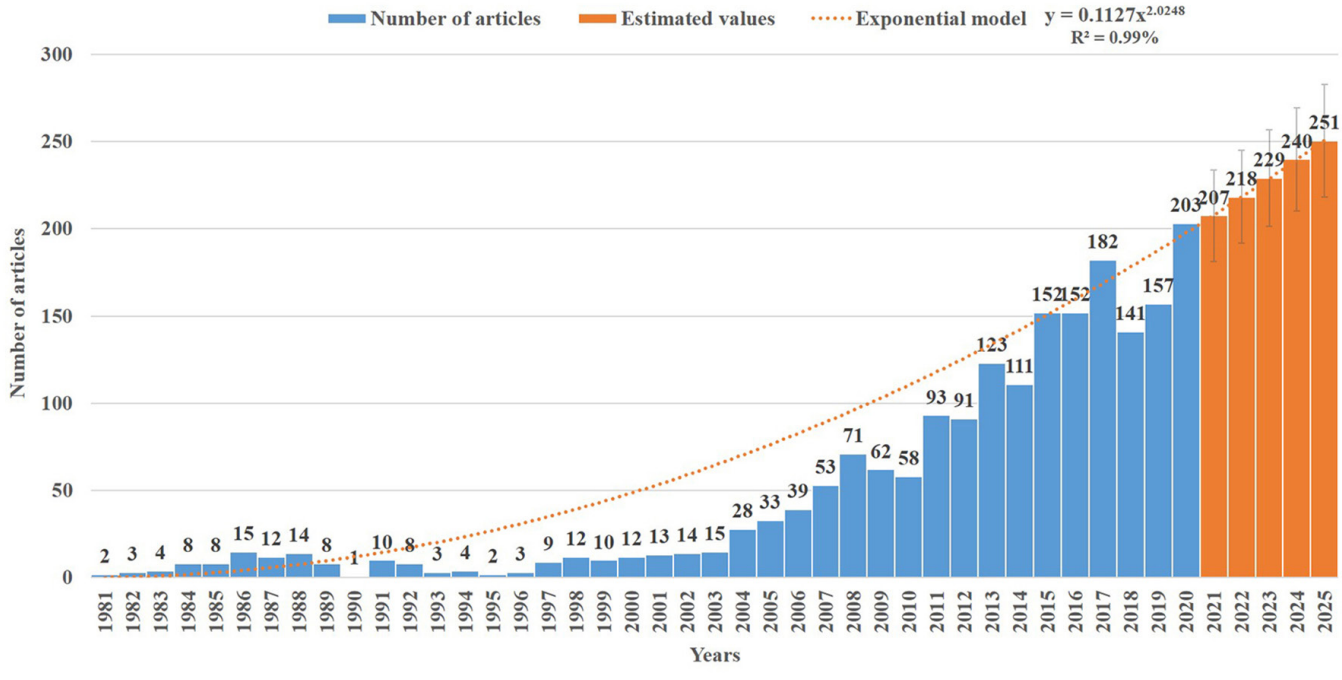

Figure 1. Number of articles published on percutaneous nephrolithotomy by years and estimation of the number of articles that can be published in the future

Dicle University (n=23), Sun Yat Sen University (n=23), Keçiören Training Research Hospital (n=20), Guangdong Key Laboratory of Urology (n=19).

Active Journals

A total of 1936 articles on PCNL have been published in 243 different journals. Out of these journals, top 35 most active journals, producing 10 articles and more, their sum of times cited and average citations per article are given in Table 1. The citation network visualization map between these journals is given in Figure 3c.. The top journal for the number of articles published was the Journal of Endourology (number of article: 376), the top journal for the number of citations was the Journal of Endourology (number of citation: 9326) and the top journal for average citations per article was European Urology (average citation per document 83.6).

Citation Analysis

The top 36 articles for the sum of times cited in the 1981-2020 period are presented in Table 2. Again, in the last column of Table 2, average citations of the articles per year are given. Accordingly, the most cited article was "The Clinical Research Office of the Endourological Society PCNL Global Study" by De la Rosette et al. (8). This study, published in 2011 in the Journal of Endourology focused on the indications, complications, and outcomes in 5803 patients (8).

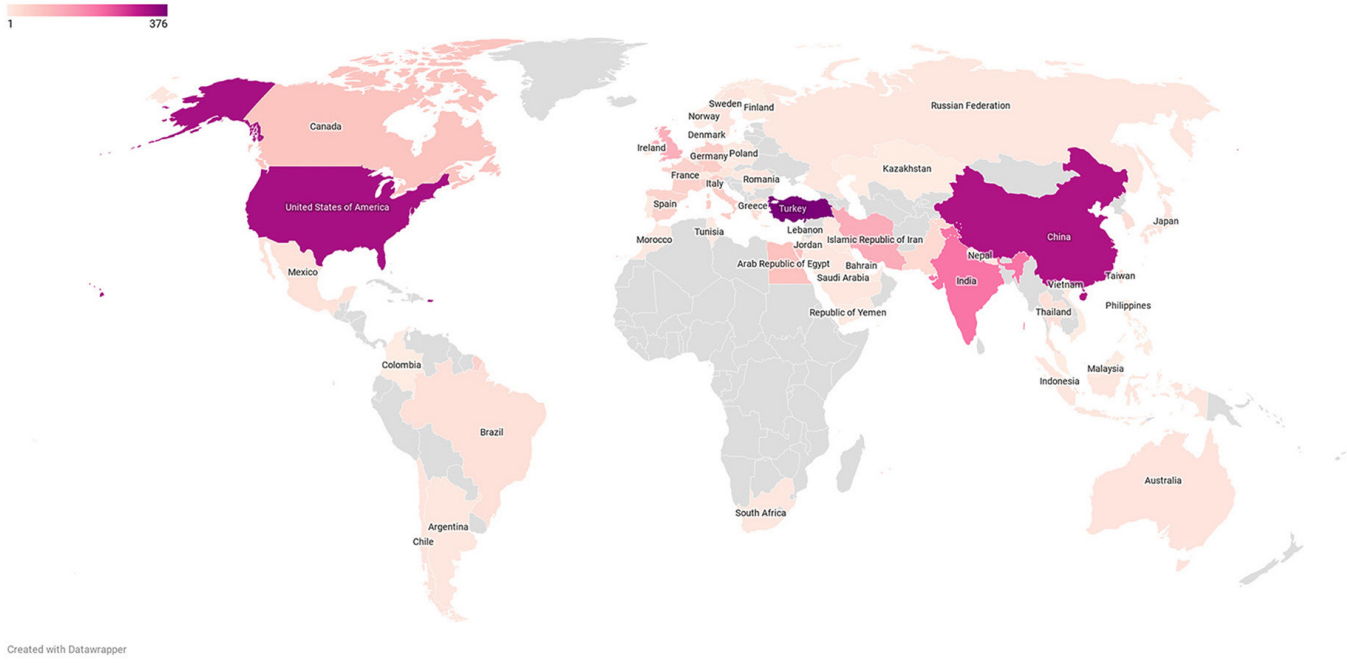

Figure 2. World map for the distribution of articles by country on percutaneous nephrolithotomy. **Footnote:** In the indicator given at the bottom left of the figure, productivity increases from green to red

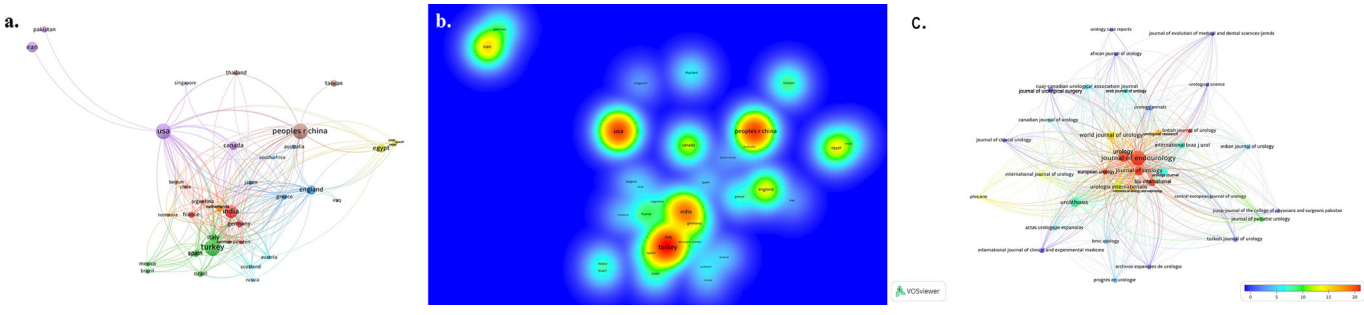

Figure 3. a. Network visualization map for international collaboration of worldwide countries on percutaneous nephrolithotomy. **Footnote:** The size of the circle shows the large number of articles, the thickness of the lines indicates the strength of relationship, and the colors show the different clusters. **b.** Density map for international collaboration of worldwide countries on percutaneous nephrolithotomy. **Footnote:** Cooperation increases from blue to red (blue-green-yellow-red). **c.** Network visualization map for citation analysis of active journals on percutaneous nephrolithotomy. Footnote: The size of the circle shows the large number of articles. The number of citations from blue to red (blue-green-yellow-red) increases

Co-citation Analysis

A total of 11068 articles were cited under the references section of all the analyzed articles. The top 8 studies, with more than 150 co-citations under the references section, were ranked as follows: Fernstrom (number of co-citations, NC: 373), Michel (NC: 279), Preminger (NC: 263), de la Rosette (NC: 251), Tefekli (NC: 192), Dindo (NC: 185), Kukreja (NC: 169), Bellman (NC: 153) (9-16).

Trend Topics

In total, 1718 different keywords were used in all 1936 articles published on PCNL. Seventy-eight keywords were used in at least 10 different articles about these words (Table 3). The trend visualization network map is given in Figure 4a and the citation network visualization map in Figure 4b. A cluster network visualization map between these keywords is given in Figure 4c.

Table 1. Most active journals on PCNL

Journals	RC	C	AC	Journals	RC	C	AC
Journal of Endourology	376	9326	24.8	Progres En Urologie	19	80	4.2
Urology	149	3699	24.8	BMC Urology	17	68	4.0
Journal of Urology	111	4393	39.6	Journal of Pediatric Urology	17	172	10.1
Urolithiasis	110	908	8.3	Actas Urologicas Espanolas	16	86	5.4
World Journal of Urology	77	1117	14.5	Arab Journal of Urology	15	105	7.0
Urology Journal	71	496	7.0	British Journal of Urology	15	349	23.3
Urologia Internationalis	71	869	12.2	Canadian Journal of Urology	15	70	4.7
BJU International	56	1748	31.2	Indian Journal of Urology	15	60	4.0
International Brazilian Journal of Urology	34	241	7.1	Journal of Clinical Urology	14	11	0.8
Urological Research	33	543	16.5	Journal of Evolution of Medical and Dental Sciences-Jemds	14	4	0.3
CUAJ-Canadian Urological Association Journal	29	141	4.9	International Journal of Urology	14	168	12.0
Urology Annals	26	71	2.7	Plos One	11	158	14.4
International Urology and Nephrology	26	450	17.3	Urology Case Reports	11	4	0.4
International Journal of Clinical and Experimental Medicine	23	15	0.7	Urological Science	11	9	0.8
Journal of Urological Surgery	21	15	0.7	African Journal of Urology	10	8	0.8
Turkish Journal of Urology	21	37	1.8	Central European Journal of Urology	10	32	3.2
Archivos Espanoles De Urologia	19	32	1.7	JCPSP-Journal of the College of Physicians and Surgeons Pakistan	10	16	1.6
European Urology	19	1588	83.6				

RC: Record count, C: Number of citation, AC: Average citation per document

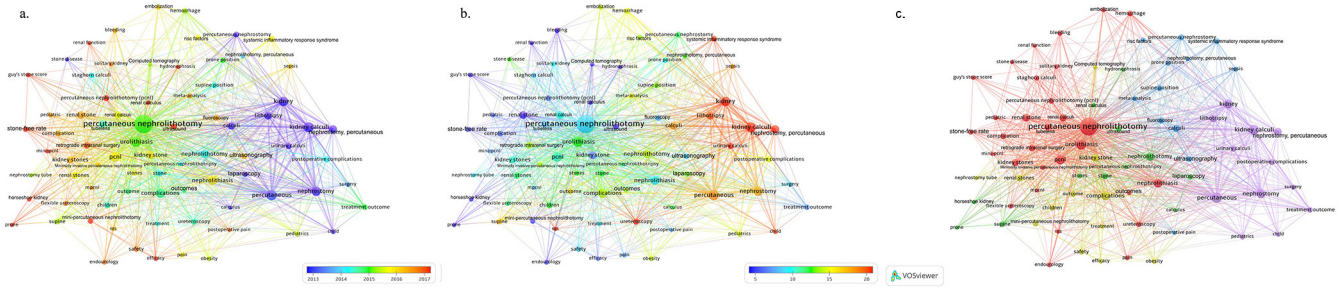

Figure 4. a. Network visualisation map for trends on percutaneous nephrolithotomy Footnote: Indicator shows current publications from blue to red (blue-green-yellow-red). **b.** Network visualization map of the most frequently cited topics on percutaneous nephrolithotomy **Footnote:** The number of citations from blue to red increases. **c.** Network visualisation map for cluster analysis based on keyword analysis on percutaneous nephrolithotomy. **Footnote:** Colors show clustering. Keywords in the same cluster are of the same color

Table 2. Top 25 most cited articles according to total citations on PCNL

No	Article	Author	Journal	PY	TC	AC
1	The clinical research office of the endourological society percutaneous nephrolithotomy global study: Indications, complications, and outcomes in 5803 patients	de la Rosette et al. (8)	Journal of Endourology	2011	430	39.09
2	First prize - factors affecting blood loss during percutaneous nephrolithotomy: Prospective study	Kukreja et al. (15)	Journal of Endourology	2004	297	16.5
3	Classification of percutaneous nephrolithotomy complications using the modified clavien grading system: Looking for a standard	Tefekli et al. (13)	European Urology	2008	292	20.86
4	The mini-perc technique: A less invasive alternative to percutaneous nephrolithotomy	Jackman et al. (23)	World Journal of Urology	1998	222	9.25
5	Percutaneous nephrolithotomy in infants and preschool age children: Experience with a new technique	Jackman et al. (24)	Urology	1998	213	8.88
6	Complications of percutaneous nephrolithotomy	Lee et al. (25)	American Journal of Roentgenology	1987	204	5.83
7	Categorisation of complications and validation of the clavien score for percutaneous nephrolithotomy	de la Rosette et al. (12)	European Urology	2012	187	18.7
8	Percutaneous nephrolithotomy with ultrasonography-guided renal access: Experience from over 300 cases	Osman et al. (26)	BJU International	2005	186	10.94
9	The guy's stone score-grading the complexity of percutaneous nephrolithotomy procedures	Thomas et al. (27)	Urology	2011	180	16.36
10	Estimated blood-loss and transfusion rates associated with percutaneous nephrolithotomy	Stoller et al. (28)	Journal of Urology	1994	167	5.96
11	Post-percutaneous nephrolithotomy extensive hemorrhage: a study of risk factors	El-Nahas et al. (29)	Journal of Urology	2007	164	10.93
12	Single-step percutaneous nephrolithotomy (microperc): The initial clinical report	Desai et al. (30)	Journal of Urology	2011	162	14.73
13	Stone and pelvic urine culture and sensitivity are better than bladder urine as predictors of urosepsis following percutaneous nephrolithotomy: A prospective clinical study	Mariappan et al. (31)	Journal of Urology	2005	148	8.71
14	Endoscopic combined intrarenal surgery in galdakao-modified supine valdivia position: a new standard for percutaneous nephrolithotomy?	Scoffone et al. (32)	European Urology	2008	146	10.43
15	Percutaneous nephrolithotomy - extraction of renal and ureteral calculi from 100 patients	Clayman et al. (33)	Journal of Urology	1984	145	3.82
16	Vascular complications after percutaneous nephrolithotomy: Are there any predictive factors?	Srivastava et al. (34)	Urology	2005	138	8.12
17	Minimally invasive PCNL in patients with renal pelvic and calyceal stones	Lahme et al. (35)	European Urology	2001	129	6.14
18	Percutaneous nephrolithotomy for complex pediatric renal calculus disease	Desai et al. (22)	Journal of Endourology	2004	128	7.11
19	Prospective randomized study of various techniques of percutaneous nephrolithotomy	Feng et al. (37)	Urology	2001	128	6.1
20	A nephrolithometric nomogram to predict treatment success of percutaneous nephrolithotomy	Smith et al. (38)	Journal of Urology	2013	122	13.56
21	Modified supine versus prone position in percutaneous nephrolithotomy for renal stones treatable with a single percutaneous access: a prospective randomized trial	De Sio et al. (39)	European Urology	2008	119	8.5
22	The percutaneous nephrolithotomy global study: classification of complications	Labate et al. (40)	Journal of Endourology	2011	116	10.55
23	The all-seeing needle: Initial results of an optical puncture system confirming access in percutaneous nephrolithotomy	Bader et al. (41)	European Urology	2011	114	10.36
24	Percutaneous nephrolithotomy: Variables that influence hemorrhage	Turna et al. (42)	Urology	2007	114	7.6
25	Operating times and bleeding complications in percutaneous nephrolithotomy: A comparison of tract dilation methods in 5537 patients in the clinical research office of the endourological society percutaneous nephrolithotomy global study	Yamaguchi et al. (43)	Journal of Endourology	2011	113	10.27

PY: Publication year, TC: Total citation, AC: Average citations per year

Table 3. Top 78 most used keywords in articles published on PCNL

Keywords	Number of uses	Keywords	Number of uses	Keywords	Number of uses
Percutaneous nephrolithotomy	717	Fluoroscopy	25	Pain	15
Percutaneous	135	Children	24	Pediatric	15
Urolithiasis	126	Ultrasound	24	Surgery	15
Kidney calculi	121	Ureteroscopy	24	Embolization	14
Pcnl	103	Hemorrhage	22	Child	13
Kidney	94	Percutaneous nephrostomy	22	Efficacy	13
Nephrostomy	92	Treatment outcome	22	Guy's stone score	13
Complications	91	Ultrasonography	22	Renal calculus	13
Nephrolithiasis	86	Supine	21	Risk factors	13
Nephrolithotomy	60	Systemic inflammatory response syndrome	21	Solitary kidney	13
Nephrostomy, percutaneous	59	Safety	20	Stones	12
Renal stone	55	Staghorn calculi	20	Nephrolithotomy, percutaneous	11
Lithotripsy	54	Stone-free rate	19	Nephrostomy tube	11
Kidney stone	52	Outcome	18	Percutaneous nephrolithotripsy	11
Renal calculi	51	Bleeding	17	Postoperative pain	11
Calculi	44	Mini-percutaneous nephrolithotomy	17	Renal function	11
Kidney stones	41	Pediatrics	17	Treatment	11
Tubeless	39	Prone position	17	Calculus	10
Renal stones	34	Flexible ureteroscopy	16	Computed tomography	10
Retrograde intrarenal surgery	34	Minimally invasive percutaneous nephrolithotomy	16	Horseshoe kidney	10
Complication	28	Outcomes	16	Hydronephrosis	10
Urinary calculi	28	Sepsis	16	Mini-PCNL	10
Percutaneous nephrolithotomy (PCNL)	27	Endourology	15	MPCNL	10
Postoperative complications	27	Laparoscopy	15	Prone	10
Supine position	27	Meta-analysis	15	Rirs	10
Stone	26	Obesity	15	Stone disease	10

Discussion

According to the data presented in our study, there has been an exponential increase in the number of PCNL-related publications recently. Between 1981 and 2003, 9 articles on average were published annually, while the number of studies on PCNL have significantly increased after 2004 reaching in average 157 articles annually between 2015 and 2019 with a peak in 2020 (203 articles). Regression analysis results show that the growing number of articles will continue exponentially in the coming years.

With a look into the distribution of publications among different countries, 12 out of the 20 most active countries on PCNL are developed countries, whereas the rest are developing countries. It is quite interesting that Turkiye is the most active country in producing publications ranking in the top 5 with China, India, Iran and Egypt. Developed countries, such as Canada, Germany, Italy, France, Spain, Taiwan and the Netherlands follow. We think that this situation may be related to the habits of patients living in these regions to apply to health institutions and for this reason it is known that the time-case distribution directly affects the level of scientific analysis. It has been shown in the literature that the developed countries have a critical role in bibliometric analysis and effective publications in many fields of medicine with a significant level of correlation to their economic power (5,6). Our study, on the other hand, presents a moderate level of significance between article productivity and indicators of economic development according to correlation

analysis results. The age interval of societies that encounter urinary stone disease depends on climate conditions, nutritional habits and genetic background (17). We think that this leads to a huge variety in the level of scientific activities in different geographies. In connection, we also believe that this situation may have led to an uneven distribution of countries involved in bibliometric studies.

In some studies in the literature, it has been stated that geographical neighborhoods are effective in international cooperation (5-7). One may conclude that these countries had also preceded international cooperation.

As for the keyword analysis results, 5 clusters in different colors come up in PCNL-related topics. The mostly cited keywords are systemic inflammatory response syndrome, retrograde intrarenal surgery, sepsis, lithotripsy, ureteroscopy, kidney, kidney calculi, and urinary calculi. Analysis of trending topics indicates that recently the most studied keywords are mini PCNL, stone-free rate, Guy's stone score, retrograde intrarenal surgery, prone, horseshoe kidney, ultrasound, renal calculus, renal function, hydronephrosis, postoperative pain, efficacy, and safety. In our study, it was observed that the increasing level of interest in PCNL was intensively studied to provide an effective and safe surgical approach for patients.

Success rates of PCNL depend closely on many factors, including the clinical experience of the institution, use of proper surgical equipment, patient-related anatomical factors, stone size and localization. Large series indicate an average success rate of 85-93% (18). Our study concluded that keywords depicting the consequences of this surgical intervention, such as efficacy and stone-free rate are searched with a growing interest in the scientific community working on PCNL. However, with the changing success rates, the medical community has grown with interest in which patient groups might benefit more from PCNL. In this context, it has been observed that the Guy's scoring system has been used with increasing trend for quantitative assessment of kidney stones by using stone and patient characteristics. Although PCNL has been shown as a minimally invasive treatment strategy, it involves many complications ranging from blood loss to adjacent organ injuries and renal pelvic perforations to fever and urinary fistulas. Large-scaled studies reported complication rates at the level of 14.5% (19). It is quite critical that patients get the least harm from this surgical procedure. Therefore, words safety, renal function and postoperative pain are quite trendy. However, surgical techniques that affect both the efficacy and reliability of PCNL are quite important. As a direct consequence of this, it was possible to see in our study that mini PCNL and prone position are the other words most often searched recently.

It has been thought that there are mainly two reasons why mini PCNL has been highly regarded in the medical community. One because the patients apply to health institutions earlier due to improving socioeconomic conditions in many parts of the world, because of which there has been an increase in the prevalence of small to medium sized kidney stones. And two, because there is minimized PCNL surgical equipment available for less traumatic surgery thanks to the technological developments. In a quite comprehensive meta-analysis by Zhu et al. (20), authors looked into eight publications and 749 patient results and reported that mini PCNL provides a more effective and reliable treatment modality versus PCNL. In another current study, Thapa and Niranjan (21) reported that mini PCNL provides a more effective and lower risk operation than PCNL considering lower bleeding and hospitalization times. The decision of whether to use PCNL in the prone or supine position is still controversial. In a relatively current systematic review and meta-analysis by Birowo et al. (22), concluded that surgical experience is quite an important factor with no significant difference between the two techniques in terms of hospitalization and surgical times. In the same study, it was reported that the prone position had a higher stone-free rate yet with higher major complication rate compared to the supine position. Our study has put forth that together the technological developments and different surgical techniques for treating kidney stones and miniaturized surgical equipment, PCNL will become more popular a more reliable and effective approach.

This comprehensive study on PCNL is the first bibliometric research. We are of in the opinion that the use of comprehensive statistical methods such as keyword cluster analysis, trending keyword analysis, correlation and regression analysis in addition to descriptive statistics and citation analyses are the strength of our study.

Study Limitations

The main limitation of our study is the use of only the WoS database in the literature review. PubMed and Scopus databases were not used in our study. This is mainly because citation and co-citation analysis cannot be performed with the PubMed database for an effective pick of studies and journals. The Scopus database may also include studies with a relatively lower impact level. Recent bibliometric analysis revealed that WoS is a more preferred alternative (5,6). The main reason is that the WoS database indexes articles published in journals with a higher impact (5). Therefore, our study used only the WoS database.

Conclusion

This comprehensive bibliometric study on PCNL that has been increasing trend in more articles every other day in the literature, provides an abstract of 1936 articles published on PCNL between 1975-2020. It is noted that publication has recently focused on

more effective and safer surgical techniques. In this context, it has been observed that surgical techniques and preoperative patient analyzes related to PCNL have attracted considerable interest in our century.

Ethics

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any author.

Informed Consent: For this type of study formal consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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References

1. Alelign T, Petros B. Kidney Stone Disease: An Update on Current Concepts. Adv Urol 2018:3068365.
2. Sarıkaya K, Şenocak Ç, Çiftci M, İbiş MA, Bozkurt ÖF. The effectiveness of percutaneous nephrolithotomy for the treatment of large impacted upper ureteral stones. Anatolian Curr Med J 2021;3:165-170.
3. Patel SR, Nakada SY. The modern history and evolution of percutaneous nephrolithotomy. J Endourol 2015;29:153-157.
4. Vicentini FC, Gomes CM, Danilovic A, Neto EA, Mazzucchi E, Srougi M. Percutaneous nephrolithotomy: Current concepts. Indian J Urol 2009;25:4-10.
5. Demir E, Comba A. The evolution of celiac disease publications: a holistic approach with bibliometric analysis. Ir J Med Sci 2020;189:267-276.
6. Doğan G, Karaca O. Análise bibliométrica no campo da anestesiologia no período de 2009-2018 [A bibliometric analysis of the field of anesthesia during 2009-2018]. Braz J Anesthesiol 2020;70:140-152.
7. Van Eck NJ. Waltman L. Software survey: VOS viewer, a computer program for bibliometric mapping. Scientometrics 2010;84:523-538.
8. De la Rosette J, Assimos D, Desai M, Gutierrez J, Lingeman J, Scarpa R, Tefekli A; CROES PCNL Study Group. The Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study: indications, complications, and outcomes in 5803 patients. J Endourol 2011;25:11-7.
9. Fernström I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol 1976;10:257-259.
10. Michel MS, Trojan L, Rassweiler JJ. Complications in percutaneous nephrolithotomy. Eur Urol 2007;51:899-906; discussion 906.
11. Preminger GM, Assimos DG, Lingeman JE, Nakada SY, Pearle MS, Wolf JS Jr; AUA Nephrolithiasis Guideline Panel). Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. J Urol 2005;173:1991-2000.
12. De la Rosette JJ, Opondo D, Daels FP, Giusti G, Serrano A, Kandasami SV, Wolf JS Jr, Grabe M, Gravas S; CROES PCNL Study Group. Categorisation of complications and validation of the Clavien score for percutaneous nephrolithotomy. Eur Urol 2012;62:246-255.
13. Tefekli A, Ali Karadag M, Tepeler K, Sari E, Berberoglu Y, Baykal M, Sarilar O, Muslumanoglu AY. Classification of percutaneous nephrolithotomy complications using the modified clavien grading system: looking for a standard. Eur Urol 2008;53:184-190.
14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.
15. Kukreja R, Desai M, Patel S, Bapat S, Desai M. Factors affecting blood loss during percutaneous nephrolithotomy: prospective study. J Endourol 2004;18:715-722.
16. Bellman GC, Davidoff R, Candela J, Gerspach J, Kurtz S, Stout L. Tubeless percutaneous renal surgery. J Urol 1997;157:1578-1582.
17. Kölükçü E, Parlaktaş BS. Our results with flexible ureterorenoscopy in treatment of upper calyceal stones in obese patients. J Health Sci Med 2019;2:79-83.
18. Nguyen DD, Luo JW, Tailly T, Bhojani N. Percutaneous Nephrolithotomy Access: A Systematic Review of Intraoperative Assistive Technologies. J Endourol 2019;33:358-368.
19. Tsai SH, Chung HJ, Tseng PT, Wu YC, Tu YK, Hsu CW, Lei WT. Comparison of the efficacy and safety of shockwave lithotripsy, retrograde intrarenal surgery, percutaneous nephrolithotomy, and minimally invasive percutaneous nephrolithotomy for lower-pole renal stones: A systematic review and network meta-analysis. Medicine (Baltimore) 2020;99:e19403.
20. Zhu W, Liu Y, Liu L, Lei M, Yuan J, Wan SP, Zeng G. Minimally invasive versus standard percutaneous nephrolithotomy: a meta-analysis. Urolithiasis 2015;43:563-570.
21. Thapa BB, Niranjan V. Mini PCNL Over Standard PCNL: What Makes it Better? Surg J (N Y) 2020;6:e19-e23.
22. Birowo P, Tendi W, Widyahening IS, Rasyid N, Atmoko W. Supine versus prone position in percutaneous nephrolithotomy: a systematic review and meta-analysis. F1000Res 2020;9:231.
23. Jackman SV, Docimo SG, Cadeddu JA, Bishoff JT, Kavoussi LR, Jarrett TW. The "mini-perc" technique: a less invasive alternative to percutaneous nephrolithotomy. World J Urol 1998;16:371-374.
24. Jackman SV, Hedican SP, Peters CA, Docimo SG. Percutaneous nephrolithotomy in infants and preschool age children: experience with a new technique. Urology 1998;52:697-701.
25. Lee WJ, Smith AD, Cubelli V, Badlani GH, Lewin B, Vernace F, Cantos E. Complications of percutaneous nephrolithotomy. AJR Am J Roentgenol 1987;148:177-180.
26. Osman M, Nordahl GW, Heger K, Michel MS Alken P, Knoll T. Percutaneous nephrolithotomy with ultrasonography-guided renal access: experience from over 300 cases. BJU Int 2005;96:875-878.
27. Thomas K, Smith NC, Hegarty N, Glass, JM. The Guy's stone score—grading the complexity of percutaneous nephrolithotomy procedures. Urology 2011;78:277-281.
28. Stoller ML, Wolf JS, Lezin MA. Estimated blood loss and transfusion rates associated with percutaneous nephrolithotomy. J Urol 1994;152:1977-1981.
29. El-Nahas AR, Shokeir AA, El-Assmy AM, Mohsen T, Shoma AM, Eraky I, El-Kenawy MR, El-Kappany HA. Post-percutaneous nephrolithotomy extensive hemorrhage: a study of risk factors. J Urol 2007;177:576-579.

30. Desai MR, Sharma R, Mishra S, Sabnis RB, Stief C, Bader M. Single-step percutaneous nephrolithotomy (microperc): the initial clinical report. J Urol 2011;186:140-145.

31. Mariappan P, Smith G, Bariol SV, Moussa SA, Tolley DA. Stone and pelvic urine culture and sensitivity are better than bladder urine as predictors of urosepsis following percutaneous nephrolithotomy: a prospective clinical study. J Urol 2005;173:1610-1614.

32. Scoffone CM, Cracco CM, Cossu M, Grande S, Poggio M, Scarpa RM. Endoscopic combined intrarenal surgery in Galdakao-modified supine Valdivia position: a new standard for percutaneous nephrolithotomy? Eur Urol 2008;54:1393-1403.

33. Clayman RV, Surya V, Miller RP, Castaneda-Zuniga WR, Smith AD, Hunter DH, Amplatz K, Lange PH. Percutaneous nephrolithotomy: extraction of renal and ureteral calculi from 100 patients. J Urol 1984;131:868-871.

34. Srivastava A, Singh KJ, Suri A, Dubey D, Kumar A, et al. Vascular complications after percutaneous nephrolithotomy: are there any predictive factors? Urology 2005;66:38-40. doi: 10.1016/j.urology.2005.02.010.

35. Lahme S, Bichler KH, Strohmaier WL, Götz T. Minimally invasive PCNL in patients with renal pelvic and calyceal stones. Eur Urol 2001;40:619-624.

36. Desai MR, Kukreja RA, Patel SH, Bapat SD. Percutaneous nephrolithotomy for complex pediatric renal calculus disease. J Endourol 2004;18:23-27.

37. Feng MI, Tamaddon K, Mikhail A, Kaptein JS, Bellman GC. Prospective randomized study of various techniques of percutaneous nephrolithotomy. Urology 2001;58:345-350.

38. Smith A, Averch TD, Shahrour K, Oponda D, Daels FPJ, Labate G, Turna B, de la Rosette JJ; CROES PCNL Study Group. A nephrolithometric nomogram to predict treatment success of percutaneous nephrolithotomy. J Urol 2013;190:149-156.

39. De Sio M, Autorino R, Quarto G, Calabro F, Damiano R, Louie M, Grabe M, Rosette On Behalf Of The Croes Pcnl Study Group J. Modified supine versus prone position in percutaneous nephrolithotomy for renal stones treatable with a single percutaneous access: a prospective randomized trial. Eur Urol 2008;54:196-202. doi: 10.1016/j.eururo.2008.01.067.

40. Labate G, Modi P, Timoney A, Cormio L, Zhang X, et al. The percutaneous nephrolithotomy global study: classification of complications. J Endourol 2011;25:1275-1280.

41. Bader MJ, Gratzke C, Seitz M, Sharma R, Stief C, Desai M. The "all-seeing needle": initial results of an optical puncture system confirming access in percutaneous nephrolithotomy. Eur Urol 2011;59:1054-1059.

42. Turna B, Nazli O, Demiryoguran S, Mammadov R, Cal C. Percutaneous nephrolithotomy: variables that influence hemorrhage. Urology 2007;69:603-607.

43. Yamaguchi A, Skolarikos A, Noor Buchholz NP, Chomon GB, Grasso M, Saba P, Nakada S, de la Rosette J; Clinical Research Office Of The Endourological Society Percutaneous Nephrolithotomy Study Group. Operating times and bleeding complications in percutaneous nephrolithotomy: a comparison of tract dilation methods in 5,537 patients in the Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study. J Endourol 2011;25:933-939.

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Risk Factors for Complications in Simple Nephrectomy: 17-Year Results from Single Institution

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

Simple nephrectomy is a common but potentially risky surgery for benign kidney diseases. This study aims to enhance the quality of care for these patients by identifying the preoperative factors that influence the surgical outcomes. We found that American Society of Anesthesiologists score, preoperative hemoglobin level and male gender were associated with higher complication rates and longer hospital stays. We suggest that patients with these risk factors should receive individualized treatment and that elective laparoscopic surgery should be preferred whenever possible.

Abstract

Objective: To determine which preoperative patient characteristics are predictive of intraoperative complications (IOC) and postoperative complications (POC) in patients undergoing nephrectomy for non-oncological diseases.

Materials and Methods: Demographics, pre-operative characteristics, the surgical technique and perioperative outcomes of 295 adult patients who had underwent simple nephrectomy between 2002 and 2019 in a single reference institution were analyzed retrospectively. Univariate and multivariable statistical analyses were performed to determine the factors affecting POC (Clavien-Dindo score ≥1) and IOC. All statistical analyses were performed using the Statistical Package for the Social Sciences v. 24.0 (SPSS Inc., Chicago, IL, USA) software for Windows.

Results: The mean age of the patients was 44.84±15.51 years, with a female-to-male ratio of 154/141. The statistically significant factors associated with IOC in the multivariable analysis were male gender, higher American Society of Anesthesiologists (ASA) score and urgent surgical intervention (p=0.002, p=0.001, p=0.021, respectively). In multivariable analysis, preoperative anemia, emergency surgery and open surgery were found to be statistically significant and associated with POC (p<0.001, p=0.004, and p=0.049, respectively).

Conclusion: Improved surgical outcomes can be achieved through treatment adapted to individual preoperative characteristics such as ASA score, pre-operative hemoglobin level and male gender. An elective laparoscopic approach should be used whenever possible.

Keywords: Nephrectomy, laparoscopic nephrectomy, intraoperative complications, postoperative complications

Introduction

Nephrectomy for benign disease is a surgical technique that involves the removal of a non-functional kidney. The loss of kidney renal function may be caused by a variety of benign conditions (1). Some of these causes are of preventable nature. Patients undergoing simple nephrectomy represent a very diverse group that require thorough pre-operative planning. Some individual cases present major challenges for physicians at every step of the process.

Currently, nephrectomy for benign disease remains a major standard surgical procedure with a risk of severe complications, including death. The term "simple" has been criticized in the relevant literature as potentially misleading. "Non-radical" or "benign" nephrectomy terms are more precise given

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that complication rates are not lower than their "radical" counterparts (1,2).

The objective of this study was to determine which pre-operative patient characteristics are predictive of intraoperative complications (IOC) and postoperative complications (POC) complications in patients undergoing nephrectomy for non-oncological diseases.

Materials and Methods

This retrospective study was approved by the Institutional Ethics Committee (approval number: 2020/03-28) and conducted in accordance with the principles of the World Medical Association Declaration of Helsinki's Ethical Principles for Medical Research Involving Human Subjects.

A total of 295 adult patients who underwent simple nephrectomy for benign diseases from April 2002 to December 2019 at our institution are included in this study. Nephrectomy due to renal trauma were not included. Demographic data, pre-operative health status and perioperative outcomes were analyzed retrospectively.

Complications occurred within 30 days of surgical intervention were evaluated using the Clavien-Dindo classification (3). Tools such as the American Society of Anesthesiologists (ASA) score and Charlson Comorbidity Index (CCI) were used to determine the general health status of pre-operative patients. Renal function was assessed by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation and patients were classified into three groups as eGFR >90 mL/min/1.73 m^2, eGFR between 60 and 90 mL/min/1.73 m^2 and eGFR <60 mL/min/1.73 m^2 (4). According to the WHO, hemoglobin levels <12 g/dL for women and <13 g/dL for men are indicators of anemia (5).

Laparoscopic cases include trans peritoneal, retroperitoneal and hand-assisted laparoscopic procedures. Simple nephrectomies performed for pyelonephritis or recurrent urinary tract infections were classified as the infectious group; whereas simple nephrectomies performed for conditions such as persistent flank pain, hematuria, dyspnea and alike were classified as the non-infectious group. Univariate and multivariable statistical analyses were performed to determine factors affecting POC (Clavien-Dindo score ≥1) and IOC.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences v. 24.0 (SPSS Inc., Chicago, IL, USA) software for Windows. Chi-square test was used for nominal data; Mann-Whitney U test was used for non-parametric variables, while t-test was used for parametric variables in univariate analysis. Mean ± standard deviation was used for parametric variables, while the median and interquartile range were used for non-parametric variables. Binary logistic regression analysis and the backward stepwise model were used for multivariable analysis. A p-value less than 0.05 was considered statistically significant.

Results

The mean age of the patients was 44.84±15.51 years, with a female-to-male ratio of 154/141. Two female and two male patients underwent surgery twice for both sides at different times. Twenty-three patients (7.8%) required emergency surgery, whereas seven patients (2.4%) underwent bilateral nephrectomy at the same session. The median follow-up period was 61 (12.75 to 127.5) months. Patient demographics and pre-operative characteristics are shown in Table 1.

The most common indications for surgery were persistent flank pain, followed by urinary tract infection and hypertension. Most cases were performed by the open surgical approach (n=195, 66.1%). Among these minimally invasive surgical approaches, 65 (22%) were performed with a trans peritoneal approach, 20 (6.8%) were performed retroperitoneal and 15 (5.1%) were performed with hand-assisted laparoscopic approach. The median estimated blood loss was 50 (50-85) mL. Blood transfusion was required in 46 patients (15.6%). The most common pathological diagnosis was pyelonephritis (56.3%), followed by atrophic renal degeneration (36.3%). Perioperative and post-operative variables are shown in detail in Table 2.

The number of patients with Clavien-Dindo grade 1, grade 2, grade 3, grade 4 and grade 5 complications were 4 (1.4%), 63 (21.4%), 9 (3%), 1 (0.3%) and 3 (1%), respectively. The most common grade 1 complication was a fever that required antipyretics, which developed in 3 (1%) patients. Among the grade 2 complications, 27 patients (9.1%) developed postoperative UTI, which required treatment by appropriate antibiotics and 29 (9.8%) patients required blood transfusion. The incision site infection requiring revision in 5 (1.6%) patients was the most common grade 3 complication. As a grade 4 complication postoperative sepsis developed in a patient with the diaphragm injury treated with repair and thoracic tube drainage, which has recovered after intensive care treatment. Three patients were lost due to sepsis (n=1) disseminated intravascular coagulation (n=1) and duodenal injury, which was identified postoperatively (n=1) (Figure 1). Factors such as the male gender, higher CCI, high ASA score, low preoperative eGFR, preoperative anemia were significantly associated with POC in univariate analysis (p=0.042, p=0.003, p<0.001, p=0.004, p<0.001, respectively).

Table 1. Patient characteristics			
Parameters			
Gender; n (%)	**Female**	154 (52.2)	
	Male	141 (47.8)	
Age, year, mean (SD)		44.84 (15.51)	
BMI, kg/m^2, mean (SD)		25.49 (4.31)	
CCI; n (%)	**0**	194 (65.8)	
	1-8	101 (34.2)	
ASA score; n (%)	**1**	73 (24.7)	
	2	175 (59.3)	
	3	47 (15.9)	
Preoperative GFR, mL/min/1.73 m^2; n (%)	**>90**	98 (33.4)	
	60-90	119 (40.3)	
	<60	78 (26.3)	
Preoperative Hb; n (%)	**Normal**	199 (67.5)	
	Anemic	96 (32.5)	
Surgical side; n (%)	**Right**	128 (43.4)	
	Left	160 (54.2)	
	Bilateral	7 (2.4)	
Preoperative hydronephrosis; n (%)	**Positive**	201 (68.1)	
	Negative	94 (31.9)	
Anticoagulant use; n (%)	**Positive**	16 (5.4)	
	Negative	279 (94.6)	
Ipsilateral stone disease; n (%)	**Positive**	161 (54.6)	
	Negative	134 (45.4)	
History of ipsilateral renal intervention; n (%)	**Positive**	100 (33.9)	
	Negative	195 (66.1)	
History of abdominal surgery; n (%)	**Positive**	122 (41.4)	
	Negative	173 (58.6)	
Character of surgery; n (%)	**Urgent**	23 (7.8)	
	Elective	272 (92.2)	
Kidney size, mm, median (IQR)		100 (85-140)	
Surgical indication; n (%)	**Non-infectious presentation**	**Persistent flank pain**	151 (51.1)
		Hematuria	3 (1)
		Dyspnea secondary to enlarged kidney	3 (1)
		Colorenal fistula	1 (0.3)
		Retroperitoneal mass invasion	2 (0.7)
	Infectious presentation	**Recurrent urinary tract infection**	50 (16.9)
		Recurrent pyelonephritis	22 (7.5)
		Perinephric abscess	12 (4.1)
		Xanthogranulomatous pyelonephritis	6 (2)
	Hypertension		33 (11.2)
	PKD		11 (3.8)

ASA: American Society of Anesthesiologists, CCI: Charlson comorbidity index, GFR: Glomerular filtration rate, Hb: Hemoglobin, IQR: Interquartile range, PKD: Polycystic kidney disease, SD: Standard deviation

Table 2. Perioperative and postoperative results		
Parameters		
Operation time; min, mean (SD)		146.9 (55)
Blood loss mL, median (IQR)		50 (50-85)
Intraoperative complications; n (%)		32 (10.8)
Length of hospital stay, day, median (IQR)		3 (2-4)
Operation technique; n (%)	Open	195 (66.1)
	Laparoscopic	100 (33.9)
Hiler lymphadenopathy; n (%)	Positive	35 (11.9)
	Negative	260 (88.1)
Specimen weight, gr, median (IQR)		210 (119-404.5)
Pathological diagnosis; n (%)	Pyelonephritis	166 (56.3)
	Atrophic kidney	107 (36.3)
	PKD	11 (3.7)
	Neoplasia	5 (1.7)
	Other	6 (2)
Postoperative complications; n (%)	Clavien 1	4 (1.4)
	Clavien 2	63 (21.4)
	Clavien 3	9 (3)
	Clavien 4	1 (0.3)
	Clavien 5	3 (1)

IQR: Interquartile range, PKD: Polycystic kidney disease, SD: Standard deviation

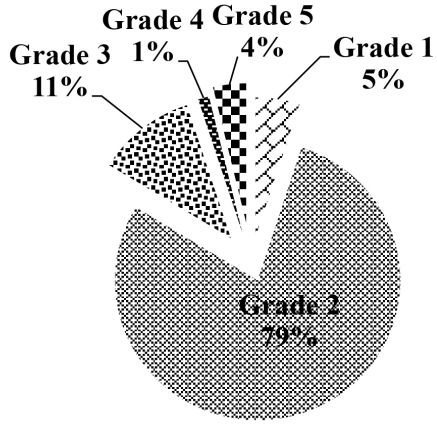

Figure 1. Post-operative complications according to Clavien-Dindo classification

Surgical factors such as simultaneous bilateral surgery, history of prior abdominal surgery, urgent character, open approach, pre-operative increased kidney size, simple nephrectomy indicated for recurrent infection and polycystic kidney disease were significantly associated with POC in univariate analysis as well (p=0.028, p=0.018, p<0.001, p=0.001, p=0.025, p<0.001, respectively) (Table 3). In multivariable analysis, pre-operative anemia, emergency surgery and open surgery were found to be statistically significant and associated with POC (p<0.001, p=0.004, and p=0.049, respectively) (Table 3).

The IOC rate was 10.8% (n=32). The most common IOC was adrenal injury (n=19). Other IOCs were the spleen (n=1), liver (n=1), diaphragm (n=3), aorta (n=1), colon (n=1), duodenum (n=2) and pancreas (n=1) in bleeding requiring transfusion (n=3). Male gender, higher CCI, high ASA score, pre-operative anemia, bilateral surgery and emergency surgery were the factors associated with IOC in the univariate analysis (p=0.001, p=0.002, p<0.001, p=0.009, p=0.021, p=0.006, respectively). Male gender, higher ASA score and emergency surgery were the statistically significant factors associated with IOC in multivariable analysis (p=0.002, p=0.001, p=0.021, respectively) (Table 4).

The two chronologically categorized groups were compared to analyze the changes in trends in surgical techniques and the change in post-operative outcomes. The rate of laparoscopic simple nephrectomy increased significantly, while the rate of POC decreased significantly between 2011 and 2019 compared to the years 2002 to 2010 (22.7% vs. 46.1%, p<0.001; 32.5% vs. 21.3%, p=0.031; respectively) (Figure 2).

Discussion

The etiology of non-functional kidney may vary from one geographic area to another. Most causes are preventable and

fall under public health area of interest. In most series, stone disease and urinary tract infections, among the other causes, are reported as the major causes of simple nephrectomies. Previous studies have focused on the correlation between definitive pathological findings and complication rates. The focus of our study was on the preoperative characteristics of patients that can be predictive of IOC and POC. Considering that our center provides care to a diversely represented population, findings

Table 3. Univariate and multivariaable analysis of factors affecting POC

Parameters		Univariate analysis			Multivariable analysis	
		Positive	Negative	p	OR (95% CI)	p
Gender (%)	Female	22.1	77.9	**0.042***	-	0.692
	Male	32.6	67.4			
Age, year, mean (SD)		47.09 (15.79)	44.01 (15.36)	0.130†	-	-
BMI, kg/m², mean (SD)		24.48 (4.34)	25.82 (4.27)	0.081†	-	-
CCI (%)	0	21.6	78.4	**0.003***	-	0.320
	1-8	37.6	62.4			
ASA score (%)	1	17.8	82.2	**<0.001***	-	0.375
	2	24	76			
	3	53.2	46.8			
Preoperative GFR, mL/min/1.73 m² (%)	>90	21.4	78.6	**0.004***	-	0.739
	60-90	22	78			
	<60	41.6	58.4			
Preoperative Hb (%)	Normal	15.2	84.8	**<0.001***	15.344 (5.265-44.722)	**<0.001**
	Anemic	52.1	47.9			
Surgical side (%)	Right	25.8	74.2	**0.028***	-	0.156
	Left	26.3	73.7			
	Bilateral	71.4	28.6			
Preoperative hydronephrosis (%)	Positive	26	74	0.375*	-	-
	Negative	31.1	68.9			
Anticoagulant use (%)	Positive	31.3	68.7	0.773*	-	-
	Negative	26.9	73.1			
Ipsilateral stone disease (%)	Positive	28.6	71.4	0.538*	-	-
	Negative	25.4	74.6			
Ipsilateral renal intervention (%)	Positive	34	66	0.057*	-	-
	Negative	23.6	76.4			
Previous abdominal surgery (%)	Positive	34.4	65.6	**0.018***	-	0.110
	Negative	22	78			
Character of surgery (%)	Urgent	78.3	21.7	**<0.001***	12.542 (2.266-69.420)	**0.004**
	Elective	22.8	77.2			
Operation technique (%)	Open	33.3	66.7	**0.001***	3.517 (1.008-12.275)	**0.049**
	Laparoscopic	15	85			
Kidney size, mm, median (IQR)		110 (96-162.5)	100 (80-140)	**0.025‡**	-	0.582
Surgical indication (%)	Non-infectious Presentation	20.3	79.7	**<0.001***	-	0.546
	Hypertension	6.1	93.9			
	PKD	54.5	45.5			
	Infection Presentation	43	57			

POC: Postoperative complications, ASA: American Society of Anesthesiologists, CCI: Charlson Comorbidity index, GFR: Glomerular filtration rate, Hb: Hemoglobin, IQR: Interquartile range, PKD: Polycystic kidney disease, SD: Standard deviation, OR: Odds ratio, CI: Confidence interval. Bold values indicate statistically significance, *: Chi-square test, †: Student's t-test, ‡: Mann-Whitney U test

Table 4. Univariate and multivariable analysis of factors affecting IOC						
Parameters		**Univariate analysis**			**Multivariable analysis**	
		Positive	**Negative**	**p**	**OR (95% CI)**	**p**
Gender (%)	**Female**	5.2	94.8	0.001*	**3.917 (1.632-9.401)**	0.002
	Male	17	83			
Age, year, Mean (SD)		46.69 (17.52)	44.62 (15.27)	0.477†	-	-
BMI, kg/m², Mean (SD)		24.43 (4.03)	25.65 (4.34)	0.219†	-	-
CCI (%)	**0**	6.7	93.3	**0.002***	-	0.413
	1-8	18.8	81.2			
ASA score (%)	**1**	4.1	95.9	**<0.001***	-	**0.001**
	2	9.1	90.9		**2.349 (0.647-8.525)**	
	3	27.7	72.3		**8.755 (2.238-34.253)**	
Preoperative GFR, mL/min/1.73 m² (%)	**>90**	6.1	93.9	0.126*	-	-
	60-90	11.9	88.1			
	<60	15.6	84.4			
Preoperative Hb (%)	**Normal**	7.6	92.4	**0.009***	-	0.570
	Anemic	17.7	82.3			
Surgical side (%)	**Right**	9.4	90.6	**0.021***	-	0.484
	Left	10.6	89.4			
	Bilateral	42.9	57.1			
Preoperative hydronephrosis (%)	**Positive**	9.9	90.1	0.390*	-	-
	Negative	13.3	86.7			
Anticoagulant use (%)	**Positive**	12.5	87.5	0.688*	-	-
	Negative	10.8	89.2			
Ipsilateral stone disease (%)	**Positive**	9.9	90.1	0.582*	-	-
	Negative	11.9	88.1			
Ipsilateral renal intervention (%)	**Positive**	9	91	0.465*	-	-
	Negative	11.8	88.2			
Previous abdominal surgery (%)	**Positive**	11.5	88.5	0.771*	-	-
	Negative	10.4	89.6			
Character of surgery (%)	**Urgent**	30.4	69.6	**0.006***	**3.518 (1.208-10.250)**	**0.021**
	Elective	9.2	90.8			
Operation technique (%)	**Open**	13.3	86.7	0.055*	-	-
	Laparoscopic	6	94			
Kidney size, mm, Median (IQR)		120 (87.5-187.5)	100 (89-140)	0.525‡	-	-
Surgical indication (%)	**Non-infectious presentation**	8.9	91.1	0.512*	-	-
	Hypertension	9.1	90.9			
	PKD	18.2	81.8			
	Infection presentation	14	86			

IOC: Intraoperative complications, ASA: American Society of Anesthesiologists, CCI: Charlson Comorbidity index, GFR: Glomerular filtration rate, Hb: Hemoglobin, IQR: Interquartile range, PKD: Polycystic kidney disease, SD: Standard deviation, OR: odds ratio, CI: Confidence interval. Bold values indicate statistically significance, *: Chi-square test, †: Student's t-test, ‡: Mann-Whitney U test

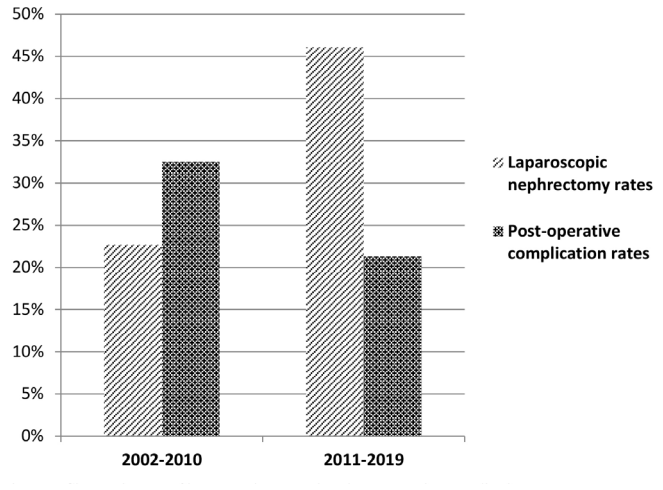

Figure 2. Changes in rates of laparoscopic approach and post-operative complications

of this study may guide health-care providers in our region. A recent article by Ames et al. (6) shows that this topic remains relevant. Their study demonstrates that causes of kidney loss may vary considerably among healthcare providers. Local patient characteristics should be considered when developing prevention and treatment strategies for a non-functional kidney.

In their series of 1039 benign nephrectomies from 112 institutions, Zelhof et al. (2) reported IOC and POC rates of 5.2% and 11.9%, respectively. Compared with 1095 T1 radical nephrectomies in the same study, simple nephrectomies were associated with a higher risk of IOC and POC (5.2% vs. 3.7% and 11.9% vs. 10%, respectively). These complication rates were inconsistent with those reported earlier in a single centre study with a relatively high number of patients comparing simple and radical nephrectomies, in which the authors described simple nephrectomy as an easier procedures (7). Being the largest series of benign nephrectomies compared to radical procedures, Zelhof et al. (2) provided strong data on the issue of previously inconsistent findings from mostly single center studies (7-9). It serves as a reference for the interpretation of our results. The study indicates that among the pathologies, stone disease had the highest risk of IOC and POC. The conversion rate to open surgery was found to be higher in stone and inflammatory diseases. Laparoscopy achieved better intra- and post-operative outcomes compared to open surgery. Our results show a significant association between open surgery and POC, but not with IOC. Manohar et al. (10) published similar inferior results for the open approach compared with laparoscopic surgery. As per our analysis, stone disease was not statistically associated with POC and IOC. Given that surgeries after infectious causes was significantly associated with POC in univariate analysis. The history of inflammation and perirenal fibrosis affects the outcome more than the history of stone disease alone. This finding is supported by numerous publications in one of which routine excision outside the Gerota's fascia is recommended to minimize complications (10-12). Due to the aforementioned reasons, laparoscopic nephrectomy performed for inflammatory etiology is considered challenging (9).

Our data showed no association between POC and IOC and the history of prior ipsilateral interventions despite published articles on this topic (13,14). Male sex has been strongly associated with IOC. It appears that the much dense and firm Gerota's fascia may have contributed to the difficult dissection in some cases. The phenomenon of "toxic fat" needs to be clarified in future studies.

Anemia is strongly associated with POC. Patients probably required transfusion more often, contributing to Clavien ≥2 grade complications. Anemia was significantly associated with IOC only in the univariate analysis.

In a recent retrospective study of 149 Nephrectomy for stone disease, Danilovic et al. (15) identified that a higher ASA score, emergency surgery, kidney size ≥12 cm and preoperative abscess were associated with POC Clavien >1. In our results, emergency surgery was associated not only with POC but also with IOC. A higher ASA score was associated with IOC instead of POC. Such discrepancy between the mentioned study and our findings may be explained by broader inclusion criteria and a higher number of patients in our cohort.

Our data demonstrate a significant association in the multivariable analysis of IOC and POC with emergency surgery. There is a rationale to avoid surgery in an urgent setting in favor of elective surgery (15,16). It is a good strategy to stabilize the affected renal unit as well as the patient before intervention whenever emergency nephrectomy is indicated.

In a recent article by Lubennikov et al. (16) investigated 108 bilateral nephrectomy patients for autosomal dominant polycystic kidney disease (ADPKD), approximately 80% of patients required surgery for infected cysts and pyelonephritis. An overwhelming 46.2% of the 39 patients who underwent emergency bilateral nephrectomies suffered a lethal outcome. In our series, bilateral nephrectomies of the same session were performed electively in limited cases for ADPKD in end-stage kidney disease patients. Bilateral nephrectomy was significantly associated with complications only in the univariate analysis. Such a result could be due to the limited number of patients (n=7). Considering the convincing findings from other studies, the same session bilateral nephrectomy should be approached with great caution.

Study Limitations

The main limitation of our study is its retrospective and non-randomized design. Past clinical decisions may have been biased according to the preferences of the primary surgeon at the time frame of the procedure. Differences in thresholds for parenteral antibiotic treatment inception and transfusion throughout the extensive time interval of the study could have contributed to the rates of Clavien >1 POC. Nevertheless, our results provide a valuable insight into the dynamics of practice in our institution over the past 17 years. Prospective randomized trials must further investigate the variables responsible for complications in nephrectomy for benign diseases.

Conclusion

The findings of this study will be useful to improve the quality of care in simple nephrectomy patients. Treatment plan should be tailored on an individual basis, particularly in male patients and those with higher ASA scores. Treatment of pre-operative anemia would reduce the need for post-operative transfusion rates. Necessary measures must be taken to avoid an emergency nephrectomy. An elective approach combined with laparoscopic surgery promises the best outcomes.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Institutional Ethics Committee (approval number: 2020/03-28).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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References

1. Raman JD, Sooriakumaran P, Cadeddu JA, Rane A. Radical and non-radical nephrectomy: no place for 'simple'. BJU Int 2009;103:855-856.
2. Zelhof B, McIntyre IG, Fowler SM, Napier-Hemy RD, Burke DM, Grey BR, British Association of Urological S. Nephrectomy for benign disease in the UK: results from the British Association of Urological Surgeons nephrectomy database. BJU Int 2016;117:138-144.
3. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.
4. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-470.
5. Cappellini MD, Motta I. Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin Change With Aging? Semin Hematol 2015;52:261-269.
6. Ames KS, Baky F, Blair S, Sanchez J, Franklin W, Barefoot A, Mears J, Magness P, Johnson B, Bakare T, Hudak S, Antonelli J, Hutchinson R, Lotan Y, Woldu SL. Simple Nephrectomy in a Tertiary Care Safety Net Hospital-Patient Characteristics, Causes, Cost, and Renal Function Implications. Urology 2021;149:98-102.
7. Connolly SS, O'Brien MF, Kunni IM, Phelan E, Conroy R, Thornhill JA, Grainger R. Is simple nephrectomy truly simple? Comparison with the radical alternative. Ir J Med Sci 2011;180:177-179.
8. Hemal AK, Gupta NP, Wadhwa SN, Goel A, Kumar R. Retroperitoneoscopic nephrectomy and nephroureterectomy for benign nonfunctioning kidneys: a single-center experience. Urology 2001;57:644-649.
9. Hsiao W, Pattaras JG. Not so "simple" laparoscopic nephrectomy: outcomes and complications of a 7-year experience. J Endourol 2008;22:2285-2290.
10. Manohar T, Desai M, Desai M. Laparoscopic nephrectomy for benign and inflammatory conditions. J Endourol 2007;21:1323-1328.
11. Duarte RJ, Mitre AI, Chambo JL, Arap MA, Srougi M. Laparoscopic nephrectomy outside gerota fascia for management of inflammatory kidney. J Endourol 2008;22:681-686.
12. Angerri O, Lopez JM, Sanchez-Martin F, Millan-Rodriguez F, Rosales A, Villavicencio H. Simple Laparoscopic Nephrectomy in Stone Disease: Not Always Simple. J Endourol 2016;30:1095-1098.
13. Greenstein A, Kaver I, Chen J, Matzkin H. Does preoperative nephrostomy increase the incidence of wound infection after nephrectomy? Urology 1999;53:50-52.
14. Carrillo-Cordova LD, Jimenez-Villavicencio JM, Vitar-Sandoval J, Sarabia-Estrada RC, Rivera-Astorga H, Lemus-Mena GR, Sanchez-Meza E, Carrillo-Cordova JR, Camilo-Martinez EJ, Rosas-Ramirez A, Virgen-Gutierrez JF, Jaspersen-Gastelum J, Garduno-Arteaga ML. Comparison of results of open simple nephrectomy secondary to lithiasis in patients with and without nephrostomy. Cirugia Y Cirujanos 2017;85:325-329.
15. Danilovic A, Ferreira TAC, Maia GVA, Torricelli FCM, Mazzucchi E, Nahas WC, Srougi M. Predictors of surgical complications of nephrectomy for urolithiasis. Int Braz J Urol 2019;45:100-107.
16. Lubennikov AE, Petrovskii NV, Krupinov GE, Shilov EM, Trushkin RN, Kotenko ON, Glybochko PV. Bilateral Nephrectomy in Patients with Autosomal Dominant Polycystic Kidney Disease and End-Stage Chronic Renal Failure. Nephron 2021;145:164-170.

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Is A One-Question Visual Analog Scale A Screening Tool That Can Be Used to Assess Female Sexual Dysfunction Before Implementing A Female Sexual Function Index?

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

In the literature, there is only one study in which the evaluation of female sexual function in women was made using visual analog scale (VAS). However, in this study, Likert scale was used instead of the classical VAS. In our study, classical VAS was used to evaluate female sexual function.

Abstract

Objective: To validate the use of a single-question visual analog scale assessing sexual dysfunction as a screening tool before implementing the female sexual function index (FSFI).

Materials and Methods: The study included 141 sexually active women over 18 years of age who were diagnosed with OAB or UI. A female sexual function-visual analog scale (FSF-VAS) was defined and developed as a one-question form in which participants were asked to mark their sexual function on a 10 cm visual analog scale. The cut-off values for the FSF-VAS in predicting FSD were determined by receiver operating characteristic curve analysis and Youden's index.

Results: A positive, moderately strong correlation was found between the FSFI score and FSF-VAS (rs=0.741). We found a cut-off value for FSF-VAS as 5.95 for in predicting both FSFI score of <25 [area under the curve (AUC) (confidence interval (CI) 95%): 0.886 (0.827-0.945)] and FSFI score of <26.55 [AUC (CI 95%): 0.893 (0.834-0.952)]. FSF-VAS value was below 5.95 in 82 of 141 (58.1%) patients who participated in the study.

Conclusion: Using the FSFI for only those with a FSF-VAS score of 5.95 or lower will reduce the clinician's Workload save time, and also spare patients from the embarrassment caused by the questions in the FSFI.

Keywords: Female sexual function index, female sexual function, visual analog scale

Introduction

Female sexual dysfunction (FSD) is a significant multidimensional health problem with biological and psychological components, which is thought to be highly prevalent in society. Although the true prevalence of FSD is unknown, approximately 50% of women have at least one sexual complaint (1). The International Consensus Development Conference on Female Sexual Dysfunctions recommended a FSD model that includes four major components (desire disorder, arousal disorder, orgasmic disorder, and sexual pain disorder), as described in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and the International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10) (2). In 2000, the Female Sexual Function index (FSFI), which is a multidimensional self-report instrument, was developed to measure female sexual function

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(FSF), based on the FSD model. Satisfaction and lubrication were added to the four components (desire, arousal, orgasm and sexual pain) in the FSD model, and a 19-question assessment form was created (3). In 2010, a six-question form (FSFI-6) was developed, in which each item was evaluated with a single question (4). However, no validation studies, which are important to assess the structural validity, have investigated the unidimensional nature of the FSFI-6 (5).

Although the FSFI is the gold standard in evaluating FSF in daily practice (6), the fact that it is a 19-item test can cause difficulties in implementation. Therefore, in our study, we answer the question of whether we can detect patients with sexual dysfunction with the use of a visual analog scale (VAS) with a single question and then evaluate only those patients with the FSFI. Because of the high prevalence of FSD in patients with overactive bladder (OAB) and urinary incontinence (UI), we selected this group of patients for this study (7).

Materials and Methods

Study Design

The study included 141 sexually active women who had been diagnosed with OAB and UI. None of the patients mentioned any sexual dysfunction problems, and they were not questioned on this issue. All participants were asked to complete the self-report FSFI questionnaire and the FSF-VAS individually in turn. The inclusion criteria for the selected participants were that they had to be between 18-60 years old, be sexually active, be able to complete the questionnaires and be willing to participate in the study. The exclusion criteria for the selected participants were having neurological or psychiatric disease, having genitourinary disorder that may cause chronic pelvic pain and painful sexual intercourse, and having drug therapy that may cause sexual dysfunction. All participants were informed about and anonymity and confidentiality.

Data Collection and Definitions

Clinical data, including age, educational status, menopause status, and primary diagnosis, were retrieved from the Gazi University Female Urology Department database retrospectively. Considering the socio-cultural sensitivities of the society we live in, the definition of "sexually active" was done as having a regular sexual life with a partner/husband. The FSFI was used as a reference gold standard measurement tool to evaluate the FSF. The patients were asked to fill in a 19-question hard -copy FSFI questionnaire, which was validated in Turkish (8). For the definition of FSD in FSFI, values of <26.55 and <25, which were previously determined in the literature, were used (9,10). The FSF-VAS was defined and developed as a one-question form, where participants were asked to rate their sexual function on a 10 cm visual analog scale. The patients were asked to complete the FSF-VAS form first, followed by the FSFI questionnaire. Participants were observed during the completion of FSF-VAS form to ensure that measuring instruments were not used.

Statistical Analyses

All statistical analyses were performed with the R version 4.0.4 through R Studio version 1.4.1106. Spearman's correlation analysis was performed to evaluate the correlation between the questionnaire scores. The cut-off values for the FSF-VAS were determined with a receiver operating characteristic (ROC) curve analysis and Youden's index and were reported using the sensitivity, specificity, and area under the curve (AUC) with 95% confidence intervals [95% confidence intervals (CIs)]. A significance level of α=0.05 was set for all analyses.

Ethics Statement

The study protocol was approved by the clinical research ethics committee of our university (Gazi University Clinical Research Ethics Committee - date: 17.10.2012; approval number: 341).

Results

The baseline characteristics are summarized in Table 1. The mean age was 44.6±7.95. The mean FSFI and median FSF-VAS scores were 21.3±(5.0) and 5.2 (4.0-7.0), respectively.

The correlations between the FSFI score and FSF-VAS were evaluated with Spearman's correlation analysis. A moderately

Table 1. Baseline characteristics

	n=141
Age (year) (mean ± SD)	44.6±7.95
Educational status n (%)	
Illiterate	3 (2.1)
Literate	3 (2.1)
Primary school	57 (40.4)
Middle/High school	37 (26.2)
Bachelor's degree	41 (29.1)
Menopause n (%)	
No	96 (68.1)
Yes	45 (31.9)
Primary diagnosis n (%)	
Overactive bladder	21 (14.9)
Stress incontinence	26 (18.4)
Urgency incontinence	28 (19.9)
Mixed incontinence	66 (46.8)
FSFI score (mean ± SD)	21.3±(5.0)
FSF-VAS [median (IQR)]	5.2 (4.0-7.0)

FSFI: Female sexual function index, FSF: Female sexual function, VAS: Visual analog scale, SD: Standard deviation, IQR: Interquartile range

strong positive correlation was found between the FSFI score and FSF-VAS r_s=0.730, p<0.001).

The patients were divided into two groups according to their FSFI scores: <25 vs. ≥25 and <26.55 vs. ≥26.55. A ROC analysis was performed to determine the cut-off values of the FSF-VAS to predict the FSFI scores <25 and <26.55 (Table 2). The cut-off values for predicting FSFI score of <25 were found to be 5.95 for the FSF-VAS [AUC (CI 95%): 0.888 (0.836-0.941); p<0.001].

Table 2. Receiver operating curve analysis of FSFI score and FSF-VAS by using different cut-off values of FSFI

	FSF-VAS	
	AUC	**Cut-off value**
FSFI (<25 vs. ≥25)	0.886	5.95
FSFI (<26.55 vs. ≥26.55)	0.893	5.95

FSFI: Female sexual function index, FSF: Female sexual function, VAS: Visual analog scale, AUC: Area under curve, CI: Confidence interval

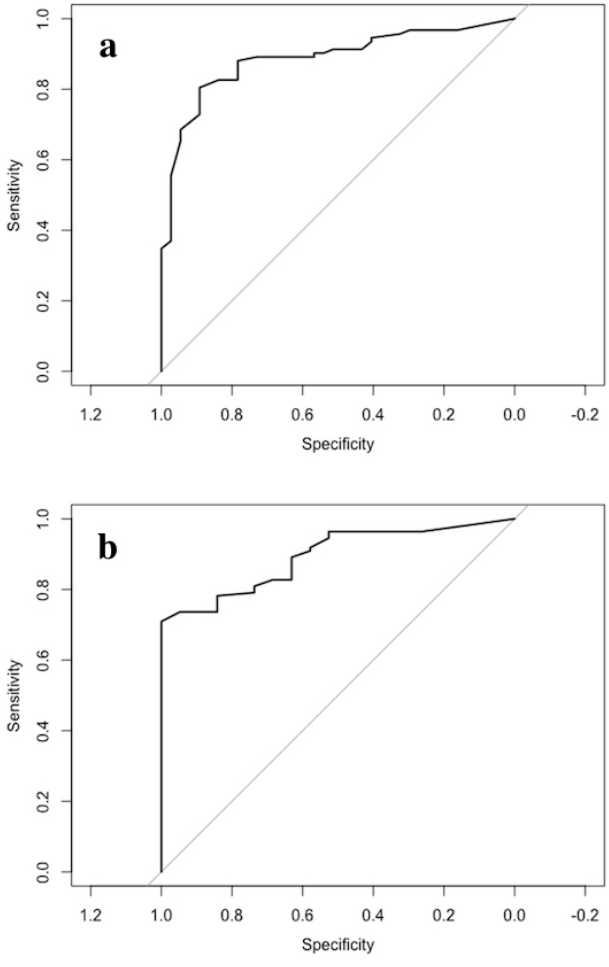

Figure 1. Receiver operating curves of FSF-VAS in predicting FSFI <25 (a) and FSFI <26.55 (b)

FSFI: Female sexual function index, FSF: Female sexual function, VAS: Visual analog scale

The sensitivity and specificity of the cut-cutoff values for FSF-VAS were 0.80 and 0.89, respectively (Figure 1a). The cut-off values for predicting FSFI score of <26.55 were found to be 5.95 for FSF-VAS [AUC (CI 95%): 0.893 (0.834-0.952); p<0.001]. The sensitivity and specificity of the cut-off values for FSF-VAS and FSF-Score were 0.70 and 1 (Figure 1b). When the FSF-VAS cut-off value was taken as 5.95 in predicting FSD, it was found that 82 (58.1%) patients were below this value.

Discussion

In our study, a moderately strong correlation was found between FSFI and FSF-VAS. We used two cut-off values for FSFI, 25 and 26.55, to evaluate FSD. Accordingly, we found a cut-off value for FSF-VAS of 5.95 for predicting FSD.

Evaluating FSD is often a challenge for both healthcare professionals (HCPs) and patients and often results in fears of "opening a can of worms" among HCPs. Structural, healthcare organizational and personal factors are intertwined parameters that influence the approach of HCPs to the evaluation of FSD (11). Women are prevented from talking about their sexual lives due to feeling embarrassed, and lack of time, training and tools, and limited training options are the barriers inhibiting HCPs, and, in addition, being unaware of or having misconceptions about conditions that may impact sexual function are barriers inhibiting patients (12). Awareness of sexual dysfunction among women is also quite limited. It was reported that 31.3% of those who did not seek help the condition indicated that they did not know that the sexual dysfunction they experienced was a medical condition, 28.9% "thought it was normal" to have FSD, and 14.1% did not think that a medical provider would be able to assist them with this issue (13). However, a recent study performed in France found that, despite it being an embarrassing subject, 93% of the patients would have welcomed the question "how is your sexuality these days?" (12). This may indicate that a short, clear, and non-specific screening question about sexual life may not be as intrusive as some might assume. Instead of resorting to long questionnaires cumbersome in practice, our practical approach would ease the possible stress of the detection of FSD for both the physician and patient, especially with women who do not even voice complaints. We think that the FSF-VAS can be used as a screening test that is simple to apply without causing delays in outpatient clinic conditions or discomfort to those who attend the clinic. The FSFI has questions related to the six domains of FSD. However, since there are also socio-cultural and psychological aspects related to FSD in addition to these domains, the VAS may also include these aspects.

The VAS was first developed by Hayes (14) in 1921 as a "graphic rating method" to overcome the limitations of ordinal

measures from Likert-type scales. The VAS has a wide range of uses in different areas in daily urological practice (15-17). The only study in the literature that evaluated the psychometric properties of the FSFI applied to the VAS was conducted by Wolpe et al. (18) in 2015. The 10 cm line on the VAS was divided into five parts for each question, with each 2 cm segment equal to one alternative on the Likert response format. Correlations between FSFI-Likert and FSFI-VAS were evaluated on a question basis, and the correlation coefficient was found to be below 0.7 in only three questions. When evaluated as the total score, a strong correlation was found between FSFI-Likert and FSFI-VAS, with a correlation coefficient of 0.87. The study also revealed that the internal consistency, construct validity, discriminant validity, and reproducibility of the FSFI-VAS were adequate (18). Unlike this study, in our study, we evaluated the relationship between the FSFI-Likert total score and the one-item FSF-VAS and found a moderately strong correlation between them, with a correlation coefficient of 0.74.

In 2000, when the FSFI was first developed, no cut-off value was specified for FSD, but several cut-off values were defined afterwards (3). In a study by Oksuz and Malhan (8) in 2005, who performed validity and reliability analysis of the Turkish version of the FSFI, the mean score was found to be 25.52 in the control group and 22.45 in the FSD group. The same authors diagnosed women with an FSFI score of <25 as having sexual dysfunction in their prevalence study (9). In 2010, Wiegel et al. (10) conducted a study with 568 female participants to determine the cut-off value for FSD. An FSFI score of 26.55 was found to be the optimal cut-off value to distinguish those who have sexual dysfunction issues from those who do not. In another validation and reliability study conducted in 2019 and involving Spanish women, the cut-off value for FSD determination was found to be 24.95 (19). In line with these studies, we preferred to use cut-off values of 25 and 26.55 for FSD. To predicting FSD, we found the cut-off value for FSF-VAS to be 5.95 for both FSFI scores 25 and 26.55.

Two recent studies in the literature that are methodologically similar to our study developed scales to predict a FSFI score of <26.55 to determine FSD. In a study by Mollaioli et al. (20), the authors asked patients to rate their orgasmic intensity on a one-question VAS, the "Orgasmometer-F." It was found that a cut-off value of 5 in the Orgasmometer-F had a high AUC, sensitivity and specificity in differentiating between women with and without sexual dysfunction (AUC=0.9, p<0.0001; sensitivity: 86.5%, specificity: 80.4%, positive predictive value: 75.4%, negative predictive value: 89.5%. In another study by Jara et al. (21,22), an 11-item menopause rating scale, which had been previously described and translated into many languages (21), was used to determine FSD. It was found that a score of >1 for item number 8 identified women with and without sexual dysfunction, with an AUC of 0.70, 78% sensitivity, 62% specificity (22).

Study Limitations

Our study was a cross-sectional observational study. Note that the cut-off values determined for FSD may not reflect the general population since our study was conducted only in female patients with OAB and UI. Our study included young and old and pre- and postmenopausal women. Since there may be different cut-off values for FSD in this group of patients, it would be more appropriate to perform separate analysis for each group, but, due to the small number of patients, we could not perform a separate analysis for each group.

Conclusion

The FSF-VAS value of 5.95 may be a parameter that can be used in the screening of sexual dysfunction in women, since there is a strong correlation between the FSFI score and FSF-VAS, and the FSF-VAS also predicts the cut-off values for FSD with high sensitivity and specificity. Due to the difficulty of implementing the FSFI as a screening tool in daily urological practice, using the FSFI for only those with a FSF-VAS score of 5.95 or higher will reduce the clinician's workload, save time and spare patients from the embarrassment caused by the questions in the FSFI.

Ethics

Ethics Committee Approval: The study protocol was approved by the clinical research ethics committee of our university (Gazi University Clinical Research Ethics Committee - date: 17.10.2012; approval number: 341).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.O., Design: İ.Ş., Data Collection or Processing: E.C.B., S.Ç., Analysis or Interpretation: M.Y.K., S.Ç., Literature Search: M.Y.K., M.O., İ.Ş., Writing: M.Y.K., E.C.B.

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

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

References

1. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999;281:537-544.
2. Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, Goldstein I, Graziottin A, Heiman J, Laan E. Report of the international consensus

development conference on female sexual dysfunction: definitions and classifications. J Urol 2000;163:888-893.

3. Rosen CB, J. Heiman, S. Leiblum, C. Meston, R. Shabsigh, D. Ferguson, R. D'Agostino, R. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191-208.
4. Isidori AM, Pozza C, Esposito K, Giugliano D, Morano S, Vignozzi L, Corona G, Lenzi A, Jannini EA. Outcomes assessment: Development and validation of a 6-item version of the Female Sexual Function Index (FSFI) as a diagnostic tool for female sexual dysfunction. J Sex Med 2010;7:1139-1146.
5. Neijenhuijs KI, Hooghiemstra N, Holtmaat K, Aaronson NK, Groenvold M, Holzner B, Terwee CB, Cuijpers P, Verdonck-de Leeuw IM. The Female Sexual Function Index (FSFI)—a systematic review of measurement properties. J Sex Med 2019;16:640-660.
6. Okobi OE. A Systemic Review on the Association Between Infertility and Sexual Dysfunction Among Women Utilizing Female Sexual Function Index as a Measuring Tool. Cureus 2021;13.
7. Moore CK. The impact of urinary incontinence and its treatment on female sexual function. Curr Urol Rep 2010;11:299-303.
8. Oksuz E, Malhan S. Reliability and validity of the Female Sexual Function Index in Turkish population. Sendrom 2005;17:54-60.
9. Oksuz E, Malhan S. Prevalence and risk factors for female sexual dysfunction in Turkish women. J Urol 2006;175:654-658.
10. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005;31:1-20.
11. Dyer K, das Nair R. Why don't healthcare professionals talk about sex? A systematic review of recent qualitative studies conducted in the United Kingdom. J Sex Med 2013;10:2658-2670.
12. Zéler A, Troadec C. Doctors Talking About Sexuality: What Are the Patients' Feelings? Sex Med 2020;8:599-607.
13. Ibine B, Sefakor Ametepe L, Okere M, Anto-Ocrah M. "I did not know it was a medical condition": Predictors, severity and help seeking behaviors of women with female sexual dysfunction in the Volta region of Ghana. PloS One 2020;15:e0226404.
14. Hayes M. Experimental developement of the graphics rating method. Physiol Bull 1921;18:98-99.
15. Kuehhas FE, Miernik A, Sharma V, Sevcenco S, Javadli E, Herwig R, Szarvas T, Schoenthaler M, Schatzl G, Weibl P. A prospective evaluation of pain associated with stone passage, stents, and stent removal using a visual analog scale. Urology 2013;82:521-525.
16. Lukacz ES, Lawrence JM, Burchette RJ, Luber KM, Nager CW, Buckwalter JG. The use of Visual Analog Scale in urogynecologic research: a psychometric evaluation. Am J Obstet Gynecol 2004;191:165-170.
17. Pineda-Murillo J, Martínez-Carrillo G, Hernández-León O, Viveros-Contreras C, Torres-Aguilar J. The Erectile Function Pineda Visual Analog Scale (EFP-VAS): An alternative to the International Index of Erectile Function (IIEF-5). Rev Int Androl 2019;18:101-106.
18. Wolpe RE, Queiroz AP, Zomkowski K, Sperandio FF. Psychometric properties of the Female Sexual Function Index in the visual analogue scale format. Sex Health 2017;14:213-220.
19. Pérez-Herrezuelo I, Hita-Contreras F, Martínez-Amat A, Aibar-Almazán A, Cruz-Díaz D, Wangensteen R, Ochoa AA, Díaz-Mohedo E. The female sexual function index: reliability and validity in Spanish postmenopausal women. Menopause 2019;26:401-408.
20. Mollaioli D, Di Sante S, Limoncin E, Ciocca G, Gravina GL, Maseroli E, Fanni E, Vignozzi L, Maggi M, Lenzi A. Validation of a Visual Analogue Scale to measure the subjective perception of orgasmic intensity in females: The Orgasmometer-F. PLoS One 2018;13:e0202076.
21. Heinemann LA, Potthoff P, Schneider HP. International versions of the menopause rating scale (MRS). Health Qual Life Outcomes 2003;1:1-4.
22. Jara D, Fuenzalida A, Figueroa R, del Prado M, Flores D, Blümel JE, Chedraui P. Is the Menopause Rating Scale accurate for diagnosing sexual dysfunction among climacteric women? Maturitas 2009;62:321-323.

ORIGINAL RESEARCH
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A Guideline-Oriented Ontological Decision Support System for Diagnosis and Treatment of Urinary Incontinence (UrInO-DSS): A System Framework

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

This study is a foreground to design a guideline-oriented ontological clinical decision support system for urinary incontinence, called UrInO-DSS. An ontology for urinary incontinence management will be designed on the basis of a clinical practice guideline. The system will offer a tool to help clinicians manage patients who suffer from urinary incontinence.

Abstract

Objective: To design an ontology-based clinical decision support system based on a clinical guideline for urinary incontinence.

Materials and Methods: The study will be conducted in four phases: Updating the adapted clinical guideline for urinary incontinence for Iranian clinicians; Developing an ontology based on the adapted guideline; Developing a guideline-oriented ontological decision support system for urinary incontinence; and evaluating both the ontology and the decision support system. The GRADE-Adolopment methodology will be used for updating the adapted guideline. The researcher will deploy Protégé 5.5.0 ontology editor for developing the ontology. The rules will be extracted from the adapted guideline for urinary incontinence, and the rule language will be Semantic Web Rule Language. Ontology consistency will be evaluated with Pellet reasoner. The system will be evaluated and analyzed by the GUIDES checklist.

Results: The results of the study will be published and disseminated in peer-reviewed journals.

Conclusion: UrInO-DSS will offer a tool to support clinicians in providing personalized treatment for patients who suffer from urinary incontinence. It can also help the residents and medical students to learn how to diagnose and manage urinary incontinence in the best way. The system can be implemented as an international decision support system for the diagnosis and management of urinary incontinence.

Keywords: Biological ontologies, decision support systems, clinical, practice guidelines as topic, urinary incontinence

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Introduction

Urinary incontinence (UI) is one of the most prevalent urologic disorders, particularly among female patients (1). A cohort study predicted 8.5 percent global prevalence of incontinence in 2018 (2). The total prevalence of UI in developing countries was 27.5%, according to a recent meta-analysis study in 2020 (3).

UI is a multifactorial condition. Some of the most common risk factors for UI are obesity, parity, age, urinary tract infection (UTI), a history of hysterectomy, menopause, and type of delivery (1,4,5). Diagnosis of UI and its type is one of the most complex and controversial issues in managing urological diseases (6,7). Background risk factors like bladder dysfunction or neurological conditions can complicate the diagnosis. However, many concomitant disorders, such as functional bowel disorder, affect the diagnosis and management of incontinence.

Recognition and usage of accurate, reliable, and up-to-date information in practice is another challenge for physicians where reducing medical errors is a priority. The lack of time should also be added to these concerns. Clinical Practice Guidelines (CPGs) are one of the evidence-based resources for managing diseases and assist physicians in reliable and appropriate decision-making and improve patient care. However, remembering all the recommendations of guidelines, accommodating them with patient history and physical examination and tests while considering complications and risk factors, and finally making the best decision can be burdensome for physicians and, in some cases, may lead them to bias in decision-making.

Nowadays, developing high-quality and ease-to-use computer-interpretable clinical guidelines are necessary for patient care (8). Clinical Decision Support System (CDSS), as the best evidence-based source, according to Alper and Haynes (9), are valuable tools for this purpose. A CDSSES can include clinical guidelines, summaries of evidence, and syntheses while integrating with patient information and ultimately becoming the most credible and best support in clinical decision making. This approach fulfills the requirements for complementarity of Evidence-Based Medicine (EBM) and personalized care (10). To this end, it is necessary to improve the interoperability and knowledge sharing among systems, and ontology can play a crucial role. In healthcare, an ontology, by creating semantic relationships between disease/disorders, symptoms, medications, and other related concepts, allows the CDSS to imitate the physician's reasoning and offer the appropriate recommendations based on patient information (11). Ontologies can be built according to the information available in clinical guidelines and domain knowledge and applied in a knowledge-based system to manage diseases. Simultaneously, when developing a CDSS, structural and content differences in the management of diseases/disorders should be considered.

Ontology-based CDSSs are widely designed and used in medical sciences (12-15). In urology, most ontology-related studies are in the field of prostate cancer (16,17). But as our best knowledge, no ontology-based decision support system has been developed for UI. Many decision support systems are designed for the diagnosis and management of UI, but neither is ontology-based (18,19). In the absence, we design a guideline-oriented ontological CDSS for the UI, called UrInO-DSS.

Materials and Methods

This study aims to design, develop and evaluate a guideline-oriented ontological clinical decision support system for UI. This system will support clinicians in the diagnosis and management of UI according to guideline recommendations. The goal of the system is to use it in the primary and secondary care setting. Ethical approval was obtained from the Ethics Committee of the Tabriz University of Medical Sciences under Grant (TBZMED.REC.1398.132).

Study Design

This study involves four phases: 1) updating the adapted UI clinical practice guideline for Iranian clinicians; 2) developing an ontology based on adapted CPG; 3) designing and developing a clinical decision support system for UI based on developed ontology and 4) evaluating the system.

Phase 1: Updating the Adapted Clinical Practice Guideline for UI

We used the GRADE-Adolopment methodology for updating the adapted guideline for UI (20). An adapted clinical practice guideline for managing UI entitled "Clinical practice guideline: Female Urinary Incontinence" has been used since 2013 (21). Updating this guideline is under development in collaboration with the Urogynecology Knowledge Management Unit of the Research Center for Evidence-Based Medicine (RCEBM) and Urology Department. The guideline updating team included female urologists, urogynecologists, clinical librarians, and guideline methodologists. The expert panel assessed and confirmed clinical questions (PICOs) of the adapted clinical guideline and other related PICOs for updating the guideline. According to the PICOs, we searched and screened the most updated and recent relevant guidelines for all new and updated recommendations. Tables 1-3 presents the PICOs. New, updated, and consistent recommendations were selected from the guidelines. If the answers to some outcomes of PICOs were not available in the recommendations of the guidelines, *de novo* systematic reviews were conducted to get the answers.

A draft of the updated guidelines was translated to Persian. Guideline developers and experts assessed the translated draft, and necessary modifications and edits were made. If any specific recommendation needed to be adapted, further research was

conducted to find evidence-based relevant studies. Then based on the results of the studies and considering the cultural and organizational setting, the necessary modifications were made. The expert panel was assembled consisted of urologists, female urologists, urogynecologists, neuro-urologists, gynecologists, midwives, physiotherapists, nurses, health economists, epidemiologists, pharmacists, representatives of the patients, and other We are currently creating GRADE evidence tables and Evidence to Decision (EtD) frameworks and grading the strength of the recommendations. The grading strength of recommendations will be done electronically by guideline developers and the panelists through GRADEpro (http://gradepro.org). The strength of recommendation will be rated according to the GRADE system to "Strong" and "Weak" (22). The panel will approve the final draft of the adapted CPG for implementation in the setting.

Phase 2: Ontology Development Based on the Adapted Clinical Practice Guidelines for UI

Reusability, interoperability, easy sharing, and formality of knowledge are known as the features and benefits of ontology. These benefits make ontologies a suitable approach for knowledge representation and management in CDSSs. Due to the critical role of guidelines and pathways in practice, a significant number of systems have focused on developing ontologies based on guidelines and pathways and applying them to the system.

Ontologies can represent both conceptual knowledge and procedural knowledge. Conceptual knowledge represents the specific domain concepts and their relationship, whereas procedural knowledge represents the procedures and measures needed to be taken (23). Conceptual knowledge will be extracted from adapted clinical guidelines, articles, the website of reputable and well-known universities and scientific associations. The ontology will be developed according to the Kuziemsky and Lau (24) approach. The accuracy of the concept will be confirmed by experts (25). The information extracted from adapted clinical practice guidelines for UI diagnosis and management will be used for ontology development of procedural knowledge.

In the process of ontology development, we searched and reviewed the available related ontologies. To the best of our knowledge, there was no ontology for UI. However, we will use standard ontologies such as Symptom Ontology, Human Disease Ontology (DOID), Clinical Signs and Symptoms Ontology (CSSO) and Unified Medical Language System (UMLS) for selecting and using standard concepts in the development of our ontology. The ontology will be developed on the basis of UI diagnosis and management process, and it will represent concepts for the UI and related examinations, tests and procedures. A bilingual ontology will be developed.

For the process of UI diagnosis and management, the ontology consists of the domain ontology and patient ontology. Overall, the ontology includes five main classes: Demographic_Information, Clinical_Assessment, Diagnosis, Treatment and Patient (Figure 1).

Note that the Patient class represents patients' personal information collected and updated in the form of ontology concepts. Patient information will be gathered through CDSS (Phase 3) and will be updated based on the system recommendations and physician's final decisions. These updates will be applied in the form of a system input to the ontology. Additional sub-classes, individuals, and properties will be defined and created during ontology development. The Delphi method will be used for eliciting and collecting experts' opinions. Protégé 5.5.0 ontology editor (https://protege.stanford.edu) and Web Ontology Language (OWL) are used for ontology development. The rules will be modeled using SWRL. The rules will follow adapted CPG for UI. The rules will fall into two categories: the rules for UI diagnosis, and UI treatment.

Phase 3: Designing and Developing a CDSS for the Diagnosis and Management of UI Based on the Developed Ontology

To design an efficient system, it is necessary to assess the system and end-users requirements (26). Users' characterizations, requirements, and the workflow for diagnosis and treatment of UI should be identified and analyzed. There are valuable and standard tools for requirement acquisition, such as interviews, observation techniques, focus group discussions and others (27). In this study, interviews with stakeholders, observation, and prototyping will be used for gathering requirements. Part of the requirements that can be implemented through the ontology will be met with the developed ontology. The remaining requirements will be implemented in the system

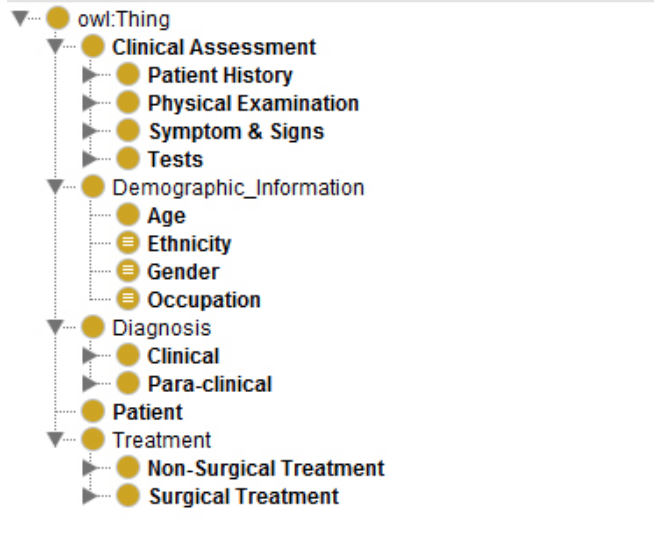

Figure 1. A sample of class hierarchy for urinary incontinence ontology

design. Considering the process of UI management is shown in Figure 2, a knowledge-based decision support system will be designed using the ontology developed in phase 2.

The system will operate according to the latest adapted CPG in UI for Iranian clinicians. The system recommendations and decisions will be based on clinical practice guideline rules (CPG rules). The ontology will be updated with the latest updates and changes as needed and, consequently, will be applied to the system. A significant portion of these changes will be patient information and their personalized diagnosis and treatment that will automatically be added to the ontology through the system. Patient medical information, such as their symptoms and signs, laboratory tests, urodynamic tests, and vital signs, will be added to the patient ontology.

Patient information is collected through the user interface in a database. The latest data from the repository database will then be synchronized automatically to the ontology. In the following steps, electronic health record (EHR), laboratory test ordering system, and urodynamic test system will be connected to this system and the required information from these systems, such as personal patient information, patient history, results of the patient's tests, and examinations, will be semantically integrated into the ontology. Patients and their guardians will receive oral information about the system operation, and a written informed consent form was obtained from the patient upon admission. Diagnosis and treatment of the individual patient will be based on their mapped information in the ontology and enable personalized patient care. Based on the patient ontology and rules, the systems recommended management options are offered to the physician. Considering the patient's condition, the physician offers the patient the appropriate management options, discusses each option's benefits and risks according to Number Needed to Treat (NNT) and Number Needed to Harm (NNH). The final decision will be made by the physician based on a shared-decision making. Ultimately, personalized diagnosis and management of the patient will be added to the ontology.

Three security dimensions, including confidentiality, availability and integrity, will be considered in the system design (26). Users' access level to authorized information will be possibly based on permission management. The data access permission will be based on the data protection regulations of the Ministry of Health of Iran. The architecture of the prototype system is shown in Figure 3.

Phase 4: System Evaluation

Evaluation of UrInO-DSS will be carried out in two steps: 1) evaluation of the developed ontology and content validation and 2) evaluation of the designed system.

The developed ontology will be evaluated for correctness based on three metrics: Accuracy, completeness, and consistency (25).

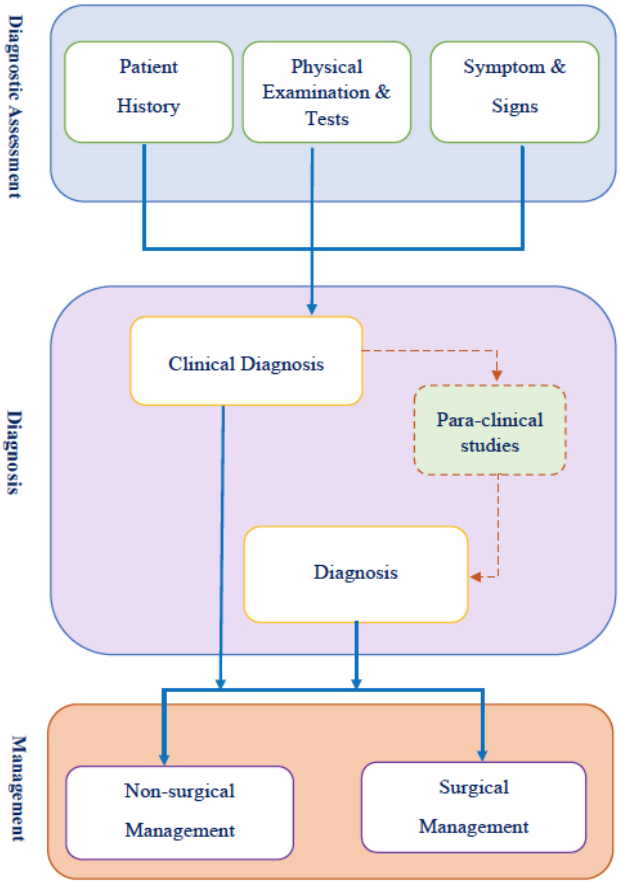

Figure 2. Process of managing urinary incontinence

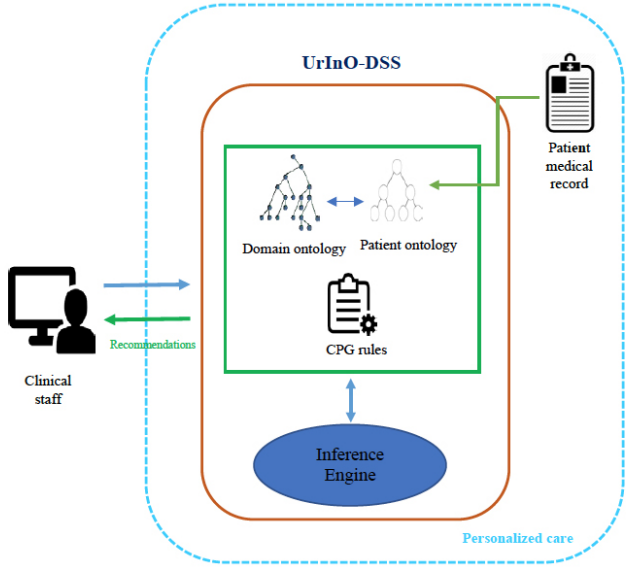

Figure 3. Architecture proposed for the system

Table 1. Clinical questions (PICOs): Diagnostic assessments of UI	
PICO-1: Physical examinations	
P (Population)	Adult women with suspected urinary incontinence
E (Exposure)	Physical examinations
C (Comparison)	Other exposures; None
O (Outcomes)	More accurate diagnosis of urinary incontinence
PICO-2: Valid questionnaires & Bladder diaries	
P (Population)	Adult women with suspected urinary incontinence
E (Exposure)	Patient questionnaires
C (Comparison)	Other exposures; None
O (Outcomes)	More accurate diagnosis of urinary incontinence
PICO-3: Diagnostic tests	
P (Population)	Adult women with suspected urinary incontinence
E (Exposure)	Diagnostic tests
C (Comparison)	Other exposures; None
O (Outcomes)	More accurate diagnosis of urinary incontinence
PICO-4: Urodynamics	
P (Population)	Adult women with suspected urinary incontinence
E (Exposure)	Urodynamics
C (Comparison)	Other exposures; None
O (Outcomes)	More accurate diagnosis of urinary incontinence
PICO-5: Imaging	
P (Population)	Adult women with suspected urinary incontinence
E (Exposure)	Imaging
C (Comparison)	Other exposures; None
O (Outcomes)	More accurate diagnosis of urinary incontinence
UI: Urinary incontinence	

Table 2. Clinical questions (PICOs): Non-surgical interventions for UI	
PICO-1: Lifestyle interventions	
P (Population)	Adult women with female urinary incontinence
I (Intervention)	Lifestyle modifications
C (Comparison)	Any other interventions; Sham interventions; None
O (Outcomes)	Cure, improving quality of life, reducing adverse effects
PICO-2: Behavioural and Physical therapies	
P (Population)	Adult women with female urinary incontinence
I (Intervention)	Pelvic floor muscle training, bladder training, ...
C (Comparison)	Any other interventions; Sham interventions; None
O (Outcomes)	Cure, improving quality of life, reducing adverse effects
PICO-3: Pharmacological management	
P (Population)	Adult women with female urinary incontinence
I (Intervention)	Pharmacological interventions
C (Comparison)	Placebo; None
O (Outcomes)	Cure, improving quality of life, reducing adverse effects
UI: Urinary incontinence	

Pellet reasoner will be used to determine the ontology consistency. The accuracy and the clinical content of the developed ontology will be validated by domain experts independently and based on adapted CPG and International Continence Society (ICS) terminologies. The completeness evaluation will be performed in collaboration with experts and ontology developers. Experts will include a urologist, a female urologist, a urogynecologist and a physiotherapist.

Statistical Analysis

The system will be evaluated and analyzed using the GUIDES checklist during the development (28). The GUIDES checklist is a tool to help system developers for a successful guideline-based CDSS implementation. The GUIDES checklist is a valuable tool that provides a detailed understanding of the elements contributing to an effective guideline-oriented decision support system. The checklist includes 16 factors that affect the success of CDSS in the four domains (Table 4). The technical evaluation will be performed by system developers, a member of the guideline developers, a urologist, a female urologist, and a urogynecologist during development. The electronic version of the checklist will be used to collect data (www.guidesproject.org). In an iterative process, checklist results will be used to upgrade the system to achieve a successful and well-structured system.

In the first phase of testing the system, the system will be used as a standalone system in the urology department of a referral teaching hospital for urological disorders. Patient information will be mapped between the local database and the UrInO-DSS. The system will be tested and evaluated by eight clinicians (29) including three urologists, two female urologists, a urogynecologist, a physiotherapist and a family physician. They will first be trained on how to use the system. We will define a set of test scenarios for diagnosing and managing various types of UI. The clinicians will use the system to get recommendations

Table 3. Clinical questions (PICOs): Surgical management for UI	
PICO-1: Traditional anti-incontinence surgeries	
P (Population)	Adult women with female urinary incontinence
I (Intervention)	Traditional surgeries
C (Comparison)	Any other interventions; Sham surgeries; None
O (Outcomes)	Cure, improving quality of life, reducing adverse effects
PICO-2: Mid-urethral mesh sling	
P (Population)	Adult women with female urinary incontinence
I (Intervention)	Mid-urethral mesh sling procedures
C (Comparison)	Any other interventions; Sham surgeries; None
O (Outcomes)	Cure, improving quality of life, reducing adverse effects
PICO-3: Artificial urinary sphincters	
P (Population)	Adult women with female urinary incontinence
I (Intervention)	Artificial urinary sphincters
C (Comparison)	Any other interventions; Sham surgeries; None
O (Outcomes)	Cure, improving quality of life, reducing adverse effects
PICO-4: Injectables	
P (Population)	Adult women with female urinary incontinence
I (Intervention)	Injectables
C (Comparison)	Any other interventions; Sham surgeries; None
O (Outcomes)	Cure, improving quality of life, reducing adverse effects
UI: Urinary incontinence	

on the solution for these scenarios. Finally, we will ask the clinicians to fill out the GUIDES checklist. In the next phase of system implementation, as future work, we plan to evaluate the effectiveness of UrInO-DSS in a trial study.

Results

The results of the study will be published and disseminated in peer-reviewed journals.

Discussion

Regarding the high prevalence of UI with different pathophysiology and the high number of patient referrals, a well-designed decision support system helps the clinical staff make a decision and manage the disorder. Our system, called UrInO-DSS, offers a tool to support clinicians in providing personalized treatment for patients suffering from UI. The system will cover all stages of the UI diagnosis and the management process. Because of the complexities of diagnosing and treating UI, UrInO-DSS can help residents and medical students learn how to manage UI in the best way.

The Standardization Steering Committee (SSC), a committee of the ICS, seeks to promote the standard of the terms related to incontinence and Lower Urinary Tract Dysfunction (LUTD). The results of these standardization of terminologies are presented in numerous articles (30). The terminologies are updated periodically on the ICS official website and in published articles. The developed ontology for UI can be a valuable tool in achieving this goal. In collaboration with the ICS, the standard terms of incontinence and LUTD could be used in the ontology building. Simultaneously, this ontology can gather and integrate vocabularies related to UI and LUTD from various sources and it can be a reference for standardization and updates of UI terminologies for better management.

Because ontologies organize domain knowledge into concepts and the relationships between them, they standardize concepts and integrate data extracted from different sources and create a common knowledge structure that can be shared between specialists and other individuals. It is possible to reuse and share the ontology, and to enrich the concepts of ontology over time. Based on the above, ontologies can play a crucial role in "knowledge management, data integration and decision support" (31). The use of CPGs in the construction of ontologies has been increasingly used in CDSSs recently. The evaluation of these systems indicates the initial useability and performance of these systems (32,33).

As far as we know, this is the first ontology developed for UI. The ontology could provide the basis for developing more effective and reliable knowledge-based systems in the field of incontinence and LUTD in the future. A strength of this study is applying bilingual ontology in the system. The ontology could be modified for any country with a different language.

Study Limitations

The limitation of the study may be that in the first phase, the system does not support full interoperability with the EHR, laboratory test ordering system, and urodynamic test system.

Conclusion

Although UrInO-DSS is being developed on the basis of an adapted CPG, with modifications to the knowledge base, the system can be implemented in any healthcare setting. Using ontology in the system and storing personalized care information

Table 4. The GUIDES checklist (28)		
Domains	**Focuses on**	**Factors**
CDSS context	The circumstances in which CDSS can be potentially successful	- CDSS can achieve the planned quality objectives
		- The quality of the patient data is sufficient
		- Stakeholders and users accept CDSS
		- CDSS can be added to the existing workload, workflows and systems
CDSS content	The factors shaping the success of the advice produced by the CDSS	- The content provides trustworthy evidence-based information
		- The decision support is relevant and accurate
		- The decision support provides an appropriate call to action
		- The amount of decision support is manageable for the target user
The CDS system	Features belonging to the CDSS tool	- The system is easy to use
		- The decision support is well delivered
		- The system delivers the decision support to the right target person
		- The decision support is available at the right time
The CDSS implementation	Factors affecting the integration of CDSS into practice settings	- Information to users about the CDSS and its functions is appropriate
		- Other barriers and facilitators to compliance with the decision support advice are assessed/addressed
		- Implementation is stepwise and the improvements in the CDSS system are continuous
		- Governance of the CDSS implementation is appropriate

CDSS: Clinical Decision Support System

could pave the way for establishing an international CDSS for diagnosis and management of UI and exchanging information among experts. In future work, we plan to evaluate the effectiveness of UrInO-DSS in the diagnosis and management of UI in a trial study.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of the Tabriz University of Medical Sciences under Grant [TBZMED.REC.1398.132].

Informed Consent: A written informed consent form was obtained from the patient upon admission.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.H., Concept: F.S.G., S.D., S.H., Design: F.S.G., S.D., L.R.K., M.R.F.D., S.H., Data Collection or Processing: F.S.G., M.R.F.D., Analysis or Interpretation: F.S.G., S.V.d.V., Literature Search: F.S.G., Writing: F.S.G., L.R.K., S.V.d.V., S.H.

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References

1. Milsom I, Gyhagen M. The prevalence of urinary incontinence. Climacteric 2019;22:217-22.
2. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int 2011;108:1132-1138.
3. Mostafaei H, Sadeghi-Bazargani H, Hajebrahimi S, Salehi-Pourmehr H, Ghojazadeh M, Onur R, Al Mousa RT, Oelke M. Prevalence of female urinary incontinence in the developing world: A systematic review and

meta-analysis-A Report from the Developing World Committee of the International Continence Society and Iranian Research Center for Evidence Based Medicine. Neurourol Urodyn 2020;39:1063-1086.

4. Danforth KN, Townsend MK, Lifford K, Curhan GC, Resnick NM, Grodstein F. Risk factors for urinary incontinence among middle-aged women. Am J Obstet Gynecol 2006;194:339-345.
5. Moosavi SY, Samad-Soltani T, Hajebrahimi S, Sadeghi-Ghyassi F, Pashazadeh F, Abolhasanpour N. Determining the risk factors and characteristics of de novo stress urinary incontinence in women undergoing pelvic organ prolapse surgery: A systematic review. Turk J Urol 2020;46:427-435.
6. Cundiff GW, Harris RL, Coates KW, Bump RC. Clinical predictors of urinary incontinence in women. Am J Obstet Gynecol 1997;177:262-266; discussion 266-7.
7. Resnick NM, Brandeis GH, Baumann MM, DuBeau CE, Yalla SV. Misdiagnosis of urinary incontinence in nursing home women: prevalence and a proposed solution. Neurourol Urodyn 1996;15:599-613; discussion 613-8.
8. Latoszek-Berendsen A, Tange H, van den Herik HJ, Hasman A. From clinical practice guidelines to computer-interpretable guidelines. A literature overview. Methods Inf Med 2010;49:550-570.
9. Alper BS, Haynes RB. EBHC pyramid 5.0 for accessing preappraised evidence and guidance. Evid Based Med 2016;21:123-125.
10. Chow N, Gallo L, Busse JW. Evidence-based medicine and precision medicine: Complementary approaches to clinical decision-making. Precis Clin Med 2018;1:60-64.
11. Sanchez E, Toro C, Artetxe A, Gra+Ýa M, Sanin C, Szczerbicki E, Carrasco E, Guijarro F. Bridging challenges of clinical decision support systems with a semantic approach. A case study on breast cancer. Pattern Recognition Letters 2013;34:1758-1768.
12. Hassan MM, Mokhtar HM. AutismOnt: an ontology-driven decision support for autism diagnosis and treatment. Egyptian Informatics Journal 2022;23:95-103.
13. Krishnan R, James M, editors. Mellrak: an Ontology Driven CDSS for Symptom Assessment, Risk Assessment and Disease Analysis of Breast Cancer. 2021 International Conference on Software Engineering & Computer Systems and 4th International Conference on Computational Science and Information Management (ICSECS-ICOCSIM); 2021: IEEE.
14. Nisheva-Pavlova M, Mihaylov I, Hadzhiyski S, Vassilev D, editors. Ontology-based decision support system for dietary recommendations for type 2 diabetes mellitus. International Conference on Computational Science; 2021: Springer.
15. Jing X, Min H, Gong Y, Sittig DF, Biondich P, Robinson D, Law T, Wright A, Nahr C, Faxvaag A, Rennert L, Gimbel R. A systematic review of ontology-based clinical decision support system rules: usage, management, and interoperability. medRxiv 2022.
16. Hussain S, Abidi SSR, editors. Integrating healthcare knowledge artifacts for clinical decision support: Towards semantic web based healthcare knowledge morphing. Conference on Artificial Intelligence in Medicine in Europe; 2009: Springer.
17. Chen Y, Yu C, Liu X, Xi T, Xu G, Sun Y, Zhu F, Shen B. PCLiON: An Ontology for Data Standardization and Sharing of Prostate Cancer Associated Lifestyles. Int J Med Inform 2021;145:104332.
18. Koutsojannis C, Lithari C, Nabil EA, Bakogiannis G, Hatzilygeroudis I, editors. Managing urinary incontinence through hand-held real-time decision support aid2010 2010: Springer.
19. Lopes MHBdM, Marin HdF, Ortega NRS, Massad E. The use of expert systems on the differential diagnosis of urinary incontinence. Revista da Escola de Enfermagem da USP 2009;43:704-710.
20. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, Brignardello-Petersen R, Neumann I, Falavigna M, Alhazzani W, Santesso N, Zhang Y, Meerpohl JJ, Morgan RL, Rochwerg B, Darzi A, Rojas MX, Carrasco-Labra A, Adi Y, AlRayees Z, Riva J, Bollig C, Moore A, Yepes-Nuñez JJ, Cuello C, Waziry R, Akl EA. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol 2017;81:101-110.
21. Unit IUKM. Clinical practice guideline: Female Urinary Incontinence. Tabriz, Iran: Tabriz University of Medical Sciences; 2013.
22. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. BMJ 2008;336:1049-1051.
23. Prcela M, Gamberger D, Jović A. Semantic web ontology utilization for heart failure expert system design. Stud Health Technol Inform 2008;136:851-856.
24. Kuziemsky CE, Lau F. A four stage approach for ontology-based health information system design. Artif Intell Med 2010;50:133-148.
25. Hlomani H, Stacey D. Approaches, methods, metrics, measures, and subjectivity in ontology evaluation: A survey. Semantic Web Journal 2014;1:1-11.
26. Sommerville I. Software engineering 10th ed. Boston: Pearson Education Limited; 2016.
27. Hegade P. Design for Requirements Engineering. Journal of Engineering Education Transformations. 2020;33:219-224.
28. Van de Velde S, Kunnamo I, Roshanov P, Kortteisto T, Aertgeerts B, Vandvik PO, Flottorp S; GUIDES expert panel. The GUIDES checklist: development of a tool to improve the successful use of guideline-based computerised clinical decision support. Implement Sci 2018;13:86.
29. Kushniruk AW, Patel VL. Cognitive and usability engineering methods for the evaluation of clinical information systems. J Biomed Inform 2004;37:56-76.
30. D'Ancona C, Haylen B, Oelke M, Abranches-Monteiro L, Arnold E, Goldman H, Hamid R, Homma Y, Marcelissen T, Rademakers K, Schizas A, Singla A, Soto I, Tse V, de Wachter S, Herschorn S; Standardisation Steering Committee ICS and the ICS Working Group on Terminology for Male Lower Urinary Tract & Pelvic Floor Symptoms and Dysfunction. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn 2019;38:433-477.
31. Bodenreider O. Biomedical ontologies in action: role in knowledge management, data integration and decision support. Yearb Med Inform 2008:67-79.
32. Madhusanka S, Walisadeera A, Dantanarayana G, Goonetillake J, Ginige A, editors. An Ontological Clinical Decision Support System Based on Clinical Guidelines for Diabetes Patients in Sri Lanka. Healthcare; 2020: Multidisciplinary Digital Publishing Institute.
33. Shen Y, Yuan K, Chen D, Colloc J, Yang M, Li Y, Lei K. An ontology-driven clinical decision support system (IDDAP) for infectious disease diagnosis and antibiotic prescription. Artif Intell Med 2018;86:20-32.

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Protective Effects of Ellagic Acid on Testicular Ischemia-Reperfusion Injury in Rats

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

In experimental studies, many agents have been studied to prevent ischemia-reperfusion injury in testicular torsion. Ellagic acid appears to have protective effects against experimental testicular ischemia-reperfusion injury in rats.

Abstract

Objective: This study aimed to investigate the protective effects of ellagic acid on testicular ischemia/reperfusion injury in rats.

Materials and Methods: Twenty-one Sprague-Dawley rats were randomly divided into three groups: sham, ischemia/reperfusion (I/R), I/R + ellagic acid (EA). All animals underwent left scrotal exploration. In all groups except the sham group, the left testes were rotated 720 degrees clockwise for 3 h and 3 h reperfusion. 10 mg/kg ellagic acid was administered intraperitoneally to the I/R+E group before reperfusion. Then, the left orchiectomy was performed. The testes underwent biochemical and histological examination.

Results: There was a significant difference between the sham and the I/R, I/R+EA groups according to the Cosentino system ($p<0.001$, $p=0.036$), and there was no difference between the I/R and IR+EA groups ($p=0.319$). A significant difference was found between sham and I/R groups according to Johnsen spermatogenesis score ($p<0.001$), but there was no significant difference between sham and I/R+EA groups ($p=0.063$). Superoxide dismutase, catalase, malondialdehyde, total oxidant status values were statistically different between I/R and I/R+EA groups ($p=0.001$, 0.002, 0.002, 0.001 respectively).

Conclusion: Ellagic acid has a protective effect against testicular ischemia/reperfusion injury in rats.

Keywords: Ellagic acid, ischemia/reperfusion injury, testis

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Introduction

Testicular torsion is a surgical emergency that can cause loss of testicular function and infertility. The incidence of torsion is estimated at 3.8 per 100.000 (0.004%) for boys under the age of 18 (1). Testicular damage development is directly related to the duration of the torsion. Therefore, surgical detorsion should be applied as soon as possible and the first 4 to 8 h are defined as the golden windows for testicular salvage (2). However, 27% testicular atrophy and 36-39% subfertility were reported in long-term follow-up after torsion (3,4). Testicular damage may occur due to the direct effect of interruption of blood flow during torsion or due to the formation of oxygen-derived free radicals by ischemia/reperfusion (I/R) injury (4). Experimental studies have been conducted with many potential agents to prevent reperfusion injury. Antioxidant drugs (Vitamin E, taurine, apocynin, quercetin, alpha lipoic acid, selenium, ascorbic acid, etc.), non-steroid anti-inflammatory drugs (ibuprofen, dexetoprofen), phosphodiesterase type 5 inhibitors (sildenafil, tadalafil), nitric oxide, neutrophil elastase inhibitors, platelet-rich plasma are some agents used in these studies (5,6). Ellagic acid (EA) is a potent polyphenol antioxidant found in fruits and natural sources such as grapes, nuts, strawberries, raspberries, honey, green tea (7). It has chemo preventive, antiapoptotic, radical scavenging properties in the previous studies (8). EA has been experimentally shown to have protective effects on testicular damage induced by chemotherapeutic agents such as cisplatin, adriamycin, doxorubicin (8-10). Furthermore, it has been reported that EA has protective effects against kidney and ovarian I/R injury in rats (11,12). However, there is no study in the literature investigating the effects of EA on experimental testicular I/R injuries. In this study, we evaluated the protective effects of EA on testicular I/R injury in rats.

Materials and Methods

Twenty-one male Sprague-Dawley female rats (12 weeks old, weight 250-300 g) were obtained from the Karadeniz Technical University Laboratory Animals Research Centre (Trabzon, Turkiye). This study was approved by the Animal Experiments Local Ethics Committee of Karadeniz Technical University (Trabzon, Turkiye) (approval number/ID: 2018/20). The same environment and nutritional conditions were provided for all the animals. Rats were entrained under a 12:12 h dark: Light cycle (lights on 6 am-6 pm) with stable temperature (21±2 °C) and humidity (60±5%). The rats had sterile water and food available ad libitum. The surgical protocol was performed at Karadeniz Technical University, Faculty of Medicine, Surgical Applications Center. A biochemical was examined in the Biochemistry Department of Karadeniz Technical University, Faculty of Medicine, histological was examined in the Pathology Department of University of Health Sciences Turkiye, Trabzon Kanuni Training and Research Hospital.

Experimental Protocol and Surgical Procedure

Animals were randomly divided into three groups: Sham, I/R, I/R+EA. Rats were anesthetized with xylazine (20 mg/kg) and ketamine hydrochloride (50 mg/kg). All animals underwent left scrotal exploration during the first procedure. In all groups except the sham group, the left testes were rotated 720 degrees clockwise for 3 h and sutured to the scrotum with a 4/0 prolene through the tunica albuginea and subcutaneous tissue. The incision was closed with a 4/0 prolene suture. After 3 h, using the same incision, the testis was turned round to its natural position and 10 mg/kg EA was administered intraperitoneally to the I/R+EA group before reperfusion. The testis was left for 3 h to evaluate results of I/R injury. After 3 h, the experiment was terminated, and orchiectomy was performed. The testes were divided into two transverse planes for biochemical and histological examination.

Biochemical Analysis

Tissues were washed with saline and stored at -80 °C until evaluation. In the biochemical analysis, first they were homogenized in cold phosphate-buffered saline (PBS) (0.05 M, pH 7.4), and were centrifuged at 3000 rpm for 10 min to remove debris and to obtain a clear supernatant fraction. Then, the analyses were performed in this fraction. Malondialdehyde (MDA), total oxidant status (TOS), as well as enzyme activities of superoxide dismutase (SOD) and Catalase (Cat) were measured in this fraction. MDA levels in tissue samples were determined using the method described by Uchiyama and Mihara (13). Tetramethoxypropane was used as a standard, and tissue MDA levels were calculated as nmol/10 g wet tissue. TOS levels were determined using a colorimetric TOS kitas previously described by Erel (14). Cat activity was measured by modifying the method based on the measurement of the absorbance of ammonium molybdate with H_2O_2 at 405 nm. Cat standard (Sigma C9322) was used as a standard, and tissue Cat activity was calculated as nmol/g protein (15). The SOD enzyme activity was determined by the method of Sun et al. (16). This method is based on the measurement of the absorbance of the purple-colored formazan molecule at 560 nm resulting from the reduction of nitroblue tetrazolium of $O_2^{\cdot-}$ formed by the xanthine-xanthine oxidase system. The tissue SOD activity was calculated as nmol/g protein by using the SOD standard (Sigma S8160) (16).

Histological Analysis

Testicular tissue samples were detected in 10% formaldehyde for 48 h and then underwent routine histological follow-up. 5 µm thick sections were prepared from paraffin embedded tissues and stained with hematoxylin-eosin. Then, the changes caused

by I/R were examined by light microscopy. Four-grade scale defined by Cosentino et al. (17) was used to assess histological changes (Table 1). The Johnsen (18) scoring system was used for evaluating spermatogenesis (Table 2). Histological changes and spermatogenesis scoring were evaluated randomly by a pathologist blinded to the groups.

Statistical Analysis

Data are expressed as the median (min-max). The Kolmogorov-Smirnov test was used to test normality, and the groups were compared using the Mann-Whitney U test. Statistical significance was set at $p<0.05$ (IBM SPSS Statistics 22.0). In our study, data have not followed a normal distribution.

Results

The biochemical analysis results are shown in Table 3. SOD in the I/R group decreased significantly compared with the I/R+EA group (p=0.001) but was similar in the sham and I/R+EA groups (p=0.209). The cat in the I/R group was significantly lower than the sham and I/R+EA groups (p=0.001, p=0.002). MDA and TOS in the I/R group increased significantly compared in the I/R+EA group (p=0.001, p=0.001). Although TOS was similar in the sham and I/R+EA groups (p=0.805), MDA was significantly higher in the I/R+EA group than in the sham group (p=0.01) (Figure 1).

The histological grade of testicular damage and spermatogenesis scores of all animals are shown in Table 4. Different findings were observed in different areas in each testicle on histopathological examination, the dominant one was recorded. In the I/R group, it was observed that one testicle was damaged enough to not be histologically evaluated, and therefore it was excluded from the study. There were generally nearly normal findings in the sham group. In four cases, signs of mild interstitial edema-bleeding and germ cell detachment were observed in some seminiferous tubules were observed. In the I/R group, severe interstitial edema-hemorrhage, Leydig cell detachment, contraction in tubules, intratubular edema, and germ cell detachment were observed. In the I/R+EA group, mild interstitial edema-hemorrhage, germ cell detachment, and irregularity in some tubules were observed (Figure 2). There was a statistically significant difference between the sham group and the I/R, I/R+EA groups according

Table 1. The Cosentino histological grading system

Grade	Characteristics
I	Normal testicular architecture with an orderly arrangement of germinal cells
II	Injury showed less orderly, noncohesive germinal cells and closely packed seminiferous tubules
III	Injury exhibited disordered sloughed germinal cells, with reduced size of pyknotic nuclei and less distinct seminiferous tubule borders
IV	Injury exhibited seminiferous tubules that were closely packed with coagulative necrosis of the germinal cells

Table 2. Spermatogenesis scoring system proposed by Johnsen (18)

Score	Characteristics
10	Complete spermatogenesis and normally organized tubules
9	Numerous spermatozoa present, but the germinal epithelium is disorganized
8	Only a few spermatozoa present in the section
7	No spermatozoa, but numerous spermatids present
6	Only a few spermatids present
5	No spermatozoa or spermatids, but numerous spermatocytes present
4	Only a few spermatocytes present
3	Only spermatogonia present
2	No germ cells, but only Sertoli cells present
1	No germ cells and no Sertoli cells present

Table 3. Results of superoxide dismutase (SOD), catalase (Cat), malondialdehyde (MDA), total oxidant capacity (TOC) of groups

Median (min-max)	Sham group (n=7)	I/R group (n=7)	I/R+EA group (n=7)	p-value
SOD (U/Gprotein)	42.8 (28.8-40.7)	9.94 (7.35-12.7)	34.4 (29.1-53.4)	**0.001*** 0.209& **0.001#**
Cat (U/Gprotein)	11.8 (11.6-12)	4.35 (2.97-5.09)	11.3 (11.2-11.5)	**0.002*** **0.001&** **0.001#**
MDA (nmol/Gtissue)	23.4 (21.4-27)	67.9 (66.3-68.6)	36.4 (33.9-40.2)	**0.001*** **0.001&** **0.001#**
TOS (µmol/L)	23.6 (19.9-29.4)	39.4 (35.6-43.1)	23.1 (17.4-34.6)	**0.001*** 0.805& **0.001#**

*I/R vs I/R+EA, &sham vs I/R+EA, #sham vs I/R

to the Cosentino grading system (p<0.001, p=0.036), and there was no difference between the I/R and I/R+EA groups (p=0.319). A statistically significant difference was found between sham and I/R groups according to Johnsen spermatogenesis scoring system (p<0.001), but there was no statistically significant difference between the sham and I/R + EA groups (p=0.063) (Table 5).

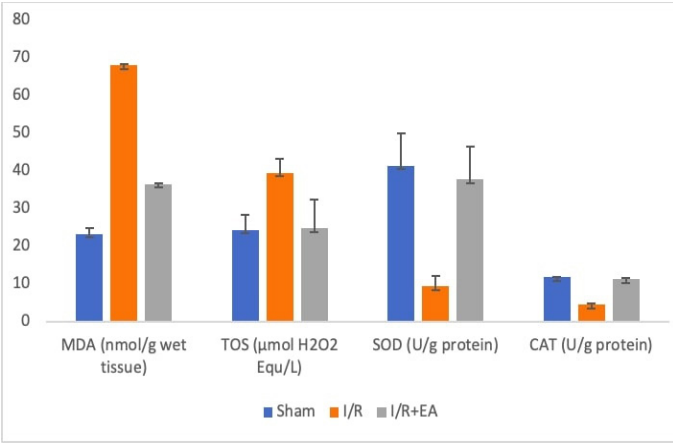

Figure 1. Results of biochemical analyses in all groups (Control: Sham group, I/R: Ischemia/Reperfusion, Ellagic Acid + T/D: Ellagic Acid+Torsion/Detorsion)

Discussion

Testicular torsion is an emergency that is frequently encountered in childhood and can cause testicular damage, infertility, and hypogonadism if detorsion is not performed within a short time (3). Although reperfusion is essential for the salvage of the testicle, it induces the formation of reactive oxygen radicals in the tissue (19). When the balance between ROS and antioxidative defense mechanisms is damaged, the amount of ROS can increase. ROS may provoke tissue damage with the development of an inflammatory response and activation of some mediators. This process causes membrane dysfunction and potential cell death by peroxidation of the phospholipid structure in cell membranes (20). Experimental testicular torsion has been shown in previous studies to cause tissue reperfusion damage (6,19). Although many agents have been studied to prevent I/R damage in the literature, there is currently no recommended agent for clinical use. This study showed that EA has protective effects on rat testicular tissue against I/R damage.

EA is a natural antioxidant substance, and its chemical name is 2,3,7,8-tetrahydroxy-chromeno [5,4,3-cde] -chromene-5,10-dione. EA is a weak acid that ionizes at physiological pH. It has two pairs of hydroxyl groups and this structure makes

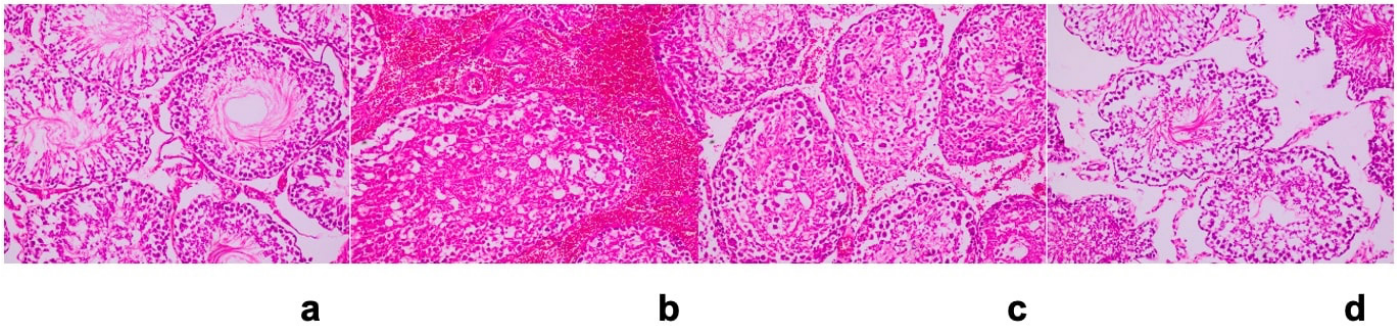

Figure 2. Histological images of rat testis sections. a) Normal testis appearance in sham group (HEx40), b) Grade IV changes in the I/R group (Interstitial hemorrhage, uncertainty in the seminiferous tubule margins, coagulation necrosis (HEx40)), c) Grade III changes in the I/R+EA group (interstitial edema-hemorrhage, seminiferous tubules detachment, border ambiguity, germ cell detachment, intercellular edema, dead germ cells, and multinucleated cells and (HEx40)), d) Grade II changes in the I/R+EA group (less regular germ cells)

Table 4. Histological examination results of testicular tissues

Animal number	Sham group (n=7)		I/R group (n=6)		I/R+ EA group (n=7)	
	Cosentino grading	Johnsen score	Cosentino grading	Johnsen score	Cosentino grading	Johnsen score
1	1	9.5	NA	NA	3	8
2	1	9.5	3	6	2	9
3	1	10	3	6	2	8
4	1	10	3	6	2	8
5	1	9.5	3.5	5.5	2	7
6	1	9.5	4	5.5	3	7
7	1	10	3.5	5.5	3	6

Table 5. Comparison of the histological scores of the groups				
	Sham (n=7)	I/R (n=6)	I/R + EA (n=7)	p-value
Cosentino grading system [Median (min-max)]	1 (1-1)*^	3.25 (3-4)*	2 (2-3)^	<0.001
Johnsen score [Median (min-max)]	9.5 (9.5-10)*	5.75 (5.5-6)*	8 (6-9)	<0.001
Kruskal-Wallis test (pair wise analysis, meaningfulness is indicated as follows: *Sham group and I/R group difference statistically significant; ^Sham group and I/R+EA group difference statistically significant)				

EA a potent antioxidant (21). In previous studies, EA has anticarcinogenic, neuroprotective, cardio-liver-skin protective and, angiogenic effects (22). EA exerts these effects by activating specific antioxidant enzymes and suppressing genes responsible for inflammation. In this process, the amount and duration of EA play an important role for treating oxidative stress (22). Daily administration of EA with diet significantly decreases the expression of cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS) and prevents the production of excessive inflammatory mediators in the tissue (23). Additionally, it has been revealed that EA may be a potential agent against human diseases due to its antiobesity, antimicrobial and antioxidant properties (24).

Although there are studies reporting the effects of EA on rat testis toxicity induced by the chemotherapeutic agents, arsenic, and monosodium glutamate, there is no study examining the effect of EA on rat testis I/R damage in literature. In a study investigating the effect of two separate EA doses (10 mg/kg, 30 mg/kg) in rats developing testicular toxicity with 10 mg/kg sodium arsenite daily, SOD and Cat were found to be significantly higher and MDA lower in EA groups compared to the toxicity group (7). In a recent study, it was revealed that EA could be a potential agent against MDA with its torsion-detorsion in rat ovaries (12). Additionally, EA was reported to lead to decreasing MDA levels in a study on cerebral ischemia (25). Ekinci Akdemir et al. (26) reported the protective effect of EA against I/R injury created in skeletal muscle. While MDA increased in the I/R group compared to S and EA+I/R group, SOD, Cat activities decreased.

On histological examination, while there were no abnormal findings in the EA groups, reduction and destruction of germinal epithelium cells, and irregularity in the arrangement of seminiferous tubule epithelium were observed in the sodium arsenite group. Testosterone values were reported to be significantly higher in the EA groups than in the sodium arsenic group. In our study, biochemical and histology results were similar, but testosterone measurement was not performed.

It has been shown that gallic acid, a monomer of EA, affects the hypothalamus-pituitary-gonadal axis and increases FSH, LH concentration, and testosterone level. In an experimental study that investigated gonadal toxicity by giving cyclophosphamide to rats, it was stated that epididymis degeneration was prevented, and a medium-normal level of sperm maturation was provided by gallic acid treatment (27). In a similar study, the effectiveness of EA in reducing the testicular toxicity of doxorubicin, which is widely used in cancer treatment, was examined. In this study, it was determined that EA significantly improved sperm parameters, serum testosterone levels, glutathione, MDA, TNF-alpha, sialic acid, and testicular cholinesterase levels in testicular tissue (10). Additionally, EA is effective in reducing the degenerative effects of doxorubicin in histopathological examinations. Similarly, in this study, the median value of the Johnsen score, in which spermatogenesis was evaluated, was 5.75 (5.5-6) in the EA+I/R group and was significantly lower than that in the I/R group [8(6-9)] ($p<0.05$). Also, there was no statistical difference between the Sham and the EA+I/R groups in terms of Johnsen score. However, there are some publications that EA has not shown positive effects on sperm parameters. In the studies of Çeribaşı et al. (9), protective effects of EA on lipid peroxidation and apoptosis on experimental adriamycin toxicity in rat testes were reported. However, in the same study, it was stated that EA had no significant protective effect on reproductive organ weight and sperm quality parameters. In this study, it was shown that EA has a more protective effect in histological evaluation than the study by Çeribaşı et al. (9). This situation can be explained by chronic adriamycin exposure (8 weeks) and different experimental models in studies.

Hypoxia that develops following testicular torsion causes some pathological changes in the tissue. The interruption of blood flow leads to venous congestion, edema, hemorrhage in the seminiferous tubules, and eventually germ cell death (28). In this study, a contraction in seminiferous tubules and necrosis of germ cells were more pronounced in the I/R group.

In the I/R study performed with torsion-detorsion in rat ovaries, the improvement was observed in MDA, SOD, glutathione reductase, and Cat enzyme activities with EA (12). In the same study, it was shown that EA is also effective in reducing tissue damage. Although biochemical results of the present study were similar to those in this study, the histopathological examination did not show a statistically significant difference in tissue

damage between the I/R and EA+I/R groups. However, in this study, the ischemia period was shorter and the EA dose was higher than this study.

Study Limitations

This study has some limitations. Firstly, testosterone levels were not measured because the experiment was terminated at the third hour after reperfusion. Secondly, apoptosis was not evaluated. Thirdly, a single dose (10 mg/kg) EA group was formed.

Conclusion

Intraperitoneal Ellagic Acid administration supports the endogenous antioxidant defense system and reduce oxidative stress in testis I/R injuries in rats. Also, it has a protective effect on spermatogenesis but has no significant protective effect on histological examination against experimental I/R injury in the rat testis.

Ethics

Ethics Committee Approval: This study was approved by the Animal Experiments Local Ethics Committee of Karadeniz Technical University (Trabzon, Turkiye) (approval number/ID: 2018/20).

Informed Consent: Not necessary.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.A.Ş., H.R.A., A.L., E.Y., T.T., M.A.R., A.Ö.G., R.E., S.K., H.K., O.D., Concept: Ç.A.Ş., H.R.A., Design: Ç.A.Ş., H.R.A., Data Collection or Processing: Ç.A.Ş., H.R.A., A.L., E.Y., T.T., M.A.R., A.Ö.G., R.E., S.K., H.K., O.D., Analysis or Interpretation: Ç.A.Ş., E.Y., Literature Search: Ç.A.Ş., E.Y., Writing: Ç.A.Ş., E.Y.

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References

1. Zhao LC, Lautz TB, Meeks JJ, Maizels M. Pediatric testicular torsion epidemiology using a national database: incidence, risk of orchiectomy and possible measures toward improving the quality of care. J Urol 2011;186:2009-2013.
2. Bowlin PR, Gatti JM, Murphy JP. Pediatric testicular torsion. Surg Clin North Am 2017;97:161-172.
3. Sessions AE, Rabinowitz R, Hulbert WC, Goldstein MM, Mevorach RA. Testicular torsion: direction, degree, duration and disinformation. J Urol 2003;169:663-665.
4. Visser A, Heyns C. Testicular function after torsion of the spermatic cord. BJU Int 2003;92:200-203.
5. Shimizu S, Tsounapi P, Dimitriadis F, Higashi Y, Shimizu T, Saito M. Testicular torsion–detorsion and potential therapeutic treatments: A possible role for ischemic postconditioning. Int J Urol 2016;23:454-463.
6. Sekerci C, Tanidir Y, Sener T, Sener G, Cevik O, Yarat A, Alev-Tuzuner B, Cetinel S, Kervancioglu E, Sahan A, Akbal C. Effects of platelet-rich plasma against experimental ischemia/reperfusion injury in rat testis. J Pediatr Urol 2017;13:317.e1-e9.
7. Mehrzadi S, Bahrami N, Mehrabani M, Motevalian M, Mansouri E, Goudarzi M. Ellagic acid: A promising protective remedy against testicular toxicity induced by arsenic. Biomed Pharmacother 2018;103:1464-1472.
8. Türk G, Çeribaşı AO, Şahna E, Ateşşahin A. Lycopene and ellagic acid prevent testicular apoptosis induced by cisplatin. Phytomedicine 2011;18:356-361.
9. Çeribaşı AO, Sakin F, Türk G, Sönmez M, Ateşşahin A. Impact of ellagic acid on adriamycin-induced testicular histopathological lesions, apoptosis, lipid peroxidation and sperm damages. Exp Toxicol Pathol 2012;64:717-724.
10. Georgy GS, Maher OW. Ellagic acid and rosmarinic acid attenuate doxorubicin-induced testicular injury in rats. J Biochem Mol Toxicol 2017;31:e21937.
11. Liu Q, Liang X, Liang M, Qin R, Qin F, Wang X. Ellagic Acid Ameliorates Renal Ischemic-Reperfusion Injury Through NOX4/JAK/STAT Signaling Pathway. Inflammation 2020;43:298-309.
12. Sayar I, Bicer S, Gursul C, Gürbüzel M, Peker K, Işik A. Protective effects of ellagic acid and ozone on rat ovaries with an ischemia/reperfusion injury. J Obstet Gynaecol Res 2016;42:52-58.
13. Uchiyama M, Mihara M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal Biochem 1978;86:271-278.
14. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38:1103-1111.
15. Goth L. A simple method for determination of serum catalase activity and revision of reference range. Clin Chim Acta 1991;196:143-51.
16. Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. Clin Chem 1988;34:497-500.
17. Cosentino MJ, Nishida M, Rabinowitz R, Cockett AT. Histological changes occurring in the contralateral testes of prepubertal rats subjected to various durations of unilateral spermatic cord torsion. J Urol 1985;133:906-911.
18. Johnsen SG. Testicular biopsy score count–a method for registration of spermatogenesis in human testes: normal values and results in 335 hypogonadal males. Hormones 1970;1:2-25.
19. Ekici S, Ekici AID, Öztürk G, Aksungar FB, Sinanoğlu O, Turan G, Lüleci N. Comparison of melatonin and ozone in the prevention of reperfusion injury following unilateral testicular torsion in rats. Urology 2012;80:899-906.
20. Memısoğullari R, Taysı S, Bakan E, Capoglu I. Antioxidant status and lipid peroxidation in type II diabetes mellitus. Cell Biochem Funct 2003;21:291-296.
21. Zafrilla P, Ferreres F, Tomás-Barberán FA. Effect of processing and storage on the antioxidant ellagic acid derivatives and flavonoids of red raspberry (Rubus idaeus) jams. J Agric Food Chem 2001;49:3651-3655.
22. Zeb A. Ellagic acid in suppressing in vivo and in vitro oxidative stresses. Mol Cell Biochem 2018;448:27-41.
23. Rosillo MA, Sánchez-Hidalgo M, Cárdeno A, Aparicio-Soto M, Sánchez-Fidalgo S, Villegas I, de la Lastra CA. Dietary supplementation of an ellagic acid-enriched pomegranate extract attenuates chronic colonic inflammation in rats. Pharmacol Res 2012;66:235-242.
24. Shakeri A, Zirak MR, Sahebkar A. Ellagic acid: A logical lead for drug development? Curr Pharm Des 2018;24:106-122.

25. Nejad KH, Dianat M, Sarkaki A, Naseri MKG, Badavi M, Farbood Y. Ellagic acid improves electrocardiogram waves and blood pressure against global cerebral ischemia rat experimental models. Electronic Physician 2015;7:1153-1162.

26. Ekinci Akdemir FN, Gülçin İ, Karagöz B, Soslu R, Alwasel SH. A comparative study on the antioxidant effects of hesperidin and ellagic acid against skeletal muscle ischemia/reperfusion injury. J Enzyme Inhib Med Chem 2016;31:114-118.

27. Oyagbemi A, Omobowale T, Saba A, Adedara I, Olowu E, Akinrinde A, Dada RO. Gallic acid protects against cyclophosphamide-induced toxicity in testis and epididymis of rats. Andrologia 2016;48:393-401.

28. Ozturk H, Ozturk H, Terzi EH, Bugdayci G, Duran A. Interleukin 10 reduces testicular damage in experimental testicular ischemia/reperfusion injury. Urology 2014;83:508.e1-e6.

ORIGINAL RESEARCH
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Pioglitazone Eases Testicular Torsion/Detorsion-Induced Ischemia-Reperfusion Injury in Rats

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

Ischemia-reperfusion-induced changes in testicular histological parameters have been shown to be improved by pioglitazone 6 mg/kg therapy. Pioglitazone can be used in emergencies such as torsion and other chronic diseases to improve testicular functions.

Abstract

Objective: This study demonstrated the protective effects of pioglitazone (Pio) on testicular torsion/detorsion-induced ischemia-reperfusion (I/R) injury.

Materials and Methods: A total of 48 male rats were randomly divided into six experimental groups of eight rats each; Control group, I/R group, Pio 3 mg/kg group, I/R treated with Pio 3 mg/kg group, Pio 6 mg/kg group, and I/R treated with Pio 6 mg/kg group. Testicular torsion was induced by twisting the left testis 720 °C in a clockwise direction (I/R groups). Both ischemia and reperfusion periods were 4 h. Single-dose 3 mg/kg Pio or 6 mg/kg Pio was administered orally two hours before reperfusion (Pio groups). Left orchiectomy was performed at the end of the protocol.

Results: In the I/R within-group analysis for mean seminiferous tubule diameter and epithelial lengths, a statistically significant difference was found only in the Pio 6 group (p=0.005; p=0.005). But Pio treatment failed to improve the levels of malondialdehyde and glutathione. Also, it did not cause any change in the non-I/R groups.

Conclusion: Considering the findings of Pio, it may be used in emergencies such as torsion and other chronic diseases.

Keywords: Testicular torsion, ischemia, reperfusion

Introduction

Torsion of the spermatic cord is a urological emergency that usually requires surgical intervention (1). Permanent damage to the testis and spermatogenesis may occur despite early surgery (2). Ischemia-reperfusion (I/R) injury due to interruption of blood flow is seen in end organs such as the testis and kidney (3). Both ischemia and reperfusion phases cause the accumulation of reactive oxygen species (ROS) after induction of lipid peroxidation and oxidative stress (4). Pharmacological agents that protect the testis in the I/R period by reducing oxidative stress have been the subject of many studies (5).

Peroxisome proliferator-activated receptors (PPARs) are subfamily nuclear hormone receptors, which regulate the transcription of several genes related to lipid metabolism, energy expenditure, atherosclerosis, infertility and inflammation (6). Pioglitazone (Pio) is a synthetic agonist of PPAR-γ that was used to reduce insulin resistance in type 2 diabetes mellitus patients (7). Several studies have revealed the protective effects of Pio on I/R damage (8-10). There is strong evidence

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that it decreases injury by increasing the antioxidant capacity, especially in the kidneys (11). In this study, we investigated the possible protective effects of Pio on testicular I/R injury by measuring malondialdehyde (MDA), which is a marker of lipid peroxidation in tissues, and reduced glutathione (GSH) levels that show intense exposure to oxidative stress, and assessment of the histological pattern of testicular tissue.

Materials and Methods

Pio's Biochemical Properties

Thiazolidinediones have beneficial effects on lipid metabolism, endothelial function, oxidative stress, and vascular inflammation in addition to their antihyperglycemic effects (12).

Thiazolidinediones have intracellular antioxidant activity (13). This property reflects its anti-oxidant effects. These compounds work as antioxidants by preventing multiple pathways that induce oxidative stress in hyperglycemic conditions, rather than by releasing free radicals. Thiazolidinediones, in particular Pio, have been discovered to be a potent glycation and protein cross-linking inhibitor as well as a strong antioxidant (14).

Animals

All experimental procedures were managed according to international ethical guidelines and were approved by the Local Ethical Committee of Trakya University (reference code 2020.02.01). A total of 48 healthy male Wistar Albino rats aged 16-20 weeks (400-500 g) were obtained from the Medical Faculty Experimental Animals and Research Laboratory. Rats were housed at the Animal Care and Research Unit under standard laboratory conditions at a relative humidity of 60%, temperature of 22±2 °C, 12-hr light-dark cycle, and fed with dry rodent chow and water ad libitum.

Study Design

A total of 48 male rats were divided into six experimental groups;

1. The control group (n=8): Rats treated only with orchiectomy.

2. I/R (n=8): Rats were subjected to four hours of ischemia then four hours of reperfusion and treated with a 0.9% saline solution orally two hours before reperfusion.

3. Pio 3 (n=8): Rats were treated with 3 mg/kg Pio (Sanovel, Istanbul, Turkiye) orally six hours before orchiectomy.

4. I/R + Pio 3 (n=8): Rats were subjected to four hours of ischemia then four hours of reperfusion and treated with 3 mg/kg Pio orally two hours before reperfusion.

5. Pio 6 (n=8): Rats were treated with 6 mg/kg Pio orally six hours before orchiectomy.

6. I/R + Pio 6 (n=8): Rats were subjected to four hours of ischemia then four hours of reperfusion and treated with 6 mg/kg Pio orally two hours before reperfusion (Figure 1).

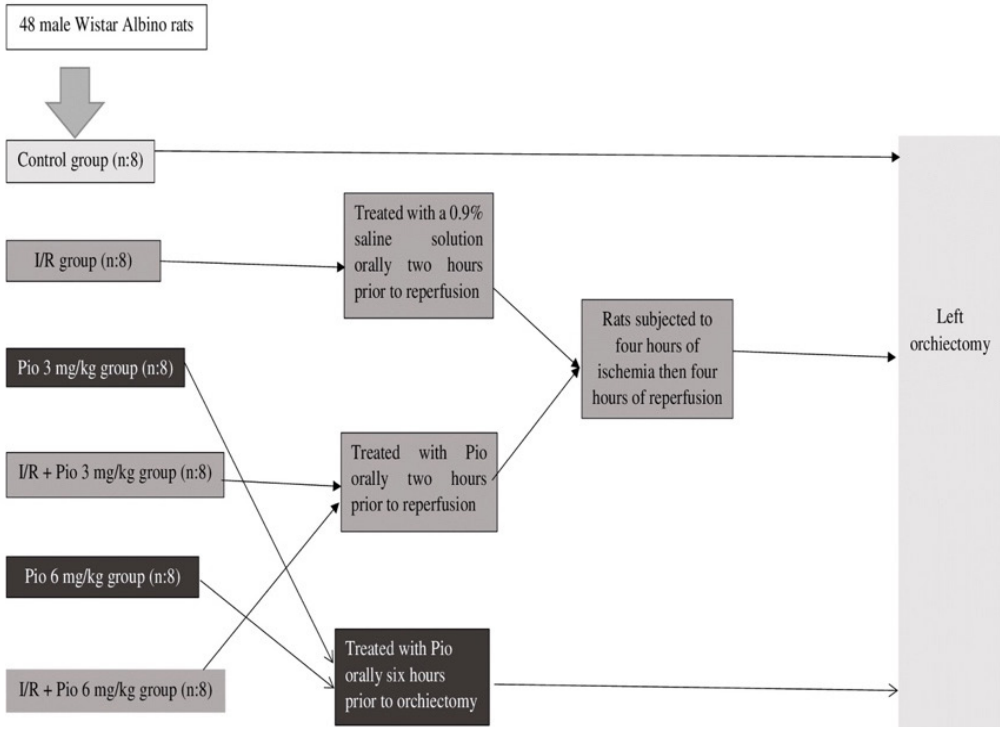

Figure 1. Study design

Surgical Procedure

All surgical operations were performed under IM administration of xylazine (10 mg/kg, Alfasan International, Woerden, Holland) and ketamine (75 mg/kg, Pfizer Pharma GMBH, Germany). The skin of the scrotum was disinfected with 10% povidone-iodine solution. The scrotum was entered with a midline incision. After the opening of the tunica vaginalis, the left testis was identified. Torsion was then induced by twisting it 720 °C in a clockwise direction (I/R groups). The torsion position was maintained by fixing the testicle to the scrotum with a 4-0 silk suture (Figure 2). Single-dose 3 mg/kg Pio or 6 mg/kg Pio was administered orally two hours before reperfusion (Pio groups). After 4 h of ischemia, the testis was returned to the normal position for a 4-hour reperfusion period. Then left orchiectomy was performed for all groups. Testes tissue samples were taken for histopathological investigation. Rats were killed by cervical dislocation at the end of the protocol.

Histopathological Study and Spermatogenesis Evaluation

The tissue samples of each rat were fixed in 10% neutral formaldehyde and then the testis was sampled by the pathologist, including the largest surface from the middle. Each tissue was prepared as 5-µm sections from each paraffin block and stained with hematoxylin-eosin (H-E). Seminiferous tubule diameters, epithelial lengths (EL) and Johnsen testicular biopsy scores were calculated. Mean seminiferous tubule diameter (MSTD) was measured in micrometers. Spermatogenesis was defined using Johnsen's mean testicular biopsy score (MTBS) criteria (15). Twenty tubules from each sample were randomly selected and scored from 1 to 10. Due to oxidative stress, EL and MSTD become shorter. These parameters are expected to deteriorate during I/R damage.

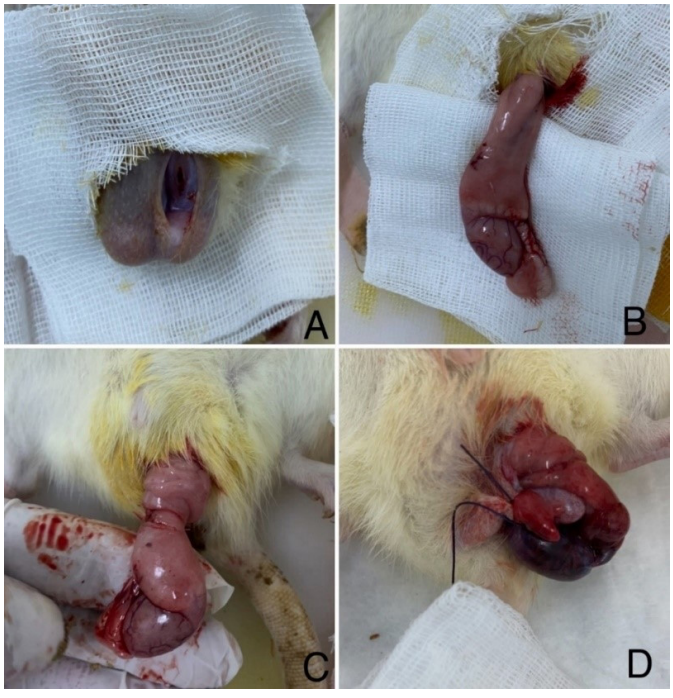

Figure 2. Surgical Procedure A. Midline scrotal incision, B. The left testicle was released from the gubernaculum, C. Twisting testicular cord 720 °C in a clockwise direction, D. The torsion position was maintained by fixing the testicle to the scrotum with a 4-0 silk suture

Biochemical Analysis

A solution of 0.15 M KCl was used for the determination of MDA and GSH levels. Homogenates of 10% (w:v) were prepared from tissue samples and 0.15 M KCl solution. The supernatants were obtained by centrifuging the homogenates at 1500xg for 10 min at + 4 °C. Supernatants were used for spectrophotometric measurements of MDA and GSH levels. The pink resulting from the reaction of MDA with thiobarbituric acid (TBA) in a hot and acidic environment was measured using the spectrophotometric method (16). The GSH level was determined according to the Ellman (17) method. The color of free sulfhydryl groups in tissue homogenates was determined spectrophotometrically by Ellman (17) reagent. Tissue protein levels were determined by the Lowry method, which is based on the principle that the alkali copper tartrate reagent complexes with peptide bonds (18). When the phenol reagent is added to the mixture treated with copper, it creates a blue-purple color and which was measured spectrophotometrically at 660 nm.

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). All data are presented as mean ± standard deviation. One-Way analysis of variance (ANOVA) followed by post-hoc Tukey multiple comparison test was used to define statistical significance in multiple group comparisons. For the comparison of quantitative data, the Kruskal-Wallis test was used for intergroup comparisons of parameters that did not have a normal distribution, and the Mann-Whitney U test was used to identify the group that caused the difference. A $p<0.05$ value was considered statistically significant.

Results

Histopathological Changes

The MSTD was significantly shorter in the groups with I/R than those without I/R ($p<0.05$). In the I/R within-group analysis, eased MSTD was seen only in the Pio 6 group. Furthermore, a statistically significant difference was found only in the Pio 6 group ($p=0.005$; $p=0.005$). The EL was significantly shorter in the groups with I/R than those without I/R ($p<0.05$). In the I/R within-group analysis, eased EL was seen only in the Pio 6 group. Moreover, a statistically significant difference was found only in the Pio 6 group ($p<0.05$; $p<0.05$). The MTBS was significantly

lower in the groups with I/R compared with those without I/R (p<0.05). The differences in the levels of MSTD, EL and MTBS were not significant between the non-I/R within-group analysis (p=0.591, p=0.674, p=0.767) (Figure 3). In the I/R within-group analysis, little ease was observed in the Pio 6 group, but it was not statistically significant (p=0.767) (Table 1).

Biochemical Analysis

The MDA was significantly higher in the groups with I/R than those without I/R (p<0.05). The differences in the levels MDA were not significant between the non-I/R within-group analysis (p=0.812). In the I/R within-group analysis, little ease was observed in the Pio 6 group, but it was not statistically significant (p=0.492). GSH was significantly lower in the groups with I/R than those without I/R (p<0.05). The differences in the levels of GSH were not significant between the non-I/R within-group analysis (p=0.996). In the I/R within-group analysis, little ease was observed in the Pio 6 group, but it was not statistically significant (p=0.845) (Table 2).

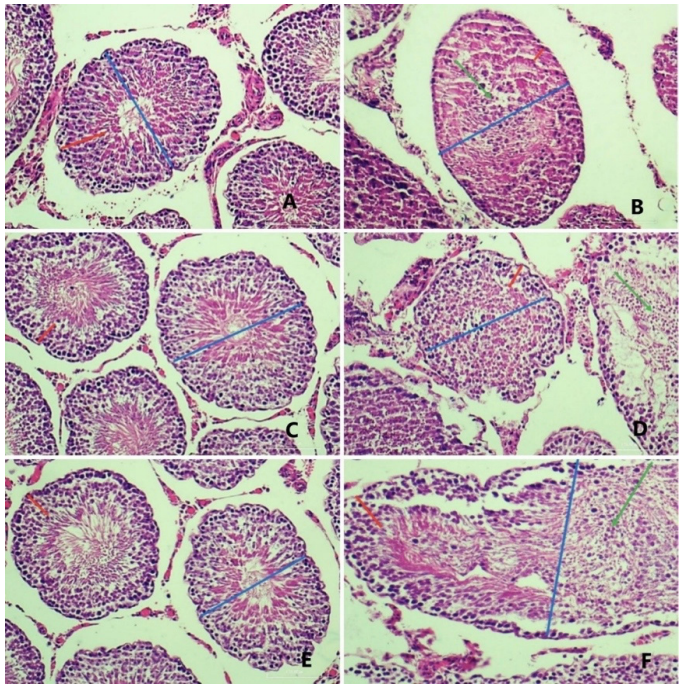

Figure 3. Histological images of hematoxylin and eosin (H & E, 100X) staining of testicular tissue, A: Control, B: I/R, C: Pio 3, D: I/R + Pio 3, E: Pio 6, F: I/R + Pio 6. I/R: Ischemia-reperfusion, Pio: Pioglitazone, Red line: Epithelial length, Blue line: Seminiferous tubule diameter, Green arrow in B, D, F: Necrosis accumulation

Discussion

Testicular torsion is a urological emergency that mostly affects young men (19). Despite early and successful surgical intervention, testicular functions are damaged by oxidative stress during I/R periods (20). The burst of mitochondrial ROS generation consumes natural antioxidants and leads to oxidative stress. Identifying medical agents to protect the testes from I/R injury would be potentially useful. Until now, many medications like oxygen radical scavengers have been successfully studied to reduce oxidative stress in animal models with I/R injury (21). But most of them are not currently in clinical use because of severe adverse effects.

I/R prompts the activation of neutrophils, increased thrombogenicity and inflammatory cytokines, the release of intracellular Ca, and the production of oxygen-derived free radicals (22). Pio was shown to reduce I/R damage by increasing the antioxidant capacity in many tissues (11,23). In a previous study, it was shown that Pio eased histopathological findings at both 1 and 3 mg/kg in testicular ischemia in rats and increased the levels of GSH and decreased levels of MDA (24). It's possible that some variables may cause this study's results to differ from ours. First unlike us, Pio was given intraperitoneally in that study. Also, pio was administered 30 min before detortion, whereas it was administered 2 h before detortion in our study. Another study revealed, Pio increased the levels of GSH at 10

Table 1. Histopathologic evaluation between groups (n=8 for each group)

Groups	MSTD (µm)	p-value	EL (µm)	p-value	MTBS	p-value
Control vs Pio 3	165-170	0.591	44.38-43.75	0.674	9.75-9.88	0.591
Control vs Pio 6	165-167.5	0.591	44.38-45.62	0.674	9.75-9.88	0.591
Pio 3 vs Pio 6	170-167.5	0.591	43.75-45.62	0.674	9.88-9.88	0.591
Control vs I/R	165-113.75	**0.001**	44.38-32.5	**0.001**	9.75-6.25	**0.001**
Pio 3 vs I/R+Pio 3	170-113.75	**0.001**	43.75-32.5	**0.001**	9.88-6.25	**0.001**
Pio 6 vs I/R+Pio 6	167.5-128.75	**0.001**	45.62-38.75	**0.001**	9.88-6.62	**0.001**
I/R vs I/R+Pio 3	113.75-113.75	**0.002**	32.5-32.5	**0.001**	6.25-6.25	0.767
I/R vs I/R+Pio 6	113.75-128.75	**0.002**	32.5-38.75	**0.001**	6.25-6.62	0.767
I/R+Pio 3 vs I/R+Pio 6	113.75-128.75	**0.002**	32.5-38.75	**0.001**	6.25-6.62	0.767

MSTD: Mean seminiferous tubule diameter, EL: Epithelial lengths, MTBS: Johnsen's mean testicular biopsy score, Pio: Pioglitazone, I/R: Ischemia-reperfusion, values are mean ± standard deviation p<0.05 was considered statistically significant
*Statistical analyses were performed between treatment groups.

Table 2. Biochemical analysis between groups (n=8 for each group)				
Groups	**MDA (nmol/mg)**	**p-value**	**GSH (nmol/mg)**	**p-value**
Control vs Pio 3	0.78-0.75	0.812	891.8-895.3	0.996
Control vs Pio 6	0.78-0.76	0.812	891.8-905.6	0.996
Pio 3 vs Pio 6	0.75-0.76	0.812	895.3-905.6	0.996
Control vs I/R	0.78-1.00	**0.001**	891.8-694.4	**0.001**
Pio 3 vs I/R+Pio 3	0.75-0.99	**0.001**	895.3-679.0	**0.001**
Pio 6 vs I/R+Pio 6	0.76-0.90	**0.001**	905.6-746.0	**0.001**
I/R vs I/R+Pio 3	1.00-0.99	0.492	694.4-679.0	0.845
I/R vs I/R+Pio 6	1.00-0.90	0.492	694.4-746.0	0.845
I/R+Pio 3 vs I/R+Pio 6	0.99-0.99	0.492	679.0-746.0	0.845

MDA: Malondialdehyde; GSH, glutathione; Pio, Pioglitazone; I/R, Ischemia-reperfusion; values are mean ± SD. p<0.05 was considered statistically significant
*Statistical analyses were performed between treatment groups.

mg/kg during renal ischemia in rats (11). Pio increased the levels of GSH at both 20 and 40 mg/kg for renal ischemia in rats in a other study (25). In this study, Pio showed improvement in histopathological findings at a dose of 6 mg/kg, but failed to improve the level of MDA and GSH. Also, it did not cause any change in the non-I/R groups. These findings may be related to the beneficial effects of spermatic cell proliferation on the seminiferous tubules.

Consensus has not yet been reached on the dose and duration of Pio for the most effective antioxidant treatment. Furthermore, randomized controlled studies on large human samples are needed in terms of the side effect profile with this effective dose.

Study Limitations

The fact that our study is an animal study is an important limitation. Studies on the effects of Pio on humans should be conducted to strengthen these findings.

Conclusion

I/R of 4 h causes severe damage in the testis. The administration of Pio improved the histopathological parameters. Moreover, further investigations with higher doses must demonstrate the potential effects of Pio in I/R injury and other diseases that affect spermatogenesis.

Ethics

Ethics Committee Approval: All experimental procedures were managed according to international ethical guidelines and were approved by the Local Ethical Committee of Trakya University (reference code 2020.02.01).

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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References

1. Schick MA, Sternard BT. Testicular Torsion. StatPearls. Treasure Island (FL) 2020.
2. Jacobsen FM, Rudlang TM, Fode M, Ostergren PB, Sonksen J, Ohl DA, Jensen CSF, Collaborative CM. The Impact of Testicular Torsion on Testicular Function. World J Mens Health 2020;38:298-307.
3. Sekulic-Jablanovic M, Petkovic V, Wright MB, Kucharava K, Huerzeler N, Levano S, Brand Y, Leitmeyer K, Glutz A, Bausch A, Bodmer D. Effects of peroxisome proliferator activated receptors (PPAR)-gamma and -alpha agonists on cochlear protection from oxidative stress. PLoS One 2017;12:e0188596.
4. Aktoz T, Caloglu M, Yurut-Caloglu V, Yalcin O, Aydogdu N, Nurlu D, Arda E, Inci O. Histopathological and biochemical comparisons of the protective effects of amifostine and l-carnitine against radiation-induced acute testicular toxicity in rats. Andrologia 2017;49.
5. Aktoz T, Kanter M, Aktas C. Protective effects of quercetin on testicular torsion/detorsion-induced ischaemia-reperfusion injury in rats. Andrologia 2010;42:376-383.
6. Elshazly S, Soliman E. PPAR gamma agonist, pioglitazone, rescues liver damage induced by renal ischemia/reperfusion injury. Toxicol Appl Pharmacol 2019;362:86-94.
7. Le P, Chaitoff A, Rothberg MB, McCullough A, Alkhouri N. Trends in pioglitazone use among U.S. adults with type 2 diabetes and suspected nonalcoholic fatty liver disease. Expert Opin Investig Drugs 2020;29:205-208.

8. Chen W, Xi X, Zhang S, Zou C, Kuang R, Ye Z, Huang Y, Hu H. Pioglitazone Protects Against Renal Ischemia-Reperfusion Injury via the AMP-Activated Protein Kinase-Regulated Autophagy Pathway. Front Pharmacol 2018;9:851.
9. Zhang XY, Xiao YQ, Zhang Y, Ye W. Protective effect of pioglitazone on retinal ischemia/reperfusion injury in rats. Invest Ophthalmol Vis Sci 2013;54:3912-3921.
10. Tawfik MK. Renoprotective activity of telmisartan versus pioglitazone on ischemia/reperfusion induced renal damage in diabetic rats. Eur Rev Med Pharmacol Sci 2012;16:600-609.
11. Zou C, Hu H, Xi X, Shi Z, Wang G, Huang X. Pioglitazone protects against renal ischemia-reperfusion injury by enhancing antioxidant capacity. J Surg Res 2013;184:1092-1095.
12. Verges B. Clinical interest of PPARI's ligands. Diabetes Metab 2004;30:7-12.
13. Da Ros R, Assaloni R, Ceriello A. The preventive anti-oxidant action of thiazolidinediones: a new therapeutic prospect in diabetes and insulin resistance. Diabet Med 2004;21:1249-1252.
14. Rahbar S, Natarajan R, Yerneni K, Scott S, Gonzales N, Nadler JL. Evidence that pioglitazone, metformin and pentoxifylline are inhibitors of glycation. Clin Chim Acta 2000;301:65-77.
15. Johnsen SG. Testicular biopsy score count--a method for registration of spermatogenesis in human testes: normal values and results in 335 hypogonadal males. Hormones 1970;1:2-25.
16. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem 1979;95:351-358.
17. Ellman GL. Tissue sulfhydryl groups. Arch Biochem Biophys 1959;82:70-77.
18. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem 1951;193:265-275.
19. Talebi H, Farahpour MR. Testicular torsion and reperfusion: Germ cell DNA damage and development. Andrologia 2019;51:e13243.
20. He M, Li M, Zhang W. Prognosis of testicular torsion orchiopexy. Andrologia 2020;52:e13477.
21. Kolukcu E, Firat F, Deresoy FA, Katar M, Atilgan D. The effects of pirfenidone on ischaemia-reperfusion injury in testicular torsion-induced rat model. Andrologia 2020:e13922.
22. Belhan S, Yildirim S, Karasu A, Komuroglu AU, Ozdek U. Investigation of the protective role of chrysin within the framework of oxidative and inflammatory markers in experimental testicular ischaemia/reperfusion injury in rats. Andrologia 2020;52:e13714.
23. Qiu L, Jiang X, Wen L, Hu Q, Deng Y. [Pioglitazone decreases the levels of inflammatory cytokines in SD rats with traumatic brain injury via up-regulating PPARgamma]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 2016;32:182-184.
24. Mahmoud NM, Kabil SL. Pioglitazone abrogates testicular damage induced by testicular torsion/detorsion in rats. Iran J Basic Med Sci 2019;22:884-892.
25. Singh AP, Singh N, Bedi PM. Pioglitazone ameliorates renal ischemia reperfusion injury through NMDA receptor antagonism in rats. Mol Cell Biochem 2016;417:111-118.

REVIEW
Urooncology

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Solitary Fibrous Tumor of the Prostate: What is the Optimal Treatment? Description of A Case and Review of the Pertinent Literature

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Abstract

A solitary fibrous tumor (SFT) originating from the prostate has been rarely reported, presenting the 44th case. We evaluated a 44-year-old man who presented with a two-year history of pressure in the lower abdomen. On magnetic resonance imaging, a 48×66 mm, well-circumscribed mass was observed. 12-core prostatic needle biopsy was performed. Histological examination reported hypocellular and hypercellular areas composed of bland spindle cells arranged in a haphazard pattern. One or two mitotic figures were observed per 10 high-power-fields. Immunohistochemistry analysis showed a strong expression of CD34, STAT-6, and vimentin by tumor cells. We conducted a surveillance protocol for the patient due to the avoidance the surgery. Although there was an increase of approximately 2 cm in tumor diameter, no change was detected in tumor cellularity, number of mitosis, and other histopathological findings in complementary prostatic needle biopsy after three years of follow-up. A literature review of all prostatic SFTs was performed on histopathological features, treatment modality, and reported recurrence and progression data to identify optimal treatment. Local recurrence was reported in five (11.6%) cases and metastasis in two (4.7%) cases. Twenty-two patients underwent radical surgery with a negative margin. None of these had local recurrence and metastasis was reported in only one. Palliative surgery was reported in 18 patients, including five with local recurrence. However, six had no local recurrence or metastasis during the reported follow-up period. Careful surveillance can be conducted in informed patients if there is no malignancy in the histopathologic examination. In all other cases, surgery is strongly advised and should be radical rather than palliative.

Keywords: Solitary fibrous tumor, prostate, immunohistochemistry, STAT6

Introduction

Solitary fibrous tumor (SFT) is a mesenchymal tumor of interstitial dendritic cells (1). Although it was initially considered to be a mesothelioma originating from the pleura, currently, it is reported in many locations due to the widespread presence of dendritic cells outside the thorax. SFTs originating from the prostate have been reported highly infrequently, and this is the 44th case to date.

SFTs are generally benign, although some may show malignant behavior (2). All reported cases have been surgically treated, but there is no standard treatment approach for these very rare tumors, particularly with regard of the benefit of radical surgery. Almost half of the reported cases were treated with palliative surgery, whereas others received radical surgery. Also, surveillance was attempted in one case (3). This report aims to present a rare case and the results of 36 months of surveillance firstly. Secondly, we reviewed all prostatic SFTs in the literature regarding histopathological features, treatment modality, and reported recurrence and progression data to identify the optimal treatment based on the available information.

Case Presentation

Case A 44-year-old man presented with a two-year history of pressure in the lower abdomen. He had no lower urinary tract symptoms (LUTS), or hematuria, and no constipation. He had

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no history of major medical illness. A rectal exam revealed a huge, firm prostate without nodule or induration. His renal function, prostate-specific antigen level, and urine analyses were also within normal limits. On dynamic, gadolinium-enhanced magnetic resonance imaging (MRI) of the abdomen, a 48×66-mm well-circumscribed mass with homogeneous enhancement was observed at the right anterolateral aspect of the prostate (Figure 1a, b). Twelve-core prostatic needle biopsy was performed.

On histological examination of biopsy specimens, the tumor was detected in all six transrectal prostate biopsies of the right prostate lobe and two biopsy specimens from the left lobe. The tumor had hypocellular and hypercellular areas, composed of bland spindle cells arranged in a haphazard pattern. The stroma consisted of a variable number of dense wire-like hyaline collagen deposits, with tumor cells arranged either singly or in small clusters next to the dense collagen (Figure 2a). The spindle-shaped cells had ill-defined borders and scanty eosinophilic cytoplasm. The nuclei were ovoid or elongated, with blunt or tapered ends and contained finely dispersed chromatin or had inconspicuous nucleoli (Figure 2b). Mitotic figures were infrequent. One or two mitotic figures were observed per 10 high-power fields (HPF). No atypical mitotic figure are encountered. These cells did not show prominent atypia or pleomorphism. No lymphovascular invasion or tumor necrosis was observed. Residual prostate parenchyma adjacent to the tumor was noted in some biopsy specimens.

Immunohistochemistry (IHC) analysis showed a strong expression of CD34, STAT-6, and vimentin by tumor cells (Figure 2c, d). Tumor cells were also immunoreactive for CD99, bcl-2, and progesterone (PR) (Figure 3a-c). No staining was observed for CD56, SMA, desmin, pancytokeratin, synaptophysin, CD31, S100, CD117, or DOG1. The proliferation rate, measured by Ki-67 nuclear staining, was evaluated as 5% in hot spots (Figure 3d).

These findings identified an SFT of the prostate. Radical surgery was discussed with the patient. However, he was hesitant about the possible side effects of the surgery, especially urinary incontinence and erectile dysfunction.

The findings were further evaluated according to the malignancy criteria proposed by England et al. (2) and the risk stratification model of Demicco et al. (4) and Pasquali et al. (5). This case had no malignancy criteria as suggested by England et al. (2). Furthermore, the tumor was classified as a low-risk and very low-risk using the models of Demicco et al. (4) and Pasquali et al. (5), respectively. As the biopsy revealed no malignancy and the patient was reluctant to surgery, conservative management was adopted. The tumor was stable on consecutive computed tomography (CT) and MRI scans, three and seven months after diagnosis. However, two years later, CT scan showed that the size of the mass had increased and at that time measured as 77x62x60 mm^3, without any emerging symptoms. Approximately 1 cm additional growth was observed in the tumor (77x82 mm) in the 36th month CT images (Figure 1c, d). Three years after the initial biopsy, confirmatory prostate needle biopsy was performed. According to the histopathological evaluation of the follow-up biopsy, the tumor had the same features as when it was first diagnosed. Histologically, the spindle-shaped tumor cells were dispersed singly or in small groups within the collagenized fibrous stroma. There were no cytological atypia and pleomorphism in follow-up biopsies. The mitotic activity was the same as in the first biopsies. No atypical mitotic figures, tumor necrosis, or lymphovascular invasion were found. These findings indicated that tumor histopathology remained stable during the follow-up (Figure 2e-h).

Literature Review and Discussion

A literature search was conducted in MEDLINE using the following search parameters "(((solitary) AND (fibrous)) AND (tumor)) AND (prostate)." Forty-three cases were identified in 26 reports (3,6-31). Patient age, presenting symptoms, treatment modality, and microscopic findings in terms of malignancy criteria, follow-up time, recurrence, and metastasis information were noted. The cases were evaluated according to the malignancy criteria proposed by England et al. (2) (size >10 cm, mitotic activity >4/10 HPFs, nuclear pleomorphism, infiltrative boundaries, and the presence of necrosis) and divided into two groups (based on the presence of any criterion or none).

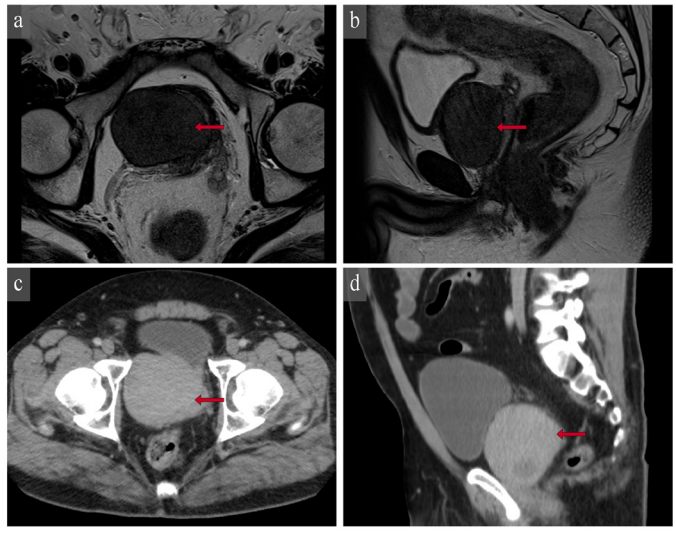

Figure 1. (a) Axial T2WI, **(b)** Sagittal T2WI. On dynamic gadolinium-enhanced magnetic resonance imaging (MRI) of the abdomen, a 48×66 mm well-circumscribed mass and homogeneous enhancement was observed at the right anterolateral side of the prostate. **(c)** Axial CT, **(d)** Sagittal CT images at three years of follow-up. CT scan showed that the size of the mass was increased and measured as 77x82 mm. The arrows indicate the mass

CT: Computed tomography

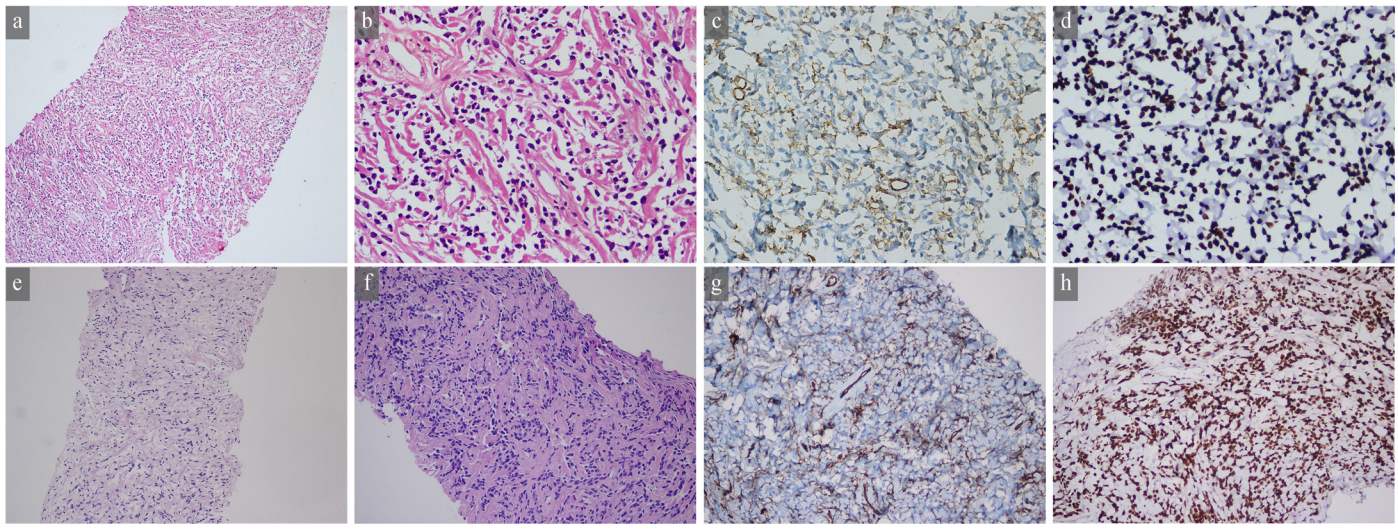

Figure 2. Images from the initial histopathology examination; **(a)** Tumor tissue with haphazard pattern ("patternless pattern") (HEx100). **(b)** High-power view showing oval or elongated nucleus with scant cytoplasm of spindle tumor cells (HEx400). **(c)** Diffuse CD 34 positivity in tumor cells (CD34x400). **(d)** Strong STAT-6 nuclear expression of tumor cells (STAT-6x400). Images of histological assessment of the third-year follow-up biopsy; **(e)** Tumor tissue with haphazard pattern ("patternless pattern") (HEx100). **(f)** High-power view showing oval or elongated nucleus with scant cytoplasm of spindle tumor cells (HEx200). **(g)** Diffuse CD 34 positivity in tumor cells (CD34x200). **(h)** Strong STAT-6 nuclear expression of tumor cells (STAT-6x400)

Demographic characteristics and pathological results of these cases are summarized in Table 1. Most patients were older and suffered from LUTS, with an average tumor size of 8 cm.

Preference of Surgical Procedure

Recurrence and metastasis information was not reported for 15 patients. Local recurrence without metastasis was reported in five (11.6%) patients and metastasis in two (4.65%) patients. Twenty-two (51.2%) patients underwent radical surgery with a negative margin. None of these had local recurrence; metastasis was reported in only one case. Palliative surgery (enucleation or transurethral resection) was reported in 17 (39.5%) patients and radical surgery with a positive margin in one case (6). All the five local recurrences were reported in these cases. However, six of them had no local recurrence or metastasis during the reported follow-up.

Histopathology

Local tumor relapse was reported in five (11.6%) cases without distant metastasis (6,8,15,23,25). Three of them had at least one malignant criterion (mitosis in 7/10 HPFs in one case, nuclear atypia and necrosis in two cases) (6,8,15). The malignant criteria were not clearly specified in the other two cases (23,25). Tumor size was <10 cm in all.

Distant metastasis was reported in two cases (3,6). Both of them had at least one malignant criterion (mitosis in 13/10 HPFs in one case, mitosis present in more than 10/10 HPFs in the other; tumor necrosis in both; hypercellularity in one). Tumor sizes were 6 cm and 9 cm, respectively. Radical surgery with a negative margin was reported in one of them and unspecified in the other.

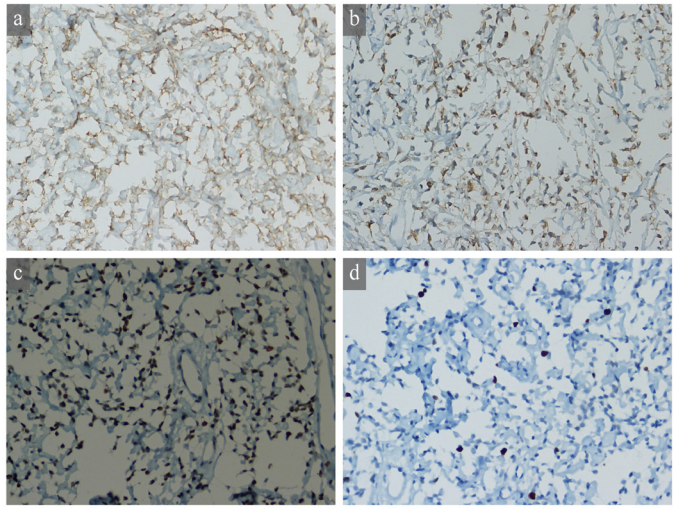

Figure 3. (a) Tumor cells diffusely positive for CD99 (CD99x400). **(b)** Tumor cells diffusely positive for bcl-2 (Bcl-2x400). **(c)** Diffuse, strong progesterone nuclear expression in tumor cells (PRx400). **(d)** Nuclear expression of Ki-67 in some tumor cells (Ki-67x400)

In one of four patients reported by Bakhshwin et al. (6) high-risk SFT by two prognostic systems Salas et al. (32) and Pasquali et al. (5). The patient underwent radical prostatectomy following transurethral resection of the tumor with pT0 disease. However, the patient had a recurrence at the bladder neck and subsequent biopsy-proven metastatic disease to the right obturator lymph node (6). Additionally, Tanaka et al. (3) reported

distant metastasis in their case, although the initial prostatic needle biopsy reported stromal spindle cells with no mitosis. On follow-up MRI approximately ten months later, the mass had increased in size, another prostatic needle biopsy was performed and now showed that tumor cells with round and short spindle-shaped nuclei with some mitoses were present. A total resection of the mass was performed. In the permanent pathological examination, the tumor was found in the muscularis of the prostatic urethra or the bladder. The tumor consisted of spindle cells with fascicular and storiform patterns of growth, and mucinous degeneration and some necrosis were observed in the background. The tumor was hypercellular, and a significant number of mitoses (more than 10/10 HPFs) were present.

Table 1. Summary of demographic characteristics and pathology results of all cases in the literature

	n	**43**
Age	Median (range) years	58 (28-78)
Presentation symptoms		
	Unknown, n (%)	6 (14.0)
	Asymptomatic, n (%)	2 (5.4)
	LUTS, n (%)	27 (73.0)
	Hematuria, n (%)	2 (5.4)
	Urinary retention, n (%)	4 (10.8)
	Constipation, n (%)	2 (5.4)
Tumor diameter		
	Unknown, n (%)	14 (32.5)
	Average (range) cm	8 (1.5-20)
	<10 cm, n (%)	18 (41.9)
	≥10 cm, n (%)	11 (25.6)
Average mitosis/10 HPF		
	Unknown, n (%)	15 (34.9)
	<1, n (%)	15 (34.9)
	1-4, n (%)	5 (11.6)
	≥5, n (%)	8 (18.6)
At least one malignant criterion		
	Unknown, n (%)	6 (14.0)
	Yes, n (%)	19 (44.2)
	No, n (%)	18 (41.9)
Radical surgery with negative margin		
	Unknown, n (%)	4 (9.3)
	Yes, n (%)	21 (48.8)
	No, n (%)	18 (41.9)
Follow-up		
	Unknown, n (%)	15 (34.9)
	Not-specified, n (%)	2 (4.6)
	Median (range) months	18 (2-168)
Local recurrence		
	Unknown, n (%)	15 (34.9)
	Yes, n (%)	5 (11.6)
	No, n (%)	22 (53.4)
Metastasis		
	Unknown, n (%)	15 (34.9)
	Yes, n (%)	2 (4.7)
	No, n (%)	26 (60.5)

HPF: High-power field, LUTS: Lower urinary tract symptoms

In contrast, six cases did not have any tumor recurrence; hence, radical surgery and negative margin were not performed (10,12,19,21,25,30). Median follow-up was 48 (12-168) months in these cases. Three of them had no malignant criterion (10,12,19). However, the others also had at least one malignant criterion (21,25,30). Nair et al. (21) reported a 10 cm tumor that was enucleated with an abdominoperineal approach. They had no evidence of loco-regional recurrence at follow-up after two years. They reported that there was a non-encapsulated tumor on microscopic examination with extended margins containing hyper- and hypo-cellular areas, spindle-shaped with bland nuclei having dispersed chromatin and inconspicuous nucleoli. The mitotic rate was 1/50 HPFs. Pins et al. (25) reported one of two cases, who was treated suprapubic prostatectomy. He had no recurrence after 21 months, though hypercellularity, nuclear atypia, and mitosis 20/50 HPFs were detected in his pathological examination. Xu et al. (30) reported three malignant prostatic SFTs in their study comparing mesenchymal tumors of the prostate. The tumor sizes were 7.6, 19 and 18 cm in largest diameter, respectively. The first was treated with radical prostatectomy with negative margin and excisional biopsies were performed for the others. The last had no information about the follow-up, but the first two cases were followed for six and 84 months without recurrence and metastasis. All tumors had necrosis, and the average mitosis was 5/10 HPFs.

Paraneoplastic Syndromes

On rare occasions SFT can present with paraneoplastic syndromes, the most commonly described being non-islet cell hypoglycemia (33). However, none of the authors reported hypoglycemia in cases of prostatic SFT.

Conclusion

Although there is little data, we suggest that probably the optimal treatment for prostatic SFT is radical surgery with a negative surgical margin. Surgeons should avoid partial resection of the tumor due to the risk of recurrence and metastasis. The malignancy criteria reported by England et al. (2) are a generally useful tool for predicting the prognosis of the disease. However, we did not observe that the tumor diameter affected the results

in the literature. Contrarily, an excessive number of mitosis per HPF seems to be a poor prognostic factor. Surveillance should be performed in patients without malignancy criteria, particularly in cases with very low mitosis rates. Here we report the longest and un-complicated surveillance in the literature. However, one should be careful that insufficient sampling of the tumor with needle biopsies may not show where mitosis is high and nuclear atypia, hypercellularity, or necrosis is present. Close follow-up with repeated biopsy and imaging may be a treatment option in patients younger age and those without malignancy criteria.

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Authorship Contributions

Surgical and Medical Practices: H.Y., A.T.E., Concept: H.Y., A.T.E., Design: H.Y., İ.E.A., Data Collection or Processing: H.Y., İ.E.A., E.Ö., Analysis or Interpretation: H.Y., İ.E.A., Literature Search: H.Y., C.Ö., A.T.E., Writing: H.Y., İ.E.A., C.Ö., E.Ö., A.T.E.

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References

1. Westra WH, Grenko RT, Epstein J. Solitary fibrous tumor of the lower urogenital tract: a report of five cases involving the seminal vesicles, urinary bladder, and prostate. Hum Pathol 2000;31:63-68.
2. England DM, Hochholzer L, McCarthy MJ. Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. Am J Surg Pathol 1989;13:640-658.
3. Tanaka Y, Nakamoto A, Inada Y, Narumi Y, Hirose Y, Azuma H. A case of malignant solitary fibrous tumor of the prostatic urethra. BJR Case Rep 2018;4:20180034.
4. Demicco EG, Wagner MJ, Maki RG, Gupta V, Iofin I, Lazar AJ, Wang WL. Risk assessment in solitary fibrous tumors: validation and refinement of a risk stratification model. Mod Pathol 2017;30:1433-1442.
5. Pasquali S, Gronchi A, Strauss D, Bonvalot S, Jeys L, Stacchiotti S, Hayes A, Honore C, Collini P, Renne SL, Alexander N, Grimer RJ, Callegaro D, Sumathi VP, Gourevitch D, Desai A. Resectable extra-pleural and extra-meningeal solitary fibrous tumours: A multi-centre prognostic study. Eur J Surg Oncol 2016;42:1064-1070.
6. Bakhshwin A, Berry RS, Cox RM, Li R, Reynolds JP, Rubin BP, McKenney JK. Malignant solitary fibrous tumour of the prostate: four cases emphasising significant histological and immunophenotypical overlap with sarcomatoid carcinoma. Pathology 2020;52:643-648.
7. Bhargava P, Lee JH, Gupta S, Seyal AR, Vakar-Lopez F, Moshiri M, Dighe MK. Radiologic-pathologic findings of solitary fibrous tumor of the prostate presenting as a large mass with delayed filling-in on MRI. Radiol Case Rep 2012;7:634.
8. Cheng Q, Chang X, Chen W, Qin J, Ai Q, Li H. A rare case of solitary fibrous tumor arising from prostate located inside of bladder. Urol Case Rep 2019;24:100880.
9. Galosi AB, Mazzucchelli R, Scarpelli M, Lopez-Beltran A, Cheng L, Muzzonigro G, Montironi R. Solitary fibrous tumour of the prostate identified on needle biopsy. Eur Urol 2009;56:564-567.
10. Gilbert B, Csillag A, Desai D, McClintock S. Prostate preserving resection of a rare giant peri-prostatic solitary fibrous tumor. Urol Case Rep 2020;32:101167.
11. Herawi M, Epstein JI. Solitary fibrous tumor on needle biopsy and transurethral resection of the prostate: a clinicopathologic study of 13 cases. Am J Surg Pathol 2007;31:870-876.
12. Ishii T, Kuroda K, Nakamura K, Sugiura H. Solitary fibrous tumor of the prostate. Hinyokika kiyo Acta urologica Japonica 2004;50:405-407.
13. Joe BN, Bolaris M, Horvai A, Yeh BM, Coakley FV, Meng MV. Solitary fibrous tumor of the male pelvis: findings at CT with histopathologic correlation. Clin Imaging 2008;32:403-406.
14. Kelly PM, Baxter GM. Solitary fibrous tumour of the prostate. Br J Radiol 1998;71:1086-1088.
15. Liu YT, Song FX, Xiang L, Chang H. Solitary fibrous tumor of the prostate: a case report and 5-year follow-up. Asian J Androl 2019;21:421-422.
16. Manica M, Roscigno M, Naspro R, Sodano M, Milesi L, Gianatti A, Da Pozzo LF. Recurrent retroperitoneal solitary fibrous tumor: a case report and review of the literature. Tumori 2020;300891620974763.
17. Matos J, Paparo F, Calcagno T, Marinaro E, Introini C, Rollandi GA. Solitary Fibrous Tumor of the Prostate. Urology 2020;141:e43-e44.
18. Mentzel T, Bainbridge TC, Katenkamp D. Solitary fibrous tumour: clinicopathological, immunohistochemical, and ultrastructural analysis of 12 cases arising in soft tissues, nasal cavity and nasopharynx, urinary bladder and prostate. Virchows Arch 1997;430:445-453.
19. Mishra A, Corkum MT, Pautler SE, Wehrli B, Winquist E. Images - Solitary fibrous tumor of the prostate. Can Urol Assoc J 2020;14:E613-E614.
20. Moureau-Zabotto L, Chetaille B, Bladou F, Dauvergne PY, Marcy M, Perrot D, Guiramand J, Sarran A, Bertucci F. Solitary fibrous tumor of the prostate: case report and review of the literature. Case Rep Oncol 2012;5:22-29.
21. Nair B, Nambiar A, Hattangadi SB, Sukumar S, Saifuddin MS. Solitary fibrous tumour of prostate: evaluation and management of a rare tumour. Scand J Urol Nephrol 2007;41:442-444.
22. Nishith N, Gupta M, Kaushik N, Sen R. Solitary Fibrous Tumor of the Prostate: A Diagnostic Challenge: A Case Report. Iran J Pathol 2020;15:41-44.
23. Oguro S, Tanimoto A, Jinzaki M, Akita H, Yashiro H, Okuda S, Kuribayashi S, Kameyama K, Mukai M. Imaging findings of solitary fibrous tumor of the prostate: a case report. Magn Reson Imaging 2006;24:673-675.
24. Osamu S, Murasawa H, Imai A, Hatakeyama S, Yoneyama T, Hashimoto Y, Koie T, Ohyama C. Solitary Fibrous Tumor of the Prostate Which Was Initially Misdiagnosed as Prostate Cancer. Case Rep Urol 2017;2017:3594914.
25. Pins MR, Campbell SC, Laskin WB, Steinbronn K, Dalton DP. Solitary fibrous tumor of the prostate a report of 2 cases and review of the literature. Arch Pathol Lab Med 2001;125:274-277.
26. Ronchi A, La Mantia E, Gigantino V, Perdona S, De Sio M, Facchini G, Franco R, De Chiara A. A rare case of malignant solitary fibrous tumor in prostate with review of the literature. Diagn Pathol 2017;12:50.
27. Sekine H, Ohya K, Kojima S, Mizuguchi K. Solitary fibrous tumor of the prostate. Int J Urol 2001;8:137-138.
28. Takeshima Y, Yoneda K, Sanda N, Inai K. Solitary fibrous tumor of the prostate. Pathol Int 1997;47:713-717.
29. Talvitie H, Astrom K, Larsson O, Ahlen J, Bergh A, Egevad L. Solitary fibrous tumor of the prostate: a report of two cases. Pathol Int 2011;61:536-538.
30. Xu Y, Li Z, Shi J, Fu Y, Zhu L, Fan X, Foo WC. Clinicopathological features to distinguish malignant solitary fibrous tumors of the prostate from prostatic stromal tumors. Virchows Arch 2021;478:619-626.
31. Yang W, Sun F, Liu H, Wang G, Shi P, Shao Z, Guo F. Solitary fibrous tumors of the prostate: A case report. Oncol Lett 2015;10:1617-1619.

32. Salas S, Resseguier N, Blay JY, Le Cesne A, Italiano A, Chevreau C, Rosset P, Isambert N, Soulie P, Cupissol D, Delcambre C, Bay JO, Dubray-Longeras P, Krengli M, De Bari B, Villa S, Kaanders J, Torrente S, Pasquier D, Thariat JO, Myroslav L, Sole CV, Dincbas HF, Habboush JY, Zilli T, Dragan T, Khan RK, Ugurluer G, Cena T, Duffaud F, Penel N, Bertucci F, Ranchere-Vince D, Terrier P, Bonvalot S, Macagno N, Lemoine C, Lae M, Coindre JM, Bouvier C. Prediction of local and metastatic recurrence in solitary fibrous tumor: construction of a risk calculator in a multicenter cohort from the French Sarcoma Group (FSG) database. Ann Oncol 2017;28:1979-1987.

33. Robinson LA. Solitary fibrous tumor of the pleura. Cancer Control 2006;13:264-269.