The Diagnostic Accuracy of Transvaginal Ultrasound for Detection of Ureteral Involvement in Deep Infiltrating Endometriosis

A Systematic Review and Meta-Analysis

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Abbreviations

AUC, area under the curve; DIE, deep infiltrating endometriosis; DOR, diagnostic odd ratio; LR, likelihood ratio; MRI, magnetic resonance imaging; TVU, transvaginal ultrasound

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This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made. *Objective*—The aim of this study is to determine the accuracy of transvaginal ultrasound (TVU) for the diagnosis of ureteral involvement in women with deep infiltrating endometriosis (DIE).

Methods—The meta-analysis included primary studies comparing the use of TVU for diagnosing endometriotic involvement of the ureter, using laparoscopic surgery and histological diagnosis as the reference standard. Search was performed in several databases (Scopus, Web of Science, and PubMed/MEDLINE). The studies' quality and bias risk were assessed using the Quality Assessment of Diagnostic Accuracy Study-2 (QUADAS-2). Diagnostic performance was estimated by assessing pooled sensitivity and specificity.

Results—A total of 496 citations were found. Six articles were ultimately selected for this systematic review and meta-analysis after the inclusion and exclusion criteria were applied. Pooled sensitivity and specificity were 0.81 (95% CI: 0.42–0.96), 1.00 (95% CI: 0.93–1.00). The heterogeneity observed was high for both sensitivity and specificity. Overall risk of bias was low.

Conclusion—TVU is a valuable tool for the pre-operative identification of ure-teral involvement by DIE.

Key Words-endometriosis; ureter; ureteral; kidney; ultrasound

Deep infiltrating endometriosis (DIE) is described as an infiltrative growth of ectopic endometrial stroma and glands extending throughout the peritoneal cavity or organ serosa at least 5 mm depth.¹ Painful symptoms, functional impairment of organs, and infertility can be seen in many patients. Moreover, it can present with dysmenorrhea, dyspareunia, and painful menstrual cycles.

Ureteral endometriosis is usually asymmetrical and affects the left ureter more frequently.² Ureteral lesions can be extrinsic or intrinsic. The most common type, accounting for 80% of cases, is extrinsic endometriosis, in which the lesion is adjacent to the ureter and may compress it. On the other hand, intrinsic endometriosis involves endometrial glands located in the uroepithelium,

submucosal layer, and adventitia of the ureter. Both types can coexist, and each type could present other focal points.²

The actual prevalence of endometriosis is uncertain. However, it is estimated that this disease may affect 5 to 45% of women in their reproductive age and is associated with significant morbidity. It has a very high prevalence in developed countries. DIE is a major public health concern; it is the most severe form of endometriosis with an estimated prevalence of 1% of women in their reproductive age and 14 to 20% in women with endometriosis.³ About 1 to 5.5% of patients with DIE have the urological tract affected, including the urinary bladder (prevalence: 70–85%) and ureter (prevalence: 9–23%).⁴ Almost 90% of patients with ureteral endometriosis have other sites affected as well.⁵

Sometimes symptoms caused by DIE are not specific and often lead to misdiagnosis. Pelvic examination may show tender nodules and fibrosis; however, it is not very accurate for determining the extension of the disease. Until today, the reference standard for the diagnosis of endometriosis and DIE is surgical evaluation followed by histopathological confirmation. However, DIE in retroperitoneal regions could be missed with laparoscopy. An expert TVU has demonstrated more accurate detection rates of endometriosis than laparoscopy and provides a preoperative assessment of the extent of the disease, especially in cases of DIE.^{6,7} However, the diagnosis of ureteral endometriosis can be very difficult, as it can be clinically silent or asymptomatic in about 30% of patients. Sometimes it may present itself with non-specific symptoms such as dysmenorrhea, dyspareunia, and non-cyclic pelvic pain.^{8,9} The involvement of the ureter can sometimes lead to a ureteral obstruction, leading to hydronephrosis and kidney function impairment.⁴

Although radiological methods have been proposed, there is no agreement on which diagnostic technique is most useful to assess ureteral endometriosis. The implementation of TVU is proving that it could be fundamental for the diagnosis of this disease. Another diagnostic tool used is magnetic resonance imaging (MRI), which proves to be very useful when differentiating from other malignant masses in the endometrium or abdominal cavity and making differential diagnosis of other gynecological diseases. Patients may temporarily benefit from medical therapy, but surgery is mandatory when there is a ureteral obstruction.¹⁰ Surgical options may be conservative ureterolysis or radical approaches, such as ureterectomy or ureteroneocystostomy depending on the type of location and length of ureteral involvement.⁴ The surgery is associated with the location and expansion of the disease. Sometimes the surgery might require multiple specialized surgeons, capable of accomplishing the most radical procedure.

The aim of this systematic review and metaanalysis is to evaluate the use of TVU in the diagnosis of ureteral involvement in DIE in patients with suspected endometriosis, using laparoscopy and histopathological confirmation as a reference standard. We did not aim to compare TVU with MRI.

Material and Methods

Protocol and Registration

The systematic review and meta-analysis according to preferred reposting items for systematic reviews and meta-analysis (PRISMA) and synthesizing evidence from diagnostic accuracy tests (SEDATE) guide-lines.^{11,12} The inclusion and exclusion criteria and quality assessment were specified beforehand. Protocol was not registered.

Data Sources and Search

Two authors using four databases (Web of Science, PubMed/MEDLINE, The Cochrane Library, and SCOPUS) to identify potentially eligible studies identified studies that were published between January 2000 and January 2022. The search terms were as follows: "endometriosis," "ureter," "ureteral," "ureteric," and "ultrasound." The language research was restricted to English only. We did not aim to compare TVU with MRI.

Study Selection and Data Collection Process

Two authors screened the articles by title and abstract to exclude the articles that were not relevant to the topic being studied, such as those focusing on MRI instead of ultrasound as the diagnostic method, as well as abstracts related to laparoscopic surgeries, treatments, and the prognosis of the disease. Furthermore, reviews, letter, case reports and case series that contained one case or less than 10 were also excluded. Full-text articles were gathered to identify eligible studies. The reviewers applied the following inclusion criteria

- A. Prospective and retrospective cohort studies
- B. Women with endometriosis and ureteral involvement
- C. Participants that were suspected to have endometriosis
- D. TVU used as the index test performed by expert sonographer or gynecologist
- E. Laparoscopy (visual inspection with histopathological confirmation) used as the reference standard
- F. Enough data reported to construct a 2×2 table of diagnostic performances.

We searched the reference list of papers ultimately included in this review for additional studies that could have been missed in the electronic search. In the event of missing significant data, the author was contacted for further information.

Diagnostic accuracy results and further information that was useful about patients and procedures were obtained from the selected primary studies independently by both authors. In case of disagreement concerning study selection and data collection, both authors came to a consensus among themselves.

Risk of Bias Assessment

The quality of the evidence and the risk of bias were evaluated with Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The QUADAS-2 included four different domains: patient's selection, index test (TVU), reference standard test (surgical findings), and flow and timing.¹³

The risk of bias and concerns regarding applicability were classified for each domain as high, low, or unclear. The results of the quality assessment were used to evaluate the overall quality of the studies included and to find the potential sources of heterogeneity. Two authors independently assessed the methodological quality of the studies using a quality assessment standard criterion. In the event of any disagreement between the authors, the decision was made by consensus.

The risk of bias in the patient selection domain has been determined by the inclusion and exclusion criteria of the study. All studies that did not include a consecutive cohort of patients prospectively were considered as having high risk of bias. Moreover, studies were considered to have a risk of bias if a study had inadequate exclusions, such as excluding women who did not have an image technique done or had poor quality imaging.

The index test domain was assessed based on the description of the TVU technique and sonographic criteria for defining ureteral involvement. Risk of bias was considered low when the studies described the technique and criteria used for diagnosing the involvement of the ureters and the number of lesions present.

The reference standard domain was evaluated based on the method used in the study as the reference standard for the diagnosis of ureteral involvement in DIE. The reference standard test was considered as the correct test if it was laparoscopic surgery with descriptions of the findings suggestive of ureteral involvement and histopathological confirmation of the lesions. A lack of blinding surgeons to the sonographic findings was not considered as high risk of bias.

The flow and timing domain refers to the time elapsed between the index test and the reference standard test. An interval higher than 3 months was considered a potential risk of bias.

Statistical Analysis

Data on the use of TVU for the diagnosis of infiltrating endometriosis affecting the ureters was collected. The test was considered positive if a lesion affecting any of the ureters or ureteral dilatation was seen with a TVU. A negative test was considered when no alterations were observed.

The reference test used was laparoscopic surgery with histopathological extraction confirming the disease. Primarily, we evaluated the pooled sensitivity, specificity, the positive and negative likelihood ratios (LR+ and LR-) and the diagnostic odd ratio (DOR = LR+/LR-) of TVU for the detection of DIE affecting the ureters. Calculations were done taking into account the number of ureters and not the number of patients because of this was the information that could be extracted from the studies.

The presence of heterogeneity for the sensitivity and specificity of the diagnostic method was evaluated through graphs by drawing a forest plot of sensitivity and specificity and using the Cochran's Q and the I^2 statistics. A test for heterogeneity studies the null hypothesis, in which all studies have evaluated the same effect. If P < .1 heterogeneity was established. According to Higgins et al, I^2 values of 0 to 40%, 30 to 60%, 50 to 90%, and 75 to 100% indicate that heterogeneity may not be important, moderate, substantial, or considerable, respectively.¹⁴ In case of moderate or high heterogeneity, a meta-regression was extracted. In the meta-regression, sample size, prevalence of ureteral involvement in DIE and year of publication were analyzed.

Summary receiver-operating-characteristics curve (sROC) were plotted to illustrate the relationship between sensitivity and specificity of the diagnostic tool, and the area under the curve (AUC) was calculated. We have plotted a Fagan nomogram for the evaluation of the post-test probabilities. The Fagan nomogram is a graphical tool for estimating how much the result of a diagnostic test changes the probability that a patient has a disease. The Fagan plot consists of a vertical axis on the left with the pre-test probability, an axis in the middle representing the likelihood ratio, and a vertical axis on the right representing the post-test probability (LR Negative, negative likelihood ratio; LR Positive, positive likelihood ratio). The pre-test probability in our meta-analysis was the mean prevalence of ureteral involvement of the studies included. Publication bias was assessed using Deek's method.¹⁴

Analyses were performed using meta-analytical integration of diagnostic accuracy studies (MIDAS) and METANDI commands in STATA 12th version for Windows (Stata Crop., College Station, TX); when P < .05, statistical significance was considered.

Results

Search Results

A flowchart summarizing literature identification and selection of studies is shown in Figure 1. The electronic search identified 496 citations (258 in PubMed, 91 in Web of Science, and 147 in Scopus). After the removal of 210 duplicate records, 286 citations remained. Sixty-eight articles were excluded after reading the title because they were not related to the topic addressed. Two-hundred and one studies were further excluded after reading the title and abstract because of the following reasons: main topic was treatment or surgical techniques, case reports, case series with small sample size, revision articles, and letters to the editor, and opinion.

The full text of 17 papers was read. Eleven articles were excluded due to the following reasons: insufficient data to construct a 2×2 table or the study reported data by patient and not by ureter involvement. Six articles ultimately remained to be analyzed in our meta-analysis.^{15–20}

Characteristics of Included Studies

Table 1 summarizes the main characteristics of the primary studies included in our meta-analysis. Data about 834 patients was available. Eighty-eight patients have at least one ureter affected. The total number of ureters affected was 93. Some cases were single or multiple unilateral lesions, and other cases were bilateral lesions. Multiple lesions on a single ureter were considered to affect one ureter for analytical purposes.

Five studies included a non-consecutive series of patients.^{15–18,20} In one study, this information was not reported.¹⁹ The diagnostic test used to conduct these studies was a TVU, and all studies used laparoscopic surgical findings with histopathological confirmation as the reference test, our reference standard. In four articles there was one single ultrasound expert examiner.^{15,16,19,20} In one study, there were multiple observers, also stated as expert examiners.¹⁸ One study did not report how many observers participated in the study.¹⁷

In three studies, the observers were blinded to the patients' clinical data.^{15,18,19} In one article, the observer was not blinded to these data.²⁰ Furthermore, two of the articles did not mention whether their observers were blinded or not to clinical complaints.^{16,17}

Qualitative Synthesis

The evaluation of the risk of bias and concerns regarding applicability of the selected articles is shown in Figure 2. According to the patient's selection dominion, three studies were considered to have a high risk of bias because of study design (retrospective cohort study) or because the sonographers were not blinded to the patient's history and to the results



Figure 1. Flow chart summarizing inclusion in the systematic review and meta-analysis of studies evaluating the accuracy of transvaginal ultrasound for the diagnosis of DIE with ureteral involvement.

of previous images.^{16,19,20} Regarding the index test dominion, five articles presented a low risk of bias for the index test¹⁵⁻²⁰ and one study was unclear.¹⁹

For the reference test dominion, the risk of bias was low for the six articles included because all of them used the correct reference standard we set as the -and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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Table 1. Characterist	ics of the A	rticles Inclu	ided in the Sys	stematic Review	According 1	to the PICO Crite	eria.				
Study	Country	Study Design	Multicenter	Consecutive Recruitment	Total (n)	Number of Patients	Number of Ureter	Index Test	Number of Observers	Blinded Observers	Reference Test
						Affected (n)	Affected (n)				
Vimercati (2012) ¹⁵	Italy	Prosp	No	No	06	∞	œ	TVU	Multiple	Yes	LPS with histology
Pateman (2015) ¹⁷	ХD	Prosp	No	No	345	14	14	TVU	N/A	N/A	LPS with histology
Exacoustos (2014) ¹⁶	Italy	Prosp	No	No	104	24	28	TVU	Single	N/A	LPS with histology
Zannoni (2017) ¹⁸	Italy	Prosp	No	No	47	31	31	TVU	Multiple	Yes	LPS with histology
Yin (2020) ¹⁹	China	Retro	No	N/A	198	6	10	TVU	Single	Yes	LPS with histology
Bindra (2022) ²⁰	India	Retro	No	No	50	2	2	TVU	Single	No	No LPS with histology

-PS, laparoscopy; N/A, data not available; Prosp, prospective; Retro, retrospective; TVU, transvaginal ultrasound

confirmation diagnosis of the ureteral involvement and expert surgeons performed the surgical procedures. Finally, regarding the flow and timing dominion, the risk of bias was unclear in only one of the articles, since this article did not mention or define the time interval that elapsed between the TVU and LPS.¹⁷ The other five articles presented a low risk of bias concerning flow and timing since each article mentions the time flow that conceded between each diagnostic tool.^{15,16,18–20}

The applicability concerns for all the six studies were deemed low for patient selection, index test, and the reference test.

Quantitative Synthesis

According to the studies analyzed, the sonographic signs of ureteral involvement are ureteral dilatation, abnormal peristalsis, the presence of an endometriotic nodule close to the ureter, compromising it, and hydronephrosis (Figures 3 and 4).

Pooled sensitivity and specificity of TVU for the diagnosis of DIE affecting the ureters were 0.81 (95% CI: 0.42–0.96) and 1.00 (95% CI: 0.93– 1.00), respectively. We observed high heterogeneity for sensitivity as well as specificity (Figure 5). This high heterogeneity means that there is high variability in our data. Meta-regression analysis showed that this heterogeneity could be explained by the different prevalence among studies (Figure 6). In this figure, it can be observed that the prevalence P value is <.01 for sensitivity and <.05 for specificity. This means that variation in prevalence is associated with different sensitivity and specificity, and, therefore, high variability in these figures among different studies.

The pooled positive likelihood ratio (LR+) was 818.6 (95% CI: 9.5–70,610.4) and the negative likelihood ratio (LR-) was 0.20 (95% CI: 0.05–0.8). The Diagnostic Odds Ratio (DOR) was 4194 (95% CI: 20–886,703).

Hierarchical summary receiver–operating characteristics curve is shown in Figure 7. The area under the curve (AUC) was 0.99 (95% CI: 0.98–1.00).

The mean prevalence of ureteral involvement was 10% (95% CI: 2–33%) which was calculated based on the sum of all patients found in each article and the sum of their corresponding ureters multiplied by two. Fagan's nomogram showed that a positive

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Risk of bias					Applicability Concerns		
Study	Patients selection	Index test	Reference test	Flow/timing	Patient selection	Index test	Reference test
Vimercati (2012) ¹⁵	٢	٢	٢		;	٢	٢
Pateman (2015) ¹⁶	٢	٢	•	•	٢	٢	٢
Exacoustos (2015) ¹⁷	8	٢		٢	٢	٢	•
Zannoni (2017) ¹⁸	٢	٢	•	•	٢	٢	•
Yin (2020) ¹⁹	8	:	©			:	
Bindra (2022) ²⁰	8	٢	٢	٢	٢	٢	٢

Figure 2. Qualitative characteristics for evaluation of the quality of the 6 studies included in this systematic review and meta-analysis. Happy face = low risk of bias, serious face = unclear, sad face = high risk of bias.

test for TVU increases from a pretest probability of 10% to a post-test probability of 99%. Meanwhile, a negative test showed a significant decrease from 10 to

2% in the pretest probability (Figure 8). No publication bias has been observed (P = .31).

Figure 3. Transvaginal ultrasound depicting a dilated ureter (asterisk) with stenotic point (arrow), indicating an intrinsic involvement of the ureter.



Discussion

Summary of Findings

Our results show that TVU has a very high sensitivity and specificity for the diagnosis of the involvement of the ureter or ureters in cases of DIE. Although significant heterogeneity was observed. This heterogeneity could be explained by different disease prevalence among the studies analyzed. It is interesting to note that, traditionally, it has been considered that the sensitivity and specificity of a diagnostic test are not influenced by disease prevalence. However, this concept has been challenged.²¹ This could be explained by several factors, such as examiner knowledge about the disease, symptoms distribution, patient care pathway, the spectrum of patients analyzed, an adequate

Figure 4. Transvaginal ultrasound depicting a parametrial endometriotic nodule contacting the ureter, indicating an extrinsic involvement of the ureter.



reference standard, inadequate exclusions, and verification bias. $^{\rm 22}$

In addition, as mentioned previously, a positive result on the diagnostic test significantly increases the probability of having the disease. Meanwhile, a negative result significantly diminishes the probability of having the disease. On the other hand, we believe that the quality of the studies included in this systematic review and meta-analysis is acceptable.

It should be noted that the diagnostic odd ratio, defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease, is very high, which means that TVU has a great ability to identify the truly affected patient. However, the 95% CI for this figure is very wide. The small number of patients

Figure 5. Forest plots demonstrating pool sensitivity and specificity of Transvaginal Ultrasound in the diagnosis of affected ureters in DIE. Only the first author of each study is given.





Figure 6. Meta-regression analysis performed.

included in this meta-analysis can explain this wide confidence interval.

Interpretation of Results

The true prevalence of ureteral involvement in endometriosis is uncertain. There is a large variability in the literature published, with a prevalence of 0.3 to 12% in most studies,^{23,24} but some studies have reported up to 23%, representing 30 to 50% of patients with DIE.⁴ Therefore, diagnosing ureteral involvement may be a sign of an extended pelvic disease with the corresponding clinical implications. Out of the urinary tract, the bladder is the most commonly affected organ, accounting for 85% of all urinary tract site involvement.⁴ The evaluation of the bladder may be easier, but it should not be performed isolated from the whole evaluation of the genitourinary system.

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Figure 7. Summary receiver-operating characteristics curves (—) showing performance of TVU in detecting ureteral involvement in women affected with DIE. O, study estimates; ◊ summary point; , 95% confidence region; ..., 95% prediction region.



The ureteral involvement does not have a specific clinical presentation, and half of the population may be asymptomatic.⁵ This involvement may be the first stage of a complete urinary tract disease, which may lead to a ureteral stenosis, hydroureter and hydronephrosis.²⁵ Around 30% of the women with ureteral endometriosis at the moment of diagnosis will already have lost ipsilateral kidney function by 25 to 50%.^{26,27} For this reason, a clinical diagnosis may be difficult but it should not be missed due to the possible loss of renal function, especially in women with DIE. Some other symptoms related to ureteral involvement have been reported, such as abdominal flank pain, gross hematuria, dyspareunia and dysmenorrhea, highlighting the importance of clinical examination of these women, to not miss a possible UTE involvement.²⁸

On the other hand, the laparoscopic surgical approach is nowadays the recommended access to ureteral endometriosis.⁴ Many different surgical strategies have been described to free the ureter, and therefore, a suspicion of its involvement may be important to the surgical plan. Procedures such as ureterolysis, ureterectomy with uretero-ureteral anastomosis, uretero-neocystostomy, and excision of

Figure 8. Fagan nomogram for the detection of ureteral involvement in DIE with TVU, based on negative (\rightarrow) , and on positive (\rightarrow) detection of ureteral involvement using a TVU in women with DIE. LR-, Negative likelihood ratio; LR+, Positive likelihood ratio; prob, probability.



other endometriosis lesions.²⁸ Laparoscopic surgery of the ureter is considered a complex procedure and it should be performed by well-trained surgeons.^{29,30} In many hospitals, gynecologists do not have expertise over the urinary tract organs and may need help from a multidisciplinary team, including urologists. Furthermore, the presence of pelvic endometriosis by itself is a risk factor for complications during gynecological surgical procedures. Urinary tract complications, such as ureter-disruption or bladder incision are part of the worst complications in these common surgeries. Studies have been made to evaluate the risk of genitourinary system disruption during gynecological surgeries. For example, in the event of hysterectomy, this risk is higher when an endometriosis is diagnosed compared with nonendometriosis patients.³¹ Other complications, such as urinary tract obstruction, bleeding, or postoperative fistula formation, were also higher in this study when endometriosis was diagnosed preoperatively.

Therefore, assuming the ureteral involvement may be a silent disease and its possible clinical relevance to the patient outcome, and considering the complexity of the surgery, it is very important to diagnose ureteral endometriosis involvement to assure a correct surgical strategy and avoid severe complications. In fact, some authors consider that ultrasound evaluation of the ureters is mandatory in all women suspected as having pelvic endometriosis.³²

It is important to evaluate the feasibility of the TVU to correctly identify the ureters.^{33,34} Multiple studies in the literature have proven to be able to diagnose endometriosis in a feasible way compared with other techniques such as MRI.^{35,36} The nodules in the anterior compartment can be well described due to the feasible measurement of the different parts of the bladder, urethra, and the tract of the ureters. The cystoscopy is an invasive procedure, which should be used to confirm nodules once we have diagnosed them through an ultrasound exam.³⁴ Out of all the image diagnostic techniques, ultrasound analysis is considered as accurate and the most cost-efficient.³⁷ It should be borne in mind that transvaginal ultrasound is more widely available than MRI. Furthermore, MRI is more expensive than TVU. Certainly, TVU requires experience to reach a good diagnostic performance, but this is also true for MRI imaging reading. Our data confirm that TVU is accurate for detecting ureteral involvement. However, we should note that our findings are based on studies in which ultrasound was performed by expert examiners. This fact could overestimate the actual diagnostic performance of TVU in general practice. On the other hand, the learning curve of TVU seems not to be too long. It is necessary to perform between 30 and 50 TVU to properly identify the ureters in real time.^{38,39} However, we must stress that we did not compare TVU with MRI. Thus, we cannot ascertain with our data whether TVU is better or worse than MRI for diagnosing ureteral involvement in patients with DIE.

Strengths and Limitations

We consider that the main strength of our metaanalysis is that it is the first meta-analysis that has analyzed qualitatively and quantitatively the TVU diagnosis of ureter involvement in endometriosis. We must also highlight the correct methodology.

The main limitation of this meta-analysis is the small number of studies included, only six and, as consequence, the very small number of patients. From a methodological point of view, the heterogeneity between them could also increase the risk of bias and therefore the results.

Conclusions

Transvaginal ultrasound is a very useful diagnostic tool for the diagnosis of endometriosis and DIE affecting the ureters.

Informed Consent Statement

Patient consent was waived due to study design. Institutional Review Board (IRB) was waived due to study's design.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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