JOURNAL OF UROLOGICAL SURGERY

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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.

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5. Abstract

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

6. Letter to the Editor

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

7. Supplement

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

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CONTENTS

Water Vapor Thermal Therapy (Rezum™) for Benign Prostate Hyperplasia: Initial Experience from Turkiye

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

Rezum™ system is a safe minimal invasive treatment modality for benign prostate hyperplasia treatment. This is the first study from Turkiye that reports the initial short-term results of Rezum™ therapy.

Abstract

Objective: Rezum™ system is a safe minimal invasive treatment modality for benign prostate hyperplasia (BPH) treatment. The aim of this study was to evaluate the short-term results of Rezum™ therapy in our center.

Materials and Methods: We retrospectively collected the data of 28 patients with symptomatic BPH who underwent Rezum™ therapy in our center. All patients' pre-operative and post-operative; post-void residual volume (PVR), Q_{max}, international prostate symptom score (IPSS), quality of life (QoL) score, serum total prostate-specific antigen levels were obtained. The number of injections administered during the procedure, operation time, catheter removal time, complications and mean duration of follow-up was recorded.

Results: Our study group consisted of 28 patients with a mean age of 65.1±8.9 years, median prostate volume 64 [interquartile range (IQR) 44.8-89.5] mL. The median procedure time was 12 (IQR 11-13.8) minutes, the median catheter removal time was 6.5 (IQR 5-8.8) days for our study group. None of the patients had experienced Clavien-Dindo 3 complications. Pre-operative median Q_{max} and PVR were 8 (IQR 6-9) mL/s and 110 (IQR 80-187.5) cc and post-operative Q_{max} and PVR were 12.5 (11-14.8) mL/s and 40 (IQR 18.8-70) cc, respectively. We observed a significant increase in IPSS and QoL score at post-operative 3rd month after the Rezum™ therapy.

Conclusion: Rezum™ procedure is an effective and safe treatment for symptomatic BPH in the short term. Rezum™ system provides a significant increase in Q_{max} and significant decrease in PVR and IPSS. QoL scores after the 3rd month of the procedure is significantly lower compared to the pre-operative status.

Keywords: Benign prostate hyperplasia, Rezum™ (water vapor therapy), minimal invasive treatment

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Introduction

Benign prostate hyperplasia (BPH) related lower urinary tract symptoms (LUTS) increase with age affects 6% of the male population (1-3). Symptoms, health-related quality of life (QoL) and urinary flow rates worsen and eventually some of the men experience acute urinary retention and need for surgery due to progressive increase in prostate volume (4). In case of pharmacotherapy failure and presence of BPH-related complications surgical treatment modalities such as open adenomectomy, laser enucleation of the prostate and transurethral resection of the prostate (TURP) should be considered (5). TURP has been considered as the gold standard surgical treatment option for BPH (6). Although TURP is a

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valuable option in improving urinary symptoms; risks of acute complication and long-term adverse effects such as ejaculatory and erectile dysfunction, *de novo* incontinence have been demonstrated (7). There are several treatment modalities for BPH with a broad spectrum of cost, invasiveness and efficacy. Rezum™ (Boston Scientific, Marlborough, MA) was a relatively new minimal invasive treatment modality and approved by Food and Drug Administration (FDA) in 2015. Since FDA clearance, Rezum™ system has been adopted by many urologists in Europe and United States (5,8). Clinical improvement in QoL, sustained relief of LUTS and durability of treatment response leads wide adoption of Rezum™ system throughout the world (9). Rezum™ system use a radiofrequency generator that converts water into water vapor. The convective conduction of heat in prostate tissue causes coagulation necrosis of prostate cells (10). Convective thermal energy that stimulates targeted tissue ablation without an effect on outside the targeted zone, offers Rezum™ a strong safety profile when compared to other minimal invasive surgical treatment modalities such as transurethral microwave thermotherapy (TUMT) and transurethral needle ablation of the prostate (TUNA) (10,11). Rezum™ therapy reduces prostate tissue volume associated with BPH, including hyperplasia of lateral, central zone and/or a middle lobe without morphologic limitations (12). Various anatomical variants, such as intravesical prostatic protrusion can be treated without interfering sexual function (13). Moreover, Rezum™ therapy does not have a steep learning curve and relatively easy to perform for the surgeon. Rezum™ procedure can be performed under local or sedoanalgesia in operating room or even in office setting (9). Steam delivered by the needle which is located at the tip of the Rezum™ device dispersed around the prostate tissue by the guidance of a cystoscope for 9 seconds for each injection. This steam leads to cell death and necrosis that in turn results in shrinking of the treated tissue up to 40% (10). This provides the patient; relief of LUTS and improvement in QoL without interfering with sexual function (9). Rezum™ procedure is shown to be effective in treating 30-80 mL prostates (with or without median lobe) for men ≥50 years old and today there are increasing data exists that shows that Rezum™ is a potentially good option for larger prostates or men with urinary retention (14,15). Rezum™ procedure is also applicable for the ablation of median lobe and enlarged central zone which is presented by elevated bladder neck (13). The aim of this study was to report our short-term (3rd month) results of the Rezum™ procedure in our center.

Materials and Methods

Between October 2020 and February 2022; 28 patients with moderate-to severe LUTS underwent Rezum™ (Boston Scientific, Marlborough, MA) procedure in our center. Our study group consisted of patients with IPSS score ≥8 (moderate and severe LUTS) and prostate size ≤130 cc in whom were considered for surgical intervention due to the ineffective pharmacotherapy treatment. Patients with a permanent urinary catheter due to the urinary retention after the trial without the catheter were also included in this study. Four of 28 patients (14.3%) had indwelling foley catheter pre-operatively due to acute urinary retention after the trial without the catheter. Because it was impossible to compare the mean peak urinary flow rate (Q_{max}) before and after the Rezum™ procedure, these 4 patients with pre-operative indwelling catheter due to acute urinary retention parameters excluded in the study. Patients with urinary infection, suspicious digital rectal examination finding, prostate volume >130 mL, history of previous pelvic radiotherapy were excluded. Patient demographic variables, pre-operative, and post-operative 3rd month PSA levels, post-void residual urine (PVR), Q_{max} values, international prostate symptom score (IPSS) and QoL scores were recorded. This study was approved by the Acıbadem Mehmet Ali Aydınlar University Institutional Review Board (İstanbul, Turkiye), (decision number: 2022-09/07) and signed informed consent was collected from all subjects.

The Rezum™ Procedure

All procedures were performed by a dedicated urology team in the operating room under sedoanalgesia. Pre-operative urine cultures and standard pre-operative laboratory examinations were obtained for all patients. Pre-operative prophylactic antibiotherapy according to local practice guidelines was administered to all patients. All procedures were performed in the lithotomy position. After the cleaning of the surgical field and proper draping; Rezum™ device was introduced into the urethra with 30-degree optic cystoscope to access the hyperplastic prostate tissue with the water delivery instrument. Initially, routine cystoscopy was performed to evaluate the bladder and the prostatic lodge. After this step, the vapor needle penetrated the prostate under direct visualization. Subsequently, water vapor was dispersed into the prostate adenoma for 9 seconds. Rapid escalation of the temperature to 70° celcius throughout the adenoma by the dispersion of the heat lead to cell necrosis.

The injections were initiated 1 cm below the bladder neck, downwards to the prostatic urethra to the proximal edge of the verumontanum and performed at each centimeter. In the case of median lobe presence, 1 or more injections may be performed in this lobe. The number of water vapor injections relies on the prostatic urethral length, median lobe presence and prostate volume. During the procedure, the urethral length was measured with a view finder, which is located at the tip of the instrument while retracting from the bladder neck to the verumontanum. The field of view finder used a scale that is 5 mm in diameter. In each 1 cm, a steam injection was performed typically at 9 and 3 o'clock for the lateral lobes and 6 o'clock on the median

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lobe. Although we did not expect any bleeding; an 18-F 3-way silicone Foley catheter was placed at the end of the procedure to be at the safe side at the beginning of our experience.

Statistical Analysis

SPSS v.21 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Shapiro-Wilk tests and probability plots were used to assess normality. Results were presented mean ± standard deviation for normally distributed variables, median [interquartile range (IQR)] for non-normally distributed variables. Categorical variables are presented along together with frequency and percentage. Differences between the two paired groups were tested using the Wilcoxon test. All tests are two-sided and the significance level was set as $p<0.05$.

Results

Rezum™ therapy was performed in 28 patients. Pre-operative characteristics are summarized in Table 1. Mean patient age was 65.1 ± 8.9 years, median PSA level was 2.6 (IQR 1.4-4.4) ng/mL, median prostate volume which was identified with urinary system ultrasonography was 64 (IQR 44.8-89.5) cc. The pre-operative median Q_{max} and Q_{ave} values were 8 (IQR 6-9) mL/s and 4 (IQR 3-5) mL/s respectively. All patients in our study were under alpha-blocker treatment for a median time of 45.5 (IQR 35-50) months and 5 patients were under 5-alpha reductase inhibitors, 4 patients were under phytotherapeutic serenoa repens as well. Preoperative median IPSS and QoL scores were 2 (IQR 2-3) and 5 (IQR 4-5) respectively. The operation time is defined as the time between the transurethral insertion of the instrument to

foley catheterization at the end of the procedure. The median operative time was 12 (IQR 11-13.8) minutes. The median number of injections given during the procedure was 6 (IQR 5-7). An 18 F 3-way silicone Foley catheter was positioned at the end of the procedure in the cases. In 2 patients concomitant bladder stone (bladder stones for 1 and 1.5 cm maximal diameter) laser lithotripsy was performed at the same session with Rezum™ therapy. All patients were discharged on post-operative day 1. Alpha-blocker treatment continued for 2 months and then was stopped. Clavien-Dindo grade 1 complications were encountered in 13 (46.4%) patients. Transient hematuria developed in 1 patient after the procedure and resolved spontaneously in a few days without any intervention. Three patients reported catheter-related mild discomfort which was managed conservatively with non-steroidal anti-inflammatory suppositories. Acute urinary retention developed after the catheter removal in 9 (32.1%) patients. In these patients, recatheterization was performed for an additional median 7 (IQR 5.5-9.5) days. For these 9 patients; spontaneous micturition was observed after catheter removal without any adverse event with a median 100 (IQR 60-120) cc PVR at post-operative 3rd month. In 2 patients post-operative urinary tract infection developed (Clavien-Dindo grade 2) which required oral antibiotics for 2 weeks. Clavien-Dindo grade ≥3 complications were not encountered in our study group and none of the patients required definitive TURP or any other surgical intervention for BPH management during the post-operative 3-month follow-up. Three months after the Rezum™ procedure; a significant increase in Q_{max} and Q_{ave} values and reduction in IPSS and PVR was identified (respectively $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). The QoL score also showed a significant

Table 1. Characteristics of the study group				
Categories	Patient n	n (%)	Mean ± SD	Median (IQR)
Age, year	28		65.1±8.9	65.5 (58.3-72)
BMI, kg/m²	28		30.8±3.3	31 (28-32.8)
ASA score	28		2.1±0.5	2 (2-2)
Pre-operative urinary ultrasound prostate volume, cc	28		67±26.7	64 (44.8-89.5)
Pre-operative urinary retention	28	4 (14.3%)		
Pre-operative catheterization	28	4 (14.3%)		
Total prostate lobe injection	28		6.2±1.5	6 (5-7)
Operative time, minutes	28		13.6±4.2	12 (11-13.8)
Post-operative foley catheter removal time, day	28		7.3±3.6	6.5 (5-8.8)
Spontaneous micturition after catheter removal	28	21 (75%)		
PMR after catheter removal, cc	28		172.9±178.9	70 (32.5-300)
Post-operative re-catheterization	28	9 (32.1%)		
Post-operative re-catheterization, day	9		7.4±2.2	7 (5.5-9.5)
Spontaneous micturition after removal of re-catheterization	9	9 (100%)		
PMR after catheter removal (for patients that required recatheterization), cc	9		95.7±46.5	100 (60-120)
n (%): Frequency (percentage), BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range				

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decrease after the Rezum™ procedure (p<0.001) (Table 2, Figures 1, 2). There was no significant difference between PSA values in pre-operative and post-operative 3rd month (p=0.058) (Table 2). Four patients with pre-operative indwelling catheter due to urinary retention were catheter free from the time of catheter removal with a median 80 (IQR 37.5-400) cc PVR at post-operative 3rd month.

Discussion

Recently, surgeons, and patients both shown an interest in minimal invasive methods for BPH management. Many minimal invasive surgical treatment options have emerged over the past decades; but high retreatment rates, procedure related sexual dysfunction and/or patient related anatomical variations like presence of middle lobe, have remained a common obstacle to their wide adoption. Although high-intensity focused ultrasound, TUNA, TUMT, prostate stent implantation, Aqua-ablation and selective prostate artery embolization (PAE) occur in the literature; new methods such as Urolift™ and Rezum™ became more popular in clinical practice. Rezum™ therapy can be performed in the presence of median lobe in contrast to urethral stents and prostatic urolift (PUL) (9). Unlike PAE and aquaablation; Rezum™ procedure can be an appliable in the day-
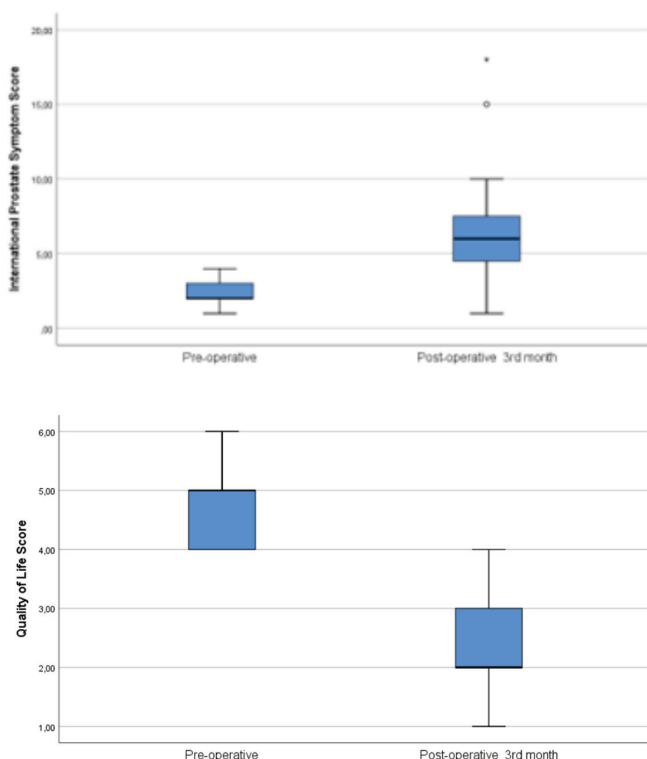
Figure 1. Change in IPSS and QoL score pre-operative and post-operative 3rd month

IPSS: International prostate symptom score, QoL: Quality of life
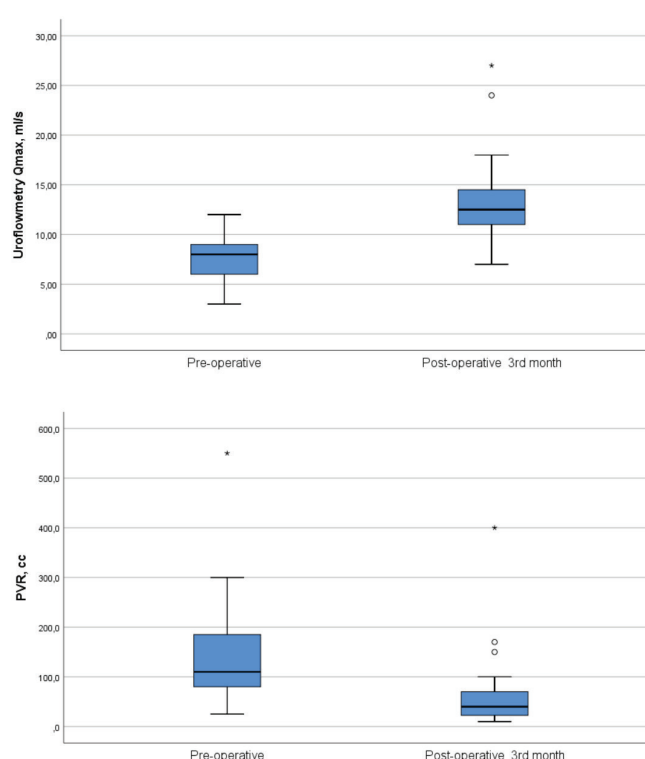
Figure 2. Change in Q_{max} (mL/s) and PVR (cc) score pre-opeative and post operative 3rd month

PVR: Post-void residual volume

Table 2. Comparisons of measures pre-operative and post-operative 3rd month				
Categories	**Patient n**	**Pre-operative**	**Post-operative 3rd month**	**p[1]**
		Median (IQR)	**Median (IQR)**	
IPSS	28	2 (2-3)	6 (4.3-7.8)	<0.001
QoL score	28	5 (4-5)	2 (2-3)	<0.001
Uroflowmetry Q_{max}, mL/s	24*	8 (6-9)	12.5 (11-14.8)	<0.001
Uroflowmetry Q_{ave}, mL/s	24*	4 (3-5)	7 (5.3-8)	<0.001
PVR, cc	24*	110 (80-187.5)	40 (18.8-70)	<0.001
PSA (total)	28	2.6 (1.4-4.4)	2.3 (1.3-3.6)	0.058
[1]Wilcoxon test; *4 patient had preoperative catheterization, IPSS: International prostate symptom score, QoL: Quality of life, Q_{max}: Peak urinary flow, Q_{ave}: Average urinary flow, PVR: Post-void residual urine, PSA: Prostate-specific antigen				

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case setting (15-18). Addition to this; operative time is short, and it can be performed in out-patient setting or office and thereby probably reduce the overall cost. Rezum™ procedure improves the clinical outcomes without bleeding or compromising sexual function. Due to the minimal adverse effects of Rezum™; an overall cost-effectiveness was observed in the studies (19,20). Randomized control trials have shown that; Rezum™ provides a mean IPSS improvement of 48% and reduces the LUTS (both storage and voiding symptoms) up to 5 years without negative impact on sexual function (9). To achieve similar results with pharmacotherapy; patient adherence to a combination of many prescription regimens which, which cause sexual dysfunction are required (21-23). Additionally, to produce similar outcome measures with PUL; permanent implants are necessitated, but in this scenario retreatments rates are higher (24). Rezum™ procedure can be also performed in local anesthesia which may be advantageous for older patients with major comorbidity. Moreover, Rezum™ serve as a suitable option in terms of short operative time (9,25). In the European Association of Urology (EAU) guideline, Rezum™ therapy is mentioned as a minimal invasive surgical technique for BPH (5). Today, American Urological Association (AUA) guideline recommend Rezum™ to patients with <80 cc prostate volume (Recommendation Grade: C) (26). However, there are increasing data show that Rezum™ can be used for treating large prostates (15). Coagulative necrosis created by water vapor leads to shrinking of the prostate up to 40% in several weeks (10). This effect is stated in a magnetic resonance imaging study; that showed a one-third decrease in the entire prostate and transition zone volumes (27). Dixon et al. (28) reported their 2 years of follow-up Rezum™ experience in 65 patients. They determined the clinical improvement in IPSS (55.7% reduction), QoL (59% reduction), Q_{max} (44.6% improvement) and benign prostatic hyperplasia impact index (BPHII) (30.5% improvement), PVR (19.8% reduction) and international index of erectile function score as early as post-operative 1-month. They detected the maximal improvement at 3rd month and this improvement was sustained for 24 months (28). Roehrborn et al. (29) conducted a study on 53 patients with 12 months follow-up in 2017. They showed a 36.4% improvement in Q_{max} values compared to the baseline parameters without compromising erectile function. Mollengarden et al. (25) reported their single surgeon Rezum™ experience in 129 patients. In this study, they detected a 51.4% improvement in Q_{max} values and 45.2% reduction in IPSS during the post-operative 6th month (25). Rezum™ can also be performed in patients with urinary catheter due to urinary retention. Johnston et al. (15) reported the first United Kingdom trial in 2020 210 patients and 12-months follow-up. In this study, mean prostate volume was 56.9 cc and 25 of the 210 cases were pre-operatively catheterized. They reported that ultimately 202 men (96%) were catheter free or on intermittent

self-catheterisation in their study population and have shown the efficacy of Rezum™ in patients with urinary catheter due to urinary retention (15). Some studies have shown that Rezum™ can be performed in large (≥80 cc) prostates. Bole et al. (14) reported their single center experience in 2020. Their study group consisted of 182 patients and 47 of these patients had prostates ≥80 cc. Addition to this; 59 of the 182 patients had pre-operative urinary retention. They reported the post-operative catheter-free rates 88% for small-sized prostates and 83% for large-sized prostates (14). To date, one multicenter randomized controlled clinical trial was conducted to assess the efficacy of Rezum™ by McVary et al. (9), which reported the 5-year outcomes in 2021. This study consisted of 197 patients from 15 centers in the USA with 5-years follow-up. In this trial, significant improvement of LUTS was noticed <3 months after Rezum™ therapy and this improvement is durable through 5 years. In this study, Q_{max} and IPSS-QoL scores increased 44% and 45%, respectively. However, IPSS and BPHII of the study population both decreased 48%. They stated that; during the 5-years of follow-up alleviation of LUTS secondary to BPH was sustainable without any cases with de novo sexual dysfunction. In this randomized controlled trial, surgical retreatment rate at the end of the study was reported 4.4% (9). Moreover, there are several advantages of Rezum™ therapy over other minimal invasive treatment modalities. Unlike TURP or Holmium laser enucleation of the prostate, which has steep learning curves, Rezum™ therapy is a simple procedure to perform and easy to learn. Additionally, Rezum™ therapy can be performed as an alternative to pharmacotherapy to decrease the side effects of medical therapies. Gupta et al. (22) reported their outcomes of Rezum™ therapy compared to the cases with medical therapy of prostatic symptom study treated with doxazosin and/or finasteride for 36 months. In this study, they stated that Rezum™ therapy provides an equivalent, prolonged IPSS improvement compared to the combination therapy (doxazosin + finasteride) and was found to be superior to the monotherapy. Moreover, in the pharmacotherapy arm, clinical progression was 5 times greater compared to Rezum™ (22). Rezum™ can be performed in cases with median lobe and large-sized prostate unlike PUL therapy (30). In the randomized controlled trial conducted by McVary et al. (9), Rezum™ therapy provided similar significant improvement in patients with median lobe (58 patients, 30.1% of the study group) compared to the patients without median lobe with an additional 1.6±0.7 injections to this lobe. Rezum™ therapy has a short operative time with an average of 8 min and can be performed in an out-patient setting (25). Most of the cases do not require general or regional anesthesia. This procedure can be performed using oral or intravenous sedation, urethral local anesthesia with or without prostatic block (9,10,31). One of the most advantageous issues of Rezum™ over other surgical and medical treatment is the preservation of the

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ejaculatory and sexual functions. To date, *de novo* erectile or ejaculatory dysfunction has not been reported in the literature after Rezum™ therapy (9). The reported post-operative complications in the literature related to this procedure are generally minor (Clavien-Dindo grade I-II) irritative symptoms. These irritative symptoms may be attributable to the acute inflammatory response in the prostate tissue after Rezum™ therapy. These irritative symptoms subside in 2-3 weeks (9,12,14,15,23,28,29).

Although there are no strict contraindications exist, Rezum™ is not recommended for patients with penile implant, artificial urinary sphincter, and radiation therapy history. Moreover, to date, the effectiveness of Rezum™ therapy for patients with previous invasive treatments (TURP, PVP etc.) has not been clinically tested in the studies. For TURP, resected prostate material can be evaluated for the identification of incidental prostate cancer, which is reported up to 13% in the studies (32,33). The lack of pathological evaluation of the prostate material may be considered a disadvantage of Rezum™. Regarding the existing literature, retreatment rate of Rezum™ therapy (due to missed median lobe, bladder neck contracture etc.) reported with the incidence of 1% to 2.3% (15,25,28).

There is no consensus on the timing of catheter removal time in the literature. Dixon et al. (28) reported an average of 3.8 days for catheter removal time. Johnston et al. (15) reported an average catheter removal time of 3-5 days, but in cases with previous urinary retention and large-sized prostates, they kept the catheter for a longer time. Moreover, Bole et al. (14) reported the catheter removal time for 3 days up to 4 weeks and stated that, catheter removal time should be adjusted according to the prostate volume and presence of previous urinary retention.

Conclusion

Rezum™ procedure (Water vapor therapy) is an effective and safe procedure for symptomatic BPH in the short-term follow-up. Rezum™ system provides a significant increase in Q_{max} values and a significant decrease PVR and IPSS. The QoL scores after the 3rd month of the procedure are significantly lower compared to the pre-operative status.

Ethics

Ethics Committee Approval: This study was approved by the Acıbadem Mehmet Ali Aydınlar University Institutional Review Board (İstanbul, Turkiye), (decision number: 2022-09/07).

Informed Consent: Signed informed consent was collected from all subjects.

Peer-review: Externally and internally peer-reviewed.

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Determining an Approach to Small Testicular Masses by Examining Scrotal Doppler Ultrasonography and Serum Tumor Markers

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

The place and importance of ultrasound in testicular masses is indisputable in the literature, as in our study. However, radical orchiectomy is often performed in small testicular masses due to low patient compliance and insufficient diagnostic differentiation of ultrasound. In this study, we found that very few testicular masses were malignant in our clinic, so we emphasized the necessity of a conservative approach in patients.

Abstract

Objective: In our study, we retrospectively analyzed the pathology results of radical orchiectomy operations performed in our clinic and to correlate preoperative color Doppler ultrasonography (CDUSG) findings with small-testicular masses (SmTM) with negative serum tumor markers (STM).

Materials and Methods: Male patients (n=98) who underwent radical orchiectomy between January 2010 and January 2021 to treat intratesticular solid lesions that were detected via CDUSG were evaluated retrospectively. All patients were evaluated in terms of age, atrophic testis, echogenicity, size of tumoral lesions, testicular palpability, preoperative STM and postoperative pathology results.

Results: Expression of at least one STM was elevated in 58 (59.2%) patients preoperatively. STM elevation continued to occur in 25 (25.5%) patients postoperatively; furthermore, 81 (82.7%) patients presented with malignant pathology. The mean age of patients was 39.47±15.20 years, whereas the mean age of patients with benign pathology was higher than patients with malignant pathology (p=0.008). The mean size of malignant lesions was significantly greater than that of benign lesions (5.4 vs 3.5 cm; p=0.033). Statistically elevated STM, lower age, heterogeneity in CDUSG, and large lesion size were found as parameters predicting malignancy. Although lesions in 9 (45%) of 20 STM-negative patients with a lesion smaller than 3 cm were benign, benign pathology was detected in 6 (75%) of 8 STM-negative patients with a lesion smaller than 1.5 cm.

Conclusion: CDUSG plays an important role in detecting small non-palpable masses. Especially in STM-negative patients with a SmTM, CDUSG can reasonably guide the decision-making phase although it cannot provide definitive diagnosis. Radical orchiectomy, which is the traditional approach for all solid testicular lesions, leads to unnecessary treatment in patients with benign lesions, so testicular-sparing surgery should be preferred in STM-negative non-palpable SmTMs because the risk of cancer is low.

Keywords: Testicular cancer, ultrasonography, small testicular masses, testis-sparing surgery, radical orchiectomy

Introduction

Germ cell tumor (GCT) of the testis is the most common solid tumor in men aged 15-35 years. GCT is a unique neoplasm where biochemical markers play a critical role. Biochemical serum tumor markers (STM) in testicular tumor are alpha-fetoprotein, b-human chorionic gonadotropin and lactate dehydrogenase. At the time of diagnosis, approximately 60% of patients with GCT appear to have at least one of these 3 tumor markers elevated (1). STM in patients with testicular cancer is integral in patient management, contributing to diagnosis, staging and risk assessment, evaluation of response to therapy, and detection of relapse. Historically, approximately 90% of testicular palpable solid masses were found to be malignant GCT, but today it has been reported that >60% of SmTM are benign (2). According to the European Association of Urology (EAU) guidelines, radical

orchiectomy is still considered the gold standard approach to treat malignant testicular masses or masses of unknown origin (3). Most of these tumors are palpable and 95% of palpable masses are malignant (4,5). Owing to the increasing use of scrotal ultrasound in the evaluation of urological problems such as infertility, scrotal pain, or trauma, the number of incidentally detected non-palpable testicular masses is increasing and most of these masses are hypoechoic (6,7). However, over the last two decades, the treatment of testicular tumors has begun to shift in favor of conservative surgery. SmTM, defined in the literature as non-palpable masses <2 cm in diameter, is a constant dilemma for urologists. Owing to the existing oncological evidence in the literature (additional treatment with radical orchiectomy) and the side effects of radical orchiectomy-such as hypogonadism, infertility, and male body image deterioration-there has been a shift from radical inguinal orchiectomy, which has been the general approach to intratesticular masses (8). In the study, we retrospectively examined the pathological results of radical orchiectomy patients in our clinic, compare these results with preoperative correlate preoperative color Doppler ultrasonography (CDUSG) findings and determine the most accurate surgical approach that should be considered for these patients, especially in STM-negative patients with SmTM.

Materials and Methods

Male patients who underwent inguinal radical orchiectomy between January 2010 and January 2021 due of intratesticular solid lesions detected in CDUSG were evaluated retrospectively. Our study was conducted at a single tertiary center. All patients were evaluated in terms of age, atrophic testis, vascularity, echogenicity, size of testicular masses, testicular palpability, before the operation STM and postoperative pathology results. Parameters correlated with malignancy were determined according to the results. Pathological subtypes and incidence rates were determined. CDUSG characteristics of pathological subtypes were compared. The probability of malignancy was determined by forming two separate groups for non-palpable STM-negative SmTM smaller than 3 cm and smaller than 1.5 cm. Patients previously diagnosed with testicular cancer (n=2), patients with a history of previous inguinal/scrotal surgery (n=1), a history of other concomitant malignancies (n=1), and chronic diseases [cirrhosis (n=1), hepatosteatosis (n=1), gynecomastia (n=0), or hormonal disorder (n=1)] that may lead to elevated marker levels were excluded from the study.

Statistical Analysis

Independent samples t-test was used to compare the numerical preoperative parameters (the age and lesion diameters) between malignant and benign solid lesions and chi-square was used for categorical parameters (ultrasonic features and pathological

results). P<0.05 indicated statistical significance. Statistical analysis was performed using SPSS v24.0 statistics software.

Results

The demographic information of the patients and their preoperative STM and postoperative tumor pathologies are shown in Table 1. At least one STM was elevated in 58 (59.2%) patients preoperatively. Tumor marker elevation continued in 25 (25.5%) patients postoperatively. In total, 81 (82.7%) of 98 patients had a malignant pathology. Although the mean age of all patients was 39.47±15.20 years, the mean age of patients with benign pathology was higher than the patients with malignant pathology (p=0.008). The mean size of malignant lesions was significantly larger than benign lesions (5.4 vs 3.5 cm) (p=0.033). In the preoperative CDUSG evaluation of the patients, vascularity increase was detected in 74 (75.5%) patients, whereas microcalcification was found in 28 (28.8%) patients. Hypervascularization was detected in 62 (76%) patients (p=0.6) and microcalcification was found in 22 (27%) patients (p=0.49) with malignant lesions. CDUSG echogenicity showed that 5 (29.4%) of the benign masses were hyperechoic, whereas only 3 (3.7%) of the malignant masses were hyperechoic (p=0.00). While 32 (39%) of malignant masses were heterogeneous, only 2 (11%) of benign masses were heterogeneous. Statistically elevated tumor markers, lower age, heterogeneity, and large lesion size were found as parameters predicting malignancy (Table 1). Pathological subtypes of all malignant and benign lesions are shown in Table 2. The most common pathological subtype was MGCT (mixed-GCT) detected in 33 (33.6%) patients. The second most common subtype was seminoma in 31 (31.6%) patients. Seventeen of the MGCT cases (51.5%) and 21 of the seminomas (67.7%) were hypoechoic. In other words, the most common CDUSG finding in both subtypes was hypoechogenicity. Although 13 of the patients had other pathologies such as atrophy or epididymorchitis, lymphoma was detected in 5 patients, NGCT (non-germ cell) in 5 patients, and paratesticular tumor (liposarcoma) was detected in 1 patient. Heterogeneity was the most common finding in 4 (80%) patients with lymphoma. Although the lesions in 11 (48%) of 20 STM-negative patients with a lesion smaller than 3 cm were considered benign, lesions in 6 (75%) of 8 STM-negative patients with a lesion smaller than 1.5 cm were benign (p=0.00).

Discussion

Historically, approximately 95% of testicular palpable solid lesions were found to be malignant GCT. Today, early-stage GCT is a highly curable malignancy, with a reported 5-year survival rate of approximately 91% (9). Despite these good oncological evidence, it is also important to consider the side

effects of radical orchiectomy (testosterone deficiency, sexual dysfunction, infertility, and modified body appearance) and avoid overtreatment in patients with benign masses. More than 60% of SmTM cases were reported to be benign (10). EAU guidelines state that testis-sparing surgery can be performed in meta-synchronous contralateral tumors or in cases with normal preoperative testosterone levels, solitary testis, and tumor volume of less than approximately 30% of testicular volume, but even in these cases, testicular intraepithelial neoplasia (TIN) rate in the same testis is high (at least up to 82%). The TIN rate is 3-5% in the contralateral testis, and malignancy is observed in half of these cases within 5 years (11-14). This requires long-term follow-up after testis-sparing surgery. Conservative

surgery is avoided in SmTM owing to low patient compliance, the pathologist's lack of experience in frozen section evaluation, and the surgeon's lack of partial orchiectomy experience (14).

In addition to these challenging conditions, conservative surgery is a viable alternative to radical surgery, particularly in selected patients with normal contralateral testis. Important points are the size of the mass, clinical picture, non-palpable feature, tumor marker negativity, or absence of radiological suspicion of malignancy. This approach has increased the importance of SmTM recently. This is because SmTMs are generally non-palpable, STM-negative, and it is difficult to distinguish whether they are malignant or benign using CDUSG or magnetic resonance imaging (15,16).

Table 1. Demographic characteristics and lesion-related pre-op CDUSG characteristics of benign and malignant patients

Parameters	All	Malignant	Benign	p
Number	98	81 (82.7%)	17 (17.3%)	
Age (years)	39.47±15.20	37.63±13.94	48.24±18.16	0.008[t]
Lesion diameter (cm)		5.40±3.29	3.50±3.22	0.033[t]
Side				
Right	59 (60.7%)			
Left	37 (37.8%)			
Bilateral	2 (2%)			
USG findings of the mass echogenicity				
Hypoechoic	52 (53%)	43 (53%)	9 (52%)	0.06[k]
Hyperechoic	8 (8.1%)	3 (3.7%)	5 (29.4%)	0.00[k]
Heterogeneous	34 (34.6%)	32 (39%)	2 (11%)	0.02[k]
Isoechoic	4 (4%)	3 (3.7%)	1 (5.8%)	0.14[k]
Vascularity	74 (75.5%)	62 (77%)	12 (70%)	0.6[k]
Microcalcification	28 (28.5%)	22 (27%)	6 (35%)	0.49[k]
Pre-op STM-positive	58 (59.2%)	58 (59.2%)	0 (0%)	0.00[k]
Post-op STM-positive	25 (25.5%)	25 (25.5%)	0 (0%)	0.00[k]
≤1.5 cm STM-negative*	8 (8.2%)	2 (25%)	6 (75%)	0.00[k]
≤3 cm STM-negative*	23 (23.5%)	12 (52%)	11 (48%)	0.00[k]

[t]: Independent sample t-test, [k]: Chi-square statistic, *: Non-palpable, STM: Serum tumor marker, CDUSG: Correlate preoperative color Doppler ultrasonography, USG: Ultrasonography

Table 2. Pathological subtypes and preoperative CDUSG characteristics

Pathological subtypes	Heterogeneous	Hyperechoic	Hypoechoic	Isoechoic	Total	p-value
Seminomatous	6 (19.4%)	2 (6.5%)	21 (67.7%)	2 (6.5%)	31 (31%)	
NSGCT	6 (60.0%)	1 (10%)	3 (30%)	0 (0%)	10 (10%)	
MGCT	15 (45.5%)	0 (0%)	17 (51.5%)	1 (3%)	33 (33%)	
Other	2 (15.4%)	4 (30.8%)	6 (46.2%)	1 (7.7%)	13 (13%)	
NGCT	0 (0%)	1 (20%)	4 (80%)	0 (0%)	5 (5%)	
Lymphoma	4 (80%)	0 (0%)	1 (20%)	0 (0%)	5 (5%)	
Paratesticular tumor	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	p=0.028[k]
Total	34 (34.7%)	8 (8.2%)	52 (53.1%)	4 (4.1%)	98 (100%)	

CDUSG: Color Doppler ultrasonography characteristics, MGCT: Mixed germ cell tumor, NSGCT: Non-seminamatous germ cell tumor other (atrophic testis, epididymorchitis...), paratesticular tumor: Liposarcoma, [k]: Chi-square statistic

A recent systematic review reported that approximately 80% of non-palpable masses had a benign histology (17). Corrie et al. (18) reported that the incidence of benign mass was 51.8% among 27 non-palpable testicular masses detected by CDUSG. In a similar study by Sheynkin et al. (19), tumor prevalence was found to be 75%. In a recent study by Shilo et al. (20), 69% (palpable and non-palpable) of testicular tumors smaller than 2.5 cm were benign. Esen et al. (21) found that 7 (53.8%) of 13 non-palpable lesions were benign. Gentile et al. (22) reported that 86.7% (13/15) of the patients had benign pathology, while De Stefani et al. (10) reported that only 2 (9.5%) of 21 cases were malignant. Ates et al. (23) reported that 93.3% of patients with tumors <2.5 cm had benign pathology (14/15). High % of benign pathologies in this series is due in part to the exclusion of lesions with malignant sonographic features. Bojanic et al. (24) found that 35.7% of the patients had GCT, whereas stromal tumors and various lesions were found in 64.3% of the patients, specific data on the differentiation of malignant and benign lesions were not reported. In this study, 11 (48%) of 23 STM-negative patients with a lesion smaller than 3 cm had benign pathology, whereas this rate was 75% in STM-negative patients with a lesion smaller than 1.5 cm (6 of 8 patients) (p=0.00). This result is in agreement with previous studies. The fact that we encountered only 2 STM-negative patients with a lesion smaller than 1.5 cm (25%) makes us question the applicability of over- and more severe treatments, such as radical orchiectomy, in these patients (worsening cosmetic body appearance, organ loss, decreased hormone levels, and fertility). We believe that conservative treatments (ultrasonography, marker close follow-up or partial orchiectomy with simultaneous frozen) should be preferred in these patients.

Of course, not all non-palpable masses should be considered benign, but the fact that the vast majority of these tumors are benign and they are suitable for organ-sparing surgery in terms of size makes radical orchiectomy overtreatment in these cases (24). The small number of cases and the lack of long-term follow-up makes it impossible to establish a guideline for non-palpable testicular tumors. After informing the patient in detail before the operation (letting the patient know that radical orchiectomy may be preferred during the procedure, radiotherapy may be needed, infertility may occur, etc.), performing inguinal exploration, partial orchiectomy and frozen pathological evaluation (25), completion of partial orchiectomy in patients with benign results, and performing radical orchiectomy otherwise may be considered a good option.

The overall incidence of testicular tumors is reported to be 2-3 per 100,000 and shows an increasing trend, albeit slowly (26). Apart from hematological malignancies, testicular tumors are the most common malignancies in men in the 3rd and 4th decades (27,28). In this study, the mean age of 98 testicular tumors was 39.47±15.20, which was consistent with the literature. The incidence of bilateral involvement in testicular tumors is reported to be 1-4% (2,3). In this study, bilateral involvement was observed in 2 (2%) patients. It has been reported that most testicular tumors are GCT with a high rate of 90-95% (29). In our series, the pathology of 13 (13%) patients resulted as atrophic testis, epididymorchitis, and ischemic necrosis (other). The remaining 85 patients had tumoral pathologies. 74 (87%) of these patients were reported as GCT. However, the rate of lymphomas, which is reported as 2-3%, in the literature, was 5% in our series (30). In this study, the rates of both lymphoma and GCT were similar to those reported in the literature. Secondary tumors of the testis are very rare. No secondary tumors were detected in our series. Metastases of the prostate, lung, and gastrointestinal system carcinomas are the most common metastases, which constitute 2.3% of all testicular tumors (26,31). No carcinoma metastasis was observed in our series.

In the general approach to intratesticular solid lesions, all lesions are considered malignant unless otherwise indicated (3). The first step in further evaluation is to identify for STM and perform a CDUS (6). Ultrasound is a valuable tool for distinguishing intratesticular masses from paratesticular masses and distinguishing solid masses from cystic masses (32). CDUSG is used to show the vascularity and echogenicity of the masses, and presence of microcalcification. Based on CDUSG findings, the surgeon determines the treatment process (radical orchiectomy, partial orchiectomy, or close follow-up of the mass). Hypoechoic findings increase the suspicion of testicular cancer. 95% of testicular cancer cases have hypoechoic features (33). In our study, we found that approximately 92% of malignant pathologies had hypoechoic (pure hypoechoic + heterogeneous) features. Generally, studies report that non-cystic seminoma subtypes are more homogeneous and hypoechoic, whereas non-seminoma and cystic tumors are more heterogeneous and hyperechoic (34). In our series, 21 (67.7%) of 31 patients with seminomatous GCT (SGHT) and 17 (51.5%) of 33 patients with MGCT were pure hypoechoic, whereas 6 (60%) of 10 patients with non-seminamatous GCTs were heterogeneous. We found that hypoechoicity, heterogeneity, vascularity, and microcalcification in CDUSG was more common in malignant pathologies. However, except for heterogeneity, the difference was not statistically significant (p>0.05). These results cannot be generalized to the whole population; thus, none of these features alone is sufficient to diagnose a malignant testicular mass, but these features play an important role in the surgeon's decision for radical orchiectomy.

Study Limitations

The biggest limitation of our study is the small number of patients and its retrospective nature. In order for these results

to be valid for the whole population, multicenter prospective studies with more patients are needed.

Conclusion

CDUSG plays an important role in detecting small non-palpable masses. Especially in STM-negative patients with an SmTM, CDUSG can reasonably guide the decision-making phase although it cannot provide a definitive diagnosis. Radical orchiectomy, which is the traditional approach for all testicular solid masses, may lead to unnecessary overtreatment in patients with benign masses. Conservative treatments provide good hormonal, sexual and body appearance results in patients with benign lesions. For this reason, partial orchiectomy or close follow-up can be considered in the first place if the patient is compatible and willing, if there is no evidence of metastatic disease, if non-palpable and incidentally detected, if STB is negative, if frozen pathological evaluation can also be performed.

Ethics

Ethics Committee Approval: Our study is retrospective and was prepared using data from our hospital system, so ethics committee approval was not required.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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

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Specific Effects of Some Metabolic Syndrome Components on Kidney Stone Formation: A Multicentric Multidisciplinary Study

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

Kidney stones can develop because of specific changes in the kidney tissue due to various diseases such as type 2 diabetes, hypertension, metabolic syndrome, and non-alcoholic fatty liver. Particularly, a triple mechanism is recognized between metabolic syndrome, non-alcoholic fatty liver disease and syndrome, and atherosclerosis the formation of kidney stones. To our results; triglyceride level and waist circumference were found to have a statistically significant effect on kidney stone formation. The formation of kidney stones caused by these risk factors in the patient can be prevented by eliminating these factors through preventable or treatable modifications.

Abstract

Objective: In this study, we examined the effects of dyslipidemia, obesity, non-alcoholic fatty liver disease and atherosclerosis on kidney stone formation.

Materials and Methods: Patients were divided into two groups; group 1; 300 patients having kidney stones or not group 2; 528 patients. Among these patients' triglyceride, cholesterol, high-density lipoprotein and low-density lipoprotein values; non-alcoholic fatty liver disease, atherosclerosis, waist circumference and subcutaneous adipose tissue thickness were recorded.

Results: It was determined that the presence of non-alcoholic fatty liver disease, atherosclerosis, high-density lipoprotein, low-density lipoprotein and cholesterol levels and subcutaneous adipose tissue thickness did not have any effect on developing kidney stones. However, triglyceride level and waist circumference had a statistically significant effect on kidney stone formation.

Conclusion: Considering that the presence of high triglyceride and low waist circumference levels can cause kidney stones in the patient; then the formation of kidney stones can be avoided by eliminating these factors through preventable or treatable modifications.

Keywords: Atherosclerosis, dyslipidemia, kidney stones, non-alcoholic fatty liver, obesity

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Introduction

Kidney stone disease is a common health disorder worldwide. The lifetime incidence of developing a symptomatic kidney stone is 5-10% (1). The prevalence of kidney stones has been increasing worldwide in the recent years, and indeed in the Asian countries too, probably because of the westernization of Asian culture (2). The kidney stone formation is multifactorial, and it is revealed in epidemiological studies that male gender, age, race, climate, occupation, and obesity are the factors involved in this process (3,4).

Primarily, one or more factors are effective in kidney stone formation, including anatomical, metabolic, and nutritional causes. Additionally, kidney stones can also develop because of specific changes on the kidney tissue due to various diseases such as type 2 diabetes, hypertension, metabolic syndrome, and non-alcoholic fatty liver (5-8). Particularly, a triple mechanism

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is recognized between metabolic syndrome, non-alcoholic fatty liver disease syndrome, and atherosclerosis and the formation of kidney stones (9).

The pathophysiological mechanism that may clarify the underlying relationship between metabolic syndrome and kidney stone formation is not unclear. However, altered urine components decreased urine pH, decreased citrate excretion and increased uric acid and calcium excretion may be the cause of uric acid and calcium stones, in patients with metabolic syndrome (10-12).

It is obvious that there is a strong relationship between metabolic syndrome and kidney stone formation. However, there are very few studies in the literature that separately evaluate the effects of metabolic syndrome components, including dyslipidemia, obesity, hepatic manifestations of non-alcoholic fatty liver and cardiac manifestations of atherosclerosis (13). Such an inadequacy in the literature forced the requirement that these components should be evaluated specifically. In this study, we aimed to examine the effects of the above-mentioned factors on kidney stone formation and to protect patients from developing kidney stones by preventing and treating risk factors.

Materials and Methods

This study was conducted retrospectively after being reviewed and approved by the Institutional Review Board (approval number: 276). Informed consent was obtained from all patients when they were enrolled; in addition, the principles of the Declaration of Helsinki were followed. Our study was conducted jointly with 3 different urology clinics who collected the data and 1 radiology clinic who evaluated computed tomography (CT); it has been carried out in a multicentric and multidisciplinary manner. All patients were admitted to the urology outpatient clinic between January 2018 and May 2020 and had stone protocol (low-dose) non-contrast abdominopelvic CT with suspicion of kidney stones was reviewed. And those having triglyceride, cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) results were included in the study. Finally, they were divided into 2 groups concerning kidney stone formation: Group 1, with stone or group 2, without stone, regardless of the stone size. The study was conducted with 828 patients, 300 patients in group 1 and 528 patients in group 2.

The patients between the ages of 18-80, of both genders, and those who reported no alcohol usage in their anamnesis to exclude alcohol-induced fatty liver disease were included. Those with artefacts in their CT, with solitary kidney or kidney anomalies, nephrocalcinosis, kidney failure, known cancer diagnosis, non-renal urinary tract stones, cirrhosis or related ascites, acute or chronic hepatitis, and chronic liver disease were excluded from the study.

Stone protocol CT for urinary stone disease was applied (Siemens Healthcare, Germany). The patient was in the supine position when the imaging was performed. Images were taken between the diaphragmatic dome and inferior pubic ramus in sagittal and coronal sections with a slice thickness of 5 mm.

Non-alcoholic fatty liver definition was defined as mean CT liver attenuation ≤40 Hounsfield units by measuring at least 5 liver segments. The presence of atherosclerosis was accepted as arterial-wall calcifications on CT, abdominal aorta involving the main iliac arteries. Waist circumference was determined by measuring the abdominal circumference the cross-section passing through the umbilical level on CT. Subcutaneous adipose tissue thickness was determined by taking the average of 3 measurements performed suprapubically at the intersection of both midclavicular lines and the iliac crest at the level of the umbilicus.

Statistical Analysis

The SPSS 23.0 (SPSS, Chicago) package program was used in the statistical analysis of data. Measures of central tendency and distribution such as number, percentage, mean and standard deviation were used for descriptive statistics, while Pearson's chi-square test was used to determine the differences between categorical variables. The compliance of numerical variables to normal distribution was tested by the Shapiro-Wilk normality test, and the difference between normally concordant independent variables was determined by the Student's t-test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 973 patients were examined with a view to being included in our study group. After the exclusion criteria were implemented, 828 patients were included in the study. Of these, 379 (45.7%) were female and 449 (54.2%) were male, with a mean age of 45.59 (17.14) years. As for the age range, 117 of the patients (14.1%) were <30 years; 452 (54.5%) were between 30 and 60 years and 259 (31.2%) were more than 60 years of age. The patients were divided into 2 groups as those with kidney stones (group 1), consisting 300 patients (36.2%), and those without kidney stones (group 2), consisting of 528 patients (63.7%). The demographic data of the patients are presented in Table 1. According to these results, there were statistically significant differences between the two groups with respect to age and gender.

The effects of some components of metabolic syndrome on kidney stone formation are shown in Table 1 and Figures 1-3. According to these results, it was determined that the presence of non-alcoholic fatty liver and atherosclerosis, as well as HDL, LDL and cholesterol levels and subcutaneous adipose tissue

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thickness had no effect on the development of kidney stones. However, triglyceride level and waist circumference were found to have a statistically significant effect on kidney stone formation. A statistically significant correlation was determined between the increase in triglyceride level (p=0.007) and the decrease in waist circumference (p<0.001) and kidney stone formation.

Considering the subgroup analysis of the age and gender parameters statistically significant among the factors affecting the kidney stone formation; the effect of gender distribution in group 1 patients was examined on the patients with or without non-alcoholic fatty liver disease and the correlation is shown in Table 2. Hence, it was concluded that non-alcoholic fatty liver disease had no effect on male and female patients who developed kidney stones.

Table 3 however, shows the relationship between gender distribution in group 1 patients and patients with or without atherosclerosis. According to these results, atherosclerosis was found to be statistically significantly less in male patients with stones (p=0.048).

Considering the subgroup analysis of the age in group 1 patients, the relationship between age and non-alcoholic fatty liver is shown in Table 4. According to these results, a statistically significant level of non-alcoholic fatty liver was determined in <30 years old group 1 patients (p=0.006).
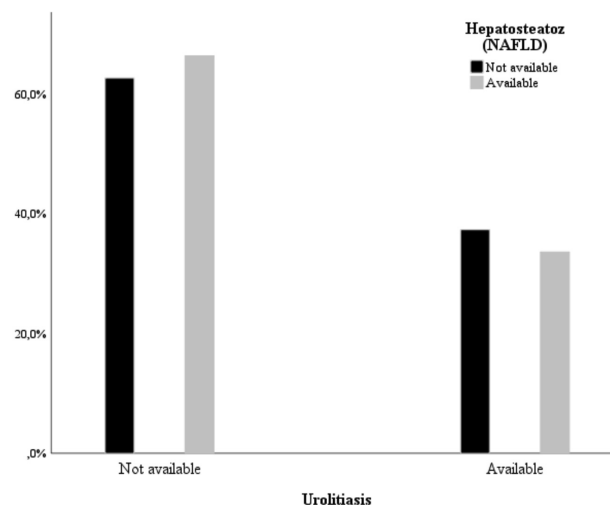
Figure 1. Relationship between non-alcoholic fatty liver disease and kidney stones

(NAFLD: Non-alcoholic fatty liver disease
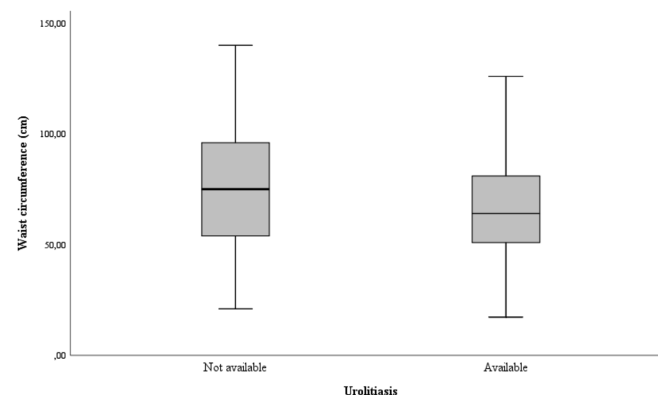
Figure 2. The effect of waist circumference on kidney stone formation
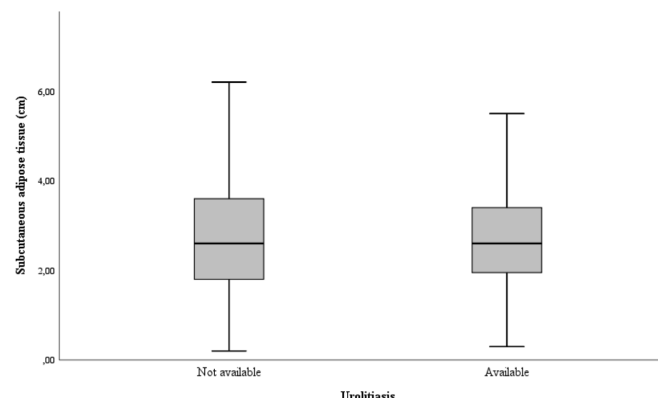
Figure 3. The effect of subcutaneous adipose tissue on kidney stone formation

Table 1. Demographic data and effects of some components of metabolic syndrome on kidney stone formation			
	Group 1	Group 2	p-value
Gender (n, %)			
Male	195 (43.4)	254 (56.6)	**<0.001**
Female	105 (27.7)	274 (72.3)	
Age (n, %)			
<30	58 (49.6)	59 (50.4)	**0.001**
30-60	167 (36.9)	285 (63.1)	
>60	75 (29.0)	184 (71.0)	
Non-alcoholic fatty liver (n, %)			
Yes	218 (37.3)	366 (62.7)	0.310
No	82 (33.6)	162 (66.4)	
Atherosclerosis (n, %)			
Yes	180 (38.1)	293 (61.9)	0.189
No	119 (33.6)	235 (66.4)	
Triglyceride; mean (SD)	167.80 (113.71)	142.19 (97.30)	**0.007**
HDL; mean (SD)	48.64 (18.72)	49.19 (16.94)	0.739
LDL; mean (SD)	107.46 (38.35)	106.99 (35.45)	0.892
Cholesterol; mean (SD)	185.62 (43.39)	182.89 (43.55)	0.525
Waist circumference (cm)	66.93 (22.36)	75.13 (24.72)	**<0.001**
Subcutaneous adipose tissue thickness (cm)	2.86 (1.80)	2.84 (1.94)	0.842
HDL: High density lipoprotein, LDL: Low density lipoprotein, SD: Standard deviation			

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Table 5 shows the relationship between the age distribution of patients in group 1 and the presence of atherosclerosis. According to these results, atherosclerosis was observed at a lower frequency in patients more than 60 years old in group 1 (14.6%) with respect to those ≤60 years old (p=0.038).

Discussion

No significant relationship was found between non-alcoholic fatty liver disease and kidney stone formation according to the results of our study, although there are studies in the literature indicating a significant correlation between them. For example, Nam (9) reported 19% higher prevalence of kidney stones in patients with non-alcoholic fatty liver disease. Again, Zeina et al. (14) obtained similar results in their study and concluded that the rate of kidney stones in patients with non-alcoholic fatty liver was significantly higher with an odds ratio of 3.4.

In a study conducted with 100 patients suspected of kidney stones due to renal colic, Paz et al. (15) determined a significant correlation between non-alcoholic fatty liver disease and kidney stones, especially in male patients. However, in our study, no

significant relationship was found between kidney stones and non-alcoholic fatty liver disease in the gender subgroup analysis, although it was more common in men.

Kim et al. (16) examined patients diagnosed with kidney stones ultrasonographically and the correlation between non-alcoholic fatty liver and kidney stones was determined only in male patients. Additionally, this correlation was observed only in patients under 50 years old. In comparison to this study, there was no correlation between kidney stones and non-alcoholic fatty liver disease in terms of gender in our study. However, the diagnosis of kidney stones was made by CT, which is the strength of our study as it is the gold standard method in this field, and a significant correlation was found between non-alcoholic fatty liver and kidney stones in patients under the age of 30.

The risk of kidney stones is associated with peripheral arterial vascular disease. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, an increase in carotid artery vascular wall thickness was determined in patients with kidney stones (17). Patel et al. (18) showed that calcification in the abdominal aorta on CT was associated with hypocitraturia, low urine pH and presence of kidney stones. According to the CT assessment of atherosclerosis in the abdominal aorta in our patients, no relationship was detected between kidney stone formation and the presence of atherosclerosis in the patient groups with and without stones. In the gender subgroup analysis, an inverse relationship was found between the presence of atherosclerosis and kidney stone formation in male patients with stones, and this inverse relationship increased significantly in patients >60 years old.

There are risk factors and mechanisms that seem independent from each other, such as insulin resistance, affecting the formation of kidney stones (17). For example, insulin contributes to ammonia production in the renal tubules (19). In case of insulin resistance developing with obesity, impaired insulin function causes altered ammonia synthesis and results in low urine pH; that is, it contributes to the favored urine acidity for uric acid crystallization and stone formation (20). Similarly, obesity is one of such risk factors. Waist circumference is a metric indicator of visceral obesity. Inflammatory cytokines released from adipocytes increase with the increase in subcutaneous adipose tissue (21). When the two patient groups in our study were compared, subcutaneous adipose tissue thickness displayed no effect on developing kidney stones; and we observed that waist circumference was significantly higher in the group without stones.

Inflammation, oxidative stress and lipotoxicity play a negative roles in the development of kidney stones (16). Inflammatory markers and pro-inflammatory cytokines may be elevated in patients with kidney stones. Lipotoxicity is another mechanism defined for altered kidney function, cellular damage and

Table 2. Relationship between gender distribution in group 1 patients and non-alcoholic fatty liver disease

	NAFLD (+)	NAFLD (–)	p-value
Group 1; male (n, %)	59 (44.4)	136 (43.0)	0.796
Group 1; female (n, %)	23 (20.7)	82 (30.6)	0.051

NAFLD: Non-alcoholic fatty liver disease

Table 3. Relationship between gender distribution in group 1 patients and atherosclerosis

	Atherosclerosis (+)	Atherosclerosis (–)	p-value
Group 1; male (n, %)	81 (38.4)	113 (47.7)	**0.048**
Group 1; female (n, %)	38 (26.6)	67 (28.4)	0.702

Table 4. The relationship between age distribution of group 1 patients and non-alcoholic fatty liver disease

Age	NAFLD (–)	NAFLD (+)	p-value
<30 (n, %)	7 (100.0)	51 (46.4)	**0.006**
30-60 (n, %)	46 (34.3)	121 (38.1)	0.454
>60 (n, %)	29 (28.2)	46 (29.5)	0.817

NAFLD: Non-alcoholic fatty liver disease

Table 5. The relationship between age distribution of patients in group 1 and atherosclerosis

Age	Atherosclerosis (–)	Atherosclerosis (+)	p-value
<30 (n, %)	1 (100.0)	57 (49.1)	0.496
30-60 (n, %)	49 (36.3)	117 (37.0)	0.883
>60 (n, %)	69 (31.7)	6 (14.6)	**0.038**

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hypoammoniagenesis in patients with kidney stones (7). Dyslipidemia is an independent risk factor for kidney stone formation, as it causes low urine pH (22). As for the lipid profile of our patient groups, cholesterol, HDL and LDL levels had no effect in both groups, whereas triglyceride level was significantly higher in the group with stones, in line with the abovementioned mechanism.

Study Limitations

Our study has some limitations. The most important is the bias risk of the CT performed in patients. Additionally, the retrospective design of our study, incomplete data regarding liver function tests of the included patients and types of renal stones of group 1 patients are the other limitations.

Conclusion

The high prevalence of metabolic syndrome or its components reveals the significance of our study, which has important results that may affect public health, based on the increased morbidity and mortality due to these risk factors. Kidney stones may be the result of a systemic disease and may have developed as a consequence of the relationship of many metabolic risk factors. The formation of kidney stones caused by such risk factors in the patient can be prevented by eliminating these factors through preventable or treatable modifications.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Local Ethics Committee Institutional Review Board (approval number: 276).

Informed Consent: Informed consent was obtained from all patients when they were enrolled.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL RESEARCH

General Urology

Is an Academic Title an Aim or a Device? Publication Productivity of Urologists in Turkiye

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

As it is known, producing a scientific publication requires a long effort and endeavor. Scientific researches play a key role not only in the contribution of individuals at the academic level but also contribute to the development of countries. This study is a unique study to evaluate publication productivity of urologists by comparative analysis of parameters affecting the quality of publications in Turkiye for the first time. This bibliometric study showed that the number and quality of publications of urologists in Turkiye are very low. Relatively younger and at the beginning of their academic level and also tertiary care physicians publish more and receive more citations for their publications.

Abstract

Objective: The publication performance is an objective indicator for individuals and institutions as well as science policy and healthy implementation of the country. We revealed the quality of the publications and citations of current urologists in Turkiye.

Materials and Methods: The publication and citation status of 1200 urologists working in Turkiye between the years 2016-2020 were included in the study. Socio-demographic characteristics of urologists like age, title, type of city, geographical region of the city, and type of hospital they work in and the number of publications, citations, indexed journal publications, and the first author publication status were examined in December 2020. The Social Security Insitution database was used for sociodemographic characteristics of urologist; while PubMed and Google Scholar were used for information on publications.

Results: The median age of the urologists was 44 (30-76) years. The median number of publications, index journal publication, the first author publication, and citations were 1 (0-68), 1 (0-66), 0 (0-24), and 1 (0-1025) for the years specified, respectively. The publication status was significantly higher in the groups the age range of 30 and 40 years, associate professors (odds ratio 44.61 and 35.97, respectively) (p<0.001).

Conclusion: Publications produced in the field of urology in our country are still not of sufficient quality. Urologists between the ages of 30-40 years old, associate professors, and who working in tertiary care hospitals have published more articles and received more citations to these publications.

Keywords: Number of citations, number of publications, publication quality, urologist

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Introduction

Scientific research is a planned and systematic study that collecting, interpreting, and evaluates data to contribute to producing knowledge in various types of documents, such as journal articles, conference proceedings, research reports, and books for the benefit of society (1). The publication and citation are objective indicators of the scientific performance of individuals and institutions as well as science policy and healthy implementation of the country (2).

The number of publications, especially scientifically indexed international journals with higher impact factors and the number of citations to the publications are known as the main factors in the performance evaluation of the researchers. The relative citation ratio is another predictive value for publication quality, which is obtained by dividing the average citation rate per publication in a subject area of a country by the average citation rate per publication in the relevant field worldwide (3).

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There has been an increase in bibliometric studies, especially recently, with the help of the online database. Although there are national or international bibliometric studies in different fields of science as well as medicine in the literature; to the best of our knowledge, there were no bibliometric research that included publication productivity urologists in Turkiye (3-6). Therefore, we investigated the quality of the publications and citations in the field of urology and demographic parameters affecting the publication productivity of current urologists in Turkiye.

Materials and Methods

This study was approved by the Local Institutional Ethics Review Committee (protocol number: 2020/443). We included and evaluated the publications of a total number of 1.200 urologists between January 2016 and December 2020 in this study. Since this is a bibliometric study, informed consent of participants was not conducted in this study. Socio-demographic characteristics of urologists, such as age, title, type of city, geographical region, and the type of hospital they work in examined comparatively with the number of publications, the number of citations of those publications, the number of publications published in MEDLINE index journals, and the number of first-the author publications. The Social Security Institution database was used for sociodemographic characteristics of urologists; and PubMed and Google Scholar databases were used for information on features of publications. The group of age and titles of urologists, and the cities, geographic regions, and hospital types of the urologist worked in are categorized accordingly seen in Table 1.

Statistical Analysis

All statistical analyses were performed using the SPSS 22.0 (IBM Corp, Chicago, USA) software. Kolmogorov-Smirnov test was applied to examine the normality of variables. After the distribution of normality was checked, quantitative data were presented as median (minimum-maximum) and categorical variables were expressed as numbers and percentages to define the parameters. Comparison of categorical variables was accomplished using Pearson chi-square or Fisher's Exact tests. Logistic regression analysis was performed for multivariable analyses. The confidence interval (CI) was 95% and the level of significance was considered at the value of p<0.05.

Results

The median age of a total number of 1.200 urologists' was 44 (30-76) years. Thirty-four percent of urologists were between the ages of 30-40 and 60.4% of urologists were specialists. Of the urologists, 43.3%, 37.7%, and 30.3% were working in three metropolitan cities (Ankara, İstanbul, and İzmir), in the Marmara Region, and in state hospitals, respectively. The median number of publications, index journal publications, the first author publications, and citations in the relevant years were 1 (0-68), 1 (0-66), 0 (0-24), and 1 (0-1025), respectively.

The highest number of median publications was 3 (0-51) in 30-40 years old, 10 (0-51) in associate professors, 1 (0-68) in the three biggest metropolitan cities, 3 (0-25) in the Eastern Anatolia Region, and 6.5 (0-47) in university hospital groups. Although similar results in the number of citations, the number of the index journal publications, and the number of first-author publications were seen, only the median number of citations in the private university hospital group was higher 22 (0-1025). The number of publications and citation parameters according to the demographics of urologists is shown in Table 1.

There were no publications, indexed journal publications, the first author publications, and citations to their publications in 44.2%, 47.2%, 72.2%, and 48.4% of urologists in the relevant years, respectively. Seventy-six point five percent and 69.1% of urologists in 30-40 years old had publications and citations, whereas, urologists in 61 and over years old had 31.3% and 26.7% had publications and citations, respectively (p<0.001). The higher the first author and the indexed journal publication rate was seen in 30-40 years old group. Ninety-two point four percent and 91.7% of associate professors had publications and citations, respectively, whereas, almost only one of three specialists had publications and citations. Eighty-seven point five percent and 85.5% of urologists working in university hospitals and private university hospitals had publications, respectively. Eighty-five point one percent of urologists working in university hospitals had indexed journal publications and 55.1% of urologists working in private university hospitals had the first author publication. The distribution of publication, citation, indexed journal publication, and the first author publication status according to demographics are presented and summarized in Table 2 and Table 3. In multivariable regression analyses, age ranges, titles, and hospital types, urologists' work was a predictive factor in publication status. Among age ranges, the odds ratio (OR) of 30-40 years old compared to the years of 61 and over the group was 44.61 (95% CI 22-71-87.66), and it was seen that as increased age range decreased, the rate of publication status (p<0.001). On the basis of titles of urologists, although all academic staff had higher OR than specialists, the associate professor group had the highest OR (OR 35.97, 95% CI 16.62-77.80) (p<0.001). As it was seen publication status was higher in the university hospital group in univariate analyses, urologists working in education and research hospitals were more likely to produce publication when it was compared to urologists work in secondary care state hospitals (OR 5.34, 95% CI 3.28-8.71). Multivariate analysis of publication status according to the demographics of urologists is shown in Table 4.

Discussion

Criteria in the scientific evaluation of countries are the number of scientific publications, the number of citations, the number of citations per publication, the amount of patents, innovative utility models, entrepreneurship, and national and international projects. Hence, this bibliometric research was a unique study to evaluate publication productivity of urologists since by comparative analysis of parameters affecting the quality of publications in Turkiye for the first time.

Especially, the number of citations is more important than the number of publications in scientific evaluation. Turkiye addressed publications, especially in clinical science, had a low relative citation ratio when it was compared to the world average (0.25 vs. 1.0) (7). Because of this, the publication impact value of Turkiye is below the average of the world and it was ranked 51st in the world (2.92 vs 6.2). Switzerland is excluded from the top 10 according to the total number of publications, while it is at the top of the world in terms of publication impact value. Fifty-five percent and 48% of the publications produced worldwide and in Turkiye were cited, respectively. In a study comparing publications of countries between 2010 and 2015, was stated that although the number of publications from Turkiye is in the upper-middle rank, whereas the number of citations was in the middle-lower rank, which revealed that relatively lower impact studies had been conducted. Obviously, it is seen that the quality of relevant Turkiye addressed scientific publications

Table 1. Distribution of the number of publication, indexed journal publication, the first author publication, and citation of urologists according to demographics of urologists					
	Frequency n (%)	Number of publication med (min–max)	Number of indexed journal publication med (min–max)	Number of the first author publication med (min–max)	Number of citation med (min–max)
Age ranges (y)					
30–40	408 (34.0)	3 (0–51)	2 (0–44)	0 (0–24)	7 (0–512)
41–50	400 (33.3)	1 (0–48)	0 (0–41)	0 (0–15)	0 (0–51)
51–60	261 (21.8)	0 (0–68)	0 (0–66)	0 (0–14)	0 (0–1.025)
61 and over	131 (10.9)	1 (0–68)	0 (0–23)	0 (0–4)	0 (0–237)
Titles					
Specialist	725 (60.4)	0 (0–34)	0 (0–32)	0 (0–18)	0 (0–19)
Assist. Prof.	121 (10.1)	6 (0–34)	4 (0–32)	1 (0–18)	19 (0–382)
Assoc. Prof.	145 (12.1)	10 (0–51)	7 (0–44)	2 (0–24)	36 (0–512)
Prof.	209 (17.4)	4 (0–68)	3 (0–66)	0 (0–11)	10 (0–1.025)
Cities					
Metropolitan cities*	520 (43.3)	1 (0–68)	1 (0–66)	0 (0–24)	2 (0–1.025)
Others&	680 (34.3)	1 (0–44)	1 (0–43)	0 (0–15)	0 (0–512)
Geographic Regions					
Marmara	453 (37.7)	1 (0–68)	1 (0–66)	0 (0–24)	1 (0–1.025)
Aegean	152 (12.7)	0 (0–33)	0 (0–30)	0 (0–10)	0 (0–220)
Mediterranean	104 (8.7)	1 (0–19)	0 (0–16)	0 (0–15)	2.5 (0–112)
Black Sea	147 (12.3)	1 (0–23)	0 (0–19)	0 (0–14)	0 (0–269)
Central Anat.	199 (16.5)	2 (0–37)	1 (0–31)	0 (0–19)	4 (0–382)
Eastern Anat.	78 (6.5)	3 (0–25)	2 (0–18)	0 (0–8)	6 (0–156)
Southeastern Anat.	67 (5.6)	1 (0–19)	1 (0–16)	0 (0–8)	1 (0–163)
Hospital types					
University H.	248 (20.7)	6.5 (0–47)	5 (0–44)	0 (0–24)	18.5 (0–512)
Educ and Res H.	203 (16.9)	3 (0–51)	2 (0–44)	0 (0–13)	9 (0–222)
Private H.	316 (26.3)	0 (0–25)	0 (0–23)	0 (0–15)	0 (0–251)
Private Univ H.	69 (5.8)	5 (0–68)	3 (0–66)	1 (0–11)	22 (0–1.025)
State H.	364 (30.3)	0 (0–33)	0 (0–32)	0 (0–18)	0 (0–199)
Total	1.200 (100)	1 (0–68)	1 (0–66)	0 (0–24)	1 (0–1.025)

*: States for Ankara, İstanbul, and İzmir, &: States for rest of the cities other than that metropolitan cities, N: Number; %, percent, min-max: Minumum-maximum, Assist. Prof: Assistant Professor, Assoc. Prof.: Associate Professor, Prof.: Professor, H.: Hospital, med.: Median, Educ.: Education, Res.: Research, Univ.: University, Anat.: Anatolia

(impacts of publication, citation per publication, etc.) is clearly low compared to similar countries in terms of population, the number of academic staff and universities, schooling rate, and socio-economical level (8). To the best of our knowledge, there were no data in relative citation ratio of other fields in medical science publication addressed from Turkiye. Here, in our study, we found that urologists got the number of median one citation and publications in the relevant years.

Countries with a high socioeconomic level correlate with the higher citation/publication rates and h indexes since they have better technical facilities, allocate more funds for scientific research and have deeper scientific traditions (9). The USA was among the top three during the years 2010 to 2015, while China ranked 5th in 2010 and 2nd in 2015 by increasing the number of publications by 122% (8). Considering the publication productivity of our country, it is seen that the publications addressed to Turkiye have increased gradually over the years. In the 2010 to 2015 period, Turkiye also increased the number of publications by 39% and is still ranked in the first 20s. Between the years 2010 to 2015, most of the publications produced in

Table 2. Distribution of publication and citation status according to demographics of urologists							
	Frequency n (%)	Publication			Citation		
		No, n (%)	Yes, n (%)	p	No, n (%)	Yes, n (%)	p
Age ranges (y)							
30-40	408 (34.0)	96 (23.5)	312 (76.5)	**<0.001**	126 (30.9)	282 (69.1)	**<0.001**
41-50	400 (33.3)	199 (49.8)	201 (50.2)		208 (52.0)	192 (48.0)	
51-60	261 (21.8)	145 (55.6)	116 (44.4)		151 (57.9)	110 (42.1)	
61 and over	131 (10.9)	90 (68.7)	41 (31.3)		96 (73.3)	35 (26.7)	
Titles							
Specialist	725 (60.4)	455 (62.8)	270 (37.2)	**<0.001**	492 (67.9)	233 (32.1)	**<0.001**
Assist. Prof.	121 (10.1)	19 (15.7)	102 (84.3)		24 (19.8)	97 (80.2)	
Assoc. Prof.	145 (12.1)	11 (7.6)	134 (92.4)		12 (8.3)	133 (91.7)	
Prof.	209 (17.4)	45 (21.5)	164 (78.5)		53 (25.4)	156 (74.6)	
Cities							
Metropolitan cities*	520 (43.3)	218 (41.9)	302 (58.1)	0.33	240 (46.2)	280 (53.8)	0.38
Others&	680 (56.7)	312 (45.8)	368 (54.2)		341 (50.1)	339 (49.9)	
Geographic regions							
Marmara	453 (37.8)	207 (45.7)	246 (54.3)	**0.005**	224 (49.4)	229 (50.6)	**0.01**
Aegean	152 (12.7)	82 (53.9)	70 (46.1)		89 (58.6)	63 (41.4)	
Mediterranean	104 (8.7)	44 (42.3)	60 (57.7)		48 (46.2)	56 (53.8)	
Black Sea	147 (12.3)	71 (48.3)	76 (51.7)		77 (52.4)	70 (47.6)	
Central Anat.	199 (16.6)	76 (38.2)	123 (61.8)		82 (41.2)	117 (58.8)	
Eastern Anat.	78 (6.5)	22 (28.2)	56 (71.82)		28 (35.9)	50 (64.1)	
Southeastern Anat.	67 (5.6)	28 (41.8)	39 (58.2)		33 (49.3)	34 (50.7)	
Hospital types							
University H.	248 (20.7)	31 (12.5)	217 (87.5)	**<0.001**	38 (15.3)	210 (84.7)	**<0.001**
Educ and Res H.	203 (16.9)	51 (25.1)	152 (74.9)		62 (30.5)	141 (69.5)	
Private H.	316 (26.3)	196 (62.0)	120 (38.0)		208 (65.8)	108 (34.2)	
Private Univ H.	69 (5.8)	10 (14.5)	59 (85.5)		12 (17.4)	57 (82.6)	
State H.	364 (30.3)	242 (66.5)	122 (33.5)		261 (71.7)	103 (28.3)	
Total	1200 (100)	530 (44.2)	670 (55.8)		581 (48.4)	619 (51.6)	

*: States for Ankara, İstanbul, and İzmir, &: States for rest of the cities other than that metropolitan cities, N: Number, %, per cent, min-max: Minumum-maximum, Assist. Prof.: Assistant Professor, Assoc. Prof.: Associate Professor, Prof.: Professor, H.: Hospital, med.: Median, Educ.: Education, Res.: Research, Univ.: University, Anat.: Anatolia, chi-square test was performed and p<0.05 was considered statistically significant and marked in bold

Turkiye, same as in the world, were produced in the field of medical science. Whereas, most of the publications produced worldwide were in the field of biochemistry and molecular biology, but in Turkiye, mostly from the surgical disciplines. The number of publications produced in the field of urology and nephrology was ranked in 10th but, they were in 43rd place according to the impact value of publications (8).

Studies have shown that the publication of medical science in Turkiye about 40-44% of total publications. Eighty-five percent, 28%, and 17.33% of these publications were produced by university hospitals, training and research hospitals, and state, private and military hospitals, respectively (10). In our study, similar to the previous results, it was observed that urologists working in university and research and education hospitals published more, received more citations to their publications, had more publications in index journals and were more the first authors in the publications. This situation can be explained by the deep-rooted data history of the universities, the continuity

Table 3. Distribution of indexed journal publication and the first author publication status according to demographics of urologists							
	Frequency n (%)	Indexed journal publication			The first author publication		
		No, n (%)	Yes, n (%)	p	No, n (%)	Yes, n (%)	p
Age ranges (y)							
30-40	408 (34.0)	116 (28.4)	292 (71.6)		244 (59.8)	164 (40.2)	
41-50	400 (33.3)	207 (51.7)	193 (48.3)	**<0.001**	280 (70.0)	120 (30.0)	**<0.001**
51-60	261 (21.8)	151 (57.1)	110 (42.1)		222 (85.1)	39 (14.9)	
61 and over	131 (10.9)	96 (73.3)	35 (26.7)		121 (92.41)	10 (7.6)	
Titles							
Specialist	725 (60.4)	479 (66.1)	246 (33.9)		622 (85.8)	103 (14.2)	
Assist. Prof.	121 (10.1)	22 (18.2)	99 (81.8)	**<0.001**	56 (46.3)	65 (53.7)	**<0.001**
Assoc. Prof.	145 (12.1)	14 (9.7)	131 (90.3)		48 (33.1)	97 (66.9)	
Prof.	209 (17.4)	55 (26.3)	154 (73.7)		141 (67.5)	68 (32.5)	
Cities							
Metropolitan cities*	520 (43.3)	235 (45.2)	285 (54.8)	0.36	360 (69.2)	160 (30.8)	0.09
Others&	680 (22.4)	135 (49.2)	345 (51.8)		507 (74.5)	173 (25.5)	
Geographic Regions							
Marmara	453 (37.8)	224 (49.4)	229 (50.6)		326 (72.0)	127 (28.0)	
Aegean	152 (12.7)	83 (54.6)	69 (45.4)		117 (77.0)	35 (23.0)	
Mediterranean	104 (8.7)	54 (51.9)	50 (48.1)		90 (76.9)	24 (23.1)	
Black Sea	147 (12.3)	74 (50.3)	73 (49.7)	**0.01**	106 (72.1)	41 (27.9)	0.37
Central Anat.	199 (16.6)	81 (40.7)	118 (59.3)		141 (70.9)	58 (29.1)	
Eastern Anat.	78 (6.5)	25 (32.1)	53 (67.9)		49 (62.8)	29 (37.2)	
Southeastern Anat.	67 (5.6)	29 (43.3)	38 (56.7)		48 (71.6)	19 (28.4)	
Hospital types							
University H.	248 (20.7)	37 (14.9)	211 (85.1)		127 (51.2)	121 (48.8)	
Educ and Res H.	203 (16.9)	59 (29.1)	144 (70.9)		117 (57.6)	86 (42.4)	
Private H.	316 (26.3)	206 (65.2)	110 (34.8)	**<0.001**	264 (83.5)	52 (16.5)	**<0.001**
Private Univ H.	69 (5.8)	15 (21.7)	54 (78.3)		31 (44.9)	38 (55.1)	
State H.	364 (30.3)	253 (69.5)	111 (30.5)		328 (90.1)	36 (9.9)	
Total	1200 (100)	570 (47.5)	630 (52.5)		867 (72.2)	333 (27.8)	

*: States for Ankara, İstanbul, and İzmir, &: States for rest of the cities other than that metropolitan cities, N: Number, %, per cent, min-max: Minumum-maximum, Assist. Prof.: Assistant Professor, Assoc. Prof.: Associate Professor, Prof.: Professor, H.: Hospital, med.: Median, Educ.: Education, Res.: Research, Univ.: University, Anat.: Anatolia, chi-square test was performed and p<0.05 was considered statistically significant and marked in bold

of the academic vision, and the use of their socio-economic, cultural, and scientific advantages.

Onat (11) revealed as a reason for the quantitative and qualitative decline of publications in advancing ages that decreased interest and encouragement in academic research due to insufficient government support for research, performance-based clinical functioning, and not finding enough time to conduct research. It has been observed that in our study, young urologists (30-40 years old) and associate professors because the effect of promotion criteria to becoming associate professors have more publications even in indexed journals, get more citations to their publications and are mostly the first authors in their publications.

International co-authored papers and multicenter collaboration positively affect the publication productivity and citation rate. Furthermore, it is known that the geographically improved region has better publication quality and productivity (12). In our study, in contrast to expected, urologists working in Eastern Anatolia, a relatively lower developed region has higher the number of publications (median: 3) and citations (median: 6). However, it was not statistically significant in multivariate analyses (p=0.79). We can explain that there was no geographic centralization in terms of publication productivity in the field of urology in our country.

Study Limitations

We also have some limitations to our study. Although we included a great number of urologists and their publications in this study, it was still sampled about one out of three of all urologists. We did not investigate which study with the highest number of citations conducted by urologists was multicenter or international collaboration.

Conclusion

It has been observed that the publications produced in the field of urology in our country are still not of sufficient quality. Young urologists tend to produce more publications especially due to the criteria for academic promotion. To increase the value of academic vision, the interest and awareness of academicians for the higher scientific quality of publication productivity can be increased with events organized by the Higher Education Council and universities by encouraging the scientists to produce science and technology.

Table 4. Multivariate analysis of publication status according to demographics of urologists				
	p*	Multivariate analysis		
		OR	95% CI	p
Age ranges (y) (comparison to years of 61 and over)				
30-40		44.61	22.71-87.66	**<0.001**
41-50	**<0.001**	6.47	3.41-12.26	**<0.001**
51-60		2.44	1.32-4.51	**0.004**
Titles (comparison to specialist)				
Assist. Prof.		5.19	2.49-10.81	**<0.001**
Assoc. Prof.	**<0.001**	35.97	16.62-77.80	**<0.001**
Prof.		22.57	11.60-43.90	**<0.001**
Geographic Regions (comparison to Southeastern Anat.)				
Marmara				
Aegean				
Mediterranean	**0.005**	0.99	0.92-1.06	0.79
Black Sea				
Central Anat.				
Eastern Anat.				
Hospital types (comparison to state h.)				
University H.		2.62	1.33-5.17	**0.005**
Educ and Res H.	**<0.001**	5.34	3.28-8.71	**<0.001**
Private H.		0.97	0.63-1.49	0.9
Private Univ H.		2.44	0.96-6.17	0.059
*: States for p-value of publication status of urologists obtained from chi-square test, N: Number, %, per cent, min-max: Minumum-maximum, Assist. Prof.: Assistant Professor, Assoc. Prof.: Associate Professor, Prof.: Professor, H.: Hospital, Educ.: Education, Res.: Research, Univ.: University, Anat.: Anatolia, OR: Odds ratio, CI: Confidence interval, logistic regression analysis was performed and p<0.05 was considered statistically significant and marked in bold				

Ethics

Ethics Committee Approval: This study was approved by the Local Institutional Ethics Review Committee (Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee Approval, protocol number: 2020/443, date: 13.10.2020).

Informed Consent: Since this is a bibliometric study, informed consent of participants was not conducted in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Multidisciplinary Collaborative Operations of Urology and Other Surgical Specialties: Thirteen Years of Experience at a Single Center

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

The multidisciplinary evaluation is known be an essential component of today's medical practice. The urology department requires to be in communication with other surgical branches throughout the preoperative, intraoperative and postoperative periods due to the close neighboring of numerous organs and iatrogenic injuries. This is the first study in the literature to present a review of cases in which multidisciplinary surgeries were performed with the involvement of urology and other surgical specialties.

Abstract

Objective: Operative procedures performed collectively by urology and other surgical specialties were investigated in this study.

Materials and Methods: In this study, surgeries performed out at a single center throughout the 13 years' period between May 2008 and February 2021 were examined retrospectively, the operations performed by the urology department and other surgical branches jointly, the procedures executed and the reasons for perioperative consultation were reviewed through operative reports. The number of performed surgeries, their types, frequencies, the status of whether emergency or elective were observed separately and tables were created by determining the most frequently done collaborative operations.

Results: The total number of patients having collective surgeries was 472. Three hundred twenty-two of these consisted of operations in cooperation with general surgery, 94 with obstetrics and gynecology, 40 with cardiovascular surgery, 9 with orthopedics, 5 with thoracic surgery and 2 with plastic and reconstructive surgery branches.

Conclusion: Operations performed in collaboration with other surgical specialties reveal a multidisciplinary contribution in the assessment, treatment planning and surgical management of patients. The success of surgical treatment is closely related to the continuity of interdisciplinary communication and collective evaluations during and after surgery and before the surgery. As there are many surgical procedures performed by urology as part of a team with other branches, the review of these operations will help make more accurate and faster collaborative decisions in similar future cases that may be encountered.

Keywords: Multidisciplinary operations, multidisciplinary evaluation, urology, perioperative consultation

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Introduction

The multidisciplinary approach, in modern age medical practice, where specialization in a branch is gradually increasing, makes it inevitable for the relevant disciplines to evaluate cases together and to cooperate in decisions and practices to better understand patients and diseases and to find more accurate solutions (1). In today's medical practices, interdisciplinary communication and collaboration appear in both medical and surgical treatments. The multidisciplinary assessment, observed to be used in most of the surgical medicine practices, particularly within the oncological patient group, has improved the success related to the treatment and management of disease (2).

Communication between specialties is of great importance in relation to correct and effective coordination of treatment

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plans for both outpatients and inpatients. Upon review of the multidisciplinary evaluation with respect to patients requiring surgery, this includes the gradual processes ongoing before, during and after the operation. Thus, consultation of the relevant specialties before, during and after surgery, exchange of ideas, considering the recommendations throughout the determination of the management plan and its application may considerably affect the success of the treatment (3).

For emergency or elective surgeries, the surgeons of the relevant branches have to be involved in the operation due of emergency trauma within the operative field or conditions resulting from iatrogenic causes in the adjacent tissues concerning other specialties during the procedure. Also, in case of the primary disease impacting the organs of other branches, it may be necessary to evaluate the case collectively before surgery and subsequently to perform a collaborative surgery (4).

Due to the wide neighborhood of urogenital structures with respect to other organs, there are a considerable number of emergency or elective collective surgeries performed by the urology department with other surgical branches.

In our study, we, as the urology clinic, aim to review the surgeries performed by the urology department and other surgical branches collaboratively by screening 13 years of operative data and to publish the related data. This study is the only one on this subject examining the multidisciplinary approach of urologic surgical operations.

Materials and Methods

Between May 2008 and February 2021, the operations at University of Health Sciences Turkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital involving the Clinic of Urology and other surgical branches were scanned through the hospital automation system. By reviewing the surgical procedure names and the operative notes, the number of surgeries performed collaboratively, their types, frequencies, the status of whether emergency or elective were examined separately and tables were created by determining the most frequently done operations. Upon establishing the reason for including the other surgical branch throughout the surgery, pathologies, or the suspicion of iatrogenic damage, the purpose of the consultation request was recorded. The types of most commonly performed cooperative surgeries and the proportion of consultation requests in collective surgeries were demonstrated. Operations involving two different surgical branches simultaneously were included in the study, whilst similar procedures performed on the same patient more than once were documented as one case. Surgeries performed by two specialties together because of two completely independent indications (for example coexistence of bladder tumor and inguinal hernia) were excluded. Ethics

committee approval for the study dated 2021 and numbered 195 was obtained from University of Health Sciences Turkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee. This study was conducted in accordance with the principles of the Declaration of Helsinki. Statistical analysis was not performed in our study.

Results

In our study investigating the operations involving urology and other branches, the total number of cases meeting the criteria was 472. Three hundred twenty-two of these cases consisted of operations in cooperation with general surgery (GS), 94 with obstetrics and gynecology (OB-GYN), 40 with cardiovascular surgery (CVS), 9 with orthopedics, 5 with thoracic surgery and 2 with plastic and reconstructive surgery (PRS) branches.

The species having the most collaborative surgical procedures with urology was GS. Of the 322 common cases, 108 were emergency operations and 214 were elective surgeries. GS was involved in 65 cases, whilst urology was included in 257 cases secondarily. The types of the surgeries performed collectively by urology and GS branches, their frequencies, the status of emergency or elective are provided in Table 1. It was observed that in 81 (31.5%) of the perioperative urology consultations requested by GS was due to iatrogenic organ damage. Ureteral injury was detected in 41 cases (50.6%), which constituted half of the iatrogenic injuries, bladder injury in 24 patients (29.6%), and urethral injury in 11 patients (13.6%). Additionally, Double J stent (DJs) implantation was applied by urology to protect the ureters in 33 (34.3%) cases that were operated by GS due to invasive mass. When the pathological results of 47 patients with rectal tumor, one of the most common conditions requiring consultation, were examined, it was observed that 30 patients (63.8%) were staged as T3-T4 according to TNM staging, and 22 patients (46.8%) were stage 3-4 patients. The reasons for

Table 1. Pathologies in joint operations of urology and general surgery branches and their frequencies

Emergency procedures		Elective procedures	
Clinical condition	Number of patients (%)	Clinical condition	Number of patients (%)
GSW-SW	38 (35.2)	Rectal tumor	47 (22)
Acute abdomen	22 (20.4)	Abdominal masses	44 (20.6)
Blunt trauma	14 (12.9)	Colon surgeries	35 (16.4)
Fournier gangrene	13 (12)	Fistules	18 (8.4)
Evisceration	9 (8.3)	Renal tumor	14 (6.5)
Other	12 (11.2)	Other	56 (26.1)
Total	108	Total	214
GSW: Gunshot wounds, SW: Stab wounds			

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consultations requested in the joint operations of GS and urology branches, the most common pathologies encountered, performed procedures and the rates are given in Table 2.
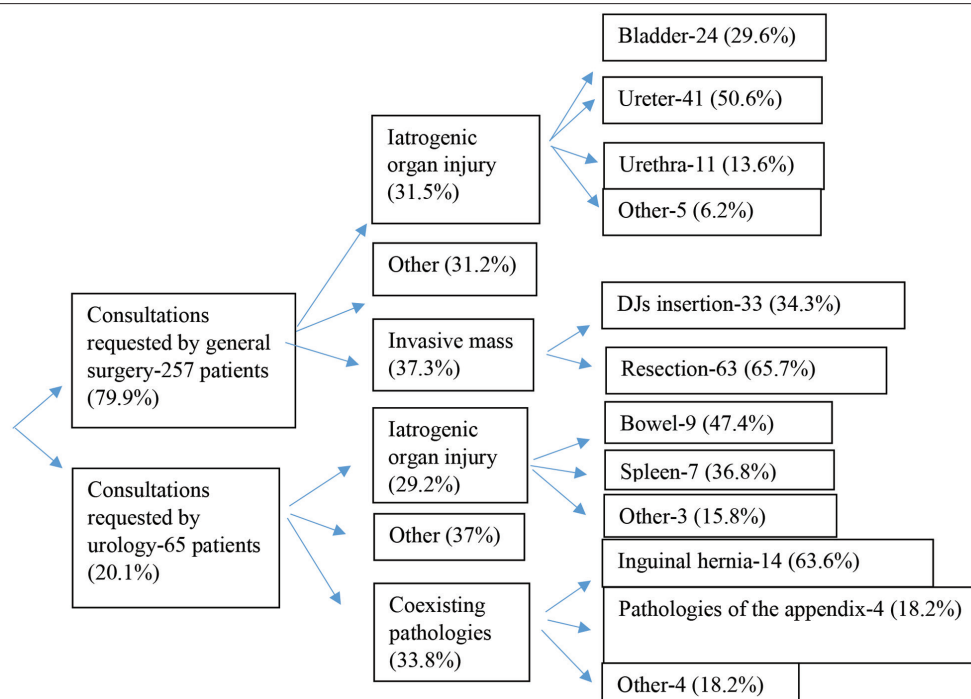
It was revealed that the specialty performing the second most frequent surgical operations with urology was the OB-GYN with 94 cases. Whilst 20 of these cases were emergency operations, 74 of them were planned as elective operations. The most common diseases and their frequencies in mutual surgeries are listed in Table 3. Among the operations performed collectively by urology and OB-GYN, it was observed that 58 cases (61.7%) were associated with iatrogenic injuries, of which 38 (66%) had bladder injury and 20 (34%) had ureteral injury. As there were 14 patients who underwent DJ insertion to protect the ureters without the presence of injury, 5 cases were identified to have simultaneous cystectomy due to an invasive genital mass. When the pathology results of 17 patients with ovarian tumor, which is one of the most common conditions requiring consultation, were examined, it was determined that 9 patients (53%) had stage 2B tumors according to the FIGO classification, 4 patients (23.5%) had stage 3 tumors, and 4 patients (23.5%) had stage 1 tumors. The reasons and frequencies of consultation requests in collaborative surgeries of urology and OB-GYN branches are summarized in Table 4.

We observed that the number of operations performed together by the specialties of urology and CVS was 40 and 16 of these (38.3%) were due to iatrogenic injuries in urology

procedures. It was determined that consultations requested in the perioperative period were most frequently due to injuries of the inferior vena cava, followed by the renal artery and other vessels. Whilst emergency surgery was carried out in 10 of 24 patients without iatrogenic injury due to gunshot wounds and stab wounds, CVS was included in the operations of 6 patients (25%) in relation to venous thrombus caused by kidney tumor. Examining the pathology results of 12 patients with kidney tumors, which is one of the most common conditions requiring consultation, 8 patients (66.7%) were found to have stage 3-4 disease. A total of 2 (16.7%) required intraoperative consultation because of renal artery and vein injury during radical nephrectomy resulting in stage 2 renal cell carcinoma. It was observed that renal vein damage occurred in 1 patient (8.3%) during open partial nephrectomy, and 1 patient (8.3%) was referred to CVS due to vena cava inferior damage during laparoscopic radical nephrectomy. The procedures involving urology and CVS branches together, their clinical features and frequencies are summarized in Tables 5 and 6.

There were 5 operations detected for engaging urology and thoracic surgery specialties, collectively. In 4 of these cases, the consultation was requested because of pleural injury. For one patient, diaphragm and pleural injury occurred simultaneously and along with thoracic surgery, GS was required to attend the operation. Of the 5 patients, 3 during nephrectomy for non-functioning kidney due to renal stone, 1 during radical

Table 2. Reasons and frequencies of the consultations requested in collaborative operations of urology and general surgery branches

DJs: Double J stent

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nephrectomy because of kidney tumor, 1 while having percutaneous nephrolithotomy developed pleural injury. Upon perioperative evaluation, primary repair and thoracostomy were mostly applied to the patients.

The number of surgeries in which the branches of urology and orthopedics attended in cooperation was determined to be 9, of these, 1 was elective and 8 of them were documented as emergency operations due to trauma. Whilst most cases were surgeries involving numerous clinics due to multitrauma, bladder repair performed for 5 patients was revealed to be the most frequently performed urological procedure.

There were 2 operations identified which were carried out in collaboration with urology and PRS specialties. These cases were revealed to be reconstructive surgeries, previously done due to Fournier's gangrene and subsequently performed for closure of wound defects.

Discussion

Recently, a multidisciplinary approach has become critical in treatment planning, decision-making and follow-up, especially

for geriatric and oncology patient groups. For this purpose, multidisciplinary case evaluation committees have been established at hospitals, especially in elective cases, and these practices have entered our practice (5).

It is recognized that a multidisciplinary decision-making process may significantly reduce the extensive variation in decisions made by independent healthcare professionals (6). Multidisciplinary decision-making has become essential for centers providing oncological treatment. A treatment plan is formed with the joint assessment of both the surgical, internal and oncology departments. For surgical units, requiring consultation among themselves and the patient group requiring collaborative treatment is not negligible. Due to the wide breadth of the surgical field for urology, it should stay in contact with many branches.
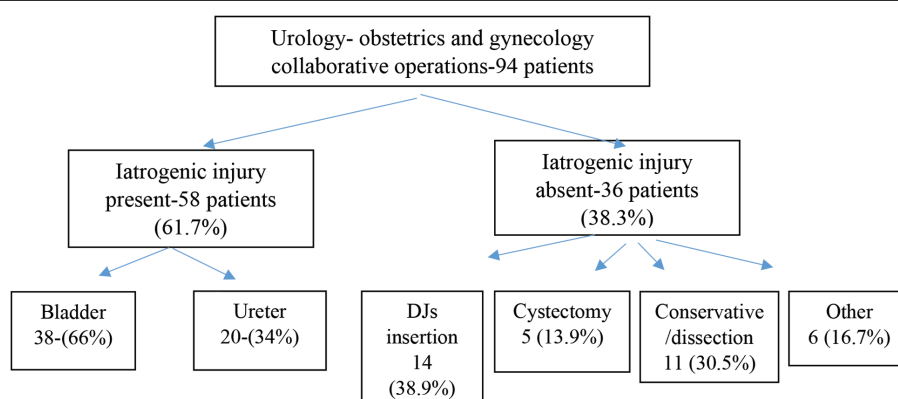
On examination of the branches operating jointly with urology, surgeries in collaboration with GS were demonstrated to be performed most frequently. It is possible to explain this situation with the variety of operations carried out by the specialty of GS and its wide area to the organs covered by urology. Especially in a center where oncological surgery is regularly performed,

Table 3. Pathologies in collective operations of urology and obstetrics and gynecology branches and their frequencies

Emergency operations		Elective operations	
Clinical condition	Number of patients (%)	Clinical condition	Number of patients (%)
Delivery/C section	8 (40)	Ovarian tumors	17 (22.9)
Hemorrhage	7 (35)	Myoma/endometriosis	12 (16.2)
Pelvic mass	2 (10)	Cervical tumors	11 (14.9)
Other	3 (15)	Delivery/C section	11 (14.9)
		Other gynecological malignancies	9 (12.2)
		Other	14 (18.9)
Total	20	Total	74
C section: Cesarean delivery			

Table 4. Reasons and frequencies of the consultations requested in joint surgeries of urology and obstetrics and gynecology branches

DJs: Double J stent

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interdisciplinary work is inevitable with respect to the surgical procedure of invasive masses (7). In our study, it was observed that most of the collective operations performed using the GS branch were not emergency surgeries, but nearly half of the them were surgeries performed out under elective conditions for stage 3-4 intra-abdominal cancer cases.

In our study, we found that approximately 1/3 of the operations performed jointly with GS were due to iatrogenic injuries. Perioperative consultation was required most frequently because of ureteral injuries. Although the most common cause of damaged ureters is iatrogenic injuries, any trauma occurring in the ureters may lead to severe sequelae (8). Whilst it is generally seen as a rare complication of colorectal surgeries, in the literature, it is stated that its incidence is increasing gradually and it is associated with high morbidity, mortality and the length of hospital stay (9). Ureteral injuries, in addition to appearing in the procedures of other branches requiring difficult dissection, are conditions that may be encountered even in the operations performed out by primary urology such as kidney tumor surgery (10). As risk factors leading to iatrogenic injury, factors such as situations disrupting the normal anatomy, malignancies,

previous surgery, radiotherapy history, diverticulitis and endometriosis have been indicated (11).

In consideration of the risk factors, iatrogenic ureteral injuries should be kept in mind as a complication that may occur in tertiary level treatment centers providing oncological surgery, and care must be taken to detect them in the intraoperative period.

It was reported in the literature that the bladder is the most frequently affected organ of the urinary system with respect to iatrogenic injuries (12). Bladder injury ratings of up to 4.5% have been documented for GS operations, especially in abdominal cytoreductive surgeries, and these rates were revealed to be between 0.12-0.41% in small-large bowel surgeries and rectal procedures (13,14). In our study, among the operations performed by GS and urology clinics collectively due to iatrogenic injury, we established that bladder injuries were the second in place.

With respect to the surgeries carried out by the OB-GYN, bladder, and ureter injuries may develop associated with the neighborhood of organs. It has been documented that the rate of ureteral injury in hysterectomy operations varies between 0.02% and 0.6%, depending on the type of hysterectomy procedure (15). It was determined that two-thirds of the surgeries performed by the OB-GYN in collaboration with urology at our center were related to iatrogenic organ damage.
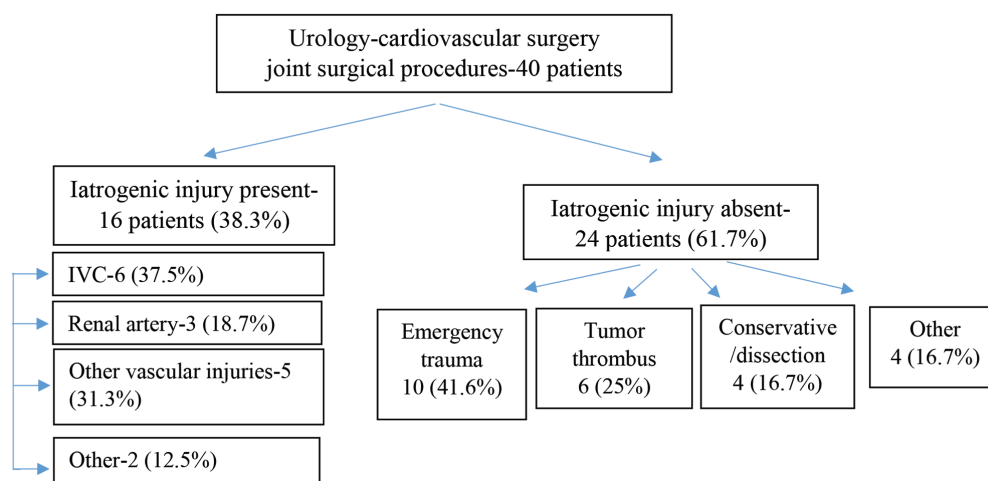
In centers performing advanced operations in terms of gynecologic oncology, because of invasive masses, the requirement for resection in relation to both adjacent organ injury and invasion confirms the necessity of preoperative and intraoperative consultation. Whilst ovarian tumor surgeries took the first place among the elective procedures done

Table 5. Pathologies in collaborative operations of urology and cardiovascular surgery branches and their frequencies

Clinical state	Number of patients (%)
GSW/SW	13 (22.9)
Renal tumor	12 (16.2)
Retroperitoneal lymph node dissection	5 (14.9)
Kidney transplant surgery	4 (14.9)
Other	6 (18.9)
Total	40
GSW: Gunshot wounds, SW: Stab wounds	

Table 6. Reasons and frequencies of the consultations requested in collective operations of urology and cardiovascular surgery branches

IVC: Inferior vena cava

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cooperatively at our center, uterine myoma surgeries and cervix tumors followed the lead. Five patients who underwent radical cystectomy for bladder invasion without any iatrogenic injury were identified. It is imperative that the decision for a major surgery such as radical cystectomy and urinary diversion, which will subsequently affect the quality of life and subsequent, should be made before surgery following interdisciplinary evaluation and obtaining their informed consent along with an explanation of the possible risks to the patients.

Inserting a DJ into the ureter for protection is revealed to be a significant situation that both GS and OB-GYN perform in cooperation with urology or necessitates a consultation. In our study, it was established that approximately one-third of the joint surgeries of GS, OB-GYN and urology, not caused by iatrogenic damage, were operations for prophylactic insertion of DJs. Nevertheless, it was reported in the literature that prophylactic stenting did not reduce the rate of ureteral injury (16). Yet, in complicated cases, the reasons for the preference of this practice include visualization of the ureter and aiding in the dissection during the operation by providing ease at palpation (17). It also provides an advantage in detecting ureteral damage if it occurs (18). Complications such as stent migration, oblivion, irritation, and cost analysis along with the risks of surgery should be carefully evaluated and prophylactic stenting should be applied in complicated cases (19).

On review of the collaborative surgeries concerning CVS and urology branches, it was revealed that they were performed after requesting perioperative consultation for iatrogenic vascular injury in 16 patients (38%). Intraoperative vascular injuries are commonly encountered. Decision-making occurs in a very short time frame following a life-threatening intraoperative vascular injury. Identifying the source of hemorrhage, initiating first-line hemostatic measures, and applying operative repair maneuvers and techniques have proven to be crucial for maintaining haemodynamic stability and cessation of bleeding (20).

Inferior vena cava (IVC) injuries were observed to be first in line amongst iatrogenic vascular injuries for urological surgeries carried out in cooperation with CVS at our hospital. Bleeding from IVC is one of the most frightening situations a surgeon may be involved in. The management of small venous tears may be easy, whereas in large defects, Satinsky clamps are used to partially or completely occlude the IVC and injury is primarily repaired by 4-0/5-0 polypropylene sutures (21). For patients with inadequate primary repair, as may also be predicted on preoperative assessments, more complex vascular reconstructions (vascular patch graft, tube-interposition graft) may be required (22).

At our hospital, apart from iatrogenic reasons, it was noted that the most common operation performed collaboratively by

urology and CVS clinics was radical nephrectomy procedures performed out due to renal tumor accompanied by a thrombus in the renal vein or vena cava. In renal cell carcinoma, venous involvement develops as a tumor thrombus in the renal vein on the affected side with the potential to extend into the IVC and even the right atrium. At the time of diagnosis, approximately 10% of the patients have predisposition for tumor thrombus in the renal vein or IVC and more frequently on the right side (22,23).

In our study investigating the joint operations of urology branch and other specialties, it was demonstrated that for most surgeries, the requirement for consultation could be anticipated before the operation. Upon examining the surgical procedures under 2 groups as emergency and elective cases, in elective operations we believe that for pathologies involving more than one specialty without any iatrogenic damage or unexpected situation during the surgery, it is necessary to form a collaborative surgical decision with an interdisciplinary evaluation before surgery. This highlights the significance of risk calculation and preoperative discussion related to possible scenarios along with obtaining informed consent from the patient. For instance, as ureteral damage or resection in the operation of a tumor invading the ureter or located closely may necessitate the insertion of a ureteral stent or nephrostomy, before surgery, it would be required to notify the patient and to receive informed consent from the patient.

We consider that being aware of the surgical procedures involving at least two branches and of the conditions in which the consultation is needed during the operation is also crucial for the training of surgical residents. With the increase in specialization, appreciating comprehensive assessments, holistic evaluation of the patients preoperatively and intraoperatively, and when necessary, asking for opinions of other branches or requesting a consultation must be a fundamental part of the residency training process.

Study Limitations

The limitations of our study include examining the results of only one center, designed retrospectively and not specifying the percentage of consultation or iatrogenic damage on a case-by-case basis. However, upon review of the literature, it may be concluded that it is the only study on multidisciplinary surgeries of urology with other surgical branches. Further studies containing more detailed and extensive case series may be conducted in the future.

Conclusion

Evaluation, treatment planning and management of surgical patients, whose care is predicted to require the involvement

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of different branches, should be conducted multidisciplinary prior to surgery along with the application of the joint decisions taken, and consultation requests must not be avoided during surgery when necessary. As the urology branch has an intensive collaboration with other surgical specialties, investigation of the reasons for perioperative consultation will play an important role in determining more planned treatment management.

Ethics

Ethics Committee Approval: Ethics committee approval for the study dated 2021 and numbered 195 was obtained from University of Health Sciences Turkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Y., E.G., Concept: U.S., E.G., Design: H.P., H.Y., Data Collection or Processing: U.S., Analysis or Interpretation: U.S., E.G., Literature Search: H.P., H.Y., Writing: U.S., H.P.

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

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External Validation of CHOKAI and STONE Scores for Detecting Ureter Stones in the Eastern Turkish Population

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

It is known from previous studies that STONE and CHOKAI scores are effective in predicting ureteral stones in patients with renal colic. In our study, we showed that the CHOKAI score is more sensitive and specific than the STONE score in predicting ureteral stones.

Abstract

Objective: To investigate the effectiveness of CHOKAI and STONE scoring systems in predicting ureter stones in patients admitted to emergency and urology departments.

Materials and Methods: This was a single-center prospective observational study. Patients over the age of 18 years with back, flank, or lower abdominal pain and suspected of ureteral stones and performed non-contrast abdominal computed tomography for diagnostic imaging were included. Each patient's CHOKAI and STONE score was calculated on their medical interviews and physical and laboratory findings. Receiver operating characteristic analysis was used for the sensitivity and specificity of the scoring systems at optimal cut-off values.

Results: Of the 348 patients in the study, 228 were detected with ureteral stones. For the CHOKAI score, the area under the curve (AUC) at an optimal cut-off point of 8 was 0.923 [95% confidence interval (CI), 0.894-0.952], with a sensitivity of 0.842, and specificity of 0.975, a positive likelihood ratio (LR+) of 33.68, and a negative likelihood ratio (LR-) 0.162. For the STONE score, the AUC at an optimal cut-off point of 9 was 0.847 (95% CI, 0.807-0.887), with a sensitivity of 0.697 and specificity of 0.900, an LR+ of 6.97, and an LR- 0.336.

Conclusion: The CHOKAI score is more sensitive and specific than the STONE score in predicting ureteral stones. Using the CHOKAI score in routine practice will reduce radiation exposure and cost and prevent time loss for serious differential diagnosis.

Keywords: Renal colic, ureter stone, scoring system

Introduction

Flank pain due to ureteral stones is essential for admission to the emergency department (ED) and urology clinics. Its lifetime prevalence is approximately 10-15% (1). In this population, the need for urological intervention in the early period is around 10% (2). The non-contrast helical computed tomography (NCCT) is the most sensitive radiological tool for detecting urinary system stone disease (3). Whereas, repeated computed tomography (CT) scans cause increased radiation exposure, as recurrence rates of ureterolithiasis are high.

Moore et al. (4), for predicting ureter stones created the STONE score to reduce CT-related radiation toxicity. It includes the following five parameters between 0-13 points: Gender, timing, ethnicity, nausea/vomit, and microscopic hematuria (Table 1). This score divides patients into low (0-5), moderate (6-9), and high (10-13)-risk categories for the probablity of ureteral stones. After that, a low-dose CT protocol was developed to reduce radiation exposure of intermediate and high-risk groups on the STONE score (5). It also showed the need for alternative diagnoses for low-risk group. The addition of hydronephrosis detected by ultrasound (US) to the STONE score, STONE-

plus was developed and further strengthened for detecting ureteral stones (6). Ethnic variation (black and non-black) was a restricting issue in STONE scoring, and it was stated that hydronephrosis concurrently encouraged the diagnosis. Due to these limitations, a new scoring named CHOKAI was produced. The CHOKAI scoring consists of age, sex, pain duration, nausea/vomit, microscopic hematuria, hydronephrosis and history of urolithiasis (Table 1). The sensitivity and specificity of the CHOKAI scoring for determining urolithiasis were 93%, and 90%, respectively (7).

Because of the large number of patients presenting to ED and urology clinics with flank pain, these scoring systems are valuable in facilitating differential diagnosis and reducing increased radiation exposure. Therefore, our aim was to investigate the efficacy of these scoring systems in predicting ureterolithiasis in our patient population.

Materials and Methods

This prospective study was conducted in our clinic between November 2020 and January 2022. The Local Institutional Ethics Committee approved the study (approval number: 2020/01.01). Patients who applied to the emergency and urology departments with lower abdominal, back or flank pain and underwent NCCT were included in the study. Patients under 18 years of age, with unstable vital signs, urinary stone surgery history (within one year), trauma, under urological treatment, referred from other hospitals for urolithiasis treatment, insufficient examination, active malignancy, and declining to participate in the study were excluded.

After the study protocol was established, a questionnaire was created asking questions about the pain duration, nausea/vomiting, previous history of urinary stone, and informed consent of patients or their caregivers. Urinalysis was then performed to investigate microscopic hematuria. US examination was performed using Mindray DC-7 (Shenzhen Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China) to detect hydronephrosis. After the initial US was performed, the physician recorded findings, and NCCT imaging was applied to approve the determination of urolithiasis. NCCT reported by the radiologist was approved as the definitive diagnosis. NCCTs were reported by the responsible radiologist on the day of the procedure. NCCT scans were reviewed by the relevant researchers concurrently with the report. Radiologists were unaware of initial US findings; NCCT reports routinely reported with prediagnosis of urolithiasis. After making a definitive diagnosis, CHOKAI and STONE scores were calculated and entered into the forms.

Statistical Analysis

All statistical analyzes were performed using SPSS Statistics software version 26.0 (IBM, Armonk, NY, USA). Categorical variables were expressed as numbers and percentages. Continuous variables are indicated as appropriate means and standard deviation, or median and interquartile range. Receiver operator characteristics (ROC) curve defined optimal thresholds via area under the curve (AUC). The Youden index was used to define the optimum cut-off values of the CHOKAI and STONE scores for predicting of ureterolithiasis, at maximum sensitivity and specificity. Positive likelihood ratio (LR+), and negative likelihood ratio (LR-) also were calculated at the optimal cut-off scores. P-value <0.05 was defined as statistical significance.

Results

Of the 388 eligible patients, 40 were excluded; thus, final analyses were performed with 348 patients (Figure 1). Ureteral stones were present in 228 (65.5%) patients in NCCT, and no stones were detected in 120 (34.5%) patients. The demographic and clinical characteristics of patients are demonstrated in Table 2. All the participants were of non-black ethnicity. The mean age was 36.7±13.4 years. The number of male patients was 225 (64.7%), and the number of female patients was 123 (35.3%).

The ROC curve analysis was used for the diagnostic accuracy of the CHOKAI and STONE scores (Figure 2). The optimum cut-off

Table 1. CHOKAI and STONE score categories			
Category	**Characteristic**	**Points**	
		CHOKAI score	**STONE score**
Age	≥60 years	0	-
	<60 years	1	-
Gender	Female	0	0
	Male	1	2
Race	Black	-	0
	Non-black	-	3
Duration of pain to presentation	>24 h	0	0
	6-24 h	0	1
	<6 h	2	3
Nausea and vomiting	No	0	0
	Only nause	1	1
	Vomiting	1	2
Urinary stone history	No	0	-
	Yes	1	-
Microscopic hematuria	No	0	0
	Yes	3	3
Hydronephrosis on US	No	0	-
	Yes	4	-
Total points		0-13	0-13
US: Ultrasound			

value for the CHOKAI score was assigned to be 8, with an AUC of 0.923 [95% confidence interval (CI) 0.894-0.952]. The highest sensitivity was 0.842, specificity was 0.975, LR+ was 33.68, and LR- was 0.162. The optimum cut-off value for the STONE score was assigned to be 9, with an AUC of 0.847 (95% CI, 0.807-0.887). The highest sensitivity was 0.697, specificity was 0.900, LR+ was 6.97, and LR- was 0.336 (Table 3).

Of 120 patients without ureteral stones, 117 were estimated correctly in the CHOKAI scoring system and 108 in the STONE scoring system. One hundred ninety-two patients with the CHOKAI scoring and 159 patients with the STONE scoring were classified correctly in patients with ureteral stones. According to the STONE score risk categories, ureteral stone diagnosis rates were 37.5% in the low-risk group, 52.5% in the moderate risk group and 97.7% in the high-risk group, respectively (Table 4).

Discussion

The present study found that both CHOKAI and STONE scores have good performance for detecting ureteral stones in our flank pain patient population. However, the CHOKAI score has better results due to its higher sensitivity and specificity.

The presence of hydronephrosis in the US has a significant 4-point effect on the 13-point CHOKAI scoring. In the STONE plus study, Daniels et al. (6) added US to the STONE scoring system. They reported that the US increased the rate of

diagnosing ureteral stones, especially in low and moderate-risk groups (6). However, Sternberg et al. (8), reported that the detection of hydronephrosis on US was not specific for ureteric stones and they focused on the need for NCCT because stone size and location give significant data for ureter stone management. However, the cumulative radiation exposure and cost burden from repetitive CT must be considered. Sternberg et al. (8) believed that the STONE scoring system could be helpful in determining the imaging modality. For increased radiation exposure when diagnosing ureterolithiasis, the European Association of Urology and the American Association of Urology encourage the use of low-dose CT, which has similar sensitivity and specificity as NCCT (9,10). By using the STONE score Moore et al. (5), produced beneficial criteria for using low-dose CT.

In a retrospective study conducted with 157 Turkish patients, the effectiveness of STONE, modified STONE, and CHOKAI scores were analyzed. The specificity and sensitivity values of STONE, modified STONE, and CHOKAI scores for the diagnosis of ureteral stones were 64.71, 71.70; 70.59, 87.74; and 66.67, 90.57, respectively, and the CHOKAI showed the best performance (11). In addition, the effectiveness of STONE and CHOKAI scores was evaluated in a recent prospective study conducted on a Turkish population of 105 patients. They reported that the AUC for the CHOKAI score was 0.788 (95% CI: 0.697-0.862, p<0.001) and 0.615 (95% CI: 0.515-0.709, p=0.087) for the STONE score and the CHOKAI score has a better diagnostic accuracy than the STONE score (12). Similarly, in our study in the eastern Turkish patient population, the sensitivity and specificity of the CHOKAI and STONE scores for predicting ureteral stones were 0.842, 0.975, and 0.697, 0.900, respectively. The absence of black patients can explain the low effectiveness of the STONE score in our and other Turkish societies.
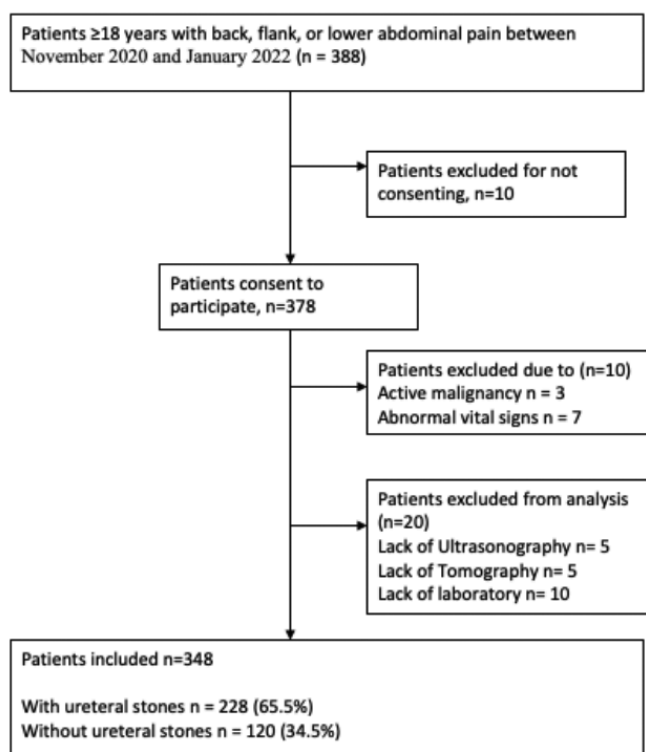

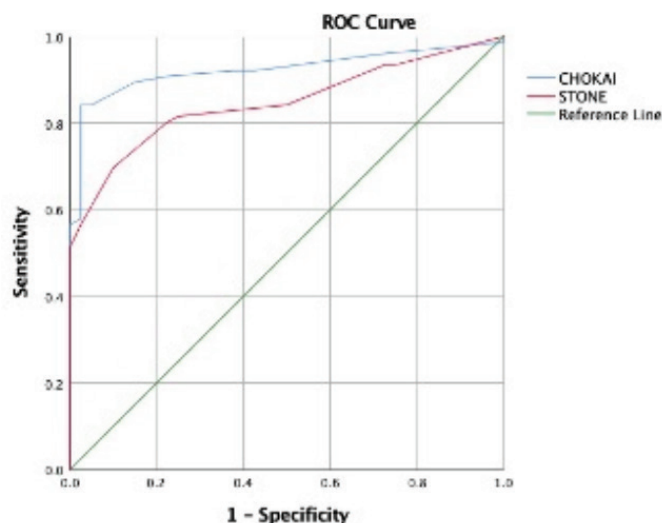Figure 1. The flowchart of patient inclusion and exclusion criteria

Figure 2. The area under the curve with receiver operating characteristic curves of the CHOKAI and STONE scores at the optimal cut-off point

For an ideal diagnostic test, LR+ is >10 and/or LR- <0.1 (13). Fukuhara et al. (7), in their multicenter prospective study, reported LR+ of 9.3 (95% CI, 3.7-23) and LR- of 0.079 (95% CI, 0.036-0.17) in the CHOKAI score for an optimum cut-off value of 6 and stated that "it is a good prediction test for ureterolithiasis". But the reported LR+ value was below 10. However, in our study, the optimal cut-off value for the CHOKAI score was 8, with LR+ 33.68 and LR- 0.162. Therefore, we can advocate stronger that the CHOKAI score is an ideal diagnostic test with these data. The larger sample size in our study than in other studies may have contributed to this difference. However, the other studies were generally managed only in ED, and in our research, all US and patient evaluations were performed by specialist urologists in the urology clinic. Therefore, it might be another factor affecting the results.

Table 2. Demographic and clinical characteristics of the patients

	Stone group (n=228)	No stone group (n=120)	Total (n=348)
Age (years), mean ± SD	37.7±13.7	34.8±12.5	36.7±13.4
Gender, n (%)			
Male	165 (72.4)	60 (50)	225 (64.7)
Female	63 (27.6)	60 (50)	123 (35.3)
Race, n (%)			
Black	0		
Non-black	228 (100)	120 (100)	348 (100)
Duration of pain to presentation, n (%)			
>24 h	66 (28.9)	72 (60)	138 (39.7)
6-24 h	30 (13.2)	12 (10)	42 (12.1)
<6 h	132 (57.9)	36 (30)	168 (48.3)
Nausea and vomiting, n (%)			
No	129 (56.6)	96 (80)	225 (64.7)
Only nause	27 (11.8)	12 (10)	39 (11.2)
Vomiting	72 (31.6)	12 (10)	84 (24.1)
Urinary stone history, n (%)			
No	114 (50)	96 (80)	210 (60.3)
Yes	114 (50)	24 (20)	138 (39.7)
Microscopic hematuria, n (%)			
No	36 (15.8)	105 (87.5)	141 (40.5)
Yes	192 (84.2)	15 (12.5)	207 (59.5)
Hydronephrosis on US, n (%)			
No	18 (7.9)	114 (95.0)	132 (37.9)
Yes	210 (92.1)	6 (5.0)	216 (62.1)
CHOKAI score, median (IQR)	11 (3)	2 (3)	9 (9.75)
STONE score, median (IQR)	11 (4)	5.5 (3.5)	8 (6)
Disposition, n (%)			
Hospitalization	16 (7.0)	26 (21.7)	42 (12.1)
Discharge	212 (93.0)	94 (78.3)	306 (87.9)
SD: Standard deviation, IQR: Interquartile range			

Table 3. Diagnostic accuracy of the CHOKAI and STONE scores at the optimal cut-off score

Score (optimal cut-off value)	AUC (95% CI)	Sensitivity	Specificity	LR+	LR-	p
CHOKAI (8)	0.923 (0.894-0.952)	0.842	0.975	33.68	0.162	<0.001
STONE (9)	0.847 (0.807-0.887)	0.697	0.900	6.97	0.336	<0.001
LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, CI: Confidence interval, AUC: Area under the curve						

Table 4. External validation of STONE score distribution and risk category diagnosed with ureteral stone

STONE score risk category	STONE score distribution n (%)	Ureteral stone validating with STONE score n (%)
Low risk (0 to 5 points)	96 (27.6)	36 (37.5)
Moderate-risk (6 to 9 points)	120 (34.5)	63 (52.5)
High-risk (10 to 13 points)	132 (37.9)	129 (97.7)

Study Limitations

Our study has some limitations:

1. It was conducted single-center, and only eastern Turkish patients were included. Thus, the features of the CHOKAI may vary in different populations.

2. This study was carried out during the daytime working hours when the researchers were actively working. Therefore, it does not reflect the entire patient population in the emergency or urology departments.

3. The US is an operator-dependent modality, so that it may have affected the study results.

Conclusion

Both CHOKAI and STONE scores effectively diagnose when ureteral stones are suspected. However, the CHOKAI score is more sensitive and specific than the STONE score predicting ureteral stones. Therefore, using the CHOKAI score in routine practice will reduce radiation exposure and cost and prevent time loss for serious differential diagnosis.

Ethics

Ethics Committee Approval: This prospective study was conducted in our clinic between November 2020 and January 2022. The Local Institutional Ethics Committee approved the study (approval number: 2020/01.01).

Informed Consent: Prospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.O., E.D., Concept: F.O., Design: F.O., Data Collection or Processing: E.D., Analysis or Interpretation: F.O., Literature Search: F.O., E.D., Writing: F.O.

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A Predictive Model for the Risk of Infertility in Men Using Machine Learning Algorithms

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> ### What's known on the subject? and What does the study add?
>
> Machine learning is used for creating different predicion models in recent years. It is a technique that uses past experiences to improve their decisions without the need of human intervention. In our study different machine learning algorithms was used for building a prediction model for the risk of infertility in men.

Abstract

Objective: Infertility is a worldwide problem and causes considerable social, emotional and psychological stress between couples and among families. This study is aimed at determining the machine learning classifier capable of developing the most effective predictive model to determine the risk of infertility in men by genetic and external factors.

Materials and Methods: The dataset was collected at Ondokuz Mayıs University in the Department of Urology. The model was developed using supervised learning methods and by algorithms like decision tree, K nearest neighbor, Naive bayes, support vector machines, random forest and superlearner. Performances of the classifiers were assessed with the area under the curve.

Results: Results of the performance evaluation showed that support vector machines and superlearner algorithms had area under curve of 96% and 97% respectively and this performance outperformed the remaining classifier. According to the results for importance of variables sperm concentration, follicular stimulating hormone and luteinizing hormone and some genetic factors are the important risk factors for infertility.

Conclusion: These findings, whenever applied to any patient's record of infertility risk factors, can be used to predict the risk of infertility in men. The predictive model developed can be integrated into existing health information systems which can be used by urologists to predict patients' risk of infertility in real time.

Keywords: Classification, superlearner, prediction model, infertility, genetic factors

Introduction

The World Health Organization defines infertility as 12 months of frequent, unprotected intercourse without pregnancy (1). Infertility is a medical and social problem effect about 15% of couples and 40% of these couples are infertile because of male factor (2). Infertility is a worldwide problem and is estimated that only in Turkiye 10-15% couples are infertile (3). Male infertility is a highly heterogeneous disorder and genetic factors play an important role in male infertility. Karyotypic abnormalities, cystic fibrosis transmembrane conductance regulator gene mutations and microdeletions on the Y chromosome are well-known genetic causes of azospermic or severely oligozoospermic men (4,5). There are diverse external factors for infertility, including age, smoking, obesity etc. (3).

The prediction contains variables in the dataset to conduct analysis and find patterns, which describe the data structure that can be interpreted by humans (6). Machine learning is a fast-growing field, which explores how computers can automatically learn to recognize complex data structures and make a conclusion based on a set of observed data (7).

Nowadays, machine learning applications are a part of our daily lives in different areas, for example, web searches,

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spam/email filtering, face recognition programs, and speech recognition programs (8). Machine learning has been used for the classification of different medical data and these results show that the performance of this study was produced promising results for different data sets. However, gathering and inventorying of more complex data types, the discovery of new diseases, and the development of new diagnostic methods have raised the need for machine learning methods in the medical area, which provides new ways for interpreting the complex data sets that researchers faced (9,10).

Machine learning has been separated into different subfields that deal with different types of learning tasks. Supervised learning is the most common used in practice and can be grouped into classification and regression. There are many algorithms for classification tasks with an increasing number and different features day by day, some classification algorithms commonly used are decision trees (DT), K nearest neighbor (KNN), Naive Bayes (NB), support vector machines (SVM), random forest (RF) (11,12).

There are different algorithms which can be used in research. The main question is which algorithm will fit on your data well? For statistics and machine learning, ensemble methods use multiple learning algorithms to obtain better predictive performance than could be obtained from any learning algorithm. Superlearner (SL) allows researchers to use multiple algorithms to outperform a single algorithm in non-parametric statistical models. Therefore, there is no need to decide which single technique to use for prediction. Instead, there is a method to use several candidate learners together at different weights by incorporating cross-validation. Cross-validation is an important evaluation technique used to assess the generalization performance of a machine learning model (13-15).

This study focuses on diagnosing the risk factors for male infertility disease by machine learning algorithms. The present study aims to compare different machine learning classifiers with different training and testing proportions. Additionally, the results were used to compare SL algorithm and see the advantages of this algorithm.

Materials and Methods

In this study we provided informed consent form patients and Ethics approval was given by the Ondokuz Mayıs University Medical Research Ethical Committee (2017/208, issued June 22, 2017). The dataset for the study was collected from 587 infertile and 57 fertile patients between 2007-2018 and published partially in two separate studies (16,17). A total of eleven attributes (ten attributes and one class attribute), age, hormone analysis, follicular stimulating hormone (FSH) level, luteinizing hormone (LH) level, routine semen parameters, total

testosterone level, sperm concentration, and genetic variations. A total of five categorical and five numerical values are present in the data.

In the pre-processing step, the data set was checked for missing values. The attribute gr/gr+b2/b3 is dropped out from the analysis and for numerical data Z-score normalization is used to scale the data. First, 80% of the collected data was used to train the algorithms and the remaining 20% was used for testing the performances also these split ratios used in the study are 70-30% and 60-40%.

After removing the missing values, the final data set composed of 329 (85.5%) infertile and 56 (15.5%) fertile patients. We performed the classification using R, which is open-source statistical software. In the pre-processing step "Plyr" and "ggplot2" were used and analyses were carried out by "caret", "SL", "e071" and "part" packages for classification. A 10-fold cross-validation method was used to test the validity of the analysis.

Machine Learning Algorithms Used for Classification

This study focuses on six different machine learning algorithms that are DT, RF, NB, KNN, SVM and an ensemble method called SL.

1. Decision Tree

The algorithm uses a tree-like model, which starts at the root and builds the tree by choosing the most informative attribute at each step (18). The internal node and the root node are points with the name of the attribute; the sides are labeled by the most informative attribute values and a leaf node is displayed with different classes. The leaf corresponds to the decision outcomes (19). For attribute selection measures, the decision is chosen by the highest gain ratio. The training data set is used while creating DT with the C4.5 algorithm. For each node in the tree, the class that divides the sample into the best subsets is determined and this is the highest gain ratio. For continuous variables, this algorithm can be used as well (20). The rpart (recursive partitioning and regression trees) package is used for classification trees (21).

2. Random Forest

This algorithm is a type of ensemble learning that uses a combination of tree estimators. The principle is random sampling by building sub-trees and random subsets of features considered when splitting nodes. The samples are drawn by replacement, which is known as bootstrapping and the final model is the majority vote from the creating trees in the forest (22).

From the original dataset set, a sample of N is drawn to construct each tree. When the attributes have been selected, the algorithm forms a repetitive partitioning of the covariates.

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The best split is chosen as the one optimizing the classification and regression tree [CART (Classification and Regression Tree)] splitting criterion, which is the gini index along with the mtry preselected directions (23). This process is repeated until each branch contains less than a pre-specified number of node sizes of observations. After this step, the prediction at a new point is computed by averaging observations falling into the branch of the new point. Each M tree gives a prediction, which is simply the majority class of the M predicted three (22).

3. Naive Bayes

The NB classifier is based on applying bayesian theorem. A probabilistic model estimates the conditional probabilities of the dependent variable from the training data and uses them for classification. This classifier assumes that the attributes are independent between the features and are equally important (24). This classifier predicts the class membership probability of examples by using the naive conditional independence assumption (25). The Bayesian generalized linear model (bglm) is a Bayesian function for generalized linear modeling by different distributions (26).

4. K Nearest-neighbor

This classifier is a method on learning by comparing a given test data set with a training data set, which resembles it. Here the samples of training data set are defined by n attributes, where each example indicates a point in n-dimensional space. This algorithm searches for the K training data samples nearest to the unknown example (7).

The performance of a KNN classifier depends on the choice of K and the distance metric. Without foreknowledge, this classifier applies Euclidean distances as the measurement of the closeness between examples. As in other classifiers majority vote assign the class label (27). Usually, the K parameter in the classifier is chosen experimentally. For each model, different numbers of nearest neighbors are chosen and the parameter with the best accuracy is given to define the classifier (28).

5. Support Vector Machine

This algorithm is mostly used for classifying linear and non-linear patterns. Linear patterns can be easily separated in low dimensions, whereas non-linear patterns can't be easily separated. For this task, a set of mathematical functions known as kernels is used. The basic idea for SVM is the use of an optimal hyperplane, which can be used for classification, to solve linearly separable patterns. The optimal hyperplane is selected from the set of hyperplanes for classifying patterns that maximize the margin of the hyperplane. That is the distance from the hyperplane to the closest point of each pattern by maximizing the margin it can correctly classify the given patterns (29).

For non-linear separable patterns, the kernel functions return the inner product between two points in a higher feature space. The training occurs in the feature space, and the data points just appear inside the dot products with other points. This is called the "kernel trick," where the non-linear pattern becomes linearly separable (30). The kernel function converts the data into the desired format and for this different kernel is used for non-linear patterns (31).

6. Superlearner

This algorithm is a cross-validation based method, which chooses one or weight of more optimal learners that perform asymptotically as well or better than any candidate learner. This prediction algorithm, which applies a set of candidate learners to the observed data, can include as many candidate learners to the model if computationally feasible (13,14). Different algorithms can be adapted to SL algorithm such as RF, SVM, NB (14).

The training set trains the estimators and the validation set estimates the performance of these estimators. The cross-validation selector selects the best performance for the learner on the validation set for the SL algorithm. In v-fold cross-validation, the training set is divided into v mutual sets of as nearly equal size. The v set and its complementary validation and training sample give v split the learning sample into training and corresponding validation sample. For every v split, the predictor is applied to the training set, and its risk is estimated by the corresponding validation set. Each learner, risks, and the validation set are averaged, resulting in cross-validated risk. The predictor is selected by the minimum cross-validated risk. The calculated risk is a measure of performance and the model getting minimized risk is the model with the minimum errors in prediction. This algorithm provides a weighted model using candidate learners. If the model is obtained with a single learner, this gives the discrete SL algorithm. There is no limitation for candidate learners, which is the main advantage of this algorithm (15).

Performance Evaluation

The performance of the algorithms selected for the study is evaluated using area under curve (AUC). The reason is to find common criteria to compare the performances of all algorithms. AUC measure the entire area under the receiver operating characteristic (ROC) curve. The ROC curve is a graph showing the performance of a classification model at all classification thresholds (32). Also, the performance metric which can be adopted by the confusion matrix like accuracy, sensitivity and specificity values have been evaluated for the algorithms (33).

Accuracy= (TP+TN)/(TP+FP+FN+TN)x100 (1)

Sensitivity= TP/(TP+FN)x100s (2)

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Specificity= TN/(FP+TN)x100 (3)

In the equations, TP defines the number of true positives; FN defines the number of false negatives; TN defines the number of true negatives; the last is FP, which defines the number of false positives (34).

Statistical Analysis

The genetic data for the diagnosis of infertility was evaluated in terms of supervised machine learning algorithms. The C4.5, KNN, NB, SVM and RF algorithms were used as classifiers and compared with the SL algorithm according to the AUC performance criteria. The C4.5 decision tree algorithm was implemented using the J48 decision tree algorithm, KNN algorithm was implemented using Euclidean distance, NB algorithm was implemented using the NB classifier, the SVM algorithm was implemented using radial basis kernel, RF algorithm was implemented using bootstrapping while SL algorithm was implemented using different weights simultaneously all available on R program. The models were trained for different split ratios and 10-fold cross-validation was used.

Results

All classifiers and different split ratios of the overall performance of the dataset are shown in Table 1. The split ratio of 80-20% using the RF algorithm showed better accuracy among all other classifiers whereas SVM showing an AUC of 95% that is the best classifier. The split ratio of 70-30% using SVM showed a performance of 95% whereas the split ratio of 60-40% using RF showed a performance of 94% among all other classifiers. The results of sensitivity and specificity show a good performance for all different proportions as well.

According to these results in Figure 1, showing the importance of variables after analysing the data set. Here the first line is sperm concentration following by FSH and LH hormones in the line. Genetic factors sy1291, gr/gr2 and b2/b3 are the important genetic factors according to these findings.

Using the SL algorithm, the predictive model developed using the risks of different algorithms and coefficients yielded an AUC of 96% following by discrete SL and RF with an AUC of 95%. The coefficient is how much weight SL put on that model in the weighted-average. The lowest risk is yield by RF given below in Table 2. As seen from the table, bglm will not give any contribution to the analysed model. The weighted model consists of RF, KNN and rpart. Therefore, SL performed as the best algorithm as AUC 97% (Table 3). These performance is discrete SL and RF at AUC 96%, respectively.

Discussion

In this study, a machine learning-based prediction model for infertility in men was developed based on genetic data. This study demonstrated that the RF algorithm has higher accuracy than the NB, SVM, DT and KNN algorithms, irrespective of different split ratios. According to the results, it was discovered that different split ratios can change the classifier used for analysis. The accuracy was highest for RF for a split ratio of 80-20% whereas the NB classifier showed a poor accuracy of 89%. In a study by Noi and Kappas (35) it was shown that the larger the training sample size, the higher the accuracy. Our findings support this result too, where they obtained 90-95% accuracy for analyzing different data sizes and split ratios for balanced and unbalanced data sets in their studies. The highest

Table 1. Performance metrics for infertility data set

Split ratio	Performance metrics	Infertility data set				
		C4.5	KNN	NB	SVM	RF
80-20%	Accuracy	0.9342	0.9079	0.8947	0.9342	0.9605*
	Sensitivity	0.9385	0.9385	0.8923	0.9692	0.9846
	Specificity	0.9091	0.7273	0.9091	0.7273	0.8182
	AUC	0.9244	0.9069	0.8727	0.9594*	0.9209
70-30%	Accuracy	0.9123	0.9035	0.8596	0.9561*	0.9386
	Sensitivity	0.9082	0.9388	0.8469	0.9694	0.9694
	Specificity	0.9375	0.6875	0.9375	0.8750	0.7500
	AUC	0.9237	0.9435	0.8903	0.9534*	0.9298
60-40%	Accuracy	0.8954	0.8824	0.8889	0.8889	0.9346*
	Sensitivity	0.8855	0.9313	0.8779	0.9618	0.9695
	Specificity	0.9545	0.5909	0.9545	0.4545	0.7273
	AUC	0.9200	0.9221	0.9302	0.9323	0.9458*

*The best performance of the model, according to these results, KNN: K nearest neighbor, AUC: Area under curve, NB: Naive Bayes, SVM: Support vector machines, RF: Random forest

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performance is adopted by SVM, RF and KNN for the split ratio of 60-40%. The results of our dataset showed that the highest performance was obtained by SVM using RBF as kernels and RF classifiers that supports findings in literature (36). In conformity with the results obtained the performance is increased using RF algorithm for the genetic data set. RF is an important algorithm for medical data sets (37,38). One of the biggest problems in machine learning is which algorithm to use and the ideal split ratio for training and testing data. This study answers these questions by using different classifiers that compared with the SL algorithm that applies weighted candidate learners to the model.

The SL algorithm picks one or more optimal learners, which are called candidate learners, to build the algorithm. RF algorithm is a candidate learner, which puts the biggest weight because
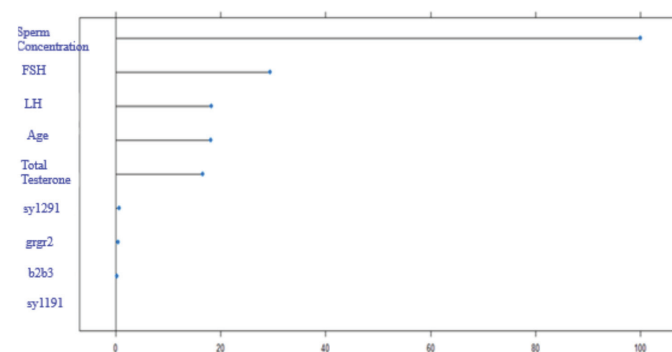
Figure 1. The importance of variables for infertility data set

FSH: Follicular stimulating hormone, LH: Luteinizing hormone

Table 2. Risk and coefficient results for superlearner		
	Infertility data set	
	Risk	Coefficient
SL.RF_All	0.0589*	0.5810*
SL.KNN_All	0.0625	0.2327
SL.bglm_All	0.0788	0.0000
SL.SVM_All	-	-
SL.rpart_All	0.0613	0.1862
*Minimum risk and Coefficient		

Table 3. The area under curve results for superlearner	
	Infertility data set
SL	0.9653*
Discrete SL	0.9597
SL.RF_All	0.9597
SL.KNN_All	0.9321
SL.bglm_All	0.9465
SL.SVM_All	-
SL.rpart_All	0.9304
*The best performance of the model	

of the lowest risk in the model for the SL algorithm. KNN and rpart put the next important weights in the model as candidate learners. According to these findings, the best performance is obtained by the SL algorithm of 97% AUC. In a previous study by van der Laan et al. (15), different candidate learners like RF, least squares method, least angle regression and delete/change/addition set to the model for the diabetes dataset set and the smallest risk was obtained by delete/change/addition.

The variable importance analyses show that the sperm concentration is the most important variable. The Polymorphism genes are, respectively, in order of sy1291, gr/gr, and b2/b3. As a matter of fact, in reference by Kumar and Singh (39), it is stated that the important factor for infertility is due to semen parameter values not within normal limits. Information on the importance of variables and because of infertility data analysis the results support the literature. For example, Hicks et al. (40), a male infertility prediction study, used sperm videos. As mentioned, sperm parameters play an important role in infertility. The reported algorithms used in this study are simple linear regression, RFs, Gaussian process, sequential minimal optimization regression, elastic net, and random trees. Here, the error rate for RF is different compared to the other mentioned algorithms. RF algorithm is a an ensemble learning algorithm in which multiple models are combined to solve a particular problem (41).

One in six couples worldwide experiences infertility (42). It has been reported that the emotional status of couples who apply to a physician with infertility is deteriorates, and their susceptibility to depression increases (42). About a quarter of couples cannot continue their infertility treatments due to the burden of treatment (43). We think that the prediction of infertility, which has a complex nature and affects many areas such as the emotional conditions of couples, other health problems and the health system expenditures of the states, is of great importance for clinicians. Therefore, the development of models with high predictive ability will also improve clinical approaches for infertility treatment. These study findings, whenever applied to any patient's record of infertility risk factors, can be used to predict the risk of infertility in men. The predictive model developed can be integrated into existing health information systems which can be used by urologists to predict patients' risk of infertility in real time.

Conclusion

The results of the study show that different split ratios affect the performance also it can change the algorithm that be used. The SL algorithm is a weighted model that consists of different candidate learners. According to the results, the algorithm with the highest performance and minimum risk are linked to each other.

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A researcher builds a model, by using different algorithms while different classifiers show different performances. However, there are too many algorithms in the literature. Choosing the best algorithm requires time and expertise. At this stage, SL is an important tool and recommended for achieving high performance and as a guide to the researcher. In this study, the model was obtained using five candidate learners and their performances were compared. SL gives the researcher time and expertise in solving data sets. However, different models can be established by evaluating different algorithms. In later studies, it is planned to conduct studies by trying combinations of different algorithms and using bigger sample data sizes. Simulation finding could be a good study to conduct.

Ethics

Ethics Committee Approval: In this study we provided informed consent form patients and Ethics approval was given by the Ondokuz Mayıs University Medical Research Ethical Committee (2017/208, issued June 22, 2017).

Informed Consent: In this study we provided informed consent form patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Relationship of Seminal Plasma Anti-Müllerian Hormone Concentration with Sperm Morphology and Sperm DNA Damage

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

Recent investigations have demonstrated that seminal plasma anti-Müllerian hormone (AMH) was associated with sperm count and motility. There was no relation between both semen and blood AMH levels and Kruger morphology and sperm DNA breaks. Observing high numbers of TUNEL-positive sperm in groups, including the normozoospermic group, points to the importance of detecting DNA breaks in idiopathic infertility cases. Both DNA fragmentation testing and conventional semen analysis can be used together for the evaluation of male fertility potential.

Abstract

Objective: This study examines the relationship between seminal plasma anti-Müllerian hormone (AMH) levels and sperm morphology and sperm DNA fragmentation.

Materials and Methods: Semen and blood samples were obtained from volunteers. There were four patient groups that are normozoospermia (n=46), oligoasthenoteratozoospermia (n=18), azoospermia (n=19) and teratozoospermia (n=68), based on semen analysis results. Serum follicle-stimulating hormone, luteinizing hormone, testosterone, serum and seminal plasma AMH levels were measured. DNA fragmentation of sperm was assessed by the TdT-mediated dUTP nick-end labeling (TUNEL) test.

Results: Azoospermic group showed the highest blood AMH levels. The seminal AMH level of normozoospermic patients was found to be significantly lower compared to the oligoasthenoteratozoospermia group. No significant associations between seminal AMH, sperm morphology, and sperm DNA damage were observed. No significant difference was observed among the groups regarding sperm DNA fragmentation.

Conclusion: A large number of TUNEL-positive cells in normozoospermic patients demonstrates that DNA damage of sperm may also occur in normal sperm parameters individuals. The measurement of serum and seminal AMH levels does not provide any additional benefit during the evaluation of male infertility.

Keywords: Sperm, seminal plasma, anti-müllerian hormone, TUNEL

Introduction

Infertility affects about a quarter of couples in the world (1). The male-originated factors lead to half of the cases (1). Additionally, 50% of the causes of male infertility are still not entirely determined (2). Low fertility can be detected in men, even with normal semen parameters (3). Even though sperm parameters are normal, 15.5% of men may have idiopathic infertility (4).

Anti-Müllerian hormone (AMH) is a routinely used test since it indicates ovarian oocyte reserve in women and has been proven to be associated with various diseases. AMH is thought to play a role in spermatogenesis in which there is a direct link to the AMH type 2 receptor, which shows both autocrine and

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paracrine properties. AMH has been advised as a distinct and indirect marker for Sertoli cell function and spermatogenesis, respectively (5). Several studies have determined an association between AMH and sperm motility in men (6,7). But Aksglaede et al. (5) showed that AMH was not an accurate marker for evaluating semen quality (5).

Sperm cells are part of the important elements that transfer their genetic material to future generations. Although sperm cells have normal morphology and motility, DNA damage could occur. The known cause of DNA damage in spermatozoa is unresolved DNA nicks resistant to resolution in the remodeling of chromatin formed during spermatogenesis. Researched factors that cause DNA damage to spermatozoa are; programmed cell death, which is for eliminating defective germ cells, poor or atypical chromatin packaging, and lastly, oxidative stress due to the overproduction of reactive oxygen species (ROS) by infections, advanced paternal age, scrotal heat stress, exposure to xenobiotics or radiation, and so on (8). The DNA damage of sperm is generally measured by the TdT-mediated dUTP nick-end labeling (TUNEL) method, single-cell gel electrophoresis (Comet assay) and sperm chromatin structure assay (9). TUNEL assay is an important test that is used to detect DNA damage induced by ROS and unsuccessful apoptosis (3). The breaking of sperm DNA strand occurs in each ejaculate, and ROS can also induce these breaks. A high rate of damaged DNA was determined in the infertile patient's spermatozoa's cells with the TUNEL method, and significant low pregnancy rates were found in these patients (10).

Although seminal plasma AMH and its relationship with sperm count and motility were examined in previous studiesto the best of our knowledge, the association of seminal AMH with sperm morphology has been investigated to the healthy men. Therefore, we studied the possible relationship between serum and seminal AMH with sperm parameters, sperm morphology, and sperm DNA damage in men.

Materials and Methods

Study Population

This cross-sectional study was conducted by the Pamukkale University Local Clinical Research Ethics Committee (approval number: 60116787-020/8324). Two hundred four volunteer patients attended the study, and their semen and blood samples were collected between 26.07.2018-12.07.2019. Semen samples were examined. According to the results of semen analysis, the patients were classified into four groups that were teratozoospermia (n=68), normozoospermia (n=46), azoospermia (n=19) and oligoasthenoteratozoospermia (n=18). Patients with a history of cryptorchidism, chemotherapy, and cancer treatment (n=5), oligoteratozoospermia (n=14), asthenoteratozoospermia (n=21), oligozoospermia (n=10) were excluded from the study (Figure 1).

Semen Analysis

After 3-5 days of sexual abstinence, semen samples were obtained from the masturbation method. According to WHO 2010 guidelines, semen volume, total sperm count, the percentage of spermatozoa with rapid progressive motility, vitality, and percentage of normal spermatozoa were analyzed, as indicated volume ≥1.5 mL, concentration ≥15 million/mL, total count ≥39 million, progressive motility ≥32%, viability ≥58%, and normal morphology >4% (11). After the incubation period, the semen sample that became suitable for counting was dropped in the sperm counting chamber (Makler, Israel), and the sperms were counted using a phase-contrast microscope (Labomed, CXL, USA) for 100 fields under 40X magnification. The Preparing Semen Smears were stained the Diff-Quik method for Kruger morphology The slides were counted using a light microscope at 100X magnification. In each slide, 400 sperm cells were inspected, and the amount of normal, head, midpiece, and tail abnormalities were analyzed (Figure 2).
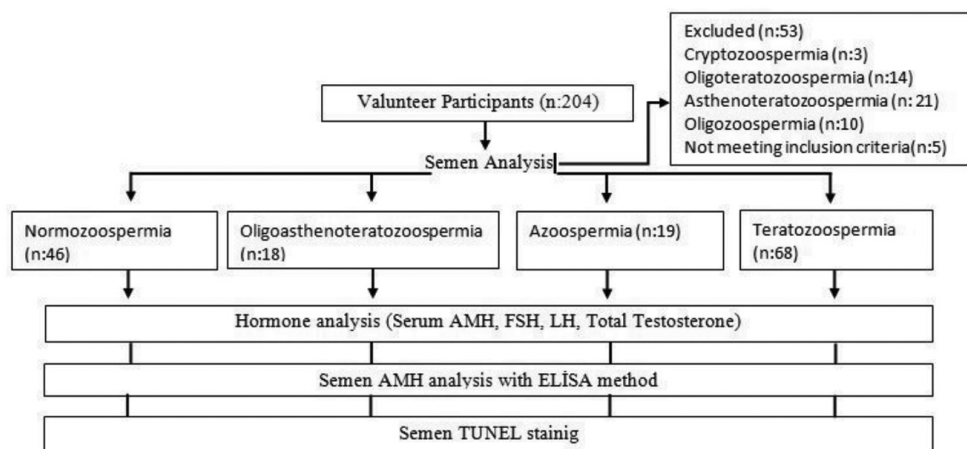

Figure 1. Flow chart of the overall experimental design

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Hormone Analysis

Blood samples were collected between 8 and 10 am and centrifuged at 24 °C for 10 min at 1000 g. Semen samples were centrifuged at 1000 g for 20 min, and the seminal plasma was removed from the cell component. The total testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and were interpreted in the Hormone Laboratory, Pamukkale University Hospital. Serum and semen AMH was measured using ELISA commercial kit (Elabscience, E-EL-HO317, USA) according to the manufacturer's instructions. Provided the micro ELISA plate in this kit has already been pre-coated with an antibody specific to Human AMH. Standards and samples were combined into appropriate micro ELISA plate wells and added with the specific antibody. Later incubated each microplate well was contained Avidin-Horseradish Peroxidase conjugate and biotinylated detection antibodies specific for Human AMH. The Substrate Reagent was added to each well, only those wells that contain Human AMH, biotinylated detection antibody. Adding stop solution was used to terminate the enzyme-substrate reaction. The spectrophotometry was employed todetermine the optical density at a wavelength of 450 nm.

TUNEL Assay

The TUNEL assay was used to determine apoptosis-related DNA strand breaks in spermatozoa, using the BIOTnA TUNEL Apoptosis Assay Kit (Biotna Biotech, 0160TA3081, TAIWAN). Briefly, one droplet of the liquefied sperm sample was air-dried onto a poly-lysine-coated glass slides, fixed with 4% paraformaldehyde. The cells were dehydrated by passing through an increasing alcohol series. The glass slides were stored at 4 °C. After storage, slides were rehydrated through a decreasing alcohol series. The cell slides were covered with sufficient drops of 3% Hydrogen Peroxide Block and were incubated for 5 min. The slides were first permeabilized with 0.2% Triton X-100 in PBS-Tween for 30 min. The slides were incubated with proteinase K for 15 min, then incubated in TdT Reaction Mixture for 1 h at 37 °C to allow DNA elongation. After stopping the enzyme-reaction, the DNA elongation was revealed by incubation of the cells with an anti-digoxigenin antibody coupled to peroxidase for 30 min. The peroxidase was revealed with diaminobenzidine. The sperm nuclei were counterstained with hematoxylin. slides were followed under a light microscope. On each slide, 200 cells were counted. Sperms with brown nuclei were evaluated as TUNEL positive. The apoptotic index was calculated by the following formula: Apoptotic index: (positive cells x 100)/total number of cells.

Statistical Analysis

Continuous variables are given as mean ± standard deviation, and categorical variables are represented as numbers and percentages. Shapiro-Wilk test was used for the data relevance to a normal distribution. When parametric test assumptions were provided one-way variance analysis was used; when parametric test assumptions were not provided, Kruskal-Wallis variance analysis was used to compare independent group differences. The relationships between the continuous variables were analyzed by Spearman correlation analysis, and the differences between categorical variables were examined with the chi-square test. P<0.05 value was evaluated as statistically significant.
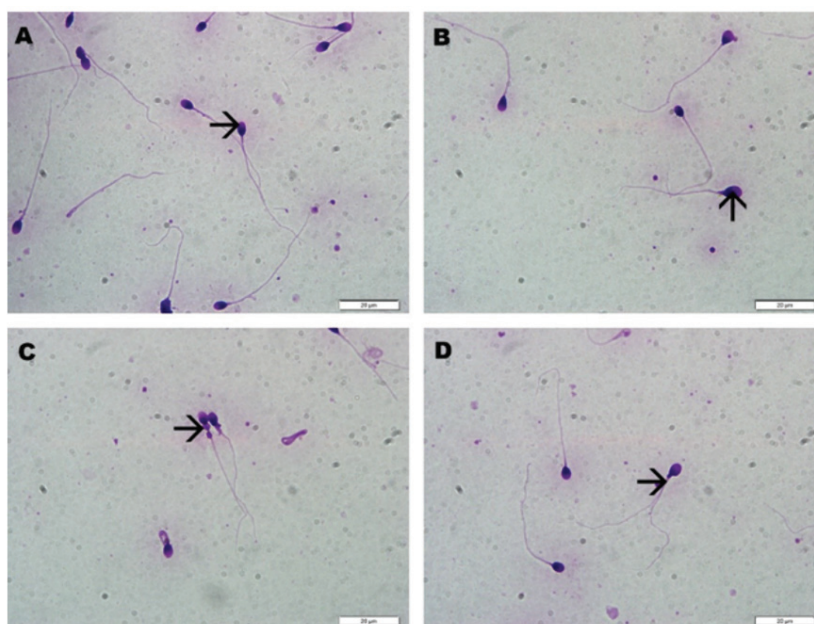
Figure 2. Morphological characteristics under light microscope A) Normal morfologia (arrow), B) Head anomaly (arrow), C) Midpiece Defect (arrow), D) Tail anomaly (arrow). Diff-Quick staining 100X

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Results

Sperm Parameters

All groups of semen characteristics can be seen in Table 1. Semen volume was detected to be significantly lower in the azoospermia group than in the normozoospermic group (p=0.0001). The concentration was significantly higher in the normozoospermic group compared to other groups (p=0.0001). A statistically significant difference was observed between the total sperm count, total motile sperm count, total progressively motile sperm count (p=0.0001). Total motile sperm count and total progressively motile sperm count was statistically higher in the normozoospermic group than in the other groups. No significant difference was found between the normozoospermic, oligoasthenoteratozoospermic and teratozoospermic groups in the number of non-progressive motile sperm. The ratios of immobile sperm were significantly different between the groups. The rate of immobile sperm was significantly in the oligoastenoteratozoospermic group and is followed by the teratozoospermic group. When the normozoospermic group was compared with the other groups, the rate of immobile sperm was found to be significantly lower (p=0.0001). In the evaluation of Kruger morphology, the head anomaly was found to be the highest in the teratozoospermic group (90.68±5.13) and then in the oligoastenoteratozoospermic and normozoospermic groups (89.39±22.51), (82.1±6.37), respectively. A statistically significant difference was observed in the results (p=0.0001) (Table 2).

Hormone Analysis Results

FSH levels were significantly higher in the azoospermic group (18.55±17.5) U/L compared with the normozoospermic group (4.45±2.3) U/L (p=0.001) (Table 3). The FSH level of the oligoasthenoteratozoospermic group (8.51±6.07) U/L was detected as higher than the teratozoospermic group (4.42±3.78) U/L (Table 3). LH levels were significantly higher in the azoospermia group (8.51±6.07) U/L, compared to normozoospermic (5.19±2.06) U/L and teratozoospermic (5.47±2.43) U/L groups (Table 3). In the azoospermic group, a positive correlation was found between the high blood AMH level (955.1±1300.89) pg/mL and the blood FSH (8.51±6.07) U/L, (r=0.845, p=0.000) and LH (11.57±8.89) U/L, levels (r=0.701, p=0.001) (Table 3). Comparison of testosterone levels among the groups showed no significant difference (Table 3). The blood AMH level was highest in the azoospermia group (955.1±1300.89) pg/mL (Table 3). The study showed that the blood AMH level was lower in the teratozoospermic group (522.47±1003.22) pg/mL than the oligoteratoasthenozoospermic group (681.38±703.74) pg/mL (Table 3) (Figure 3).

Table 1. Comparison of semen parameters among four groups in study population (n=151)

	Normozoospermia		Oligoasthenoteratozoospermia		Azoospermia		Teratozoospermia		p
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Semen volume (mL)	3.83±1.56	3.5 (1.5-10.2)	3.2±1.7	2.85 (1.4-7.4)	2.02±1.35	2 (001-4.5)	3.38±1.66	3 (0.7-9.7)	0.0001*
Sperm concentration (10⁶/mL)	98.22±48.2	91.5 (24-265)	3.97±2.88	3.55 (0.1-12.5)	0±0	0 (0-0)	71.6±48.02	61.5 (0.01-230)	0.0001*
Total sperm count (10⁶)	343.74±156.35	294.5 (84-840)	11.18±7.49	11.4 (0.37-30)	0±0	0 (0-0)	221.75±160.94	183.5 (0.02-722)	0.0001*
Total motile (%)	71.26±11.02	73 (46-91)	33.06±9.25	37 (14-43)	0±0	0 (0-0)	66.24±10.61	65 (45-88)	0.0001*
Sperm count (10⁶)	238.59±106.54	217 (54-609)	3.69±2.53	3.75 (0.05-8.8)	0±0	0 (0-0)	150.96±123.15	120 (22-554)	0.0001*
Total progressively motile sperm count (10⁶)	210.59±106.72	186 (42-546)	2.18±1.39	2.05 (0.03-4.8)	0±0	0 (0-0)	128.95±111.7	102 (18-504)	0.0001*
Progressively motile (%)	61.74±12.29	62 (34-86)	20.11±6.9	21 (8-31)	0±0	0 (0-0)	54.13±12.26	53 (32-80)	0.0001*
Non-progressively motile (%)	11.11±8.95	10 (3-64)	12.89±4.48	13.5 (4-22)	0±0	0 (0-0)	12.09±4.95	11 (4-26)	0.0001*

SD: Standard deviation, significance level*: p-value <0.05

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There was also a significant difference in seminal AMH (pg/mL) levels between the groups (p=0.043) (Figure 4). Among the groups, normozoospermic patientswith seminal AMH levels were significantly lower than the oligoasthenoteratozoospermic group. There was no correlation between the blood and seminal AMH levels of the groups (p>0.05) (Table 3). In azoospermic patients, it was found that as the sperm volume increased, the semen AMH level also increased (r=0.658, p=0.006).

Analysis of DNA Damage

TUNEL results were similar among the groups. (Table 3) (Figures 5, 6). While there was a negative correlation (r=-0.337, p=0.016) between the head anomaly rate of Kruger morphology and the presence of TUNEL-negative cells in teratozoospermic patients, a positive correlation was found between the neck and tail anomaly (r=0.323, p=0.021, r=0.297, p=0.035, respectively) (Figure 5).

Discussion

In this study, there was no relationship between both semen and blood AMH levels and Kruger morphology and sperm DNA breaks. The presence of TUNEL-positive cells in all groups indicates the existence of DNA breaks.

Andersen et al. (7) found that individuals have very different AMH levels in seminal plasma from each other, and they suggested that seminal plasma AMH might be used as a marker for sperm production, but the predictive value gap is limited (7). Serum AMH levels are useful clinic parameters for infants and children in predicting testicular function (12). Because AMH is present in just mature Sertoli cells, it may be a marker for semen quality (7). It was reported that subfertile men have low levels of AMH compared with normal men (13-15). However, other studies didn't show consistent data for this association (16,17). Aksglaede et al. (5) showed that AMH concentration

Figure 3. Comparison of blood AMH values between groups. Blood AMH levels of teratozoospermia patients were significantly lower than oligoastenothetospermia group. Significance level*: p<0.05

AMH: Anti-Müllerian hormone
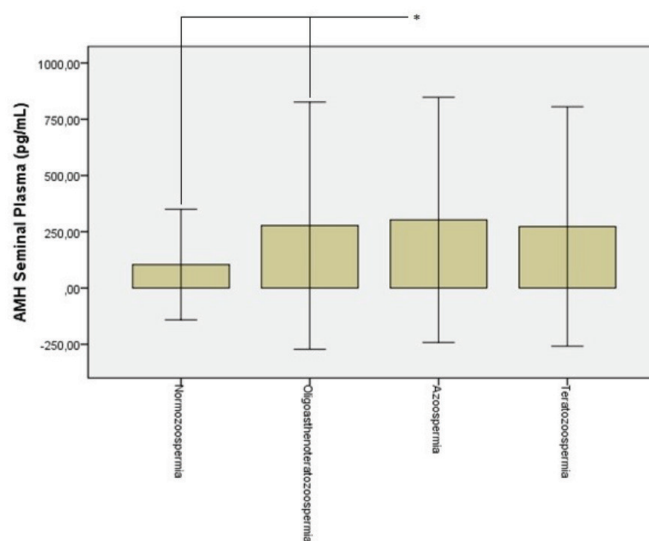
Figure 4. Comparison of semen AMH values between groups. Semen AMH levels of normozoospermic patients were significantly lower than oligoasthenoteratozoospermia group. Significance level*: p<0.05

AMH: Anti-Müllerian hormone

Table 2. Comparison of normal, head, neck and tail anomalies according to Kruger criteria between groups								
	Normozoospermia		Oligoasthenoteratozoospermia		Azoospermia		Teratozoospermia		
	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	p
Normal morfologia (%)	4.63±0.83	4 (4–7)	0.76±0.83	1 (0–3)	0±0	0 (0–0)	2.16±1.05	3 (0–3)	0.0001*
Head anomalies (%)	82.15±6.37	82 (58–92)	89.39±22.51	96 (0–98)	0±0	0 (0–0)	90.68±5.13	92 (72–100)	0.0001*
Midpiece defects (%)	8.3±3.27	8.5 (3–20)	2.76±1.68	2 (1–6)	0±0	0 (0–0)	4.5±2.49	4 (0–15)	0.0001*
Tail defects (%)	4.93±3.84	4 (1–25)	1.82±1.13	1 (1–4)	0±0	0 (0–0)	2.71±2.93	2 (0–16)	0.0001*
SD: Standard deviation, significance level*: p-value <0.05								

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Table 3. Comparison of FSH, LH, testosterone, AMH and TUNEL values between groups

	Normozoospermia		Oligoasthenoteratozoospermia		Azoospermia		Teratozoospermia		p
	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	
FSH (U/L)	4.45±2.3	4.08 (0–11.02)	8.51±6.07	6.63 (1.28–25.57)	18.55±17.5	14.6 (0.42–62.5)	4.42±3.78	3.69 (0.86–28.83)	0.0001*
LH (U/L)	5.19±2.06	5.3 (0–11.65)	6.48±4.33	6.29 (0.1–19.14)	11.57±8.98	10.08 (0.69–34.39)	5.47±2.43	5.16 (0.1–17.12)	0.001*
Total testosterone (ug/L)	4.1±1.72	4.19 (0–8.49)	4.08±2.07	3.92 (0.1–8.94)	3.3±1.74	3.35 (0.11–8.22)	4.53±1.8	4.2 (1.24–10.31)	0.072
AMH serum (pg/mL)	525.15±849.85	236.8 (24.45–3552)	681.38±703.74	457.3 (0.58–2743)	955.1±1300.89	487.25 (8.44–4879)	522.47±1003.22	126.6 (1.46–4402)	0.018*
AMH seminal plasma (pg/mL)	104.11±245.65	36.11 (0–1522)	277.13±549.45	79.27 (0–2027)	302.76±544.92	57.68 (11.38–2075)	273.07±532.12	50.55 (7.15–2209)	0.043*
TUNEL (AI %)	26.26±21.87	21 (1–94)	22.29±16.84	18.5 (2–66)	-	-	18.98±17.82	12 (1–68)	0.163

SD: Standard deviation, significance level*: p-value <0.05

in serum could not associate the concentration of sperm, healthy males sperm motility, total sperm count, and they argued that the WHO criteria are still the gold standard method for evaluating semen quality (5). In our study, the azoospermic group showed the highest blood AMH levels. When the groups were compared within themselves, blood AMH highs were found undoubtedly lower in the teratozoospermic group in contrast to the oligotretoasthenozoospermic group. Considering these data, we consider that blood AMH checking in male patients may be misleading for evaluating infertility.

Small-scale studies showed a positive correlation between the AHM of seminal plasma and the concentration of sperm (6,18,19), but this correlation was not supported by other studies (13-20). Actually, opposite results were shown in terms of seminal AMH and the motility of sperm (19,20).

It appears that apoptosis in Sertoli and germ cells is regulated differently in the testis. While FSH deprivation-elevated DNA fragmentation without any effect on caspase activity, it had no impact on Sertoli cells (21).

Against these results, FSH levels in the oligoasthenoteratozoospermic group were significantly higher than those in the teratozoospermic group in the present study. LH levels were significantly higher in the azoospermia group compared to normozoospermic and teratozoospermic groups. The testosterone retraction in the testis is a reason for caspase activity and DNA fragmentation in Sertoli cells; however, it does not show any effect in germ cells (21). Related to this information, we found no significant difference between groups for testosterone levels in our study.

Duvilla et al. (22) showed that the seminal AMH mean value was calculated as 97.08 (±135.15) pmol/L in patients with normal parameters, 62.02 (±93.33) pmol/L in oligozoospermia patients, 13.12 (±31.94) pmol/L (n=67) in azoospermia patients (22). Kang-sheng et al. (23) studies focused on comparing of the AMH level of serum and seminal via FSH, LH, testosterone, and prolactin serum levels in infertile and fertile male groups. A positive
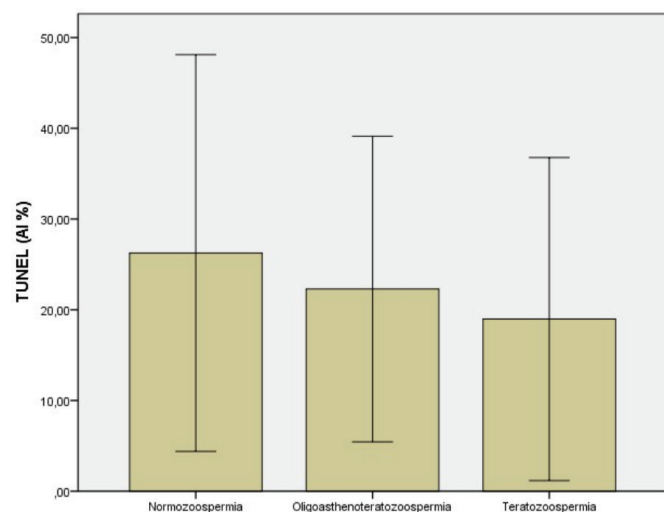
Figure 5. Comparison of sperm DNA fragmentation in normozoospermia (n=46), Oligoasthenoteratozoospermia (n=18) and teratozoospermia (n=68). Significance level*: p<0.05

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correlation was shown the AMH level with sperm motility, class A sperm ratio, and sperm viability (p<0.05); however, it was not correlated with the sexual hormone level (p>0.05) (23). Contrary to this study, seminal plasma AMH concentration was very low in normozoospermic patients. We found that semen AMH levels were significantly lower in the normozoospermic patients than the oligoasthenoteratozoospermic group. We determined that as the sperm parameters improved, semen AMH levels decreased.

AMH promotes early-stage sperm maturation. Spermatogenesis is a consecutive process of cell maturation and differentiation. This hormonedependent process is regulated by a hypothalamic-pituitary-gonadal axis. Hormones in this process are the mixture of gonadotropin (GnRH) released from the hypothalamus, FSH and LH secreted from the pituitary gland, and T secreted by interstitial cells. Instead of directly interacting with spermatogenetic cells, FSH and T first bind to receptors on Sertoli cells, then feed the spermatogenic cells through a paracrine system. AMH secreted by Sertoli cells is seen in seminal plasma, but rarely passes through the blood-testis barrier. Therefore, the level of AMH in seminal plasma is much higher than that in serum. According to Kang-sheng et al. (23) the level of seminal AMH was higher than the level of serum AMH (p<0.01), and they announced that seminal AMH and serum AMH has not correlated (r=0.026, p>0.05) (23). Our study showed that there was a lower concentration of serum AMH levels compared with semen AMH levels. A correlation could not show blood and semen AMH levels in any group in accordance with that of the Kang-sheng et al. (23) (p>0.05).

To analyze the integrity of sperm DNA, a more objective marker of sperm function is recommended, unlike standard sperm parameters such as sperm motility (24,25). The high DNA fragmentation that we found in our study, even in normozoospermic patients, proves this recommendation. While our research shows a negative equation (r=-0.337, p=0.016) between the head anomaly rate of Kruger morphology and the presence of TUNEL-positive cells in teratozoospermic patients,

a positive correlation was found between the neck and tail anomaly rates. These data showed us that DNA damage is inversely related to sperm morphology.

In a study conducted on 40 asthenozoospermic and 40 normozoospermic patients, sperm samples were analyzed. TUNEL-positive and motile sperm counts showed an inverse correlation (26). Irvine et al. (27) showed that ROS could trigger the breaking of sperm DNA strands, and this happens in each ejaculate. Henkel et al. (10) examined DNA fragmentation of semen samples taken from the IVF program. A significant correlation was found between the motile sperm count and TUNEL staining. Furthermore, they observed a low pregnancy rate in patients with high DNA fragmentation. Although, a direct correlation could not determine among the TUNEL-positive spermatozoa percentage and pregnancy or fertilization rate, patients with a high percentage of TUNEL-positive spermatozoa were found to have a lower pregnancy rate compared to patients with a low percentage (10). Unlike these studies, a significant difference between the groups regarding DNA fragmentation was not observed in our study. Saleh et al. (28) investigated and compared the DNA fragmentation indices of patients with normal and abnormal sperm parameters. They found that the index of DNA fragmentation was significantly surplus in infertile men who had normal sperm parameters (28). TUNEL positivity was found to be high in normozoospermic patients in our study; thus, our research also supports this study.

Study Limitations

Serum and semen AMH levels are affected by BMI. The limitation of our study is that the BMI values of the patients cannot be determined.

Conclusion

In conclusion, we did not find the possible relationship between blood and seminal AMH levels and sperm parameters.
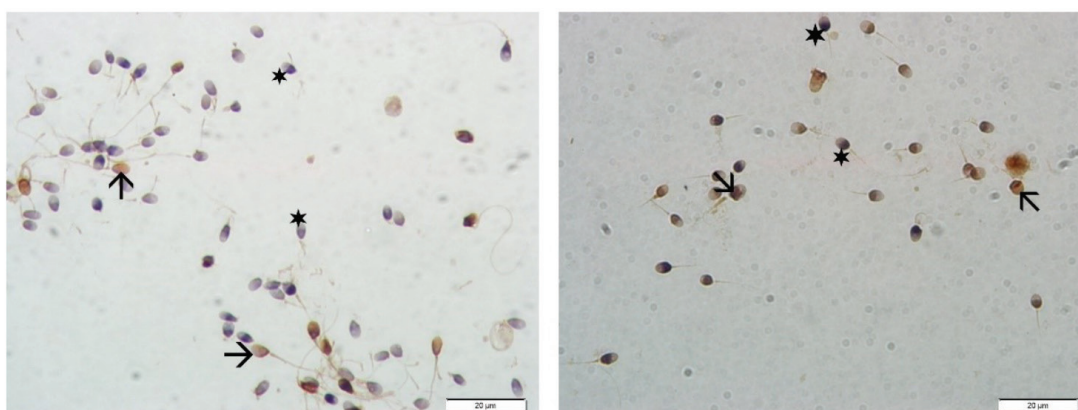
Figure 6. TUNEL staining, as TUNEL-positive (arrow), and TUNEL-negative cells (*), 100X

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TUNEL-positive cells were observed in all groups, and the highest number was detected in the normozoospermic group. Because of the limited number of cases between groups, it is important to confirm these results with higher case numbers in future studies. Observing high numbers of TUNEL-positive sperm in groups, including the normozoospermic group, points to the importance of detecting DNA breaks in idiopathic infertility cases. Consequently, it can be considered that DNA fragmentation testing and conventional semen analysis can be used for evaluating male fertility potential.

Ethics

Ethics Committee Approval: This cross-sectional study was conducted by the Pamukkale University Local Clinical Research Ethics Committee (approval number: 60116787-020/8324, date: 01.02.2018).

Informed Consent: Informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ç., T.T., İ.V.F., Concept: N.Ç., T.T., G.A.M., Design: G.T., N.Ç., C.K., Data Collection or Processing: G.T., N.Ç., C.K., Analysis or Interpretation: N.Ç., C.K., İ.V.F., G.A.M., Literature Search: G.T., N.Ç., C.K., Writing: G.T., N.Ç., C.K., T.T., İ.V.F., G.A.M.

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

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Effects of COVID-19 Lockdown on People's Sexual Lives in Turkiye

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

Previous studies showed that negative effects such as anxiety, fear and depression due to COVID-19 lockdown might negatively affect sexual life. According to the data of this study conducted among Turkish participants, sexual deterioration was observed in 15% of the individuals. Additionally, this study demonstrated that while anxiety plays a role in women, the Marriage adjustment score was significant in married men.

Abstract

Objective: To evaluate the impact of coronavirus disease-2019 (COVID-19) lockdown on the sexual lives of couples who live in Turkiye.

Materials and Methods: One hundred ninety-three sexually active participants. While sexual functions were evaluated with the international erectile function index-15 in men and the female sexual function index in women, Hamilton anxiety scale (HAM) was used to measure anxiety level. Married people filled out the Marriage adjustment test (MAT) questionnaire. The effects of the quarantine period on the relationship were evaluated with a questionnaire created specifically for this study.

Results: Sexual improvement and worsening were observed in 8.8%, and 15%, respectively. It did not change for 76.2%. Sexually deteriorated subjects had a higher HAM score (p=0.003). The MAT score was lower in sexually deteriorated subjects (p=0.004). The rate of sexual worsening was higher in women than in men (28.6% vs. 12%, p=0.02). Women's HAM scores were higher (p=0.002). The MAT score was also found to be higher in women (p=0.0037). 58% of sexually deteriorated participants did not feel safe at home during the COVID-19 period, whereas all of those sexually improved participants felt safe at home.

Conclusion: During the COVID-19 lockdown period, sexual deterioration was detected in 15% of sexually active people. This worsening was associated with the HAM score. Additionally, it was revealed that feeling safe at home is related to sexual life. While the relationship between sexually worsening and the MAT score was significant in men, it was revealed that the level of anxiety in women affected sexual life more significantly.

Keywords: COVID-19, lockdown, sexual health

Introduction

While the coronavirus disease-2019 (COVID-19) pandemic is affecting the whole world, its social and psychological effects still continues. The first lockdown in Turkiye started on April 29, 2020 and lasted until May 17, 2020. Afterward, these lockdown periods are repeated when case numbers reach threatening levels. Especially in the first half of the 2020, the lack of vaccines and uncertainties in the prognosis and treatment of the disease created negative effects such as widespread fear, anxiety, and depression in society at the time of the first lockdown (1,2). Additionally, social isolation, economic problems, fear of job

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loss, and many other factors have seriously affected people of all ages. Such a relationship between sexual life and severe stress has been reported in the previous studies and has been observed in this pandemic as well (3,4). A study from Italy examined the sexual life of couples during the first lockdown period and interestingly showed that sexual life was improved in most people (3). In this study, we evaluated how the sexual life of couples was affected during the first lockdown period in Turkiye.

Materials and Methods

This single-center, cross-sectional study was conducted between 10 and June 25, 2020. Ethics committee approval was obtained (2022.064.IRB1.033) and patient consent forms were filled out online. Participants over the age of 18 of both sexes who were sexually active and had been in a relationship for at least six months were included in the study. Individuals who were sexually inactive, living alone, COVID-19 positive, were excluded from the study.

For the study, an online questionnaire was designed in Google Form. The survey link was shared with all friend groups of the authors of this study with the help of social media accounts (Facebook™, Instagram™ Inc., Menlo Park, CA, USA) and communication applications (Whatsapp™, Inc., Menlo Park, CA, USA). Among the respondents, 193 participants who met the inclusion criteria were included in the study.

Demographic data (age, body mass index, gender, sexual orientation, occupation, marital status, education) of all participants were included in the survey. The female sexual function index (FSFI-19) (5) for women and the international erectile function index (IIEF-15) (6) for men were used to evaluate sexual functions. Married participants additionally completed the Marital adjustment test (MAT) questionnaire (7). All participants completed the Hamilton anxiety scale (HAM) (8) to measure their anxiety levels. Finally, a separate questionnaire created by the authors was used to examine the impact of the COVID-19 pandemic and the quarantine process on couples (Table 1). "Improvement of sexual life" was defined based on, the response to question 4: "Do you feel improvement in your sexual life during this period?" Participants who answered "a lot" or "too much" was accepted as "improvement of sexual life." While those who answered as "much" or "too much" the question "Do you feel that your sexual life has deteriorated during this period?" were defined as those whose sexual life deteriorated.

Statistical Analysis

Responses were downloaded and analyzed from Google Form. Categorical data were evaluated with Fisher's exact test, while

the Mann-Whitney U test was used to compare continuous variables that did not show normal distribution. Normally distributed continuous variables were evaluated with the t-test.

Results

Sexual improvement was observed in 17 (8.8%) of 193 participants and worsening in 29 (15%), no change in 147 (76.2%) of the 193 participants (Table 2). No significant differences were observed between these three groups in terms of age, gender, marriage rates, the duration of relationship and working area. The MAT score of the sexually worsened participants was found to be lower than people who had sexually improved and not-changed (40.2±19.5 vs. 55.9±10.2 vs. 49.5±13.8, p=0.004). The sexually worsened group had a higher HAM score (14.8±13.5 vs. 5.2±4.6 vs. 7.1±8.1, p=0.003) compared to those who improved and did not change. This difference was more significant when comparing their sex life as very improved to those who described their sex life as "much worse" (18.2 vs. 2.8, p<0.001).

The rate of sexually worsening was higher in women than in men (28.6% vs. 12%, p=0.02) (Table 3). Although the rate of sexual improvement was higher in women than in men, no statistical difference was found (17.1% vs. 7%, p=0.09). There was no improvement or worsening in the sexual life of 81% of men and 54.3% of women (p=0.002). Women's HAM score was higher than men's. (12.2±10.3 vs. 7.2±8.87, p=0.002). The

Table 1. A questionnaire was designed to assess the impact of the COVID-19 pandemic on couples' relationships
1. Do you feel safe at home?
2. Do you feel safe outside the home?
3. Do you think that your sex life as a couple has deteriorated during this period?
4. Do you think that your sex life as a couple has improved during this period?
5. Do you feel safe with your partner at home?
6. Do you feel dissatisfied with your partner at home?
7. Do you feel happy with your partner at home?
8. Do you feel uncomfortable with your partner at home?
9. How comfortable do you feel with your partner at home?
10. How satisfied do you feel with your partner at home?
11. Do you think that your couple problems have decreased during this period?
12. Do you feel unhappy with your partner at home?
13. Do you think that your couple problems have increased during this period?
14. Do you feel more nervous towards your partner during this period?
15. Do you feel more calm towards your partner during this period?
Responses: "No"- "Not Much"- "So and So" -"Much" - "Very Much", COVID-19: Coronavirus disease-2019

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MAT score was also found to be higher in women (56.7±6.7 vs. 47.3±15.5, p=0.0037). MAT scores among sexually worsened, improved, and unchanged participants were 40.2±19.4, 55.9±10.2, and 49.5±13.8 (p=0.04). The MAT score of sexually worsened men was lower than those who improved and did not change (31.5±18.1), (57.4±11.3, 48.8±13.9, p<0.0001). There was no difference between those who continued to work and others (flexible working, retired, unemployed) in terms of changes in their sexual lives (Table 4).

Although the rate of married people was higher in the sexually worsened group compared to the sexually improved group (82.8% vs. 70.6%), no significant difference was observed (p=0.33). The rate of those who felt safe outside the home was similar between the two groups (27.6% and 35%, respectively). However, while the rate of people who felt safe outside the home in the sexually worsened group was 58%, all people from the sexually improved group felt safe at home (100%).

Discussion

This study was planned as the Turkish version of the original study conducted in Italy (3). The survey questions were translated into Turkish and conducted as a separate study in Turkiye with the approval of the authors of the original article. Both populations were mostly similar in terms of demographics (age, marital status, duration of relationship, education level, working life), although there were some differences. In our study, men were in the majority. Additionally, while most our participants stated that their sexual life was not affected during this period, 8.8% said it improved and 15% stated that it worsened. In the study conducted in Italy, these rates were 22%, 49%, and 29%, respectively. Compared to our study, the percentage of patients in the original study whose sexual lives had worsened was similar, while the percentage of patients whose sexual lives had improved was much higher.

Table 2. Demographic data of patients with improvement, worsening, or no changes in their sexual life				
	Worsening n=29 (15%)	Improvement n=17 (8.8%)	No change n=147 (76.2%)	p-value
Age	42.6±11.6	37.4±7.4	43±11.3	0.14
BMI	26.1±4.6	23.7±3.4	26±3.2	0.054
Gender				
Female n (%)	10 (34.5)	6 (35.3)	19 (12.9)	0.004
Male n (%)	19 (65.5)	11 (64.7)	128 (87.1)	
Sexual orientation				
Heterosexual n (%)	26	16	144	
Homosexual n (%)	1	1	1	
Bisexual n (%)	2	0	2	
Son n (%)	16 (55.2)	9 (52.9)	107 (72.8)	0.06
Married n (%)	24 (82.8)	12 (70.6)	119 (81)	0.55
Cohabitants n (%)	24 (82.8)	11(64.7)	122 (83)	0.42
Years of stable relationships				
<5 years n (%)	9 (31)	9 (53)	29 (19.7)	0.002
>5 years n (%)	20 (69)	8 (47)	118 (80.3)	
Occupation				
Student n (%)	0	0	0	
Retired n (%)	3 (10.3)	0	12 (8.1)	
Unemployed n (%)	0	2 (11.7)	1 (0.7)	
Working at the usual workplace n (%)	16 (55.2)	8 (47.1)	71 (48.3)	
Smart working n (%)	10 (34.5)	7 (41.2)	63 (42.9)	
Questionnaire				
IIEF (mean, SD)	44.3±23	67.6±7.7	61.1±16.4	<0.001
FSFI (mean, SD)	36.7±28.09	76.1±4.1	69.4±24.1	0.001
MAT (mean, SD)	40.2±19.4	55.9±10.2	49.5±13.8	0.004
HAM (mean, SD)	14.8±13.5	5.2±4.6	7.1±8.1	0.003
BMI: Body mass index, IIEF: International index of erectile function, FSFI: Female sexual function index, MAT: Marital adjustment test, HAM: Hamilton anxiety scale, SD: Standard deviation				

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In the same study, it was also reported that the couples who showed improvement in their sexual lives were happier and more satisfied when they were at home, and the increase in the time they spent together and the number of things they had in common was an important factor in this. However, being unemployed, working from home, and having children were identified as risk factors for people whose sexual life worsened. For those who had children, homeschooling via the internet was found to be effective as the time allocated to children at home increased while the time that couples could spare for each other decreased. In our study, we found that variables such as gender, marital status, relationship time, and work-life balance were similar when comparing participants whose sexual life worsened and those who improved. We also observed that the HAM score of the sexually worsening group was higher than that of the sexually improved and unchanged groups. Previous studies have showed that factors such as stress, fear, and anxiety decrease sexual desire, frequency of intercourse, orgasm, and libido (9-12). In Constantini et al.'s (3) study, the authors indicated that the sexual life of people who have problems such as fear, anxiety, and depression caused by COVID-19 and lockdown was worsened. Interestingly, in our study, when compared to the sexually worsened and improved groups, the rate of those who felt safe outside home was similar, while the rate of those who did not feel safe at home was significantly higher in the sexually worsened group. In this study, which was conducted in the

Table 3. Demographic data and female and male participants			
	Female n=35	Male n=158	p-value
Age	36.5±10.3	43.7±10.8	<0.001
BMI	22.4±3.1	26.6±3.1	<0.001
Sexual orientation			
Heterosexual n (%)	35 (100)	151 (95.6)	
Homosexual n (%)	0	3	
Bisexual n (%)	0	4	
Son n (%)	8 (22.9)	124 (78.5)	<0.001
Education			
Primary school n (%)	0	1 (0.6)	
Secondary school n (%)	0	1 (0.6)	
High school n (%)	2 (5.7)	5 (3.2)	
Graduate school n (%)	33 (94.3)	151 (95.6)	
Occupation			
Student n (%)	0	0	
Retired n (%)	2 (5.7)	13 (8.2)	
Unemployed n (%)	5 (14.3)	5 (3.2)	
Working at the usual workplace n (%)	17 (48.6)	74 (46.8)	
Smart working n (%)	11 (31.4)	66 (41.8)	
Cohabitants n (%)	25 (71.4)	132 (83.5)	0.095
Married n (%)	21 (60)	134 (84.8)	0.002
Stable relationship			
<5 years n (%)	13 (37.1)	34 (21.6)	0.108
>5 years n (%)	22 (62.9)	124 (78.4)	
Questionnaire			
IIEF (mean, SD)	-	59.6±17.8	
FSFI (mean, range)	61.2±27.4	-	
MAT (mean, SD)	56.7±6.7	47.3±15.5	0.0037
HAM (mean, SD)	12.2±10.3	7.2±8.87	0.002
Sexual improvement n (%)	6 (17.1)	11 (7)	0.09
Sexual worsening n (%)	10 (28.6)	19 (12)	0.02
No change n (%)	19 (54.3)	128 (81)	0.002
BMI: Body mass index, IIEF: International index of erectile function, FSFI: Female sexual function index, MAT: Marital adjustment test, HAM: Hamilton anxiety scale			

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initial time of the COVID-19 pandemic, when the vaccine was not administered and there were several ambiguities about the disease, the risk of transmission from the partner at home and the fear and anxiety may have negatively affected sexual life. Mollaioli et al. (13) found that 50% of sexually active people quit their sexual activities during restrictions. The authors attributed this to two reasons: The first is the stress disorder caused by the quarantine, and the second is the difficulty in reaching their partners. Moreover, the researchers observed that people who could maintain their sexual activity had lower anxiety and depression scores compared to those without sexual activity. It has been shown in this study and other studies that anxiety and mood scores of women were affected more than men during the COVID-19 period, and its effects on sexual life were greater (13-17). In our study, the HAM score of women was higher than that of men. In line with this, more sexual worsening was observed in women than in men.

It has been shown that people with higher MAT scores feel more secure and connected in their relationships and have less relationship anxiety (18). Also, previous studies have shown the relationship between MAT and sexual life (3,19). In Constantini et al.'s (3) study, the MAT score of those whose sexual life worsened during lockdown was also lower, as in our study. Although the mean MAT scores of women in our study were higher than that

of men, the relationship between MAT scores and changes in women's sexual lives could not be demonstrated. In men, on the other hand, the MAT score was significantly lower in sexually worsened subjects than in the others. A study from Turkiye has exhibited a significant relationship between women's MAT scores and their sexual lives (20). However, in our study, the high anxiety caused by the pandemic in women probably worsened their sexual life regardless of the MAT score. According to these data, it can be said that while the relationship between the MAT score and sexual life in men is obvious, the anxiety factor plays a more critical role in the sexual life in women. Previous studies have demonstrated the effects of unemployment and dismissal on depression and anxiety symptoms (21-24). In our study, however, the effect of job status on HAM score and sexual life was not observed. This may be presumably because the people who participated in our study were mostly healthcare professionals, and in this respect, they could maintain their current job positions during this period and did not have the fear of being dismissed. In our study, the participants whose sexual life was not changed represent the majority, and this can be explained by the same reason.

The fact that many employees and employers have switched to work from home during the COVID-19 period has increased the time spent with a partner at home. However, people experience

Table 4. Comparison of participants according to working conditions

	Working at the usual workplace n=91	Smart working/unemployed/ retired/student n=102	p-value
Age	41.6±10.5	43.2±10.2	<0.05
>40 years (mean, SD)	44 (48.4)	47 (46.1)	
<40 years (mean, SD)	47 (51.6)	55 (53.9)	
Gender			
Female	17 (18.6)	18 (17.7)	<0.05
Male	74 (81.4)	84 (82.3)	
Son	65 (71.4)	67 (65.7)	<0.05
Married	76 (83.5)	79 (77.4)	<0.05
Cohabitans	77 (84.6)	80 (78.4)	<0.05
Stable relationship			
<5 years n (%)	19 (20.9)	28 (27.5)	<0.05
>5 years n (%)	72 (79.1)	74 (72.5)	
Questionnaire			
IIEF (mean, SD)	60.9±16.6	58.5±12	<0.05
FSFI (mean, SD)	63.4±24.9	58.2±29.6	<0.05
MAT (mean, SD)	42.9±13.5	42.8±12.5	<0.05
HAM (mean, SD)	7.5±8.6	8.5±9.1	<0.05
Sexual worsening	16 (17.6)	13 (12.7)	<0.05
Sexual improving/no change	75 (82.4)	89 (87.3)	

IIEF: International index of erectile function, FSFI: Female sexual function index, MAT: Marital adjustment test, HAM: Hamilton anxiety scale

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social restrictions. During this period, cultural and artistic activities at places such as cinemas, theaters, museums and performance centers stopped. Also, accessibility to places that allow people to come together, such as cafes and restaurants, was limited. Even going outside the house was restricted. In such a socially weakened period, the excess of negative psychological factors is expected to negatively affect sexual life. This study reflects the results of a survey conducted during the first months of the COVID-19 period. At currently, the period of COVID-19 has shaken the whole world both psycho-socially and economically. It should be investigated whether these staggering changes will have long-term negative effects on sexual lives.

Study Limitations

Our study has several limitations, such as: The small number of patients, the obvious difference between female and male participant rates, the fact that all those who filled out the questionnaire were limited to health professionals and friends, and the fact that HAM and MAT scores of the pre-pandemic period are not known. The lack of information regarding the underlying conditions of the patients in the study was another limitation. We were also unable to fill out a questionnaire that allowed us to examine the patients' pre-pandemic sexual life. However, we requested only sexually active people to fill out the questionnaire.

Conclusion

We found that the rate of sexually deteriorated participants during the first lockdown period of the pandemic was 15%. We also observed that those people had higher anxiety scores during this period and that not feeling safe at home was an effective factor in this. While the relationship between men whose sexual life deteriorated and the MAT score was obvious, the level of anxiety in women had a more significant effect on their sexual life.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained (Koç University Ethics Committee, date: 28.03.2022, approval number: 2022.064.IRB1.033).

Informed Consent: Informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.K., T.T., E.I., E.C., Design: E.I., E.C., Data Collection or Processing: M.K., E.K., F.Te., T.T., Analysis or Interpretation: M.K., T.T., Literature Search: M.K., Writing: M.K., F.Te., E.C., F.T., T.T.

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ORIGINAL RESEARCH

Endourology

Outcomes of Ureteral Stent Removal by Flexible Cystoscope Versus Semirigid Ureteroscope: A Prospective Randomized Clinical Trial

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

In developing countries, where the availability of expensive instruments like flexible cystoscopes may not be available everywhere, the semirigid ureteroscopes can be as comfortable as flexible cystoscopes for both patients and surgeons. The study findings can lead to increased use of semirigid urteroscope for Double J stent removal and it is very commonly available in the urology armamentarium everywhere.

Abstract

Objective: Ureteral stents are usually removed after 2-4 weeks. Classically rigid cystoscope was used for stent removal along with retrieval forceps. A flexible cystoscope is an excellent alternative to a rigid cystoscope to reduce discomfort. In this study we compared semirigid ureteroscope with a flexible cystoscope for retrieving stents.

Materials and Methods: It was a prospective randomized clinical trial including 100 patients. All patients were divided into two groups: Group A: Patients undergoing Double J stent (DJS) removal using a flexible cystoscope. Group B: Patients undergoing DJS removal using a semirigid ureteroscope. Outcome parameters compared in both groups were pain during and after the procedure, operative time, and operative difficulty.

Results: There were 70 males and 30 females in the study. Mean visual analogue scores (VAS) for pain during the procedure in groups A and group B were 5.2 ± 1.4 and 5.82 ± 1.8 (p=0.057) and after the procedure were 1.95 and 2.25 in group A and group B, respectively (p=0.253). Mean VAS scores for pain during the procedure in males in groups A and B were 5.2 ± 1.6 and 5.9 ± 1.7, respectively (p=0.080). The mean operative times in groups A and group B were 4.9 and 4.2 min, respectively (p=0.076). VAS scores for operative difficulty overall were 3.6 ± 1.1 and 2.9 ± 1.2 (p=0.058), while in males were 3.7 ± 1.0 and 2.8 ± 1.3 (p=0.002) for groups A and B, respectively.

Conclusion: Ureteral stents removal by semirigid ureteroscope is a good alternative as it is readily available, with the same degree of discomfort as flexible cystoscopes. They are inexpensive and easier to operate than flexible scopes.

Keywords: Ureteral stent, cystoscope, ureteroscope

Introduction

Ureteral stents are an integral part of urological practice. They are placed for better urinary drainage after urological procedures like ureteroscopic stone removal, percutaneous nephrolithotomy, extra-corporeal shock wave lithotripsy, and reconstructive surgeries like pyeloplasty and ureteric re-implantation. These stents are usually removed after 2-4 weeks of surgical intervention, mostly by a retrograde cystoscopic method as a short office-based procedure under topical anesthesia (1,2).

Any endoscopic intervention tends to cause pain and significant discomfort when performed under topical anesthesia, particularly in male patients because of the longer and curved urethra (3). A flexible cystoscope is an excellent alternative to a rigid cystoscope to eliminate the above limitations and is widely adopted by many urologists worldwide for stent removal (4).

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Several studies have reported better patient acceptance during flexible cystoscopy because of reduced pain and discomfort (5,6). However, these studies have mostly compared diagnostic cystoscopy only, without any adjuvant procedure. Besides, there are only very few studies assessing the incidence of pain during cystoscopic stent removal (1,4). Though the duration of stent removal is shorter than flexible diagnostic cystoscopy, there is a need to introduce an adjuvant instrument to grasp the ureteral stent. This factor can confound the perception of pain. Moreover, a flexible cystoscope has a higher purchase cost than that of a rigid scope (7).

Many times, the removal of the stent is impossible by cystoscope due to urethral stricture or other reasons. In such cases, alternate instruments could be either a flexible cystoscope or a narrow caliber semirigid ureteroscope. A semirigid ureteroscope is widely available with the urologist for ureterorenoscopy. It has a narrow diameter (7.5-9 Fr) and a working channel that can be used to introduce a stent retrieval instrument. It is also inexpensive compared to a flexible cystoscope and has a longer life. This study was designed to compare the surgical outcomes of ureteral stent removal with semirigid ureteroscope and flexible cystoscope, focusing primarily on male patients.

Materials and Methods

Data Sources and Patient Selection

The study was conducted at the Department of Urology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) from March 2018 to August 2019. The research was conducted in accordance with the Helsinki Declaration. The ethical clearance was taken from the Institutional Ethics Committee, JIPMER, Puducherry with approval number JIP/IEC/SC/2/302/2013. A total of 100 patients were included in the study after written informed consent. All adult patients above 18 years with unilateral Double J stent (DJS) *in situ* for 2-4 weeks, due for stent removal were included. Patients with migrated stents, severe co-morbidities, encrusted stents, post-renal transplant, residual or bilateral stones and patients with active urinary tract infection with positive urinary culture were excluded from the study. All patients who met the inclusion and exclusion criteria were included in the study after obtaining informed consent. Patients were blinded to the type of instrument used in stent removal and randomized into the following two groups by allocation concealment and closed envelope.

1. Group A: Patients undergoing DJS removal using a flexible cystoscope.

2. Group B: Patients undergoing DJS removal using a semirigid ureteroscope.

Surgical Procedure

Stent removal was performed under local anesthesia after instillation of 10 mL Lignocaine jelly 2% for 5 min in all patients using either a flexible cystoscope (group A) or Semirigid Ureteroscope (group B). The diameter of the flexible cystoscope used was 15 Fr, and the semirigid ureteroscope was 9/7.5 Fr. Immediately after the procedure, all patients were asked to mark the degree of pain using the visual analog pain score (VAS). No pain was graded as 0 points, and the most intractable pain ever felt as 10 points. Surrogate markers for pain (peak SBP and pulse rate were also documented before, during and after the procedure. Blood pressure and HR were recorded by attaching the monitor and pulse oximeter to the patient before starting the procedure in the operative room. So the continuous monitoring was done. Any change in the parameters during the procedure compared to those before starting it was noted and compared. Operative time was calculated from the time of insertion of the stent removal device to the removal of the device and stent. The degree of difficulty, as felt by the operator, was measured using VAS. Score 1 as no difficulty and score five as most problematic. The parameters recorded included pain scores, operative time, and operative difficulty.

Sample Size Calculation

The sample size was estimated with an expected difference in the mean of pain score as 1.0 with a standard deviation of 1.5 between the procedures. The sample size was estimated at a 5% level of significance and 90% power. Hence, a sample size of 50 was allotted in each group with 20% attrition rate anticipated. G powder was used for calculating the sample size (8).

Statistical Analysis

The distribution of data on the VAS score of pain, operative difficulty, and operative time was expressed as mean with standard deviation or median with range, whichever was appropriate. The comparison between the groups was done using independent Student's t-test or Mann-Whitney U test. The distribution of data related to the complication was expressed as frequencies and percentages. Subgroup analysis for male patients was done separately. All statistical analysis was carried out at a 5% level of significance, considering p-value <0.05 as significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 19. Armonk, NY: IBM Corp.

Results

The stents were successfully removed in all 100 patients. Overall, there were 70 male and 30 female patients in the study. The gender ratio in groups A and B was 36:14 and 34:16, respectively, and the mean age was 40.1 and 40 years, respectively (range 18

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to 70). There was no statistical difference in sex ratio, mean age, and stented time between the groups (Table 1).

The data of the outcome parameters of all 100 patients were available for the final analysis. There was no complication reported in our study population. Mean VAS for pain during the procedure in groups A, and B were 5.2±1.4 and 5.82±1.8 (p=0.057). The mean VAS scores for pain after the operation were 1.95 and 2.25 in groups A and B, respectively (p=0.253) (Table 2).

Other surrogate markers for patient discomfort and pain were also measured like change in systolic blood pressure (SBP) and heart rate (HR). Mean changes in SBP in groups A and B were 7.3 and 8.3 (p=0.120), and that of HR was 6.6 and 7.6, respectively (p=0.260).

The mean operative times in groups A and group B were 4.9 and 4.2 min, respectively (p=0.076). VAS for operative difficulty, as reported by surgeons, was 3.6±1.1 and 2.9±1.2 in group A and group B, respectively (p=0.058).

Since we had an equal number of male patients in both groups, we performed a subgroup analysis of male patients separately. Out of 70 male patients in the study, groups A and B had 36 and 34 patients, respectively (Table 3). Mean VAS scores for pain during the procedure in males in groups A and B were 5.2±1.6 and 5.9±1.7, respectively (p=0.080). The mean VAS scores for pain after the procedure for males in groups A and B were 1.9±1.4 and 2.3±1.5, respectively (p=0.252), and mean operative time was 5.3±2.2 and 4.4±1.8 min, respectively (p=0.066). The VAS for operative difficulty, as reported by surgeons, were 3.7±1.0 and 2.8±1.3 for groups A and B, respectively, and the difference was significant (p=0.002).

Table 1. Demographic data and cause of stent placement

Variable		Group A (flexible cystoscopy) n=50	Group B (semirigid ureteroscopy) n=50	p-value
Gender ratio (Male: Female)		36:14	34:16	0.450
Mean age in years (SD)		40.1 (12.1)	40 (10.5)	0.252
Mean duration of DJs *in situ* in days (SD)		25.2 (7.8)	27.6 (6.5)	0.120
Cause of stent placement	URSL	34 (68%)	32 (64%)	
	Post pyeloplasty	5 (10%)	4 (8%)	
	PCNL	7 (14%)	4 (8%)	
	ESWL	4 (8%)	10 (20%)	
SD: Standard deviation, URSL: Ureteroscopic lithotripsy, PCNL: Percutaneous lithotripsy, ESWL: Extracorporeal shock wave lithotripsy, DJS: Double J stent				

Table 2. Outcome parameters

Variable	Group A (flexible cystoscopy) n=50	Group B (semirigid ureteroscopy) n=50	p-value
Mean pain on VAS during the procedure (SD)	5.2 (1.4)	5.82 (1.8)	0.057
Mean pain on VAS after the procedure	1.95 (1.2)	2.25 (1.4)	0.253
Mean operative time in minutes (SD)	4.9 (2.0)	4.2 (1.9)	0.076
Mean score on VAS for operative difficulty (SD)	3.6 (1.1)	2.9 (1.2)	0.058
SD: Standard deviation, VAS: Visual analogue scale			

Table 3. Outcome analysis in males

Variable	Group A (flexible cystoscopy) n=36	Group B (semirigid ureteroscopy) n=34	p-value
Mean pain VAS during the procedure (SD)	5.2 (1.6)	5.9 (1.7)	0.080
Mean pain VAS after the procedure	1.9 (1.4)	2.3 (1.5)	0.252
Mean operative time in minutes (SD)	5.3 (2.2)	4.4 (1.8)	0.066
Mean VAS for operative difficulty (SD)	3.7 (1.0)	2.8 (1.3)	0.002
SD: Standard deviation, VAS: Visual analogue scale			

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Discussion

In our study, the pain on VAS and other markers for discomfort during and after the procedure were similar for patients who had stent removal by flexible cystoscope and semirigid ureteroscope in both males and females. Operative time and difficulty in removing the stent was also identical in both males and females. On comparing the surgeon's difficulty in male patients, it was found that removing a ureteral stent through a flexible cystoscope was significantly difficult than removing it through a semirigid ureteroscope (p=0.002). The difficulty with flexible cystoscopy was mainly due to difficult maneuverability compared to the semirigid ureteroscope, which is easy to handle and orient inside the bladder.

Several studies have documented that flexible diagnostic cystoscopy is better than rigid cystoscopy (RC) for better patient tolerance and pain perception. Denholm et al. (5) demonstrated in their study of 200 patients that flexible cystoscopy under local anesthesia was well tolerated and had lower morbidity compared with RC under general anesthesia. Flannigan et al. (6) reported similar outcomes in their cohort of 53 patients. Several authors also reported that flexible cystoscopy is well tolerated in females as well. Gee et al. (7) randomized 36 women to flexible and RG with comparable pain scores in both groups. In a similar randomized trial, Quiroz et al. (9) showed that urinary frequency and duration of urinary burning post-procedure occurred more frequently in the FC group, although these symptoms were transient. Besides, office FC and RC are generally well tolerated in women with overall low morbidity, different from this study, in all above studies, only diagnostic cystoscopy was compared without any adjuvant procedure.

Researchers have also evaluated FC for the adjuvant procedure like ureteral catheters insertion, removal of ureteral stents and foreign bodies, and treatment of small bladder tumors with the Nd: YAG and fragmentation of bladder calculi with a pulsed-dye laser (10). Kaabneh et al. (11) showed in their study of 600 patients that operative pain score, lower abdominal pain score, dysuria, urgency, and hematuria were less in male patients subjected to DJS removal using flexible cystoscopy. However, a statistically significant outcome was not seen in female patients.

A flexible cystoscope has high initial and maintenance costs. A systematic review conducted by Canales et al. (12) found that Olympus cystoscopes require repair every 2 to 3 years. The distal deflection tip, specifically the outer bending rubber, is the most common site of flexible cystoscope damage. Despite significant improvements in the deflection apparatus, the number of repairs has not changed significantly with time.

Söylemez et al. (2) randomized 67 patients of stent removal to a flexible cystoscope and ureteroscope. There were no statistical differences in the two groups regarding mean operative pain score, irritative voiding symptom scores, and hematuria. They reported higher prices for buying and maintenance of flexible scope. Besides, ureteroscope offered an added advantage in the removal of mildly up-migrated ureteral stents under local anesthesia.

Jeong et al. (13) compared ureteral stent removal by rigid cystoscope and flexible cystoscope in 104 male patients. They reported that the VAS pain score was lower, and the satisfaction scale score was more in the flexible cystoscope group compared with the rigid cystoscope, and the difference was statistically significant.

Similar to our study, Lai et al. (14) prospectively compared the removal of ureteral stents by rigid ureteroscope and flexible cystoscope in a cohort of 300 patients. They reported no statistical difference between both the techniques of stent removal in terms of operative time, pain scores, hematuria after stent removal, and irritable symptoms. They reported a significantly higher cost per use for stent removal by flexible cystoscopy (US dollars 107.9 versus 28.2). However, this study did not compare the surgeon's perspective on difficulty level in stent removal by both the above techniques.

Flexible cystoscopes have a higher cost, and their durability is lower than the semirigid ureteroscopes. Moreover, the flexible cystoscopes and their accessory instruments are liable to easy wear and tear. These factors increase the per use cost of flexible cystoscopy (14). Thus, stent removal by semirigid ureteroscopes is a good alternative as it is equal in discomfort, more comfortable to operate, and inexpensive than the flexible cystoscopes. Moreover, the ureteroscopes are readily available in every health setup.

Study Limitations

There were some limitations to our study. First, the sample size was relatively small. Second, it was a single-center study. A multi-center study with a larger sample size can give better results.

Conclusion

Ureteral stents removal by semirigid ureteroscope is a good alternative as it is readily available, with the same degree of patient discomfort as flexible cystoscopes. Moreover, they are inexpensive and easier to operate than flexible scopes.

Ethics

Ethics Committee Approval: The ethical clearance was taken from the Institutional Ethics Committee, JIPMER, Puducherry with approval number JIP/IEC/SC/2/302/2013.

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Informed Consent: A total of 100 patients were included in the study after written informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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

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Children with Non-Neurogenic Lower Urinary Tract Dysfunction Require Less Frequent and Number of Botulinum Toxin Injections Than Neurogenic Ones

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

Despite having different etiologies, neurogenic bladder and non-neurogenic lower urinary tract pathologies have similar clinical presentation and common symptoms. In our study, we aimed to point out the clinical outcome differences (duration of response and requirement for repeat injections) in different patient groups. In addition, the number of patients is considerably high for a single institute. There is only one study including a group larger than 89 patients (257 patients). The other studies were mostly conducted in patient groups of less than 60 cases.

Abstract

Objective: To evaluate pediatric patients with lower urinary tract dysfunction (LUTD) who received bladder or external sphincter botulinum toxin A (BTX) injection in terms of effectiveness and permanence.

Materials and Methods: We analyzed 80 patients treated with intradetrusor (n=48) n or intrasphincteric (n=32) BTx injection between May 2007 and December 2019. We divided the patients into 2 groups: Neurogenic bladder (NB) and LUTD. Clinical assessment of results was mainly done with Dysfunctional Voiding and Incontinence Symptoms Score (DVISS) and quality of life questionnaires and dryness status. Uroflowmetry with electromyography and video-urodynamic study was performed postoperatively.

Results: Mean age and follow-up time were 123.0±48.3 and 30.1±5.8 months. For bladder BTx (NB: 18 patients; LUTD: 30 patients), the response rate was 79.1% (n=38). NB patients' response duration was shorter (32 vs 87 weeks) and required subsequent multiple injections more (55% vs 23%) than the LUTD group. For sphincter BTx (NB: 13 patients; LUTD: 19 patients) clinical improvement was found in 75% (n=24) n of the patients. There was no significant difference between the NB and LUTD groups. DVISS and quality of life questionnaires showed substantial decrease in the LUTD groups after bladder (p<0.001) and sphincter (p<0.05) BTx injection. NB patients showed significant dryness status in both BTx-B (pre: 3.2%, post: 82.1%, p<0.05, chi-square test) and BTx-S (pre: 0%, post: 100%, p<0.05, chi-square test) patients postoperatively.

Conclusion: This study demonstrated that BTx injection is an effective and safe treatment in pediatric patients with NB and LUTD. With its benefits, this endoscopic treatment should be kept in mind before major constructive surgeries.

Keywords: Urodynamics, botulinum toxin A, luts

Introduction

Lower urinary tract dysfunction (LUTD) denotes any deviation from normal physiological storage and emptying functions of the bladder. Symptoms can be listed as daytime frequency, incontinence, urgency, nocturia, hesitancy, straining to void, weak caliber, intermittent urination, dysuria, post-voiding dribbling (1).

The etiology of LUTD can be divided into two basic categories: Neurogenic and non-neurogenic. Neurogenic LUTD is an abnormality of bladder and/or sphincter innervation and is due to congenital anomalies or acquired conditions (2).

Neurogenic bladder (NB) treatment aims at preservation of the upper urinary tract with low bladder pressure and normal compliance. CIC and antimuscarinic medications are initial tools to manage this condition (3).

Non-neurogenic LUTD can be identified within a spectrum of conditions starting from detrusor instability to serious cases affecting the upper urinary tracts without any known neurologic cause. Treatment aims at normalizing the voiding pattern and pelvic floor activity, incontinence and urinary tract infections. Physiotherapy, biofeedback, antimuscarinic and alfa-blocker medications, antibiotics can be used depending on the type and severity of symptoms at initial diagnosis (4).

Patients who do not benefit from initial treatment modalities, would need more invasive options ranging from endoscopic injection to open surgery like bladder augmentation. Botulinum toxin (BTx) injection with cytoscopic guidance into the detrusor or external urethral sphincter (EUS) is efficient in decreasing muscle overactivity with no serious side effects by interfering with SNAP proteins and blocking neurotransmitter release into the synaptic cleft (5). This is the most up-to-date alternative that can be used before irreversible surgical treatments.

Our hypothesis in this study is that BTx application to the detrusor and/or sphincter is an effective and safe treatment in non-neurogenic and neurogenic LUTD. For this purpose, we retrospectively evaluated pediatric patients who received BTx treatment.

Materials and Methods

This retrospective clinical study (Hacettepe University Local Ethic Committee, approval number: GO-18/449, date: 15.05.2018) included 89 patients who were treated with bladder or sphincter botulinum toxin A (BTX) injection between May 2007 and December 2019. Patients were given detailed information about the procedure and informed consent was obtained.

The indication for the procedure was the absence of clinical response to treatment for detrusor and/or sphincteric overactivity [standard urotherapy, medications, clean intermittent catheterization (CIC)] in non-neurogenic and neurogenic LUTD patients. None of the NB had a history of augmentation, cathaterizable stoma, or bladder neck surgery. In LUTD patients, the decision of response to medical treatment was given after at least 6 months of continuous use of antimuscarinics. Video-urodynamic study (VUDS) was applied to all patients. VUDS was performed in patients with sterile urine culture. During the procedure, a 7 Fr cystometry and rectal catheters were placed into the bladder and rectum. The bladder was filled with saline at room temperature at a rate of 5-10% mL/min of expected bladder capacity. Cystometric capacity, bladder and detrusor

pressure, bladder compliance, bladder activity, were recorded. Bladder capacity and pressure at the initiation of reflux were recorded, if present. At the end, residual urine was calculated. Uroflowmetry (UF) with electromyography (EMG) was performed in all patients with dysfunctional voiding. Inclusion criteria for sphincter BTx were inefficient emptying with high-postvoiding residual volume, urinary incontinence and/or voiding symptoms with pathological UF pattern and EMG activity during urination in at least 2 consecutive tests.

BTX was injected into detrusor only, sphincter only and detrusor and sphincter simultaneously in 48, 32, and 9 children, respectively. BTX was injected with the guidance of a rigid cystoscope under general anesthesia in the presence of sterile urine. The total dose of BTX was 150-200 IU for the bladder with 20 injection sites sparing the trigone (6) (10 IU/kg, maximum total dose 200 IU), 50 IU for the sphincter diluted in 4 mL saline (12.5 IU/mL), were injected in 4 quadrants (3, 6, 9 12 o'clock positions) CITATION (7). Clinical outcomes were assessed with questionnaires including symptoms, postoperative UF and VUDS if parents approved. Demographic parameters (age, sex), the number of injections, clinical benefit, Dysfunctional Voiding and Incontinence Symptoms Score (DVISS), quality of life (QoL), dryness between CIC, time to initiate the effect and duration of efficacy, urodynamic parameters were recorded and compared before and after BTx injection. Efficacy parameters were continence or decrease in total number of incontinence episodes, prolonged dry time, normalized voiding pattern, decrease in DVISS score, cessation of recurrent urinary tract infections. Indications for repeat injections were recurrence of symptoms.

Statistical Analysis

In the statistical comparison of the data, chi-square test, Mann-Whitney U test, t-test were used with the Statistical Package for Social Sciences (SPSS 17.0). A p-value less than 0.05 in the 95% confidence interval was considered statistically significant.

Results

Since the number of patients who underwent simultaneous bladder and sphincter injections was small, the statistical analysis was performed in those with detrusor only and sphincter only cases. Mean age of first application and follow-up was 123.0 ± 48.3 and 30.1 ± 5.8 months, respectively. Female/male ratio was 44/36. 58% of the children had LUTD, whereas 42% of them had NB. The causes of NB were spina bifida and myelomeningocele.

Clinical improvement was observed in 83.3% (40) of who received BTx injection to the bladder (BTx-B) after a median number of 1 (1-3) injection. NB patients had a shorter duration

of response (32 vs 87 weeks) and required more injections than LUTD patients (55% vs 23%) (Table 1).

Clinical improvement after BTx injection to sphincter (BTx-S) was observed in 75% (24) children with a median number of 1 (1-2) injection with a mean duration of action of 27.8 ± 25.7 weeks. There was no statistically significant difference between NB (n=13) and LUTD (n=19) in terms of response parameters (Table 2).

The DVISS and QoL scores of the LUTD group decreased significantly in the postoperative period who underwent BTx-B and BTx-S (Table 2). NB patients were evaluated with dryness status between CIC before and after BTx injection. The results showed a statistically significant difference with 82.1% (pre: 3.2%, post: 82.1%, p<0.05, chi-square test) and 100% (pre: 0%, post: 100%, p<0.05, chi-square test) dryness after the BTx-B and BTx-S group, respectively.

Although, all patients underwent preoperative VUDS, only the parents of 29 patients allowed us to perform postoperative VUDS. The comparison of pre- and post-operative urodynamic studies in 29 children revealed increased bladder capacity (V_{max}), decreased $Pdet_{max}$ and $Pves_{max}$. However, decreases in $Pdet_{max}$ and $Pves_{max}$ were significant in LUTD patients where the increase in V_{max} was significant in NB patients (Tables 3 and 4). VUDS in these patients revealed improvement in detrusor overactivity (presence of detrusor overactivity, preoperative: 71.1% vs postoperative: 55.6%, p=0.037, McNemar test) and compliance (presence of hypocompliance, preoperative: 71.4% vs postoperative: 52%, p=0.039, McNemar test). Detrusor reflex volumes (DRV) increased after the procedure in both LUTD [from 51.00 (4.00-275.00 to 148.00 (21.00-647.00) mL, Wilcoxon signed-rank test, p=0.001] and NB (from 61.5 ± 62.4 mL to 98.4 ± 86.2 mL, paired Sample t-test, p=0.029) patients. There was no statistical significant difference in preoperative DRV patients with and without clinical response [mean preoperative DRV with and without clinical response: 72.00 (2.00-524.00), 97.75 (3.00-492.00), respectively, p=0.850, Mann-Whitney U test].

One BTx-B patient had urinary retention in the postoperative period requiring catheterization for 24 h. There was no

Table 1. Demographic parameters

Parameter	BTx-B		Sphincter Btx	
	Neurogenic bladder (n=18)	Lower urinary tract dysfunction (n=30)	Neurogenic bladder (n=13)	Lower urinary tract dysfunction (n=19)
Boy/girl	10/8	11/19	7/6	3/16
Age (median, min-max)	156 (72-324)	114 (70-205)	129 (94-180)	117 (60-208)
Number of injections (median, min-max)	1 (1-3)	1 (1-3)	1 (1-2)	1 (1-2)
Clinical benefit (yes/no)	15/3	23/7	8/5	16/3
Time to effect, week (median, min-max)	2 (0-8)	2 (0-8)	2 (0-4)	2 (0-4)
Duration of efficacy, week (median, min-max)	32 (11-120)	87 (12-465)	24 (12-64)	29 (5-96)
Single injection/multiple injections	8/10	23/7	13/0	17/2
Min-max: Minimum-Maximum, BTx: Botulinum toxin				

Table 2. Comparison of DVISS and QoL scores of LUTD patients

Parameter	BTX-B			BTX-S		
	pre	post	p	pre	post	p
DVISS (mean $\pm$ SD)	20.80 ± 6.39	10.20 ± 7.62	<0.001[a]	16.63 ± 6.12	8.16 ± 7.37	<0.001[a]
QoL (mean $\pm$ SD)	2.60 ± 0.77	1.33 ± 1.12	<0.001[a]	2.79 ± 0.78	1.16 ± 1.21	<0.001[a]
DVISS + QoL (mean $\pm$ SD)	23.51 ± 6.55	12.81 ± 7.71	<0.001[a]	19.25 ± 6.5	11.06 ± 8.04	0.00[a]
[a]: Paired sample t-test, SD: Standard deviation, BTX: Botulinum toxin A, DVISS: Dysfunctional Voiding and Incontinence Symptoms Score, QoL: Quality of life, LUTD: Lower urinary tract dysfunction						

Table 3. Comparison of preoperative and postoperative urodynamic parameters of bladder BTx injection (LUTD group) patients

Non-neurogenic LUTD (n=23)	V_{max} (mean)	$Pdet_{max}$ (mean)	$Pves_{max}$ (mean)
Preoperative	247 mL	70 cmH$_2$O	76 cmH$_2$O
Postoperative	266 mL	47 cmH$_2$O	56 cmH$_2$O
p	0.281a	0.030[a]	0.024[a]
[a]: Paired sample t-test, LUTD: Lower urinary tract dysfunction, BTx: Botulinum toxin			

urinary tract infection after the procedure and 1 patient had postoperative pain.

Nine patients who underwent simultaneous bladder and sphincter injections had a mean age of 135.89±34.09 and male-to-female distribution of 5/4. Four of 9 had neurogenic origin. Seven (77.7%) patients benefited from the treatment. None of them experienced complication.

Discussion

The BTx injection is also a very useful treatment option in LUTD and NB patients who do not respond to initial non-invasive treatment modalities with incontinence or repeated urinary infections (8). These toxins are composed of two chains and three functional domains: The light chain (LC, ~50 kDa), which is a zinc-dependent metalloprotease that cleaves the target proteins in neurons, and the heavy chain (HC), which can be further divided into the N-terminal membrane translocation domain (HN, ~50 kDa) and the C-terminal receptor-binding domain (HC, ~50 kDa). There are 7 serotypes of botulinum neurotoxins but only botulinum-A serotype is U.S. Food and Drug Administration-approved for medical uses in humans (9). There are two subtypes of botulinum-A serotype neurotoxin, onabotulinum-A (Botox@) and abobotulinum-A neurotoxin (Dysport@). The onabotulinum-A is mainly used in urology, whereas abobotulinum-A plays a critical role mainly in dermatological interventions. However, many studies on the effect of botulinum injection in the lower urinary tract is present using the abobotunlinum-A toxin (9). EAU guidelines recommend the onabotulinum-A toxin injection as a treatment option for patients with idiopathic or NB overactivity refractory to the first-line treatment with anticholinergic agents (10). In the pediatric population, the role of onabotulinum-A toxin injection is the preservation of renal function preventing the urinary infections in patients with bladder overactivity or NB. It is also recommended as a treatment option in patients with incontinence refractory to the anticholinergic agents (11). As for the dose, 5 U/kg and 10 U/kg doses have been tested in the literature (12,13). It comprises a very promising intervention as it can achieve continence, increase in maximum cystometric capacity and improvement of compliance and maximum detrusor pressure (12). Studies with higher doses (12 IU/kg, maximum 300 IU) reported similar clinical results (13). We used a dosage of 10 IU/kg (not exceeding a total dose of 200 IU) and achieved symptomatic improvement in ¾ of our patients. Recently, the experimental use of electromotive drug administration (EMDA) has been investigated with the aim of increasing drug delivery. It was hypothesized that EMDA provide better BTx delivery into the deeper detrusor muscle layers. Kajbafzadeh et al. (14) showed that the EMDA system, in moderate to severe incontinent NB patients, provided urinary continence in 70% and improvement in constipation in 77%.

In a recent review, the clinical response to intradetrusor BTx injection was reported to a range of 65-87% (6). In our study, the indication for the application of onabotulinum-A injection in the NB group was the repeated urinary infection or the urinary incontinence refractory to first-line treatment with anticholinergic agents. We evaluated the clinical improvement after the bladder injection using the dryness status. Clinical improvement was observed in 82.1% patients, which were statistically significant. Being more significant than the mentioned objective and subjective findings, we detected that many patients or the caregivers who benefited from the procedure, indicating that the timing of re-injection as the well-being starts to diminish in time. It was noticed that the effect of BTx injection lasted for 2-24 weeks in literature (6). We found that the mean duration of the effect persisted for 32 weeks for the bladder and 24 weeks for the sphincter injections. The systematic review of Hascoet et al. (12) showed that BTx injection provided improvements in urodynamic parameters as decreasing the $Pdet_{max}$ (32-54%) and increasing the V_{max} (27-162%) and compliance (28-180%). Another multicenter study in 53 NB patients reported 66% clinical improvement rate and 34% urodynamic success rate was that in fact showed discrepancy between clinical condition and laboratory tests (15). In our VUDs, only the V_{max} statistically significantly increased (pre-operatively 149 mL vs post-operatively 228 mL) (p<0.05) and the improvement in other parameters was not significant. However, the number of patients with postoperative VUD was small that decreases the reliability of the statistical analysis result. In terms of repeated injections, literature showed us great variance of rates from 9% to 47% (13). In our study, many NB patients (10/18; 55.5%) required more than 1 injection.

Regarding the group of LUTD, in the literature, clinical improvement after BTx injection for LUTD patients was 38-60%, whereas the mean efficacy duration was 32 weeks (12,16). In

Table 4. Comparison of preoperative and postoperative urodynamic parameters of bladder BTx injection (NB group) patients			
Neurogenic LUTD (n=6)	V_{max} (mean)	$Pdet_{max}$ (mean)	$Pves_{max}$ (mean)
Preoperative	149 mL	44 cmH$_2$O	43 cmH$_2$O
Postoperative	228 mL	27 cmH$_2$O	37 cmH$_2$O
p	**0.028**[a]	0.295[a]	0.557[a]
[a]: Paired sample t-test, LUTD: Lower urinary tract dysfunction, BTx: Botulinum toxin, NB: Neurogenic bladder			

a recent study, 257 patients underwent onabotulinum-A toxin injection in a fixed dosage of 100 U. Study reported 50% and 45.7% full clinical response rates in patients with enuresis and daytime incontinence, respectively. The cystometric capacity increased by 23.1%, 31.6% and 16.8% after the first, second and third injections. One patient developed post-operatively urinary retention, which was resolved with temporary CIC (16). In our study, onabotulinum-A toxin injection was applied to LUTD patients with incontinence or urinary infection refractory to first-line treatment with anticholinergic agents. Clinical benefit was investigated in 79.6% (29/39) and the mean duration of effect was 87 weeks for the bladder injection and 29 weeks for the sphincter injections. In this LUTD group, multiple injections were required in 7 of 30 BTx-B and 2 of 19 BTx-S patients. In VUDS, the post-operative improvement was statistically significant in $Pdet_{max}$, $Pves_{max}$ and compliance. We evaluated the clinical improvement by using DVISS and QoL questionnaires. All DVISS, QoL, DVISS+QoL scores were statistically significantly improved after BTx injection. The only study comparing DVISS scores in the literature was conducted in patients who received bladder injections and demonstrated well-being status up to 12 months postoperatively (17). We used this specific scoring system for the evaluation of both bladder and sphincter injections. In our study, the pre- and post-operative DVISS values were 20.67 and 10.67 (p<0.05) for the bladder, and 16.75 and 8.93 (p<0.05) for the sphincter BTx injection patients, respectively.

After the effect of onabotulinum-A in the vesical non-sympathetic synapses, the neuron starts forming new synapses to replace the blocked ones. This process is called sprouting, however the original synapses regenerate and the neo-synapses degenerate. That is the cause of the temporary effect of the intradetrusor or intrasphincteric onabotulinum-A injection (18). The effect of onabotulinum-A toxin on the target-tissue starts in only a few days and reaches its peak after 2-6 weeks. After the peak point, the effect of onabotulinum-A toxin decreases gradually to a minimum level after 6-12 months (19). Antibodies directed against onabotulinum-A toxin interfere with the biological aspects of the toxin and may lead to an antibody-induced failure. The individual dose, the immunologic quality of the onabotulinum-A preparation and the interval between injections are determined as risk factors. The cumulative dose, the treatment time and the patients' age are not presented as related to antibody induced failure factors. Therefore, it is recommended that repeat injections should be performed at least 3 months after the previous one (20). In our investigation, in both the NB and LUTD groups the time to initiate effect was 0-2 weeks and the duration of the effect was from 24-87 weeks in accordance with the mentioned pathophysiological data. In the literature, most studies present a mean effect duration of 6-10 months and a mean re-injection time after 6-9 months (21). The mean re-injection period of our population was 84

(55-154) weeks. In our study, we detected that NB patients benefited for a shorter time period (32 weeks) and required multiple injections (55%) more than LUTD patients (87 weeks, 23%, respectively). There is a lack of literature on the cause of this difference in effect duration between NB and LUTD patients. LUTD patients have a disorder which is caused by the maturation delay of detrusor function. In our perspective, onabotulinum-A injection provides a period in LUTD patients to achieve detrusor function maturation and establish a better bladder-sphincter coordination in the absence of evident neurologic origin (5). This fact could lead to a more durable result as the bladder-sphincter dyssynergia plays a principal role in the pathophysiology of non-NB overactivity. However, NB patients have a permanent congenital structural disease, which causes the formation of hypertrophic or hyperactive detrusor muscle fibers. The provoked bladder wall ischemia and the fibroproliferative changes lead to lower compliance of the bladder (1,22). These changes in the bladder wall can lead to a decreased response to the administration of BTx-A injection (20). Also, Compérat et al. (23) showed that the bladder wall structure was different between BTx injection responder and non-responder patients. In fact, minor fibrosis was found in the bladder wall of responder patients. Since we don't have histological evaluation, we can just link our findings of difference between NB and LUTD patients to the possible relationship between the clinical response (duration of well-being and number of injections) and the degree of fibrosis in the bladder wall. Antibody levels before intervention may be another possible explanation (24). However, neither ours nor the studies in the literature investigated the difference between NB and LUTD patients in terms of antibody levels. As for the sphincter BTX-A injection, there are a limited number of studies in the literature. Previous studies on the sphincter BTx injection reported improvement rates in voiding and urodynamic parameters as 45-77%, and 40%, respectively (25,26). In our study, clinical improvement was observed in 75% (24/32) of all patients. Moreover, the mean follow-up was 30.1±5.8 months and decrease in DVISS and QoL scores were significant. One must acknowledge that the mean time to effect was 2 (0-4) weeks in both groups and it is measured at the beginning of the clinical improvement and it is in accordance with the previous studies (25,26).

The onabotulinum-A injection is regarded minimally invasive, but not without complications. Previous studies have mentioned UTI (4-29%) and urinary retention (4%) as the most encountered postoperative complications (13,21). In our study, none of the patients experienced UTI after the procedure. Only 1 episode of urinary retention and 1 episode of post-operative pain were recorded.

Our experience showed that the onabotulinum-A toxin injection is an effective alternative treatment options for NB and LUTD

patients who do not respond to first-line therapy. It is a minimal invasive procedure which can easily be repeated. The clinical and urodynamic outcomes are very satisfying, whereas the cost is far lower than that of bladder augmentation procedures. Although, it cannot replace the role of bladder reconstruction, particularly for NB patients, BTx injection has provided symptomatic relief in 75% that simply means to spare these children from more invasive major augmentation procedures.

Study Limitations

There are limitations in our study. Firstly, it was a retrospective study. Additionally, VUD was not performed in all patients post-operatively. VUD is a very painful and stressful examination, especially for the children. Due to being invasive, it has its possible adverse events. Therefore, in most of the cases, parents did not agree to their children to undergo another invasive examination only for academic purposes, once the clinical benefit was well established with the use of questionnaires. Actually, most of the previous studies revealed that objective assessment tools are most of the time in consistency with the subjective ones (21,23).

Conclusion

The results of our study show that BTx injection for children with NB and LUTD is effective and safe with the potential of saving a significant number of patients from further more invasive treatment. Although it was not surprising, this study was the first to show objectively that the effect of BTx injections in LUTD patients lasts longer and this population requires less number of interventions than the NB group. Our findings need to be verified by future studies with longer follow-up in a larger groups of patients with more detailed urodynamic evaluation.

Ethics

Ethics Committee Approval: The Local Ethics Committee (Hacettepe University Ethic Committee) approved the study protocol (decision number: GO-18/449, date: 15.05.2018).

Informed Consent: Patients were given detailed information about the procedure and informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Mycobacterium bovis Associated Aneurysm of the Common Iliac Artery After Bacillus Calmette-Guérin Intravesical Treatment for Urothelial Carcinoma

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Introduction

A 54-year-old man with a non-invasive urothelial carcinoma (T1N0M0) was scheduled for transurethral resection after a 2-year treatment with adjuvant Bacillus Calmette-Guérin (BCG) instillation therapy. During this period, the patient received antibiotic therapy (Rifampicin, Isoniazid, Ethambutol) for a suspected *Mycobacterium bovis* systemic infection with B symptoms and lymphadenopathy. A culture of *Mycobacterium bovis* BCG grew from the sputum of the patient. The preoperative computed tomography (CT) showed an aneurysm of the left common iliac artery with a diameter of approximately 3.5 cm (Figure 1) and a dissection of the right common iliac artery (Figure 2). These findings had not been documented in a previous CT scan done 8 months before. The clinical and imaging findings were consistent with those of a BCG-associated mycotic aneurysm. A xenopericardial graft replacement via midline laparotomy was performed two days after diagnosis without complications. A Ziehl-Neelson staining procedure and a polymerase chain reaction (IS6110 and M65 methods) were performed on an intraoperative tissue sample and confirmed the diagnosis. The patient could be discharged home a few days after the procedure with the same established preoperative antibiotic therapy. After consultation with the infectiologists in the domo, the patient was recommended to continue the antibiotic therapy for another 4 months.

Intravesical instillation of BCG is widely used for treating superficial, early-stage bladder cancer based on its immunomodulatory effects aimed at limiting cancer progression and preventing local recurrence (1). Although being considered safe, a few typical complications may occur, such as granulomatous hepatitis or pneumonia (0.5%), hematuria (1%),

Figure 1. Shows a *mycobacterium bovis* associated aneurysm of the common iliac artery

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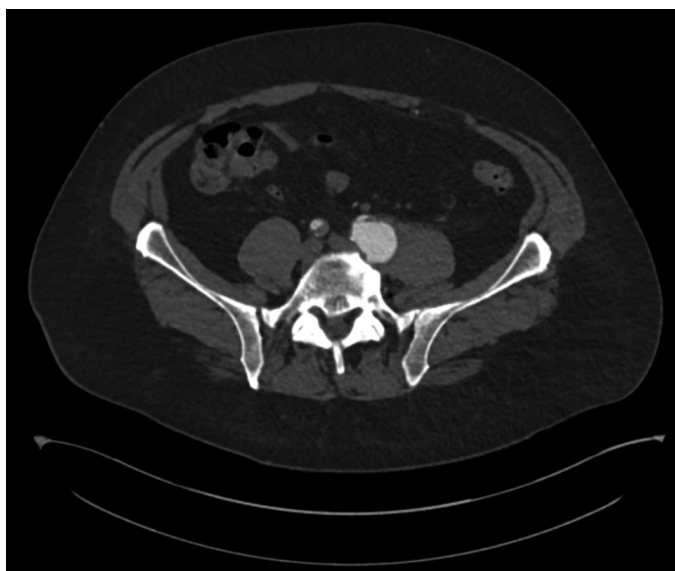
Figure 2. Shows a dissection of the right common iliac artery

fever (2.9%) and, even more common, dysuria and pollachiuria. A very rare complication, described in fewer than 50 cases in the literature, consists of *Mycobacterium bovis*-associated aortitis with subsequent mycotic aneurysm [Higashi et al. (2)]. The localization in peripheral arteries, such as the carotid and the lower-limb arteries, appears even rarer.

Written informed consent for publication was obtained from the patient.

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Life-threatening Arterioureteral Fistula Between Iliac Vessel and Ureteral Stump: A Case Report

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Abstract

Arterioureteral fistulas (AUFs) are a rare but life-threatening condition that cause massive hematuria. Radiation treatments, pelvic surgeries and chronic permanent ureteral stent use due to pelvic malignancies have been identified as the most important causes of AUFs. The number of cases in which arteriography and computed tomography angiography are insufficient and the pulsatile flow of the fistula can be observed only with ureterenoscopy is very rare in the literature. Here, we presented our 60-year-old patient with AUF, who has important risk factors such as pelvic surgery, radiotherapy and recurrent ureteral stent placement and whose pulsatile flow of the fistula was observed by ureteroscopy between the ureteral stump and iliac vessel

Keywords: Arterioureteral fistula, iliac vessel, ureteral stump

Introduction

Arterioureteral fistulas (AUFs) are a rare but life-threatening condition that cause massive hematuria. They usually occur where the ureters cross the iliac vessels (1). Radiation treatments, pelvic surgeries and chronic permanent ureteral stent use due to pelvic malignancies have been identified as the most important causes of secondary AUF (2) The most common symptom is intermittent hematuria, which can be life-threatening. AUFs are very difficult to diagnose. Failure to diagnose can be mortal. Although arteriography is defined as the gold standard diagnostic method (3), computed tomography (CT) angiography and antegrade/retrograde ureterography may also help in diagnosis despite their low detection rates. Treatment is mostly performed by endovascular interventions (4).

There are very few cases in the literature in which arteriography and CT angiography are insufficient, the pulsatile flow of the fistula can be observed only by ureterenoscopy. Here, we presented our 60-year-old patient with AUF who had significant risk factors such as pelvic surgery, radiotherapy (RT), recurrent ureteral stent placement, and pulsatile flow of the fistula observed by ureteroscopy.

Case Report

A 60-year-old female patient diagnosed with endometrial cancer 7 years ago applied to our clinic. It was learned that the patient had undergone total hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection 7 years ago. She had received whole pelvic RT (57.8 Gy) after surgery. In the follow-up of the patient, bilateral hydroureteronephrosis (HUN) (right compensatory hypertrophic and grade 3-4 HUN, left partial atrophic grade 1-2 HUN) was detected due to RT. His creatinine (Cre) level was 4.6 mg/dL in July 2019. Bilateral 4.8 Fr Double J stents (DJS) were inserted. Her bilateral ureteral stents were changed regularly. Although the patient had bilateral DJS for 1 year, the patients became oliguric, the continuation of hydronephrosis and the development of Cre progression concluded that the drainage of ureteral stents were not sufficient, so right nephrostomy was deemed appropriate. So in July 2020, bilateral DJS was removed and only right nephrostomy was inserted. Five days after this procedure, the patient presented to the emergency department with intermittent macroscopic gross hematuria. CT angiography and digital subtraction angiography (DSA) was performed with the initial diagnosis of right renal AUF and pseudoaneurysm. No pathology was identified. The

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patient's hemoglobin (Hgb) was 7.8 g/dL. Her blood pressure was 95/62 mmHg, pulse rate was 101 beats/min, and her respiratory rate was 18/min. Blood clots were observed in the bladder and patient was hospitalized. Magnetic resonance imaging showed a 10X8 cm hematoma in the left perirenal, subcapsular area and clot in the collecting system (shown in Figure 1). As the patient's hematuria continued and Hgb value decreased to 5.6 g/dL, cystoscopy and left nephrectomy were performed under emergency conditions. On the cystoscopy, hematoma in the bladder and after washing, an appearance compatible with radiation cystitis was observed in the bladder. Retrograde pyelography was not applied to the patient, since the patient was operated under emergency conditions due to a significant decrease in Hgb and there was no hematuric urine flow from either ureteral orifice. As the hematuria persisted on the 2nd postoperative day, the patient underwent intravenous contrast-enhanced CT angiography with the preliminary diagnosis of right renal arteriovenous fistula, right ureteroiliac fistula and left ureteroiliac fistula. However, no findings compatible with any active extravasation or fistula were found. Then, right renal angiography and bilateral pelvic arteriography were performed, but no pathology was found to explain the current situation. It was decided to perform repeat cystoscopy and bilateral diagnostic ureterorenoscopy (URS). Cystoscopy was applied first, no active hematuria was observed. Then, the right URS was applied. Active hematuria or ureteral clots were not observed. Then, the left stump was entered through the left orifice. Pulsatile arterial flow was observed at the midureteral level (shown in Figure 2a). The arterial level associated with the ureteral fistula was determined by retrograde ureterography (shown in Figure 2b). The vascular plug was immediately placed at the level of attachment of the left common iliac artery to the ureter for embolization by interventional radiologists via
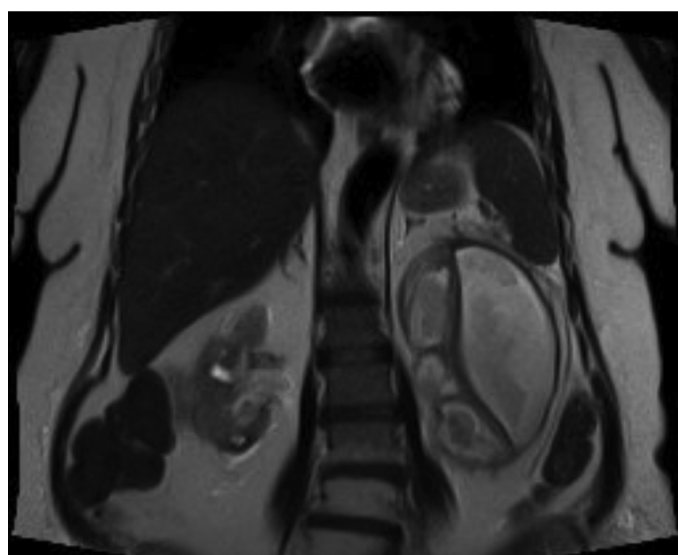
an endovascular approach (shown in Figure 2c). The patient, who had no postoperative problem, was discharged on the 5th day after the procedure. The patient did not have hematuria or fistula recurrence for a year. The patient is currently being followed up with a right nephrostomy. There is no need for hemodialysis. The cre value is at the level of 3.4 mg/dL.

Discussion

AUFs are a rare but life-threatening condition that cause massive hematuria. They typically occur where the ureter crosses the iliac vessels, close to the iliac bifurcation (1). AUFs are more common in women (4). Fistulas on the left are more common than on the right (1). While these may be vascular aneurysms or pseudoaneurysm erosion primary fistula to the ureter (15%), they are mostly secondary fistulas (85%), and they appear after urological and gynecological cancers or after radiation (5).

While pelvic surgery and radiation therapy cause fixation of the ureter to the arteries due to ischemia, inflammation and fibrosis in the artery wall by damaging the vasavasorum, placing a ureteral stent creates a basis for fistula formation by increasing the pressure and causing abrasive erosion in the ureter wall and accelerating necrosis (6,7). Recently, an increase in the incidence of AUF has been observed in parallel with the prolongation of life expectancy, the widespread use of radiation treatments, pelvic surgeries and chronic permanent ureteral stents due to pelvic malignancies (2). As the radiation dose increases, the extent of arterial damage also increases, which means more frequent AUF (8). Considering that the average time between radiation therapy and the onset of AUF is 36 months, and the average time between ureteral stent placement and the onset of AUF is 18 months, it can be said that ureteral stent placement plays a greater role in the development of AUF (9). Ureteral stents act as support against AUFs. The use of large

Figure 1. Left perirenal, subcapsular 10X8 cm hematoma and clot in the collecting system on magnetic resonance imaging
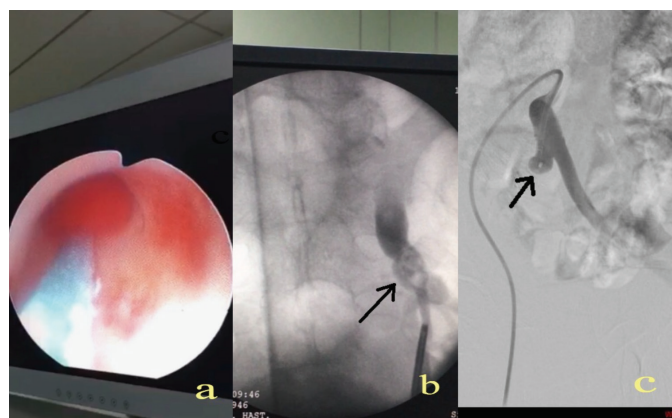
Figure 2.a. Pulsatile arterial flow at the midureteral level, **b.** Level of the artery associated with the ureteral fistula on retrograde ureterography, **c.** Vascular plug inserted through the endovascular approach at the level where the left common iliac artery connects to the ureter

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diameter ureteral stents causes ischemia by putting pressure on the ureter wall. Considering that the 7F and 12F ureteral stents have the same flow rate, care should be taken to use the smallest diameter and softest material possible during ureteral catheterization in patients with risk factors (10). Our patient also had important risk factors for AUF, such as pelvic surgery, pelvic RT and recurrent urethral stent insertion.

Unfortunately, only 22% of the patients are diagnosed correctly before treatment (11). The most common symptom up to 74% is hematuria (1). This entity, which is generally encountered with massive hematuria, may result in death, unfortunately, as it is a rare condition among the causes of hematuria (11) and is diagnosed late and even often undiagnosed.

If hematuria occurs in patients undergoing pelvic surgery, radiation and ureteral stenting, AUF should be kept in mind and pelvic angiography should be performed when the diagnosis cannot be made with imaging methods. The probability of CT Urography showing positive findings in AUF is only 22% (1). Although contrast-enhanced CT can show the enhancing mass at the point where the ureter crosses the vessel wall in the presence of a pseudoaneurysm, bleeding usually occurs with a direct fistulous connection between the artery and the ureter. This situation makes it impossible to show AUF with cross-sectional imaging (6). Studies have shown that CT helps in diagnosis only in 42% of the cases (1). DSA remains the gold standard for the diagnosis of AUF. However, it can still show the accuracy of the diagnosis to be as low as 69% (1). For DSA to indicate an active fistula, there should typically be a flow rate faster than 3 mL/s. If it is considered that abnormal findings are not observed in approximately one-third of the patients with AUF even with DSA, angiographic examinations must be evaluated with different oblique projections. This is because small pseudoaneurysms can be overlooked because of overlapping the iliac arteries. Although the diagnostic value of angiography increases with provocative maneuvers such as manipulating, removing of ureteral stents or thrombolytic applications, it should be kept in mind that these maneuvers may lead to massive hematuria and emergency intervention may be required (7). As an alternative to arteriography, diagnosis can be made by antegrade or retrograde ureterography by direct contrast extravasation from the ureter to the arterial structures. In a study, the accuracy of this method in diagnosis was found to be 52% (1). Ureterography should be considered in patients in whom AUF is highly suspicious but angiograms cannot explain the cause. It should be remembered that the suspicion is important in these patients, as our patient could not be diagnosed with angiographic studies, but diagnosed by retrograde ureterography and ureteroscopy. A mean of 2.4 instrumental examinations for patients was required to achieve the correct diagnosis (1). Mortality due to AUF varies between 7% and 23% (3).

Although open surgery accompanied by vascular ligation and/or nephrectomy preserves its place as a form of treatment (2), less invasive endovascular interventions that require a multidisciplinary approach with the cooperation of urologists and interventional radiologists have been accepted as the main treatment for treating AUFs recently (3). Malgor et al. (12) found that patients treated with open repair had a higher rate of enterocutaneous fistula (60%) and rate of early complications (27%) than the endovascular treatment. Fox et al. (13) found no difference in hematuria recurrence in patients treated with open (33%) and endovascular repair (14%). In patients with a short life expectancy, urinary diversion with percutaneous nephrostomy may be an alternative in addition to ureteral occlusion. However, it should be kept in mind that this method may progress with recurrent bleeding without arterial occlusion or repair (14). Nevertheless, endovascular repair remains the treatment of choice in the appropriately selected patient, as many patients have been successfully treated with endovascular intervention and open surgical repair is uncomplicated. We also used the embolization method with the endovascular approach in our patient in accordance with the treatment method of our age. Following the right main femoral artery entrance, the left common iliac artery was selectively catheterized using a hydrophilic guide wire and a diagnostic catheter. The arterial branch associated with the left ureter stump was embolized with a vascular plug of appropriate diameter from its origin in a way not to block the main iliac artery flow.

Ethics

Informed Consent: Informed consent was obtained from the patient who participated in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Testicular Metastasis in Renal Cell Carcinoma

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Abstract

We report on a patient, who was diagnosed with renal cell carcinoma (RCC) and presented with testicular metastasis at 5 years after the initial diagnosis, surgical interventions and systemic treatments. Although there are reports of testicular metastasis of RCC, to the best of our knowledge, our case is first who presented late recurrence in the testicular tissue despite previous tyrosine kinase inhibitor and PD1 inhibitor treatments.

Keywords: Renal cell carcinoma, testicular metastasis, case report

Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all adult malignant neoplasms and the most common sites in metastatic disease are the lungs, vertebral bones, liver and brain (1). Testis is a rare location for metastatic disease and the most common primary tumors that metastasize to the testes are reported as the prostate, lung and gastrointestinal system (2). Although RCC can metastasize to many unusual organs, testicular metastasis is an extremely rare reported issue (3).

We report on a patient, who was diagnosed with RCC and low-volume lung metastasis and presented with a testicular metastasis as the sole metastatic finding 5 years after the initial diagnosis despite tyrosine kinase inhibitor and anti PD1 inhibitor treatments.

Case Report

A 70-year-old male patient who presented with a right kidney mass was detected on ultrasonography (US) and confirmed on magnetic resonance imaging as an exophytic 58x56 mm mass with a 20x20 mm cyst (Figure 1). Staging with thorax-computed tomography showed low volume metastatic disease in bilateral lungs.

Right partial nephrectomy was performed, and the histological diagnosis of the mass was reported as RCC, clear cell type, pT1b, Fuhrman grade 2, whereas the histological diagnosis of the cyst was also reported as RCC but multilocular cystic type. Close follow-up with periodic imaging and without adjuvant treatment was recommended by the multidisciplinary tumor council.

At 1 year after the initial diagnosis, pazopanib treatment was started due to increase in the number and size of the lung nodules. After 15 months under the pazopanib treatment, solitary metastatic lesions in both lungs were resected and histological diagnosis was reported as clear cell type metastasis of RCC. At 6 months after treatment-free period, recurrent disease in the lungs was detected and nivolumab treatment was started. After 6 courses of nivolumab treatment, progressive disease in the lungs was detected and his treatment was changed to axitinib. At 1 year under the axitinib treatment he was presented with swelling in the left testicle and a left testicular mass was detected on the patient's physical examination, which has been confirmed as 34x27 mm solid mass with scrotal Doppler US. Tumor markers for testicular carcinoma were negative and histological diagnosis of the left inguinal orchiectomy was reported as clear cell type metastasis of RCC (Figure 2). Informed consent was obtained from the patient.

Discussion

Metastatic disease in the testicular tissue is a rare finding and has been reported between 0.3-3.6% in several case reports and literature reviews (4). Back in 1972, in an autopsy series with

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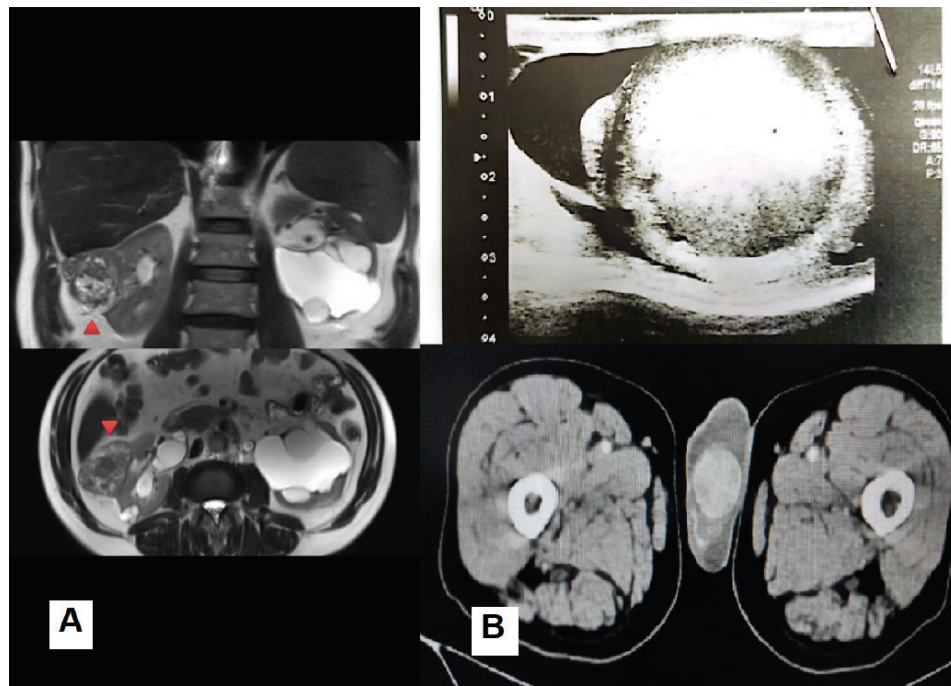
Figure 1. A. MRI of the right kidney mass, B. US and CT images of testicular mass 663x475mm (47x47 DPI)

MRI: Magnetic resonance imaging, US: Ultrasonography, CT: Computed tomography
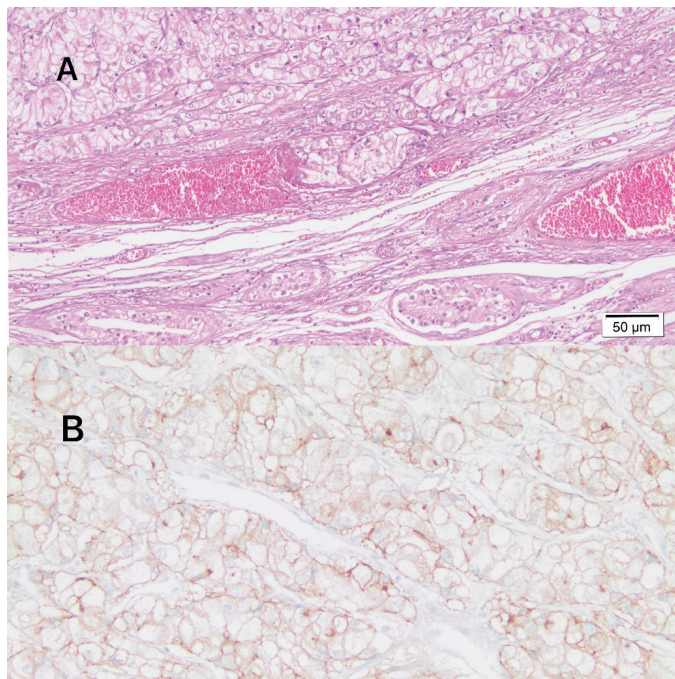
Figure 2. Histologic images of the testicular mass A. Tumor cells with clear cytoplasm adjacent to the seminiferous tubules (H&E, x100) B. Diffuse membranous staining of tumor cells with CAIX (IHC, x200) Macroscopically the tumor was a well circumscribed mass. The microscopic examination identified cells with clear cytoplasm arranged in a nested pattern with intervening delicate fibrous tissue and blood vessels (A). On immunohistochemical staining, Carbonic anhydrase IX (CAIX), was found to be positive (B) in addition to CD10, and vimentin. Histological diagnosis of the left inguinal orchiectomy was reported as clear cell RCC. 1106x1106mm (47x47 DPI)

H&E: Hematoxylin and eosin stain, IHC: Immunohistochemistry

24,000 people, metastatic disease in the testis was reported as 0.06% and the most common primary diagnosis was reported as prostate adenocarcinoma (5).

Testicles can be called a tumor sanctuary because tumor cells cannot grow easily in the testicular environment (6,7). There are some opinions explaining the rarity of testicular metastases. One of the potential reasons is that the temperature of the scrotum is lower than the normal body temperature (8). Another potential explanation might be the physiological blood testicular barrier, which is formed by Sertoli cells and protects spermatozoa's cells and prevents testicular metastasis (7).

Clinical and autopsy studies have reported that RCC can metastasize to many unusual organs (9). Testicular metastasis of RCC was reported for the first time when a patient who underwent right orchiectomy in 1943 with a pre-diagnosis of orchitis and the pathological diagnosis was not clearly understood and the patient presented with hematuria in 1945, when nephrectomy was performed in the right kidney mass and a kidney tumor was detected (10).

Theoretically, metastatic cells can come to the testicle with retrograde venous flow, arterial embolism, lymphatic pathway, and intracanalicular spread (8). Testicular metastasis of RCC is usually ipsilateral (6,11) and left testicular metastasis has been reported more common (11). It is thought that this situation may be due to tumor cells escaping retrograde to the testicle through the left spermatic venous plexus, which is directly opening to the left renal vein. However, for the right side, it is thought

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that cancer cells might migrate to the right testicle through the arterial system (7). Contralateral testicular metastasis of RCC has also been reported in the literature, and it is thought that contralateral metastases also come to the testicle through the bloodstream (11,12).

In this study, left testicular metastasis was detected 5 years after the initial diagnosis and surgical intervention. Although there are reports of testicular metastasis of RCC, to the best of our knowledge, our case is first who presented with sole metastatic lesion in the testicular tissue after previous tyrosine kinase inhibitor and PD1 inhibitor treatments for recurrent disease. The effect of testicular metastases on prognosis in RCC is not fully known due to the small number of cases.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Ö., T.T., D.F., İ.T., Concept: M.Ç., İ.T., Design: G.Ö., İ.T., Data Collection or Processing: G.Ö., M.Ç., T.T., D.F., Analysis or Interpretation: M.Ç., Literature Search: G.Ö., D.F., Writing: G.Ö., D.F., İ.T.

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

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

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