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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.

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Date of Issue Semi-annually (June and December)

Editorial

The ninth issue of Insight Urology (ISU) was published online in December 2024.

It comprises six original articles, and three review articles. It covers several fields of urology, such as andrology, endourology, kidney transplantation, and pediatric urology.

One review article was submitted by renowned international authors, namely “Phimosis in children: an unfinished story”. We are confident that you will enjoy reading and applying the knowledge in these articles to your present urological work, especially when treating phimosis in pediatric patients, benign prostatic surgeries, and performing stones treatments.

The front cover of this issue features a photograph of the National Library of Thailand (NLT). The NLT formerly known as “Vajirayana Library for the Capital City” which was established on October 12, 1905. His Majesty King Chulalongkorn was graciously pleased to establish the amalgamation of three royal libraries namely, the Vajirayana Library, the Mandira Dhamma Library and the Buddhasasanasangaha Library. At the beginning of its establishment, it was located at Sala Sahathai Samakhom Hall in the Grand Palace.

The new building of NLT was constructed on the same area and opened on October 3, 2011. The NLT has renovated the building 1 (the old building) to be remodeling of the building for comfortable and suited for modern lifestyle with new library services technology. The building has been opened since October 12, 2017.

The NLT holds the main function for acquisition, collecting and preserving of Thai intellectual and culture heritage of information resources in form of printed materials, audio-visual, electronic materials and ancient manuscripts. The library represents a National Depository, International Standard Books Number (ISBN), International Standard Serials Number (ISSN) and Press Act A.D. 2007.

The Editorial Board of ISU hopes that the cover of this issue represents the importance of documenting and preserving knowledge for our descendants. 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

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Original Article

East Coast Malaysia mini percutaneous nephrolithotomy series: an effective and safe approach to treat renal stones

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Keywords:

Percutaneous nephrolithotomy, PCNL, mini PCNL, kidney stones, retrospective, Malaysia

Abstract

Objective: This paper aims to determine the safety and efficacy of mini percutaneous nephrolithotomy (PCNL) by evaluating the postoperative pain score, postoperative length of hospital stay, stone free-rate, perioperative blood loss, and changes in renal function in patients with nephrolithiasis.

Materials and Methods: This retrospective cohort study involved patients who underwent mini PCNL at the Hospital Tengku Ampuan Afzan (HTAA), Pahang, Malaysia, from January 1st, 2019, until December 31st, 2023. Data are presented descriptively. Changes in haemoglobin and serum creatinine pre- and post-operative were compared using univariate analysis.

Results: The cohort included a total of 50 patients who underwent mini PCNL at our centre. Ninety two percent of the cases had radiopaque stones with a median size of 1.57cm³. The total operative time was 143.7±32.16 minutes, access being established in 90% of cases via the intracostal route. Four patients (8%) had complications (two (4%) were sepsis-related). Postoperative pain was reported as mild and tolerable, with a median length of hospital stay of 2 days. The stone-free rate was 96%, and the haemoglobin drop was less than 1 g/dl (MD=-0.57 (95% CI: -0.77, -0.37), p < 0.001) following mini PCNL. There was no significant change in serum creatinine observed

Conclusion: Our study determined that mini PCNL is a safe and efficacious treatment modality in the management of nephrolithiasis in this Malaysian cohort. The growing trend of mini PCNL in Malaysian urology reflects the advancements in surgical techniques and the commitment of healthcare professionals to provide the best possible care for the patients.

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Introduction

Percutaneous nephrolithotomy (PCNL) has evolved significantly since its introduction in the late twentieth century as a procedural technique for the removal of renal stones. The first successful PCNL procedure was performed in 1976 by Fernström and Johansson,¹ marking a pivotal moment in urological history. Upon its conception, the procedure was primarily used for the treatment of large renal calculi that were challenging to manage with other therapeutic modalities.²

Conventional PCNL involves a larger access tract and is performed under general anaesthesia.³ The procedure typically begins with the patient placed in a prone position. Under fluoroscopic guidance, a large calibre nephrostomy tract (usually 24-30 Fr) is created to gain access to the renal collecting system.⁴ Following the tract creation, rigid nephroscopy is used to visualise and fragment the renal calculi using either pneumatic or ultrasonic lithotripsy. Once stone fragmentation is achieved, the fragments are removed using a stone retrieval mechanism (e.g., baskets or forceps). The procedure concludes with the placement of a nephrostomy tube to drain the renal collecting system, which is usually left in place for a few days post-operatively. Although it is effective, significant morbidity is associated with PCNL due to its invasive nature. The procedure is also coupled with longer hospital stays, greater postoperative pain, and blood loss.^{2,5,6}

Miniaturization PCNL (mini PCNL), also known as minimally invasive PCNL or its modifications (including micro PCNL, super mini PCNL, and ultra-mini PCNL)⁷, utilizes a smaller access tract in comparison to the conventional PCNL.² The concept originally evolved from the use of smaller working sheaths to reduce the trauma observed during paediatric PCNL^{8,9} and can be performed under regional or general anaesthesia. It frequently results in shorter hospital stays and quicker recovery times.¹⁰ The procedure usually begins with the patient positioned either prone or supine. A smaller calibre nephrostomy tract (typically 11-20 Fr) is created under fluoroscopic or ultrasound guidance.¹¹ Flexible nephroscopy is then used to visualise and fragment the renal calculi using holmium laser lithotripsy or miniaturized pneumatic lithotripsy devices. Stone fragments are removed using various retrieval devices, and a smaller calibre nephrostomy tube

or a ureteral stent may be placed for drainage.¹¹ Mini PCNL has helped in the management of renal stones with smaller sized sheaths without compromising the stone-free rate. It also provides an excellent surgical outcome and reduced incidence of surgical complications.¹²

Although mini PCNL has significant appeal for endoscopic urologists due to the clinical benefits of a smaller tract¹¹, there were only a handful of urology centres in Malaysia performing this technique due to limited resources (e.g., lack of availability of specific sized scopes). This paper aims to determine the safety and efficacy of mini PCNL performed in our centre by evaluating the postoperative pain score and length of hospital stay, stone free-rate, perioperative blood loss, and changes in renal function in nephrolithiasis patients. The findings of the study will inform future developments in this area to improve patient experience and outcomes.

Materials and Methods

Ethical approval

The study was registered with the National Medical Research Register (NMRR) of the Ministry of Health Malaysia (NMRR ID-23-01741-FWZ (IIR)) and received ethical clearance from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (Ref.: 23-01741-FWZ (2)).

Setting and study design

This was a retrospective cohort study involving all patients who underwent mini PCNL at Hospital Tengku Ampuan Afzan (HTAA), the main tertiary referral centre for the state of Pahang, Malaysia, from January 1st, 2019, until December 31st, 2023.

Patients selection

All patients who underwent mini PCNL within the specified time period at our centre were included. This included patients with a history of failed extracorporeal short wave lithotripsy (ESWL), patients with residual renal stones following PCNL, patients with lower pole stones with unfavourable anatomy for ESWL, and patients with a nephrostomy tract. Pregnant patients, patients with uncorrected coagulopathy, congenital kidney abnormalities, and active urinary tract infections were excluded.

Data collection

All peri-operative data of interest were collected in a designated data collection form. Pre- and post-operative blood workout, urine analysis, and imaging findings were recorded. Length of hospital stay, post-operative analgesia requirement and pain score (using visual analogue score), stone free-rate (stone clearance), perioperative blood loss and changes in renal function (assessment of changes in serum creatinine) were all collected.

Mini PCNL procedure

General preparation

Preoperative evaluation included complete blood workup, urine analysis, urine culture and image studies, including kidneys, ureter and bladder (KUB) X-ray, ultrasound, and CT urography (CTU). CTU was done to evaluate the stone characteristics, renal anatomy and other visceral conditions. Stone dimensions were recorded in millimetre (mm) along the maximum length. Patients with clinical evidence of urinary tract infection were treated with antibiotics for 2 to 7 days prior to surgery. All patients were admitted 1-2 days before surgery to ensure nil by mouth (NBM) status. After adequate general anaesthesia has been achieved, the patient was placed in the lithotomy position. Prophylactic antibiotics were prescribed 30 minutes pre-surgery. Equipment

used included: rigid cystoscope, 0.035 inch guidewire, 5 Fr ureteral access sheath, 10 Fr fascia dilator, 16 Fr mini PCNL dilator, 16 Fr mini PCNL sheath, 12 Fr nephroscope, and a laser.

Cystoscopy and retrograde pyelogram

First, rigid cystoscopy was performed. The ipsilateral ureteral orifice was identified, and access obtained with a 0.035 inch guidewire and a 5 Fr retrograde-pyelography (RP) ureteral catheter was placed at the renal pelvis and a Foley's catheter was inserted. Plain image and retrograde pyelogram images were taken under fluoroscopy.

The patient was then turned prone with bolsters and padding to cover the pressure joint areas. All renal access was obtained under fluoroscopic guidance using the "eye of the needle" technique. The puncture site was chosen to maximize stone clearance, usually the calyx that gives a straight direct tract. An 18-gauge needle was passed under fluoroscopic guidance into the appropriate calyx, and its position confirmed by biplanar fluoroscopy and return of urine. A standard working guidewire was passed into the collecting system and manipulated down the ureter.

Tract access

A single step dilatation was done using a 16 Fr mini PCNL dilator over the guidewire and an outer sheath was placed into the targeted calyx (Fig. 1).



Figure 1. Single step 16 Fr dilation using a metal dilator and insertion of 16 Fr metal outer sheath followed.

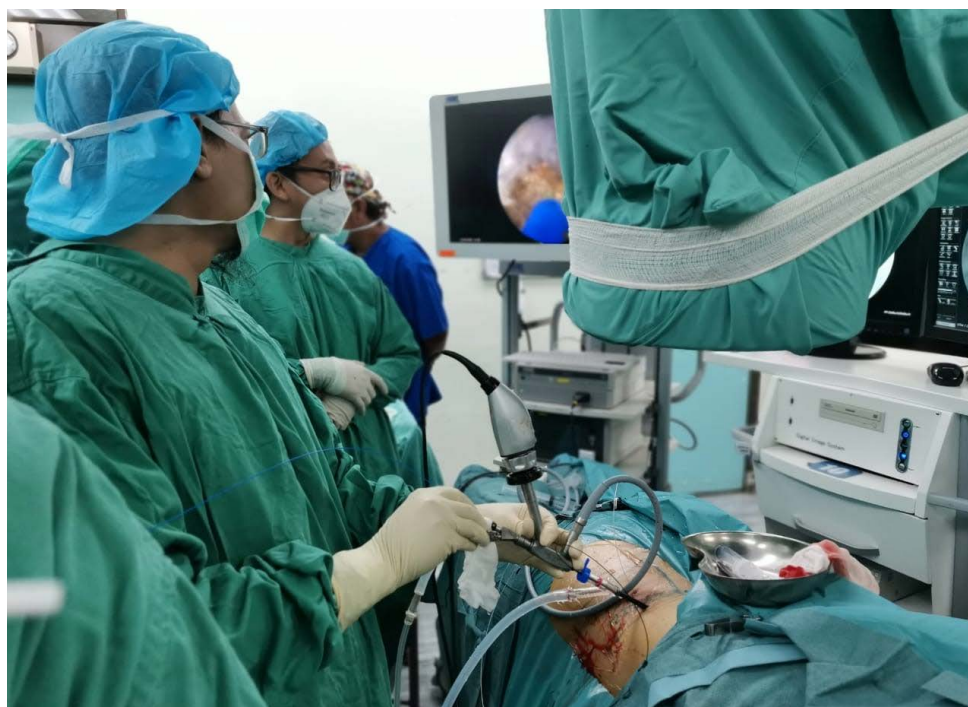


Figure 2. Mini PCNL and lithotripsy performed with Holmium-YAG laser.

Insertion of endoscope

A 16 Fr nephroscope was used to examine the renal collecting system and allow passage of irrigation fluid, preventing pressure build-up in the urinary tract. An appropriate size offset cystoureteroscope is ideal and can function as a nephron.

Lithotripsy

With a combination of lithotripsy, for example laser (Fig. 2), and manual extraction using baskets and graspers, the stone can then be removed and sent for analysis. Smaller fragmented stones will pass around the endoscope and wash out through the sheath. An initial stone-free status was defined as no visible stone under direct vision, and was checked via intra-operative fluoroscopy. After the stone had been evacuated, a guidewire was placed into the collecting system and the access sheath slowly retracted. The access tract was carefully checked for severe bleeding, and fluoroscopy was employed to check along the retrograde pyelogram angio-catheter for any stone impaction.

Post-operative care and outcomes

Operative findings, surgical duration (from insertion of puncture needle to the end of the procedure) and outcomes were recorded. The urine catheter was removed on post-operative day 1. The overall type, frequency, and dosage of analgesia requirement was also documented.

Post-operative pain was assessed using the Visual Analogue Score (VAS).

Complete blood work and biochemistry tests were performed on the day immediately post-operative. KUB X-ray was performed as a routine procedure prior to discharge to confirm the stone-free status for radiopaque stones, and renal ultrasound in the case of radiolucent stones. The length of post-operative hospital stay was calculated as the number of days from the first day post-operative to the day of hospital discharge. The initial stone-free status was checked at the end of the operation, and a final stone-free status (%) was defined as a residual stone ≤ 2 mm under renal ultrasonography 3 months after mini PCNL. In cases of residual stone fragments, ancillary procedures were done. The Clavien-Dindo grading system¹³ was used to assess any surgical-related morbidity. Patients were discharged home only if they progressed well.

Statistical analysis

Data were cleaned and analysed using Statistical Package for Social Sciences (SPSS) version 26.0. The distribution of continuous variables was checked using skewness, kurtosis, and histogram. Continuous variables with normally distributed data are presented using mean $\pm$ standard deviation, otherwise median (25th percentile, 75th percentile) are used. Categorical variables are

presented as frequency and percentage. The mean changes in haemoglobin and serum creatinine pre- and post-operative were compared using a paired sample t-test. All the tests were two-sided and statistical significance was denoted by $p < 0.05$.

Results

A total of 50 patients were included in the study with an overall mean age of 54.0 ± 12.35 years old. The majority were Malay (84.0%) and were male (54.0%). The reported median body mass index (BMI) was 26.08 (IQR: 24.09, 30.10) kg/m^2 (Table 1).

The X-ray findings found that almost all stones were radiopaque in nature (92.0%). The median stone size on CTU was 1.57 cm^3 (IQR: 1.10, 3.30). The reported total operation and prone PCNL times were 143.68 ± 32.16 minutes and 104.90 ± 34.55 minutes, respectively. The sizes of laser fibre used were 365 nm (70%) and 600 nm (28%), and in the majority of the patients access was intracostal (86%) followed by supracostal 12th (10%) and lower pole (4%).

Four patients were punctured twice. The calyces puncture sites included lower pole (70%), midpole (14%), midpole and lower pole (2%), and upper pole (14%). Eighty percent of the stones were simple in nature, followed by complex (14%), complex and impacted (4%), and lastly nephrocalcinosis (2%). The majority of the stones were distributed at the lower pole (38%) and in the renal pelvis (28%). There were three (4%) cases of incomplete stone clearance reported; one with nephrocalcinosis at the lower pole, one with a residual midpole stone due to acute angle, and one with an inaccessible upper pole due to narrow infundibulum.

Stents were placed in 27 (54%) patients post-operatively. Complications were observed in four patients, the complications reported including sepsis (2%), septic shock (2%), stent irritation (2%) and vomiting (2%). The median post-operative pain score was 2 (IQR: 2.0, 2.0). Medications used post-operatively were mostly a combination of paracetamol and tramadol (56.0%) (Table 2).

The haemoglobin decreased significantly post-operatively with a mean decrease of $0.57 \mu\text{mol/L}$ post-operatively compared to pre-operative ($p < 0.001$). There was no significant change observed in serum creatinine between pre- and

Table 1. Demographic characteristics of the patients.

Characteristics	Output
Age in years, mean $\pm$ SD	53.74 $\pm$ 12.35
Gender, n (%)	
Female	23 (46.0)
Male	27 (54.0)
BMI in kg/m^2 , median (IQR)	26.08 (24.09, 30.10)
Race, n (%)	
Malay	42 (84.0)
Chinese	2 (4.0)
Indian	3 (6.0)
Others	3 (6.0)

BMI = Body mass index, IQR = Interquartile range, SD = Standard deviation

post-operative readings ($p = 0.205$) (Table 3).

Discussion

Our study determined that mini PCNL is indeed a safe and efficacious treatment in the management of nephrolithiasis in this Malaysian cohort. The median post-operative pain score in our study cohort was 2, denoting a mild and tolerable pain. We observed that the majority of our patients required a combination of paracetamol and tramadol for adequate pain relief. Our findings are in alignment with a randomised trial by Lee et al.¹⁴ which found that patients who underwent mini PCNL reported lower pain score and less analgesia requirements in comparison to retrograde intrarenal surgery among 70 patients with renal stones bigger than 10 mm. This is potentially due to the minimally invasive nature of mini PCNL, and the smaller tract resulting from the procedure has garnered popularity as a safe and effective alternative to the conventional PCNL.¹⁵ Hence, with the ongoing advancements and a growing body of evidence supporting its efficacy¹⁶, mini PCNL is poised to become an integral part of the standard of care for kidney stone management in Malaysia.

The median post-operative length of hospital stay following mini PCNL was only two days. Our findings were echoed in a recent review paper evaluating the clinical outcomes of mini PCNL in comparison to conventional PCNL. In one review, five papers (three prospective cohort studies, one randomised controlled trial and one retrospective study) it was collectively found that mini PCNL was associated with reduced length of hospital stay.¹⁷ Flexible nephroscopy with

Table 2. Perioperative characteristics of the patients.

Characteristics	Output
Pre-operative	
Stone opacity, n (%)	
Radiolucent	4 (8.0)
Radiopaque	46 (92.0)
Size on CTU in cm ³ , median (IQR)	1.57 (1.10, 3.30)
Intra-operative	
Total operation time in minutes, mean±SD	143.68±32.16
Total prone PCNL time in minutes, mean±SD	104.90±34.55
Laterality, n (%)	
Left	29 (58.0)
Right	21 (42.0)
Size of laser fibre in nm, n (%)	
365	35 (70.0)
600	15 (30.0)
Access site, n (%)	
Intracostal	45 (90.0)
Supracostal 12 th	5 (10.0)
Number of punctures, n (%)	
1	46 (92.0)
2	4 (8.0)
Calyces punctures, n (%)	
Lower pole	35 (70.0)
Midpole	8 (16.0)
Upper pole	7 (14.0)
Nature of the stone, n (%)	
Simple	40 (80.0)
Complex	7 (14.0)
Complex, impacted	2 (4.0)
Nephrocalcinosis	1 (2.0)
Intraoperative stone distribution, n (%)	
Proximal ureter	2 (4.0)
Renal pelvis	15 (30.0)
Lower pole	19 (38.0)
Lower pole renal parenchymal stone	1 (2.0)
Lower pole + renal pelvis	4 (8.0)
Lower + midpole	2 (4.0)
Midpole	4 (8.0)
Upper pole	3 (6.0)
Stone clearance, n (%)	
Complete	47 (96.0)
Incomplete	3 (4.0)
Post-operative	
Tubeless post-op, n (%)	
Tubeless	24 (48.0)
Totally tubeless	26 (52.0)
Complication, n (%)	
Nil	46 (92.0)
Sepsis	1 (2.0)
Septic shock	1 (2.0)
Stent irritation	1 (2.0)
Vomiting	1 (2.0)

Table 2. Perioperative characteristics of the patients. (continued)

Characteristics	Output
Pain score, median (IQR)	2 (2, 2)
Medication used, n (%)	
Nil	1 (2.0)
PCM	17 (34.0)
Tramadol	2 (4.0)
PCM + tramadol	28 (56.0)
PCM + tramadol + celebrex	2 (4.0)
Total length of post-operative stay in days, median (IQR)	2 (2, 2)

CTU = computed tomography urography, IQR = interquartile range, PCM = paracetamol, PCNL = percutaneous nephrolithotomy, SD = standard deviation.

Table 3. Changes in haemoglobin and serum creatinine pre- and post-operatively.

Parameters	Timepoint	Mean $\pm$ SD	Mean difference (95% CI)	P-value
Hb (g/dl)	Pre-op	12.83 $\pm$ 1.60	-0.57 (-0.77, -0.37)	<0.001*
	Post-op	12.25 $\pm$ 1.64		
Serum creatinine (μ mol/l)	Pre-op	100.77 $\pm$ 40.40	-2.23 (-5.72, 1.26)	0.205
	Post-op	103.00 $\pm$ 42.15		

Paired sample t-test, *Statistical significance

holmium laser lithotripsy or the use of miniaturized pneumatic devices is typically utilized for stone fragmentation in mini-PCNL. Hence, this smaller calibre approach often results in shorter hospital stays, quicker recovery times, and potentially reduced morbidity in comparison to conventional PCNL.^{2,3,15,16}

We also found that up to 96% of our patients had complete stone clearance and remained stone-free for at least three months post-mini PCNL. However, a recent meta-analysis of 20 trials with a total of 4,953 people found no difference in the stone-free rates between mini PCNL and conventional PCNL.⁶ This could be due to the heterogeneity of the patient characteristics (e.g., substantial stone burden) and the level of experience and surgical skills (e.g., lack of experience with flexible nephroscopy) in the studies included in the meta-analysis. It is a generally accepted premise that mini PCNL has a significantly lower stone-free rate (but clinically comparable) when compared to the conventional PCNL, but with markedly reduced complications.^{2,3,15,18} This is evident in our study as 92% of our patients did not report any complication following mini PCNL.

Despite the observed statistical significance, the haemoglobin drop of less than 1 g/dL following mini PCNL in our study was not clinically significant. Studies mostly found that mini PCNL

were associated with less perioperative blood loss in comparison to conventional PCNL^{6,10,16,19,20}, however, Lee et al. did not find any statistical difference in perioperative blood loss between mini PCNL and retrograde intrarenal surgery.¹⁴

Additionally, we did not find any significant difference in the change of serum creatinine following mini PCNL. This contradicts a recent prospective cohort study among 46 patients with chronic kidney disease in Kashmir, which reported a statistically significant improvement in renal function.²¹ However, it is important to note that the estimated glomerular filtration rate (eGFR) was used as a parameter to assess renal function in that study, while we evaluated changes in the baseline serum creatinine in our patient pool (which was still preserved even at the preoperative stage). It is worth noting that both eGFR and serum creatinine are indexes of glomerular function, and the inclusion of specific indexes of tubular function and injury (e.g., urinary albumin-to-creatinine ratio, urinary β 2-microglobulin) would render the assessment of safety and efficacy of endourological procedures more comprehensive.²²

To the best of our knowledge, this is the first paper of its kind reporting on the clinical outcomes of mini PCNL in Malaysia. Over the past few years, the urology community in Malaysia has



witnessed a significant shift towards the adoption of mini PCNL as a standard procedure in patients with nephrolithiasis. This shift has not only improved patient outcomes but has also set a new milestone in Malaysian urology.

Despite the small sample size and it being a single centre study, our findings provide evidence, corroborated by the relevant literature, on the safety and efficacy of mini PCNL over conventional PCNL. Moving forward, we would suggest that future studies explore the use of cyclical clinical audits to monitor and sustain the safety and efficacy of mini-PCNL, ensuring optimal healthcare delivery for patients with nephrolithiasis.

Conclusions

This analytical retrospective report which assesses the clinical outcomes, safety and effectiveness of mini PCNL in Malaysian patients has shown promising results. The growing trend of the use of mini PCNL in Malaysian urology does not only signify advancements in surgical techniques, but also reflects the commitment of healthcare professionals to provide the best possible care for the patients. As more healthcare professionals and facilities embrace this technique, it is expected that the overall standard of urological care will continue to improve, leading to better outcomes for patients, nationwide and globally.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Clinical outcomes and complications of percutaneous nephrolithotomy (PCNL) in multidrug resistant (MDR) bacteriuria

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Keywords:

Renal calculi,
multidrug resistant
urine culture, MDR,
complications, PCNL

Abstract

Objective: To evaluate the outcomes and complications of percutaneous nephrolithotomy (PCNL) in patients with multidrug resistant (MDR) urine cultures in comparison with those with normal urine cultures.

Materials and Methods: A retrospective cohort study was completed in patients who underwent PCNL at Maharaj Nakorn Chiang Mai Hospital between January, 2019 and August, 2021. The medical record charts of patients were reviewed and divided into 2 groups: those with a preoperative positive multidrug resistant culture (MDR, n=37) and those with a negative urine culture (No MDR, n=73). The following data were collected: demographics, size of stones, intraoperative data, preoperative urine cultures and postoperative complications. Association between factors and postoperative complications after PCNL were identified using a binary logistic regression model.

Results: Sepsis complications occurred in 8.2% of the patients (No MDR, n=2, MDR, n=7). The results of the multivariate analysis demonstrated a significant association between a positive preoperative MDR urine culture and postoperative sepsis complications (odds ratio (OR) = 15.21, 95%CI 1.59-145.35, p = 0.018). Conversely, female patients exhibited a decreased risk in comparison to male patients (OR 0.03, 95%CI 0.001-0.75, p = 0.003).

Conclusion: The prevalence of positive MDR bacteriuria in patients who underwent PCNL in Maharaj Nakorn Chiang Mai Hospital was relatively high. The female gender exhibited a prophylactic effect, while a positive MDR urine culture emerged as a significant risk factor for postoperative complications associated with sepsis, even in the presence of appropriately administered preoperative prophylactic antibiotics.

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Introduction

Kidney stone disease is a common problem in urology that affects patients in terms of pain, quality of life and daily life function. There are several treatment methods including both minimally invasive and open surgery. According to the 2016 American Urological Association (AUA) and 2021 European Association of Urology (EAU) guidelines on the management of the condition, percutaneous nephrolithotomy (PCNL) is a minimal invasive procedure and a preferred treatment for large upper tract stones as the first-line treatment, especially those that are more than two centimeters in diameter.^{1,2} Renal calculi may be accompanied by urinary tract infection which must be treated with antibiotics before surgery. Complications of PCNL include fever, bleeding, and sepsis or septic shock which can lead to significant morbidity and even death.

Infection complications have been reported in 32% of patients undergoing PCNL, which include fever, and sepsis. Several previous studies have shown that preoperative positive urine or stone cultures, number of access points, and the need for blood transfusion are associated with postoperative infection.^{3,4} Some of the preoperative urine cultures, perioperative urines and stone cultures have been recorded as having differentiated organisms.⁵ This variety can mean that antibiotic treatment may not be able to sterilize the urine, especially in the case of bacterial resistant organisms. Bacterial resistance also increases the complexity of treatment as well as the medical costs and the length of the hospital stay. Patients who exhibit preoperative multidrug resistance are more likely to have postoperative complications.⁶ Some studies have reported that positive preoperative cultures controlled with antibiotics for at least 72 hours are sufficient to control the infections in these cases.⁷

Resistant bacteria are usually resistant to more than one antibiotic and are considered multidrug resistant (MDR) bacteria if they are resistant to at least one agent in three or more antimicrobial categories.⁸ Our observations have indicated an increase in the incidence of bacterial resistant organisms in our clinical practice. Therefore, there is an urgency to investigate the prevalence of MDR pathogens and their association with postoperative infectious complications. The findings can be used to determine the risk factors for postoperative complications for

pertinent preoperative counselling, as well as determining the role of antibiotic prophylaxis. The research objective is to evaluate the outcomes and complications of PCNL in patients with MDR urine cultures compared with those with normal urine cultures.

Materials and Methods

After approval from the Research Ethics Committee of Chiang Mai University (Study Number SUR 2563-07824), a retrospective cohort study was completed on all PCNL patients at Maharaj Nakorn Chiang Mai Hospital between January 2019 - August 2021 with patients who were 18 years or older. Urine samples were collected via midstream clean void one month prior to the operation and were then cultured. The exclusion criteria were patients in whom urine cultures were not carried out, were on antiplatelet or anticoagulant medications, had undergone prior urinary diversions e.g. PCN or DJ stent, had undergone secondary nephroscopy or failed PCNL.

Patients with MDR urine cultures were treated with culture-specific antibiotics for approximately one week and received prophylactic antibiotics just before surgery.

In a study by Patel et al. which investigated the presence of multidrug resistant bacteriuria before PCNL postoperative infection complications were able to be predicted. In this study the estimated required sample size was 115 patients to enable effective calculation of the postoperative sepsis outcome.

Multidrug bacterial resistance is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories

Sepsis was defined as two or more criteria of the quick sepsis-related organ failure assessment (qSOFA) being met, specifically: respiratory rate of ≥ 22 breaths/min, altered consciousness (Glasgow Coma Scale score of < 13), and systolic blood pressure of ≤ 100 mmHg.⁹ Data was collected from post-procedure until discharge to home.

Results

We analyzed the data of 110 patients, who were divided into 2 groups, preoperative culture with multidrug resistance (37 patients) and negative urine culture (73 patients). Patient characteristics are shown in Table 1. There were no statistically significant differences in sex, body

**Table 1.** Baseline characteristics between MDR and no MDR

Parameters	No MDR n=73	MDR n=37	P-value
Age, years mean (SD)	57.86 (10.82)	53.38 (8.99)	0.032
Sex			0.838
Male n (%)	44 (60.27)	21 (56.76)	
Female n (%)	29 (39.73)	16 (43.24)	
BMI, kg/m ² mean (SD)	22.51 (4.47)	21.78 (3.50)	0.383
Preop creatinine, mg/dl mean (SD)	1.26 (0.73)	1.56 (1.45)	0.149
Stone number mean (SD)	3.76 (3.26)	3.25 (2.66)	0.415
Stone size, cm mean (SD)	3.04 (1.53)	3.22 (2.26)	0.628
Staghorn stone n (%)			1.000
No	35 (48.61)	18 (48.65)	
Yes	37 (51.39)	19 (51.35)	
Diabetes mellitus n (%)			0.792
NO	61 (83.56)	30 (81.08)	
Yes	12 (16.44)	7 (18.92)	
Antibiotics given 30 days prior n (%)			0.015
No	11 (15.07)	0 (0.00)	
Yes	62 (84.93)	37 (100.00)	
Positive urine culture n (%)			<0.001
No	68 (93.15)	0 (0.00)	
Yes	5 (6.85)	37 (100.00)	
Number of access points n (%)			0.481
1	68 (93.15)	33 (89.19)	
>1	5 (6.85)	4 (10.81)	
Access tract n (%)			0.442
Upper pole	46 (63.01)	27 (72.97)	
Middle pole	9 (12.33)	5 (13.51)	
Lower pole	18 (24.66)	5 (13.51)	
Point access n (%)			0.015
Supracostal	11 (15.07)	14 (37.84)	
Subcostal	62 (84.93)	23 (62.16)	
History of previous procedure n (%)			0.081
No history of surgery	57 (78.08)	23 (62.16)	
History of PCNL	4 (5.48)	1 (2.70)	
History of NL	12 (16.44)	13 (35.14)	
Blood loss (ml) mean (SD)	199.73 (151.22)	206.76 (125.37)	0.808
Transfusion n (%)			0.299
No	68 (93.15)	32 (86.49)	
Yes	5 (6.85)	5 (13.51)	
Sepsis n (%)			0.006
No	71 (97.26)	30 (81.08)	
Yes	2 (2.74)	7 (18.92)	
Postoperative fever n (%)			0.004
No	35 (47.95)	7 (18.92)	
Yes	38 (52.05)	30 (81.08)	
Stone free n (%)			0.225
Stone free	38 (52.05)	14 (37.84)	
Retain stone	35 (47.95)	23 (62.16)	
Length of stay (days) mean (SD)	10.37 (2.48)	11.73 (4.74)	0.050

MDR = multidrug resistant, PCNL = percutaneous nephrostomy, NL = nephrolithotomy, SD = standard deviation

mass index (BMI), preoperative creatinine, or diabetes mellitus. Patients who had MDR and positive urine cultures received antibiotics prior to the procedure for at least 7 days or until negative urine cultures were achieved. All patients were given prophylactic antibiotics, specifically third-generation cephalosporin or specific to urine culture results. The majority of the patients underwent subcostal access: 84.9% with negative culture, 62.2% with MDR culture. The proportion of patients undergoing an upper pole calyceal approach were 63% with negative culture and 73% with MDR culture. Patients in the MDR urine culture group were more likely to develop postoperative fever.

Out of all MDR organisms, *Escherichia coli* was the most prevalent MDR organism at 43.2% (Fig. 1) with *Enterococcus faecalis* (16.2%) and *Staphylococcus saprophyticus* (8.1%). Seven out of 37 patients with positive MDR urine cultures developed postoperative sepsis, compared with 2 of 73 patients with non-MDR cultures ($p = 0.006$).

Table 2 shows the univariate analysis of factors associated with postoperative sepsis. There was an association between patients with underlying diabetes mellitus and postoperative sepsis (OR = 4.59, $p = 0.036$), and also with a positive urine culture (OR = 16.48, $p = 0.010$). There was an increased risk of postoperative sepsis with a positive MDR urine culture (OR = 8.28, $p = 0.011$). Patients with postoperative sepsis had relatively longer hospital stays and required more blood transfusions (OR = 1.22, $p = 0.037$ and OR = 6.71, $p = 0.018$) respectively. Multivariate analysis showed the female sex was associated with a decreased risk of post operative sepsis, whereas positive MDR culture was associated with postoperative sepsis. All these results are shown in Table 3.

Discussion

Current evidence suggests that most renal stones can be cleared with retrograde intrarenal surgery (RIRS) or minimally invasive surgery, with PCNL still being the first-line treatment for stones more than 2 cm. However, the procedures can be complicated by sepsis which can lead to significant morbidity and even death. Several studies have shown that sepsis complications after PCNL occurred in 0.3-9.3% of cases.¹⁰⁻¹² In this study, we found 8.2% of patients studied

developed postoperative sepsis with no mortality.

This study included a total of 45 female patients, among whom only 1 patient developed postoperative sepsis. Multivariate analysis indicated that female gender was a prophylactic factor for post-PCNL sepsis. This finding could be attributed to several factors. One possible explanation is anatomical differences between males and females with regard to the urinary tract. In the female anatomy the urethra is generally shorter, which may reduce the likelihood of bacteria ascending to the kidneys when compared to the longer male urethra. Additionally, differences in hormonal and immune responses between males and females may also play a role in influencing susceptibility to infection and the development of sepsis. However, it's important to note that individual patient characteristics and medical histories can also impact the likelihood of complications.^{13,14}

The prevalence of MDR bacteria in pre-operative urine cultures before PCNL was 34% and increased the risk of development of post-operative complications associated with sepsis fifteen-fold. This finding is concerning because MDR bacteriuria is a challenge in the treatment of patients with stones increasing the complexity and results with regard to greater prevalence of patient morbidity, longer length of stay, and higher hospital costs. Our study found that *E. coli* was the most common MDR organism and the second most common was *E. faecalis*, the same findings reported in previous studies.^{6,14} AUA 2016 and EAU 2021 guidelines recommend that the physician should always treat urinary tract infections before stone removal. In patients with clinically significant infections and obstructions, the patient should undergo drainage for several days before PCNL.¹ However, there are no evidence-based guidelines for antibiotic prophylaxis in patients with stones that have a positive MDR urine culture. In real life clinical situations, we treat infections with empirical antibiotics in accordance with the urine culture sensitivity.

The results from this study, indicate that the presence of MDR bacteria in the urine culture increases the potential for postoperative sepsis. However, if we attempt to eradicate the colonization and treat until the urine culture is negative, the renal function will continue to decrease due to the obstruction. We also know that the stone

**Table 2.** Univariate analysis for postoperative sepsis

Parameters	Odds ratio	95 % C.I. for odds		P-value
		Lower	Upper	
Age	1.01	0.95	1.08	0.742
Sex				
Male	Reference			
Female	0.16	0.02	1.34	0.092
BMI	0.93	0.77	1.13	0.480
Preop creatinine	0.91	0.40	2.09	0.823
Stone number	1.02	0.82	1.27	0.849
Stone size	1.19	0.92	1.54	0.177
Staghorn stone				
No	Reference			
Yes	1.20	0.30	0.74	0.794
Diabetes mellitus				
No	Reference			
Yes	4.59	1.10	19.06	0.036
Positive urine culture				
No	Reference			
Yes	16.48	1.98	137.34	0.010
Number of access points				
=1	Reference			
>1	3.84	0.67	22.06	0.132
Access tract				
Upper pole	Reference			
Middle pole	1 (empty)			
Lower pole	0.90	0.17	4.66	0.898
Point access				
Supracostal	Reference			
Subcostal	0.33	0.08	1.33	0.119
History of previous PCNL				
No history of surgery	Reference			
History of PCNL	1 (empty)			
History of NL	0.91	0.18	4.67	0.907
Blood loss	1.00	1.00	1.01	0.842
Transfusion				
No	Reference			
Yes	6.71	1.38	32.74	0.018
Postoperative fever				
No	Reference			
Yes	5.47	0.66	45.38	0.116
Stone free				
Stone free	Reference			
Retain stone	0.70	0.18	2.74	0.605
LOS	1.22	1.01	1.48	0.037

PCNL = percutaneous nephrolithotomy, NL = nephrolithotomy, MDR = multidrug resistant, LOS = length of stay (days)

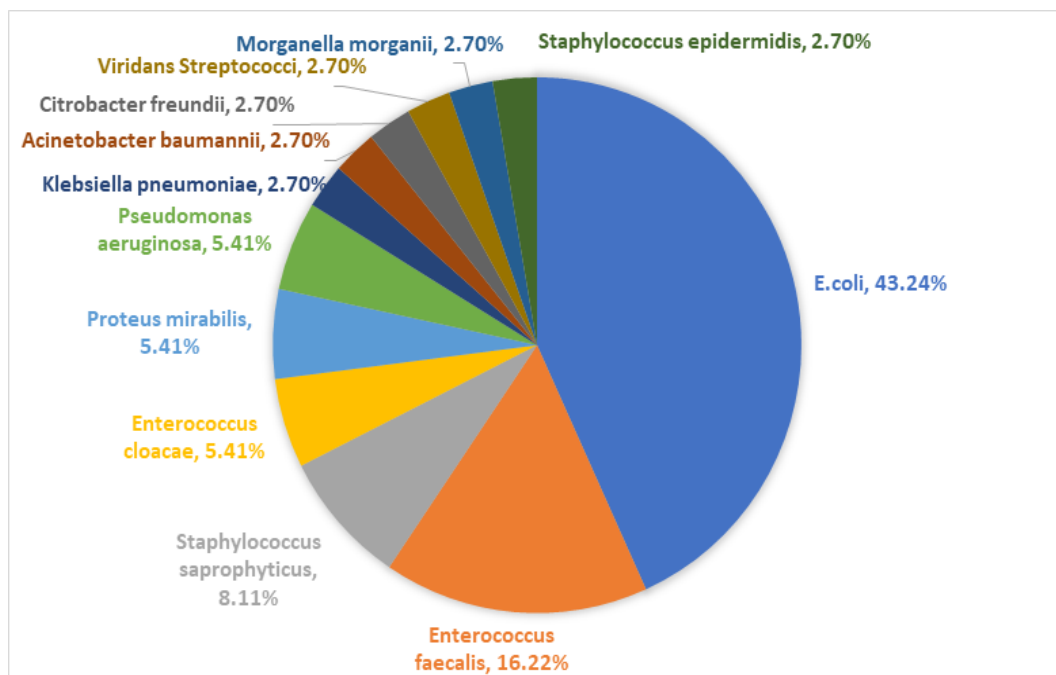


Figure 1. Multidrug resistant (MDR) pathogens

Table 3. Multivariable analysis for postoperative sepsis complications

Parameters	Odds ratio	95 % C.I. for odds		P-value
		Lower	Upper	
Sex				
Male	Reference			
Female	0.03	0.001	0.75	0.033
Preop creatinine	0.34	0.06	1.96	0.229
Stone number	1.28	0.84	1.93	0.246
Stone size	1.30	0.90	1.87	0.160
Staghorn stone				
No	Reference			
Yes	1.80	0.19	17.49	0.611
Diabetes mellitus				
No	Reference			
Yes	1.54	0.14	17.16	0.724
Blood loss	0.99	0.98	1.00	0.094
Positive MDR				
No MDR	Reference			
MDR	15.21	1.59	145.35	0.018
Postoperative fever				
No	Reference			
Yes	3.05	0.16	57.47	0.457
Stone free				
Stone free	Reference			
Retain stone	0.24	0.02	2.66	0.243
LOS	1.93	0.94	3.99	0.074

MDR = multidrug resistant, LOS = length of stay (days)



itself might be or become the cause of a persistent bacterial infection, in which case it would be wise to proceed with the PCNL with empirical antibiotic treatment. Counselling the patient about possible complications in either scenario is important. For patients without a previous history of preoperative urine cultures, assessing the prevalence of organisms can assist in determining the appropriate use of prophylactic antibiotics.

This study has some limitations. Some data was incomplete due to the retrospective nature of the study. The data was also only collected from a single-center limiting the generalization of the findings which would also be affected by the sample size being relatively small.

Conclusion

The prevalence of MDR bacteriuria in patients who underwent PCNL in our study was relatively high. This study found that female gender is a prophylactic factor, and also that preoperative MDR bacteriuria is a strong predictor of postoperative sepsis complications. Therefore, extra care and precautionary measures should be taken in treating male patients and those with positive MDR bacteriuria.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Comparison of enucleation efficiency of HoLEP with the early apical release 'En Bloc' technique between the learning curve period and after becoming proficient in HoLEP

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Keywords:

Enucleation, HoLEP, En Bloc, learning curve, proficiency

Abstract

Objective: To compare prostate enucleation efficiency using Holmium laser (HoLEP) with the early apical release 'En Bloc' technique between a learning curve and experienced group and to evaluate factors required to ensure proficiency.

Materials and Methods: A retrospective analysis was conducted on 120 patients diagnosed with benign prostatic hyperplasia (BPH) who underwent En Bloc HoLEP with early apical release by a single surgeon (CL) at Thammasat University Hospital between January 2019 and December 2023. The primary outcome was a comparison of enucleation efficiency (EE). EE was calculated by dividing the weight of enucleated prostatic tissue (g) by the enucleation time (min). Secondary outcomes were hematocrit (Hct) change, one-month postoperative maximum urine flow rate (Qmax), International Prostate Symptom Score (IPSS) reduction, catheter time (CT; day), length of hospital stay (LOS; day), morcellation efficiency (ME; calculate by dividing enucleated tissue weight (grams) by the morcellation time) and post-operative stress urinary incontinence (SUI) occurrence. The 120 cases were divided into a learning curve group of 60 cases and an experienced group of 60 cases. Mean EE & ME, post-operative Hct change, IPSS reduction, Qmax, CT, LOS and post-operative SUI were compared.

Results: The median (IQR) prostate weight in the learning curve group vs the experienced group was 66 (50.5-101) g vs 69 (50-95) g. Demographic and clinical data differed significantly between groups. Mean EE was significantly different between the learning curve group vs the experienced group (0.76 g/min vs 0.92 g/min ($p = 0.021$), respectively) after experience of 60 cases. Mean CT and LOS were decreased in the experienced group. Mean ME improved slightly but was not statistically significant.

Conclusion: The number of cases required to become proficient at the early apical released En Bloc technique of HoLEP is 60 cases.

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Introduction

Surgical treatment is considered for treatment of benign prostatic hyperplasia (BPH) when any of the following indications are present: refractory acute urinary retention¹, recurrent gross hematuria², recurrent urinary tract infection (UTI), signs of end-stage bladder decompensation (bladder calculi, bladder diverticula) or bilateral hydronephrosis with renal function impairment.³ The surgical treatment is usually a minimally invasive endoscopic procedure for example transurethral resection of the prostate (TURP). Another option is Holmium laser enucleation of the prostate (HoLEP), which has been shown to have better surgical outcomes than TURP.⁴⁻⁶

HoLEP is safe, effective, and independent of prostate size.^{7,8} Previous studies have shown that HoLEP was equally efficient as open prostatectomy and resulted in comparatively lower morbidity, catheterization time, and length of hospital stay (LOS).⁷⁻⁹ HoLEP provides better visualization, easier identification of prostate surgical capsule location, increased ability to approach the correct plane while dissecting adenoma, and better preservation of the external urethral sphincter.¹⁰

A study by Riedinger et al.¹¹ showed that prolonged operative time of transurethral surgery is associated with an increased risk of postoperative complications such as septicemia with or without shock. Extending the duration of the procedure leads to blood loss, deep vein thrombosis, or pulmonary embolism.¹²⁻¹⁵ Therefore, to achieve efficacy and safety in terms of reducing operative time for this challenging procedure, only experienced urologists should perform HoLEP, which has a steep learning curve.¹⁶

A study was carried out in Thailand into the safety and outcome of transurethral anatomical enucleation of prostate (TUAEP) using bipolar energy.¹⁷ However, no prior study has been carried out in prostate enucleation by laser energy. In this study the aim was to determine the number of cases a urologist needs to experience to become proficient at this procedure. To fulfil this aim data was collected regarding HoLEP with early apical release En Bloc technique performed by a single surgeon (CL) at Thammasat University Hospital between January 2019 and December 2023. To our knowledge, this is the first Thai study into the HoLEP learning curve.

Materials and Methods

Patient selection

Data pertinent to patients who were diagnosed with BPH underwent HoLEP with early apical release En Bloc technique between January 2019 and December 2023 were retrospectively reviewed. Prostate volume was measured before the HoLEP procedure by one of the following techniques: transrectal ultrasound, computer scan of the genitourinary system, or MRI of the prostate gland. The research was approved by the Human Research Ethics Committee of Thammasat University (Medicine): 0263/66. The protocol number MTU-EC-SU-0-263/66.

Inclusion criteria

Patients were included if they were diagnosed with BPH with an indication for surgery (refractory urinary retention, recurrent gross hematuria, recurrent UTI, renal deterioration from BPH, bladder diverticulum or bladder calculi from BPH, or BPH with troublesome symptoms) and underwent HoLEP with early apical release En Bloc technique.

Demographic data

Patients' data were collected through the Electronic Patient Health Information System (E-PHIS). The information included age (years), body weight (kg), height (m), preoperative IPSS, preoperative prostate-specific antigen (PSA), preoperative Hct (%), prostate volume (gm), and history of BPH medication use.

Surgical procedure

En Bloc HoLEP with early apical release was performed in each case by a single surgeon. Either general anesthesia or spinal anesthesia was used based on the underlying disease of the patient and expected operative time. Holmium: YAG laser (Lumenis PULSE MOSES TM) 120 W two pedal was used for the procedure. A 550- μ m end-firing laser fiber (SLIMLINE TM, Lumenis Inc.) was used. The procedure was performed using the following settings: for cutting, energy of 1.2-1.8 J, frequency of 50-60 Hz, and power of 72-90 W; for coagulating, energy of 1 J, frequency of 20 Hz, and power of 20 W, employing a long pulse energy. A 26 Fr continuous flow resectoscope (Karl Storz and Richard Wolf Shark) with a laser bridge was also used. Two types of morcellators were used to remove the prostatic tissue: the

VersaCut (Lumenis) and the Piranha (Richard Wolf) morcellators. The procedure was carried out using the standard reference technique of Dr. Fernando GS¹⁸ and self-learning from YouTube¹⁹ without a proctor.

Statistical analysis

A suitable sample size was calculated for cases in the learning curve group. In studies by Seki Narihito²⁰ and Shah HN²¹, the mean EE in the learning curve group was 0.75 g/min $\pm$ 0.3 (Mean1 $\pm$ SD), while the expected mean for the experienced group increased by 0.15 to reach 0.9 g/min $\pm$ 0.3 (Mean2 $\pm$ SD). We analyzed optimum sample size using program STATA version 15, with a set type 1 error of 0.05, power of 80%, and assuming SD1 = SD2 = 0.3. The calculated sample size was 60 cases per group, resulting in 120 cases in the study. Patient data was divided into two groups, the learning curve and the experienced group, and comparisons were made between the two groups. The student's t-test was used for normally distributed continuous data [expressed as mean and standard deviation (SD)] and the Wilcoxon Rank Sum test for skewed data [expressed as the median and interquartile range (IQR)]. Fisher's exact test was used for categorical data. Results were categorized as statistically significantly different at $p < 0.05$.

Results

A total of 120 cases were categorized into two groups: 60 cases in the learning curve group and 60 cases in the experienced group. The demographic data is shown in Table 1. The mean (SD) age of patients in the learning curve group was 71.5 (7.3) years, and in the experienced group was 70.7 (6.7) years which were not significantly different. The number of patients was highest in ASA class 2 for both groups. The median preoperative PSA (IQR) in the learning curve group was 4.8 (2.7-9) ng/ml, while in the experienced group, it was 6 (2-11.3) ng/ml, data showing no significant difference. There was no statistically significant difference in the median (IQR) prostate volume of patients in the learning curve group vs the experienced group (66 (50.5-101) vs 69 (50-95) g) ($p = 0.872$).

The mean (SD) preoperative IPSS for the learning curve group vs the experienced group were 24.9 (5.5) vs 25.8 (4.4) respectively. The median (IQR) preoperative Qmax for the learning

curve group vs the experienced group were 7.5 (5-10.7) ml/sec vs 8.1 (6.5-12) ml/sec, respectively. The indication for HoLEP in the learning curve group included urinary retention in 26 (43.33%) patients and troublesome symptoms in 26 (43.33%) patients, whereas, in the experienced group, the indications were urinary retention in 30 (50%) patients and troublesome symptoms in 25 (41.67%) patients. Of the preoperative demographic data, only ASA classification ($p = 0.021$), BMI ($p = 0.001$), medication ($p = 0.022$), and preoperative urinary retention ($p = 0.044$), showed statistically significant differences between the two groups.

Operative data are shown in Table 2. The mean (SD) EE of the learning curve group vs the experienced group was significantly different, 0.76 (0.38) g/min vs 0.92 (0.36) g/min respectively, ($p=0.021$). The median amounts of enucleated prostatic tissue in the learning curve group vs the experienced group were 44 (31-63) g vs 51.5 (30-71.5) g, respectively ($p = 0.171$). The median (IQR) morcellation times for the learning curve group vs the experienced group were 15 (10-26) min vs 11.5 (7-20) min, respectively ($p = 0.137$). The mean (SD) of morcellation efficiency in the learning curve group and the experienced group were 3.76 (3.1) g/min and 4.89 (2.81) g/min, respectively ($p = 0.05$).

The mean (SD) of catheterization time in the learning curve group and the experienced group were 3 (2.3) days and 2 (0.4) days, respectively ($p=0.0003$). The mean (SD) of LOS) in the learning curve group and the experienced group were 4 (2.1) days and 3 (0.48) days, respectively ($p = 0.0008$).

Table 2 shows the perioperative complications. The rates of high-grade complications (Clavien Dindo Classification (CDC) grade 3-4) showed no difference between the two groups. Other complications included bladder mucosal injury in 3 cases (2 cases in the learning curve group needed open cystotomy to repair), blood transfusion in 2 cases (both in the learning curve group), and severe UTI sepsis in 2 cases. Unfortunately, the rate of urethral catheter reinsertion was not collected in this study.

Post-operative data

Table 3 shows the mean (SD) improvement of Qmax in the learning curve group vs the experienced group, 17.8 (10.8) ml/sec vs 19.6 (11.4) ml/

**Table 1.** Preoperative demographic data

Variables	First 60 cases	Last 60 cases	P-value
Age, year, mean (SD)	71.5 (7.3)	70.7 (6.7)	0.540
ASA classification n (%)			0.021
1	2 (3.33)	1 (1.67)	
2	39 (65.00)	52 (86.67)	
3	19 (31.67)	7 (11.67)	
BMI, kg/m ² (SD)	25.46 (4.74)	22.86 (3.71)	0.001
Previous BPH medication n (%)			0.022
None	4 (6.67)	4 (6.67)	
Alpha-blocker	10 (16.67)	23 (38.33)	
Combination	46 (76.67)	33 (55.00)	
Indication for surgery n (%)			0.805
Urinary retention	26 (43.33)	30 (50.00)	
Bothersome	26 (43.33)	25 (41.67)	
Hematuria	3 (5.00)	3 (5.00)	
UTI	1 (1.67)	0	
Renal deterioration	3 (5.00)	1 (1.67)	
Bladder stone	1 (1.67)	1 (1.67)	
Prostate volume, g, median (IQR)	66 (50.5-101)	69 (50-95)	0.872
Pre-op IPSS, mean (SD)	24.9 (5.5)	25.8 (4.4)	0.346
Pre-op Hct, %, mean (SD)	39.6 (4.5)	38.6 (4.1)	0.198
Pre-op urinary retention, n (%)	23 (38.33)	34 (56.67)	0.044
Pre-op Qmax, ml/sec, median (IQR)	7.5 (5-10.7)	8.1 (6.5-12)	0.285
Pre-op PVR, ml, median (IQR)	52 (42-100)	68 (35-145)	0.698
Pre-op PSA, ng/ml, median (IQR)	4.8 (2.7-9)	6 (2-11.3)	0.728

SD = standard deviation, BMI = body mass index, BPH = benign prostatic hyperplasia, n = number, IQR = interquartile range, g = grams, Pre-op IPSS = preoperative International Prostate Symptom Score, Pre-op Hct = preoperative hematocrit, Pre-op Qmax = preoperative maximum urine flow rate, Pre-op PVR = preoperative postvoid residual urine, Pre-op PSA = preoperative prostate specific antigen, UTI = urinary tract infection

Table 2. Operative data

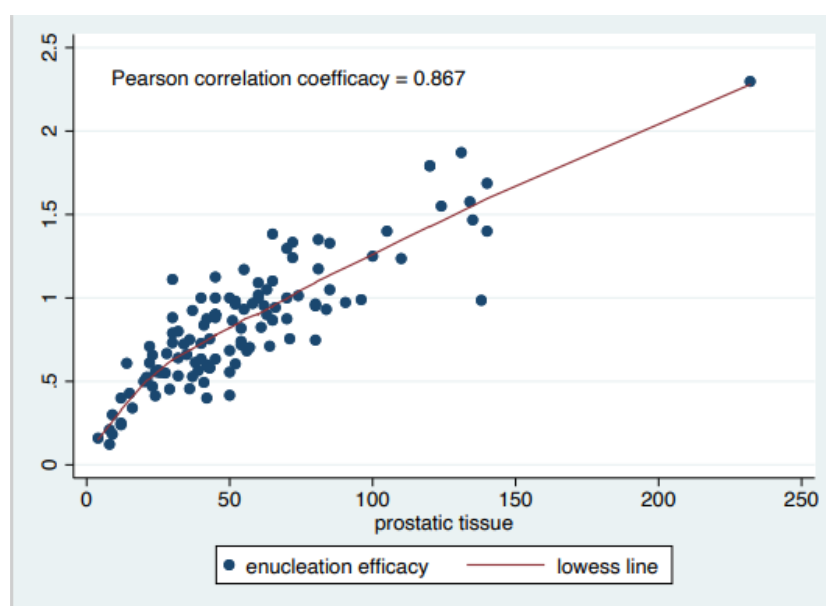
Variables	First 60 cases	Last 60 cases	P-value
Enucleation efficiency, g/min, mean (SD)	0.76 (0.38)	0.92 (0.36)	0.021
Enucleation tissue, gm, median (IQR)	44 (31-63)	51.5 (30-71.5)	0.171
Morcellation time, min, median (IQR)	15 (10-26)	11.5 (7-20)	0.137
Morcellation efficiency, g/min, mean (SD)	3.76 (3.10)	4.89 (2.80)	0.050
Hct changed, %, mean (IQR)	1.15 (0.10-2.45)	0.70 (0-2.80)	0.647
Catheter time (day), mean (SD)	3 (2.3)	2 (0.4)	0.0003
Length of hospital stay (day), mean (SD)	4 (2.1)	3 (0.48)	0.0008
CDC, n (%)			0.385
I	26 (43.33)	30 (50)	
II	8 (13.33)	5 (8.33)	
III	4 (6.67)	4 (6.67)	
IIIa	2 (3.33)	4 (6.67)	
IIIb	2 (3.33)	0 (0.00)	
IV	0 (0.00)	2 (3.33)	
IVa	0 (0.00)	0 (0.00)	
IVb	0 (0.00)	2 (3.33)	

SD = standard deviation, n = number, IQR = interquartile range, g = grams, Hct = hematocrit, CDC = Clavien Dindo Classification

Table 3. Post-operative outcomes at 1-month follow-up

Variables	First 60 cases	Last 60 cases	P-value
Improved Qmax, ml/sec, mean (SD)	17.8 (10.8)	19.6 (11.4)	0.363
IPSS reduction, mean (SD)	19.6 (6.2)	19.3 (4.4)	0.786
Post-op SUI, n (%)	9 (15.00)	14 (23.33)	0.354
Post-op hematuria, n (%)	10 (16.67)	5 (8.33)	0.269

SD = standard deviation, Qmax = maximum urine flow rate, n = number, IPSS = International Prostate Symptom Score, Post-op SUI = post-operative stress urinary incontinence, Post-op hematuria = post-operative hematuria

**Figure 1.** Enucleation efficiency and enucleated prostatic tissue.

sec, respectively. The difference was not significant ($p = 0.363$). The mean (SD) IPSS reductions in the learning curve group vs the experienced group were 19.6 (6.2) vs 19.3 (4.4), respectively with no statistically significant difference ($p = 0.786$). Postoperative SUI at 1-month follow-up in the learning curve group vs the experienced group, were 9 (15%) patients vs 14 (23.3%) patients, with no statistically significant difference ($p = 0.354$). Postoperative hematuria at 1-month follow-up in the learning curve group vs the experienced group were 10 (16.67%) patients vs 5 (8.33%) patients, which was not significantly different ($p = 0.269$).

Fig. 1. Scatter plots of operative data of HoLEP early apical release En Bloc technique. The plots show a correlation between enucleation efficiency and the weight of enucleated prostatic tissue. Larger prostate tissue resulted in a higher enucleation efficiency in comparison to smaller prostate tissue.

Fig. 2. shows the scatter plots of the operative data of HoLEP early apical release En Bloc technique. The plots demonstrated that the improvement of enucleation efficiency increased with the number of cases. The mean EE of the learning curve group was 0.76 g/min (0.38), and the mean of the experienced group was 0.92 g/min (0.36), which was an improvement of 0.16 g/min ($p = 0.021$).

Discussion

Several studies have demonstrated the advantages of anatomical endoscopic enucleation of the prostate (AEEP) using techniques such as laser or bipolar energy. These have been reported as being especially successful in the treatment of large gland prostate, which is consistent with our data (Fig. 1). However, HoLEP is one of the most challenging procedures in endourology, and due to the steep learning curve, its use has been limited. Without formal instruction, the steepness

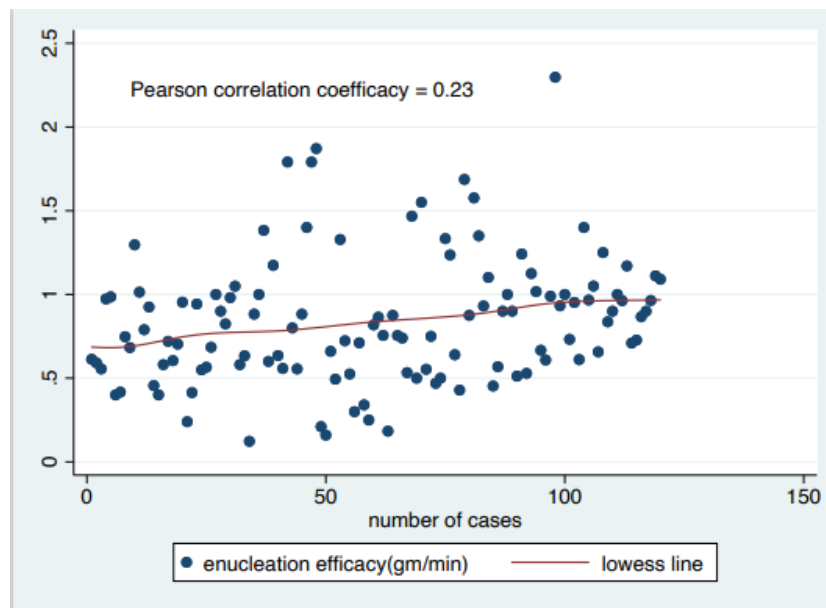


Figure 2. Learning curve parameters: enucleation efficiency and number of cases

of the learning curve is particularly difficult.^{22,23}

To date many studies have demonstrated a number of procedures used to achieve the level of proficiency necessary for successful surgery. In the case of the standard three-lobe incisional technique, the novice needs to carry out 20 cases with an experienced instructor and 40-50 in the case of the self-teaching model.²⁴⁻²⁷ However, the En Bloc technique is more challenging, proficient requiring at least 30-50 and 100 cases, with or without a proctor.^{28,29} However, the En Bloc technique is becoming a more popular option because it saves operative time and is more efficient in enucleating adenoma while using less laser energy, causing lower post-operative complications.³⁰⁻³²

Within our study, the operative data revealed a significant improvement in the mean EE of the experienced group compared to the learning group, with an increase of 0.15 g/min (from 0.76 to 0.92), a statistically significant difference ($p = 0.021$). High levels of success occurring after operating in 60 consecutive cases. Catheter time (CT) and LOS were also significantly shorter in the experienced group. This data suggests that a suitable number of procedures required for passing the learning curve in this technique is at least 60 cases, based on the improvement in EE, CT, and LOS in this study. Other studies carried out around the world also support this finding.^{22,24,33}

Even three decades after the introduction of HoLEP there is still no consensus with regard to a standard value of mean EE as a cutoff point for

gaining expertise. Another factor in the assessment during the learning curve is the stability of skills. Most studies in the multi-incisional technique demonstrate a constant surgical performance state as it reaches a plateau of EE.^{24,26,27} Unfortunately, however, our results show a different pattern as a slightly rising trend.

In Fig. 2: a gradual proportional increase in EE can be seen in parallel to the cases experienced. This figure is often seen in publications describing the development of the En Bloc learning curve.^{28,29} The result of Wenk et al.²⁹ reveals a slight but steady improvement of EE even after 500 surgical cases, results still not reaching the plateau. To attempt to explain this, we hypothesize that it is challenging to master the En Bloc technique. The enucleation state begins with one incision to seek the space between the adenoma and the surgical capsule, then dissection progresses toward the bladder neck. The most challenging step is finding a good plane and effectively lasering tissue with proper hemostasis. As the surgical field is limited, the perspective and orientation of anatomy is more complicated than in standard incisional techniques, especially without a mentor.

When surgeons gain experience by carrying out increased numbers of consecutive cases in this En Bloc technique, especially with the large prostate volume, this will facilitate reduced enucleation time. This increased familiarity with the procedure might affect gradual improvement in EE (enucleation efficiency) (g/min). This data is

consistent with results from a study by Tamalunas et al.³¹ As previously mentioned, HoLEP has a steep learning curve, requiring surgical experience for the best operative outcomes, reduced operative time, minimal perioperative blood loss, and minimal perioperative complications.³⁴ Self-learning may need more cases to achieve efficiency than in the professional guidance process.^{20,21}

The morcellation efficiency in the experienced group improved from 3.76 (3.1) g/min to 4.89 (2.81) g/min, but the results did not quite achieve statistical significance ($p = 0.05$). In our study, the first 30 cases used the VersaCut morcellator before switching to the Piranha morcellator (oscillating function), which is a more efficient device. This could also have affected the data.³⁵

The postoperative data demonstrate no statistically significant differences between the two groups in the case of Qmax improvement ($p = 0.363$), IPSS reduction ($p = 0.786$), post-operative SUI ($p = 0.354$), or post-operative hematuria ($p = 0.269$). This is consistent with the results of a study by Ito TT.³⁶ A possible cause of greater post-operative SUI in the experienced group than in the learning curve group is the operative technique. The surgeon removed the tissue around the prostate apex totally to decrease the adenoma recurrence rate, which is a different technique to that used initially, aiming to leave tissue at the apical area because of concerns about incontinence. However, the outcomes documented in this study were at 1-month follow-up. At the 6-month follow-up, the patients had normal continence, which is similar to other studies.³⁷

Overall the peri-operative complications in this study were minor, the majority occurring in the learning curve period, the incidence being comparable with another study from high-volume centers.²³ Serious post-operative complications, such as severe bladder mucosal injury (CDC IIIb) caused by a morcellator, occurred in 2 cases in the learning curve group. Those patients underwent open cystotomy for adenoma removal and bladder repair to ensure the patient's safety. Another morbidity was severe UTI sepsis (CDC IVb). These complications may have resulted from prolonged catheterization, which is a risk factor for UTI and poor health.³⁸

A limitation of this retrospective study was the limited number of cases and that only a single surgeon performed the procedure, hence all

procedures were managed without supervision. The experience of one urologist might not enable the generalization of the findings. Also, this study was based on data from 120 patients which was divided exactly into two groups. This data could potentially yield more detailed findings if it was examined as a continuous data set as the proficiency of the surgeon would assumedly improve along the linear period.

In this case the surgeon had passed proficiency in Bipolar Enucleation of Prostate (BiPoLEP), which might affect the initial phase of the learning group and limit the transferability of the findings to a novice in this technique. Future prospective studies should recruit more cases and follow up longer to provide more reliable results.

Conclusion

This study determined that because of the steep learning curve, urologists require experience of 60 cases to become proficient in Holmium laser enucleation of the prostate with the early apical release En Bloc technique. It is essential that urologists who wish to carry out this procedure should gain the necessary surgical experience.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Surgical outcomes of Holmium laser enucleation of the prostate (HoLEP) versus bipolar transurethral enucleation of the prostate (B-TUEP) in benign prostatic hyperplasia patients

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Keywords:

HoLEP, bipolar transurethral enucleation of the prostate, benign prostatic hyperplasia

Abstract

Objective: To evaluate the outcomes and safety of the surgical technique Holmium laser enucleation of the prostate (HoLEP) in comparison to bipolar transurethral enucleation of the prostate (B-TUEP) in patients with benign prostatic hyperplasia (BPH) for whom surgery was advised by a single surgeon.

Materials and Methods: Data was collected from 36 patients who underwent HoLEP between January 2021 and June 2022 and 36 patients who underwent B-TUEP between January 2023 and August 2024 in Rajavithi Hospital. Demographic characteristics, perioperative results, complications, and functional outcomes of surgery were compared between the two groups.

Results: There was no significant difference between the groups in terms of age, blood loss, resected tissue volume, complications and pathology. The operative time, the catheterization time and the length of stay were significantly longer in the HoLEP group. There was significant postoperative improvement in international prostate symptom score (IPSS), quality of life score (QoL), peak flow rate (Q-max), post-void residual urine volume (PVR) and prostate-specific antigen (PSA) in both groups. However, the improvement in the IPSS was significantly better in the B-TUEP group.

Conclusions: The outcomes of HoLEP and B-TUEP are comparable regarding safety and efficacy for the treatment of BPH patients. However, HoLEP required a longer operative time, catheterization time and length of stay than B-TUEP.

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Introduction

Benign prostatic hyperplasia (BPH) is the most common pathology affecting bladder outlet obstruction in men, the incidence of BPH increas-

ing by 50% in the last 60 years.¹ Transurethral resection of the prostate (TURP) is still the gold standard in the endoscopic surgical treatment of BPH. Currently, bipolar-TURP is being in-

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creasingly used in comparison to the long-established monopolar-TURP due to the lower risk of hyponatremia, TUR syndrome, and blood loss.² Bipolar transurethral enucleation of the prostate (B-TUEP) was implemented as a safe, effective, and durable procedure for BPH patients, and it has been shown to have superior outcomes at both short- and long-term follow-up in comparison with TURP.³ Holmium laser enucleation of the prostate (HoLEP) has been used as alternative treatment for BPH, first being described in 1995 by Gillling et al.⁴ The recent guidelines published by the European Association of Urology (EAU) recommend B-TUEP and HoLEP as surgical treatments for BPH when the gland is larger than 30 ml.^{5,6} American Urology Association (AUA) guidelines recommend HoLEP as the surgical treatment for all sizes of BPH especially in the case of patients who use anticoagulant and antiplatelet therapy.⁷ However, in the majority of hospitals of Thailand there remains a lack of laser equipment for BPH surgery. For these reasons B-TUEP has been considered as a suitable option for all patients in Thailand. Thus, the purpose of this study was to compare the perioperative data, complications and functional outcomes between HoLEP and B-TUEP in the same hospital by single surgeon.

Materials and Methods

A total of 36 patients underwent HoLEP between January 2021 and June 2022 and 36 patients underwent B-TUEP between January 2023 and August 2024 in Rajavithi Hospital for BPH surgical conditions. The study was approved by the Research Ethics Committee of Rajavithi Hospital (protocol number: 66042). In this study was cystoscopy had been carried out in every patient before either the HoLEP or B-TUEP procedure to evaluate the prostate anatomy and exclude other causes of lower urinary tract symptoms.

Data were recorded including underlying disease, mean age, operative time, tissue weight removed, catheterization time, length of hospital stay (LOS), pathologic results and complications in both groups. The data collected included the international prostate symptom score (IPSS), quality of life score (QoL), prostate-specific antigen (PSA), peak flow rate (Q-max), and post-void residual urine volume (PVR). Data were collected pre-operatively and compared with results from 1 month postoperatively. Pre-post operative hema-

tocrit (Hct) readings were also compared. Patients were monitored for complications for one month postoperatively, with follow-up continuing until the patient exhibited normal urination. Additional follow-up was conducted at three months.

Data analyses were performed using SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA). The categorical variables are presented as number and percentages, whereas the continuous variables are represented by mean $\pm$ standard deviation (SD). Comparisons between the two groups were analyzed using the chi-squared test or Fisher's exact test. Student's t-test or Mann-Whitney U test were used to compare continuous variables between two groups. Preoperative versus postoperative results in each group were compared using a Paired-t test or Wilcoxon signed rank test. A p-value less than 0.05 was statistically significant.

Whilst carrying out the HoLEP procedure, the author performed the three-lobe technique in all patients. The instrument was a 26 Fr laser resectoscope with 30-degree lens (Wolf brand). The laser device was Holmium-YAG laser 120-watt (Lumenis brand) with 550 microns of laser fiber. The laser power setting was 2J and 50Hz for cutting, with 1J and 20Hz for coagulation. The morcellator was PIRANHA (Wolf brand) connected with a 0-degree nephroscope for removal of prostatic adenoma. The irrigating fluid used was normal saline. Patients were put in the lithotomy position after general or spinal anesthesia, a 26 Fr laser resectoscope and sheath were inserted then the bladder was evaluated, and ureteric orifices, bladder neck and verumontanum were identified. The author inserted the resectoscope with an obturator lens (Wolf brand) without dilating the urethra but in the narrow urethral lumen cases we used a metal dilator before inserting the resectoscope. Firstly, the author made the inverted-U shape incision by laser around the verumontanum to identify the surgical capsule of the median lobe. Then the incision was made at 5 and 7 o'clock deep to reach the surgical capsule. After that the median lobe was enucleated to the bladder in a retrograde fashion. The left lateral lobe enucleation was initiated by mucosal incision from 5 to the 12 o'clock position at the apex of the prostate to release the adenoma tissue from the urethral sphincter then an incision was made at the anterior commissure of the prostate. The left lateral lobe was enucleated in a retrograde fashion towards the bladder. The

right lateral lobe enucleation was initiated by mucosal incision from the 7 to the 12 o'clock position at the apex of the prostate then the right lateral lobe was enucleated in a retrograde fashion to the bladder in a similar way to the left lobe. After completing enucleation of the three lobes of the prostate, the author used the laser to stop any bleeding of the prostatic fossa before morcellation. The nephroscope was changed to the same sheath and a morcellator was used to remove the floating adenoma from the bladder. At the end of operation, the author inserted a 22 Fr three-way urethral catheter with 30 mL of balloon with continuous bladder irrigation with normal saline. Urethral traction was carried out in some cases if the urine became red.

In the case of the B-TUEP procedure, the author performed the three-lobe technique in all patients. The instrument used was a 26 Fr bipolar loop resectoscope with a 30-degree lens (Wolf brand). The electrosurgery unit (Martin brand) was set to 180 watts at grade 3. The morcellator was PIRANHA (Wolf brand) connected to a 0-degree nephroscope for removal of prostatic adenoma. The operation was begun in the same way as the HoLEP procedure. Firstly, the urethral mucosa was split deep to the surgical capsule from the 5 to 3 o'clock position near the verumontanum to identify the correct surgical capsule. Then, the median lobe was enucleated retrogradely at 5 and 7 o'clock to the bladder neck using the resectoscope beak. An electrode loop was used to ensure coagulation at bleeding points. The median lobe was separated from the surgical

capsule and both lateral lobes, then the median lobe was pushed into the bladder. The 12 o'clock position of the mucosa of the prostate was resected to spilt the left and right lobes of the prostate. The left lateral lobe enucleation was initiated from the 5 to 12 o'clock position in a retrograde fashion then the adenoma was pushed into the bladder. The right lateral lobe was enucleated in the same fashion from the 7 to 12 o'clock position toward the bladder neck. After enucleation of three lobes of the prostate was completed, the author used the bipolar electrode loop to arrest any bleeding from the prostatic fossa before morcellation. The nephroscope was used with the morcellator to remove prostatic adenoma in the same way as HoLEP. At the end of operation, the author implanted a 22 Fr three-way urethral catheter with 30 mL of balloon with continuous bladder irrigation by normal saline. Urethral traction was carried out in some cases if the urine became red.

Both HoLEP and B-TUEP were performed by a single surgeon who only has previous experience in standard TURP.

Results

The demographic data and preoperative parameters of the patients who underwent HoLEP and B-TUEP are shown in Table 1. The postoperative outcomes of the patients are shown in Table 2. There were no significant differences between the groups with regard to age, blood loss (estimated by anesthesiologist which may lead to some inaccuracy), resected tissue volume, complications and pathology. Underlying diseases

Table 1. Demographic data and preoperative parameters of the patients

Data	HoLEP (n =36)	TUEP (n = 36)	P-value
Age (year)	72.08±7.81	69.11±7.75	0.110 ^A
Underlying disease	21.0 (58.3)	30.0 (83.3)	0.020 ^{*B}
Hct Preoperative (%)	40.71±5.60	39.87±5.50	0.526 ^A
PSA Preoperative (ng/ml)	5.3 (2.2-9.5)	3.9 (1.6-10.1)	0.441 ^C
IPSS Preoperative	22.8±6.65	25.25±5.54	0.228 ^A
QOL Preoperative	5.0 (4.0-5.0)	5.0 (5.0-5.8)	0.401 ^C
Q-max Preoperative (ml/sec)	8.2 (5.0-12.7)	8.1 (6.3-12.7)	0.664 ^C
PVR Preoperative (ml)	159.70±148.60	120.50±109.11	0.375 ^C

Results shown as mean ± SD, n (%) and median (IQR), * = statistically significant at p ≤ 0.05

^A = The p-value by Student's t-test, ^B = The p-value by Chi-squared test, ^C = The p-value by Mann-Whitney U test

Hct = hematocrit, PSA = prostate-specific antigen, IPSS = International Prostate Symptom Score, QOL = Quality of Life Score, Q-max = peak flow rate, PVR = post-voided residual urine volume.

Table 2. Postoperative outcomes of the patients.

Data	HoLEP (n = 36)	TUEP (n = 36)	P-value
Hct (%)	38.80±4.90	37.58±4.81	0.296 ^A
Hct loss	1.9 (0.3-3.2)	2.1 (0.7-4.1)	0.331 ^C
% Hct loss	4.6 (0.8-8.8)	6.1 (1.8-9.7)	0.265 ^C
PSA (ng/ml)	1.1 (0.6-1.6)	0.8 (0.4-1.9)	0.441 ^C
PSA decline (ng/ml)	3.8 (1.2-9.0)	3.1 (0.7-10.0)	0.479 ^C
%PSA decline	78.0 (56.8-90.8)	81.2 (48.8-89.3)	0.945 ^C
IPSS	6.35±4.05	2.85±2.46	<0.001 ^{*A}
IPSS improvement	15.55±7.23	21.50±5.19	0.027 ^{*A}
%IPSS improvement	66.82±22.25	87.43±10.54	0.009 ^{*A}
QOL	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.121 ^C
QOL improvement	4.0 (2.8-5.0)	4.5 (3.8-5.0)	0.137 ^C
%QOL improvement	81.7 (55.0-100.0)	81.7 (75.0-100.0)	0.782 ^C
Q-max (ml/sec)	17.8 (12.2-26.7)	20.4 (14.5-34.7)	0.264 ^C
Q-max Improvement (ml/sec)	11.4 (0.5-18.7)	9.4 (5.7-27.5)	0.431 ^C
%Q-max Improvement	64.1 (5.3-78.9)	60.0 (48.1-66.4)	0.928 ^C
PVR (ml)	29.0 (17.5-55.8)	32.0 (9.8-80.8)	0.965 ^C
PVR decline (ml)	50.5 (13.3-215.0)	47.0 (8.5-159.0)	0.502 ^C
%PVR decline	63.4 (39.2-93.1)	79.1 (7.0-100.0)	0.860 ^C
Operative time (minutes)	150.0 (120.0-217.5)	90.0 (60.0-150.0)	<0.001 ^{*C}
Blood loss (ml)	200.0 (62.5-300.0)	100.0 (50.0-200.0)	0.080 ^C
Catheterization (days)	2.31±0.53	1.92±0.28	<0.001 ^{*A}
Length of stay (days)	2.42±0.69	1.94±0.23	<0.001 ^{*A}
Resected tissue volume (g)	43.5 (16.3-59.8)	29.0 (11.0-49.8)	0.213 ^C
Complications	6 (16.7)	5 (13.9)	0.743 ^B
Pathology			1.000 ^B
BPH	34 (94.4)	35 (97.2)	
Prostate cancer	2 (5.6)	1 (2.8)	

Results shown as mean ± SD, n (%) and median (IQR), * = statistically significant at p ≤ 0.05

^A = The p-value by Student's t-test, ^B = The p-value by Chi-squared test, ^C = The p-value by Mann-Whitney U test

Hct = hematocrit, PSA = prostate-specific antigen, IPSS = International Prostate Symptom Score, QOL = Quality of Life Score, Q-max = peak flow rate, PVR = post-voided residual urine volume, BPH = benign prostate hyperplasia.

such as hypertension, diabetes, chronic kidney disease and cardiovascular disease were noted. All patients who took an antiplatelet or anticoagulant drug were asked to discontinue the medication before surgery. Twelve out of 36 patients in the HoLEP group and 19 out of the 36 patients in the B-TUEP group had an indwelling urethral catheter before surgery due to urinary retention. The median operative time was significantly longer in the HoLEP group, 150.0 (120.0-217.5) minutes vs 90.0 (60.0-150.0) minutes, (p < 0.001). The mean catheterization time was significantly longer in the HoLEP group, 2.31±0.53 days vs 1.92±0.28

days, (p < 0.001). The length of stay was also significantly longer in the HoLEP group, 2.42±0.69 days vs 1.94±0.23, (p < 0.001).

Preoperative and postoperative data are compared in Table 2 and Table 3. There were statistically significant differences between mean preoperative versus postoperative Hct in the HoLEP group, 40.71±5.60 % vs 38.80±4.90 %, (p < 0.001) and in the B-TUEP group, 39.87±5.50 % vs 37.58±4.81 %, (p < 0.001). However, there was no significant difference in the Hct loss between the two groups. Only 1 patient in each group required 1 unit of blood transfusion. There was

**Table 3.** Comparison between the preoperative and postoperative parameters.

Data	Preoperative	Postoperative	P-value
Hct (%) HoLEP	40.71±5.60	38.80±4.90	<0.001*
Hct (%) TUEP	39.87±5.50	37.58±4.81	<0.001*
PSA (ng/ml) HoLEP	5.3 (2.2-9.5)	1.1 (0.6-1.6)	<0.001*
PSA (ng/ml) TUEP	3.9 (1.6-10.1)	0.8 (0.4-1.9)	<0.001*
IPSS HoLEP	22.8±6.65	6.35±4.05	<0.001*
IPSS TUEP	25.25±5.54	2.85±2.46	0.005*
QOL HoLEP	5.0 (4.0-5.0)	0.0 (0.0-2.0)	<0.001*
QOL TUEP	5.0 (5.0-5.8)	0.0 (0.0-1.0)	0.007*
Q-max (ml/sec) HoLEP	8.2 (5.0-12.7)	17.8 (12.2-26.7)	0.006*
Q-max (ml/sec) TUEP	8.1 (6.3-12.7)	20.4 (14.5-34.7)	0.003*
PVR (ml) HoLEP	104.0 (34.0-238.0)	29.0 (17.5-55.8)	0.001*
PVR (ml) TUEP	88.0 (35.8-188.3)	32.0 (9.8-80.8)	0.037*

Results shown as mean ± SD and median (IQR), * = statistically significant at $p \leq 0.05$

The p-value from paired t-tests

Hct = hematocrit, HoLEP = holmium laser enucleation of the prostate, TUEP = bipolar transurethral enucleation of prostate, PSA = prostate-specific antigen, IPSS = International Prostate Symptom Score, QOL = Quality of Life Score, Q-max = peak flow rate, PVR = post-voided residual urine volume, BPH = benign prostate hyperplasia.

significant postoperative improvement in PSA, IPSS, QoL, Q-max and PVR in each group. The IPSS improvement was significantly higher in the B-TUEP than the HoLEP group, 21.50 ± 5.19 vs 15.55 ± 7.23 , ($p = 0.027$).

Pathological results of the tissue removed showed mostly BPH with the exception of 2 of the HoLEP group who were found to have prostate cancer adenocarcinoma Gleason 3+4 and adenocarcinoma Gleason 3+3, and 1 in the B-TUEP group who was found to have prostate cancer adenocarcinoma Gleason 3+3.

There were no serious complications or TUR syndrome in any patients in either group. The total rate of complications in the HoLEP group was 16.7% (6 of 36 patients), 1 patient (2.78%) required a blood transfusion of one unit, 1 patient (2.78%) had capsular perforation needing prolonged urethral catheterization, 1 patient (2.78%) had overflow incontinence from a prior neurogenic bladder, 1 patient (2.78%) had post operative bleeding after discharge for 1 week (he was readmitted for urethral traction and continuous bladder irrigation), and 2 patients (5.56%) had contracture of bladder neck at the 3 month follow up, necessitating transurethral incision of the bladder neck. Total complications in the B-TUEP group was 13.9% (5 out of 36 patients). One patient (2.78%) required one unit of blood

transfusion, 1 patient (2.78%) had post operative bleeding after discharge for 1 week (he was readmitted for transurethral fulguration at the prostatic fossa), 1 patient (2.78%) had contracture of bladder neck at the 3 month follow-up necessitating urethral dilation, and 2 patients (5.56%) had postoperative stress incontinence at the 2 week follow-up (full recovery was established at the 3 month follow-up).

Discussion

Many investigations have resulted in the emergence of various new transurethral surgical therapies including vaporization, aquablation⁸, laser and bipolar enucleation, hence the surgical treatment of BPH has diversified. A recent study has shown that HoLEP is the most common modality for enucleation, but Bipolar TURP is the most common modality for prostate resection.⁹ HoLEP was introduced in 1995 by Gilling et al.⁴ Many publications supported the effectiveness, safety, and durability of the technology involved in this treatment and HoLEP has been recommended as the surgical treatment for all sizes of BPH in American Urology Association (AUA) guidelines. However, HoLEP necessitates a steep learning curve and incurs great expense.^{10,11} A combination of bipolar energy used in TURP and the enucleation technique have resulted in

B-TUEP. B-TUEP has been reported as being a safe and effective alternative to TURP or open prostatectomy.¹²

In B-TUEP, the adenoma is completely dissected along the surgical capsule plane in the same manner to the index finger of the surgeon during open prostatectomy, which is equivalent to HoLEP and is also considered an anatomic enucleation technique.¹³

Elsaqa et al.¹⁴ reported the outcomes of a prospective trial of HoLEP versus B-TUEP in bladder outlet obstruction patients with a prostate volume more than 80 g. Seventy patients underwent HoLEP and 31 patients underwent B-TUEP. The enucleation rate in g/min was significantly higher in the HoLEP patients than in the B-TUEP group (1.9 ± 1 vs 1.1 ± 0.4 , $p < 0.001$), meaning that HoLEP was associated with a shorter operative time. Catheterization time (days) and length of hospitalization (days) were also significantly lower in the HoLEP group (1 (1–2) vs 2 (2–3), $p = 0.012$, 1.2 ± 0.7 VS 1.9 ± 0.6 , $p < 0.001$ respectively). The complication rate, drop in hemoglobin, and readmission rate were comparable between the groups.

Higazy et al.¹⁵ reported on a randomized controlled trial of the outcome of HoLEP versus B-TUEP in 120 patients. The prostate volume was 135.2 ± 34.8 ml and 125 ± 26.9 ml for HoLEP and B-TUEP, respectively. The HoLEP patients had shorter operative time of 83.43 ± 6.92 min compared with 94.7 ± 12.2 min in the B-TUEP group. HoLEP was associated with an earlier catheter removal time compared with B-TUEP (1 ± 0.23 vs 1.79 ± 1.6 days, $p = 0.02$) and shorter hospital stay (1 ± 0.24 vs 1.49 ± 0.6 days, $p = 0.01$) respectively. Postoperative IPSS, QoL, Q-max, PVR, PSA, prostate volume reduction and perioperative complications were comparable between both groups. In the cost analysis, HoLEP was more cost-effective than B-TUEP.

Li et al.¹⁶ carried out a meta-analysis of the outcome in HoLEP versus B-TUEP from 10 studies (1,725 patients). HoLEP had a significantly lower operative time ($p = 0.03$), shorter catheterization time ($p = 0.007$), lower bladder irrigation time ($p = 0.01$), and higher enucleation weight ($p = 0.01$) compared with B-TUEP. Length of stay, drop in hemoglobin, transfusion rates and complications were comparable between the two techniques. There were no statistically significant

differences in postoperative outcomes between HoLEP and B-TUEP regarding IPSS, Q-max, QoL and PVR at 1, 3, 6, 12 and 24 months.

In this present study, both HoLEP and B-TUEP showed significant improvement post-operatively in all parameters without serious complications or incidence of TUR syndrome. However, there was a significantly longer operative time, catheterization time, and length of stay in the HoLEP group which contrasted to other literature. In the author's opinion, the reason might be that using a Holmium laser to stop bleeding differs from using a bipolar loop. When compared to the conventional TURP the author needed additional bladder traction on post-op day 0, continuous bladder irrigation on day 1, stopping bladder irrigation on day 2 and removal of the urethral catheter on day 3. Thus, the mean catheterization time of HoLEP and B-TUEP might be shorter than conventional TURP. The results of this present study could differ from other studies due to the hospitals not having access to a Holmium laser for BPH surgery due to the cost of laser machine. They might perform B-TUEP instead of HoLEP for BPH patients to good effect because the surgical outcomes of the two techniques were comparable.

The limitations of this study are the relative inexperience in the carrying out of both techniques and also the relatively low number of patients. To improve the study further randomized controlled trial data would increase the generalization of the findings.

Conclusion

HoLEP and B-TUEP are equally safe and effective methods for the treatment of BPH patients who have paused anticoagulant and anti-platelet medications prior to operation. However, in this study HoLEP required a longer operative time, catheterization time and length of stay than B-TUEP.

Conflict of Interest

The authors declare no conflicts of interest.

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Original Article

External validation of Stone Probability Score for screening Loei urolithiasis patients

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Keywords:

External validation, predictive model, probability stone formation, stone probability score, screening urolithiasis patients

Abstract

Objective: Urolithiasis is prevalent in Thailand, particularly in Loei region. Early detection is vital for effective management. In 2022, Santanapipatkul et al. developed a Stone Probability Score for screening urolithiasis patients at Loei, however, external validation of this predictive model is necessary to ensure its reliability and applicability. The objective of this study is to externally validate the Stone Probability Score for Screening Urolithiasis Patients at Loei developed in 2022.

Materials and Methods: The external validation was conducted using cross-sectional data from urolithiasis patients at Loei Hospital between September 28, 2022, and December 31, 2023. Logistic regression analysis was employed to evaluate the performance of the predictive model with regard to discrimination, calibration, and multicollinearity.

Results: This validation study included 347 patients and an accuracy of 92.6% (95%CI 88.9-96.3) was achieved with an AUC pertinent to discrimination measurement resulting in a sensitivity of 96.9% (95%CI 94.2-98.6), a specificity of approximately 53.4% (95%CI 39.9-66.7), positive predictive value of 91.2% (95%CI 87.5-94.1) and negative predictive value of 77.5% (95%CI 61.5-89.2). The performance of the model was found to be consistent after external validation in three models in comparison with the previous study.

Conclusion: The external validation of SPS for Screening Loei Urolithiasis Patients exhibited excellent discrimination and calibration. The overall performance of the models was validated with high accuracy. This model can be used as a screening tool to identify individuals at risk of developing urolithiasis in the Loei region.

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Introduction

Urolithiasis is a common urological problem in Thailand, being particularly prevalent in the northeast region.¹ The major problems associated with urolithiasis are seen in patients with complications as a result of urolithiasis. Early detection

and intervention are crucial in the management of urolithiasis, as timely treatment can prevent complications.

Current practice is to separate symptoms into 2 stages: evaluation of metabolism in the 1st

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episode with recurrent stone formation as secondary a secondary stage. However, it is evident that current standard protocols for screening methods for stones in the urinary tract have yet to be established to facilitate primary prevention. Additionally, metabolic evaluation remains costly and cumbersome and is often only feasible in select hospital settings in Thailand, primarily in medical school-affiliated institutions.²

In 2022, Santanapipatkul et al. developed a predictive model for stone formation known as the Stone Probability Score (SPS) for screening urolithiasis patients in Loei. The score included eight parameters: BMI, being of male gender, a family history of urolithiasis, working in farming, working time > 8 hours/day, regular consumption of water spinach, regular consumption of bamboo shoots, eating Laab/Koi more than or equal to 3 times per week. The cut-off of probability for stone formation was 0.46 with a sensitivity of 72.41%, a specificity of 79.52%, and an area under the ROC curve of 0.83.³ This study aimed to externally validate SPS for screening Loei urolithiasis patients by Santanapipatkul et al. using external patient data.

Materials and Methods

Study design

This study is an external validation of the SPS designed in 2022 by Santanapipatkul et al. to enable the identification of urolithiasis patients in Loei. Cross-sectional data were collected from patients at Loei Hospital between September 28, 2022, and December 31, 2023. Approval for the study protocol was obtained from the Institutional Review Board of Loei Hospital (EC011/2565).

Study patients

Patients diagnosed with urolithiasis at a hospital in the Loei region between September 28, 2022, and December 31, 2023 were enrolled onto the study. A total of 347 patients were included in the study, categorized into two groups. Group 1 consisted of 300 non-migrant urolithiasis patients, who permanently reside in Loei province, while Group 2 comprised 47 immigrant urolithiasis patients, who had migrated into Loei province. Urolithiasis patients were identified based on imaging results, including ultrasound, plain KUB, IVP, or CT scan.

Data collection

The data were collected by face-to-face interview and included the following information: [1] Baseline characteristics and demographic data including sex, body mass index, comorbidities, family history of urolithiasis, past stone treatment, occupation, education, monthly income, working hours, and workplace; [2] Dietary habits including consumption of different types of food and water associated with urolithiasis.

Evaluation variables

The workplace was categorized into two groups: outdoor occupations, involving exposure to sunlight, and indoor occupations, such as office or hospital work. The amount of daily water intake was estimated by asking participants, "How many glasses of water do you drink per day?" (1 glass = 250 ml). Dietary risk factors for urolithiasis were assessed through questions about the frequency of consuming specific foods, categorized into four groups: [1] never (never consumed), [2] seldom (consumed monthly), [3] sometimes (consumed weekly), and [4] always (consumed daily). Patients were asked to recall their consumption of these specific foods over the past year.

Study determinant

The mainly focus of our validation study is to assess the SPS developed by Santanapipatkul et al. for the identification of urolithiasis patients in Loei. This SPS comprises 8 predictors, including BMI, male gender, family history of urolithiasis, occupation as a farmer, working more than 8 hours per day, regular consumption of water spinach and bamboo shoots, and eating Laab/Koi 3 or more times per week. If the probability of stone formation calculated by the SPS is greater than or equal to 0.46, we recommend further investigation for urolithiasis.

Study outcome

The primary outcome of the study was to assess the performance of the predictive model in identifying patients at risk of developing urolithiasis in the Loei region.

Statistical analysis

Statistical analyses conducted using STATA carried out in 3 models. The first model included all 347 patients enrolled onto the study model. These were then categorized into a secondary model. The secondary model consisted of 300

non-migrant urolithiasis patients who permanently reside in Loei province while the last model comprised 47 immigrant urolithiasis patients.

Logistic regression was used to evaluate the performance of all predictive models. The goodness of fit assessed by using Hosmer-Lemeshow test if $p > 0.05$ indicated that the model has high reliability perfect. The multicollinearity of the model was considered using the variance inflation factor (VIF) together with the conditional index. mean VIF of more than 1 is indicative of moderate multicollinearity. A conditional index of >30 the multi-collinearity is strong.

The external validation was performed by considering overall performance including discrimination measures then accuracy assessments, specifically sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and area under the curve (AUC). If $0.7 \leq \text{AUC} < 0.8$ the level of discrimination was acceptable, $0.8 \leq \text{AUC} < 0.9$ indicated excellent discrimination and $\text{AUC} \geq 0.9$ outstanding discrimination. We also used the Brier score, a quadratic score rule, where the squared differences between actual binary outcome range from 0 indicates a perfect model to 0.25 for a noninformative model. Calibrations refers the agreement between observed outcomes and prediction that consider calibration in the large (CITL), Calibration slope with graphical assessment of calibration is calibration plot.

However, the provided information helps to clearly understand how the model's accuracy was evaluated and referenced to assess its predictive performance in the study.

Results

Three hundred and forty-seven participants were enrolled onto the study, comprising 223 (64%) males and 124 (36%) females. The average BMI was 23.7 kg/m^2 (± 3.61) for males, 24.4 kg/m^2 (± 4.3) for females, and 23.9 kg/m^2 (± 3.9) overall. A notable portion of participants had a family history of urolithiasis (62% males, 60% females). The majority of both males (83%) and females (89%) worked as farmers. Around 60% of males and 56% of females reported working more than 8 hours per day. Consumption of water spinach varied among participants, with "sometimes" being the most common frequency reported. Similarly, bamboo shoot consumption also varied, with "sometimes" being the most fre-

Table 1. Demographic data and type of food-related to urolithiasis

Variables	Group (n=347)	
	Male	Female
Sex n (%)	223 (64)	124 (36)
Age; year (mean $\pm$ SD)	57.9 $\pm$ 11.3	55.5 $\pm$ 12.9
	57.0 $\pm$ 11.9	
BMI; kg/m ² (mean $\pm$ SD)	23.7 $\pm$ 3.61	24.4 $\pm$ 4.3
	23.9 $\pm$ 3.9	
Underlying disease n (%)	134 (60)	80 (65)
Diabetes mellitus	30 (13)	32 (26)
Hypertension	74 (33)	53 (43)
Dyslipidemia	27 (12)	22 (18)
Gout	24 (11)	4 (3)
Chronic kidney disease*	69 (31)	31 (25)
Education n (%)		
Equal to or lower than Bachelor's degree	220 (99)	123 (99)
Higher than Bachelor's degree	2 (1)	1 (0.8)
Occupations n (%)		
Farmer	187 (83)	111 (89)
Self-employed	16 (7)	4 (3.2)
Others	3 (1)	1 (0.8)
History of family urolithiasis n (%)		
Yes	139 (62)	75 (60)
No	84 (38)	49 (40)
Working times n (%)		
> 8 hours/day	133 (60)	70 (56)
≤ 8 hours/day	90 (40)	54 (44)
Eate Laab/Koi 3 or more times/week n (%)		
Yes	58 (26)	0 (8)
No	165 (74)	114 (92)
Water spinach n (%)		
Never	39 (17)	25 (20)
Seldom	84 (38)	47 (38)
Sometimes	81 (36)	43 (35)
Always	19 (9)	9 (7)
Bamboo shoot		
Never	10 (5)	9 (7)
Seldom	25 (11)	18 (15)
Sometimes	119 (53)	70 (56)
Always	69 (31)	27 (22)

SD = standard deviation, BMI = body mass index

*Chronic kidney disease is defined by a glomerular filtration rate less than 60 ml/min/1.73 m² for at least 3 months.⁴

quently reported frequency. About 26% of males and 8% of females reported consuming Laab/Koi 3 or more times per week (Table 1).

The following predictive model that separated 3 model external validation were

Model 1: Overall total of 347 participated in the study:

$$\text{SPS} = 1 / \{1 + \text{EXP} (-[-1.002 * \text{Male}) + (0.072 * \text{BMI}) + (1.172 * \text{Family history of urolithiasis}) + (1.893 * \text{Working time} > 8 \text{ hours/day}) + (1.279 * \text{Eats Laab/Koi 3 or more times/week}) + (0.170 * \text{always eat water spinach}) + (2.278 * \text{some-times eats Bamboo shoots})]\}$$

Model 2: 300 non-migrant urolithiasis patients:

$$\text{SPS} = 1 / \{1 + \text{EXP} (-[-1.294 * \text{Male}) + (0.083 * \text{BMI}) + (0.897 * \text{Family history of urolithiasis}) + (1.928 * \text{Working time} > 8 \text{ hours/day}) + (1.343 * \text{Eats Laab/Koi 3 or more times/week}) + (0.234 * \text{always eat water spinach}) + (2.211 * \text{some-times eats Bamboo shoots})]\}$$

Model 3: 47 immigrant urolithiasis patients, who migrated to Loei province:

$$\text{SPS} = 1 / \{1 + \text{EXP} (-[0.529 * \text{Male}) + (-0.082 * \text{BMI}) + (71.289 * \text{Family history of urolithiasis}) + (1.162 * \text{Working time} > 8 \text{ hours/day}) + (17.200 * \text{Eats Laab/Koi 3 or more times/week}) + (0.301 * \text{always eat water spinach}) + (36.621 * \text{some-times eats Bamboo shoots})]\}$$

For each individual model in our study, the predicted probability of SPS was calculated using these formulae, leading to the AUC, goodness of

Table 2. The accuracy assessment and goodness of fit of the predictive models in the validation of SPS.

Number in cohort	Model	AUC (%)	Standard error	Asymptotic normal (95% confidence interval)	P-value	VIF	CI
347	1	92.6	0.019	88.9-96.3	0.336 ^a	1.05 ^b	20.67 ^c
300	2	92.3	0.022	87.9-96.5	0.648 ^a	1.05 ^b	20.70 ^c
47	3	95.5	0.029	89.8-100	0.941 ^a	1.09 ^b	20.62 ^c

^a = Hosmer-Lemeshow test, ^b = Variance inflation factor, ^c = Conditional index

SPS = Stone Probability Score, AUC = area under the curve, VIF = variance inflation factor, CI = conditional index

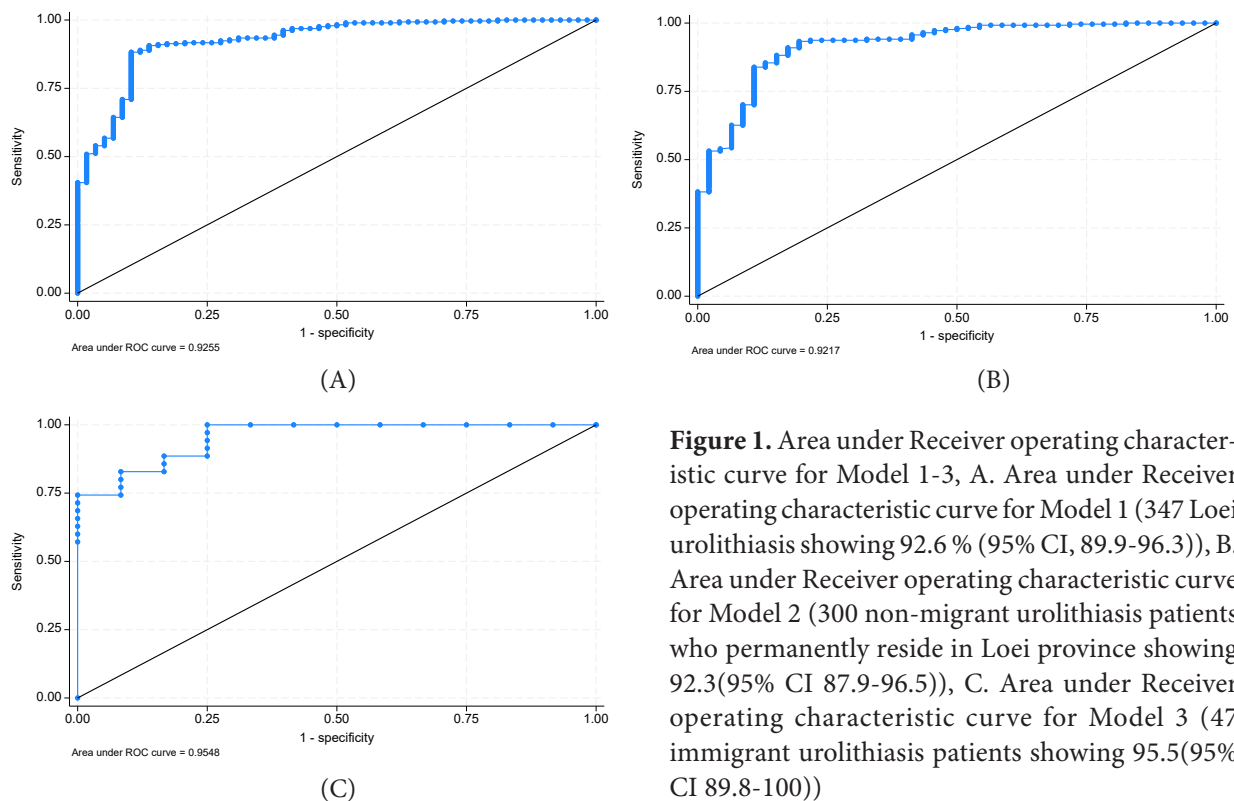


Figure 1. Area under Receiver operating characteristic curve for Model 1-3, A. Area under Receiver operating characteristic curve for Model 1 (347 Loei urolithiasis showing 92.6 % (95% CI, 89.9-96.3)), B. Area under Receiver operating characteristic curve for Model 2 (300 non-migrant urolithiasis patients who permanently reside in Loei province showing 92.3(95% CI 87.9-96.5)), C. Area under Receiver operating characteristic curve for Model 3 (47 immigrant urolithiasis patients showing 95.5(95% CI 89.8-100))

Table 3. Performance measure of external validation all 3 models.

Performance measure	External validation		
	Model 1 (n=347)	Model 2 (n=300)	Model 3 (n=47)
Overall			
Brier score	0.072	0.068	0.058
Cragg & Uhler's R ² (%)	79.6	56.7	79.6
Discrimination			
C stat	92.6	92.3	95.5
Discrimination slope	0.486	0.475	0.695
Sensitivity (%)	96.9 (94.2-98.6)	97.6 (94.9-99.1)	100 (90-100)
Specificity (%)	53.4 (39.9-66.7)	50 (34.9-65.1)	75 (42.8-94.5)
PPV (%)	91.2 (87.5-94.1)	91.5 (87.5-94.5)	92.1 (78.6-98.3)
NPV (%)	77.5 (61.5-89.2)	79.3 (60.3-92)	100 (66.4-100)
Calibration			
Calibration in the large	0	-0	0
Calibration slope	1	1	1
H-L test	0.336	0.648	0.941

PPV = positive predictive value, NPV = negative predictive value

fit by Hosmer-Lemeshow statistical and multi-collinearity issue about VIF and CI as shown in table 2 and fig. 1. The AUCs in all 3 models are much higher in our validation.

External validation

From the table 2, predictive accuracy of the three models as described by the system proposed by Santanapitakul et al was significantly higher in our study. Firstly, a total of 347 patients in the original data set was used in the first model in table 1 showed an AUC of approximately 92.6% (95% CI 88.9-96.3). Secondly, the first model was split into 2 groups of urolithiasis patients, 300 non-migrant who permanently reside in Loei province showed an AUC of 92.3 (95% CI 87.9-96.5) and the final model had 47 immigrant urolithiasis patients and showed 95.5 (95% CI 89.8-100) if an AUC greater than 0.9 suggests outstanding discrimination between the presence and absence of SPS.

From the table 3, overall model performance in the study of 347 patients was greater than in the other two models. We evaluated the overall performance using the Brier score, which was found to be 0.072, according to Cragg & Uhler's R² about 79.6%. For the discrimination measure have shown sensitivity approximately 96.9% (95%CI 94.2-98.6) while specificity may be 53.4% (39.9-66.7) when we consider about PPV is 91.2% (95%CI 87.5-94.1) and NPV probably 77.5% (95%CI 61.5-89.2).

The secondary model was split and from the group of 300 patients the Brier score was 0.068 whereas Cragg & Uhler's R² less than the first model about 56.7%. This model has highly sensitivity 97.6% (95%CI 94.9-99.1) but the specificity was poorer at about 50% (95%CI 34.9-65.1) while the PPV and NPV were 91.5% (95%CI 87.5-94.5), 79.3% (95%CI 60.3-92) respectively.

Finally, the model from the 47 immigrants with urolithiasis had a Brier score of 0.058 but coincidentally the Cragg & Uhler's R² is the same as in the first model at about 79.6%. The discrimination measure showed that the 100% of sensitivity (95%CI 90-100) was not consistent with the specificity at only 75% (95%CI 42.8-94.5) with a PPV of 92.1 (95%CI 78.6-98.3) and NPV of 100% with a 95%CI 66.4-100.

The calibration of all three models by the E:O ratio is 1.000 meaning the ratio of predicted accuracy (E) to actual accuracy (O) is 1.000 indicating that the model predicts accurately or predictions closely match the actual outcomes. CITL is 0.000 meaning a phenomenon that is fully independent of discrimination value is 0.000. This could suggest that the first model and last model are well-calibrated including being balanced and unbiased on a large scale. However, the second model was -0.000 but the discrimination will be unaffected and calibration slope is 1.000 indicating the model calibration is perfect without any bias or adjustment needed as shown in Fig. 2.

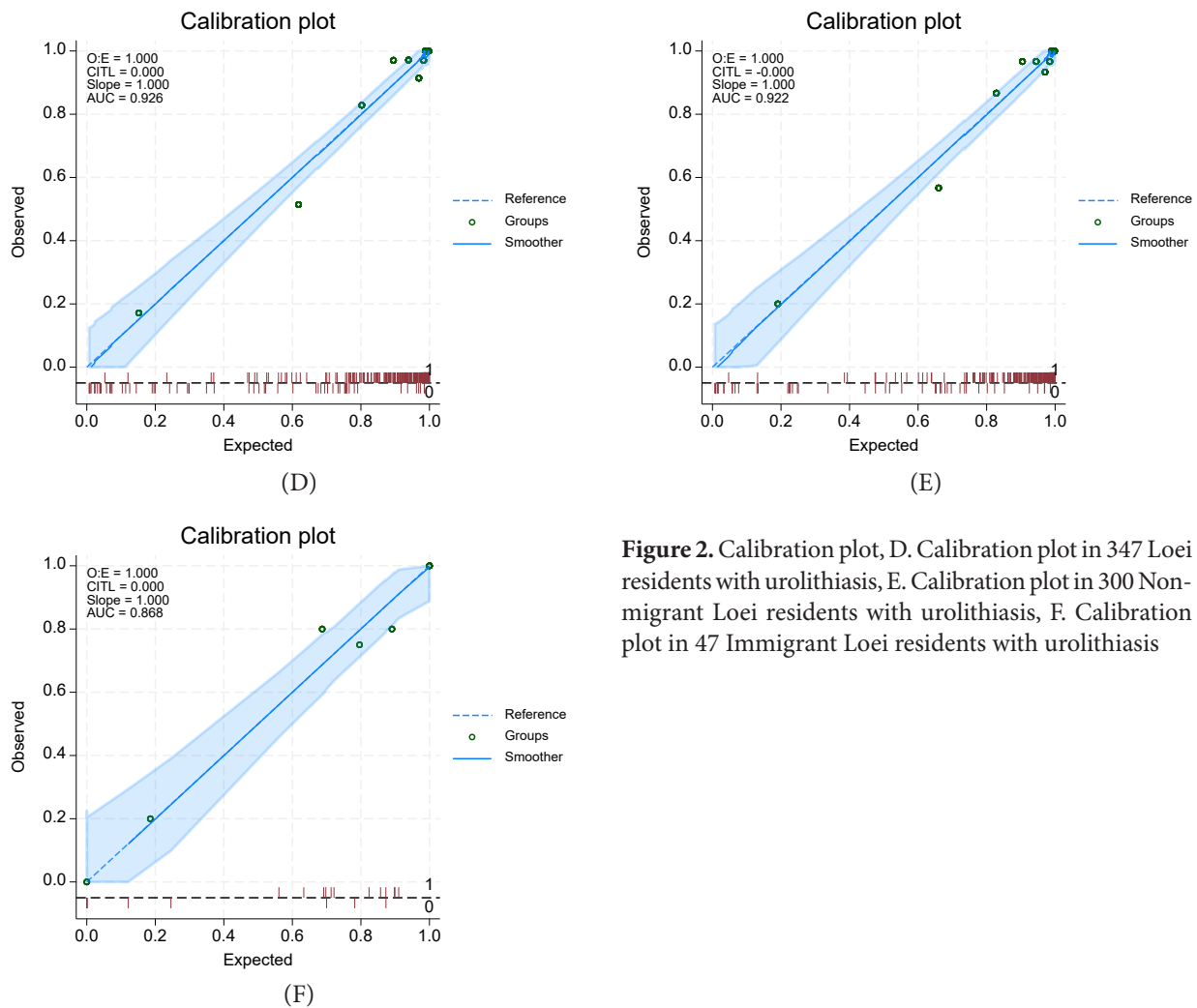


Figure 2. Calibration plot, D. Calibration plot in 347 Loei residents with urolithiasis, E. Calibration plot in 300 Non-migrant Loei residents with urolithiasis, F. Calibration plot in 47 Immigrant Loei residents with urolithiasis

Discussion

Loei has a very high prevalence of urolithiasis patients⁵ which is negatively associated with health and expenditures. To decrease the cost and prevalence of urolithiasis, prevention and control of stone formation are important factors.

Todate many studies have identified predictors for the recurrence of stone after the first episode^{6,7} However, there is limited research into screening for primary prevention of stone formation. One notable study in this regard is by Okita et al., which introduced a nomogram for the prediction of potential candidates for stone episodes.⁸ This nomogram suggests an optimal cut-off value for the probability of a stone episode (>28%), demonstrating a sensitivity of 79%, a specificity of 76%, and an area under the curve of 0.860, indicating satisfactory discrimination for screening of a population. Based on the current data, it is apparent that multiple risk factors are linked to stone formation. This observation in-

dicates that each geographical area may have distinct risk factors contributing to the occurrence of stones.⁹ Hence, we conducted a study utilizing the SPS for screening Loei urolithiasis patients.

This study found that among the 347 Loei patients with urolithiasis, the predictive model demonstrated good discrimination ability and calibration in an external validation setting. The accuracy of the model showed an AUC of 92.6% (95%CI 88.9-96.3). Overall performance measured by Brier score was 0.0072 while Cragg & Uhler R^2 about 79.6% with discrimination measurement, a sensitivity of 96.9% (95%CI 94.2-98.6), a specificity of approximately 53.4% (95%CI 39.9-66.7), a positive predictive value of 91.2% (95%CI 87.5-94.1) and a negative predictive value of 77.5% (95%CI 61.5-89.2).

Additionally, when analyzing subgroups within the Loei urolithiasis population, including non-migrants we found the Brier score to be 0.068 whereas Cragg & Uhler's R^2 was less than

the first model at 56.7%. This model had a high sensitivity of 97.6% (95%CI 94.9-99.1) but poor specificity of about 50% (95%CI 34.9-65.1) while the PPV and NPV were 91.5% (95%CI 87.5-94.5), and 79.3% (95%CI 60.3-92), respectively. Analysis of the immigrant Loei patients showed a Brier score of 0.058 but coincidentally the Cragg & Uhler's R^2 is the same as in the first model at about 79.6%. The discrimination measures were 100% sensitivity (95%CI 90-100) and a lower specificity of 75% (95%CI 42.8-94.5), a PPV of 92.1 (95%CI 78.6-98.3) but a NPV of 100% but wide of 95%CI 66.4-100. In summary, we suggest that these models still exhibited good discrimination ability and calibration.

These results suggest that the SPS may be applied effectively in the northeastern region of Thailand, especially in the Loei province. The extended area outside Loei is due to similar dining habits and traditions in other provinces in the northeast.

One limitation of our study is that its cross-sectional nature only provides a snapshot of a population at a specific point in time, without a longitudinal follow-up., however, the aim of the study was to validate a scoring system which had been developed in previous research so that in this case the cross-sectional approach was valid.

Conclusions

The external validation of SPS for the Screening of Urolithiasis Patients in Loei showed that the screening process exhibits excellent discrimination and calibration. The overall performance of the models was validated with a high degree of accuracy. This model can be used as a screening tool to identify individuals at risk of developing urolithiasis in the Loei region.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Efficacy of *Orthosiphon aristatus* (Cat's Whiskers) and an alpha-blocker for stone expulsion in patients with urinary tract calculi undergoing extra corporal shockwave lithotripsy

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Keywords:

Extra corporal shockwave lithotripsy, ESWL, treatment success rate, stone free rate; *Orthosiphon aristatus*, Cat's Whiskers, alpha-blockers

Abstract

Objective: To evaluate the efficacy of a herbal treatment, *Orthosiphon aristatus* (Cat's Whiskers) and alpha blockers with regard to stone free and treatment success rates in patients with urinary tract calculi undergoing extra corporal shockwave lithotripsy (ESWL).

Materials and Methods: Data pertinent to 84 patients who underwent ESWL for treatment of KUB stones were prospectively analyzed. Patients were randomized into two groups: Group 1: patients received the medicinal herb *Orthosiphon aristatus* post ESWL and Group 2: patients received an alpha-blocker (Doxazocin 2 mg) post ESWL. Both groups used the same medication throughout the 3-month period of the study. All patients were followed-up every 2 weeks after ESWL for 3 months with x-ray and blood tests and urine tests to evaluate results and complications.

Results: The stone free rate was 47.6% in the medical herb *Orthosiphon aristatus* group and 45.2% in the alpha-blocker group. Treatment success rates were 69.0% in the *Orthosiphon aristatus* group and 54.8% for alpha-blockers group. The differences in stone free rate and treatment success rate were not statistically significantly different ($p = 0.827, 0.261$) and the rate of complications in the *Orthosiphon aristatus* group was not statistically significantly different from the other group ($p = 1.000$).

Conclusion: Treatment with *Orthosiphon aristatus* medical expulsive therapy after ESWL give similar results of stone free rate as the group taking alpha-blockers. Both treatments are equally safe methods of medical expulsive therapy.

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Introduction

Extracorporeal shock wave lithotripsy (ESWL) has been used as a treatment of urolithiasis since 1980.¹ As a minimally invasive

procedure, the efficacy of ESWL is accepted worldwide especially in the treatment of small renal or ureteric calculi.² However, some patients require repeat ESWL treatment due to the failure

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or limitation of stone fragmentation. The success of ESWL treatment depends on several factors including stone size, stone number, stone composition, and renal function. The success rate of ESWL has a wide variation ranging from 46% to 91%.³⁻⁸ The results of ESWL are measured by taking into consideration stone fragmentation and clearance, which have been found to be influenced by certain predicting factors such as stone size, stone location, skin-to-stone distance (SSD), stone composition, severity of obstruction, urinary tract anatomy, obesity, and ESWL machine type.⁹⁻¹⁷ Greater success of ESWL was observed in cases of patients aged ≤ 40 years, with a stone size of ≤ 10 mm, a stone surface area of ≤ 50 mm and a location in the upper calyx.¹⁸

The main mechanism employed is the cavitation phenomenon. When a shock wave generated by an extracorporeal shock wave lithotripter interacts with a solid, it can produce cavitation bubbles at the interface between the solid and the surrounding liquid. The implosion of the cavitation bubbles plays an important role in the disintegration of the stone

Other studies related to Orthosiphon aristatus (Cat's Whiskers)

One study was carried out in patients with renal stones with patients taking an Orthosiphon aristatus (Cat 'Whiskers) infusion every day 3 times a day for 2-6 months. The results were promising. In 23 cases the size of stones reduced, 40% of the stones were expelled, and the symptoms improved by 20%.¹⁹ Another study into the effect of cat's whisker grass in reducing the size of kidney stones in an area in the North-east of Thailand also showed promising results.²⁰ One report described a study into the treatment of kidney stones in patients who were given a decoction prepared from dried Cat's whisker grass leaves. The concentration of the solution was 0.5% and patients were given 300 ml once a day for 1-10 months. Nine cases were found to have a good clinical response. It was found that the patient's urine was more alkaline, which suggests that it should help to reduce the occurrence of uric acid stones. An increase in uric acid excretion was also noted after consumption of a tea prepared from Orthosiphon grandifloras.²¹ Recently, a study showed a reduction in stone size in patients which was probably related to an increased excretion of calcium and uric acid.²² In *in vitro* experiments

it was shown that the antilithogenic activity of grandiflorus might be due to its diuretic activity.

It has also been demonstrated that methoxyflavonoids from Orthosiphon act as antagonists at adenosine A₁ receptors. Some studies revealed that adenosine A₁ receptor antagonists can induce diuresis and sodium excretion.²³ Since adenosine A₁ receptors are expressed in the afferent arterioles, glomerulus, proximal tubules, and collecting ducts adenosine antagonists could directly inhibit sodium reabsorption in the proximal tubules or indirectly by promoting afferent arteriole dilatation.²⁴

Other studies related to alpha-blockers

The giving of an alpha-blocker after shock wave treatment to break up kidney stones appears to clear the fragments faster in more people and reduce the need for extra treatments. It has been shown that alpha-blockers might cause fewer unwanted events than usual care or a placebo.²⁵

There is a modest increase in stone-free rates in those receiving alpha-blockers following ESWL, with a reciprocal modest risk reduction for steinstrasse (stone street), pain and auxiliary procedures. However, alpha-blockers do not reduce the risk of requiring retreatment.²⁶

This study was the first study in patients with urinary tract stones who have taken Orthosiphon aristatus after treatment with ESWL. The aim of the study is to compare stone free rate, treatment success and prevalence of complications between treatment with the medicinal herb Orthosiphon aristatus and alpha blockers following ESWL. The hypothesis is that the herbal treatment in combination with ESWL improves the stone free rate to the same extent as alpha-blockers in combination with ESWL

Materials and Methods

A prospective, randomized, trial was conducted between July 2024 and September 2024 at Uttaradit Hospital. This study was approved by the Ethics Committee of Human Research (ECID: 4 /2567) and approved by the Ethics Committee for Research in Human Subjects in the Fields of Thai Traditional and Alternative Medicine (TAMEC)

From the original cohort 90 patients, 6 patients were excluded due to loss of follow up, the remaining 84 patients were enrolled in the study. All patients had radiopaque renal or ureteric



calculi. Written consent was given by all participants. Demographic data including age, sex, body mass index (BMI), stone size, and stone location were noted. As shown in Table 1, the patients were randomly divided into 2 groups. In the first group (Herbal Medicine group), the patients received Orthosiphon aristatus in the form of 500 mg capsules with 2 capsules being taken twice a day after the ESWL session and then the herbal treatment was continued to the end of the study. In the second group, the patients were given 2 mg Doxazocin before bed time after each ESWL session. Blood pressure, and oxygen saturation were monitored during the procedures.

All patients given ESWL were treated as outpatients under intravenous analgesia; pethidine 25 mg. A SEIMEN model MODULARIS machine was used for the ESWL, with 3,000 shots of shock waves given at the rate of 60-90 shockwaves/minute with the energy beginning at 8 and progressing up to 15 kilovolts. Patients were followed up at the outpatient department every 2-3 weeks after ESWL for 3 months with a plain film kidney ureter bladder (KUB) x-ray. ESWL was repeated if no stone fragmentation occurred or residual stone fragments were larger than 4 mm. Patients were permitted a maximum of 3 sessions of ESWL, 2-3 weeks apart. The primary outcome was stone free rate at 3 months after ESWL.

Stone free was defined as the complete clearance of stone or no visible stone seen on plain film KUB. Clinically insignificant residual fragments (CIRF) was defined as residual fragments of stone 4 mm or less on plain film KUB. The secondary outcome was the treatment success rate, defined as the complete clearance of stone (stone free) or CIRF on plain film KUB after 3 months. Inclusion criteria were patients above 18 years old, with a radiopaque renal or ureteric calculi size over or equal to 4 mm. The exclusion criteria were patients who were pregnant, suffered from uncontrolled coagulopathy, or urinary tract infection, and those with Diabetes mellitus and heart disease.

Statistical analysis was carried out using Statistical Package for Social Sciences STATA V 16.0 by Stata Corp. Categorical variables were compared using the Chi-square test. Continuous data are presented as mean and standard deviation (SD), which were compared using a Fisher's exact test

Results

A total of 84 patients were enrolled onto the study and randomly divided into two groups, 42 patients being allocated into each arm. There were no statistical differences between the 2 groups with regard to age, sex, BMI, stone size and stone location (Table 1).

The mean ages of the Orthosiphon aristatus group and the alpha-blocker group were 58.8 years and 55.9 years respectively, p -value 0.528. The mean BMI of the Orthosiphon aristatus group and the alpha-blocker group were 24.2 kg/m² and 24.9 kg/m² respectively, p = 0.370. The mean size of the stones in the Orthosiphon aristatus group and the alpha-blocker group were 1.61 mm and 1.32 mm respectively, p = 0.248. Fifty-two patients (61.90%) had a renal stone and thirty-two patients (38.09%) a ureteric stone. Patients with renal stones in the Orthosiphon aristatus group and the alpha-blocker group numbered 27 patients (64.9%) and 25 patients (59.5%) respectively. Patients with ureteric stone in the Orthosiphon aristatus group and the alpha-blocker group totaled 15 patients (35.71%) and 17 patients (40.47%) respectively.

There was no statistical difference between the stone free rate of the Orthosiphon aristatus group and the alpha-blocker group (p = 0.227). The overall treatment success rate in the Orthosiphon aristatus group was not significantly higher than in the alpha-blocker group (69.0% vs 54.8%, p = 0.261) (Table 2).

When we analyzed complications associated with treatment, it was found that there were no significant differences between the two sample groups as regards complications (p = 1.000). The specific complications in the Orthosiphon aristatus group were 13 (30.9%) gross hematuria and 7 (16.7%) colicky pain whereas in the alpha-blocker group they were 13 (30.9%) and 8 (19.1%) (Table 3).

Two patients (4.7%) in each group were treated with ureterorenoscopy to remove residual stones, 2 patients (4.7%) in the Orthosiphon aristatus group required a transurethral procedure for removal of a stone from the bladder after failure to pass spontaneously through their urethra, the same number required ureterorenoscopic lithotripsy in the alpha-blocker group. There were no significant differences in any of the auxiliary treatments (Table 4).

Table 1. Demographic data

General Data	Orthosiphion aristatus (n=42)	Alpha-blocker (n=42)	P-value
Gender			
Male n (%)	26 (61.9)	31 (73.8)	0.175
Female n (%)	16 (38.1)	11 (26.2)	
Age (years) (mean±SD)	(58.8±10.8)	(55.9±11.7)	
Body mass index (BMI) (kg/m ²) (mean±SD)	(24.2±3.9)	(24.9±3.6)	
Underlying disease			
Yes n (%)	25 (59.5)	24 (57.1)	1.000
No n (%)	17 (40.5)	18 (42.9)	
GFR (ml/min/1.73 m ²)			
<60 n (%)	7 (16.7)	1 (2.4)	0.188
60-89 n (%)	27 (64.30)	29 (69.0)	
>90 n (%)	8 (19.0)	12 (28.6)	
(mean±SD)	(74.9±17.5)	(91.2±75.9)	
Stone size (cm) (mean±SD)	(1.61±0.5)	(1.32±0.6)	0.248
Stone position			
Upper calyx n (%)	6 (14.3)	4 (9.5)	0.815
Middle calyx n (%)	4 (9.5)	2 (4.8)	
Lower calyx n (%)	8 (19.1)	10 (23.8)	
Renal pelvis n (%)	5 (11.9)	7 (16.7)	
Other n (%)	19 (45.2)	19 (45.2)	

SD = standard deviation

Table 2. Outcomes of the study

	Orthosiphion aristatus (n=42)	Alpha-blocker (n=42)	P-value
Stone free n (%)	20 (47.6)	19 (45.2)	0.827
CIRF* n (%)	9 (21.4)	4 (9.5)	0.227
Treatment success** n (%)	29 (69.0)	23 (54.8)	0.261

*Clinically Insignificant Residual Fragment (CIRF) is residual stone fragment less than or equal to 4 mm after treatment, **Treatment success defined as stone free and CIRF in combination

Table 3. Complications associated with treatment

Complications	Orthosiphion aristatus (n=42)	Alpha-blocker (n=42)	P-value
UTI n (%)	0 (0)	1 (2.8)	1.000
Persistent gross hematuria n (%)	13 (30.9)	13 (30.9)	1.000
Stone street with colicky pain n (%)	7 (16.7)	8 (19.1)	1.000
Serum potassium level n (%) (>5.0 ng/dl) (mean±SD)	0 (0.0)	0 (0.0)	1.000

SD = standard deviation

Discussion

ESWL is the treatment of choice for urolithiasis with small size stone, due to the minimally invasive nature of the procedure. The mechanisms involved in ESWL treatment for stone disintegra-

tion are compressive fracture, spallation, acoustic cavitation, and dynamic fatigue, of which cavitation is the most important.^{27,28}

There were several factors found which could interfere with the success of ESWL treatment, for

Table 4. Auxiliary procedures

Procedures	Orthosiphon aristatus (n=42)	Alpha-blocker (n=42)	P-value
URSL n (%)	0 (0)	2 (4.7)	0.114
TUL n (%)	3 (7.1)	0 (0.0)	
PCN or ureteral stent indwelling n (%)	0 (0.0)	0 (0.0)	
Open surgery n (%)	0 (0.0)	0 (0.0)	

URSL = ureterorenoscopic lithotripsy, TUL = transurethral lithotripsy, PCN = percutaneous nephrostomy

example, in stone related factors stone size, stone number, stone composition, and in patient related factors intrarenal anatomy or stone location especially in the case of lower caliceal stones. Therefore, the choice of treatment which is the minimally invasive, while treating the condition effectively in each patient is an important issue that urologists should consider.

The findings of many studies currently being carried out will improve ESWL outcomes and promote a higher success rate of treatment for the maximum benefit for urolithiasis patients. This will ultimately mean that in more and more cases invasive surgery can be avoided.

The use of many medicinal herbs post-ESWL has resulted in improvements in outcomes of treatment. For example *Andrographis paniculata* tablets were shown to be beneficial in the treatment of post-ESWL urinary tract infection. In this study post-ESWL pyuria and hematuria in patients were significantly reduced after receiving *Andrographis paniculata* when compared to pre-ESWL values.²⁹

Muangman et al. conducted a study on patients with Renal stones in Ramathibodi Hospital by having patients take an *Orthosiphon aristatus* infusion every day 3 times a day for 2-6 months. The results were promising. The size of 23 stones decreased, 40% of the stones fell off, and the symptoms improved by 20%. Premkamol et al. has studied the effect of *Orthosiphon aristatus* in reducing the size of kidney stones, and found that *Orthosiphon aristatus* can reduce the size of renal stones. Chronic symptoms including tightness of the stomach, waist pain, joint pain, fatigue, headache, lateral burning, and leg pain have all been alleviated in patients after treatment with *Orthosiphon aristatus*. From the results of the study, it was shown that *Orthosiphon aristatus*

could contribute to the reduction of the size of kidney stones and that it was also good for patients with kidney stones who have suffered from physical torture and mental suffering, and also have insufficient money for medical expenses.¹⁹

Based on the current best evidence, this alpha-blocker may improve stone clearance and reduce auxiliary treatments and major adverse events after ESWL.²⁹

In our study, there was no statistically significant difference in overall stone free rate between the *Orthosiphon aristatus* group and the alpha-blocker group ($p = 0.827$), but the results did show that CIRF in the *Orthosiphon aristatus* group were closer to significance than in the control group ($p = 0.227$). It is reasonable to assume that if the period of follow up were longer, some CIRF may be passed and incidence of the stone free rate may increase over time.

The treatment success rate (stone free rate and CIRF) was not significantly higher in the *Orthosiphon aristatus* group than in the alpha-blockers group (69.0%: 54.8%, $p = 0.261$).

Conclusions

In this study treatment with *Orthosiphon aristatus* did not result in a significant difference in the improvement of the stone free rate or treatment success rate after ESWL in this study in comparison with the alpha-blocker.

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Conflict of Interest

The authors declare no conflict of interest.

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Review Article

First implantation: preparation, setup and implantation for malleable penile prosthesis

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Keywords:

Implantation, preparation, set up, malleable, penile prosthesis

Abstract

Treatment for erectile dysfunction (ED) is becoming more common in Thailand. The spectrum of treatment varies from non-invasive techniques such as medication, to counseling for invasive treatment such as injection and finally to penile prosthesis implantation. As the demand for penile implant surgery increases it is increasingly crucial to ensure thorough preparation and patient care in order to minimize the risk of harmful complications, for example device infection. This review article aims to provide guidance on various aspects of the surgical process, including pre- and intra-operative patient preparation, essential equipment and supplies, and step-by-step surgical techniques. It also offers key pointers for post-operative care. This article may be valuable for those looking to start performing penile prosthesis surgery or for those seeking to improve their current practices. Literature was reviewed from PubMed and Google scholar databases. This article provides crucial information on patient selection, pre-operative counseling, surgical setup and technique, and post-operative care for malleable penile prosthesis implantation. A penile prosthesis is an excellent option for men with refractory ED as opposed to medical treatment or with contraindications to medical management. However, this operation is still relatively uncommon in Thailand. Malleable prostheses offer advantages including being cost-effective, having a low risk of malfunction, and being easier to implant in comparison to inflatable implants. This review aims to encourage, reassure, and convince new implanters to complete all spectrums of ED treatment.

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Introduction

Roughly one-third of patients with erectile dysfunction (ED) (30-35%) may not experience positive results from treatment with phosphodiesterase-5 inhibitors (PDE5i).¹ Challenges such as insufficient dosage, inappropriate dose adjustments, and titration may explain this lack of

response. Despite proper use of PDE5i, some ED patients may still not respond.² Aging, advanced cardiovascular issues, uncontrolled diabetes, metabolic syndrome, late-onset hypogonadism, and previous pelvic surgeries are known factors that can significantly decrease the effectiveness of PDE5i treatment for ED.³

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Penile prosthesis implantation is becoming an increasingly popular treatment option for men with refractory ED and is being performed internationally by urologists. However, this operation remains relatively rare in Thailand. A known issue in surgical training is that many trainee surgeons lack exposure to practical surgical training. Unfortunately, there is no simulation or cadaveric model available to supplement the training of residents, fellows, and low-volume penile prosthesis surgeons to enhance their procedural knowledge and confidence in penile prosthesis placement.

The malleable penile implant is often considered to result in lower levels of satisfaction compared to the three-piece inflatable penile prosthesis implant.⁴ However, it possesses unique benefits, including ease of use and being more cost effective, and is also associated with fewer mechanical complications than inflatable prostheses. A previous study showed that the malleable prosthesis can achieve excellent clinical outcomes in patients with both erectile dysfunction and Peyronie's disease.⁵ In a recent study, Habous et al.⁶ found that the size of the malleable penile implant (9.5 and 11 mm vs. 13 mm) does not significantly impact patient satisfaction (75.7% vs. 88.6%).

Additionally, a review of satisfaction rates for both the inflatable penile prosthesis (IPP) and malleable penile prosthesis (MPP) demonstrated that the average satisfaction rate for IPP and MPP were 86.2% and 75.1%, respectively.⁷ These findings can play crucial roles in decision-making for new implant surgeons and patients. This article provides details about patient selection and evaluation, pre-operative preparation, and also reviews different surgical techniques. The author hopes that this article will serve as a driving force to encourage, reassure, and convince new implanters.

Materials and Methods

Literature was reviewed using PubMed and Google Scholar databases. "Penile prosthesis", "Malleable penile prosthesis", "Surgical preparation penile prosthesis", "Surgical technique penile prosthesis" and "Complication penile prosthesis" were included in the search terms. Articles from well-known high-volume implanters, specifically Steven K Wilson, Tobias S Köhler, Paul Petit, Jean F Eid, and Daniar Qsmonov, and their references during 1980-2023 were selected for

extraction. The results are described in narrative fashion.

Results

Patient selection and evaluation

One of Dr. Wilson's favorite pieces of advice for novice implanters is, "NEVER IMPLANT A STRANGER." Implantation of a penile prosthesis is the most invasive and less frequently chosen option, but once these devices are placed, patients and their partners are generally satisfied with the resulting erections, as reported by Levine et al.⁸, with 96% of patients and 91% of partners expressing satisfaction. However, a negative outcome, or even a positive outcome with an unsatisfied patient, can have significant adverse physical and emotional effects on both the patient and the surgeon.

Before proceeding with penile prosthesis implantation, the implanter and the patient must consider various factors to determine whether the patient is a suitable candidate for an implant.

Dos for implant discussion

- Do document the failure or contraindication of treatment with Phosphodiesterase 5 inhibitors (PDE5i). Ensure that patients are aware of second-line treatments such as vacuum devices and intracavernous injections.

- Do ensure that patients fully comprehend the risks associated with infection. Primary procedures have infection rates ranging from 0.6% to 8.9%, with more complex procedures, such as excising Peyronie's plaques or implanting in severe corporal fibrosis, showing higher rates.^{9,10} Wilson and Delk¹¹ observed a staggering nine-fold increase in infection rates among spinal cord injury patients with implants. It is important for patients to recognize and act on any symptoms of infection, such as increasing pain at the surgical site or over prosthetic parts, fever, cellulitis, fluctuance around device components, and purulent drainage from the wound, particularly after pressing on implant parts. In cases of confirmed infection around an implant, removal of the entire device is necessary.

- Do discuss the issue of penile implant length. It is important to clarify that a penile implant will not make the penis longer. One major concern among patients who have undergone penile implants is the perceived decrease

in length compared to their natural erections when they were younger. According to a study by Devici¹², there were no significant differences in penile length after surgery when compared to preoperative measurements. However, it is essential for surgeons to effectively communicate with patients and manage their expectations. It should be emphasized that a prosthetic erection does not result in any engorgement or increase in glans size. Patients should also be informed that penile sensitivity, sexual desire, and ejaculatory function will not be affected by the surgery.^{13,14}

- Do inform patients about the choice of implant. Malleable devices are the easiest to implant, are cost-effective, simple to use, and require less technical skill and surgical knowledge for implantation. However, they may not be the best choice for patients with a short penis because the implant tends to cause the penis to stick out from the body's plane and may not provide sufficient length for bending the organ. In the long term, the implant can compress the erectile tissue in the corporal body and create a "finger in the glove" appearance. Three-piece inflatable devices are more realistic and result in high satisfaction rates, however they require patients to practice operating them and demand greater surgical skill for implantation. In 12 studies (20,161 patients; median age 57 years), survival of an IPP device was 93.3% at 1 year, 91.0% at 3 years, 87.2% at 5 years, 76.8% at 10 years, 63.7% at 15 years, and 52.9% at 20 years.¹⁵

Patient non-psychological factors

There are various factors that can affect the success of surgery, specifically the severity of any underlying condition, previous procedures having been performed on the surgical site, any co-morbidities (such as diabetes, cardiovascular or pulmonary diseases) and medication that may hinder healing. It is crucial to carefully consider these factors and assess the potential risks and benefits of undergoing surgery. However, patients with poorly controlled diabetes should not automatically be excluded from surgery for the rest of their lives. Instead, it may be more logical to have a discussion with the patient about the possibility of a higher risk of infection compared to someone without diabetes or with well-controlled diabetes, and then allow the patient make an informed decision. Habous et al.¹⁶ found that

in 902 patients (685 MPP, 217 IPP), the mean HbA1c level was 8.0%, with 81% of men having a HbA1c level of >6%. The overall infection rate was 8.9% (80/902). Using ROC analysis, they determined that an HbA1c threshold level of 8.5% predicted infection with a sensitivity of 80% and a specificity of 65%.

Preoperative preparation

The best practice statement of the American Urological Association recommends the use of two intravenous (IV) antibiotics before incision, specifically an aminoglycoside in combination with either a 1st or 2nd generation cephalosporin or vancomycin.¹⁷ The Center for Disease Control and Prevention (CDC) recommends that hair not be removed unless it will interfere with the operation, and if hair is to be removed it is done immediately before the operation with electric clippers rather than shaving.¹⁸ Chlorhexidine scrub solution needs to be used for preoperative skin preparation. Unlike iodophor-based preparations, chlorhexidine is not inactivated by blood or serum proteins, and it has been demonstrated that it has a greater residual activity than traditional povidone-iodine after a single application.¹⁹

Equipment and procedure setup

- Position: The patient is positioned supine in a modified "frog-legged" position.

- Skin Preparation: Prior to penile implant surgery, the skin is prepared by scrubbing with a Chlorhexidine solution for 5-10 minutes.²⁰ This step, performed by the surgeon or assistant, involves hand-scrubbing and donning sterile gown and gloves for optimal hygiene. The skin is prepped from the belly button to the upper thigh, with lateral areas extended to the flanks and thighs for thorough coverage.

- Hand scrub duration: Optimum hand scrub duration has been studied in orthopedic surgeons who carried out long duration hand scrub prior to total joint replacement surgery.²¹ In the case of arthroplasty procedures lasting less than 90 minutes surgical hand disinfection using Hibiscrub for a 5 min. hand-scrub was equally as effective as one of 10 min. Longer procedures (more than 90 min.) colony counts were significantly higher on subjects who had scrubbed for 10 min than on those who only scrubbed for 5 (p < 0.05). This data needs to inform the procedures

in penile prosthesis implantation as well.

- **Foley catheter:** To facilitate bladder emptying and assist in locating the urethra during the procedure, a Foley catheter is inserted after the surgical site is draped. Additionally, the incision is isolated from the surrounding skin using 3M Ioban.

- **Incision options:** Selecting the right incision for an implant is crucial. The three options, subcoronal, infrapubic, and penoscrotal, all have disadvantages and advantages.

Infrapubic incision: This technique results in less scrotal dissection/swelling but limits exposure in obese patients and increases the risk of dorsal nerve injury.

Subcoronal incision: Advantages are less discomfort postoperatively, and facilitates operation under local anesthesia. Disadvantages include limited exposure and intraoperative complications are difficult to correct (urethral injury, proximal perforation).

The penoscrotal approach: This offers optimal exposure for all patients, even those who are obese, it also poses a risk of scrotal manipulation resulting in discomfort and bruising. Despite this, the author's experience shows that this method is more convenient than others due to greater exposure and corporal length measurement, avoiding neurovascular injury and reducing intra operative complications. Penoscrotal incision is used in more than 80% of all placements of inflatable penile prostheses (IPPs) worldwide.²²

- **Incision preparation:** The penoscrotal skin is excised either vertically or transversely, and the overlying Dartos is dissected to expose the

corpora cavernosa with the urethra identified. To maintain the position of the penis cephalad, a Lone Star (Scott) retractor is used along with elastic stay hooks, which are loosely positioned at 5, 7, 11, and 1 o'clock, and tightly at 3 and 9 o'clock. (Fig. 1)

- **Absorbable Stay Sutures:** Absorbable stay sutures (Vicryl 3-0) are placed before the corporotomy. Corporotomies should be made as proximal as possible on the corpus cavernosa. However, corporotomies that are too proximal create an impossible angle for distal dilatation.

- **Corporal dilatation:** The procedure for corporal dilation commences with the use of Metzenbaum scissors to dilate the distal corpora cavernosa, with a lateral turning and angling motion (Fig. 2). A Brooks dilator, size 11 from Coloplast, Minneapolis, MN, USA, is then carefully passed through both distal and proximal regions, staying consistently lateral. The aim is to extend into the mid-glans distally and the lateral crux of the corpora proximally, until reaching the inferior pubic ramus. To protect the fossa navicularis during distal dilation, the surgeon should use their non-dominant hand to bend the glans contralaterally while dilating with their dominant hand. Each side is then sequentially dilated using Brooks dilators until the implant reaches the desired size (9.5, 11, and 13 mm).

- **Measurement Tests:** There are two tests to ensure accurate measurement. The "field goal test" involves placing two Brooks dilators proximally inside the corpora with comparisons being made regarding their depth and angle to check for

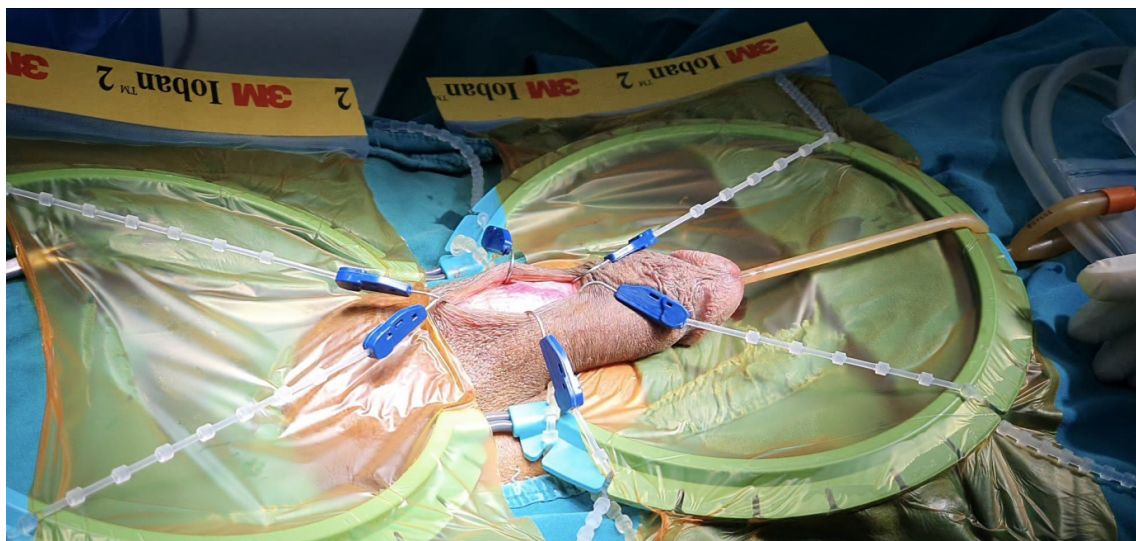


Figure 1. Penoscrotal incision. 6 Stay hooks with Lone star retractor.

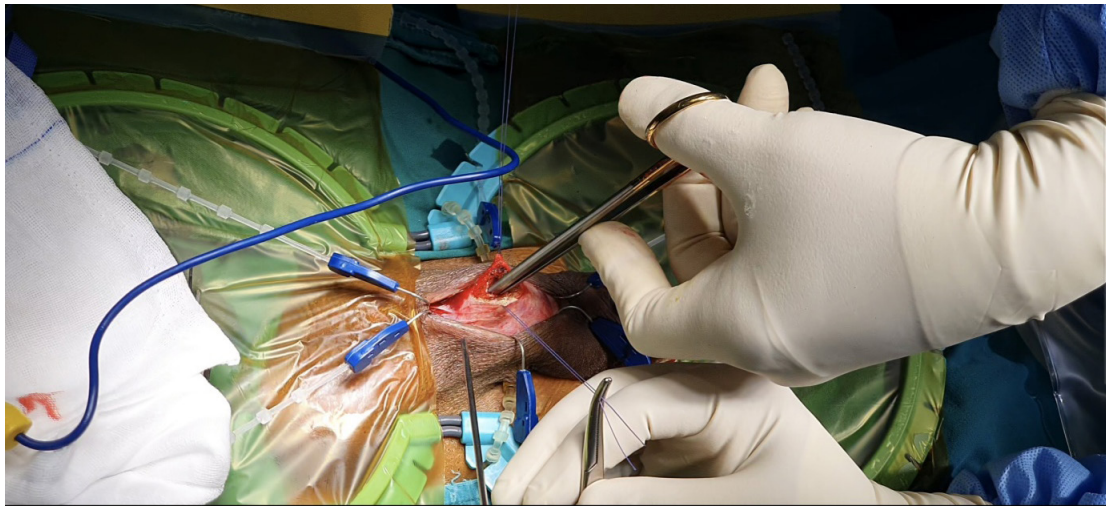


Figure 2. Corporal dilatation begins with distal corpora cavernosa dilation using Metzenbaum scissors turned and angled laterally.



Figure 3. Field Goal test.

crossover or perforation (Fig. 3). The “distal fluid challenge test” involves inserting a filled Asepto syringe into the corporotomy and injection from the syringe distally.

A failed test will result when fluid shoots out around the Foley catheter at the meatus, indicating a perforation into the urethra. If there is no false dilatation, corporal measurement needs to be performed with a Furlow dilator proximally and distally.

Implant preparation

The Coloplast Genesis® and Boston Scientific Tactra® are two comparable implant options. Both allow for the proximal end to be trimmed and end caps to be added in order to achieve the desired length. However, the Coloplast Genesis®

stands out by offering a hydrophilic coating, which enables rapid absorption of antibiotics into the implant when submerging it in an antibiotic solution.²³ To ensure proper infection prevention, an additional 1,000 ml of injectable saline mixed with 500 mg vancomycin and 80 mg gentamicin needs to be kept nearby and used for irrigation and instrumentation submersion throughout the procedure. It's worth noting that the effectiveness of this antibiotic irrigation technique has not yet been fully explored through a prospective, randomized trial.²⁴ Once the appropriate rod and rear tip extenders (RTE) have been selected, it's recommended to use the shortest RTE possible when placing the implants into the corporal body. Implants need to be placed into corporal bodies. The implant should be sized so that there

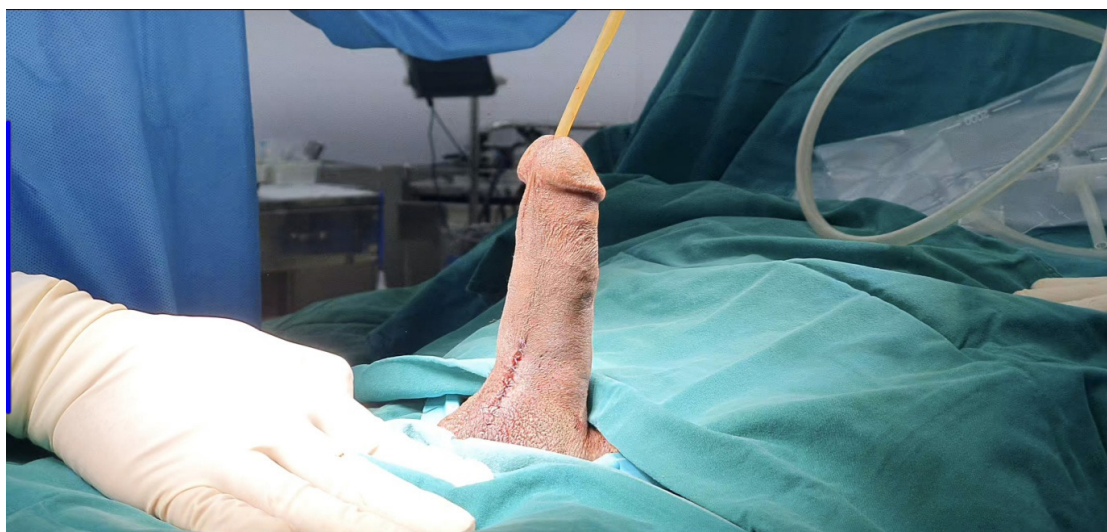


Figure 4. Implant fitted to corporal length. Incision closed.

is not excessive pressure on the glans of the penis which could lead to pain and give potential for erosion (Fig. 4).

To secure the closure of the corporotomy, the stay sutures on both sides need to be carefully tied in a horizontal mattress style. In the event that any part of the cylinder is visible, additional sutures are needed to fully close the corporotomy without disturbing the cylinders. The use of absorbable sutures allows for a multi-layered closure. Another advancement in penile lengthening techniques is ventral phalloplasty, where the penoscrotal web is removed during implantation.²⁵ The use of a drain after IPP implantation is a topic currently under debate and requires further investigation.²⁶ However, a study by Osmonov et al.²⁷ found that the placing of a scrotal drain for 72 hours following the surgery significantly reduces the rates of hematoma and infection compared to no drain placement.

Postoperative care

Köhler/Wilson's protocol

Patients are admitted for 24 hours for observation. On the morning after surgery the catheter and drain need to be removed. Recommended medication involves 10 days of a post operative antibiotic, and NSAIDs or opioids also given as required. Local wound dressing with normal saline solution needs to be carried out once daily with the wound being wrapped with sterile gauze. Showers or any submergence in water need to be avoided until the wound is completely healed. Patients are encouraged to place the penis in the upright position in underwear for 3 months to

allow the capsule to form around the implants, hence ensuring the implant erection is in the upward position. Patients need to be informed about indicators of infection, especially with regard to severe pain, discharge, swelling or fever.

Conclusion

Penile prosthesis surgery requires significant preparation on behalf of both surgeon and patient, comprising a series of steps that begin before the patient even arrives at the hospital and extending throughout the pre- and intra-operative stages. To ensure success, the surgeon must have access to the appropriate instruments, have a meticulously arranged aseptic operating room, skillfully execute the surgical technique and ensure appropriate post-operative care. These critical factors significantly impact the ease of the procedure and ultimately contribute to improved outcomes for the patient.

Conflict of Interest

The author declares no conflict of interest.

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Review Article

Mind the gap in kidney care: translating what we know into what we do

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Abstract

Historically, it takes an average of 17 years to move new treatments from clinical evidence to daily practice. Given the highly effective treatments now available to prevent or delay kidney disease onset and progression, this is far too long. The time is now to narrow the gap between what we know and what we do. Clear guidelines exist for the prevention and management of common risk factors for kidney disease, such as hypertension and diabetes, but only a fraction of people with these conditions worldwide are diagnosed, and even fewer are treated to target. Similarly, the vast majority of people living with kidney disease are unaware of their condition, because in the early stages it is often silent. Even among patients who have been diagnosed, many do not receive appropriate treatment for kidney disease. Considering the serious consequences of kidney disease progression, kidney failure, or death, it is imperative that treatments are initiated early and appropriately. Opportunities to diagnose and treat kidney disease early must be maximized beginning at the primary care level. Many systematic barriers exist, ranging from patient to clinician to health systems to societal factors. To preserve and improve kidney health for everyone everywhere, each of these barriers must be acknowledged so that sustainable solutions are developed and implemented without further delay.

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Introduction

At least 1 in 10 people worldwide is living with kidney disease.¹ According to the Global Burden of Disease study, in 2019, >3.1 million deaths were attributed to kidney dysfunction, making it the seventh leading risk factor for death worldwide (Fig. 1 and Supplementary Fig. S1).² However, global mortality from all kidney diseases may actually range between 5 and 11 million per year if the estimated lives lost, especially in lower-resource settings, from acute kidney injury and from lack of access to kidney replacement therapy for kidney failure (KF) are also counted.³ These high global death rates reflect disparities in prevention, early detection, diagnosis, and treatment of chronic kidney disease (CKD).⁴ Death rates from CKD are especially prominent in some regions, and particularly high in Central Latin America and Oceania (islands of the South Pacific Ocean), indicating the need for urgent action.⁵

CKD also poses a significant global economic burden, with costs increasing exponentially as CKD progresses, not only because of the costs of dialysis and transplantation, but also because of the multiple comorbidities and complications that accumulate over time.^{6,7} In the United States, Medicare fee-for-service spending for all beneficiaries with CKD was \$86.1 billion in 2021 (22.6% of the total expenditure).⁸ Data from many lower-resource settings are absent, where most costs are paid for out of pocket. A recent study from

Vietnam reported that the cost of CKD per patient was higher than the gross domestic product per capita.⁷ In Australia, it has been estimated that early diagnosis and prevention of CKD could save the health system \$10.2 billion over 20 years.⁹

Although there is regional variation in the causes of CKD, the risk factors with the highest population-attributable factors for age-standardized CKD-related disease-adjusted life years were as follows: high blood pressure (51.4%), high fasting plasma glucose level (30.9%), and high body mass index (26.5%).¹⁰ These risk factors are also global leading risk factors for death (Fig. 1). Only 40% and 60% of those with hypertension and diabetes, respectively, are aware of their diagnosis, and far smaller proportions are receiving treatment and at target goals.^{11,12} Moreover, at least 1 in 5 people with hypertension and 1 in 3 people with diabetes also have CKD.¹³

A large proportion of CKD can be prevented through healthy lifestyles, prevention and control of risk factors, avoidance of acute kidney injury, optimization of maternal and child health, mitigation of climate change, and addressing social and structural determinants of health.³ Nevertheless, the benefits of some of these measures may only be seen in generations to come. In the meantime, early diagnosis and risk stratification create opportunities to institute therapies to slow, halt, or even reverse CKD.¹⁴ Concerningly, CKD awareness was strikingly low among individuals

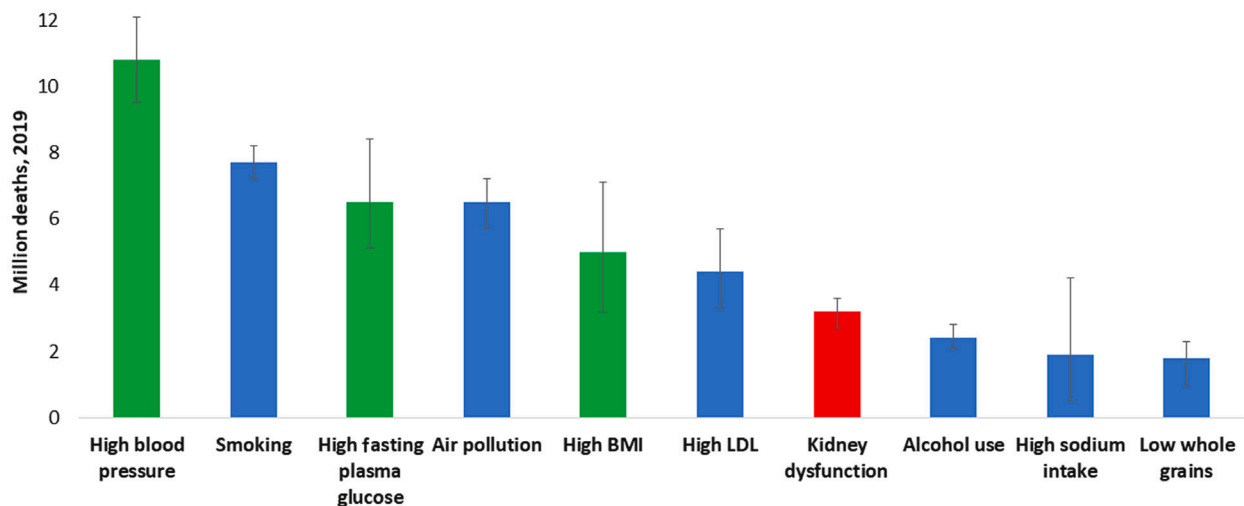


Figure 1. All ages, top 10 global risk factors for death, 2019. Kidney dysfunction (defined as estimated glomerular filtration rate <60 ml/min per 1.73 m² or albumin-to-creatinine ratio ≥ 30 mg/g) was the seventh leading global level 3 risk factor for death in 2019. The 3 leading global risk factors for kidney disease, including hypertension, diabetes, and overweight/obesity, are also leading global risk factors for death; therefore, holistic strategies are required to address all risk factors simultaneously. Ranking is depicted by millions of deaths attributed to the risk factors. Error bars depict the confidence range. Global ranking of kidney dysfunction stratified by World Bank income category and gender is shown in Supplementary Fig. S1. Data obtained from the Global Burden of Disease Study.² BMI = body mass index, LDL = low-density lipoprotein.

with kidney dysfunction, with $\approx 80\%$ to 95% of patients being unaware of their diagnosis across world regions (Fig. 2).^{15–20} People are dying because of missed opportunities to detect CKD early and deliver optimal care!

More important, CKD is a major risk factor for cardiovascular disease, and as kidney disease progresses, cardiovascular death and KF become competing risks.²¹ Indeed, the Global Burden of Disease study data from 2019 showed that more people died of cardiovascular disease attributed to kidney dysfunction (1.7 million people) than from CKD itself (1.4 million people).² Therefore, cardiovascular disease care must also be a priority for people with CKD.

Gaps between knowledge and implementation in kidney care

Strategies to prevent and treat CKD have been built on a strong evidence base over the past 3 decades (Fig. 3).^{19,22} Clinical practice guidelines for CKD are clear; however, adherence to these guidelines is suboptimal (Fig. 2).^{15,19,20}

Regardless of the cause, control of major risk factors, particularly diabetes and hypertension, forms the foundation of optimal care for CKD.^{19,23} Beyond lifestyle changes and risk factor control, the initial pharmacologic classes of agents proven to provide kidney protection were the renin-

angiotensin-aldosterone system inhibitors in the form of angiotensin-converting enzyme inhibitors (ACEIs) and the angiotensin receptor blockers.^{14,19} However, despite decades of knowledge that these medications have important protective effects on kidney and heart function in people with CKD, their use has remained low based on real-world data from electronic health records (Fig. 2). For example, in the United States, ACEI or angiotensin receptor blocker use was reported in the range of 20% to 40% at ≥ 15 years after the last approvals of these agents for patients with CKD and type 2 diabetes.²⁴ Although more recent data show improvement in prescribing rates to 70% in this population, just 40% persist on an ACEI or angiotensin receptor blocker for at least 90 days.²⁰ These data illustrate gaps in both prescribing kidney protective medication and continuity of care over time, potentially related to cost, lack of patient education, polypharmacy, and adverse effects.²⁵

Although initial enthusiasm for sodium-glucose cotransporter 2 (SGLT2) inhibitors focused on their benefits for diabetes and cardiovascular disease, unprecedented therapeutic benefits have clearly been observed for CKD as well. The relative risk reductions with SGLT2 inhibitors approach 40% for substantial decline in estimated glomerular filtration rate, KF, and death in popu-

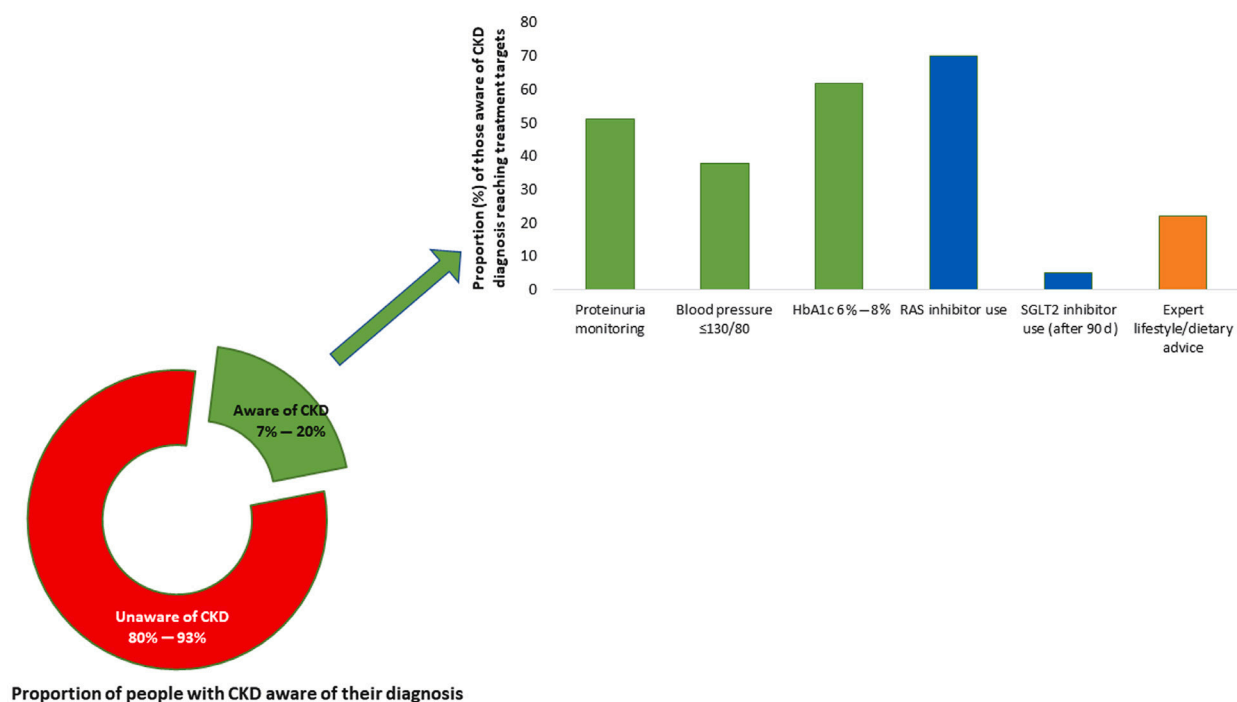


Figure 2. Proportion of people with chronic kidney disease (CKD) who are aware of their diagnosis and are receiving appropriate guideline-recommended care. The proportion of people with CKD who are aware of their diagnosis varies globally, with rates ranging from 7% to 20%. As CKD stage worsens, knowledge of CKD increases. Among those with a diagnosis of CKD, the average proportion of patients receiving appropriate medication to delay CKD progression (renin-angiotensin-aldosterone system [RAS] inhibitors and sodium-glucose cotransporter 2 [SGLT2] inhibitors) is suboptimal as are those reaching target blood pressure, diabetes control, and nutrition advice. The treatment targets depicted in the figure follow the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines.¹⁵ Most data come from higher-resource settings; these proportions are likely lower in lower-resource settings. Data are shown for proportions of patients reaching blood pressure of $<130/80$ mm Hg. Data compiled from previous studies.^{15–20} HbA1c = hemoglobin A1c.

lations with CKD of several causes, heart failure, or high cardiovascular disease risk.^{26,27} These benefits accrued on top of standard-of-care risk factor management and renin-angiotensin-aldosterone system inhibitor. Risks of heart failure, cardiovascular death, and all-cause mortality were also reduced in patients with CKD.²⁶ Addition of SGLT2 inhibitor to renin-angiotensin-aldosterone system inhibitors could delay the need for kidney replacement therapy by several years, depending on when they are started.²⁸ Moreover, for every 1000 patients with CKD treated with an SGLT2 inhibitor on top of standard therapy, 83 deaths, 19 heart failure hospitalizations, 51 dialysis initiations, and 39 episodes of acute kidney function worsening can be prevented.²⁹

Concerningly, marked underuse of these and other guideline-recommended therapies, including SGLT2 inhibitors, persists (Fig. 2).^{20,24} In the CURE-CKD registry, only 5% and 6.3%

of eligible patients with CKD and diabetes, respectively, continued on SGLT2 inhibitor and glucagon-like peptide-1 receptor agonist at 90 days.¹⁸ Notably, lack of commercial health insurance and treatment in community-based versus academic institutions were associated with lower likelihoods of SGLT2 inhibitor, ACEI, or angiotensin receptor blocker prescriptions among patients with diabetes and CKD.²⁰ In low- or middle-income countries (LMICs), the gap between evidence and implementation is even wider given the high cost and inconsistent availability of these medications, despite availability of generics.³⁰ Such gaps in delivering optimal treatment for CKD are unacceptable.

In addition to the SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists have been demonstrated to reduce the risks of CKD progression, KF, cardiovascular events, and deaths, on top of the standard of care with renin-angiotensin-aldosterone system inhibi-

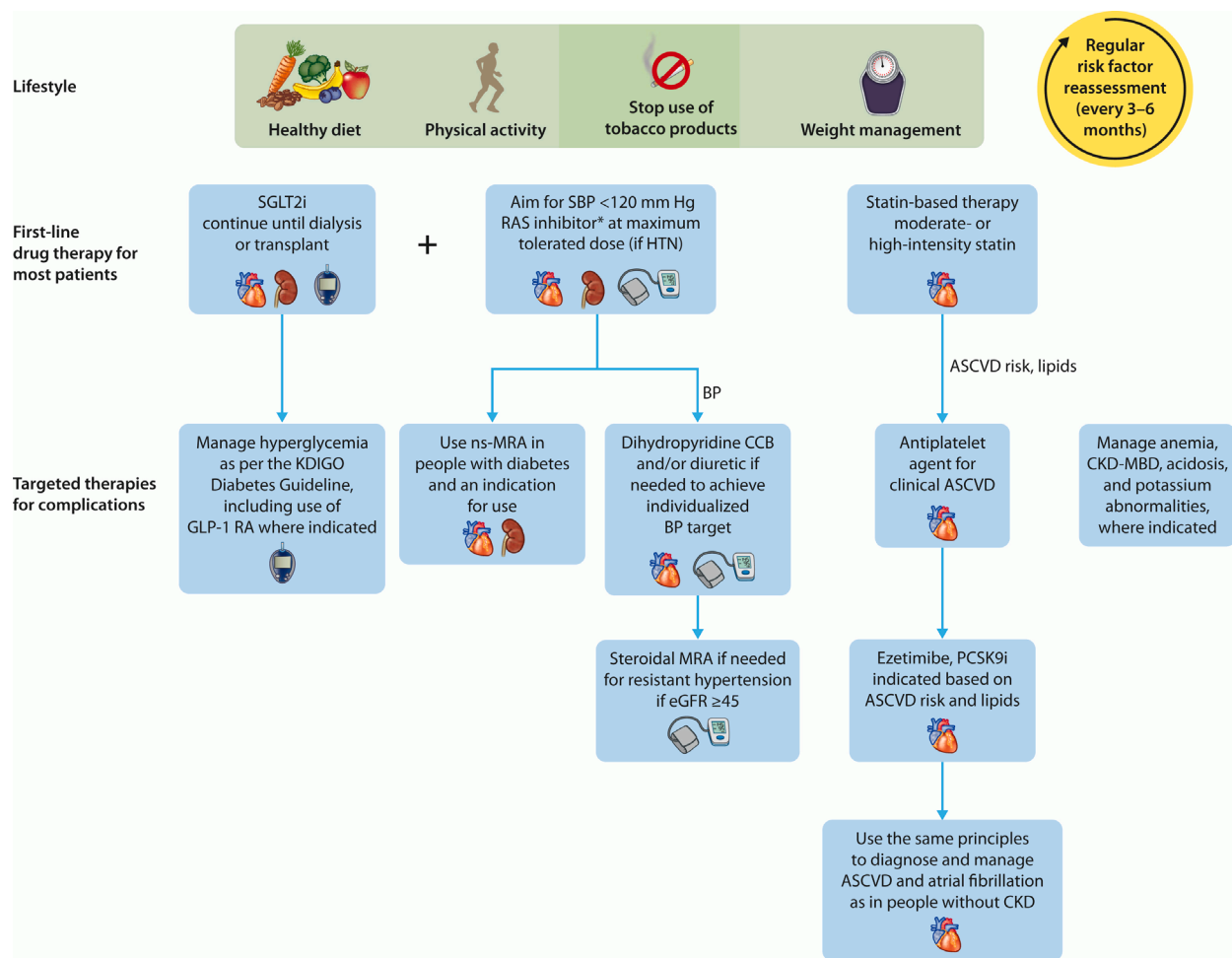


Figure 3. Recommended optimal lifestyle and therapeutic management for chronic kidney disease (CKD) in diabetes. Illustration of a comprehensive and holistic approach to optimizing kidney health in people with CKD. In addition to the cornerstone lifestyle adjustments, attention to diabetes, blood pressure (BP), and cardiovascular risk factor control is integral to kidney care. *Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker should be first-line therapy for BP control when albuminuria is present; otherwise dihydropyridine calcium channel blocker (CCB) or diuretic can also be considered. Figure reproduced from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. <https://doi.org/10.1016/j.kint.2023.10.018>.²² Copyright© 2023, Kidney Disease: Improving Global Outcomes (KDIGO). Published by Elsevier Inc. on behalf of the International Society of Nephrology under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). ASCVD = atherosclerotic cardiovascular disease, CKD-MBD = chronic kidney disease-mineral and bone disorder, eGFR = estimated glomerular filtration rate, GLP-1 RA = glucagon-like peptide-1 receptor agonist, HTN = hypertension, MRA = mineralocorticoid receptor antagonist, ns-MRA = nonsteroidal mineralocorticoid receptor antagonist, PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor, RAS = renin-angiotensin-aldosterone system, SBP = systolic blood pressure, SGLT2i = sodium-glucose cotransporter 2 inhibitor.

tors, in type 2 diabetes.³¹ A growing portfolio of promising therapeutic options is on the horizon with glucagon-like peptide-1 receptor agonists (NCT03819153, NCT04865770), aldosterone synthase inhibitors (NCT05182840), and dual-to-triple incretins (Supplementary Table S1).^{26,32} Furthermore, the evidence is already clear that in patients with CKD and diabetes, glucagon-like

peptide-1 receptor agonists reduce cardiovascular events, are safe and effective glucose-lowering therapies, and aid with weight loss.³²

Historically, it has taken an average of 17 years to move new treatments from clinical evidence to daily practice.³³ With millions of people with CKD dying each year, this is far too long to wait.

BARRIERS TO APPROPRIATE MEDICATION PRESCRIBING AND USE IN CKD

PATIENT OR DISEASE-RELATED	Self-care and empowerment	Health literacy	Trust in health care system	Polypharmacy	High health expenditure	Language and communication	Misinformation
CLINICIAN	Knowledge	Risk perception	Time pressure	Burnout	Bias	Guideline overload	Patient complexity
SOCIO-ECONOMIC	High medication costs	High medication copays	Racism	Poverty	Education	Transportation	Geography
HEALTH SYSTEM	Time pressure on clinicians	Misaligned incentives	Care fragmentation	Poor communication	Preauthorization requirement	Missing guidelines, lack of support	Quality-of-care standards
POLICY	Lack of UHC	Lack of public awareness	Lack of NCD policies	Lack of CKD policies	Lack of early detection	Essential medicines lists	Quality of medication
GLOBAL	Inequities	Drug prices, nontransparency	Research representation	CKD in children	Community-driven research	CKD not globally prioritised	Focus on dialysis and transplant

Figure 4. Depiction of the spectrum of factors impacting implementation of timely and quality kidney care. CKD = chronic kidney disease, NCD = noncommunicable disease, UHC = universal health coverage.

Closing the “Gap” between What We Know and What We Do

Lack of policies, global inequities

Health policy

Since the launch of the World Health Organization Action Plan for Non-Communicable Diseases (NCDs) in 2013, there has been global progress in the proportion of countries with a national NCD action plan and dedicated NCD units.³⁴ However, CKD is only incorporated into NCD strategies in approximately one-half of countries.⁴ Policies are required to integrate kidney care within essential health packages under universal health coverage (Fig. 4).³⁰ Multisectoral policies must also address the social determinants of health, which are major amplifiers of CKD risk and severity, limiting people's opportunities to improve their health.³ Lack of investment in kidney health promotion, along with primary and secondary prevention of kidney disease, hinders progress.¹⁴

Health systems

Two major goals of universal health coverage are to achieve coverage of essential health services and reduce financial hardship imposed by health care. However, universal health coverage alone is

insufficient to ensure adequate access to kidney care.³ Health systems must be strengthened and quality of care must also be prioritized, as poor quality care contributes to more deaths than lack of access in low-resource settings.³⁵ Quality care requires a well-trained health care workforce, sustainable availability of accurate diagnostics, reliable infrastructure, and medication supplies and should be monitored in an ongoing process of quality improvement (Fig. 4). The quality of medications, especially in LMICs, may be an additional barrier to successful management of CKD.³⁶ Regulation and monitoring of drug manufacturing and quality standards are important to ensure safe and effective therapies. Strategies to support regulation and quality assurance will need to be developed in local contexts and guidance, as outlined elsewhere.³⁷

Establishing a credible case for CKD detection and management based on risks, interventions and outcomes, and costs, based on real-world data, will help to translate theoretical cost-effectiveness (currently established primarily in high-income countries with minimal data from elsewhere) into economic reality.^{30,38} Screening should include evaluation of risk factors for CKD,



eliciting a family history, recognizing potential symptoms (usually advanced-fatigue, poor appetite, edema, itching etc.), and measuring blood pressure, serum creatinine, urinalysis, and urine albumin/protein to creatinine ratios, as outlined in established guidelines.^{19,39} Addressing CKD upstream beginning in primary care should lower costs over time by reducing CKD complications and KF. Medications required for kidney care are already included in the World Health Organization Essential Medication List (Table 1). These must be provided at national levels under universal health coverage.⁴⁰ Pharmaceutical companies should provide these at affordable prices.

Challenges in primary care, clinical inertia

Health care professionals

A shortage of primary care professionals is compounded by inconsistent access to specialists and allied health professionals in both high-income countries and LMICs. Defining roles and responsibilities for kidney care is essential. Solutions may include multidisciplinary team care (primary care physicians, pharmacists, advanced practitioners, nurses, therapists, educators, nutritionists, and mental health professionals) with well-established mechanisms of collaboration of all elements and promptly available communication technologies within health systems and between professionals to support care and decision-making.^{41,42} Brain drain in low-resource settings is complex and must be tackled.

Mobilization of community health workers yields cost savings in infectious disease programs in LMICs, and may facilitate early detection, diagnosis, and management of NCDs.⁴³ Protocolized CKD management, possibly supported by electronic decision-support systems, lends itself well to interventions at the community level, with integration of primary care physicians and backup from nephrology and other professionals.^{44,45} In some environments, pharmacists, for example, could identify people with diabetes or hypertension, at risk of CKD, based on their prescriptions, and could offer testing on site and reference if needed.⁴⁶ Pharmacists can also provide medication reconciliation and medication advice for safety, effectiveness, and adherence. Social workers and pharmacists can help patients with medications access programs.⁴⁶

Challenges for clinical inertia

Clinical “inertia,” commonly blamed for low prescribing rates, has many facets (Fig. 4).⁴⁷ Many knowledge gaps regarding CKD exist among primary care clinicians.⁴⁸ Such gaps are remediable with focused public and professional education. Additional factors include fear of medication adverse effects, misaligned incentives within the health system, excessive workload, formulary restrictions, and clinician burn-out.⁴⁷ Furthermore, discrepancies in guideline recommendations from different professional organizations may add to confusion. A major impediment to optimal care is the time constraints imposed on individual clinicians. The average primary care practitioner in the United States would require ≈ 26.7 hours per day to implement guideline-recommended care for a 2,500 patient panel.⁴⁹ Innovation is required to support guideline implementation, especially for primary care practitioners who must implement many different guidelines to meet the needs of various patients. Electronic health records, reminders, team-based nudges, and decision support tools offer a promising support for quality kidney care in busy clinical practices.⁵⁰ The extra time and effort spent negotiating preauthorizations or completing medication assistance program requests, along with need for frequent monitoring of multiple medications, however, also hinder appropriate prescribing.²⁵ Many primary care practitioners have only a few minutes allocated per patient because of institutional pressure or patient volume. “Inertia” can hardly be applied to clinicians working at this pace. The number of health professionals must increase globally.

Visits for patients with CKD are complex as multimorbidity is high. Patients are often managed by multiple specialists, leading to fragmentation of care, lack of holistic oversight, and diffusion of responsibility for treatment. Multidisciplinary care improved transition to kidney replacement therapy and lowered mortality in single and combined outcomes analyses.⁵¹ Novel models of “combined clinics” with on-site collaboration and coparticipation (nephrologist-cardiologist-endocrinologist) may prove to be of substantial benefit for patients, in terms of reduced fragmentation of care, logistics, and cost saving.

Table 1. Essential medicines for patients with kidney disease

Medication/technology	Example	Reason	On WHO model list of essential medicines
ACE inhibitor	Enalapril, lisinopril	Delays CKD progression, benefits cardiovascular disease and stroke	Yes
Angiotensin receptor blocker	Losartan, telmisartan	Delays CKD progression, cardiovascular disease, and stroke	Yes
Calcium channel blocker	Amlodipine, verapamil	Blood pressure control	Yes
Loop diuretics	Furosemide, torsemide	Good when GFR is low, good for heart failure	Yes
Thiazide diuretics	Hydrochlorothiazide, metolazone, indapamide	Good for BP, especially in the Black population	Yes
SGLT2 inhibitor	Empagliflozin, canagliflozin, dapagliflozin	Diabetes control, delays CKD progression, cardiovascular disease, and death	Yes
GLP1 agonist	Semaglutide	Diabetes control, weight loss	No
Mineralocorticoid inhibitor	Spironolactone, finerenone	Delays CKD progression, reduces heart failure risk Caution: risk of hyperkalemia in patients with kidney disease	Yes/no
β -Blocker	Bisoprolol	Prevention and treatment of ischemic heart disease	Yes
Statins	Simvastatin	Prevention of CAD in patients with CKD, transplant	Yes
Aspirin		Secondary prevention of MI in patients with CKD, transplant	Yes
Fixed-dose combinations (polypill) ^a	Aspirin + atorvastatin + ramipril	Simultaneous management of CKD and cardiovascular disease and risk factors where indicated ^a	Yes
	Aspirin + simvastatin + ramipril + atenolol + hydrochlorothiazide		Yes
	Aspirin + perindopril + amlodipine		Yes
Oral hypoglycemic medication	Gliclazide, metformin, SGLT2 inhibitors	DM management Caution with dosing and glomerular filtration rate	Yes
Insulin	Long and short acting	DM management	Yes

ACE = angiotensin-converting enzyme, BP = blood pressure, CAD = coronary artery disease, CKD = chronic kidney disease, DM = diabetes mellitus, GFR = glomerular filtration rate, GLP1 = glucagon-like peptide-1, MI = myocardial infarction, SGLT2 = sodium-glucose cotransporter 2, WHO = World Health Organization.

^a Polypills containing aspirin may not be appropriate for patients with early CKD without other cardiovascular indications.

Patient centeredness

Health literacy

Self-care is the most important aspect of kidney care. A patient's ability to understand his/her health needs, make healthy choices, and

feel safe and respected in the health system, and psychosocial support are important to promote health decision-making (Fig. 4). Communication should start from good communication that requires quality information and importantly



confirmation of “understanding” on the side of the patient and often family. Electronic apps and reminders may become useful tools to support patients by improving disease knowledge, promoting patient empowerment, and improving self-efficacy, although it is unlikely that one size will fit all.⁵² Insufficient patient health information, poor communication, and mistrust, among other elements, are important barriers, especially in marginalized and minoritized communities, where CKD is common.³⁰ Patients may also be confused by contradictory recommendations for care between health care professionals, as well as conflicting messaging in lay media. Innovative platforms to improve communication between patients and clinicians about CKD are promising and may promote optimal prescribing and adherence.^{53,54}

To overcome barriers and promote equity, patient perspectives are essential to designing and testing better health strategies. Collaborative care models must include patients, families, community groups, diverse health care professionals, health systems, government agencies, and payers.³⁸ Advocacy organizations and local community groups and peer navigators, having trusted voices and relationships, can be conduits for education and may provide input for development of patient tools and outreach programs.⁵⁵ Most important, patients must be at the center of their care.

Cost and availability of medication

In high-income countries, people without health insurance and those with high copays paradoxically pay the most for even essential medications.³⁸ Across LMICs, kidney disease is the leading cause of catastrophic health expenditure because of reliance on out-of-pocket payments.⁵⁶ Across 18 countries, 4 cardiovascular disease medications (statins, ACEIs, aspirin, and β -blockers), all often indicated in CKD, were more available in private than in public settings, mostly unavailable in rural communities, and unaffordable for 25% of people in upper middle-income countries and 60% of people in low-income countries.⁵⁷ Newer therapies may be prohibitively expensive worldwide, especially where generics may not yet be available. In the United States, the retail price for a 1-month supply of an SGLT2 inhibitor or finerenone is $\approx$ \$500 to

\$700; and for glucagon-like peptide-1 receptor agonists, $\approx$ \$800 to \$1200 per month.³⁸ Reliance on out-of-pocket payment for vital, life-saving basic medications is unacceptable (Fig. 4).

Special considerations

Not all kidney diseases are the same. Much of what has been discussed here relates to the most common forms of CKD (e.g. diabetes and hypertension). Some forms of CKD not yet completely understood have different risk profiles, including environmental exposures, genetic predisposition, and autoimmune or other systemic disorders. Highly specialized therapies may be required. Pharmaceutical companies should be accountable to ensure that research studies include disease-representative participants with appropriate race, ethnicity, and sex and gender representation, that effective drugs are made available after studies, and that the balance between profit and prices is fair and transparent. Many novel therapies are offering new hope for diverse kidney diseases; and once approved, there must be no delay in extending the benefits to all affected patients (Supplementary Table S1).

An important group often overlooked is children with kidney diseases. This group is especially vulnerable in LMICs, where nephrology services and resources are limited, and families must often make the choice to pay for treatment for 1 child or support the rest of their family.⁵⁸ Children with CKD are also at high risk of cardiovascular disease, even in high-income settings, and more attention is required to control risk factors and achieve treatment targets.⁵⁹

Fostering innovation

Implementation science and knowledge translation

Given that we know how to treat CKD based on a rigorous evidence base, we must now optimize implementation.⁶⁰ Implementation research aims to identify effective solutions by understanding how evidence-based practices, often developed in high-income countries, can be integrated into care pathways in lower-resource settings. The management of CKD lends itself to implementation research: optimal therapeutic strategies are known, outcomes are easily measurable, and essential diagnostics and medications should already be in place. Eliciting local patient

preferences and understanding challenges are crucial components of such research. Ministries of health should commit to overcoming identified barriers and scaling up successful and sustainable programs.

Polypills as an example of simple innovation

Polypills are attractive on multiple levels: fixed doses of several guideline-recommended medications are present within 1 tablet (Table 1); lower price; reduced pill burden; and simplicity of the regimen.⁶¹ Polypills have been shown to prevent cardiovascular disease, and to be cost-effective for patients with CKD.⁶² More studies are needed, but given the alternatives of costly kidney replacement therapy or early death, it is likely that polypills will prove cost-effective to reduce CKD progression.

Harnessing digital technologies

Integration of telehealth and other types of remotely delivered care can improve efficiency and reduce costs.⁶³ Electronic health records and registries can support monitoring of quality of care and identify gaps to guide implementation and improve outcomes within learning health care systems. Artificial intelligence may also be harnessed to risk stratify and personalize medication prescribing and adherence.⁶⁴ The use of telenephrology for communication between primary care and subspecialists may also prove of use and benefit for patient treatment.⁶⁵

Patient perspectives

Multiple methods support elicitation of patient preferences for CKD care, including interviews, focus groups, surveys, discrete choice experiments, structured tools, and simple conversations.^{66,67} At present, many of these are in research stages. Translation into the clinic will require contextualization and determination of local and individual acceptability.

The journey of each person living with CKD is unique; however, challenges and barriers exist in common. As examples of lived experiences, comments solicited from patients about their medications and care are outlined in Box 1 and Supplementary Table S2. These voices must be heard and headed to close gaps and improve quality of kidney care everywhere.

Call to action

A stalemate in kidney care has been tolerated far too long. The new therapeutic advances offer real hope that many people with CKD can survive without developing KF. The evidence of clinical benefit is overwhelming and unequivocal. We cannot wait another 17 years for this evidence to trickle into clinical practice.³³ The time is now to ensure that all who are eligible to receive CKD treatment equitably receive this care.

Known barriers and global disparities in access to diagnosis and treatment must be urgently addressed (Fig. 4). To achieve health equity for people with and at risk of kidney diseases, we must raise awareness from policy makers to patients and the general population, harness innovative strategies to support all cadres of health care workers, and balance profits with reasonable prices (Table 2). If we narrow the gap between what we know and what we do, kidney health will become a reality worldwide.

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Box 1. Barriers impacting medication use as expressed by people living with kidney disease.

"I have to pay for my medications so I either settle for less expensive options or ration the regular dose."

"I am seeing doctors of different specialties each of whom prescribe separate regimens which makes me concerned about drug interactions."

"As an experienced patient, I sometimes stop, or modify the dose of the prescribed medications without referring to my doctors. If they do ask, I would tell them that I am in full compliance."

"Over time, the dose and varieties of my medication keep increasing. I am not sure whether it's because of condition worsening or medications becoming less effectiveness."

"My knowledge of medication mostly comes from a peer patient who appears to be very knowledgeable about this stuff."

**Table 2.** Examples of strategies to improve implementation of appropriate CKD care

Domain	Potential solutions
Health policy	Include NCD and CKD as health care priorities; ensure sustainable financing; monitor disease burdens and outcomes; registries; multisectoral action; promote kidney health through public health measures; achieve SDGs
Health systems	Integrate CKD care into primary care under UHC; establish quality standards; include necessary diagnostics and medications in national essential medication/diagnostic lists; monitoring and evaluation; reduce brain drain; monitor equity; simplify and streamline guidelines
Quality assurance	Regulation and monitoring of medication quality, especially of generics. Monitoring of health outcomes and care processes to permit iterative improvement
Health care professionals	Reduce time pressure; improve knowledge; broaden scope of practice (e.g. pharmacists); engage community health workers
Patient empowerment	Health literacy; education; community engagement; involvement in research design and conduct
Medication cost	Quality generics; reduce prices; UHC for essential medications
Implementation research	Identify barriers within local contexts; test solutions to overcome barriers
Polypills	Reduce cost; lower pill burden
Digital technologies	Electronic pill boxes, bags, bottles; blister pack technology; ingestible sensors; electronic medication management systems; patient self-report technology; video-based technology; motion sensor technology; telemedicine; smartphone apps; electronic health records

CKD = chronic kidney disease, NCD = noncommunicable disease, SDG = sustainable development goal, UHC = universal health coverage.

Conflict of Interest

VL is chair of the Advocacy Working Group, International Society of Nephrology, no financial disclosures. KRT has received research grants from the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases, National Heart, Lung, and Blood Institute, National Center for Advancing Translational Sciences, National Institute on Minority Health and Health Disparities, director's office), the US Centers for Disease Control and Prevention, and Trave Therapeutics; and consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk. She is chair of the Diabetic Kidney Disease Collaborative for the American Society of Nephrology. RC-R is a member of the Steering Committee of World Kidney Day, a member of the Diabetes Committee of the Latin-American Society of Nephrology and Hypertension (SLANH), and a member of the Latin American Regional Board, International Society of Nephrology. He is a member of the Steering

Committee of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial (AstraZeneca), the Study of Diabetic Nephropathy with Atrasentan (SONAR) (Abbvie), A Non-interventional Study Providing Insights Into the Use of Finerenone in a Routine Clinical Setting (FINE-REAL) (Bayer), and CKD-ASI (Boehringer). He has received research grants from AstraZeneca, GlaxoSmithKline, Roche, Boehringer, and Novo Nordisk; and has received honoraria as a speaker from AstraZeneca, Bayer, Boehringer Ingelheim, and Amgen. All the other authors declared no competing interests.

Appendix

Members of the World Kidney Day Joint Steering Committee:

Alessandro Balducci, Vassilios Liakopoulos, Li-Li Hsiao, Ricardo Correa-Rotter, Ifeoma Ulasi, Latha Kumaraswami, Siu Fai Lui, Dina Abdellatif, and Ágnes Haris.

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Figure S1. Ranking of kidney dysfunction as a cause of death stratified by world-income category and gender by level 2 risk factors for death.

Data from Global Burden of Diseases Study: <https://vizhub.healthdata.org/gbd-results/>



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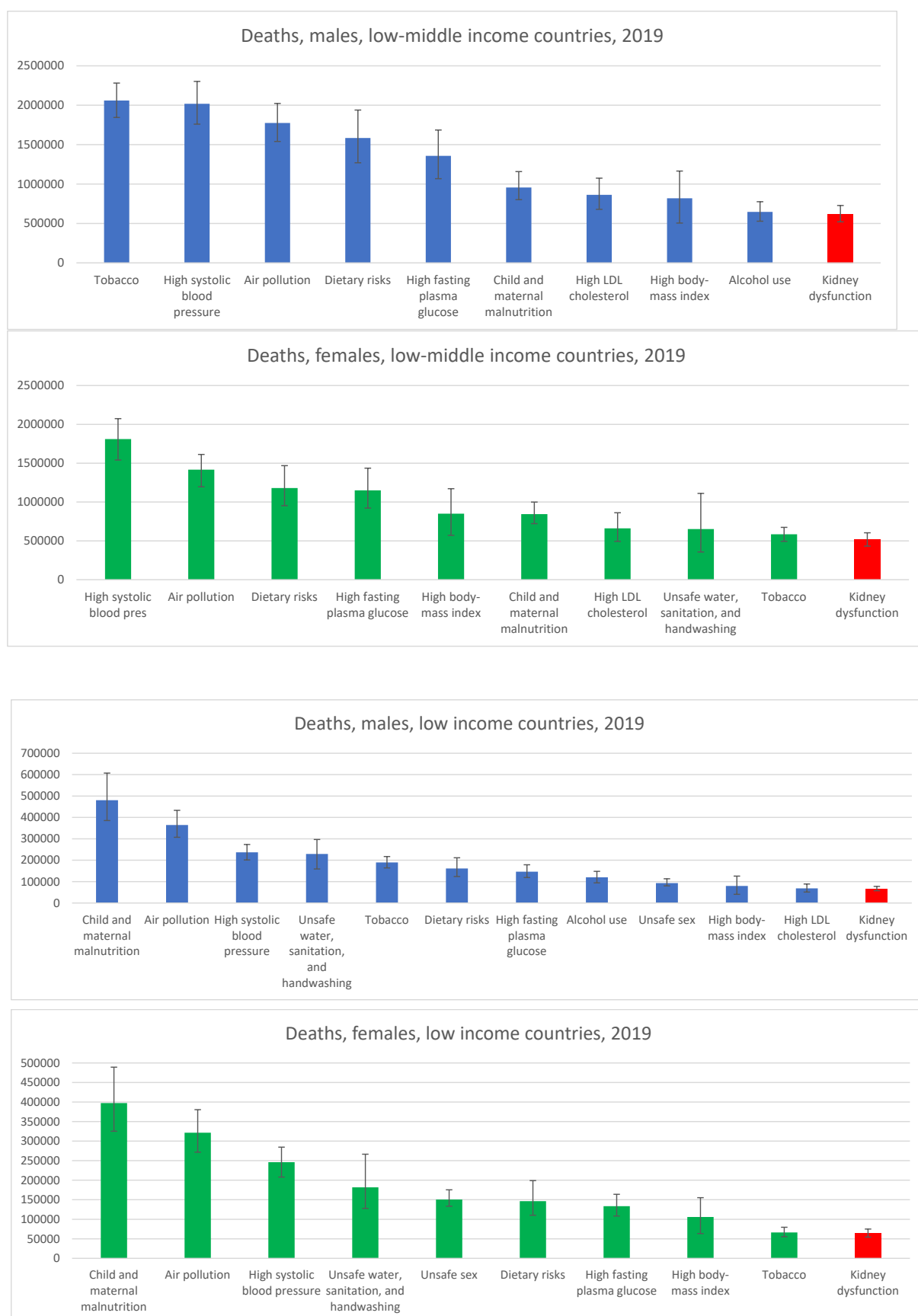


Table S1. Approved and emerging novel therapeutic agents for various kidney diseases.

Medications (Class)	Conditions	Status	Clinical Trials
Inaxaplin (APOL1 inhibitor)	Two APOL1 variants FSGS	Emerging	NCT04340362
Sparsentan (Endothelin A receptor antagonist)	FSGS	Emerging	DUPLEX (NCT03493685)
	IgAN	Approved	PROTECT (NCT03762850)
Budesonide (Corticosteroid)	IgAN	Approved	NEFIGARD (NCT03643965)
Atrasentan (Endothelin A receptor antagonist)	IgAN	Emerging	ALIGN (NCT04573478)
Sibeprenlimab (APRIL inhibitor)	IgAN	Emerging	VISIONARY (NCT05248646)
Narsoplimab (MASP-2 inhibitor)	IgAN	Emerging	ARTEMIS-IgAN (NCT02682407)
Iptacopan (Factor B inhibitor)	IgAN	Emerging	APPLAUSE-IgAN (NCT04578834)
	aHUS	Emerging	APPELHUS (NCT04889430)
Ravulizumab (long acting anti-C5 monoclonal antibody)	aHUS	Approved	ALXN1210-aHUS311 (NCT02949128)
Dapagliflozin/ Empagliflozin (SGLT2-i)	CKD/ DKD	Approved	DAPA-CKD (NCT03036150) EMPA-kidney (NCT03594110)
Canagliflozin (SGLT2-i)	DKD	Approved	CREDENCE (NCT02065791)
Finerenone (non-steroidal mineralocorticoid receptor antagonists)	DKD	Approved	FIGARO-DKD (NCT02545049) FIDELIO-DKD (NCT02540993)
	CKD	Emerging	FIND-CKD (NCT05047263)
Ziltivekimab (Antibody Mediated IL-6 Inhibition)	CKD	Emerging	RESCUE (NCT03926117) RESCUE II (NCT04626505)
	Atherosclerotic CVD in CKD		ZEUS (NCT05021835)
Semaglutide (GLP-1 receptor agonist)	DKD	Emerging	FLOW (NCT03819153)
Voclosporin (Calcineurin inhibitor)	Lupus nephritis	Approved	AURORA1/2 (NCT03021499)
Belimumab (anti-BAFF monoclonal antibody)	Lupus nephritis	Approved	BLISS-LN (NCT01639339)
Anifrolumab (anti-interferon α antibody)	Lupus nephritis	Emerging	IRIS (NCT05138133)
Daratumumab (anti-CD38 monoclonal antibody)	Lupus nephritis	Emerging	NCT04868838
Avacopan (C5a receptor antagonist)	ANCA vasculitis	Approved	ADVOCATE (NCT02994927)

aHUS = atypical haemolytic uremic syndrome, CKD = chronic kidney disease, DKD = diabetic kidney disease, FSGS = focal segmental glomerulosis, IgAN = IgA nephropathy

Table S2. Patient comments on accessibility, affordability, knowledge, facilitators and barriers to optimal kidney care.

Patient comment/category		Cost	Side effects, interaction	Patient empowerment	Safety	Source of information	Comfort level to query	Delay new therapy	New hope	Policies/ prevention	Education	Fragmentation of care	Lack of specialists
HK1	The medication is not covered by UHC or insurance policies, I cannot afford to take the most effective medications as recommended by my doctors. I decide to not to take the medication, settle for less expensive option or start to ration the regular dose.	x											
HK2	Given the side effects, not taking medication to the extent possible would be the best policy.		x										
HK3	I do not feel any side effects and question about the medication effectiveness.		x	x									
HK4	I am concerned or unsure about the interactions among the medications taken especially as I am seeing doctors of different specialties each of whom prescribe separate regimens of their own.		x										
HK5	I can stop taking my medication when my laboratory results improve or when I start to feel better.			x									
HK6	All over-the-counter medications are generally safe for me to take.		x								x		
HK7	The dose and varieties of medication keep increasing. I am not sure whether it's because of condition worsening or less effectiveness of medication.		x										
HK8	I am sceptical about adding new medications to my existing regimen and have the natural tendency of resisting any new additions or dose increase.				x								
HK9	As an experienced patient, I sometimes stop, or adjust the dose of the medication prescribed without telling my doctors. Or if they do ask, I would tell them that I am in full compliance.			x									
HK10	My knowledge of medication mostly comes from a peer patient who appears to be very knowledgeable about this stuff.					x							
UK1	People need confidence to tell clinicians about side effects of medications and clinicians can offer education and encouragement to explain medications (and also encourage people not to stop taking them without discussion)		x				x						

Patient comment/category		Cost	Side effects, interaction	Patient empowerment	Safety	Source of information	Comfort level to query	Delay new therapy	New hope	Policies/prevention	Education	Fragmentation of care	Lack of specialists
UK2	In England we have prescription charges on certain medications unless you are on dialysis. These charges, about £10 each and can be a barrier for some. Yet in Scotland, Wales, and Northern Ireland there are no charges.	x											
UK3	New medicines can take a very long time to reach patients even after approval from the regulators as payers can be reluctant							x					
UK4	New medications such as those which may delay CKD have been greeted with excitement by many.								x				
UK5	A universal focus on preventative approaches to CKD, including exercise, diet, emotional support as well as medications is one that's likely to be most patient-centred but needs a plan.									x			
HN1	From the perspective of kidney patients in Honduras/Latin America, access to medicines is crucial to our quality of life and survival. For this we mention some points of importance related to access to medicines and what this means, based on our current experience based on the theme of World Kidney Day 2024, "Kidney health for all: Advancing equitable access to care and optimal medication practice "	x											
HN	In the absence of solid programs/policies regarding the management of comprehensive kidney disease, as in Honduras, isolated programs exist for renal care, where the action is mostly geared to dialysis treatment only. Government responsibility for public assistance covers 85% of the renal population, 12-13% is covered by the social security system, and about 3% privately. Currently in Honduras, the law that does not cover the interests of kidney patients and it must be updated and revised in order to manage the comprehensive program of kidney disease.	x								x			
HN	There is a significant diversity observed in the other countries of Latin America in health policies regarding Renal Health Programs promoted by SLANH, however many of them have shortcomings ranging from timely and early diagnosis, lack of coverage and accessibility to medicines. In Latin America, in recent years n most	x								x			

Patient comment/category		Cost	Side effects, interaction	Patient empowerment	Safety	Source of information	Comfort level to query	Delay new therapy	New hope	Policies/ prevention	Education	Fragmentation of care	Lack of specialists
	countries the focusing on the accessibility of medication has been on price rather than the benefit, effectiveness and quality of medicines.												
HN	In Honduras, access to medicines is limited due to economic barriers and the type of health system that is managed. Many patients struggle to obtain the medications they need, but they cannot always be obtained and the costs of the low-income patient are inaccessible. Even though the Ministry of Health has a basic set of medicines, it does not meet the needs and does not adjust to the growth of the renal population, therefore they are insufficient.	x											
HN	In Honduras, the absence of programs defined in primary care for the early or opportune detection of chronic diseases such as kidney, and having a fairly collapsed health system, has led to the increases in kidney disease in the last decade, and this has been deepened with the lack of health budget. ItFor these reasons patients are unable to obtain appropriate treatments of quality and with the regulatory requirements that are required. On the other hand, the lack of specialized professional resources affects us directly since medical cares is given only in case of extreme urgency and this means that in many cases very advanced complications are already detected.	x								x			
HN	In Latin America, some countries which have developed a national public health coverage such as Argentina and Uruguay do not have major deficits but the rest of the countries have many deficiencies within their public systems in terms of timely medical attention. There is lack of education regarding the disease for patients.	x								x	x		
HN	We have very few specialized health professionals in the renal area and most are concentrated in the main cities of the country in Honduras, little or none in the other areas where the number of patients affected by kidney disease is growing, and this directly affects the patient since they have to migrate to the cities to be able to be treated affecting their quality of life or they have to abandon treatment for not									x			x

[illegible]

Patient comment/category		Cost	Side effects, interaction	Patient empowerment	Safety	Source of information	Comfort level to query	Delay new therapy	New hope	Policies/ prevention	Education	Fragmentation of care	Lack of specialists
	adequate medical care with accessibility to the best health practices by renal specialists and the appropriate effective and quality timely medication.												
IN1	Patients are well advised on need for medications at all stages. When prescription changes more information on need for change for better outcome is needed.										x		
IN2	Co-relation between medications and the dietary requirements need to be established		x		x								
IN3	Cost is a huge factor for the poor as well as middle -income patients	x											
IN4	Exceptional drugs for rare diseases like eculizumab must be made available at reasonable costs world-wide	x								x			



Invited Review Article

Phimosis in children: an unfinished story

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Keywords:

Phimosis, children, physiologic, pathologic, corticosteroids, circumcision

Abstract

Phimosis is a condition in which prepuce cannot be fully retracted behind the glans of the penis, which is common in boys and can occur at any age. Physiologic phimosis is a normal condition that occurs at birth and generally resolves with age as a child grows, which may take until adolescence to be completely retracted. In most cases, external hygiene is adequate care. Whereas pathologic phimosis is a condition in which the foreskin cannot be retracted at an age when retraction normally should be possible or when a previously retractable foreskin becomes non-retractable. This type of phimosis usually occurs in older children and possible ballooning of the foreskin when voiding. It can result from lichen sclerosus, recurrent episodes of balanitis or balanoposthitis, and inappropriate retraction of the foreskin. Topical corticosteroids can loosen the tissues in non-scarred prepuce in approximately 80% of cases. Phimosis can cause complications such as obstructed voiding, urinary tract infection, paraphimosis, and penile cancer. Various classifications; Kikiros, Kayaba, and Sookpotarom, have been developed to assess the severity of phimosis, making it easier to understand and compare the condition across different patients. If a patient experiences complication from phimosis that do not resolve with topical steroids, circumcision should be considered as an option. While pediatric circumcision has been shown to offer benefits in reducing the risk of urinary tract infections, HIV, sexually transmitted diseases, and penile cancer, routine neonatal circumcision is not recommended. Newborn circumcision while controversial is a familial decision and should be based on informed consent.

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Introduction

Phimosis is a condition in which prepuce cannot be fully retracted behind the glans of the penis. It can occur in both children and adults. Phimosis is either physiologic or pathologic.

Physiologic phimosis is a normal condition which occurs at birth. Only 4% of male newborns have retractile foreskins.¹ Inner epithelial lining of the prepuce fuses with the glans of the penis, but the boys still void normally without prepuce ballooning. As the boys grow into

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adolescence, keratinization of the inner prepuce and intermittent penile erection cause the foreskin to gradually become retractile. Only 10% of 3-year-old boys have fully retractile foreskins.² Although physiologic phimosis usually resolves as the boys grow up, it can cause complications like balanoposthitis, urinary tract infection, and penile cancer in some cases. Thus, parents and adult patients need to be aware of the risk of malignancy if the phimosis is left untreated.^{1,2} However, penile cancer is rare, as the incidence is about 1% of all male cancers over the age of 60 in the Western population. The incidence of penile cancer in Thailand reported in 2014 was 0.2-2.3/100,000 in ages between 35-60 and 3.2-7/100,000 in ages over 60 years.³ The cause of penile cancer is largely attributed to poor hygiene.

Pathologic phimosis (true phimosis) is a condition in which the foreskin cannot be retracted at an age when retraction normally should be possible or when a previously retractable foreskin becomes non-retractable. This type of phimosis, which usually occurs in older children, looks like a contracted fibrous ring around the preputial outlet with possible ballooning of the foreskin when voiding. It can result from balanitis xerotica obliterans, also known as lichen sclerosus⁴, after recurrent episodes of balanitis or balanoposthitis, and from inappropriate retraction of the foreskin before the age when physiologically appropriate. The incidence of the pathologic phimosis is unknown. Topical corticosteroids can loosen the tissues in non-scarred prepuce in approximately 80% of cases.²

History taking and physical examination

Symptoms that children present with include inability to retract the prepuce, tight foreskin, obstructed voiding, ballooning when voiding, and urinary tract infections.⁵ Although these conditions are mostly benign, physicians should be alert to possible emergency conditions such as paraphimosis.^{2,5}

Physicians should review the history of the following phimosis complications.

1. Balanoposthitis, infection of the prepuce and glans
2. Preputial pain or pain in erection
3. Weak urine flow or painful urination
4. Acute urinary retention

5. Urinary tract infection

6. Previous history of paraphimosis

By physical examination, a normal prepuce should appear healthy, with pink mucosa. Scar tissue or white fibrotic ring on the prepuce could indicate balanitis xerotica obliterans. Erythema or edema could be infection or inflammation. The smegma, a thick white sebaceous secretion with desquamated epithelial skin cells, collects underneath the foreskin and can form lumps. Such lump can accumulate between the foreskin and shaft and are referred to as Keratin pearls. Physicians should also inspect for signs of paraphimosis.⁴

Prevalence of the phimosis

Previous studies found that the prevalence of phimosis in older boys was higher in Asian countries than in Western countries.⁶ In the U.K., 15% of boys at age 6 months, 50% at age 1 year, 80% at age 2 years, and 90% at age 3 years could fully retract their prepuce. Similarly, 90% of Danish boys could retract their prepuce at age 3 years. In contrast, in Japan, 61.6% of boys at age 3 years could not fully retract the prepuce, and 35% were completely un-retractable. In Taiwan, 50% of boys at age 7 years still had phimosis.⁶ In Thailand, 68% of boys at age 3-4 years had phimosis, 54% at age 5-6 years, and 40% at age 11-12 years.⁷

The preputial development

When a fetus is 8 weeks old, prepuce is formed as a thickening ring of epidermis, which then grows forward to cover the base of the glans penis. At 12 weeks, the frenulum develops. At age 16 weeks, the prepuce grows forward to the tip of the glans penis. The epidermis of the inner part of the prepuce fuses with the epidermis of the glans which is lined with squamous epithelial cells. Desquamation and rearrangement of the squamous cells create a space between the glans penis and the prepuce. The degree to which these developmental processes have progressed at the time of birth varies, but complete separation between the glans and the prepuce at birth is uncommon, which is why a normal newborn's prepuce is non-retractable.^{8,9}

Normal separation may be complete at any age up to adolescence, often around the age of 5 years. It is affected by histological changes, hormones, and stretching caused by erections. In

addition to these factors, penile growth and the effect of smegma as it moves distally between the glans and foreskin aids in natural separation. If the foreskin is redundant, erections may not be able to stretch it, resulting in prolonged phimosis.¹⁰ Smegma accumulating under the prepuce can become a risk factor for penile cancer.⁸ If retracted forcefully, the glans and prepuce might tear, which can lead to bleeding, infection, and pathologic phimosis. Older boys who cannot completely retract the prepuce may have just a few strands of tissue connecting it to the glans, in which case a slight force is sufficient to complete the separation.

Lichen sclerosus and phimosis

Lichen sclerosus, also known as balanitis xerotica obliterans (BXO) is a chronic inflammatory dermatitis which produces whitish scars around the opening of the prepuce, and white plaque on the glans and urethral meatus. It can cause phimosis, meatal obstruction, and obstructive voiding symptoms. The degree of phimosis does not indicate the presence of lichen sclerosus, but histology revealing homogenized collagen and subepidermal lymphocytes does; physical examination is insufficient for diagnosis.¹¹ Steroid treatment is the mainstay medicine treatment but over 40% recurrence rates are known despite aggressive medical therapy, so this group of patients need surgery.¹² In the worst cases, Lichen sclerosus may invade the urethra to cause stricture disease requiring surgical reconstruction.

Classification of severity of phimosis

1. Kikiros and Woodward classification (Fig. 1)

Kikiros and Woodward defined 6 classifications of phimosis severity. Type 0 is full and easy retraction, not tight behind the glans. Type I is full retraction but tight behind the glans. Type II is partial exposure of the glans. Type III is partial retraction which exposes only the meatus. Type IV is slight retraction but neither meatus nor glans are exposed. Type V is no retraction at all.¹³

2. Kayaba classification (Fig. 2)

Similarly, Kayaba defined 5 classifications of phimosis severity. Severity is evaluated by gently retracting the prepuce without traumatic force when the patient is in the supine position. Type I cannot be retracted at all. Type II exposes only the urethral meatus when retracted. Type III exposes the glans halfway to the coronal sulcus. Type IV exposes the glans above the coronal sulcus. Type V exposes the whole glans. Meanwhile, physicians need to identify the tight ring that prevented the prepuce from being retracted or constricted around the glans or penile shaft during retraction. In a study of Japanese boys, Kayaba found that almost 50% of boys younger than 6 months were Type I and none were Type IV. Less than 10% of boys older than 5 years were Type I or II. Only 60% of boys 11-15 years old were Type IV.¹⁴

3. Sookpotarom classification (Fig. 3)

In Thailand, Sookpotarom et al. defined grades of phimosis. Grade 0 is foreskin can be fully retracted. Grade 1 is foreskin can be fully retracted but has a phimotic ring behind the glans.

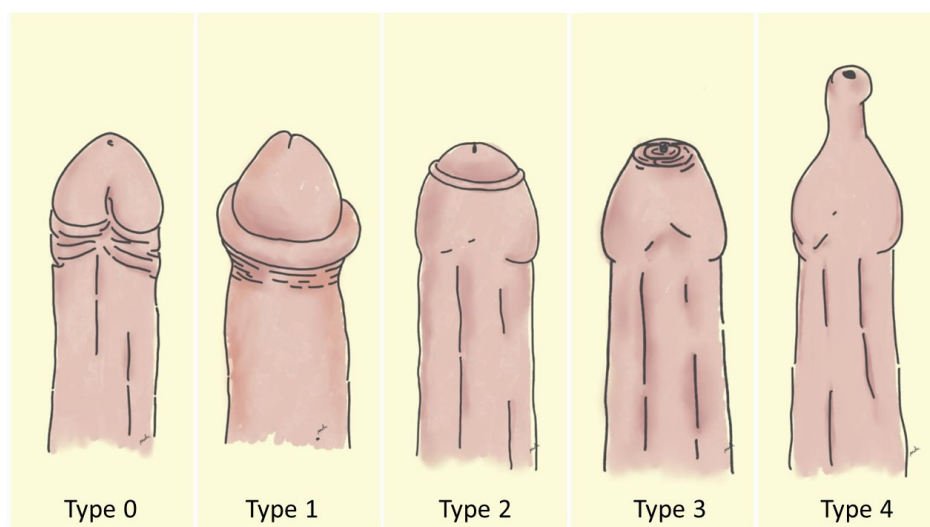


Figure 1. Kikiros and Woodward classification

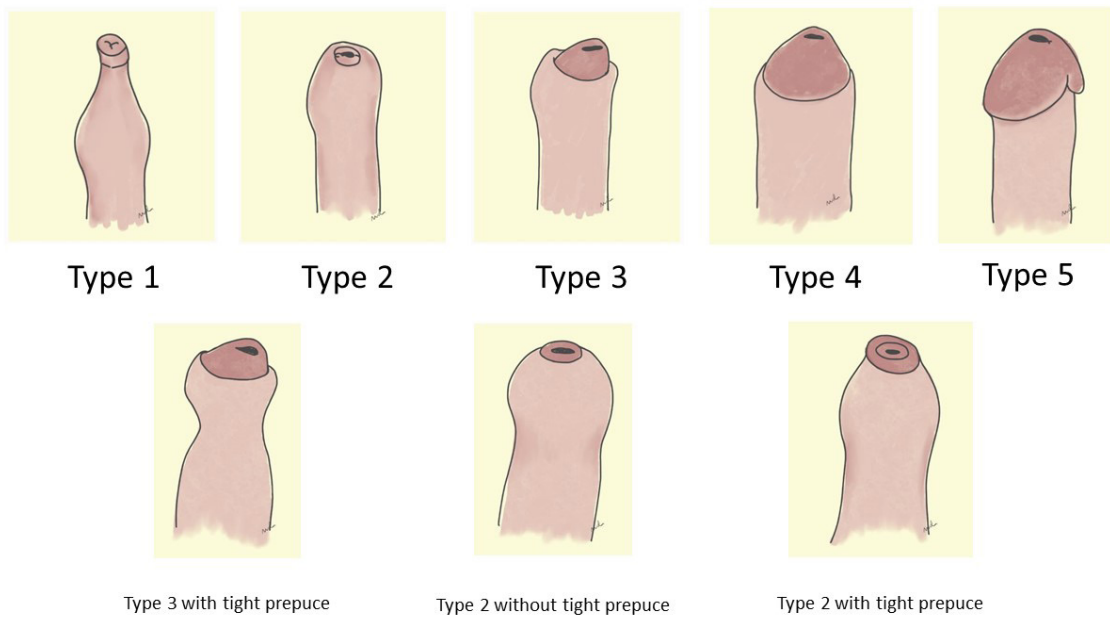


Figure 2. Kayaba classification

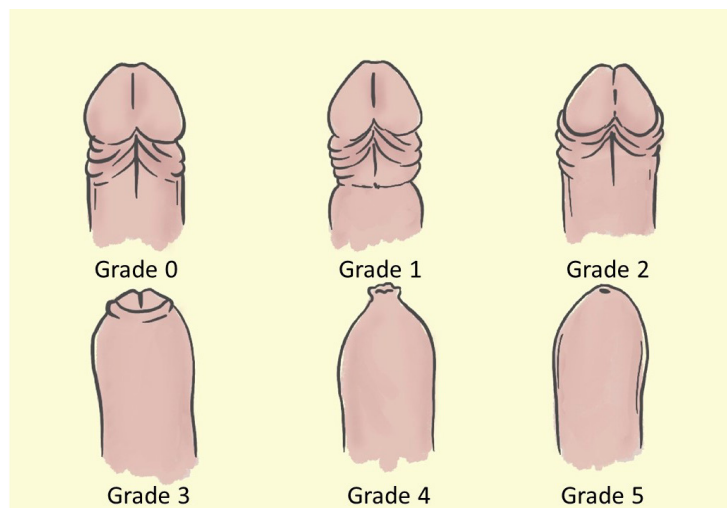


Figure 3. Sookpotarom classification

Grade 2 is foreskin can be partially retracted exposing most of the glans. Grade 3 is foreskin can be partially retracted but exposes only meatus. Grade 4 is foreskin can be retracted very little with puckering and cannot expose meatus. Grade 5 is foreskin cannot be retracted.¹⁵

Management

Appropriate preputial hygiene care

For an uncircumcised penis, the prepuce should be left alone until it shows ability to be retracted. Before reaching this time, it is not necessary to clean underneath the prepuce and the prepuce should not be forcefully retracted, which can cause pain, bleeding, and scars. The

American Academy of Pediatrics recommends cleaning only the external skin. When the prepuce can be retracted, parents should gently retract it as far as possible without pain, and clean during bathing, and they should teach their children to do it themselves.²

Topical corticosteroid with gently manual retraction

Jorgensen and Svensson¹⁶, and Kikiros and colleges¹³ reported benefits of topical steroids in phimosis treatment in 1993. Many recent studies have demonstrated that topical corticosteroid with gentle manual retraction of the foreskin was 66-96% successful after 4-8 weeks of treatment.



This method was most successful in patients aged 4-8 years, which can reduce the psychological effect of circumcision in this phallic period. Patients with a history of previous balanoposthitis had lower success rates. This method is safe and cost-effective. It may increase the long-term cure of phimosis at least 6 months after treatment. Meta-analysis showed that this method had higher efficacy than placebo with manual retraction. The success rate of topical steroid in the meta-analysis was about 84%. The risk of adverse effects was not different between corticosteroid, placebo, and no treatment.^{17,18}

Topical corticosteroids are usually applied 1-3 times daily (less frequently with high-potency formulations) for 4-6 weeks, at the junction of the prepuce and the glans of the penis, followed by gentle retraction.¹⁹ The potency of topical corticosteroids ranges from most potent (class I) to least potent (class VII). Steroids can cause skin atrophy, striae, telangiectasia, acneiform eruptions, hypertrichosis, contact dermatitis, and pigmentation changes. Moreover, steroids can promote fungal growth when used for over 1 month, particularly on the thinner skin of the face, axillae, and genitalia. High-potency steroids may cause adrenal suppression by suppressing the hypothalamic-pituitary-adrenal axis when applied on an extensive skin surface, using occlusive dressings, or for long periods, especially in children. However, skin atrophy and systemic side effects of long-term high dose topical corticosteroid are rare.²⁰

Studies of the efficacy of various topical steroids have not yet determined the optimal active ingredients and dosage. Table 1 compares studies relating to the efficacy of topical corticosteroids on phimosis. Generally, parents are advised to apply steroid on the prepuce after maximal atraumatic retraction twice daily; in the morning and in the evening.²¹ Previous studies demonstrated that medium to high potency topical steroids; such as Triamcinolone, Betamethasone, Mometasone, Clobetasone and hydrocortisone were effective.²² The most popular, including in Thailand, was 0.05 % betamethasone valerate cream.¹⁵ The success rates of high-potency topical steroids (e.g., betamethasone, clobetasol) were no higher than rates of low to medium-potency steroids.^{18,23}

A few studies also demonstrated the effect of manual retraction without a topical steroid

by observing placebo groups. The success rates were between 20-76%, which was lower than rates using topical steroids.¹⁹

The possible mechanisms of action of topical steroids to treat phimosis differ and are controversial. Firstly, glucocorticoids can inhibit humoral inflammatory response and affect the function of endothelial cells, granulocytes, and fibroblasts resulting in anti-inflammatory and immunosuppressive effects. Secondly, glucocorticoids can inhibit collagen synthesis and have antiproliferative effects on the epidermis, resulting in skin thinning.²⁴⁻²⁶

Although topical corticosteroid with manual retraction shows high efficacy and cost-effectiveness in the treatment of pediatric phimosis, the phimosis can recur after discontinuing the steroid. The recurrence may result from parents or children not continuing to perform daily manual retraction and poor genital hygiene.^{24,27} After circumcision of the failure cases, the most pathological condition reported is dermal fibrosis.

Circumcision

Routine neonatal circumcision is not recommended, but current evidence suggests that the health benefits outweigh the associated risks. The benefits of this procedure support providing access to the procedure for families who decide to pursue it. Therefore, when counseling families, physicians should explain risks and benefits without bias and emphasize that neonatal circumcision is an elective procedure. Physicians must ensure that parents understand all risks and benefits thoroughly before making the decision. Parents should practice good penis hygiene whether or not they opt for circumcision.²⁸

Pediatric circumcision: myth or fact?

Outside the cultural and religious significance, true benefits of newborn circumcision are still controversial. Neonatal circumcision can prevent balanoposthitis, urinary tract infection, some sexually transmitted diseases, and cervical and penile cancer, but it can cause pain requiring local or general anesthesia, bleeding, wound infection, or devastating complications like glanscectomy. Similar benefits can be achieved through good genital hygiene and protection during sex. Moreover, a child who loses his prepuce loses his chance to use the prepuce for urogenital recon-

struction, such as for urethral stricture, in the future. The ethics of performing circumcision on infants raises questions about consent and autonomy. Balancing parental rights and a child's future choices is a critical aspect of the circumcision debate. Knowledge about phimosis would eliminate unnecessary circumcision in children. Physicians should explain this to parents.²⁹ The family decision should be based on appropriate counseling regarding the pros and cons.

The benefit of circumcision as a prophylactic treatment

Prevent urinary tract infection

Phimosis causes colonization of pathogens underneath the prepuce which can result in balanoposthitis and urinary tract infection. A previous study demonstrated that boys whose urethral meatus was tightly covered by prepuce had a higher incidence of urinary tract infection. Circumcision may reduce the incidence of urinary tract infections during the first year of life.⁶ Wiswell et al.'s study reported an increased risk of UTI in uncircumcised boys 9.91-fold higher for ages 0 to 1 year, 6.56-fold higher for ages 1 to 16 years, and 3.41-fold higher for ages over 16 years. The estimated risk during the entire lifetime is 3.65-fold higher for uncircumcised males. The number needed to treat was 4.29.³⁰

Prevent sexually transmitted diseases (STD)

Pediatric circumcision was found to reduce the risk of HIV infection, however, the reduction in risk of other STDs is controversial. Previous studies revealed that male circumcision may reduce the risk of syphilis, gonorrhea, and chancroid, but not genital herpes.⁶

Prevent Human Immunodeficiency Virus (HIV)

Male circumcision can reduce HIV transmission in heterosexuals by 55-76% because the HIV-1 receptors of the superficial Langerhans cells are more prevalent in the prepuce than in the penis. Moreover, a circumcised penis is less susceptible to minor trauma during intercourse.⁶ However, routine male circumcision did not improve the prevalence rates significantly. The WHO currently recommends male circumcision as a key strategy for preventing heterosexual HIV transmission, but this advice is targeted specifically at regions with high HIV incidence and low circumcision rates.³¹

Prevent penile cancer

About 25-75% of penile cancer patients have phimosis. Penile cancer usually occurs in men who have poor penis hygiene. Smegma that accumulates underneath the prepuce can cause chronic irritation, which leads to penile cancer. Neonatal circumcision reduces the risk of penile cancer; however, previous studies demonstrated that hygiene is sufficient to reduce risk of penile cancer, and circumcision is not necessary. Therefore, routine neonatal circumcision to prevent penile cancer is not recommended. Adult circumcision differs because adults have been exposed to smegma longer.⁶

The indication of pediatric circumcision

Absolute indications for circumcision are pathological phimosis related to lichen sclerosus which tends to resist topical steroids, recurrent balanoposthitis, or symptomatic therapy-resistant phimosis. Further indications are antenatal history of significant hydronephrosis, known reflux, etc. Another indication is boys at risk of urinary tract infections due to congenital upper tract abnormalities such as vesicoureteral reflux.¹⁰ Preputial ballooning during voiding is not an indication for surgery. Absolute contraindications are infection, congenital anomalies of the penis such as hypospadias or epispadias, hooded foreskin, ventral curvature of the penile shaft, peno-scrotal webbing, prematurity, and congenital megaprepuce. Relative contraindications are concealed penis, bleeding disorders; hemophilia A, sickle cell disease, etc., and jaundice.⁶ The severely concealed penis should not be treated at birth but surgical reconstruction with circumcision can be performed after 6 months of age if parents desire. From the author's perspective, if a 3-year-old boy with phimosis fails betamethasone treatment and is experiencing ballooning of the foreskin during urination or recurrent balanitis, we would recommend offering circumcision or a dorsal or ventral slit procedure (as described in the La Vega Slit technique) to address the issue.³²

The circumcision techniques⁶

Sleeve technique

The external and internal prepuce is incised. Then, subcutaneous attachments are separated between Buck's fascia and the prepuce. Finally, the excess skin is excised.



Dorsal slit

The prepuce is cut along the midline, then cut circumferentially at 2-3 mm distal to the corona.

Plastibell

After the dorsal slit, a Plastibell device is placed between the glans and the prepuce. A Suture is looped around the prepuce at the groove of the plastibell, then tied tightly to stop the blood supply to the prepuce. Excess skin beyond the suture is cut off.

Mogen clamp

The prepuce is pulled toward the distal of the glans and a Mogen clamp is clamped at the prepuce. Then the prepuce is cut away from the clamp. It is critical to lyse all of the preputial adhesions and divide the frenulum to prevent inadvertent injury to the glans during the procedure.

Gomco clamp

After a dorsal slit is done, a clamp is placed around the prepuce and tightened to crush the prepuce leading to hemostasis. The prepuce is cut distal to the clamp.

For newborn circumcision, the author typically uses either a Gomco or Mogen clamp. After the procedure, the penis is dressed with a single wrap of Surgicel and lightly covered with Coban, which is removed within 24 hours. Vaseline is then applied during diaper changes. If there is a tendency for the penis to retract after circumcision, I instruct the family on how to expose the penis by pressing down with two fingers on each side (similar to forming a "V" shape). This allows direct application of ointment to the wound, helping to prevent postoperative adhesions and, in the worst cases, the formation of a cicatrix.

Pediatric circumcision is generally performed under general or local anesthesia. It is not recommended to use only sucrose and a pacifier. Non-pharmacologic techniques are inadequate for preventing peri-operative and post-operative pain. Some studies reported using tissue glue instead of suture to reduce operative time.³³

For a free-hand circumcision, the author typically uses a dorsal and ventral slit technique. Then, place 5-0 Monocryl sutures at the 6 o'clock and 12 o'clock positions, splay the tissue, and mark the excess skin on each side. The excess skin is then carefully removed using cautery for hemostasis. Next, a 5-0 Monocryl was used for suturing in a continuous fashion on each side to complete the repair. Following the procedure, a gentle compressive bio-occlusive dressing was

done and instruct the family to remove it if it hadn't come off within the first three days. If it remains, they can work it off gradually after each bath over the next four days. I recommend applying Vaseline during each diaper change and scheduling a follow-up visit in 6 weeks.

Surgical procedures to resolve phimosis without removing the foreskin, known as preputioplasty, include Y-V plasty, transversal widening on the dorsal side, triple incision plasty, longitudinal incision and transverse closure, lateral preputioplasty, sutureless prepuce plasty, four V-flap repair, and Z-plasty reconstruction.³⁴ These methods result in good outcomes, but phimosis can potentially recur.

Complications from circumcision are uncommon, between 1-4% of cases, with bleeding being the most common. Risk of sexual dysfunction after circumcision is still controversial. Complications that have been reported are trapped penis, redundant foreskin, preputial adhesions, meatal stenosis, urethrocuteaneous fistula, glangular necrosis, penile amputation, and hypospadias, but these complications are rare.³⁵ Pediatric circumcision can lead to psychological trauma in the phallic period, between 3-6 years old.³⁶

Conclusion

Phimosis is a common genital occurrence in young boys. Physicians should explain phimosis to parents. Newborn circumcision while controversial is a familial decision and should be based on informed consent. Additionally, in the face of absolute indications, which are pathological phimosis related to lichen sclerosus, recurrent balanoposthitis, or symptomatic therapy-resistant phimosis, antenatal history of significant hydronephrosis, known reflux, boys who are at risk of urinary tract infections due to congenital upper tract abnormalities such as vesicoureteral reflux.

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Conflict of Interest

The authors declare no conflicts of interest.

Table 1. Demonstrates studies about the efficacy of topical corticosteroids on phimosis.

Study	Participant	Method	Classification of potency and duration	Result	Other
Jorgensen et al. (1993) ¹⁶	54 boys with phimosis (mean age 6.9 years)	Open trial with 0.05% clobetasol propionate once daily for 1-3 months	Class I	Success rate 70%	No side effect
Kikiros et al. (1993) ¹³	63 boys with phimosis	Steroid ointment: Betamethasone valerate 0.05% (42 patients), 1% hydrocortisone 1% (18 patients), 2% hydrocortisone (3 patients) was applied three times daily for 4 weeks	Betamethasone valerate 0.05%: class II 1% Hydrocortisone: class VII 2% Hydrocortisone: class VII	37 patients in 0.05% betamethasone valerate group showed an initial improvement. 2 patients using 2% hydrocortisone and 16 using 1% hydrocortisone ointment showed improvement, but 2 of the latter group ultimately required circumcision.	Recurrent 6 patients in 0.05% betamethasone group
Orsola et al. (2000) ³⁷	137 boys (median age 5.4 years)	0.05% betamethasone cream applied twice a day for 4 weeks. evaluated after 5 weeks and at 6 months. In primary phimosis ≤ 5 years, success 95.4% >5 years, success 82.3%	Class II	At 5 weeks, 82% had successful result, 12% had a partial response, and 6% were failures. 25 patients underwent a second course of treatment. At 6 months, 90% had a successful without recurrence. 13 patients had recurrent or persisted	In recurrent groups, non-compliant with the suggested daily foreskin care
Lund et al. (2000) ³⁸	137 boys	RCT to 0.1% betamethasone (n=66) vs placebo (n=71) twice daily for 4 weeks	Class V	Success rate 74% VS 44% at 4 weeks	Treatment effect persists for at least 18 months
Letendre et al. (2009) ²⁴	43 boys (age 3-12 years)	RCT of 2-month twice daily treatment with emollient cream (placebo) vs 0.1% triamcinolone	Class III-IV	Success rate 48% in placebo and 90% in triamcinolone group at 8 weeks. Success rate 39% in placebo group and 76% in the triamcinolone group at 12 weeks (p<0.05)	After long-term follow-up, recurrence is frequent with triamcinolone 47% at 2 months and 76% at 4 months but not statistically significant
Reddy et al. (2011) ³⁹	260 boys age up to 15 years (mean age 34 months)	Betamethasone dipropionate (0.05%) on gently stretched prepuce twice a day	Class II-III	91% showed a successful outcome at end of 4 weeks, which was maintained in 77% over a mean follow-up of 25.4 months. The long-term failure rate was 23%	42 (17.8%) boys had recurrence of phimosis, 24 (57.14%) of these occurred within 6 months, while others were seen as late as 34 months. No side effect

Table 1. Demonstrates studies about the efficacy of topical corticosteroids on phimosis. (continued)

Study	Participant	Method	Classification of potency and duration	Result	Other
Lee et al. (2013) ⁴⁰	88 boys with Kikiris grade 4-5 (average age of 2.82±1.78 years)	0.05% clobetasol propionate cream was applied with massage and retracting the foreskin 20 times twice a day, after washing or bathing, for 4 consecutive weeks	Class I	Success rate 68%	No side effect
Sookpotarom et al. (2013) ¹⁵	47 patients, 23 boys (average age of 16.65 ± 4.052 months (11-24 months)) were given 0.025 % betamethasone cream. Another 24 boys in control group (average age of 18.42 ± 5.030 months (10-24 months))	RCT between valerate 0.025 % betamethasone cream vs 0.05 % betamethasone valerate cream twice a day for 2 months	No classified for this regimen	Success rate in the half-strength group (0.025 % strength) was significantly lower than 0.05 % betamethasone group (p = 0.0003)	
Makhija et al. (2018) ²²	100 boys (mean age 3.9 (1.5-12) years old)	0.1% mometasone applied three times a day for 6 weeks	Class IV-V	Success rate 84% at 6-weeks	
Chamberlin et al. (2019) ⁴¹	46 boys (Mean age 5.9-6.6) with Sookpotarom grade 4-5	Randomized open-label trial comparing 1% hydrocortisone cream in 21 boys vs 0.1% triamcinolone cream in 25 boys for 12 weeks.	Hydrocortisone: Class VII Triamcinolone: Class VI	Successful treatment in the hydrocortisone group was 30.8% at 4 weeks, 53.8% at 8 weeks, and 61.5% at 12 weeks. Successful treatment in the triamcinolone group was 31.6% at 4 weeks, 52.6% at 8 weeks, and 68.4% at 12 weeks (p=0.99)	
Chung et al. (2021) ⁴²	45 boys with Kikiris grade 4-5 (Mean age 46.64 months)	24 boys received Methylprednisolone aceponate and 21 boys received Hydrocortisone butyrate for 4-8 weeks.	Methylprednisolone aceponate: No classified Hydrocortisone butyrate: Class V	77.8% success. Recurrence of phimosis in 8.6% which can show remission after additional topical steroid therapy. Success rate of the MPA group was higher than that of the HCB group (91.7% and 61.9% respectively, p=0.029).	No side effect

Table 1. Demonstrates studies about the efficacy of topical corticosteroids on phimosis. (continued)

Study	Participant	Method	Classification of potency and duration	Result	Other
Zhou et al. (2021) ⁴³	1499 boys (age 2-12) Kikiros grade 4-5	0.1% mometasone furoate twice a day for 4 weeks. Patients were re-evaluated at the end of weeks 2, 4, 8, and 6 months follow-up.	Class IV	71.1% responded at the end of week 4. The long-term success rate was 66.0% over a mean follow-up of 26.9 months.	No systemic side effects, 23 cases developed local erythema or burning sensation. 138 cases had recurrence of phimosis, of which 81 (58.7%) recurred within 8 weeks, while 57 (41.3%) recurred after 8 weeks
Zhou et al. (2022) ²¹	1689 boys with Kikiros grade 4-5 and had complications of phimosis. Age 1.9 -13.2 years (mean 57-58 months)	798 patients were administered 0.1% mometasone furoate twice daily for 4 weeks. 797 patients were administered 0.1% mometasone furoate once daily for 4 weeks. Evaluate at 3 months.	Class IV	Success rate was 65.8%	No difference in efficacy between once daily and twice daily dose at 4 weeks.

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3.2 Not previously published

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4.2 Creative and beneficial to all readers

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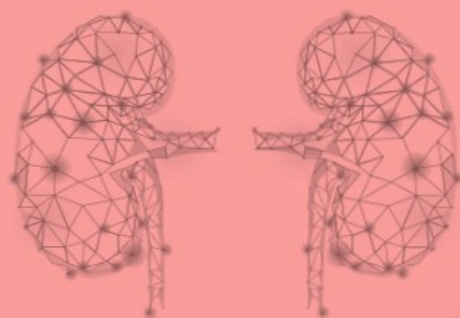
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