

# Predictors for Kidney Stones Recurrence Following Extracorporeal Shock Wave Lithotripsy (ESWL) or Percutaneous Nephrolithotomy (PCNL)

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**Background:** Stone recurrence after extracorporeal shock wave lithotripsy (ESWL) or percutaneous nephrolithotomy (PCNL) are common. Predictors for kidney stones vary among populations and areas.

**Objective:** To determine predictors for kidney stones recurrence after ESWL or PCNL.

**Material and Method:** A retrospective cohort study was conducted at a university hospital. The study cohort was patients aged more than 18 years, diagnosed with kidney stones, who were treated with ESWL or PCNL between 2006 and 2009. Medical files were reviewed for clinical profiles, stone characteristics, composition, type of treatment, presence of stone after treatment, stone reappearance, and related laboratory data. Predictors were determined by a multivariable poisson regression and presented as incidence rate ratios (IRRs) with 95% confidence interval.

**Results:** From a cohort of 252 patients, 240 who had at least one follow-up and with complete plain kidney ureters and bladder (KUB) film or intravenous pyelogram (IVP) were included in analysis. At three years, the total incidence rate of recurrence was 46 per 1,000 person-months. After a multivariable poisson regression clustering by type of stone composition, independent predictors for stone recurrence were age  $\leq 50$  years (adjusted IRR = 1.3, 95% CI = 1.2-1.4,  $p < 0.001$ ), ESWL treatment (adjusted IRR = 2.1, 95% CI = 2.1-2.2,  $p < 0.001$ ), stones located in lower calyx as compared to renal pelvis (adjusted IRR = 8.7, 95% CI = 2.9-25.9,  $p = 0.001$ ), multiple stones (adjusted IRR = 5.9, 95% CI = 4.8-7.5,  $p < 0.001$ ), and stone size larger than 20 mm (adjusted IRR = 1.4, 95% CI = 1.2-1.6,  $p < 0.001$ ).

**Conclusion:** After stone removals, patients with these predictors should closely be followed up for regular clinical evaluations.

**Keywords:** Predictors, Kidney stones, Post treatment, Reformation, Incidence rate, Nephrolithotomy

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Kidney stone disease is a significant problem in urological diseases, often leading to morbidity such as pain, hematuria, infection, deterioration of renal function, and renal failure<sup>(1)</sup>. The global prevalence of kidney stones ranged from 6% to 15%<sup>(2)</sup>. Reported incidences of kidney stones were between 114 and 270 per 100,000<sup>(3)</sup>. Currently, the safe and effective treatments of kidney stones are extracorporeal shock wave lithotripsy (ESWL) and percutaneous

nephrolithotomy (PCNL). Both treatments are used widely due to their minimal invasion, leading to a decrease in open surgery<sup>(1)</sup>. ESWL is considered as the first alternative treatment for kidney stones smaller than 3 cm in diameter<sup>(4,5)</sup>. During treatment, energy penetrates the body and focuses shock waves to disintegrate stones into fragments<sup>(6,7)</sup>. PCNL is a technique to remove stones directly through a tube under nephroscopy and is usually implemented for kidney stones larger than 3 cm, mostly staghorn stones, hard stones, infected stones, complex urinary stones, including those with failed treatment by ESWL<sup>(8-10)</sup>. After treatments, however, stone reformation is commonly found in 40 to 50% within five years, 50 to

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60% within ten years for recurrence<sup>(11)</sup> and 5.2 to 41% within 1 to 2 years for regrowth<sup>(12-14)</sup>.

The exact etiology of stone formation is complex. Stone formation is caused by the imbalance between an excessive concentration of factors promoting urinary crystallization and a defective concentration of factors inhibiting crystal formation<sup>(2)</sup>. Previous studies reported various risk factors for stone recurrence. However, the results are conflicting. Some studies reported prognostic factors of stone recurrence such as gender, history of stone recurrence and type of treatment<sup>(15,16)</sup>. Additional factors including age, family history, underlying disease<sup>(17)</sup>, body mass index (BMI)<sup>(18)</sup>, urine calcium level, urinary tract infection (UTI)<sup>(19)</sup>, urine specific gravity<sup>(20)</sup>, uric acid levels<sup>(21)</sup>, and stone compositions<sup>(22,23)</sup>, and increased the risk of stone recurrence in other studies<sup>(24,25)</sup>.

ESWL and PCNL have been introduced as the procedure for treating kidney stones in Thailand since 1987 and 1994, respectively. Stone recurrence is still the main problem after stone removals. Study focusing on patient's prognosis is somehow rare. The authors aimed to determine potential predictors for stone recurrence following ESWL or PCNL. The results may be useful for providing proper preventive strategies or for essential clinical evaluations and management.

### Material and Method

A retrospective cohort study was conducted in patients aged over 18 years diagnosed with kidney stone and treated with ESWL (MODULITH® SLX-20) or PCNL between 2006 and 2009, at the Urological Unit, Chiang Mai University Hospital. Patients who had stone free or complete clearance of the stone after these two treatments were included. They were appointed to follow-up at three months for stone

examination and then every year for three years for stone recurrence evaluation. All plain kidney ureters and bladder (KUB) films were reviewed by the same urologist and radiologist. Stones appeared on radiograph after certain stone free period were defined as "recurrent stones". Stone sizes were calculated by adding the diameters of all stones within one kidney. The consecutive three years of patients' medical files after treatment were reviewed. Two hundred forty patients had at least one follow-up and with complete plain KUB film and/or intravenous pyelogram (IVP) film results and were included for the analysis.

Study variables were focused on gender, age, BMI, underlying diseases, urine pH, urine specific gravity, history of urinary tract infection, type of treatment, stone compositions, stone size, number, location, and urinalysis report. Data were analyzed by a standard statistical package. The present study protocol was approved by The Research Ethics Committee of Chiang Mai University Medical School.

Predictors for kidney stones recurrence following ESWL or PCNL were analyzed in two steps. First, a univariable poisson regression was performed to detect predictors with p-value less than 0.20. Second, a backward stepwise multivariable poisson regression was used to determine significant prognostic factors from variables selected from the first step. Incidence rate ratios (IRRs) with 95% confidence interval were used to identify the importance of each predictor. A p-value less than 0.05 was considered statistically significant.

### Results

Of 252 patients with kidney stones, 240 patients were eligible. Among these, 119 were treated with ESWL and 121 with PCNL (Fig. 1). By KUB film or IVP at three months follow-up, the total

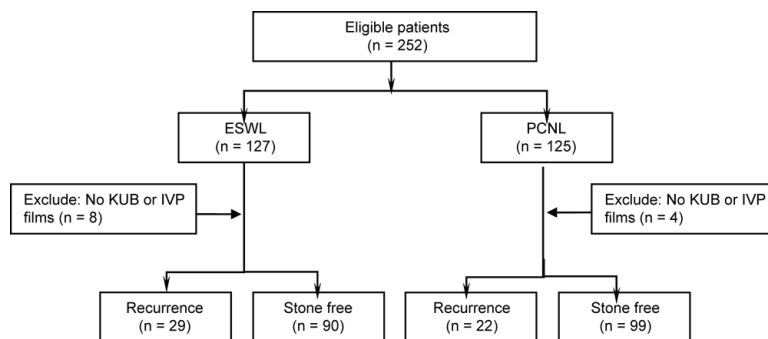


Fig. 1 Study flow diagram for kidney stone patients after ESWL or PCNL at three years of follow-up

incidence rate of recurrence was 46 per 1,000 person-months. The incidence rates of stone recurrence after the ESWL or PCNL of the present study population are shown in Table 1. The stone size in ESWL group was 14.5 mm and 31.5 mm in PCNL group. The majority of stone compositions were calcium stone (133 cases,

68.2%), the rest were mixed stones (34 cases, 17.4%), and non-calcium stones (28 cases, 14.4%).

By a univariable poisson regression, factors that increased the incidence of stone recurrence with p-value less than 0.20 were age  $\leq$  50 years ( $p = 0.086$ ), BMI  $>$  25 kg/m<sup>2</sup> ( $p = 0.139$ ), ESWL treatment ( $p = 0.021$ ),

**Table 1.** Incidence rate of stone recurrence after ESWL or PCNL at three years

Characteristics	Recurrence	Follow-up time (month)	Incidence rate <sup>a</sup>	p-value
Gender				
Female	32	3,120	10.2	0.496
Male	19	2,256	8.4	
Age (year)				
$\leq$ 50	31	2,616	11.8	0.086
$>$ 50	20	2,760	7.2	
BMI (kgs/m <sup>2</sup> )				
$\leq$ 25	7	804	8.7	0.139
$>$ 25	26	1,968	13.2	
Underlying disease				
No	36	4,128	8.7	0.297
Yes	15	1,248	12.0	
Urinary pH				
$\leq$ 5.5	18	1,848	9.7	0.415
$>$ 5.5	29	1,272	22.7	
Urine specific gravity				
$\leq$ 1.025	2	132	15.2	0.766
$>$ 1.025	45	3,000	15.0	
Urinary tract infection				
No	49	5,100	9.6	0.791
Yes	2	276	7.2	
Type of treatment				
PCNL	22	2,784	7.9	0.021
ESWL	29	2,592	11.2	
Stone size (mm)				
$\leq$ 20	19	2,628	7.2	0.020
$>$ 20	32	2,748	11.6	
Stone location				
Renal pelvis	2	1,056	1.8	0.034
Upper calyx	3	360	8.3	
Middle calyx	5	564	8.8	
Lower calyx	41	3,396	12.1	
Stone number				
Single stone	5	1,560	3.2	$<$ 0.001
Multiple stones	41	3,396	12.1	
Stone composition				
Calcium stone	24	3,000	8.0	0.994
Mixed stones <sup>b</sup>	6	756	7.9	
Non calcium stones <sup>c</sup>	5	660	7.6	

<sup>a</sup> Incidence rate per person-month

<sup>b</sup> Mixed stones: more than one stone compositions

<sup>c</sup> Non calcium stones: uric acid stone, struvite stone, and cystine stone

stone size larger than 20 mm ( $p = 0.020$ ), stone located in the lower calyx ( $p = 0.011$ ), and multiple stones ( $p < 0.001$ ) (Table 2). These factors were analyzed in the next step. Results from multivariable poisson regression clustering by type of stone compositions indicated that independent prognostic factors of stone recurrence were; age  $\leq 50$  year (adjusted IRR = 1.3, 95% CI = 1.2-1.4,  $p < 0.001$ ), ESWL treatment (adjusted IRR = 2.1, 95% CI = 2.1-2.2,  $p < 0.001$ ), stone size larger than 20 mm (adjusted IRR = 1.4, 95% CI = 1.2-1.6,  $p < 0.001$ ), stones located in the lower calyx when compared to renal pelvis (adjusted IRR = 8.7, 95% CI = 2.9-25.9,  $p = 0.001$ ), and multiple stones (adjusted IRR = 5.9, 95% CI = 4.8-7.5,  $p < 0.001$ ). Near significant prognostic factors were stones in the middle calyx (adjusted IRR = 2.4, 95% CI = 0.7-7.7,  $p = 0.142$ ) and in the upper calyx (adjusted IRR = 3.3, 95% CI = 0.4-25.8,  $p = 0.248$ ) (Table 3).

## Discussion

Stone sizes larger than 20 mm, located in lower calyx, multiple stones, age  $\leq 50$  year, and ESWL treatment were the significant prognostic factors of stone recurrence following these two treatments. This confirmed the findings of the previous studies<sup>(20,26)</sup>, that larger stone tended to recur or reform than smaller stone because the larger stone fragments remained after ESWL treatment causing more stone dust or microscopic residual stone debris left in the collecting system, which may serve as nuclei for new stones<sup>(27)</sup>. These stone dust particles may be too small to be visualized by plain KUB films and are therefore interpreted as “stone free”. In the nuclei development process, the crystal grows and aggregates leading to a new stone formation in the collecting duct of kidney leading to clinically detected recurrence<sup>(28)</sup>.

Recurrence was explained by multiple stones in previous studies<sup>(25,29)</sup>. This may be noted that the higher number of residual stones, the greater chance of recurrence<sup>(14)</sup>.

Similar to previous studies<sup>(14,30)</sup>, stone location, especially in the lower calyx, was another significant predictor of stone recurrence. The results could be explained by the fact that stones located in lower calyx are in the lowest position of the kidney which is the area where residual fragments are mostly collected and at the same time, they are difficult to remove<sup>(8,30)</sup>. These residual fragments may further develop into larger stones and may lead to stone recurrence<sup>(22)</sup>.

Similar to previous studies<sup>(20)</sup>, stone recurrence was more commonly observed in younger

**Table 2.** Univariable incidence rate ratio (IRR) of stone recurrence after ESWL or PCNL at three years

Factors	IRR	95% CI of IRR	p-value
Female	1.2	0.8-1.8	0.496
Age $\leq 50$ year	1.6	0.9-2.8	0.086
BMI $> 25$ kgs/m <sup>2</sup>	1.5	0.8-2.7	0.139
Underlying disease	1.3	0.9-2.1	0.297
Urinary pH $> 5.5$	2.3	0.8-1.8	0.415
Urinary specific gravity $> 1.025$	1.0	0.5-2.8	0.766
Urinary tract infection	1.1	0.5-2.5	0.791
ESWL (vs. PCNL)	1.3	1.1-2.2	0.021
Stone size $> 20$ mm	1.6	1.1-2.4	0.020
Stone location <sup>a</sup>			
Upper calyx	4.6	0.9-24.1	0.065
Middle calyx	4.8	0.7-26.3	0.105
Lower calyx	6.7	1.5-26.4	0.011
Multiple stones	3.8	1.9-7.2	$< 0.001$
Stone composition <sup>b</sup>			
Calcium stone	1.1	0.5-1.9	0.939
Mixed stones	1.0	0.4-2.2	0.912

<sup>a</sup> Compared to renal pelvis

<sup>b</sup> Compared to non calcium stones

**Table 3.** Multivariable<sup>a</sup> incidence rate ratio (IRR) of stone recurrence after ESWL or PCNL at three years

Factors	Multivariable IRR	95% CI of IRR	p-value
Age $\leq 50$ year	1.3	1.2-1.4	$< 0.001$
ESWL (vs. PCNL)	2.1	2.1-2.2	$< 0.001$
Stone size $> 20$ mm			
Stone location <sup>b</sup>	1.4	1.2-1.6	$< 0.001$
Upper calyx	3.3	0.4-25.8	0.248
Middle calyx	2.4	0.7-7.7	0.142
Lower calyx	8.7	2.9-25.9	0.001
Multiple stones	5.9	4.8-7.5	$< 0.001$

<sup>a</sup> Poisson regression clustered by stone compositions

<sup>b</sup> Compared to renal pelvis

stone formers. Age could be associated with a recurrence of kidney stones because the urine of younger people had a strong capacity of crystallization inhibition<sup>(31)</sup>.

The previous extracorporeal shock wave lithotripsy has been reported in 1996<sup>(8)</sup> and 2003<sup>(29)</sup> as the predictors for stone recurrence, because of residual fragments or microscopic sand particles that may act as foci for new stone formation<sup>(29)</sup>. However, current ESWL equipment is highly efficient to

disintegrate stones into minute fragments, which consequently will be removed through ureter, leading to lesser opportunity of stone recurrence.

Struvite stones with urease-producing micro-organism results in increasing urinary concentration of ammonium and carbonate ions, and give urine alkaline pH, leading to rapid stone formation and high recurrence or regrowth rate<sup>(17)</sup>. However, the present study comprised a small number of patients with struvite stones. This may explain the insignificance of stone compositions in the present study.

Body mass index and urine pH were not related to stone reforming and were not determined as the prognostic factor of stone recurrence. These findings were consistent with the results of previous studies<sup>(18,20)</sup>. Other prognostic factors reported in previous studies including, gender<sup>(16)</sup>, urine specific gravity<sup>(20)</sup>, history of UTI<sup>(25)</sup>, were not identified in the present study. This may be due to population differences or stone compositions differences among study areas<sup>(20)</sup>.

As an observational design, other potential factors reported in previous studies such as dietary modification<sup>(18)</sup>, drug therapies<sup>(20)</sup>, fluid intake<sup>(15,16)</sup>, and metabolic evaluation<sup>(16)</sup> were not planned in data collection. However, such information was not always available even in routine practice.

Readers should be aware that three years follow-up in the present study may not be sufficient to observe total stone recurrence. However, the results may reveal short-term evidence. By longer time of observation, additional prognostic factors could be detected as well as a long-term recurrence rate.

### Conclusion

During the three years of follow-up, the incidence rate of recurrence was 46 per 1,000 person-months. The stone size larger than 20 mm, located in lower calyx, multiple stones, age  $\leq$  50 year, and ESWL treatment were significant prognostic factors of kidney stones recurrence following ESWL or PCNL. The findings may be useful to identify high-risk patients in order to provide proper monitoring and investigation to prevent stone.

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### Potential conflicts of interest

None.

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## ปัจจัยทำนายการกลับเป็นซ้ำของนิ่วในไตภายหลังรักษาด้วยวิธีสลายนิ่วหรือวิธีเจาะนิ่วผ่านเนื้อไต

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**ภูมิหลัง:** การกลับเป็นซ้ำของนิ่วในไตภายหลังรักษาด้วยวิธีสลายนิ่วหรือวิธีเจาะนิ่วผ่านเนื้อไตพบได้บ่อย ซึ่งพบว่าหลากหลายปัจจัย

**วัตถุประสงค์:** เพื่อศึกษาปัจจัยทำนายการกลับเป็นซ้ำของนิ่วในไตภายหลังรักษาด้วยวิธีสลายนิ่วและวิธีเจาะนิ่วผ่านเนื้อไต

**วัสดุและวิธีการ:** การศึกษานี้เป็นการศึกษาย้อนหลังในโรงพยาบาลมหาวิทยาลัย โดยศึกษาในผู้ป่วยที่อายุตั้งแต่ 18 ปีขึ้นไป ได้รับการวินิจฉัยเป็นนิ่วในไตและรักษาด้วยวิธีสลายนิ่วและวิธีเจาะนิ่วผ่านเนื้อไตระหว่างปี พ.ศ. 2549 และ พ.ศ. 2552 เก็บรวบรวมข้อมูลจากประวัติการรักษาของผู้ป่วย ลักษณะของนิ่ว องค์ประกอบของนิ่ว ชนิดของการรักษานิ่ว นิ่วที่เกิดขึ้นหลังการรักษา และสัมพันธ์กับข้อมูลจากห้องปฏิบัติการ ปัจจัยทำนายการกลับเป็นซ้ำของนิ่วในไตภายหลังรักษาด้วยวิธีสลายนิ่วและวิธีเจาะนิ่วผ่านเนื้อไตใช้สถิติ poisson regression และรายงานผลเป็นอัตราอุบัติการณ์ (IRRs) กับระดับความเชื่อมั่น 95%

**ผลการศึกษา:** ในจำนวนผู้ป่วยทั้งหมด 252 ราย 240 ราย ที่มีผลฟิล์ม KUB หรือ IVP ครบสมบูรณ์ที่ใช้ในการวิเคราะห์เมื่อติดตาม 3 ปี พบอัตราอุบัติการณ์การกลับเป็นซ้ำ 4.6 ต่อ 1,000 คน-เดือน ภายหลังการวิเคราะห์แบบ multivariable poisson regression ซึ่ง cluster โดยองค์ประกอบของนิ่ว ผลการศึกษาพบว่า ผู้ป่วยอายุน้อยกว่าหรือเท่ากับ 50 ปี (adjusted IRR = 1.3, 95% CI = 1.2-1.4,  $p < 0.001$ ), วิธีสลายนิ่ว (adjusted IRR = 2.1, 95% CI = 2.1-2.2,  $p < 0.001$ ), นิ่วที่อยู่ในตำแหน่ง lower calyx เมื่อเปรียบเทียบกับ renal pelvis (adjusted IRR = 8.7, 95% CI = 2.9-25.9,  $p = 0.001$ ), และนิ่วที่มีจำนวนหลายก้อน (adjusted IRR = 5.9, 95% CI = 4.8-7.5,  $p < 0.001$ ) และนิ่วที่ขนาดใหญ่กว่า 20 มิลลิเมตร (adjusted IRR = 1.4, 95% CI = 1.2-1.6,  $p < 0.001$ )

**สรุป:** ภายหลังการรักษานิ่วในไตผู้ป่วยที่มีปัจจัยทำนายเหล่านี้ควรจะได้รับการติดตามดูแลอย่างใกล้ชิดเพื่อจะได้รับการรักษาต่อไป

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