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Journal Policies

Insight Urology is the official journal of the Thai Urological Association under Royal Patronage. We accept submissions on interesting urological topics from physicians and all medical providers. The topics must not have been previously published.

Objectives

1. To enhance medical research in urology
2. To instigate academic discussions in urology
3. To distribute dedicated works and research in urology

Our experts and native English speakers will review all chosen topics. All of the content and opinions in this journal belong solely to the authors, and do not express the opinions of the editors or the Thai Urological Association under the Royal Patronage.

Owner The Thai Urological Association under the Royal Patronage (TUA)

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Date of Issue Semi-annually (June and December)

Editorial

The eighth issue of *Insight Urology* (ISU) was published online in June 2024. It comprises five original articles, two review articles, and one case report. It covers several fields of urology, such as general urology, oncologic urology, endourology, and robotic surgeries.

Two review articles were submitted by renowned international authors, namely "**Cardiovascular risk and urolithiasis: underestimated or unknown relationship?**" and "**Transforming urology: exploring the innovations and utilizations of robotic systems**". We are confident that you will enjoy reading and applying the knowledge in these articles to your present urological work, especially when treating stones in adult patients and performing robotic surgeries.

The front cover of this issue features four photographs of the National Archives of Thailand (NAT), which was established in 1916 as a section of the National Library of Thailand. It officially became the NAT on 18 August 1952. The NAT is responsible for collecting and preserving public and other historical records and making them available to the public. The NAT collection consists of over 1 million historical government and public records dating from the reign of King Rama III to the present.

The photograph on the upper left is the **Office Building of the NAT**, located in Samsen Road, Dusit District, Bangkok. The photograph on the lower left is of the **Prince Bijitprijakara Room** for written documents, while the photograph on the lower right is of the **stair to the second floor** displaying four important pictures. The photograph on the upper right is of the **Prince Purachatra Room** for photographs, maps, and plans. Additionally, there are also other National Archive buildings in each region of Thailand.

The Editorial Board of ISU hopes that the cover of this issue represents the importance of documenting and preserving knowledge for our descendants. The father of Thai history, **Prince Damrong Rajanubhab**, once stated, "**A man who thinks he knows enough is a dead man walking, for as the world continues to spin, we must keep learning in order to stay in the world without being foolish.**" Likewise, we sincerely believe that Thai urologists must keep striving to improve their knowledge in the same way in order to enhance their treatment and practices.

No reserve. No retreat. No regret.

Assoc. Prof. Phitsanu Mahawong, M.D.
Editor in Chief of Insight Urology

Contents

Original Article

Comparative outcomes between adjuvant and salvage radiotherapy in prostate cancer after minimally invasive radical prostatectomy

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Keywords:
Prostate cancer, adjuvant, salvage, radiotherapy, radical prostatectomy

Abstract

Objective: Radical prostatectomy (RP) is the standard treatment in clinically localized prostate cancer. However, the timing of postoperative radiotherapy (RT) in patients with adverse pathologic features or PSA persistence remains controversial. The objective of this study is to compare the survival outcomes and treatment complications between adjuvant radiotherapy (aRT) and salvage radiotherapy (sRT) in patients after minimally invasive RP.

Materials and Methods: This retrospective study reviewed the clinical data in patients who underwent minimally invasive RP in our institution between January 2012 and April 2021. The patients were divided into three groups: no RT, aRT, and sRT. Patient demographic data, pathological reports, RTOG/EORTC toxicity scores, functional outcomes, and survival outcomes were compared between aRT and sRT groups.

Results: A total of 487 patients were included in the study. One-hundred and thirty-three patients (27.3%) received postoperative RT. The pathological stage and positive margin rate were significantly higher in the aRT group. Five-year ADT-free survival (78.8% vs 80%, p = 0.68), 5-year metastasis-free survival (80.2% vs 92.2%, p = 0.38), and 5-year overall survival (97.1% vs 100%, p = 0.68) were no different between groups. There were no significant differences in continence, potency, genitourinary or gastrointestinal toxicities between groups.

Conclusions: Timing of postoperative RT does not affect survival. Functional outcomes and radiation toxicity were comparable between patients undergoing aRT and sRT.

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Introduction

Prostate cancer is the fifth most common malignancy in men in Thailand.[1] Radical prostatectomy (RP) is the standard treatment for clinically localized prostate cancer in a patient with a long-life expectancy. However, biochemical recurrence (BCR) occurred in 20-40% of patients after RP within 10 years.[2] BCR is an independent risk factor for the development of metastasis, prostate cancer-specific mortality, and overall mortality.[2]

Postoperative radiation therapy (RT) has an important role in reducing recurrence and increasing survival.[3-5] There are 2 major types of postoperative RT. Adjuvant RT (aRT) which is started after the patient's recovery, aiming to reduce the disease recurrence in patients at a high-risk of recurrence based on the adverse pathological features. Salvage RT (sRT) which is administered after the detection of BCR, aims to treat recurrent disease. Oncological benefits from the treatment should be balanced with the adverse effects of the treatment.

Currently, based on large randomized controlled trial studies, the role of aRT was found to be limited.[6-8] aRT did not demonstrate superior outcomes over sRT in terms of disease progression, and also increases the risk of genitourinary toxicity (GU) including urethral stricture, incontinence, and hematuria.[6-8]

This study aimed to investigate and compare the treatment outcomes between aRT and sRT including disease control rates and radiation-related complications in prostate cancer patients after minimally invasive (laparoscopic and robot-assisted) RP.

Materials and Methods

Study populations

After approval of the study protocol from the institutional review board and the ethics committee (Protocol Number: 659/64), all medical records of the patients who underwent minimally invasive RP in our institution between January 2012 and April 2021 were retrospectively reviewed. The patients were divided into three groups: those who did not receive postoperative RT, those who received aRT, and those who received sRT.

Patients in the aRT group received RT at the prostatic fossa (55.2-70.2 Gy in 30-39 fractions) after they recovered from surgery without having BCR. Patients in the sRT group received an RT dose of 66-79.2 Gy in 33-39 fractions when they had BCR which was defined as an increase in the serum PSA level of more than 0.2 ng/ml twice after surgery. The decision regarding treatment is based on surgeon and patient preference after consideration of the pathological results and disease staging.

Surgical techniques

The surgical techniques have been described previously.[9] Briefly, all the procedures were performed by the conventional transperitoneal approach with 5-trocar insertion. Robot-assisted RP was performed by the da Vinci Si Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). Pelvic lymphadenectomy was performed using the standard template in the patients who had a high risk of metastasis following the nomogram. Neurovascular bundles were preserved in the selected patient. Urethro-vesical anastomosis was performed with the continuous suture by two V-loc 3/0 sutures.

The patients were followed up at 1, 3, 6, and 12 months after surgery and then subsequently every 6 months. Serum PSA, continence, and potency status were recorded.

Outcome measurement and statistical analyses

Demographic data, pathological reports, and functional outcomes after surgery from all patients were analyzed. These parameters were also compared between the aRT and the sRT group. Pathological staging was classified following the 2017 American Joint Committee on Cancer AJCC Staging 8th edition.[10] Continence was defined as no pad used or use of a protective pad. Potency was defined as being able to have an erection sufficient for sexual intercourse with or without using a phosphodiesterase type 5 inhibitor.

The primary outcomes of this study were the oncological results among the patients who received postoperative RT. Androgen deprivation therapy (ADT)-free survival, metastasis-free survival, and overall survival were compared between the aRT group and sRT group. ADT-free survival was defined as a patient who did not receive ADT after complete adjuvant or salvage treatment which included patients who received ADT in combination with RT.

The secondary outcome was to compare the adverse effects of radiation therapy between aRT and sRT groups. The genitourinary (GU) and gastrointestinal (GI) tract toxicity grades were allocated in accordance with the guidelines published by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC)[11] throughout the follow-up period.

This study also compared the results from a subgroup of patients with "high-risk features" defined as patients with pTstage 3-4 or Gleason grade group 4-5 or positive surgical margin status.

Statistical analysis was carried out using STATA version 17 (StataCorp, College Station, Texas, USA). Categorial variables were compared using the chi-square or Fisher exact test and presented as number and percentage. Continuous variables were compared using the Wilcoxon rank sum test and presented as median and interquartile range (IQR).

Survival was analyzed using the Kaplan-Meier method. Survival in the study group was compared using the log-rank test, with the significance level set at 5%. Results are presented as survival at various time points with their associated 95% confidence interval (CI).

Results

A total of 501 patients with clinically localized prostate cancer underwent minimally invasive RP in our institution during the study period. Eight patients were excluded due to incomplete medical records and six patients with variant histology were also excluded from the study. Among the remaining patients, 354 patients did not receive postoperative RT, 63 patients received aRT, and 70 patients received sRT (Figure 1).

Demographic data of all patients are presented in Table 1. The median age was 67 years. The median preoperative PSA was 10.1 ng/ml. Most of the patients were at pT2 stage (54.7%) and had a Gleason score of 7 (67.5%). The positive surgical margin rate was 41.1%. The median follow-up duration was 3.7 years.

Comparisons of aRT and sRT group

In the group of patients who received postoperative RT, comparative outcomes between the aRT and sRT group are shown in Table 2. Patients in the aRT group had significantly higher pathological staging and positive surgical margin rate ($p = 0.03$, and $p < 0.001$ respectively). The median time after surgery to RT was 5 months in

Table 1. Patient characteristics of total populations at baseline (N=487)

Variables	
Age (years), median (IQR)	67 (62-71)
BMI (kg/m^2), median (IQR)	24.1 (22.3-26.4)
Preoperative PSA (ng/dl), median (IQR)	10.1 (7.1-15.3)
Pathological T stage, n (%)	
pT2	266 (54.7)
pT3a	152 (31.3)
pT3b	65 (13.4)
pT4	3 (0.6)
Gleason score, n (%)	
6	87 (17.9)
7	328 (67.5)
8-10	71 (14.6)
Follow-up duration (years), median (IQR)	3.7 (2-5.6)
Positive margin rate, n (%)	200 (41.1)

IQR = interquartile range, PSA = prostate specific antigen

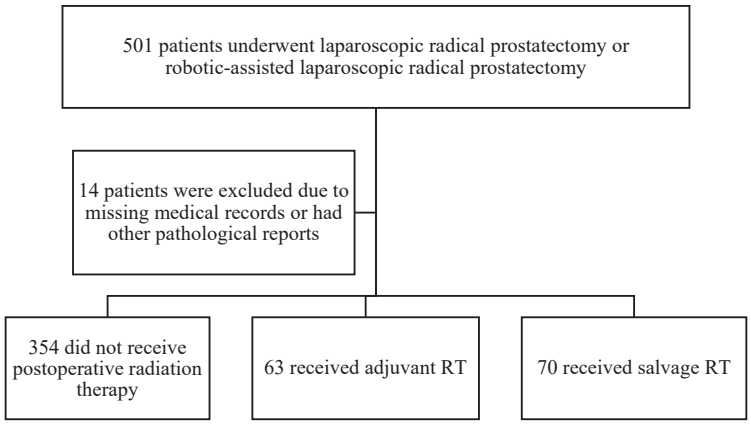


Figure 1. Trial population

Table 2. Baseline patient characteristics of postoperative RT populations (n=133)

	Adjuvant RT (n=63)	Salvage RT (n=70)	P-value
Age (years), median (IQR)	68 (62-71)	66 (62-70)	0.39
BMI (kg/m^2), median (IQR)	24.2 (22.3-26.6)	25.3 (23.5-26.9)	0.14
Preoperative PSA (ng/dl), median (IQR)	14.6 (7.8-20.7)	10.8 (7.6-17)	0.21
Pathological T stage, n (%)			0.03
pT2	20 (31.8)	35 (50)	
pT3a	23 (36.5)	25 (35.7)	
pT3b	20 (31.8)	10 (14.3)	
pT4	0	0	
Gleason score, n (%)			0.13
6	3 (4.8)	9 (12.9)	
7	40 (63.5)	47 (67.1)	
8-10	20 (31.8)	14 (20)	
Time to postoperative radiation (months), median (IQR)	5 (3-6)	21 (12-34)	-
Length of follow-up (years), median (IQR)	4.6 (3.2-6.3)	5 (3.4-7.1)	0.78
Combined ADT, n (%)	21 (33.3)	23 (32.9)	0.95
Positive margin rate, n (%)	54 (85.7)	35 (50)	<0.001
Continence, n (%)			
Months 1	0/43 (0)	9/63 (14.3)	0.01
Months 3	9/44 (20.5)	17/58 (29.3)	0.31
Months 6	21/47 (44.7)	31/59 (52.5)	0.42
Months 12	25/45 (55.6)	45/60 (75)	0.04
Potency, n (%)			
Months 1	0/6 (0)	3/43 (7)	0.50
Months 3	1/9 (11.1)	5/42 (11.9)	0.95
Months 6	1/7 (14.3)	7/39 (18)	0.81
Months 12	1/5 (20)	7/33 (21.2)	0.95

IQR = interquartile range, BMI = body mass index, PSA = prostate specific antigen, RT = radiation therapy, ADT = androgen deprivation therapy

the aRT group and 21 months in the sRT group. The median (IQR) PSA level at the time of sRT was 0.28 (0.21-0.49) ng/dl.

One-third of patients in both groups received ADT in combination with RT (33.3% in the aRT group and 32.9% in the sRT group). The duration of additional ADT was between 6 months to 2-3 years in all patients. Continuous ADT was required if the disease couldn't be controlled during the treatment. Continence rates were significantly better in the sRT group at 1, and 12 months after surgery (p = 0.01, and p = 0.04 respectively). Potency was no different between groups. Median follow-up was 4.6 years in the aRT group and 5 years in the sRT group.

There were 9 deaths (1.85%) in the total population during the follow-up period. Eight patients were from the non-postoperative RT group (4 patients from pneumonia, 1 patient from prostate cancer, 1 patient from pancreatic cancer, 1 patient from leukemia, and 1 patient from COVID-19). Only one patient from the aRT group died from prostate cancer. None of the patients in the sRT group died during the study.

The Kaplan-Meier curves of the survival studies are shown in Figure 2. There were no significant differences in the survival rates between groups. Five-year ADT-free survival was 78.8% (95% CI 62.2-88.7) in the aRT group and 80% (95% CI 68-88.7) in the sRT group (p = 0.68). Five-year metastasis-free survival was 80.2% (95% CI 63.2-89.9) in the aRT group and 92.2% (95% CI 82.4-96.7) in the sRT group (p = 0.38). However, 10-year metastasis-free survival was significantly better in the sRT group (p = 0.01). Five-year overall survival was 97.1% (CI 83.6-97.3) in the adjuvant RT group and 100% in the salvage RT group (p = 0.68).

Toxicities from postoperative RT were compared between groups and presented in Table

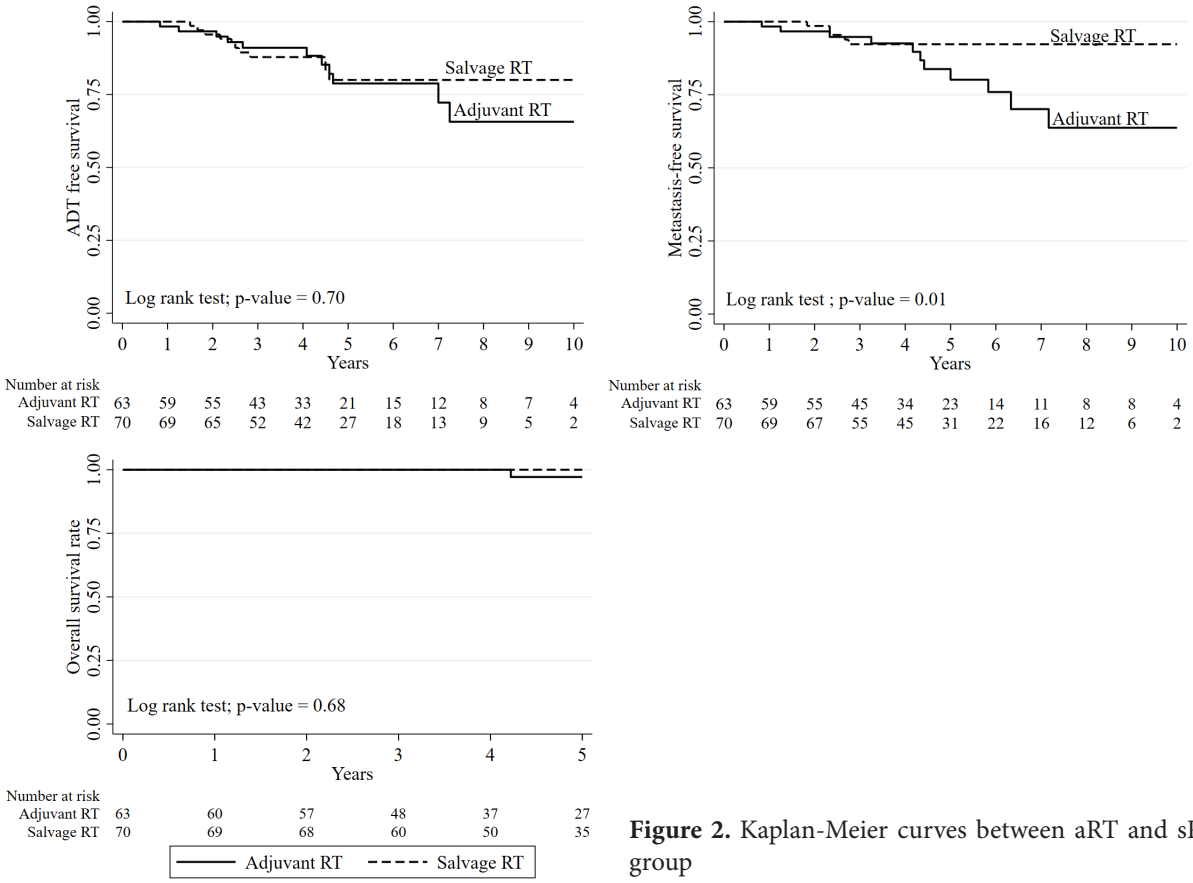


Figure 2. Kaplan-Meier curves between aRT and sRT group

Table 3. Radiation toxicity

RTOG/EORTC toxicity score	Adjuvant RT (n=63)	Salvage RT (n=70)	P-value
Acute radiation morbidity, n (%)			
Genitourinary organ			0.56
Grade 1	14 (22.2)	15 (21.4)	
Grade 2	1 (1.6)	0 (0)	
Gastrointestinal organ			0.62
Grade 1	1 (1.6)	2 (2.9)	
Late radiation morbidity, n (%)			
Genitourinary organ			0.49
Grade 1	5 (7.9)	2 (2.9)	
Grade 2	5 (7.9)	6 (8.6)	
Grade 3	0	1 (1.4)	
Gastrointestinal organ			0.17
Grade 1	0	5 (8.8)	
Grade 2	2 (3.2)	1 (1.4)	
Grade 3	1 (1.6)	1 (1.4)	

RTOG = Radiation Therapy Oncology Group, EORTC = European Organization for Research and Treatment of Cancer, RT = radiation therapy

3. Incidence of early and late GU and GI tract toxicities were not significantly different between groups. Approximately 20% of patients in each group experienced acute GU tract toxicities, the majority being grade 1. There were 3 late grade 3 toxicities that occurred in this study. Two patients experienced severe bladder telangiectasia with intractable gross hematuria treated with bladder fulguration and hyperbaric oxygen therapy. One patient had rectal mucosa necrosis that required endoscopic treatment.

Subgroup analysis of high-risk patients

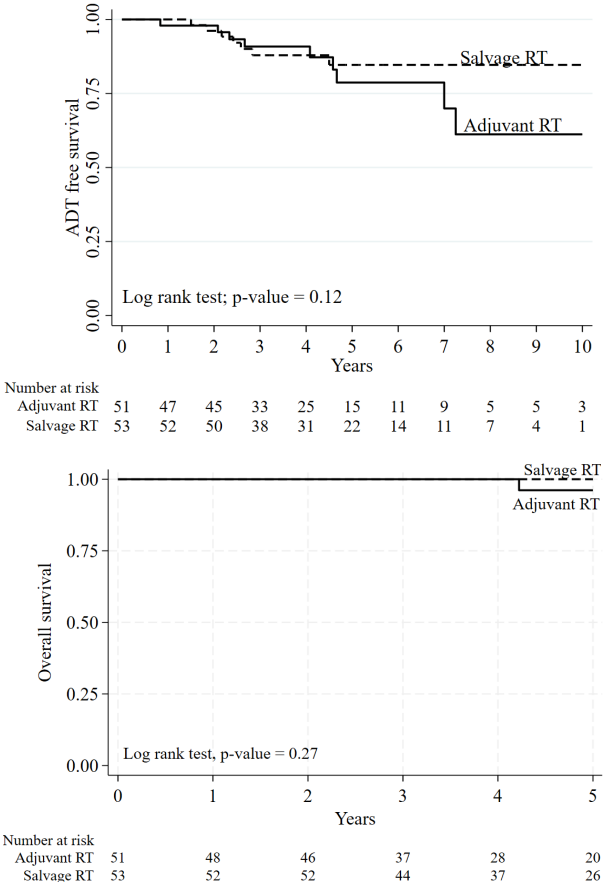
There were 51 high-risk patients in the aRT group and 53 high-risk patients in the sRT group. The continence rate was significantly better in the sRT group at 1 month after surgery (0% vs 14.6%, p = 0.02). There were no significant differences in radiation toxicities between groups in both GU toxicity and GI toxicity.

Survival rates among these 2 subgroups were not significantly different. Five-year ADT-free survival was 78.8% (95% CI 62.2-88.7) in the aRT group and 84.7% (95% CI 70-92.5) in the sRT group (p = 0.75). Five-year metastasis-free survival was 79.1% (95% CI 58-90.4) in the aRT group and 91.9% (95% CI 79.7-96.9) in the sRT group (p = 0.94). Five-year overall survival was 96.5% (CI 75.7-99.5) in the aRT group and 100% in the sRT group (p = 0.27). The Kaplan-Meier curves of the survival studies from the high-risk patient are shown in Figure 3.

Discussion

The optimum time for post-radical prostatectomy radiation therapy is controversial. Early aRT may improve biochemical progression; however, sRT can avoid unnecessary treatment with a low rate of radiation-related toxicity. There remains an ongoing debate among medical professionals regarding which of these two approaches is the most effective for treating prostate cancer after RP. The choices have mainly relied on the local protocols and the preferences of the patient and their physicians.

Previously, The American Urological Association and the American Society for Radiation Oncology (AUA/ASTRO), and the European Association of Urology (EAU) Guidelines suggest that patients who are at high risk of recurrence (pT3-T4, positive surgical margin) should be offered aRT.[12-14] aRT at the surgical bed in patients with adverse pathologic features has been shown to increase biochemical progression-free survival[4,5] and may also increase overall survival or prevent metastasis compared to observation.[5] However, not all these patients will experience the survival benefits from aRT, and some patients will have toxicity from radiation therapy. This is likely since the tissues surrounding the prostate bed have not yet fully healed after surgery. Therefore, aRT is associated with a higher risk of urinary toxicities such as urinary incontinence and urethral stricture.[6,7]



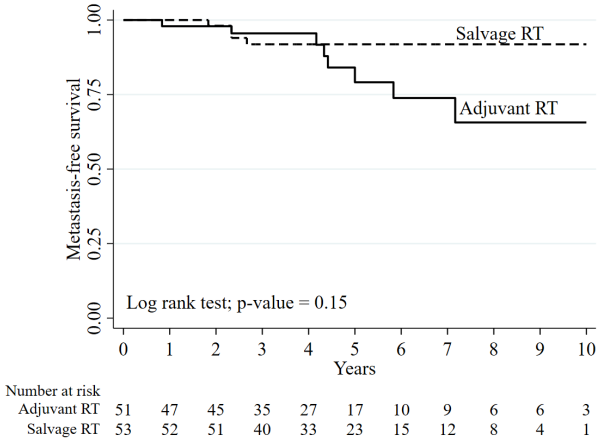


Figure 3. Kaplan-Meier curves between aRT and sRT in high-risk patients subgroup

Several studies have compared the outcomes of aRT and sRT after RP in patients with clinically localized and locally advanced prostate cancer. The results of immediate aRT within 6 months after surgery were compared with sRT that was administered when the patient had biochemical progression. The results from 3 large randomized controlled trial studies showed no statistically significant difference in the survival outcomes. This has led to a decrease in the popularity of aRT.[15]

The results from the RADICALS-RT trial[7] did not support the routine use of aRT. Five-year biochemical progression-free survival was 85% in the aRT group and 88% in the sRT group (HR 1.1; 95% CI 0.81-1.49, p = 0.56). The freedom from the non-protocol ADT at 5 years was 93% in the aRT group and 92% in the sRT group (HR 0.88; 95%CI 0.58-1.33, p = 0.53). Moreover, early and late RTOG toxicities were significantly higher in the aRT group in both GU and GI tracts. The RAVES trial[6], which is a non-inferiority trial, supported using the sRT with the comparable biochemical control with aRT, and 50% of patients in the sRT group may avoid radiation therapy. Five-year freedom of biochemical progression was 86% in the aRT group compared with 87% in the sRT group (stratified HR 1·12, 95% CI 0·65-1·90; p = 0·15). The GETUG-AFU 17 trial[8] found aRT with 6-month ADT has no benefit for 5-year event-free survival (92% vs 90%, HR 0·81, 95% CI 0·48–1·36; log-rank p = 0·42) and 5-year overall survival (96% vs 99%, HR 1.6, 95%CI 0.71-3.6, p = 0.25) over sRT with 6-month ADT.

Vale et al. reported a meta-analysis incorporating data from these 3 RCTs with a total of 2,151 patients. There was no evidence of an advantage in event-free survival with aRT compared to early sRT (HR 0.95; 95% CI 0.75–1.21, p = 0.7).[16]

In a study in Thai patients, Woranisarakul et al.[17] compared the results between aRT and sRT in 151 prostate cancer patients with adverse pathological features after radical prostatectomy. There were no statistically significant differences in 5-year BCR-free survival (78.7% vs 69.1%, p = 0.11) and 5-year metastasis-free survival (100% vs 90.6%, p = 0.05) between groups. The incidences of grade 3 to 4 late gastrointestinal and genitourinary toxicities were 5.8% and 10.8% respectively. In our study, we found that the survival rates between the two treatment groups (both the total population and the subgroup of the high-risk patients) were not significantly different. These findings are consistent with the results from all the previous studies. However, the metastasis-free survival curve showed a separation starting after 5 years of follow-up, resulting in better outcomes in the sRT group compared with the aRT group at 10 years (p = 0.01). This could be due to the high proportion of locally advanced disease and positive surgical margin patients in the aRT group which has a greater chance of being resistant to treatment and causing disease progression. Furthermore, there was no difference in both acute and late radiation toxicities. However, the continence rate was better in the sRT group only in some periods.

The combination of ADT with sRT is an important factor in survival outcomes and is still undergoing debate. The RGOT 9601 study[18] showed the benefit of adding daily 150 mg of bicalutamide for 24 months to sRT in comparison with sRT-only in recurrent prostate cancer. The 12-year overall survival rate was significantly better in the combination group, especially in the subgroup of patients with PSA > 1.5 ng/ml (HR 0.45, 95%CI 0.25-0.81, p = 0.007). The incidences of 12-year metastasis prostate cancer and prostate cancer-related death were also significantly lower in the combination group. More recently, the results from GETUG-AFU 16[19] supported the benefit of short-term ADT by using 6 months of goserelin combined with sRT over sRT alone. 10-year progression-free survival (HR 0.54, 95%CI 0.43-0.68, p < 0.0001) and metastasis-free survival (HR 0.73, 95%CI 0.54-0.98, p = 0.03) were significantly better in the combination group.

In contrast, the results from Thai patients showed a combination of ADT with aRT in high-risk prostate cancer patients after radical prostatectomy couldn't improve 10-year metastasis-free survival (p = 0.78). However, combined treatment resulted in an improving trend in improving BCR-free survival over aRT alone (HR 0.4, 95%CI 0.16-1.03, p = 0.05).[20]

Spratt et al.[21] presented a decision framework for the use of hormonal therapy combined with sRT in recurrent prostate cancer based on the pre-sRT PSA, margin status, and ISUP grade. The patient with a high risk of progression may benefit from combined long-term (2 years) ADT. For the patient at a low risk of progression, combined short-term (6 months) ADT may be sufficient.

In the patients with low-risk profiles, combined ADT may not be helpful.

The limitation of this study is its retrospective nature with a selection bias which limits the reliability of the data. Patients in the aRT group had a higher pT stage and higher positive margin rates. There is no standard rationale for combining ADT with RT. This relies on the individual decision made mutually by the surgeon and patient, the duration of ADT varying which is influenced by the evolution of treatment over time.

Conclusions

The timing of postoperative RT after radical prostatectomy does not affect survival outcomes. Functional outcomes and radiation toxicities were comparable between aRT and sRT. Our findings support the use of early sRT over aRT in patients with adverse pathological features.

Conflicts of Interest

The authors declare no conflicts of interest.

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Original Article

Effect of implementation of Enhanced Recovery After Surgery Protocol on elective open simple nephrectomy in urolithiasis

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Keywords:
ERAS protocol, elective open simple nephrectomy, urolithiasis

Abstract

Objective: To assess the impact of the implementation of an Enhanced Recovery After Surgery (ERAS) protocol in elective open simple nephrectomy in urolithiasis patients.

Materials and Methods: Data from 43 patients were collated. Sixteen were in the ERAS group and 27 in the pre-ERAS group, the division created by date of the procedure. The ERAS protocol included preoperative education, standardized perioperative care, early mobilization, and postoperative pain management. Outcomes, including length of hospital stay (LOS), first flatus, first defecation, complications, pain scores, creatinine level (Cr), glomerular filtration rate (GFR) and associated costs, were compared.

Results: The ERAS group exhibited significantly lower total LOS (3.19±0.40 days vs. 6.22±1.55 days, $p < 0.001$), earlier first flatus (1.19±0.40 days vs. 2.66±1.11 days, $p < 0.001$), first defecation (1.56±0.73 days vs. 3.11±1.28 days, $p < 0.001$), and lower postoperative ileus rates (12.5% vs. 71.43%, $p = 0.01$) than the control group. Lower pain scores at 1, 6, 24, and 48 hours post-surgery ($p < 0.05$) were also recorded in comparison to the control group. No significant differences in Cr and GFR were observed ($p > 0.05$). Although ERAS treatment costs were marginally lower, the difference was not statistically significant (23,833±3731.48 Baht vs. 23,930±3068.45 Baht, $p = 0.927$).

Conclusion: ERAS implementation in elective open simple nephrectomy for urolithiasis reduces LOS, and postoperative pain, accelerates recovery of bowel function, and allows quicker resumption of normal activities. These benefits come without increased risk of readmission or complications, and without compromising postoperative renal function. All these advantages may also result in cost savings.

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Introduction

Urolithiasis represents a significant healthcare burden worldwide. There are multiple approaches to the treatment of urolithiasis. One such approach is nephrectomy, which is indicated in patients with recurrent urinary tract infection, pain, severe hydronephrosis, pyonephrosis and fistula formation.[1]

Enhanced Recovery after Surgery (ERAS) is a modern and evidence-based approach in the field of medicine that aims to improve patient outcome. Studies in ERAS have shown a decrease in complications and hospital stays, improvements in cardiopulmonary function, earlier return of bowel function, and faster resumption of normal activities. However, it does not lead to a reduction in mortality or readmission.[2-5]

ERAS was initially introduced by Professor Kehlet and was successfully implemented in colorectal surgery for the first time in 1997.[6,7] An ERAS protocol, or fast-track surgery, can be implemented using a multidisciplinary and multimodal approach to reduce perioperative and intraoperative stress responses and promote the recovery of the function of various organs following surgery.[8]

Currently, the ERAS approach is being applied in association with various surgical procedures including colonic surgery[9], vascular surgery[10], thoracic surgery[11], and urological surgery.[12-16] The ERAS approach has been implemented in various aspects of urological surgery including laparoscopic radical nephrectomy[12], partial nephrectomy[13], radical cystectomy[14], laparoscopic radical prostatectomy[15], and adrenalectomy.[16] However, there is limited research on the successful application of ERAS in nephrectomy procedures for patients with urolithiasis.

This research aims to investigate the impact of an ERAS protocol on elective open simple nephrectomy for urolithiasis.

Materials and Methods

Patients

This research is a retro to prospective cohort study, meaning specifically that the data collection is divided into two periods: the retrospective analysis of urolithiasis patients who underwent elective nephrectomy at Loei Hospital from February 2017 to June 2020 (Pre-ERAS group) and the prospective study of urolithiasis patients who underwent elective nephrectomy at Loei Hospital from July 2020 to November 2023 (ERAS group). A total of 43 urolithiasis patients were included in the study, with 16 in the ERAS group and 27 in the Pre-ERAS group. Inclusion criteria were individuals with severe kidney impairment due to urolithiasis, those within the age range 18 to 80 years and who met the specific indications to undergo open simple nephrectomy as elective cases. Exclusion criteria included cases where adjacent organ injury was discovered during surgery and also cases with excessive bleeding leading to unstable vital signs. This study received approval from the Ethics Committee of Loei Hospital (approval number: EC023/2564).

Open simple nephrectomy

All patients underwent open simple nephrectomy using the retroperitoneal approach, with a single surgeon carrying out all the cases. For each patient, the anesthesiologist's approach involved a thorough assessment of the suitability of the patient for the preferred method of anesthesia. The primary choice was a combination of general anesthesia and epidural block. However, if an epidural block was found to be unsuitable for a patient, the anesthesiologist opted for general anesthesia and coordinated with the surgeon to enable local infiltration of 0.25% Marcaine around the surgical wound at the end of surgery. Following general anesthesia, the patient was positioned in the flank position, and after administration of antibiotic prophylaxis, the flank wall was meticulously opened layer by layer. Dissection around the kidney was completed, allowing the renal artery and vein to be exposed. The ureter was identified. Following complete separation, the kidney was then removed, and placement of a retroperitoneal drain was considered.

Pre-ERAS management

The patients in this study received traditional preoperative management, which included a 12-hour preoperative fasting period, bowel preparation before surgery, and restriction from food and fluids immediately post-surgery. Bed rest was obligatory for the first 24 hours, and then there was a gradual transition to a liquid diet and then a soft diet, along with the initiation of ambulation. Pain control involved administration of pain-relief medication when patients experienced significant

discomfort and requested it. Urinary catheters were removed on postoperative day (POD) 2 or 3, or later if patients demonstrated good ambulation. The drainage tube was removed when the volume of drainage decreased to less than 50 ml over three consecutive days.

ERAS management

Patients undergoing ERAS management received guidance and had their questions addressed by nurses and physicians regarding the rationale and practices associated with the ERAS protocol. This approach aims to reduce anxiety and uncertainties. Specifically, patients undergo a 6-9 hour preoperative fasting period, with no bowel preparation required. After surgery, if the patient awakens well, they start a soft diet and ambulation is initiated within 24 hours. Pain management involves administration of epidural analgesia or infiltration of the incision with local anesthetic (in cases where intraoperative epidural anesthesia is not performed) as needed when patients experience significant pain and request it. Removal of urinary catheters is planned on POD 1, while drainage tubes will be removed on POD 2 in cases where intraoperative drains are used and when the drainage volume falls below 50 ml for one day.

Data collection, definitions, and primary outcomes

General data collection included gender, age, BMI, and any underlying medical conditions. Stone-related data included any details about the location of the stone, the history of stone treatment, the causes of obstruction, and pathological findings.

Surgical data covered the method of anesthesia used, the duration of surgery, estimated blood loss during the procedure, the use of drainage tubes, and any intraoperative findings of abscesses in the kidney.

The outcome data included the length of hospital stay (LOS), comprising both total LOS and postoperative LOS., the first date of ambulation, the first instance of passing gas (first flatus), the commencement of bowel movements (first defecation), and the removal dates of urinary catheters and drainage tubes. Data were collected up to 2 weeks post-surgery and reported using the Clavien-Dindo classification system.

Renal function, both preoperative and postoperative, was evaluated by measuring creatinine (Cr) levels and estimating the glomerular filtration rate (GFR) using the MDRD GFR equation. Assessments were conducted on the date of admission and on POD 1.

Pain scores were recorded using the Visual Analog Scale (VAS) at 1, 6, 24, and 48 hours post-surgery, as assessed by nursing staff.

Lastly, total cost data was calculated covering pertinent expenses, including laboratory tests, imaging studies, medication, surgical costs, and service charges.

Statistical analysis

For the statistical analysis, STATA version 14 was used to analyze categorical data, such as gender and comorbidities, using counts and percentages. Group differences were compared using statistical tests, including Fisher's exact test. Continuous data, including age, BMI, operative time, and estimated blood loss were analyzed using mean values and standard deviation. Group differences in normally distributed data were analyzed using Independent t-tests, while skewed continuous data were assessed using the Mann-Whitney U test. A probability of $p < 0.05$ was used to indicate a statistically significant difference.

Pain score parameters, including basal condition pain scores and those measured at 1, 6, 24, and 48 hours postoperative, were analyzed using Repeated Measured Analysis of Variance tests to assess differences between the ERAS and Non-ERAS groups. Pairwise post hoc tests were conducted to compare differences in pain score parameters between each group. A p-value < 0.05 was considered statistically significant.

Results

Clinical features and surgical overview of participants

Forty-three patients with urolithiasis who underwent elective open simple nephrectomy for urolithiasis were enrolled onto this study, with 27 cases in the Pre-ERAS group and 16 cases in the ERAS group. The demographic data of the two groups is shown in Table 2. The findings revealed no statistically significant differences between the groups regarding demographic data including gender, age, body mass index (BMI), side, under-

Table 1. The key differences between the Pre-ERAS and ERAS protocols are as follows in patients undergoing open simple nephrectomy

Perioperative management	Pre-ERAS group	ERAS group
1. Patient education	Routine description of medical procedures	Routine description of medical procedures and explanation of the ERAS program. Promotion of its utilization is an essential component of this program
2. Preoperative fasting	Preoperative fasting starting 12 hr before surgery	Preoperative fasting starting 6-9 hr before surgery
3. Bowel preparation	Preparation of bowel using soap and water	No bowel preparation
4. General anesthesia plan	Balanced anesthesia	Balanced anesthesia in conjunction with the consideration of using epidural analgesia
5. Standard anesthesia	Intraoperative intravenous opioids are utilized for pain	Utilization of short-acting opioids, prevention of hypoxemia and hypothermia, maintaining control over intraoperative blood glucose and blood pressure, timely administration of blood products
6. Postoperative pain control	Intraoperative: intravenous injection of fentanyl/pethidine Postoperative: intravenous injection of morphine	Intraoperative: epidural nerve block or incisional infiltration, intravenous injection of fentanyl/pethidine Postoperative: epidural nerve block or incisional infiltration, intravenous injection of morphine
7. Ileus prevention	No	Gum chewing, early ambulation, bisacodyl rectal suppository, and minimal opioid usage
8. Postoperative activities	Commencement of ambulation based on the patient's individual capability to do so	Encouraging patient mobilization, starting from sitting and standing, gradually progressing to walking, once the patient begins to wake
9. Urinary catheter removal	POD 2-3	POD 1
10. Drainage tube removal	POD 4-5	If a drainage tube is inserted, it will be removed on POD 2
11. Postoperative fluid infusion	Patients receive 2,500 to 3,000 ml of fluids daily for 3 to 4 days after surgery	Controlled infusion with removal on POD1
12. Postoperative eating	Provision of fluids and food on POD 1 or until there are signs of bowel movement	Initiation of a soft diet when the patient is awake and alert

ERAS = enhanced recovery after surgery, POD = postoperative day

lying disease, history of previous surgery (ureterorenoscopy, open surgery urolithiasis), cause of obstruction, and pathological findings.

Analgesia during surgery differed between the Pre-ERAS and ERAS groups. In the Pre-ERAS group, the sole analgesic procedure used was general anesthesia, while in the ERAS group, 12 patients (75%) received general anesthesia in combination with epidural analgesia, and 4 patients (25%) received general anesthesia in combination with local analgesia. In terms of intraoperative findings (including surgical duration and estimated blood loss), there were no statistically significant differences between the two groups. Prophylactic drainage was utilized in all cases within the Pre-ERAS group, while in the ERAS group drainage was only used in 2 cases.

Comparison of renal function parameters

When comparing the preoperative and postoperative Cr and GFR values between the pre-ERAS and ERAS groups, no statistically

Table 2. Demographic data and surgical overview of participants

Variables	Pre-ERAS (n=27)		ERAS (n=16)		P-value
	n	%	n	%	
Sex					1.000[a]
Male	17	62.96	10	62.50	
Female	10	37.04	6	37.50	
Age (year) mean±SD	57.26	±10.42	58.63	±14.08	0.718[b]
<60 year	16	59.26	6	37.50	0.215[a]
>60 year	11	40.74	10	62.50	
BMI (kg/m^2) mean±SD	22.97	±4.17	21.49	±4.57	0.283[c]
Side					0.526[a]
Right	17	62.96	8	50.00	
Left	10	37.04	8	50.00	
Underlying diseases					
No	13	48.15	4	25.00	0.199[a]
Yes	14	51.85	12	75.00	
Diabetes mellitus	6	42.86	4	33.33	0.781[a]
Hypertension	10	71.43	7	58.33	0.683[a]
Dyslipidemia	4	28.57	1	8.33	0.330[a]
Chronic kidney disease*	6	42.86	5	41.67	1.000[a]
Chronic obstructive pulmonary disease	1	7.14	0	0.00	1.000[a]
Gouty arthritis	1	7.14	0	0.00	1.000[a]
Previous ureterorenoscopy	0	0.00	2	12.50	0.133[a]
Previous open surgery	2	7.41	3	18.75	0.344[a]
Causes of obstruction					
Ureteric calculi	15	55.56	6	37.50	0.347[a]
Staghorn stone	9	33.33	7	43.75	0.530[a]
Renal pelvis stone	3	11.11	1	6.25	1.000[a]
Caliceal stone	0	0.00	2	12.50	0.133[a]
Pathology					
Chronic pyelonephritis	24	88.89	14	87.50	1.000[a]
Xanthogranulomatous pyelonephritis	0	0.00	2	12.50	0.133[a]
Squamous metaplasia	1	3.70	0	0.00	1.000[a]
Urothelial cancer	1	3.70	0	0.00	1.000[a]
Caseous granulomatous pyelonephritis	1	3.70	0	0.00	1.000[a]
Anesthesia					
General anesthesia	27	100.00	0	0.00	<0.001[a]
General anesthesia with epidural analgesia	0	0.00	12	75.00	<0.001[a]
General anesthesia with local analgesia	0	0.00	4	25.00	0.015[a]
Operative time (minutes) mean±SD	105.93	±31.16	129.38	±51.15	0.068[b]
Intraoperative blood loss (ml) mean±SD	261.48	±323.20	343.75	±510.19	0.520[b]
Intraoperative pus present	6	22.22	5	31.25	0.719[a]
Prophylactic drainage	27	100.00	2	12.5	<0.001[a]

Statistical analysis was conducted using various tests: [a]Fisher's exact, [b]Independent t-test, [c]Mann-Whitney U test
*Chronic kidney disease is defined by a glomerular filtration rate less than 60 ml/min/1.73 m^2 for at least 3 months.[17]
SD = standard deviation, ERAS = Enhanced Recovery After Surgery, BMI = body mass index

significant differences were found as shown in Table 3.

Postoperative outcomes and complications

The study findings showed that patients in the ERAS group had a statistically significant shorter Total LOS and postoperative LOS in

Table 3. Comparison of renal function parameters

Variables	Pre-ERAS (n=27)		ERAS (n=16)		P-value
	Mean	±SD	Mean	±SD	
Cr level					
Preoperative Cr (mg/dl)	1.12	0.41	1.21	0.54	0.541[b]
Postoperative Cr (mg/dl)	1.11	0.42	1.31	0.63	0.231[b]
GFR level					
Preoperative GFR (ml/minute/1.73 m^2)	72.72	23.17	70.23	27.50	0.752[b]
Postoperative GFR (ml/minute/1.73 m^2)	72.90	22.79	65.77	29.54	0.381[b]

[b]Independent t-test
ERAS = Enhanced Recovery After Surgery, SD = standard deviation, Cr = creatinine, GFR = glomerular filtration rate

Table 4. Comparison of outcome

Variables	Pre-ERAS (n=27)		ERAS (n=16)		P-value
	Mean	±SD	Mean	±SD	
Total LOS (day)	6.22	1.55	3.19	0.40	< 0.001[c]
Postoperative LOS (day)	5.22	1.55	2.19	0.40	< 0.001[c]
Ambulation (day)	1.59	0.64	1.13	0.34	0.010[c]
First flatus (day)	2.66	1.11	1.19	0.40	< 0.001[c]
First defecation (day)	3.11	1.28	1.56	0.73	< 0.001[c]
Foley catheter removal (day)	2.93	1.44	1.25	0.45	0.001[b]
drainage tube removal (day)	4.70	0.67	0.25	0.68	< 0.001[b]
Cost (bath)	23,930	3068.45	23,833	3731.48	0.927[c]

Statistical analysis was conducted using various tests: [b]Independent t-test, [c]Mann-Whitney U test
ERAS = Enhanced Recovery After Surgery, SD = standard deviation, LOS = length of stay

comparison to the pre-ERAS group. Additionally, statistically significant faster ambulation, and time to first flatus, and first defecation were observed in the ERAS group when compared to the pre-ERAS group.

Regarding Foley catheter removal, it was found that the ERAS group had a statistically significant shorter duration of Foley catheterization compared to the pre-ERAS group.

In this study, two patients in the ERAS group required the placement of drainage tubes, and when compared to the pre-ERAS group, it was found that the duration of drainage tube placement was statistically significantly shorter (Table 4).

With regard to complications, in both groups only grade 1-2 complications occurred following Elective Nephrectomy, and there was no statistically significant difference in the incidence of complications between the two groups. It was observed that the incidence of ileus was statistically significantly lower in the ERAS group than in the Pre-ERAS group. However, urinary retention occurred in 2 patients in the ERAS group, while it was not observed in the Pre-ERAS group. With regard to readmissions, one case was recorded in the Pre-ERAS group, while there were no readmissions in the ERAS group (Table 5).

Pain control

It was observed in the study that the ERAS group had significantly lower pain scores at 1, 6, 24 and 48 hours in comparison to the Pre-ERAS group (Table 6).

Table 5. Comparison of complications

Variables	Pre-ERAS (n=27)		ERAS (n=16)		P-value
	Mean	±SD	Mean	±SD	
Complications					
No	7	25.93	8	50.00	0.185[a]
Yes	20	74.07	8	50.00	
Grade					
Grade 1	11	55.00	4	50.00	1.000[a]
Grade 2	9	45.00	4	50.00	
Hypotension and bradycardia	0	0.00	1	12.50	0.286[a]
Acute urinary retention	0	0.00	2	25.00	0.074[a]
Ileus	15	71.43	1	12.50	0.010[a]
Fever	6	30.00	2	25.00	1.000[a]
Attack of gout	1	5.00	0	0.00	1.000[a]
Drug allergy	1	5.00	0	0.00	1.000[a]
Urinary tract infection	7	33.33	0	0.00	0.142[a]
Required blood transfusion	3	14.29	3	37.50	0.305[a]
Number of PRC administered (units) mean±SD	1.33	+0.58	2.33	+0.58	0.101[b]
Readmission					
No	26	96.30	16	100.00	1.000[a]
Yes	1	3.70	0	0.00	

Statistical analysis was conducted using various tests, [a]Fisher's exact, [b]Independent t-test
PRC = packed red cells, SD = standard deviation

Table 6. Comparison of pain scores

Variables	Group, mean±SD, 95% CI				P-value
	Pre-ERAS	95% CI of mean	ERAS	95% CI of mean	
Pain score 1 hr	4.85±1.32	4.24-5.47	3.38±1.96	2.57-4.18	0.0052[a]
Pain score 6 hr	5.67±2.04	4.94-6.40	2.75±1.57	1.80-3.70	<0.0001[a]
Pain score 24 hr	4.19±1.27	3.68-4.69	2.75±1.34	2.09-3.41	0.0011[a]
Pain score 48 hr	3.85±1.13	3.40-4.30	2.31±1.19	1.73-2.90	0.0001[a]

[a]Repeated measured ANOVA test
ERAS = Enhanced Recovery After Surgery, CI = confidence interval, SD = standard deviation, hr = hour

Discussion

Urolithiasis is an area of public health concern in Thailand, and Loei province, one of the provinces in the north-eastern region of Thailand, has a relatively high prevalence of the disease.[18] Urolithiasis can lead to pain, infection, renal failure, and even fatalities. Nephrectomy is one of the most effective treatment approaches for management of stone diseases.

Numerous research studies have shown the effectiveness of a multidisciplinary approach in implementing ERAS protocols, resulting in a reduction in the stress response, improved quality of rehabilitation, and increased levels of patient satisfaction. The key to the success of ERAS lies in its structured approach, which comprises three phases: preoperative, intraoperative, and postoperative. These strategies are tailored to individual patients and emphasize various aspects, including a reduction in preoperative fasting, multimodal pain management, early oral intake, and early ambulation.[19,20]

At present, the appropriate perioperative ERAS protocol is typically derived from the framework of research studies conducted by experienced individuals, and subsequently tailored to the unique clinical context. In practice, however, there is a scarcity of research specifically addressing ERAS Nephrectomy in patients with urolithiasis

In this study, laparoscopic nephrectomy was not performed. This was due to the fact that patients with urolithiasis often exhibit fibrotic and inflammatory processes extending to the renal hilum and perirenal adipose tissue. These observations are in line with the findings of the study, where the majority of patients presented with chronic pyelonephritis (80.8%). Consequently, the complexity of performing laparoscopic procedures in the urolithiasis population increases, and complications associated with nephrectomy in urolithiasis patients may occur more frequently compared to those undergoing nephrectomy for renal tumors.[21]

Pain management in nephrectomy offers several modalities, including epidural analgesia, patient-controlled analgesia systems (PCAS), neuraxial techniques, transversus abdominis plane (TAP) blocks, and others. Current research suggests that a multimodal approach is frequently employed.[22] In this study, researchers chose to administer pain management through either epidural nerve block or local anesthesia. The results revealed superior pain control in the ERAS group compared to the Pre-ERAS group, as illustrated in Figure 1.

However, this study could not compare the pain scores recorded between local analgesia and epidural analgesia within the ERAS group, as the sample sizes for such comparisons as these were too small to calculate reliable statistical significance.

The decision to place a retroperitoneal drain after nephrectomy is not yet considered as part of the standard of care and depends on the judgment of the surgeon.[23,24] In this study, insertion of a drain was appropriate in approximately 12.5% of the ERAS group, due to the presence of oozing blood.

In the ERAS group, the absence of the placement of a retroperitoneal drain or the rapid removal of the Foley catheters and retroperitoneal drain (in cases where intraoperative drainage was deemed necessary), in combination with effective pain control, allowed patients in the ERAS group to become ambulant earlier, resulting in a faster return of normal bowel function. Patients in the ERAS group experienced less abdominal distension and had faster recommencement of bowel movement in comparison to the Pre-ERAS group. As a result, patients in the ERAS group had shorter lengths of stay, both total and postoperative, when compared to the Pre-ERAS group. This finding aligns with reports from prior research that applied the ERAS protocol for nephrectomy in various conditions, including renal cell carcinoma and transplantation.[25,26]

In addition, when analyzing complications related to ERAS nephrectomy, there were no statistically significant differences between the two groups. However, it was noted that the incidence of ileus was lower in the ERAS group This observation can be attributed to the ERAS protocol in this study, which involved early ambulation, minimal opioid usage, the utilization of gum chewing[27] and bisacodyl rectal suppository.[28] However, complications associated with epidural analgesia were observed in the ERAS group, including acute urinary retention, hypotension and bradycardia.[22] Nevertheless, the incidence did not show a statistically significant increase in comparison to the pre-ERAS group.

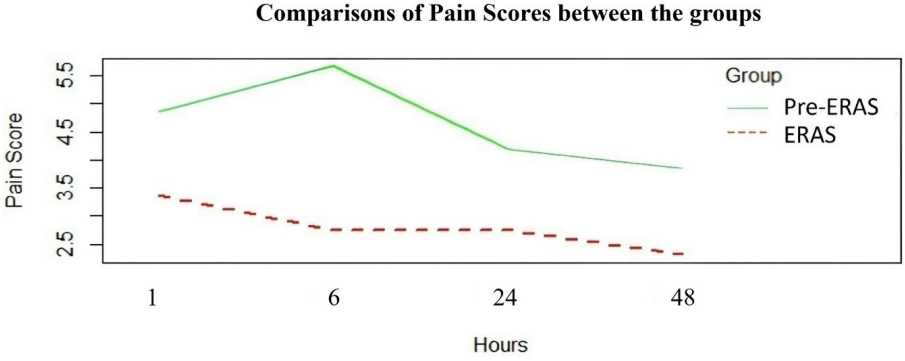

Figure 1. Comparison of Pain Scores at 1, 6, 24, and 48 Hours between Pre-ERAS and ERAS groups.

ERAS implementation did not have a significant impact on renal function, as assessed by pre- and post-operative Cr and GFR. This finding is in alignment with the results of previous research.[25]

In terms of costs, it was observed that there were lower costs associated with the ERAS group in comparison to the Pre-ERAS group, although the cost difference was not statistically significant. This is attributed to the fact that, even though the implementation of ERAS reduces inpatient hospitalization costs, it is associated with additional resource utilization, such as the cost of performing epidural nerve blocks and increased medication expense.

Conclusions

The implementation of ERAS in elective open simple nephrectomy for urolithiasis significantly reduces LOS, and postoperative pain, and results in earlier return of bowel function, faster resumption of normal activities and may result in cost savings without increasing the risk of readmission or complications, and without compromising postoperative renal function.

Conflicts of Interest

The authors declare no conflicts of interest.

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Original Article

Diagnostic properties of percent-free PSA as a predictor of prostate cancer in Thai men with total serum PSA level of 4-10 ng/ml

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Keywords:
%Free PSA, total PSA, intermediate PSA, prostate cancer, Thai

Abstract

Objective: The percent-free prostate specific antigen (%fPSA) could enhance total PSA (tPSA) with regards to early prostate cancer detection by increasing its specificity. However, due to significant physiologic differences across races, the optimal cut-off level for %fPSA may vary. We aimed to determine optimal %fPSA cut-off level for Thai men aged between 50 to 80 years whose tPSA score ranged from 4-10 ng/mL and to evaluate its corresponding diagnostic properties, specifically sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The secondary endpoint is the relationship between Gleason Grade Group and %fPSA value.

Materials and Methods: A total of 184 male patients from age 50-80 years whose tPSA was between 4-10 ng/ml were enrolled onto the study. Their %fPSA were measured before undergoing trans-rectal ultrasonography (TRUS) guided prostate biopsy, which procured at least 10 cores. All histologic reports were reviewed and confirmed for further analysis.

Results: Out of the 184 patients registered the final diagnoses were 31 (16.84%) were positive for prostate cancer and the other 153 (83.16%) had benign prostate hypertrophy (BPH). At %fPSA cut-off of ≤ 10%, the sensitivity would be 22.6%, specificity 95.4%, PPV 50.0% and NPV 85.9%. However, at a %fPSA cut-off of ≤ 20%, the sensitivity was 77.4%, specificity 32.7%, PPV 18.9%, and NPV 87.7%. The %fPSA value has a direct relationship with sensitivity and NPV whereas it is inversely proportional to specificity and PPV. Lower %fPSA is associated with higher risk of prostate cancer. The area under the curve (AUC) of ROC curve was 0.65. The incidence of prostate cancer among patients with Gleason Grade Groups 1, 2, 3, 4, and 5 were 41.94%, 32.26%, 16.13%, 6.45%, and 3.23% respectively. The mean %fPSA scores among those groups were 14.75%, 17.64%, 10.19% ,13.33%, and 15.65% respectively.

Conclusion: The decision to undergo prostate biopsy in Thai males with a tPSA score between 4-10 ng/ml can be guided by %fPSA, which proved to be an effective and useful predictive tool. The cut-off level of %fPSA ≤ 20% had the highest diagnostic properties in Thai men in our study which yielded a sensitivity of 77.4%, specificity of 32.7%, PPV of 18.9%, and NPV 87.7%. If %fPSA was ≥ 30%, there was no risk of prostate cancer in this cohort. In addition, with regard to disease severity, we found that %fPSA level is not associated with the Gleason Grade Grouping.

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Introduction

Prostate cancer is the second most common malignancy in males worldwide and the fifth highest cause of mortality[1], leading to a significant burden on healthcare systems. This emphasizes the need for early detection, one method of which – namely the process of prostate specific antigen (PSA) screening – contributes to a 21% reduction in the mortality risk.[2] Total serum PSA is currently utilized worldwide as a tumor marker for prostate cancer. Although it has a high degree of sensitivity, it lacks specificity. This is especially important in cases where the total serum PSA lies between 4-10 ng/ml since a mere 25% of incidences of prostate cancer could be identified in this group. As a result, subsequent unnecessary prostate biopsies[3,4] could lead to significant morbidity, overdiagnosis, overtreatment, and anxiety, as well as excessive cost.

The total serum PSA consists of two isoforms, the free unbound PSA and the complex PSA.[5-8] Various studies have shown promise regarding the possibility of using percent-free PSA (%fPSA) in distinguishing benign from malignant prostate disease. Studies have shown that lower %fPSA was associated with greater risk of prostate cancer, aggressive pathologic features, and biochemical recurrence after radical prostatectomy.[5-8]

Compared to the less accessible and more costly multiparametric MRI (mpMRI) of the prostate, laboratory kit for %fPSA proved to be more financially and logistically feasible. Furthermore, mpMRI of prostate has several limitations including the obesity of the patient or the inability to remain immobile, which potentially affect the quality of the images. Other contraindications include foreign implants such as pacemakers, aneurysm clips, ear implants, and other metallic instruments.

Due to its advantaeous cost implications and versatility, %fPSA could play a pivotal role in assisting the diagnosis by the physician and decision making for further management of suspected prostate cancer in the environment where healthcare resources are scarce. Nevertheless, the percent-free PSA values derived from the populations of different races could not be used in their current form[9-11] In addition, the consensus for the cut-off level of %fPSA has not been agreed[8]. One of the popular cut-off levels proposed by Catalona et al. defined significant %fPSA as ≤ 25%, which yielded a sensitivity as high as 95%. They also found that a value of %fPSA between 0 and 10% had the highest incidence of prostate cancer at 55-56%.[12]

This study aimed to determine the most appropriate cut-off level of %fPSA among Thai males whose total serum PSA ranged from 4 to 10 ng/ml, as mpMRI of the prostate are less available and more expensive. Other parameters to be established include sensitivity, specificity, positive predictive value, and negative predictive value. We also assessed the association between Gleason Grade Group and the value of percent-free PSA.

Materials and Methods

Patients

This retrospective study registered data from Thai male patients from 50 to 80 years of age whose serum PSA ranged from 4 to 10 ng/ml who visited Maharaj Nakorn Chiang Mai Hospital from 1 April 2011 to 31 December 2022. Patients with untreated urinary tract infection (UTI), untreated bleeding disorder, prostatitis, history of prior prostate surgery, and history of prior prostate cancer were excluded. The study protocol was approved by the Ethics Committee of Chiang Mai University Hospital with the study number SUR-2564-08360.

Methods

Blood samples of total PSA and free PSA were taken from patients who fulfilled the inclusion criteria and were quantitatively analyzed using a COBAS-e double sandwich electrochemiluminescence immunoassay (ECLIA) analyzer. Percent-free PSA values were then calculated by dividing free PSAs with total serum PSAs and multiplying the results by 100.

A total of 184 patients underwent trans-rectal ultrasonography (TRUS) guided biopsy for the first time during the defined period. Prostate volume was measured by TRUS prior to biopsy. Extended core biopsy was carried out, the process of which had to yield at least 10 cores of prostatic specimens. There were no MRI-guided prostate biopsies carried out in this study. The specimens would then be handled and evaluated by experienced pathologists. The procedure included use of Hematoxylin and Eosin (H&E) dye, formalin fixing, and the procurement of paraffin-embedded blocks.

The diagnosis and grading of adenocarcinoma were reported in line with the Gleason Scoring System in accordance with the definitions provided by the Consensus Conference of International Society of Urological Pathology.

Statistical analysis

The data obtained were analyzed and calculations were carried out to obtain the sensitivity, specificity, PPV, and NPV of each cut-off level. ROC curves were utilized to determine the optimum cut-off level for a screening tool for prostate cancer. Statistically significant differences were defined as $p < 0.05$. All statistical analyses were performed with STATA version 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

Data from a total of 184 patients with total PSA between 4 to 10 ng/ml were used in the study. Of those, 31 patients (16.84%) were diagnosed with prostate cancer and 153 (83.16%) were diagnosed with benign prostate hyperplasia after the results of TRUS-guided biopsies were confirmed by pathology.

The baseline characteristics significantly differed in terms of mean age between the groups (68.16 years in prostate cancer group vs 65.71 years in benign prostatic hyperplasia (BPH) group; $p = 0.012$). In addition, %fPSA was significantly lower in prostate cancer group in comparison to the BPH group ($p = 0.005$). Average prostate volume among the prostate cancer group was 38.90 ml, which was also significantly lower than the 49.55 ml in the BPH group ($p = 0.014$)(Table 1).

The highest proportion of prostate cancer (50%) was observed in the 0-10% range of %fPSA value. The highest incidence of prostate cancer (11 patients, 35.48%) was in the 10.1-15% range of %fPSA value, whereas the peak incidence of BPH (56 patients, 36.60%) was in the 15.1-20% stratum of %fPSA value. None of the patients with %fPSA ≥ 30% were diagnosed with prostate cancer (Table 2).

At a %fPSA cut-off level of ≤ 10%, the highest specificity of 95.4% and highest PPV of 50% were

Table 1. Demographic and clinical characteristics according to biopsy pathology

Parameters	BPH (n=153)	Prostate cancer (n=31)	P-value
Age (Years), mean (SD)	65.71 (4.95)	68.16 (4.61)	0.012
BMI (kg/m^2), mean (SD)	23.95 (3.25)	23.46 (3.12)	0.440
%Free PSA, mean (SD)	18.44 (6.34)	14.89 (6.50)	0.005
Total PSA (ng/ml), mean (SD)	6.60 (1.60)	6.37 (1.55)	0.472
Prostatic volume (ml), mean (SD)	49.55 (22.96)	38.90 (14.50)	0.014
Numbers of biopsy cores, mean (SD)	10.80 (2.94)	11.16 (1.66)	0.513

BMI = body mass index, SD = standard deviation, PSA = prostate specific antigen, BPH = benign prostatic hyperplasia

Table 2. %Free PSA and pathologic report

%Free PSA	BPH (n=153)	Prostate cancer (n=31)	Total (N=184)	%Ca-p	P-value
0-10	7 (4.58)	7 (22.58)	14	50.00	<0.001
10.1-15	40 (26.14)	11 (35.48)	51	21.57	0.289
15.1-20	56 (36.60)	6 (19.35)	62	9.68	0.064
20.1-25	30 (19.61)	3 (9.68)	33	9.09	0.189
25.1-30	9 (5.88)	4 (12.90)	13	30.77	0.164
30.1-35	7 (4.58)	0	7	0	0.224
35.1-40	4 (2.61)	0	4	0	0.363

PSA = prostate specific antigen, %Ca-p = percentage of patients with prostate cancer, BPH = benign prostatic hyperplasia

Table 3. Diagnostic properties of %fPSA at each cut-off level

%Free PSA	Sensitivity (%)	Specificity (%)	PPV	NPV
≤10	22.6	95.4	50.0	85.9
≤15	58.1	69.3	27.7	89.1
≤20	77.4	32.7	18.9	87.7
≤25	87.1	13.1	16.9	83.3
≤30	100.0	7.2	17.9	100.0
≤35	100.0	2.6	17.2	100.0

PSA = prostate specific antigen, PPV = positive predictive value, NPV = negative predictive value

Table 4. The relationship between Gleason Grade Group and mean %Free PSA

Gleason grade group (score)	Number of patients (n=31), n (%)	Mean %Free PSA (SD)
1 (3+3)	13 (41.94)	14.75 (5.62)
2 (3+4)	10 (32.26)	17.64 (8.48)
3 (4+3)	5 (16.13)	10.19 (3.38)
4 (4+4, 3+5, 5+3)	2 (6.45)	13.33 (1.90)
5 (4+5, 5+4, 5+5)	1 (3.23)	15.65 (0.00)

PSA = prostate specific antigen, SD = standard deviation

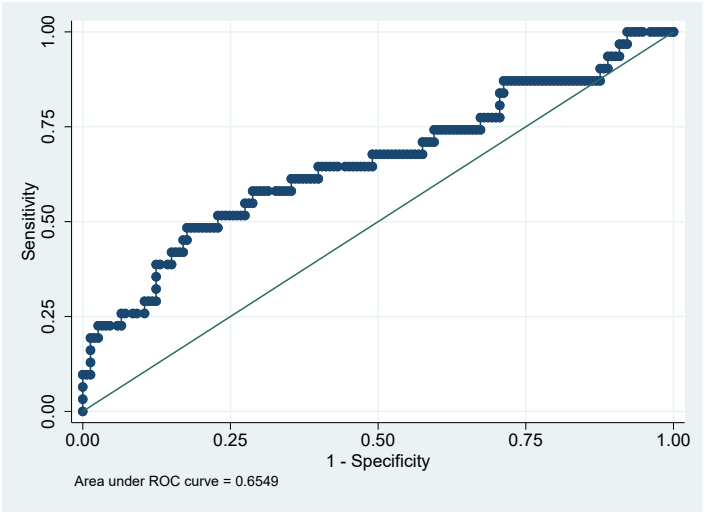

Figure 1. The receiver operating characteristic (ROC) curve

observed, which subsequently lead to a 4.6% rate of unnecessary biopsies. The sensitivity and NPV were 22.6% and 85.7%, respectively. If the %fPSA cut-off level was increased to ≤ 20%, sensitivity and NPV improved to 77.4% and 87.7% respectively. Nevertheless, its specificity and PPV also dramatically dropped to 32.7% and 18.9% respectively. The %fPSA value has a direct relationship with sensitivity and NPV whereas it is inversely proportionate to specificity and PPV (Table 3).

The number of prostate cancer patients classified as Gleason Grade Groups 1, 2, 3, 4, and 5 were 13, 10, 5, 2, and 1 respectively. The mean %fPSA in those groups were 14.75%, 17.64%, 10.19%, 13.33%, and 15.65% respectively. The incidence in each Gleason grade group decreased as the score increased. Moreover, the results revealed no significant association between severity of the disease and either Gleason grade group or mean %fPSA (Table 4).

Figure 1. shows the receiver operating characteristic (ROC) curve plot of sensitivity against 1-specificity. The area under the curve was 0.65, indicating that the %fPSA in this study can

effectively distinguish between prostate cancer and BPH.

Discussion

Analysis of the data from the 184 patients in our study showed an overall cancer detection rate of 16.8%, which is consistent with the 17.3% prevalence of prostate cancer in Thailand.[13] The demographic and characteristic data show that the average age of patients with prostate cancer was significantly higher than those with BPH, a finding which coincided with the results of the study conducted by Matsuyama et al.[14]

Several other studies also found that the average prostatic volume of those with prostate cancer was substantially smaller than those with BPH, which also corresponded with our findings.[5,10,15]

In our study, the prevalence of prostate cancer was highest in the %fPSA ≤ 10% group and dropped to zero in the group with a %fPSA ≥ 30%. In a study by Catalona et al.[12] a universal cut-off level of %fPSA ≤ 25% was proposed however, in that study there was only a minority of Asian patients (2%). Using the same cut-off level in our study, the diagnostic properties were less than the original paper, with a sensitivity of only 87.7%, specificity of 13.3%, PPV 16.9%, and NPV 83.3%. In addition, our study showed an inverse relationship between %free PSA and the detection rate of prostate cancer while total serum PSA was found to have no significant difference, a finding also being reported by Tijani et al.[16]

The concepts of race-specific cut-off level were proposed by Arai et al.[17] and Oesterling et al.[18] This would mean our study should be cross-referenced with other Asian populations rather than Caucasian. A study conducted by Matsuyama et al.[14] found that optimal cut-off level among Japanese people, a specifically Asian population, to be ≤ 17%. This concurred with our finding that the optimal cut-off level among Thai people is ≤ 20%, which yielded a of sensitivity 77.4%, specificity of 32.7%, PPV of 18.9%, and NPV 87.7%.

The ROC curve gave rise to an AUC of 0.65, which was higher than the pre-determined discrimination line. As a result, we concluded that the predictive value of %fPSA shown in our study did not occur by chance. Regarding the relationship between severity of disease and %fPSA, we found none which were significant, which is consistent with other studies by Noldus et al.[19] and Sakai et al.[20] As a result, we suggest adding %fPSA to the total serum PSA to give more information as a screening tool for prostate cancer in Thailand, especially in centers without facilities to carry out mpMRI of the prostate.

There are several limitations in this study. Firstly, it was carried out in a single center which potentially limits the transferability of the findings. Secondly, having different physicians perform TRUS-guided biopsy, due partly to the retrospective nature of the study, might result in variations in cancer detection rate. Thirdly, the relatively small sample size in this study could impact the reliability of the statistical outcomes However, the findings of this pioneering study, conducted solely among a Thai population, warrant further investigation as they highlight inter-racial differences in this field. Lastly, some patients with negative-cancer biopsy results might possibly have had undetected prostate cancers since this random TRUS biopsy procedure could potentially miss a small cancerous area. Further studies with a more accurate biopsy protocol such as MRI-ultrasound-fusion guided biopsy, which is widely acknowledged as being more precise in most recent studies, are recommended in the future.

Conclusions

The decision to undergo prostate biopsy in Thai males with tPSA between 4-10 ng/ml can be guided by %fPSA, which proved to be an effective and useful predictive tool. The cut-off level of %fPSA ≤ 20 % had the highest diagnostic properties in Thai men in our study which yielded a sensitivity of 77.4%, specificity of 32.7%, PPV of 18.9%, and NPV 87.7%. If %fPSA is ≥ 30%, there was no risk of prostate cancer. In addition, with regard to disease severity, we found that %fPSA level is not associated with Gleason grade grouping.

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Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Evaluation of therapeutic outcomes in emphysematous pyelonephritis: a single-center experience at Siriraj Hospital

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Keywords: Emphysematous pyelonephritis, metabolic acidosis, urosepsis, nephrectomy, chronic kidney disease

Abstract

Objective: Emphysematous pyelonephritis (EPN) is an acute, severe, necrotizing parenchymal and perirenal infection associated with high morbidity and mortality. The radiographic classifications, which determine the treatment strategies, however, remain controversial. Our study aimed to evaluate and compare the clinical parameters related to nephrectomy and the treatment outcomes in current practices.

Materials and Methods: We retrospectively reviewed the data from 21 EPN patients who had been diagnosed using computed tomography (CT) scans, who were admitted to Siriraj Hospital from January 2009 to December 2019. The clinical manifestations, imaging results, laboratory findings, treatment methods, and overall outcomes of each patient were reviewed and analyzed. Huang–Tseng's and Wan's classifications were used to classify the images obtained from the CT scans.

Results: Among the 21 patients with EPN, all had at least one comorbidity associated with a compromised immune response. Common manifestations included fever (74%) and initial laboratory findings showed hyperglycemia (66%), acute kidney injury (72%), and metabolic acidosis (76%). Inotropes were used in 13 patients for hemodynamic support. Eleven patients were treated with a non-nephrectomy approach, while 10 patients underwent nephrectomy. No statistical difference in treatment outcomes was observed between groups in both classification systems. Overall survival was 100% with a minimum one-year follow-up.

Conclusion: Our study demonstrated that the current treatment approach has resulted in a zero mortality rate of EPN most probably due to advancements in antibiotics, surgical techniques, and postoperative intensive care over the years. However, refining treatment strategies, considering radiographic criteria, clinical parameters, and initial treatment response, is essential in future studies to further decrease disease morbidity.

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Introduction

Emphysematous pyelonephritis (EPN) is an acute and severe necrotizing parenchymal and perirenal infection caused by gas-forming uropathogens.[1] While uncommon, it is a serious condition with high morbidity and mortality rates of up to 40%-50%.[2,3] However, over the last two decades, the mortality rate has decreased to 20% due to the introduction of a new generation of antibiotics and the use of better surgical techniques.[4]

In the past, open drainage and the use of antibiotics regardless of nephrectomy was the standard treatment.[5,6] More recently, there has been a shift towards disease classification using computed tomography (CT) scans to determine prognosis and guide appropriate treatment options. The results to date have been promising, especially when considering the role of nephrectomy regarding imaging classifications.[7,8] However, ideal management processes remain controversial and should be personalized for each patient.

In the era of modern perioperative-, intensive-, and critical-care specialists, the outcomes of EPN treatment have improved. This study aims to investigate EPN treatment outcomes at Siriraj Hospital and to compare the factors based on image classifications and the association with nephrectomy.

Materials and Methods

Following Institutional Review Board approval (Protocol Number 353/2563 (IRB4)), we conducted a retrospective review of EPN patients admitted to Siriraj Hospital between January 2009 and December 2019. A total of 21 patients were diagnosed with EPN using a CT scan. The clinical manifestations, radiographic findings, laboratory results, treatment modalities, and outcomes were reviewed and analyzed.

In our study, two image classifications were utilized to categorize patients, specifically those of Huang and Tseng[8] and Wan et al.[7] According to Wan et al., Type 1 classification is defined as EPN with parenchymal destruction and an absence of fluid content, while Type 2 refers to EPN with the presence of renal or perinephric fluid associated with a loculated gas pattern. Huang and Tseng's system categorizes EPN into four types: type 1 - gas in the collecting system only; type 2 - gas in the parenchyma without extending into the extrarenal space; type 3a - extension of gas or abscess into the perinephric space; type 3b - extension of gas or abscess into the pararenal space; and Type 4 - bilateral EPN or EPN in a solitary kidney.

Previous studies indicate that type 1 and type 2 EPN under the Huang-Tseng classification exhibit a lower mortality rate (0-10%) compared to types 3a, 3b, and 4 (20%-50%).[7,8] Therefore, in the present study, we categorized patients into two groups based on the Huang-Tseng classification: group 1 comprising type 1 and type 2, and group 2 comprising Type 3 and Type 4 EPN cases.

Additionally, we examined factors associated with nephrectomy in EPN patients. There are six laboratory factors that may result in adverse clinical outcomes: hyperglycemia, defined as initial blood glucose > 11.10 mmol/l; anemia, defined as hematocrit (HCT) < 30%; leukocytosis, defined as white blood cell (WBC) count >12x09/l; thrombocytopenia < 100x109/l; metabolic acidosis, defined as serum bicarbonate < 20 mmol/l and blood pH < 7.2; and acute kidney injury, defined as a decreased glomerular filtration rate (GFR) > 30% of baseline or serum creatinine > 0.13 mmol/l.[9] The outcomes assessed were the treatment modality, i.e., nephrectomy or non-nephrectomy (medication, ureteral stent, or percutaneous drainage), long-term renal replacement therapy (RRT), and mortality rate.

Statistical analysis

Quantitative variables are presented as mean (minimum, maximum), while qualitative variables were reported as frequency and percentage. Chi-square and Fisher's exact tests were used to compare categorical variables, and the Mann-Whitney U test was employed to compare continuous variables between radiographic classifications type 1 and type 2. Statistical significance was defined as a p-value of less than 0.05. PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, USA) was used for the statistical analysis.

Results

During a 10-year-period, a total of 21 patients were diagnosed with EPN (20 females and 1 male) at our institute. The mean age was 55.2 years (range 30-72). Seventeen patients (80%) had diabetes mellitus, with six (35%) being newly diagnosed. Other comorbidities included hyper-

tension (33%), chronic kidney disease (28%), the use of immunosuppressive drugs (23%), previous urological stones (21%), history of urological surgery (14.3%), and cirrhosis (9.5%). All patients had at least one comorbidity associated with a compromised immunologic response, (Table 1).

As shown in Table 2, the most common clinical manifestation was fever (74%), followed by tachycardia (71%), flank pain (66%), alteration of consciousness (23%), dysuria (19%), and hematuria (14%). Seven patients (33%) were diagnosed with septic shock and another seven (33%) with diabetic ketoacidosis upon initial presentation. Predominant pathogens included *Escherichia coli* (80%), Klebsiella pneumoniae (14%), and Proteus mirabilis (6%), constituting extended-spectrum beta-lactamases (ESBL) strain microorganisms, accounting for 38%. Initial laboratory abnormalities included hyperglycemia (66%), anemia (61%), leukocytosis (57%), thrombocytopenia (42%), acute kidney injury (71%), and metabolic acidosis (76%).

All patients received initial intravenous antimicrobial treatment, including meropenam (81%) and piperacillin/tazobactam (19%). Inotropic drugs were used in 13 patients (62%) to maintain hemodynamics. Eleven patients (68%) were treated with non-nephrectomy approaches while 10 (34%) underwent nephrectomy. The survival rate was 100% at one-year follow-up, no deaths being observed.

Table 1. Characteristics of 21 patients diagnosed with EPN

Characteristics	Patients with EPN (N=21)
Age (mean, range, years)	55.2 (30-72)
Sex (n, %)	
Male	1 (5)
Female	20 (95)
Total	21 (100)
Comorbidities (n, %)	
Diabetes mellitus	17 (80)
Hypertension	7 (33)
Chronic kidney disease	6 (28)
Immunosuppressive drug usage	5 (23)
Previous urological stones	4 (21)
Previous urological surgery	3 (14.3)
Cirrhosis	2 (9.5)

EPN = emphysematous pyelonephritis

Table 2. Characteristics of 21 patients diagnosed with EPN

Variables	Number (%) of patients (N=21)
Clinical features	
Fever	15 (71)
Flank pain	14 (66)
Dysuria	4 (19)
Tachycardia	15 (71)
Hematuria (microscopic, gross)	3 (14)
Alteration of consciousness	5 (23)
Septic shock	7 (33)
Diabetic ketoacidosis	7 (33)
Laboratory results	
Hyperglycemia (blood glucose > 11.10 mmol/l)	14 (66)
Anemia (Hct < 30%)	13 (61)
Leukocytosis (WBC >12x10^9/l)	12 (57)
Thrombocytopenia (platelet < 100x10^9 /l)	9 (42)
Metabolic acidosis (serum bicarbonate < 20 mmol/l)	16 (76)
Acute kidney injury	15 (71)
Treatment strategies	
Inotropic medication	13 (62)
Approaches	
Non-nephrectomy	11 (68)
Nephrectomy	10 (34)
Total	21 (100)

EPN = emphysematous pyelonephritis, WBC = white blood cells, Hct = hematocrit

Table 3. Baseline characteristics and treatment outcomes of patients with EPN classified by Wan's classification

Factors	Type 1 (n=5)	Type 2 (n=16)	P-value
Age (years) ≥ 65	2	2	0.22
Sex			1.00
Male	0	1	
Female	5	15	
Diabetes mellitus	2	11	0.32
Chronic kidney disease	2	4	0.59
Nephrectomy	3	7	0.64
Long-term RRT	2	1	0.13

EPN = emphysematous pyelonephritis, RRT = renal replacement therapy

The baseline characteristics and treatment outcomes, including nephrectomy and long-term RRT, are shown in Table 3 (Wan classification) and Table 4 (Huang-Tseng classification). No baseline differences were observed between the groups, and there was no statistical difference in treatment outcomes for both classifications. Clinical factors associated with nephrectomy were also analyzed, as shown in Table 5. No significant differences were found between the nephrectomy and non-nephrectomy groups, including in the alteration of consciousness, acute kidney injury, thrombocytopenia, and shock.

Table 4. Baseline characteristics and treatment outcomes of patients with EPN classified by Huang–Tseng's classification

Factors	Group 1 (n=9)	Group 2 (n=12)	P-value
Age (years) ≥ 65	3	1	0.27
Sex			1.00
Male	0	1	
Female	9	11	
Diabetes mellitus	6	7	1.00
Chronic kidney disease	3	3	1.00
Nephrectomy	4	6	1.00
Long-term RRT	2	1	0.53

EPN = emphysematous pyelonephritis, RRT = renal replacement therapy

Discussion

While EPN is uncommon, it remains a life-threatening condition. Over the past two decades, various studies have evaluated the prognostic factors associated with morbidity and mortality.[10-13] In 1996, Wan et al. introduced a classification system for EPN, categorizing it into two types based on radiographic criteria: type 1 which exhibited a higher mortality rate (69%) in comparison to type 2 (18%).[7] Subsequently, in 2000, Huang and Tseng classified EPN into four classes, classes 3 and 4 resulting in increased failure rates for conservative treatment (with up

Table 5. Factors associated with the nephrectomy and non-nephrectomy groups in patients with EPN

Factors	Nephrectomy (n=10)	Non-nephrectomy (n=11)	P-value
Age (years) ≥ 65	1	3	0.58
Diabetes mellitus	5	8	0.38
Chronic kidney disease	5	1	0.06
Alteration of consciousness	4	1	0.14
Diabetic ketoacidosis	5	2	0.18
Septic shock	3	5	0.65
Leukocytosis	4	8	0.19
Thrombocytopenia	5	4	0.67
Serum glucose > 11.10 mmol/l	8	6	0.36
Acute kidney injury	6	9	0.36
Metabolic acidosis			
Serum bicarbonate < 20 mmol/l	9	7	0.31
Arterial blood gas pH < 7.2	2	5	0.36

EPN = emphysematous pyelonephritis

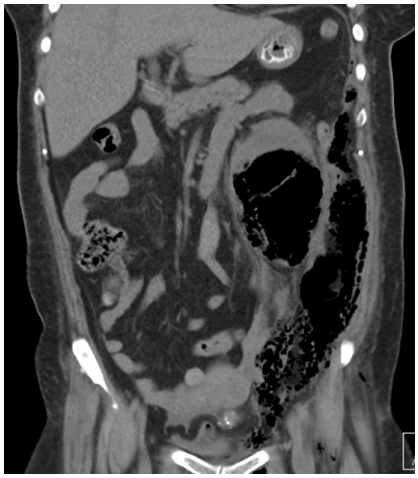
to 70%-75% of patients requiring nephrectomy) and mortality rates of 20%-50%.[8] A more recent study conducted in Taiwan by Tsu et al. in 2012 reported a reduction in the nephrectomy rate to 50% and mortality rate to 33% for EPN patients categorized by both Wan and Huang-Tseng criteria.[6] Similar results were also reported in a study by Olvera-Posada et al. in Mexico, where nephrectomy and mortality rates were reduced to 16% and 11%, respectively.[14]

The lack of established guidelines for treating EPN adds complexity to the clinical management of this condition. Historically, aggressive surgical interventions demonstrated superiority over medical treatments alone.[8] Nevertheless, morbidity and mortality were greater in early nephrectomy patients compared to those undergoing initial conservative strategies with percutaneous drainage (PCD) and antibioticstherapy.[8,14] Controversy persists over the efficacy of PCD in EPN patients.

Akpek et al. reported that 57% of patients in whom PCD was attempted experienced treatment failure, with a mortality rate of 26%.[15] In Huang and Tseng's study, 92% of patients classified as Classes 3 and 4 were reported to have PCD treatment failure, with a mortality rate of 15%. The clinical risk factors associated with poor outcome were thrombocytopenia, acute renal failure, altered mental status, and shock.[8] Additional studies by Falagas et al. and Kapoor et al. highlighted factors associated with increased mortality, namely an altered mental status, thrombocytopenia, acute renal failure, and severe hyperglycemia.[16,17] It is essential to take these factors, including imaging classification and several clinical features, into consideration when assessing treatment modalities.

Our approach involved initial resuscitation for fluid and electrolyte imbalance, hyperglycemic screening, and intravenous antibiotics in cases where urosepsis or septic shock was diagnosed. Subsequently, we monitored patients to assess their initial response to treatment. While imaging characteristics, disease extension, and clinical parameters such as mental status, severe metabolic acidosis, septic shock, or disseminated intravascular coagulation (DIC), and decreased renal function are crucial for determining the stage and severity of the disease, it is emphasized that these should not be routinely used as indicators for intervention or nephrectomy. Additional significant factors, including bacterial virulence, host immunity, hyperglycemic control, and the adequacy of blood supply for antibiotic delivery to the renal parenchyma, play pivotal roles in determining the response and necessity for surgical intervention following initial treatment.

Our study revealed no statistically significant factors associated with radiographic classifications, clinical parameters, or treatment modalities (Tables 3, 4). Intriguingly, some patients with extensive radiographic findings and challenging clinical parameters were successfully managed with a non-nephrectomy strategy. As shown in Figure 1, a patient with metabolic acidosis and extension of EPN to the anterior abdominal wall and pelvic cavity was effectively managed with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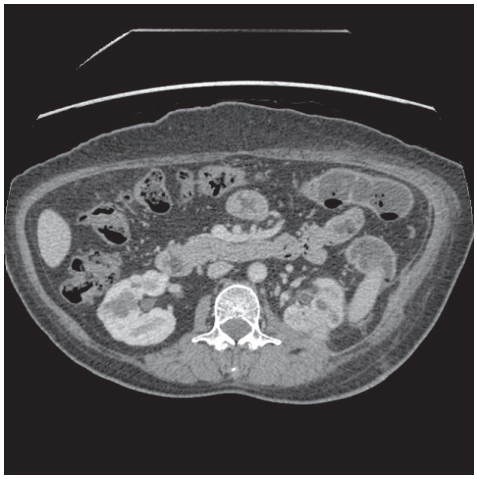
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Figure 1. (A) A 54-year-old female with left extensive emphysematous pyelonephritis extended to anterior abdominal wall and pelvic cavity. Blood gas pH was 7.24. She underwent left open drainage and was discharged with normal kidney function. (B) Follow-up imaging.

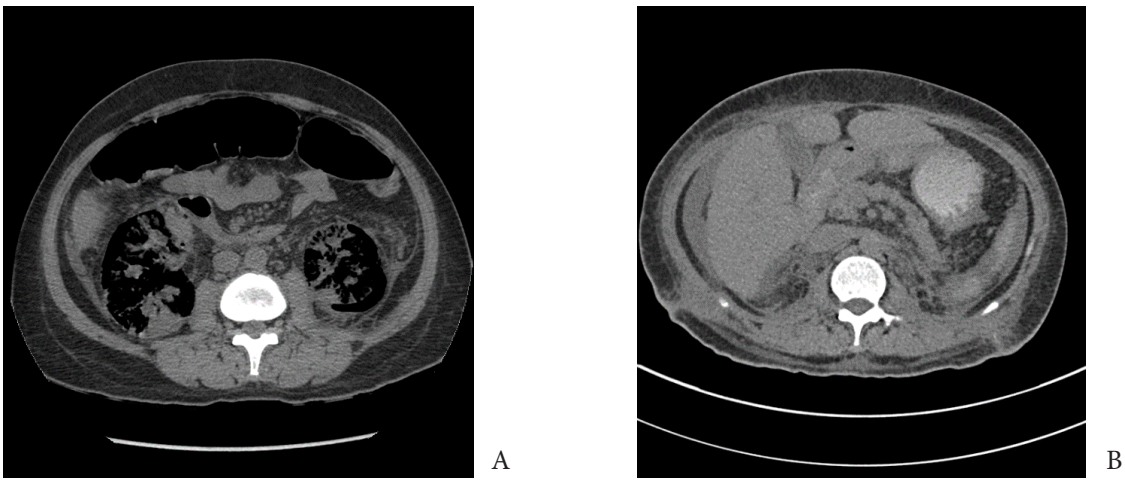

Figure 2. (A) A 51-year-old female with bilateral emphysematous pyelonephritis, blood gas showed severe metabolic acidosis (pH 7.15). She underwent bilateral nephrectomy and was discharged with long term dialysis. (B) Postoperative follow-up imaging.

intravenous antibiotics and open drainage, eliminating the necessity for nephrectomy. Conversely, some patients with less extensive radiographic findings and favorable clinical parameters eventually required nephrectomy due to worsening clinical conditions (Table 5). Similar to findings from previous studies[18-20], the initial treatment response played a crucial role in determining the treatment strategy at our institution. However, this was a retrospective study and the definition of treatment response for EPN, which is not well established, depended on individual experience.

In the present study, the nephrectomy rate was 50%, and no fatalities were observed. Perioperative care, the intervention of intensive care specialists, and the postoperative application of continuous RRT significantly contributed to positive treatment outcomes, as mentioned by Sokhal et al.[20] For instance, as depicted in Figure 2, a patient with bilateral EPN and Wan type 1 classification underwent bilateral nephrectomy due to clinical deterioration. The subsequent continuous RRT was successfully implemented, enabling the patient to survive with long-term hemodialysis. The reduction in morbidity and mortality rates of EPN over time has resulted not only from the improvement in the medication and surgical intervention approaches, but also from refined clinical judgment, improved perioperative care, and the effective application of modern technology.

The limitation of our study was its small sample size and lack of transferability as it was carried out in a single institution and as it is a relatively uncommon disease. A further multicenter study should be developed to validate the efficacy of the classifications. Our assessment of long-term outcomes was constrained by the limited follow-up period.

Conclusions

While emphysematous pyelonephritis is a life-threatening condition, the mortality rate has significantly decreased over time. It was reassuring to record a zero-mortality rate with the current treatment practices, potentially due to the current improvement in specific antibiotics, surgical techniques, and postoperative intensive care. Future studies should focus on refining treatment strategies based on radiographic criteria, clinical parameters, and the response to initial treatment to further enhance patient outcomes and reduce the morbidity associated with this disease.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Original Article

The impact of musical intervention on pain and anxiety levels during percutaneous nephrostomy tube replacement: a randomized controlled trial

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Keywords:
Percutaneous nephrostomy tube replacement, music, pain, anxiety

Abstract

Objective: Percutaneous nephrostomy tube replacement (PNTR) is a significant and frequently performed outpatient urological procedure. Patients undergoing this procedure often experience pain and anxiety. Various non-pharmacological methods are currently utilized to alleviate pain and anxiety. The objective of this study is to investigate the effects of music on pain and anxiety during PNTR .

Materials and Methods: A prospective randomized controlled trial was conducted in patients undergoing PNTR at Loei Hospital from May 1, 2023, to September 30, 2023. A total of 104 patients were randomly assigned to two groups: group 1, where patients did not listen to music during the procedure, and group 2, where patients listened to their preferred choice of music. Demographic data, vital signs, Visual Analog Scale (VAS) pain levels, State-Trait Anxiety Inventory-State Anxiety (STAI-SA), and willingness to repeat procedures were compared.

Results: The VAS pain scores in the music group were significantly lower than in the non-music group during and after PNTR (2.5 vs 5, $p < 0.005$ and 0 vs 3, $p < 0.001$, respectively). Moreover, the STAI-SA levels in the music group were significantly lower post-procedure (32.98±5.61 vs 39.98±6.18, $p < 0.001$), and the willingness to repeat the procedure was significantly higher (41 vs 22, $p < 0.001$).

Conclusion: The results of this study indicate that listening to a preferred choice of music during PNTR has the potential to reduce pain, and anxiety, and increase the willingness of patients to repeat procedure. The intervention of music serves as a cost-effective, safe, and side effect-free non-pharmacological approach to facilitate patient outcome in PNTR.

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Introduction

Percutaneous nephrostomy tube placement (PNTP) is a critical medical intervention in the management of relieving upper urinary tract obstruction associated with urosepsis, acute renal failure, and intractable pain[1], facilitating the diversion of urine from the kidney to an external collection bag.

In cases where a PNTP is employed during the wait for surgical intervention for the resolution of obstructive causes, or as a lifelong measure due to a patient not being a suitable candidate for surgery to collect the obstructive cause or when a cure for the obstructive cause cannot be achieved for the patient, regular percutaneous nephrostomy tube replacement (PNTR) every 6-8 weeks can be performed. Patients undergoing PNTR, approximately 35-64 individuals per month, often experience anxiety and discomfort during the process

There is currently a growing interest in using music to reduce anxiety and pain during outpatient urological procedures[2], for example during extracorporeal shockwave lithotripsy[3,4], transrectal ultrasound-guided prostate biopsy[5,6], cystoscopy[7,8], and urodynamic studies.[9] Music therapy has demonstrated efficacy in reducing pain and anxiety, resulting in an increased willingness to undergo the procedures again.

Despite the potential benefits of music therapy in urological surgeries, there is limited information on its application to reduce pain and anxiety during PNTR. The aim of this research is to investigate the impact of music on pain and anxiety levels throughout the PNTR procedure.

Materials and Methods

Patients

This study was conducted at Loei Hospital, focusing on patients who underwent PNTR between May 1, 2023, and September 30, 2023. Inclusion criteria included patients aged 18 years and older undergoing PNTR, proficiency in the Thai language, and who demonstrated understanding of the procedures and objectives, as evidenced by providing informed consent through signing the consent form. Patients excluded from the study included those with a history of hearing impairment, individuals with neurological conditions that impact sensory perception, and those who were unable to undergo PNTR. Approval for the study was obtained from the Ethics Committee of Loei Hospital (approval number: EC017/2566).

Study design

This study, a single-center randomized controlled trial, used a random allocation method based on a computer-generated random sequence with blocks of 4. Concealment was achieved through identical sequential opaque sealed envelopes, and the envelope draw carried out by staff before the procedure. Patients were then assigned to either group 1, not listening to music but wearing headphones for blinding purposes or group 2, listening to a preferred choice of music (e.g., traditional Thai music, country, international) with headphones during the procedure. While participants could not be blinded to their group, the medical personnel performing the PNTR and the research assistants collecting data were able to be blinded.

PNTR technique

In this study, all PNTR procedures were carried out in the operating room and a single urologist carried out all cases. The procedure followed a standardized protocol for PNTR, including informed consent, cleaning with antiseptic solution, sterile draping, and, for some participants, listening to music via headphones. During the procedure 7 ml of 1% Xylocaine without adrenaline is administered, old ties are cut, and the tube is shortened before inserting a guide wire. The old tube is then removed, replaced with a new one, and tested for proper positioning by irrigating with water. Suturing is performed, and a final test ensures the secure placement of the new urinary drainage tube.

Data collection, definitions, and primary outcomes

In this research, demographic data collection included gender, age, body mass index (BMI), underlying medical conditions, and causes of obstruction. Procedure-related data included details about the location of the PNT, pain and anxiety scores, vital signs and willingness to repeat the procedure.

The primary outcomes for this study were pain and anxiety scores. Secondary outcomes included vital signs and willingness to repeat the procedure.

Pain scores: pain was be assessed using the Visual Analog Scale (VAS) with scores ranging

from 0 to 10. The assessments were conducted three times: baseline pain evaluation before changing the PNT, procedural pain assessment immediately upon completion of suturing of the new PNT to the skin, and post-procedural pain.

Anxiety scores: anxiety was assessed using The State-Trait Anxiety Inventory-State Anxiety (STAI-SA), developed in 1970 by Spielberger and colleagues. The validity of the Thai version, established in 1983 by Nonthasak T[10], demonstrated a Cronbach's alpha internal consistency level of 0.78. The STAI-SA measures a person's feelings in a specific situation at a certain time. The STAI-SA consists of 20 statements, with total scores ranging from 20 to 80. Anxiety levels are categorized as no or low anxiety (20-37), moderate anxiety (38-44), and high anxiety (45-80).[11] The STAI-SA assessment was conducted twice: before commencing the procedure, and 10 minutes after the procedure was completed.

Vital signs: vital signs, including systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate, were measured using appropriate medical instruments. The vital signs were measured at three distinct times along with the VAS pain assessment

Willingness to repeat the procedure was evaluated after completion of the procedure. Patients were asked whether they are satisfied or dissatisfied with the idea of coming back for the next PNTR.

Statistical analysis

The statistical analysis involved descriptive statistics for the sample group undergoing PNTR, sex, age, BMI, underlying disease, side of PNT, procedural indicators, and cause of hydronephrosis. Data are presented as frequency and percentage distributions, with mean and standard deviation for normally distributed continuous variables and median with interquartile range (IQR) for non-normally distributed data.

Differences in general characteristics between the music-listening and non-music-listening groups were assessed using the Chi-square test or Fisher's exact test if expected values are less than 5 in more than 20% of cells.

STAI-SA scores, VAS pain scores, vital signs and willingness to repeat the procedure were compared between the music-listening and non-music-listening groups. The choice between an independent t-test or Mann-Whitney test was dependent on whether the data was normally or non-normally distributed.

The researchers based the statistical analysis on 4 protocols; protocol A, patients undergoing their first PNTR only, protocol B, patients undergoing 2-4 PNTR changes, protocol C, patients undergoing 5-17 PNTR and finally, protocol D, patients undergoing more than 17 PNTR. All of the above were used for comparing the differences in VAS between music and non-music therapy by two-way analysis of variance. The correlation between VAS and frequency PNTR was analyzed using Spearman correlation coefficient.

Results

A total of 108 patients were initially enrolled for the PNTR procedure, with 4 individuals (3.7%) excluded from the study. Among these exclusions, 3 did not meet the inclusion criteria, and 1 did not cooperate in completing the questionnaire. Subsequently, 104 participants were randomized and divided into two groups, each consisting of 52 individuals (Figure 1).

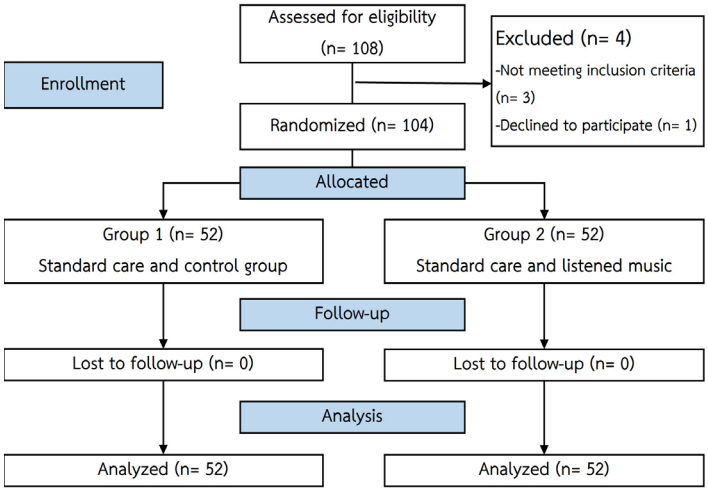

Figure 1. Flowchart of this study

Table 1. Demographic data

Variables	Control group (n=52)		Music group (n=52)		P-value
	n	%	n	%	
Sex					0.694[a]
Male	23	44.23	25	48.08	
Female	29	55.77	27	51.92	
Age (years) mean±SD	66.48	±13.66	62.71	±12.60	0.147[b]
BMI (kg/m^2) mean±SD	22.21	±4.41	22.85	±4.91	0.487[b]
Side					0.691[a]
Right	29	55.77	31	59.62	
Left	23	44.23	21	40.38	
Underlying disease					0.169[a]
No	1	1.92	4	7.69	
Yes	51	98.08	48	92.31	
Diabetes mellitus	13	25.00	13	25.00	1.000[a]
Hypertension	21	40.38	25	48.08	0.430[a]
Dyslipidemia	7	13.46	10	19.23	0.426[a]
Chronic kidney disease*	38	73.08	32	61.54	0.210[a]
Gout	7	13.46	4	7.69	0.339[a]
Bladder cancer	5	9.62	3	5.77	0.462[a]
Cervix cancer	7	13.46	7	13.46	1.000[a]
Prostate cancer	1	1.92	2	3.85	0.558[a]
Colon cancer	0	0.00	1	1.92	0.315[a]
Rectal cancer	0	0.00	1	1.92	0.315[a]
Cause of obstruction					
Ureteric calculi	16	30.77	14	26.92	0.510[a]
Renal calculi	17	32.69	13	25.00	0.530[a]
Ureteral stricture	5	9.62	4	7.69	1.000[a]
Ureteropelvic junction obstruction	0	0.00	3	5.77	0.133[a]
Benign disease**	3	5.77	4	7.69	0.689[a]
Malignant disease	11	21.15	14	26.92	0.368[a]

SD = standard deviation, BMI = body mass index
Statistical analysis was conducted using tests as indicated: aFisher'sexact, bIndependent t-test
*Chronic kidney disease is defined as a condition where the glomerular filtration rate is less than 60 ml/min/1.73 m^2 for a minimum duration of 3 months.[12]
**Benign diseases in this research include ovarian tumor, benign prostatic hyperplasia with bilateral hydronephrosis, and neurogenic bladder.

The demographic data included gender, age, BMI, the side of PNT, underlying medical conditions, and the cause of hydronephrosis. Statistical analysis reveals no statistically significant differences between the two groups when these variables are compared (Table 1).

In this study, it was observed that the systolic blood pressure of the music-listening group was lower than the non-music-listening group during and after PNTR, but the difference was not statistically significant (Table 2).

VAS pain score of the music-listening group was significantly lower than that of the non-music-listening group during and after PNTR (2.5 vs 5, $p < 0.005$ and 0 vs 3, $p < 0.001$, respectively). Additionally, statistically significant differences were observed in STAI-SA levels post- PNTR and the willingness to repeat procedure, with the music-listening group exhibiting lower anxiety (32.98±5.61 vs 39.98±6.18, $p < 0.001$) and higher willingness in comparison to the non-music-listening group (41 vs 22, $p < 0.001$) (Table 3).

Table 2. Operation time and hemodynamic parameters.

Variables	Control group (n=52)		Music group (n=52)		P-value
	mean±SD		mean±SD		
Duration of PNTR (minutes)	5.51	0.89	5.46	0.81	0.591[b]
Pre-PNTR SBP (mmHg)	139.15	22.59	141.78	21.11	0.54
Pre-PNTR DBP (mmHg)	77.53	11.78	79.76	14.06	0.382
Pre-PNTR MAP (mmHg)	101.38	16.45	104.17	17.07	0.398
Pre-PNTR HR (mmHg)	88.54	16.32	88.42	14.81	0.97
Procedural-PNTR SBP (mmHg)	140.84	22.62	138.57	19.54	0.585
Procedural-PNTR DBP (mmHg)	77.75	14.31	78.11	14.65	0.97
Procedural-PNTR MAP (mm Hg)	103.09	17.91	103.59	16.31	0.882
Procedural-PNTR HR (mmHg)	88.04	15.63	89.59	13.28	0.585
Post-PNTR SBP (mmHg)	139.53	21.92	137.25	18.98	0.571
Post-PNTR DBP (mmHg)	75.92	12.28	75.82	13.8	0.97
Post-PNTR MAP (mmHg)	101.21	17.32	100.51	15.55	0.831
Post-PNTR HR (mmHg)	88.28	15.38	87.69	14.32	0.838

SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, HR = heart rate, SD = standard deviation, PNTR = percutaneous nephrostomy tube replacement
[b]Statistical analysis was conducted using an Independent t-test

Table 3. Pain scores, anxiety scores, and willingness to repeat the procedure.

Variables	Control group (n=52)		Music group (n=52)		P-value
Pre-PNTR VAS; Median (IQR)	0	4	0	4	0.849[c]
Pre-PNTR STAI-S; mean ± SD	41.9	6.54	41.21	6.52	0.590[b]
Procedural-PNTR VAS; Median (IQR)	5	3.5	2.5	4	<0.005[c*]
Post-PNTR VAS; Median (IQR)	3	5	0	1	<0.001c*
Post-PNTR STAI-S; mean ± SD	39.98	6.18	32.98	5.61	<0.001[b*]
Willing to repeat procedure n (%)	22	42.31	41	78.85	<0.001[a*]

Statistical analysis was conducted using: [a]Fisher's exact, [b]Independent t-test, [c]Mann-Whitney U test, [*]Statistically significant
STAI-SA = State-Trait Anxiety Inventory-State Anxiety, VAS = visual analog scale, PNTR = percutaneous nephrostomy tube replacement

In this study, we investigated whether patients experience a decrease in pain during PNTR procedures. We conducted a per-protocol analysis to assess the relationship between the number of PNTR and the pre-PNTR VAS scores for pain.

Pre-PNTR process

We considered the differences between the two groups using comparisons between the 4 protocols. Two-way analysis of covariance revealed that VAS differed in the Music and Non-music therapy groups, but the results did not reach statistical significance ($p = 0.064$). The grand mean for this analysis was calculated to be 2.019231. Tukey multiple comparisons of means, also showed no statistically significant differences ($p > 0.05$) between all 4 protocols, even though the mean VAS for pain were 2.8432 for the control group and 1.0991 for the music group.

Furthermore, when analyzing the linear correlation of VAS between the control group and the music group, we found that in this population, VAS in pre-PNTR and frequency of PNTR are not linearly correlated ($p = 0.1491$)

Overall, our per-protocol analysis revealed no statistically significant differences ($p > 0.05$) in the relationship between pre-PNTR VAS in patients across different protocols and between

the control and music groups. A summary of the results are shown in Table 4.

Procedural-PNTR process

The overall mean for the number of PNTR is 4. The mean number of PNTR for each protocol (A, B, C, D) ranges from 3.308 to 4.654. The means of the two groups are 4.902 in the control group and 3.098 in the music group. The interaction in terms of the comparisons of the two groups have shown results consistent with pre-PNTR. Comparison of the VAS in Music and Non-music therapy showed also non-significant outcomes (p = 0.731)

The comparison between protocols in the Procedural-PNTR as regards VAS using Tukey multiple comparisons of means resulted in no statistically significant differences in the relationship between Procedural -PNTR VAS scores and pain among patients across different protocols and between the control and music groups. These results were similar to the linearity test that showed that VAS in Procedural-PNTR and frequency of PNTR were not linearly correlated (p = 0.4226) (Table 5).

Post-PNTR process

This process has been used to investigate the comparisons between the groups when a combination of the protocols that non-significantly corresponded to the first period before PNTP including procedural PNTR (p = 0.817). Each of protocols analysis was conducted to compare the mean scores of post-PNTR VAS across the different protocols and between groups. The grand mean for all protocols and groups combined was found to be 1.971154 whereas the correlation coefficient based on Spearman's method among VAS in post-PNTR did not show any linearity with frequency PNTR (p = 0.5244)

Table 4. The Tukey multiple comparisons of means pre-PNTR VAS.

Comparison	Difference in mean	Lower CI of mean	Upper CI of mean	Adjusted p-value of mean	Spearman's correlation coefficient (95%CI)	P-value of correlation
A-B	0.7307	1.2374	2.6989	0.7663	-0.142 (-0.326, 0.052)[a]	0.1491[b]
A-C	0.4615	1.5066	2.4297	0.9276		
A-D	0.7307	1.2374	2.6989	0.7663		
B-C	0.2692	1.6989	2.2374	0.9842		
D-B	0.0000	-1.9682	1.9682	1.0000		
C-D	0.2692	1.6989	2.2374	0.9842		

[a]spearman correlation coefficient: linear correlation between VAS before PNTP with frequency of PNTR, [b]p-value Spearman's correlation coefficient
STAI-SA = State-Trait Anxiety Inventory-State Anxiety, VAS = visual analog scale, PTNR = percutaneous nephrostomy tube replacement, CI = confidential interval

Table 5. The Tukey multiple comparisons of means using the mean procedure-PNTR VAS.

Comparison	Difference in mean	Lower CI of mean	Upper CI of mean	Adjusted p-value of mean	Spearman's correlation coefficient (95%CI)	P-value of correlation
B-A	1.1538	-0.8982	3.2059	0.4594	0.0794[b] (-0.268, 0.115)	0.4226[a]
C-A	1.0384	-1.0135	3.0905	0.5505		
A-D	0.1923	1.8597	2.2443	0.9947		
B-C	0.1153	1.9366	2.1674	0.9988		
B-D	1.3461	0.7059	3.3982	0.3215		
B-A	1.1538	-0.8982	3.2059	0.4594		

[a]Spearman's correlation coefficient: linear correlation between VAS procedural-PNTR with frequency of PNTR, [b]p-value Spearman's correlation coefficient, CI = confidential interval

The mean scores between different protocols (A, B, C, D) were compared using Tukey multiple comparisons of means. The results showed that there were no statistically significant differences ($p > 0.05$) between Protocol B and Protocol A, Protocol C and Protocol A, Protocol D and Protocol A, Protocol C and Protocol B, Protocol D and Protocol B, or between Protocol D and Protocol C (Table 6).

However, upon consideration of the comparison of mean VAS for pre-procedural, procedural, and post-procedural phases of PNTR, it is evident that the mean VAS does not decrease with an increasing number of PNTR, as shown in Table 7.

In conclusion, the analysis indicates that there were no statistically significant differences ($p > 0.05$) between the protocols, indicating that the mean pre, procedure, post-PNTR VAS did not vary significantly across different protocols according to spearman correlation coefficient in 3 periods. Moreover, an increased frequency of PNTR does not show any correlation with a reduction in pain.

Discussion

When patients undergo percutaneous nephrostomy tube placement they commonly experience pain and anxiety.[13] The actual procedure of PNTR exacerbates these symptoms. This procedure is frequently performed in a urologist's office, and patients often face increased pain and anxiety due to the alien surroundings.

Currently, there are no standard pain relief recommendations for PNTR. The common practice involves local administration of analgesic agents around the PNT insertion, at the precise location of the suture site where the PNT is attached to skin. However, there are a range of pharmacological and non-pharmacological approaches being used to reduce pain and anxiety. Pharmacological approaches have limitations, including cost, side effects, and the risk of drug dependence.[14,15] Non-pharmacological methods are attracting increasing interest due to their lower side effect profile.[16-18]

Non-pharmacological pain relief methods encompass various techniques including educa-

Table 6. The Tukey multiple comparisons of means in post- PNTR VAS.

Comparison	Difference in mean	Lower CI of mean	Upper CI of mean	Adjusted p-value of mean	Spearman's correlation coefficient (95%CI)	P-value of correlation
B-A	0.2307	-1.5546	2.0162	0.9866	0.0630 (-0.131, 0.252)[a]	0.5244[b]
C-A	0.4230	-1.3623	2.2085	0.9255		
D-A	0.4615	-1.3239	2.2469	0.9059		
C-B	0.1923	-1.5931	1.9777	0.9921		
D-B	0.2307	-1.5546	2.0162	0.9866		
D-C	0.0384	-1.7469	1.8239	0.9999		

[a]Spearman's correlation coefficient: linear correlation between VAS procedural-PNTR with frequency of PNTR, [b]p-value Spearman's correlation coefficient
CI = confidential interval

Table 7. Mean VAS for pre-procedural, procedural, and post-procedural phases of PNTR for the control group and the music intervention group across different protocols (A, B, C, D).

Protocol	Pre-PNTR VAS		Procedural-PNTR VAS		Post-PNTR VAS	
	Control group	Music group	Control group	Music group	Control group	Music group
A	2.846	2.154	4.308	2.692	2.308	1.077
B	1.250	2.214	5.583	3.857	2.667	1.286
C	1.200	3.182	5.000	3.909	3.000	0.909
D	2.750	0.929	4.833	2.000	3.417	1.071

PTNR = percutaneous nephrostomy tube replacement, VAS = visual analoque scale

tion, music therapy, mind-body techniques, relaxation training, distraction, biofeedback, humor, massage, aromatherapy, reflexology, acupuncture, therapeutic touch, and transcutaneous electrical nerve stimulation.[19]

Several studies have explored the use of music to reduce anxiety and pain during urological procedures.[2-9] Music, as a stimuli-directed intervention, stimulates the part of the brain controlling emotional responses faster than the part responsible for pain perception, increasing pain tolerance and alleviating suffering.[20,21]

This study chose to have patients listen to their preferred music because previous research by Cift A and colleagues found that providing patients undergoing shock wave lithotripsy with their preferred music choice contributed significantly to lower levels of pain and anxiety, as well as higher satisfaction levels, when compared to responses to exposure to Turkish art music and Western classical music.[22]

Despite previous research into the use of music during office-based surgical procedures, no studies have investigated its efficacy during PNTR. This study aimed to assess the impact of music on pain and anxiety during PNTR.

The study found that VAS pain score and STAI-SA scores in the music group were significantly lower than those in the non-music group, with a statistically significant proportion in the music group expressing a willingness to repeat the procedure. This finding is in alignment with other randomized controlled trials in which patients listened to music during minor urological procedures. These trials included nephrostomy tube placement by Hamidi et al.[23], extracorporeal shock wave lithotripsy by Bozkurt M and coworkers[24], and a urodynamic study by Öztürk E and colleagues.[9]

However, in a study by Cakmak et al.[25], listening to music during extracorporeal shockwave lithotripsy, found significantly lower systolic blood pressure, diastolic blood pressure, and heart rate in comparison to the non- music group. These outcomes were in contrast to the findings of this study, where although systolic blood pressure in the music group was lower than in the non-music group during and after PNTR results were not statistically significant. The lack of significant differences in vital signs may be due to the shorter duration of pain stimulation during PNTR compared to shockwave lithotripsy.

There are a few potential limitations to this study. Firstly, the absence of an evaluation regarding the success of the PNTR, a factor which could easily be incorporated into a future investigation. Secondly, an inability to assess the relationship between the type of music and the reduction in VAS pain score and STAI-SA scores, again an aspect which could be included in the future.

Conclusions

The outcomes of this study demonstrate that listening to a preferred choice of music during PNTR has the potential to reduce pain, anxiety, and increase the willingness of the patients to repeat procedure. This music intervention serves as a safe and side effect-free non-pharmacological approach.

Conflicts of Interest

The authors declare there are no conflicts of interest.

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Invited Review Article

Cardiovascular risk and urolithiasis: underestimated or unknown relationship?

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Urolithiasis, kidney stones, risk factor, cardiovascular disease, metabolic syndrome, obesity

Abstract

Objective: Urolithiasis, a multifactorial disease, is increasingly recognized for its association with cardiovascular disease (CVD), a leading global cause of morbidity and mortality. Despite the establishment of links between urolithiasis and CVD risk factors such as diabetes, obesity, and hypertension, this relationship remains underexplored. This study aims to characterize the trend of information regarding cardiovascular risk and urolithiasis through comprehensive bibliometric analysis, highlighting the importance of investigating this association further.

Materials and Methods: We searched publications between 2002 and 2022 on the Web of Science (WOS) database, filtered by exclusion criteria. Impact factor (IF) 2021 and Journal Citation Reports (JCR) were evaluated and analyzed by mapping using VOSviewer.

Results: We obtained 63 articles from 49 journals over the last two decades, identifying an increase in publications in the last two years without a rising annual trend. Gambaro G is the author of most citations (12,317), underscoring the extent of the global and interdisciplinary effort in understanding the cardiovascular implications of urolithiasis. Our findings highlight the varied impact of journals, with IFs ranging from 1 to 10.6, and point to a significant yet overlooked global research interest in the intersection between urolithiasis and cardiovascular risk. The USA was the country with the most publications (20.6%) followed by Taiwan (12.6%) and Spain (9.5%). Despite the observed increase, the rate of publications especially in high-impact journals remains low, particularly in Latin America, indicating a need for heightened research efforts in this important field.

Conclusion: This bibliometric analysis underscores a growing yet insufficient global scholarly interest in the relationship between urolithiasis and cardiovascular risk. Despite some high-impact publications, the overall scarcity points to a need for increased research efforts, particularly in underrepresented regions such as Latin

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America. The study calls for a broader interdisciplinary collaboration to further understand and address the cardiovascular implications of urolithiasis, aiming to improve patient care and outcomes in this significant public health intersection.

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Introduction

Urolithiasis, a multifactorial disease, exhibits a high prevalence in developed countries, with a higher incidence in males and a recurrence rate exceeding 60% within a 10-year period.[1] This condition has been associated with systemic disorders such as hypertension, metabolic syndrome, dyslipidemia, and chronic kidney disease.[2,3] While the diet of an individual primarily influences their metabolism, other factors, including intestinal microbiota and its impact on intestinal transit, have been linked to obesity and diabetes, conditions directly related to urolithiasis.[3]

Alleviation of, not only the disease itself but also its complications, such as acute renal injury and pyelonephritis, can be achieved through dietary modifications and adequate hydration. Medical treatments have proven effective, particularly in the case of calcium oxalate stones, which account for over 80% of cases.[1] As urolithiasis is a commonly encountered emergency condition, interventional treatments have advanced; however, the current trend in managing this disease emphasizes a global perspective that prioritizes prevention as a fundamental pillar of treatment.[4] Primary care physicians should also familiarize themselves with its epidemiology as it significantly impacts the financial and mobility burden on public health.[5] Notably, urolithiasis has been identified as an important risk factor for cardiovascular disease, although the direct relationship between urolithiasis and cardiovascular events such as acute myocardial infarction is yet to be fully understood.[2]

In this study we collated and analyzed the available literature from the last two decades regarding urolithiasis and cardiovascular risk. As this topic is not very-well known and researched in urology, we were driven to do a bibliometric analysis with the objective of providing information pertinent to this relationship and modify the current assessment of the disease into a global approach. The outcomes pointing to prevention as a main component and resulting in positive outcomes in these patients.

Materials and Methods

Database and research strategy

For our bibliometric analysis, we accessed the comprehensive Web of Science (WOS) database, which encompasses over 9,000 high-impact journals, offering extensive scope for our investigation. Our focus was on identifying the nexus between cardiovascular disease and urolithiasis. Given the dynamic nature of the WOS with constant updates, we confined our search to a single day's work, aiming to maintain data consistency.

The search strategy was meticulously constructed using specific search terms including "cardiovascular risk factors," "cardiovascular risk," "urolithiasis," and "kidney stones." We integrated Boolean operators (AND, OR) to refine our query, spanning publications from 2002 to 2022. The initial search rendered 93 studies. The selection process involved excluding 30 studies that did not meet our inclusion criteria: publication type (e.g., meeting summaries and acts), irrelevant disciplines (e.g., veterinary sciences), and out-of-scope articles. We prioritized English-language publications, acknowledging the role of English as the lingua franca of academic communication, thus narrowing our scope to original research articles and review articles. Information on authors, titles, sources, and abstracts was systematically extracted and organized in text format, facilitating subsequent bibliometric analysis and assuring extensive topical coverage.

Data analysis

Data curation and analysis were collaboratively conducted by two investigators (V.M, C.S) to bolster the precision and reliability of our findings. We scrutinized publication frequency, authorship, citation metrics, journal influence, affiliations, and geographical distribution within our dataset. For data organization and preliminary analysis, we utilized Microsoft Office Excel 2019 (Microsoft Corp., Redmond, WA, USA), arranging our findings into utilizable tables.

Data visualization

For the visualization component, we employed Microsoft Office Excel 2019 to construct tables and graphical representations, focusing on the most salient features within each category. We assessed the quality of the publications by journal Impact Factor, as indicated in the Journal Citation Reports 2021, and applied the H-index for evaluating the influence of authors and journals, referencing the Scimago Journal and Country Rank. We quantified citations per journal, author, and institution to underscore research impact.

Advanced visualization was facilitated through VOSviewer (version 1.6.18), a specialized software for generating and interpreting network maps from data. Our analysis incorporated various bibliometric measures, including co-authorship and co-citation networks, and keyword co-occurrence, providing insight into collaborative trends and thematic concentration within the field.[6,7]

Results

Global tendencies in publications

We compiled a total of 63 publications which recorded investigations into the association between cardiovascular risk and urolithiasis from 2002 to 2022. The comprehensive research strategy employed is outlined in Annex 1. Our analysis revealed a fluctuating pattern in annual publication output, with a notable peak in 2019, featuring 9 articles. This was followed by 2017 and 2022, with 7 publications in each, as depicted in Figure 1.

Data analysis by country

We collated the number of publications per country pertinent to the relationship between cardiovascular risk and urolithiasis. On figure 2, we identified the 10 countries in which most articles were published: USA leading with 13 publications, followed by Taiwan 8, Spain 6 and Japan 6. In South America, we found out that only 3 countries were writing about this subject (Brazil, Argentina and Chile) with one article each. Figure 3 showed the relationship of co-authorship per country.

The lines between the nodes indicate the co-authorship between the countries, and the thicker the line, the greater the cooperation also called total link strength (TLS). The co-authorship visualization map (Figure 3) showed that the top 4 TLS were USA (TLS: 3), England (TLS:1), Germany (TLS:1), France.[1]

Health institutes data analysis

206 health institutes were identified in papers regarding cardiovascular risk and urolithiasis. The 10 most published are shown in annex 2. The majority were from Taiwan, the top 3 according to TLS (Total link Strength) being from: National Yang Ming Chiao Tung University (TLS=30), Taipei City Hospital (TLS=30) and Chang Gung University (TLS=27). Even though institutes

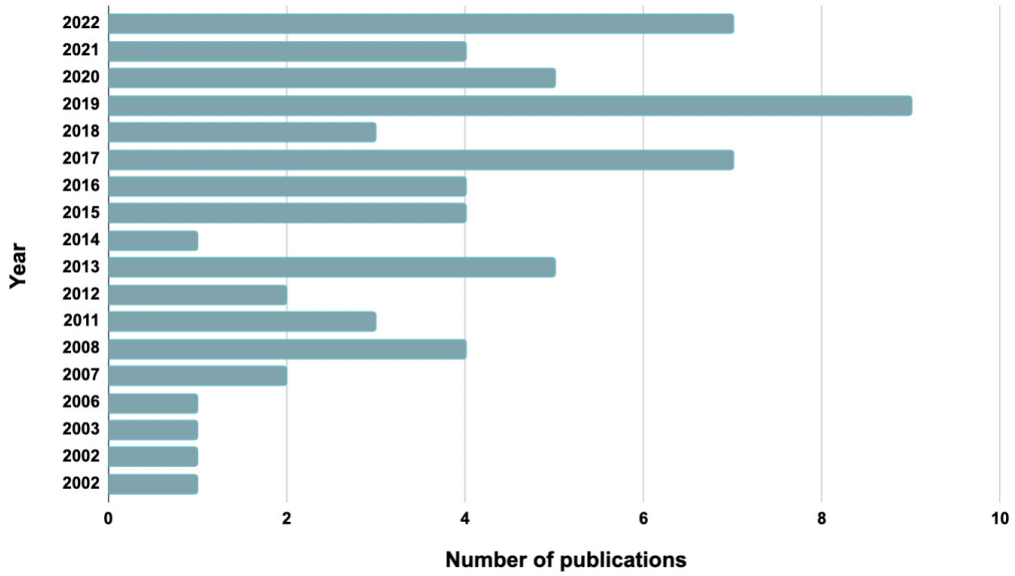

Figure 1. Number of publications per year 2002 to 2022.

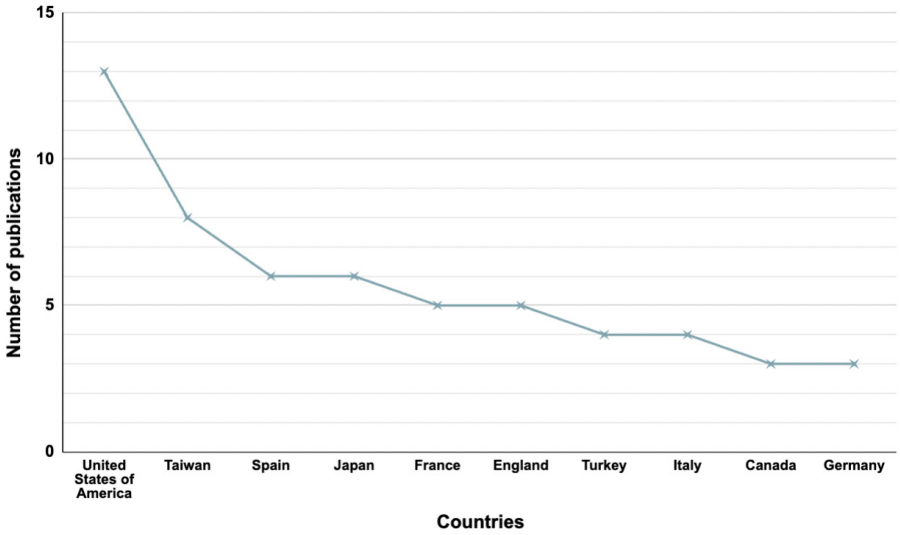

Figure 2. Top 10 countries with the highest number of publications.

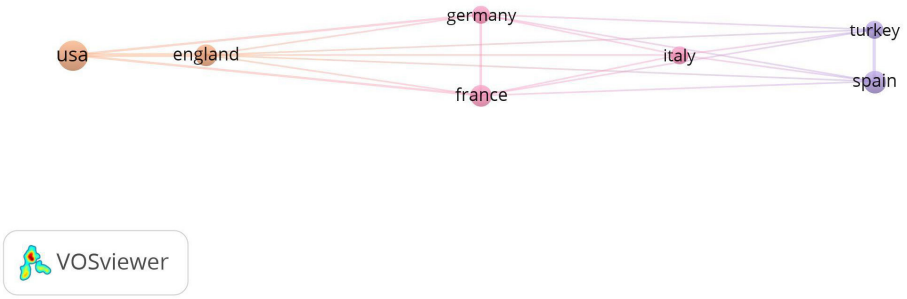

Figure 3. VOSviewer map based on co-authorship per country.

from Taiwan and France have published the same number of publications, Albert Einstein College of Medicine of the USA has the most cited studies.[2]

Authors analysis

In Annex 3, we present the top 10 authors out of a total of 370 authors who have made significant contributions to the field, based on the number of publications. Notably, these authors represent six different countries, indicating the high level of international collaboration in urolithiasis research. Each author in the top 10 has contributed two articles, although there is variability in the number of citations received for their work.

An outstanding achievement in terms of citations is attributed to Gambaro G, who amassed a remarkable total of 12,317 citations. This places him at the forefront of this field in terms of impact, demonstrating the significance and influence of his research. Moreover, Gambaro also achieved the highest H index (HI=49), indicating the broad impact and sustained level of citation of his publications. Following closely behind is Gratzke C who despite a difference of over 4,000 citations between the two authors, still highlights a significant contributions to the field.

Journal data analysis

Several journals have published articles pertinent to this topic. Table 1 shows the 10 journals which have most frequently published relevant papers, being led by Urolithiasis journal (5; 1.9%), however has fewer citations (1,600). On the other hand, Plos One journal had the highest number of citations (944,441) from only 2 publications. The highest IF was found in 2 American journals, Clinical Journal of The American Society (FI=10.6), and Journal of Urology (FI=7.6) and a Swiss journal International Journal of Molecular Sciences (FI=6.2). Only 3 out 10 journals had a q1 from JCR scoring.

Table 1. Top 10 of journals related to cardiovascular disease and urolithiasis

Rank	Journal	Country	Publications	IF (2021)	JCR (2021)	H-Index	Citations
1	Urolithiasis	USA	5	2.8	Q3	65	1,600
2	Clinical Journal of The American Society of Nephrology	USA	3	10.6	Q1	163	24,535
3	Progres en Urologie	France	3	1.0	Q4	34	1,175
4	Clinical Rheumatology	England	2	3.6	Q3	88	14,054
5	International Journal of Molecular Sciences	Switzerland	2	6.2	Q1	195	211,519
6	International Journal of Urology	Japan	2	2.8	Q3	71	5,434
7	Journal of Nephrology	Germany	2	4.4	Q2	71	4,702
8	Journal of Urology	USA	2	7.6	Q1	265	51,677
9	Plos One	USA	2	3.7	Q2	367	944,441
10	Journal of Cardiology	Japan	1	3.1	Q3	52	4,534

IF = impact factor, JCR = Journal Citation Reports

Table 2. Top 20 keywords related to cardiovascular disease and urolithi

Rank	Keywords	Frequency	TLS	Rank	Keywords	Frequency	TLS
1	Urolithiasis	49	216	11	Cardiovascular-disease	12	53
2	Nephrolithiasis	30	138	12	Disease	11	51
3	Risk	26	103	13	Chronic kidney-disease	12	47
4	Prevalence	21	101	14	Oxidative stress	8	38
5	Kidney-stones	18	95	15	Coronary-heart-disease	8	35
6	Metabolic Syndrome	17	85	16	Epidemiology	6	34
7	Association	16	73	17	Chronic kidney disease	6	32
8	Hypertension	14	65	18	Stroke	5	32
9	Obesity	12	63	19	Uric acid	6	31
10	Risk-factors	15	57	20	Metaanalysis	6	29

TLS = total link strength

Data analysis of eywords and articles

The 10 most frequently used keywords were very varied including similar terms to urolithiasis and cardiovascular disease. The most repeated keyword (49) and highest TLS (216) is "Urolithiasis" followed by "Nephrolithiasis" and "risk". We also observed a relationship between these keywords and how easily they relate to the topic of interest, table 2.

The most cited article between 2002 and 2019 was, "The pathophysiology of hyperuricemia and its possible relationship to cardiovascular disease, morbidity and mortality" by David Gustafsson in BMC Nephrology (141). 50% of the articles were reviews, table 3.

In the analysis of the co-occurrenceof keywords, we used a minimum of 5 repetitions between the words. Out of 530 keywords we organized 35 items in 4 clusters, represented by different colors in figure 4. The pink cluster (pathophysiology and risk factors) includes keywords including "Chronic kidney disease", "gout", "cardiovascular disease" among others. The purple cluster is diagnosis related and includes words like "urolithiasis", "metabolic syndrome", and "obesity". Orange group (Pathogenesis) includes words such as: "risk", "Renal Stone" and "oxidative stress". The last cluster is identified by green and contains words like "prevalence" and "meta analysis"; all related to epidemiology.

Table 3. Top 10 of the most cited articles

Author	Title	Year	Journal	Citations	Type of publication
Ziemba, JB; Matlaga, BR	Epidemiology and economics of nephrolithiasis	2017	Investigative And Clinical Urology	132	Review
Gustafsson, D; Unwin, R	The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality	2013	BMC Nephrology	141	Review
Chen, XQ; Burdett, TC; Desjardins, CA; Logan, R., et al	Disrupted and transgenic urate oxidase alter urate and dopaminergic neurodegeneration	2013	Proceedings Of The National Academy Of Sciences Of The United States Of America	94	Article
Stern, JM; Moazami, S; Qiu, YP; Kurland, I., et al	Evidence for a distinct gut microbiome in kidney stone formers compared to non-stone formers	2016	Urolithiasis	88	Article
Alexander, RT; Hemmelgarn, BR; Wiebe, N; Bello, A., et al	Kidney Stones and Cardiovascular Events: A Cohort Study	2014	Clinical Journal Of The American Society Of Nephrology	94	Article
Dincer, HE; Dincer, AP; Levinson, DJ	Asymptomatic hyperuricemia: To treat or not to treat	2002	Cleveland Clinic Journal Of Medicine	92	Review
Alvarez-Lario, B; Macarron-Vicente, J	Is there anything good in uric acid?	2011	Qjm-An International Journal Of Medicine	87	Review
Strilchuk, L; Fogacci, F; Cicero, AF	Safety and tolerability of available urate-lowering drugs: a critical review	2019	Expert Opinion On Drug Safety	86	Review
El-Zoghby, ZM; Lieske, JC; Foley, RN; Bergstralh., et al	Urolithiasis and the Risk of ESRD	2012	Clinical Journal Of The American Society Of Nephrology	85	Article
Scales, CD; Tasian, GE; Schwaderer, AL; Goldfarb, DS., et al	Urinary Stone Disease: Advancing Knowledge, Patient Care, and Population Health	2016	Clinical Journal Of The American Society Of Nephrology	87	Article

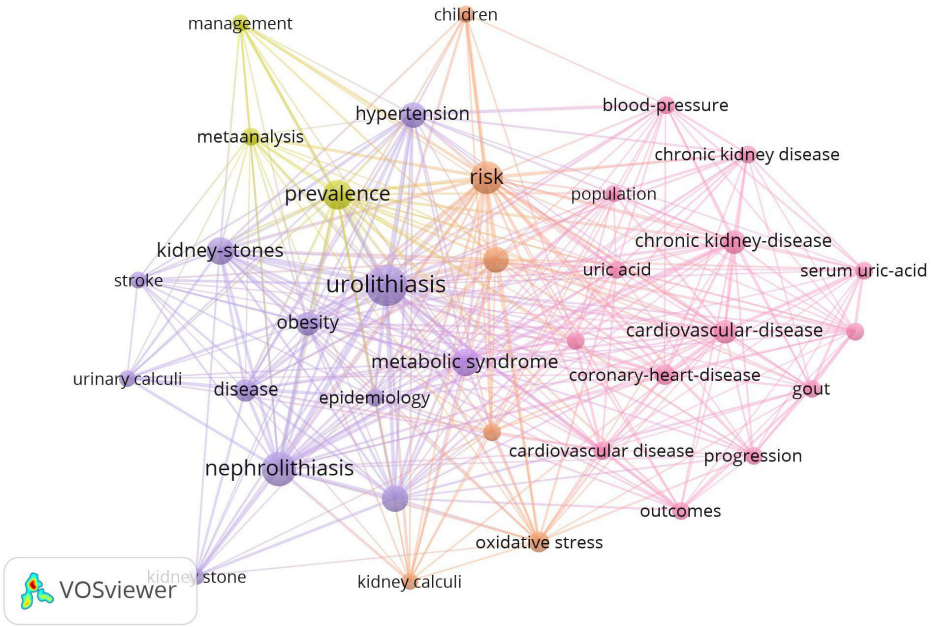

Figure 4. Relationship Map of co-occurrence and keywords.

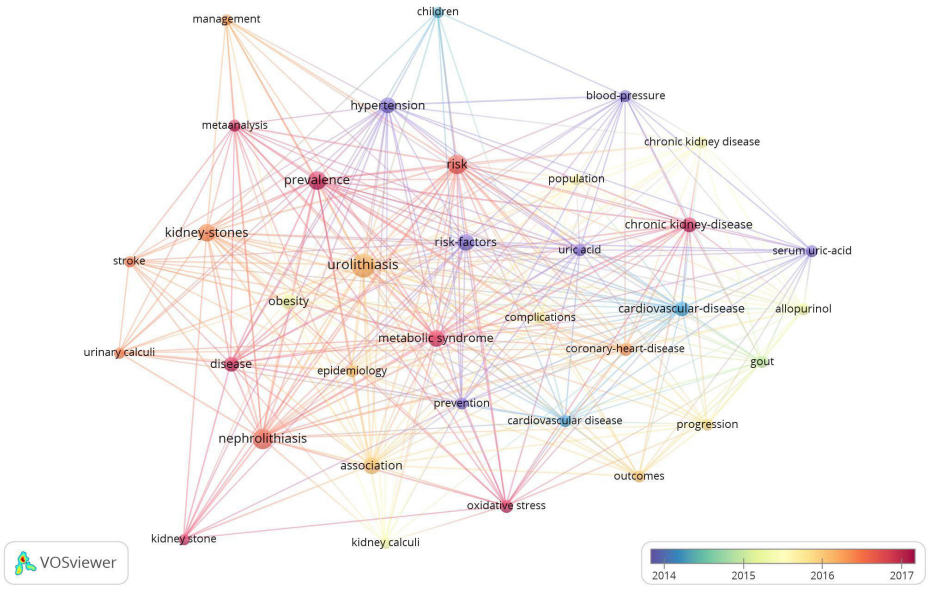

Figure 5. Map of keywords according to frequency of appearance between 2014 and 2017.

Figure 5 maps keywords according to the moment of time used, and we found the closer the time gets to today, the more technical and specific the keywords get.

Discussion

Over the past two decades, there has been an increasing trend in the examination of the relationship between cardiovascular risk and urolithiasis. However, the variation in the manifestation of cardiovascular diseases and urinary stones have made it challenging to establish a direct link.[6] Despite this, there is an accumulating bank of evidence to suggest that urolithiasis may be part of a broader systemic syndrome associated with cardiovascular risk.[8-10] From their 2014 meta-analysis, Yanqiong et al. proposed that metabolic abnormalities such as hypercalciuria, hyperuricemia, and hyperoxaluria might contribute to the formation of kidney stones due to the absence

of effective inhibitors for calcification, which are found deficient in blood and urine. For instance, abnormalities in urinary excretion—such as decreased levels of citrate and magnesium—have been observed in patients with both urolithiasis and CVD. Citrate provides a protective role by inhibiting kidney stone formation, and its reduced excretion could reflect broader metabolic dysregulation that also increases cardiovascular risk.[11] Consequently, recommendations have been made for the implementation of preventive measures and cardiovascular risk screening for all patients with urinary stones.[12,13]

Over the last two decades, there has been an increasing focus in research into the link between cardiovascular risk and urolithiasis. Despite the complex interplay between the diverse manifestations of cardiovascular diseases (CVD) and urinary stones, which makes it difficult to pinpoint a direct relationship, there is growing evidence that suggests urolithiasis might be part of a broader systemic syndrome that includes cardiovascular risk.[14,15] According to a 2014 meta-analysis by Yanqiong et al., metabolic abnormalities such as hypercalciuria, hyperuricemia, and hyperoxaluria may promote kidney stone formation due to the deficiency of effective calcification inhibitors in blood and urine.[12,13] Notably, urinary abnormalities like decreased levels of citrate and magnesium, which have been observed in patients with both urolithiasis and CVD, point to a possible metabolic dysregulation that might also elevate cardiovascular risk. Citrate, known for its role in preventing kidney stones, when found at reduced levels, could indicate broader metabolic issues. As a result, other teams have also made recommendations for implementing preventive measures and cardiovascular risk screenings for patients with urinary stones.[16]

Another significant observation is the presence of endothelial dysfunction (ED) in patients with urolithiasis. ED, a known precursor to cardiovascular problems such as atherosclerosis and hypertension, suggests a possible shared pathway involving systemic inflammatory responses and oxidative stress.[17] This finding supports the idea that improving endothelial function might simultaneously benefit conditions of both urolithiasis and CVD.

Furthermore, oxidative stress and inflammation are crucial in the development of chronic diseases, including both urolithiasis and CVD. Elevated levels of reactive oxygen species (ROS) and inflammatory cytokines can lead to tissue damage and fibrosis, affecting both vascular and renal systems. This shared pathophysiology implies that treatments targeting oxidative stress and inflammation could potentially address both urolithiasis and CVD effectively.

Additionally, disruption of calcium metabolism, common in patients with kidney stones, might also contribute to vascular calcification in CVD.[18] The formation of calcium-based kidney stones and the calcification of arterial walls involve similar biochemical processes that may be influenced by factors such as vitamin D metabolism, parathyroid hormone levels, and other calcium-phosphate regulators.[19] This overlap highlights the potential for shared therapeutic strategies in managing both kidney stones and cardiovascular complications.

It is worth noting that the majority of studies published on this topic originate from developed countries, which may be attributed to the higher prevalence of chronic diseases, including cardiovascular risk, in these regions.

Despite the significant public health impact of this issue, there has not been a consistent upward trend in annual publications worldwide. Furthermore, only a few case reports related to this topic have been published in Latin America, and significantly, a country like Colombia, which faces high cardiovascular disease mortality, has no publications addressing this relationship.[20,21] Understanding of and identifying the key risk factors contributing to cardiovascular disease is crucial for addressing this pressing public health concern.

The United States stands out as the country with the highest number of published articles, often achieving high impact factor (IF) and Journal Citation Reports (JCR) scores. Some of these publications have even secured positions among the top 100 most cited articles in urologic surgery.[22] The Journal of Urology has been one of the most productive journals in terms of citations in topics related to urinary stones, with a gradually rising IF since 2018.[23]

Among the top 10 authors with the most publications on this topic, there is a higher H index, indicating the influence and impact of their work. However, none of these authors has

published more than two articles specifically examining the relationship between cardiovascular disease and urolithiasis. The United States continues to dominate the publication landscape, even during the peak year of 2018 when the highest number of publications was observed.

In the co-occurrence analysis conducted using VOSViewer, we were able to identify four groups in the mapping and analysis of keywords. These groups range from the pathophysiological understanding of the mechanisms by which cardiovascular risk is a factor in the incidence of urolithiasis, to the importance of epidemiology in this relationship. Additionally, the overlaid visualization map reveals that recent studies are focusing on determining metabolic risk factors and prevalence, suggesting that future research should continue to explore the similarities in the pathogenesis of both diseases.

We emphasize the need for a greater number of studies and publications addressing this topic in order to establish the relationship between cardiovascular risk and urolithiasis with certainty. Furthermore, investigations of this nature should involve various fields of health sciences, including cardiology, nephrology, and internal medicine, in addition to urology and related areas.

It is important to acknowledge the limitations of our study, including the use of a single database and the restriction to English-only articles. This may result in incomplete data representation for Spanish-speaking countries in Latin America. Nevertheless, this study provides the first Colombian bibliometric analysis, shedding light on the trends over the past two decades with regard to cardiovascular risk and urolithiasis.

Conclusions

Urolithiasis transcends its local manifestations to present systemic implications, including an increasingly recognized association with cardiovascular disease. Despite the significant impact of this topic on public health, there has not been a consistent upward trend in the annual publication of investigative work globally. Moreover, in Latin America, only a few case reports have been published on this subject. Notably, a country like Colombia, which faces high mortality from cardiovascular diseases, lacks publications addressing this association. A comprehensive understanding and identification of key risk factors contributing to cardiovascular diseases are imperative if this pressing public health issue is to be addressed.

Our study underlines the urgent need for an increase in scholarly output that elucidates the relationship between cardiovascular risk and urolithiasis. Future research endeavors should span multiple health science fields, including cardiology, nephrology, and internal medicine, as well as urology and related disciplines. The limitations of our study, such as reliance on a single database and restriction to English-language articles, is acknowledged, andcould result in incomplete data representation of Spanish-speaking countries in Latin America. Nevertheless, this study presents the inaugural Colombian bibliometric analysis, illuminating trends over the past two decades in cardiovascular risk and urolithiasis. There is a call to action for the establishment of local databases to enhance scientific output and performance. Encouraging collaboration among researchers in related fields can lead to a more integrated and comprehensive approach with regard to preventive strategies and patient care, and specific recommendations for future research directions and clinical practice should be formulated based on the insights gained from this and subsequent studies.

Acknowledgements

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Conflicts of Interest

The authors declare no conflicts of interest.

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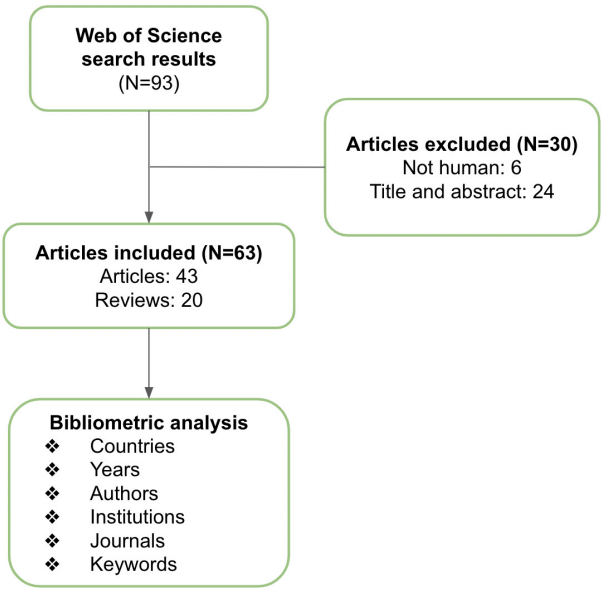
Annex 1. Flow chart of research strategy.



Annex 2. Top 10 of institutions related to publications of interest

Rank	Institutions	Country	Publications	TLS	Citations
1	Albert Einstein College of Medicine	USA	2	3	88
2	Assistance Publique Hopitaux Paris	France	3	-	-
3	Chang Gung Memorial Hospital	Taiwan	3	7	7
4	Chang Gung University	Taiwan	3	27	76
5	Institut National de La Sante et de la Recherche Medicale	France	3	-	-
6	National Yang Ming Chiao Tung Universitv	Taiwan	3	30	80
7	Sorbonne Universite	France	3	-	-
8	Taipei City Hospital	Taiwan	3	30	80
9	Taipei Medical University	Taiwan	3	9	38
10	Udice French Research Universities	France	3	-	-

TLS = total link strength

Annex 3. Top 10 of authors with the largest numbers of publications

Rank	Author	Country	Publications	H-Index	Citations
1	Agalliu I	USA	2	30	2,733
2	Aydin H	Germany	2	10	364
3	Binder H	Turkey	2	46	6,709
4	Boeker M	Germany	2	15	825
5	Cheng TT	Taiwan	2	17	1,280
6	Fichtner UA	Germany	2	2	19
7	Gambaro G	Italy	2	49	12,317
8	Goldfarb DS	USA	2	49	7,292
9	Gratzke C	Germany	2	46	8,250
10	Haymann JP	France	2	34	3,917

Invited Review Article

Transforming urology: exploring the innovations and utilizations of robotic systems

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Keywords:
Robotic surgical system, robotic urology, da Vinci, robotic advancement

Abstract

Robot-assisted surgery represents the pinnacle of minimally invasive surgical techniques, surpassing laparoscopic surgery in its efficacy. This study aimed to evaluate the current status of robotic surgery in urological practice, examining its advantages and disadvantages. A literature review was conducted using PUBMED and the pertinent articles in the field of urology selected. Various single-port and multiport robotic platforms, such as Da Vinci, Versius, Hugo RAS, Revo-I, Senhance, Mantra, Avatera, hinotori, and MicroSurge, are discussed along with their respective pros and cons. Details of the 4 robotic platforms used in our centers are also included. With an influx of diverse medical surgical robots entering the market and a competitive drive to establish the next standard of care in robotic surgery, it is inevitable that robotic surgery will soon become economically comparable to laparoscopic procedures.

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Introduction

Robot-assisted surgery currently stands as the epitome of minimally invasive procedures, boasting a distinct advantage over its predecessor, laparoscopic surgery. With technological advancements, it naturally progresses the evolution of minimally invasive techniques. The integration of high-resolution three-dimensional magnified vision, a multi-degree range of movements, tremor dampening, and instrument miniaturization enhances the dexterity and precision of surgeons, further improving the safety and efficiency of surgical techniques. These advancements build upon the already established benefits of laparoscopic surgery.[1] Commercial approval of robotic surgery by the FDA began in 2000[2], primarily with the da Vinci robotic systems from Intuitive Surgical, which dominated the market for nearly two decades. Now, as many of Intuitive Surgical's patents expire, we are entering a new era where numerous competitors are vying for a share of the robotic surgical market.

Our objective is to assess the current status of robotic surgery in urological practice, including its advantages and disadvantages in today's application landscape.

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Materials and Methods

A non-systematic literature search was conducted using PubMed/MEDLINE with the keywords "robotic surgery," "robotic surgical system," "da Vinci system," and "robotic urology." A similar search was also performed using Google Scholar. The search was specifically narrowed down to literature pertaining to urological surgery. Furthermore, relevant information was sought from the official websites of various robotic companies.

Information regarding different robotic systems

Da Vinci

Intuitive Surgical Inc. has achieved remarkable success with the introduction and sustained presence of the da Vinci Surgical System, solidifying its dominance in the robotic surgery market for the past 21 years.[3] To date, there have been four distinct generations of robotic surgical systems that have been actively operational, functioning primarily as telemanipulator systems.[4]

The da Vinci Si, X, and Xi models are characterized by their shared features, including four robotic arms mounted on a single patient cart. (Figure 1) The surgeon operates from a confined closed console, which houses finger loop controllers equipped with Endowrist Technology. Notably, all instruments utilized in these models have an 8 mm diameter, enabling seven degrees of freedom.[2] Presently, the Si system is undergoing a phase-out process and is being succeeded by the newer Xi system, which was launched in 2014. Similar to its predecessors, the Xi system boasts additional features such as a dual console, slender robotic arms, articulating instruments, and an 8 mm port hopping camera, facilitating the execution of multi-quadrant procedures.[5]

The most recent advancement is the da Vinci Single-Port (SP) system, which received FDA approval in May 2018. Its application has been documented in a variety of urological procedures, including renal surgery.[6] The da Vinci Single-Port (SP) system has been utilized in radical perineal and transperitoneal prostatectomy procedures,[7,8] and cystectomy.[9]

The SP platform comprises a 360-degree rotating boom and a single robotic arm designed to fit into a 25 mm multichannel cannula. This configuration allows for the deployment of a fully articulated 3D endoscope and three wristed 6 mm instruments, all of which fan out to prevent collisions within the surgical field[4] (Figure 2).

Figure 1. Davinci Xi

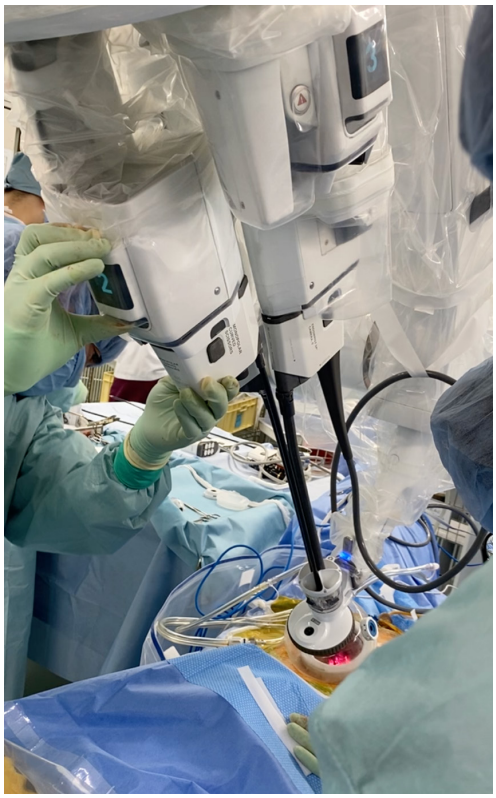

Figure 2. Da vinci SP

Furthermore, the surgeon console of the SP system features a relocation pedal, enabling the movement of the entire robotic arm while keeping the instruments in the same position.[2]

A comparison between the SP and multiport (Xi) robotic platforms of the da Vinci system has been conducted, with the conclusion that there is no significant difference between the two platforms. Additionally, it was found that the SP platform offers advantages in both pain control and shorter hospital stays.[10]

Versius

The Versius surgical system, developed by Cambridge Medical Robotics Ltd. in Cambridge, UK, received its CE mark in 2019.[11] One distinctive feature of the Versius surgical system is its setup, which consists of five lightweight portable carts, each individually mounted with a robotic arm.[3] In contrast to most robotic platforms, the surgeon console of the Versius system features an open design. It necessitates the use of 3D polarized glasses for vision and offers haptic feedback to the operating surgeon.[2] The handheld handles of the joystick offer complete control of the system, eliminating the necessity for foot pedal controls. The instruments of the Versius system are slender, with a 5 mm diameter, and are wristed, allowing for seven degrees of freedom. This system has been evaluated in various clinical settings, with approximately 66 installations worldwide to date. The first clinical series reported in India involved its use in gynecologic and upper gastrointestinal surgeries.2 Feasibility was assessed through 30 robotic radical hysterectomies using the Versius system.[12]

Hugo RAS

The Hugo™ RAS system by Medtronic features an open console that also requires the use of 3D glasses for visualization. The system comprises independent pods, with each pod containing six hinges offering seven degrees of freedom. Notably, all system components and arms, including the surgeon console, are mounted on wheels for enhanced mobility. This system is designed to be upgradable, thereby eliminating the need for purchasing newer systems and ultimately reducing costs.[13]

Revo-I

The Revo-I system, developed by Meere Company Inc. in Yongin, Korea, received approval from the Korean Ministry of Food and Drug Safety in August 2017. Subsequently, its availability has been extended to Russia and Kazakhstan.[4] The features of the Revo-I system are akin to those of the da Vinci system. The surgeon console is enclosed, and the patient cart is equipped with four arms, each allowing seven degrees of freedom. The 3D endoscope has a diameter of 10 mm, while the instruments measure 7.4 mm in diameter and can be reused up to 20 times.[14] Chang et al. published their first human study in 2018, utilizing the Revo-I system for localized carcinoma of the prostate. The study reported no major perioperative or intraoperative complications and noted the absence of any robotic malfunction throughout the duration of the study.[14]

Senhance

The Senhance system was originally developed by the Italian company SOFAR and Tuebingen Scientific, and was initially called Telelap ALFX. It obtained its CE Mark certification in 2016.[13] Later, the system was rebranded as "Senhance" after being acquired by the US company Transenterix, based in Morrisville, North Carolina, USA, in 2015. It became the first robotic system to receive FDA clearance in 2017, receiving CE approval for use in Europe after da Vinci. The Senhance system features an open console with up to four independent arms. It also incorporates a "machine vision system," which employs eye tracking 3D vision technology, enabling the camera to move in response to the movement of the instruments.[13,15] While the Senhance system offers haptic feedback and is compatible with laparoscopic trocars and many commercially available laparoscopic instruments, it lacks the "wristed" degrees of freedom that are present in most of the newer robotic systems.[4]

Mantra

The Mantra Surgical robotic system, developed by the Indian company SS Innovations, is renowned for its cost-effectiveness and versatile surgical applications, including cardiac surgery. It comprises patient-side arm carts, a Surgeon command center, and a Vision cart. The side arm

carts are individual motorized carts equipped with robotic arms featuring an Integrated Tool Interface and Instrument actuator. Each joint's actuator includes motors, harmonic drives, electro-mechanical brakes, and sensors. The Surgeon command center boasts an open console system with dual monitors: a 3D-HD monitor and a 2D touch display monitor for system control and patient-related data display. It incorporates visible active hand and foot pedal controls, as well as a head tracking system. The endoscopic camera is equipped with Chip-on-Tip technology and Motorized articulation control (four-way), providing a field of view of 75 degrees. The articulating endoscope offers the advantage of a greater range of vision, facilitating the observation of ports without moving the camera and visualizing anatomical structures without changing endoscopes. The system includes over thirty 9 mm SSI MUDRATM Endo-Surgical Instruments designed for multi-specialty procedures, including the NADI (Automated Anastomotic Connector) for coronary bypass surgery, Multi-fire Clip Appliers, and a Cardiac Endo-Stabilizer.

Avatera

The Avatera system, developed by avatera-medical GmbH in Jena, Germany, obtained its CE mark in November 2019, after which its primary focus has been on urological and gynecological surgeries.[2] The features of this system include four robotic arms fixed to a single cart, a 10mm endoscope, and single-use 5mm instruments aimed at reducing costs.[13] The surgeon console is an open system with microscope-like technology providing 3D-HD vision through the eyepiece. This design allows the surgeon's head to remain outside of the system, facilitating better communication with the surgical team. Additionally, the console features an integrated sitting arrangement and loop-like handles for instrument control.[13] Clinical data for the system are yet to be published.

Hinotori

Medicaroid developed the Hinotori Robot, a Japanese surgical system that obtained regulatory approval from the Japanese Ministry of Health, Labor, and Welfare. This system comprises three units: the surgeon cockpit, the operation unit (which features four arms in a single boom), and the vision unit. The arms of the operation unit allow for 8 degrees of freedom and feature a "docking-free" design for instruments, where the pivot of the instrument is set by software. The handles for controlling the instruments are wristed, loop-like handles (Figure 3).

MiroSurge

The Miro robotic surgery platform, developed by the German Aerospace Center, is a lightweight system weighing only 10 kg. Its robotic arm is designed to mimic the structure of the human arm, comprising a shoulder, upper arm, elbow, forearm, and wrist. A unique feature of this system is its moving fulcrum point, which enables surgeries to be performed on the moving chest wall during respiration. The instruments of the Miro robotic surgery platform offer seven degrees of freedom, with an additional option of haptic feedback available. While the platform was initially developed for minimally invasive abdominal and thoracic surgery, it has not advanced to preclinical or clinical studies.[4]

Single-port robotic platforms

As the conventional robotic system becomes more widely used across various surgical procedures, innovators have turned their attention to

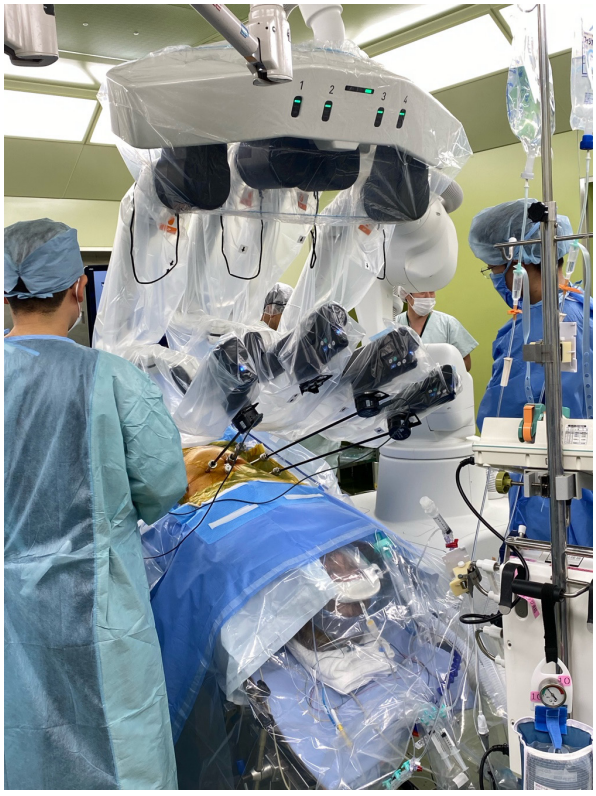

Figure 3. Hinotori

Table 1. Experiences of robotic systems in our centers

Platforms	Advantages	Disadvantages
DaVinci Xi	• Maximum mobility and flexibility • "Firefly" utilizes a near-infrared technology (ICG)	• Large & heavy cart • Non-ergonomic neck and trunk angle
Hinotori	• Human-sized & Flexible arm design (eight axes movements) • Docking-free design (pivoting)	• Single console • Only domestic market (as of 2024)
Da Vinci SP	• Single-port with flexible camera • No collision between arms outside	• Cost (platform & disposables) • Collision & limited movement inside
Hugo RAS	• Open console with specific 3D glasses for head tracking technology • Each unit of the Hugo RAS is independent and extendible with six different joints	• Limited variety of instruments • Delayed upgrade responses to the clinical feedbacks

Robotic Laparo-endoscopic Single Site (R-LESS) surgery. This approach offers several advantages, including a reduced number of incisions, improved cosmesis, decreased postoperative pain, shorter recovery times, and a lower risk of postoperative incisional hernia.[16]

In addition to the da Vinci® SP1098 platform, several other robotic systems are undergoing preclinical and human studies. These include the Single-Port Orifice Robotic Technology surgical system (SPORT) by Titan Medical (US) and the miniature in vivo robot surgical system (MIRA) developed by Virtual Incision (US). Neither of these systems is currently available for sale or use in any country.

The SPORT system features a maneuverable patient cart with a single port of 25 mm, housing two articulating arms within it. This system is considered to be cost-effective in the future due to its replaceable end effectors in the instrument.

The MIRA system offers the unique characteristic of housing the bulk of the robotic system inside the abdominal cavity during surgery, thereby reducing the extracorporeal footprint (the motor units are housed within the arm itself). It consists of two robotic arms in a central single rod, which is inserted through a small incision of 3.5 cm and can be rotated to allow access to all quadrants of the abdomen.[3]

Conclusions

In just over two decades, surgical robots have profoundly transformed the landscape of surgical specialties, making procedures significantly more efficient and surgeon-friendly. With the influx of various medical surgical robots entering the market and the race to establish the next standard of care in robotic surgery, it's only a matter of time before robotic surgery becomes financially comparable to laparoscopic surgeries. Already, it has become an indispensable tool for delivering complex surgical care, thanks to its high levels of maneuverability, magnification, and precision.

Looking ahead, future advancements and the integration of virtual and augmented reality, artificial intelligence in data analytics, deep learning, and machine learning algorithms will further enhance the safety of the surgical applications. Simultaneously, these technologies will provide ample opportunities for surgeons undergoing training to develop their skillsets, ultimately leading to improved patient outcomes and better overall surgical care.

Conflicts of Interest

The authors declare no conflict of interest.

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Case Report

An intravesical ureterocele with a large impact stone: a case report

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Keywords:
Ureterocele, ureteral stone, transurethral incision ureterocele, cystolitholapaxy

Abstract

Ureteroceles can occur asymptomatically or present with various clinical signs and symptoms. Urine stasis within the dilated distal segment can result in recurrent urinary tract infections and stone formation. This case study focusses on a 51-year-old woman who had experienced intermittent left flank and left lower quadrant pain for six months due to an intravesical ureterocele with a large impacted stone. Diagnosis was established through ultrasonography, CT scan, and cystoscopic examination. Treatment included transurethral incision of the left ureterocele followed by cystolitholapaxy using a 26 Fr Resectoscope and hook electrode with a U-shaped incision and stone fragmentation with a stone punch. The procedures resulted in a successful resolution of symptoms. A voiding cystourethrogram (VCUG) carried out 10 weeks post-surgery revealed the absence of vesicoureteral reflux (VUR).

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Introduction

A ureterocele is a cystic dilatation of the distal ureter with associated tissue defect leading into the urinary bladder.[1] Ureteroceles may present as a spectrum of clinical manifestations, ranging from being asymptomatic to causing various symptoms such as recurrent cystitis, bladder outlet obstruction, or even kidney failure. Stasis of urine within the dilated distal segment can predispose individuals to recurrent urinary tract infections and the formation of stones.[2] An intravesical ureterocele with a stone is a rare condition and may mimic vesical calculi. Management varies between centers, depending on the availability of instruments and the expertise of the surgeon. The objective of this study is to describe the clinical presentation, diagnosis, treatment, and outcome of an intravesical ureterocele complicated by a large impacted stone.

Case Report

A healthy 51-year-old women who had previously undergone a transabdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) 20 years ago, presented with mild intermittent left flank and left lower quadrant pain for 6 months. She had had dysuria for 1 week and urinalysis revealed microscopic hematuria. She was treated for acute cystitis by a general practitioner and was sent to the urology department for con-

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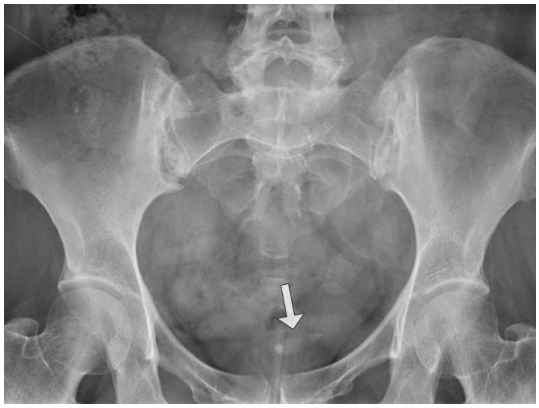


Figure 1. Plain KUB showing 10×25 mm faint radio-opaque stone in the pelvis (arrow).

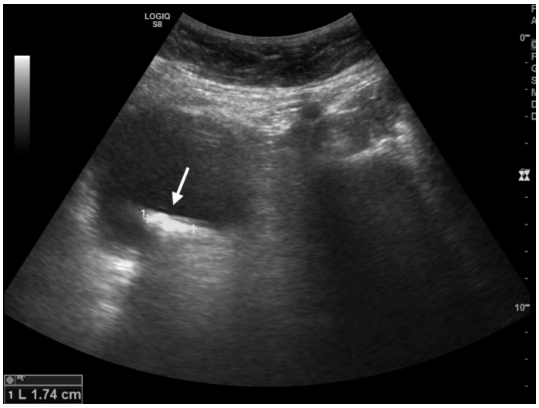


Figure 2. Ultrasound of the KUB system showing a 1.7-cm vesical calculus; VC (arrow).

sultation and further examination. She reported no history of gross hematuria, difficulty with urination, intermittency, urinary incontinence, nocturia, prior urinary tract infection or trauma associated with the perineal-pelvic organ. Plain film KUB indicated a suspected faint-opaque bladder stone approximately 1.0 x 2.5 cm (Figure 1). Ultrasound of the KUB system showed a 1.7-cm vesical calculus (VC) and 5-mm left lower calyceal stone (Figure 2).

Cystoscopic examination was performed which showed a normal urethra. There was a large impact stone with the distal end protruding into the urinary bladder at the left ureteric orifice, with a mushroom-like appearance, suggestive of ureterocele stone (Figure 3). Contrast-enhanced CT of the KUB system demonstrated a large left ureterocele with a large stone approximately 2.2 x 1.1 cm and also a small component impacted at the distal end, indicating a small left distal ureteric calculus about 4 mm. There was no evidence of hydronephrosis (Figure 4A, B). A provisional

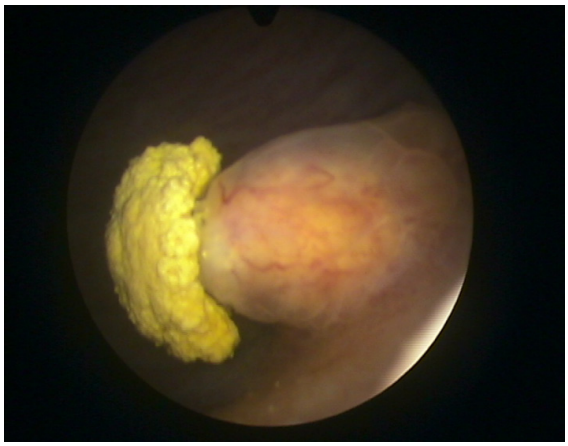
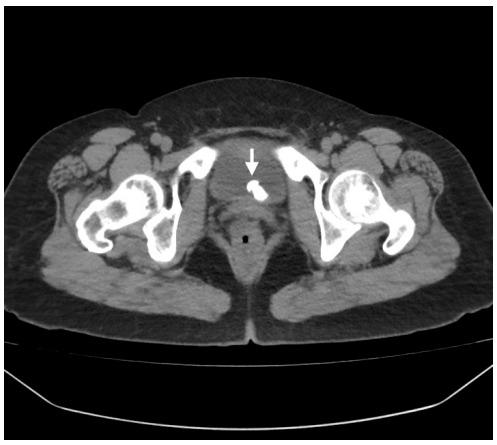


Figure 3. Cystoscopy image showing outpouching of left ureter with impacted stone projecting from the orifice.

diagnosis of intravesical ureterocele with a large impact stone was made based on the cystoscopic examination and the CT scan.

The patient was taken to the operation room for a transurethral incision of the left ureterocele and cystolitholapaxy using 26 Fr Resectoscope and a hook electrode with U-shaped incision. The



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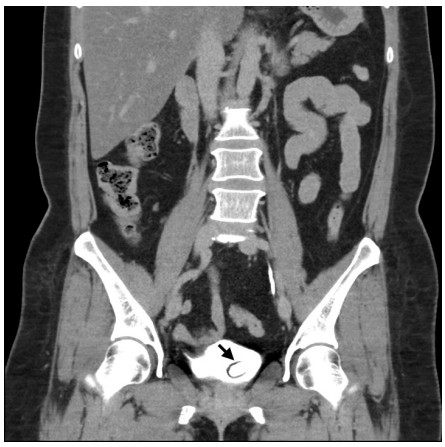

B

Figure 4. A) Contrast-enhanced CT of the KUB system demonstrating a large left ureterocele with a large stone approximately 2.2 x 1.1 cm (arrow). B) The cobra head sign in the delayed phase (arrow).

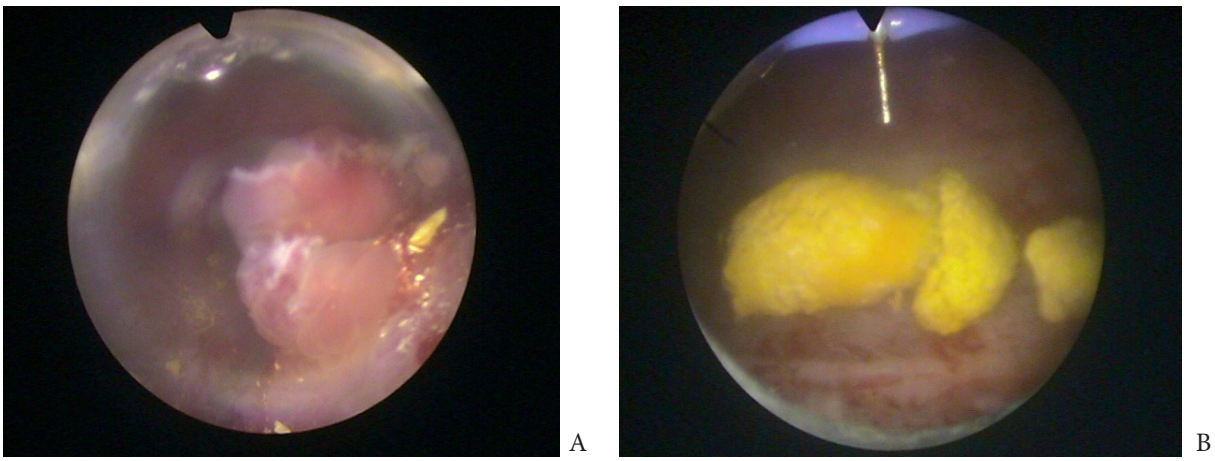

Figure 5. (A, B). Ureteric orifice incision using Collins knife to extract the impacted stone.

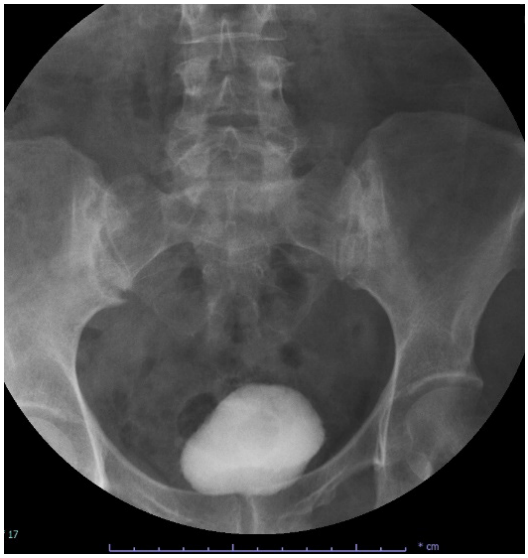

Figure 6. VCUG at 10 weeks after surgery, no VUR.

stone was extracted into the urinary bladder (Figure 5A, B). Then the stone was fragmented with a stone punch and the fragments were removed using an Ellick evacuator. Left ureteroscopy was performed using a semi-rigid uretrorenoscope 8/9.8 Fr to evaluate the ureter and the small distal ureteric calculus; however, the distal ureteric stone passed intravesically following the extraction of the ureterocele stone. A 6 Fr DJ stent was placed into the left ureter and a Foley catheter was retained postoperatively which was then removed the following day. The left DJ stent was taken off at 6 weeks after surgery. Voiding cystourethrogram (VCUG) was done at 10 weeks after surgery, there was no evidence of vesicoureteral reflux (VUR) (Figure 6). Follow up at 16 weeks after surgery found normal micturition and normal urinalysis.

Discussion

Ureterocele is a condition characterized by cystic dilatation of the distal ureter, intravesical ureter, and out-pouching into the urinary bladder. It is reported to occur at an incidence of 1 in 4000 children in Europe and the United States[1], with a four times higher occurrence in females compared to males. It was once considered exclusive to Caucasians, although cases have been reported in African and Asian populations.[2] Classification of ureteroceles includes single-system ureteroceles, associated with a single kidney, collecting system, and ureter, and duplex-system ureteroceles, associated with kidneys that have completely duplicated ureters. The orthotopic (intravesical) type is a ureterocele contained within the bladder at a normal or next to the normal site. The ectopic type is a ureterocele which extends into and opens at the bladder neck or posterior urethra. In 1954 Stephens' classification categorized affected ureterocele orifices into distinct types including stenotic ureteroceles which are located inside the bladder with an obstructing orifice, sphincteric ureteroceles which lie distal to the internal sphincter, sphincterostenotic ureteroceles which have characteristics of both stenotic and sphincteric ureteroceles, and cecoureterocele which are elongated beyond the ureterocele orifice by tunneling under the trigone and the urethra.[1] Understanding regarding these subtypes is crucial for accurate diagnosis, treatment planning, and the prediction of outcomes in patients with ureterocele-related issues.

Ureteroceles can be asymptomatic or present with various signs and symptoms ranging from recurrent cystitis to kidney failure. In adults,

diagnosis is often incidental, though symptoms like intermittent flank pain, recurrent urinary tract infections, or those due to the presence of calculi may occur.[2] Kidney and bladder ultrasonography serve as the initial imaging modality due to their extensive availability, non-invasiveness, and ability to provide valuable information about the upper and lower urinary tracts. These procedures typically identify a ureterocele as a fluid-filled cystic intravesical mass. However, to fully evaluate the lower urinary tract and assess for concomitant vesicoureteral reflux, VCUG is essential. This procedure helps identify any reflux of urine from the bladder back into the ureters and kidneys, which is commonly associated with ureteroceles. From an intravenous pyelogram (IVP) or CT urogram, the presence of an intravesical ureterocele can be identified by a characteristic imaging sign known as the "cobra head sign." This sign is indicative of the appearance of the dilated intravesical portion of the ureter, resembling the head of a cobra, while the extravesical ureter forms the body of the cobra.[3]

Treatment options include endoscopic incision, upper pole partial nephrectomy, and complete reconstruction. In our case, where the ureterocele is complicated by a calculus, it is not uncommon for stones to occur within a ureterocele in a significant proportion of cases. A study of relevant literature indicates this is the case in 5% to 40% of cases.[4,5] Many surgical techniques have been described in the literature, however, endoscopic ureterocele incision or deroofing by resectoscope with cutting current or holmium laser with stone extraction and fragmentation, are easy to perform and give good results.[6-8]

Conclusions

Transurethral ureterocele incision with U-shape by hook electrode with subsequent extraction of the stone into the urinary bladder, followed by cystolitholapaxy using a stone punch, has proven to be an effective method for treating an intravesical ureterocele complicated by a large impacted stone. This approach is minimally invasive, easy to perform, and yields favorable outcomes.

Conflicts of Interest

The authors declare no conflict of interest.

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- Materials and Methods
- Results
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- Materials and Methods
- Results
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- Acknowledgement (optional)
- Conflict of Interest
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1.3 Table (s) and legend (s)

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2.1 Interesting and pertinent

2.2 Include standard of treatment

3. Case report

Requirements:

3.1 Interesting

3.2 Not previously published

3.3 Indicates the important case aspects

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Requirements:

4.1 Questions, discussions, and opinions to published articles

4.2 Creative and beneficial to all readers

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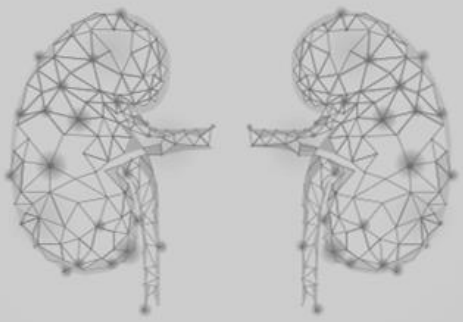

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