

# Predictive Factors Of Pyonephrosis In Renal Calculus Patients

# Mohammad Yasine Husnoo, Wan Mokhzani Wan Mokhter, Mohamed Ashraf Mohamed Daud, Zaidi Zakaria

# Background

This is a retrospective study conducted to describe the prevalence and analyse the predictive factors of patients with underlying renal calculi presenting with pyonephrosis in Hospital Universiti Sains Malaysia.

# Methods

Patients with renal calculus disease with or without pyonephrosis presenting to Hospital Universiti Sains Malaysia between January 2009 and October 2020 were evaluated. Analysis of the data was done using both univariate and multivariate analysis.

# Results

The prevalence of pyonephrosis from 1<sup>st</sup> January 2009 to  $31^{st}$  October 2020 was 120 of which 100 (83.3%) were secondary to renal calculus. A total of 139 renal calculus patients were included with 72 renal calculus patients without pyonephrosis and 67 renal calculus patients with pyonephrosis. The positive predictive factors amongst patients with renal calculus for developing pyonephrosis include diabetes mellitus (p = 0.038), non-functioning kidney (p = 0.022), staghorn calculi (p = 0.046) and moderate or severe hydronephrosis (p = 0.013). In terms of long term outcomes, 3.1% (2/65) patients passed away from urosepsis secondary to pyonephrosis and 12.3% (8/65) developed acute kidney injury (AKI) and progressed to chronic kidney disease (CKD).

# Conclusion

Our study demonstrates out of a total of 338 patients who presented to HUSM with renal calculus, a prevalence of 120 patients (35.5%) across 11 years for pyonephrosis out of which 100 patients (83.3%) were renal calculus patients who developed pyonephrosis. Factors showing statistically significant associations with the development of pyonephrosis include diabetes mellitus (p = 0.024), non-functioning kidney on admission (p = 0.02), presence of staghorn calculi (p = 0.043) and moderate or severe hydronephrosis (p = 0.013).

Dr Mohammad Yasine Husnoo MB BCh BAO, MRCS, MMED (Surgery) Department Of Surgery, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia. https://orcid.org/0000-0002-6259-5340

#### Dr. Wan Mokhzani Wan Mokhter MD, MS

Department Of Surgery, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia. https://orcid.org/0000-0002-6259-5340

Dr Mohamed Ashraf Mohamed Daud, MMED, FEBU, FRCS(Urol) Department Of Surgery, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia.

> Prof Zaidi Zakaria MBBS, MS

Department Of Surgery, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia.

https://orcid.org/0000-0002-6259-5340

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Pyonephrosis is the suppurative destruction of the renal parenchyma as a result of renal or ureteric obstruction. The causes of the obstruction can be intraluminal such as stones, or extraluminal such as compression from tumours. Pyonephrosis is a serious condition. However since it is uncommon, there is limited data in the literature regarding its prevalence. At the time of presentation, patients are usually ill and can end up with urosepsis, which comes with a mortality rate between 22% and 76%.<sup>1</sup> Consequently patients may require Intensive Care Unit admission. This may be accompanied by concomitant acute kidney injury secondary to obstruction. Therefore prompt treatment is essential to prevent damage to the renal parenchyma.

Pyonephrosis is caused by the obstruction of the ureter. The most common cause of pyonephrosis is renal calculus. In a study by Scarneciu et al, they found that 53 out of 65 cases (81.5%) of pyonephrosis were caused by renal calculus, and only 6 cases due to urological malignancy.<sup>2</sup> Pyonephrosis is an uncommon disease. In a study by Patodia et al on predictive factors for pyonephrosis, out of 501 patients with renal calculus disease, 91 patients (18.1%) developed pyonephrosis.<sup>3</sup>

Understanding the risk factors of a disease is critical, as this allows for stratification of patients to determine who is at considerable risk, allowing these patients to be counselled about their increased risk and be channelled into prompt treatment pathways. However there is not much data regarding the risk factors for pyonephrosis. Currently the only study performed is by Patodia et al They analysed retrospectively 501 patients with renal calculus disease (RCD) who required surgical intervention. They divided the patients into 2 groups: RCD patients without pyonephrosis (Group 1) including 410 patients and RCD patients with pyonephrosis (Group 2) with 91 patients. They identified that having the following features resulted in a higher risk for patients with RCD to develop pyonephrosis: a longer duration of symptoms, having a non-functioning kidney, multiple renal calculi, staghorn calculi, ureteric stones, hydronephrosis and previous kidney surgery.<sup>3</sup>

Previous data suggested that retrograde stent insertion was associated with an increased risk of infection and hence percutaneous drainage with nephrostomy was favoured instead.<sup>4</sup> However more recent studies have demonstrated equal outcomes for both.<sup>5</sup> The latest guidelines on management of pyonephrosis by the European Association of Urology and the American Urological Association state that percutaneous drainage or retrograde stent insertion are equally effective as first-line management. The choice between the two should be guided by local resources.<sup>6,7</sup>

Currently in our hospital, patients with pyonephrosis undergo retrograde pyelogram and stenting as the first therapeutic intervention. This strategy results in fewer complications in comparison to more invasive procedures such as percutaneous drainage which predispose the patient to bleeding (given that the kidney is a highly vascular organ) and seeding of bacteria into the peritoneum during the puncture procedure.<sup>8</sup> Our practice is consistent a 15-year retrospective study by Goldsmith et alwho found that Patients treated with percutaneous nephrostomy were more likely to require ICU admission and demonstrated longer length of hospital stay, even when adjusting for age, APACHE II score, and Charlson Comorbidity Index score.9 (If retrograde stenting has failed due to inability to pass the stent through the blocked ureter, nephrostomy is then considered the next step and performed by interventional radiology.

Most studies published on the treatment of pyonephrosis are primarily based on percutaneous drainage. However in our centre, we practice drainage via retrograde stent insertion. So far, despite guidelines, data regarding retrograde ureteric stent in treatment for pyonephrosis and their outcome worldwide and in Malaysia remains underreported.

At the Indira Gandhi Medical College where cystoscopy is not always available, Sood et al have performed a study on the performance of percutaneous nephrostomy in 50 kidneys on 32 patients with pyonephrosis. The success rate of their procedure was 42 out of 50 patients (84%). Outcomewise they noted that the most common complication of percutaneous nephrostomy, which is bleeding, presented as haematuria in 14% of cases.<sup>10</sup> They concluded that percutaneous nephrostomy is a suitable alternative for drainage.

Flukes et al performed a prospective study of 53 patients over a 15 months' period from January 2012 to April 2013. Their primary objective was to review the outcome of patients undertaking retrograde ureteric stenting for pyonephrosis. In their study, they demonstrated that 51 of 52 patients (98%) were successfully treated with retrograde ureteric stenting. A theoretical risk of retrograde stenting is of the worsening sepsis secondary to instrumentation. In their study, only 3 patients required ICU admission.

The European Association of Urology currently advocates either percutaneous nephrostomy or retrograde ureteric stenting for drainage of pyonephrosis.<sup>7</sup>

Currently there is no data available regarding the prevalence of patients suffering from pyonephrosis in Malaysia. There are also no defined predictive factors that can stratify and identify at-risk patients for pyonephrosis in renal calculus patients. Renal calculus patients are treated on an elective basis with some patients postponing (or treatment being delayed) treatment for years. Early identification of these high-risk patients can lead to channelling of these patients into earlier treatment pathways to treat their causative factors pre-emptively, thereby preventing the patient from developing this complication, which is associated with a substantial risk of morbidity and mortality. Early intervention can be done to improve the patients' overall outcomes.

In a retrospective study, Patodia et al noted that longer duration of symptoms, staghorn calculi, hydronephrosis, ureteric stone, multiple renal stone, non-functioning kidney, and previous kidney surgery were predictors for pyonephrosis.<sup>3</sup> Yongzhi et al also found other risk factors associated with acute renal infections in patients with calculus disease including female gender, older age, and multiple sites of stone.<sup>11</sup> We intend to analyse the predictive factors in our population as well as assessing other relevant predictive factors.

The data obtained during this study includes outcomes of patient with pyonephrosis. By obtaining data regarding outcomes for pyonephrosis, we aim to provide more accurate counselling to patients regarding the risk of this disease to their health, so that they can reach a better decision regarding the further management of their disease.

#### **MATERIALS AND METHODS**

This is a retrospective review of medical records in Hospital Universiti Sains Malaysia (HUSM) Kelantan Malaysia from 1<sup>st</sup> January 2009 to 31<sup>st</sup> October 2020. Depending on risk factors, renal calculus patients can present as renal colic, hydronephrosis or pyonephrosis. We aim to identify and determine the predictive factors for renal calculus patients to develop pyonephrosis. We therefore allocated those presenting as renal colic and hydronephrosis as our comparator group. The study population are the patients with renal calculus disease who presented at HUSM Simple random sampling will be used to select patients with renal calculus disease without pyonephrosis (Group 1). All renal calculus patients who presented with pyonephrosis will be included (Group 2). The diagnosis of the patient will be taken from the formal ultrasound or CT (Computed Tomography) imaging report and from intraoperative findings. Inclusion criteria were patients with renal calculus disease who presented to HUSM between January 2009 and October 2020 and patients diagnosed with pyonephrosis over the last 10 years. Exclusion criteria were missing patient notes and patients who did not attend follow-up.

## **Statistical Data Analysis**

Data was analysed with Statistical Package for the Social Sciences (SPSS) version 26.

Descriptive analysis was used to summarise the sociodemographic characteristics of subjects. Numerical data was presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data was presented as frequency (percentage).

Independent t test was used to compare continuous data and chi-square test was used to analyse categorical data. The statistical significance level used was p < 0.05. Data for risk factors were analysed with simple logistic and multivariate binary logistic regression to identify the predictors for pyonephrosis.

#### RESULTS

Out of a total of 338 patients who presented to HUSM with renal calculus from 1st January 2009 to 31st October 2020, 120 cases (35.5%) presented with pyonephrosis. 83.3% (100/120) of these were secondary to renal calculus, while 16.7% (20/120) were due to other causes. Of these 20 cases, there were 4 cases due to gynaecological cancer, 2 cases each of duplex kidney, ureteric cancer, ureteric stricture, neurogenic bladder and colon cancer, and 1 case each of bladder cancer, renal cancer, renal uterine fibroid, pregnancy abscess, and retroperitoneal cancer.

139 renal calculus patients were included in this study, with 72 patients in Group 1 (calculus disease without pyonephrosis) and 67 patients in Group 2 (calculus disease with pyonephrosis). The findings of the patient-related and disease-related factors from both groups are detailed in Table 1 and Table 2 respectively. A p value less than 0.05 was considered statistically significant for the univariate analyses.

Variable	Group 1 (n = 72)	Group 2 (n = 67)	p value		
Demographics					
Age (years) Mean ± Standard Deviation, Range	52.50 ± 13.95	56.66 ± 14.15	0.79		
	23 - 84	19 - 90			
Sex (Male / Female)	42/30	22/45	0.003		
Sex Ratio	1.4 : 1	1:2.05			
Race (Malay / Chinese)	69/3	65/2	1.000		
Associated co-morbidities					
Past history of urinary tract infections	0	23	< 0.001		
Gynaecological cancer	2	2	0.94		
Diabetes mellitus	16	36	< 0.001		
Chronic kidney disease	6	26	< 0.001		
Non-functioning kidney on admission	3	25	< 0.001		
Gout	2	3	0.67		
Anatomic variations of kidney	0	6	0.011		
Previous urological intervention	10	31	< 0.001		

 Table 1
 Results of data collection for patient-related factors

Variants which could be potential predictive factors from Table 1 and Table 2 and showed univariate significance were subsequently entered into a multivariate logistic regression model. These factors are shown in Table 3. A p value less than 0.05 was considered statistically significant for the multivariate analysis.

From the logistic multivariate analysis, factors shown to have statistically significant associations with pyonephrosis were diabetes mellitus (p = 0.038), nonfunctioning kidney on admission (p = 0.022), presence of staghorn calculi (p = 0.046) and presence of moderate or severe hydronephrosis (p = 0.013). Variables which showed univariate significance but were not statistically significant during multivariate analysis included: sex, history of urinary tract infections, chronic kidney disease, anatomic variations of kidney, previous urological intervention, positive urine culture for bacteremia, number of calculi and large size of renal calculi.

#### DISCUSSION

The prevalence of pyonephrosis across from January 2009 to October 2020 was 120. 83.3% (100/120) of these were secondary to renal calculus, while 16.7%

(20/120) were due to other causes. At the time of writing, there is limited evidence in the literature regarding prevalence of pyonephrosis due to the scarcity of cases.

According to Patodia et al, there was no statistically significant difference between the number of male and female patients with renal calculus presenting with pyonephrosis. With regards to age, there was also no significant discrepancy between renal calculi patients with pyonephrosis compared to their counterparts without pyonephrosis.<sup>3</sup> This is consistent with the findings in our own study.

In our study, 96.4% (134/139) of the patients over both groups were Malay with the remaining 5 patients (3.6%) being Chinese. Our study is therefore most representative of the Malay population, however further studies would be required to explore the predictive factors for pyonephrosis in renal calculi patients of Chinese background.

Pyonephrosis can present with a number of symptoms, the most frequent symptoms of which are fever, rigors and lumbar pain.<sup>12</sup> In one study, lumbar pain was noted to occur in 70% of patients with pyonephrosis, with fever, rigors and pyuria present in all their cases.<sup>13</sup> Renal angle tenderness can indicate

# Table 2 Results of data collection for disease-related factors

Variable	Group 1 (n = 72)	Group 2 (n = 67)	p value		
Clinical presentation					
Lumbar pain	55	44	0.163		
Radiation of pain to groin	19	21	0.519		
Cloudy urine	3	11	0.016		
Pyuria	0	17	< 0.001		
Urinary frequency	15	18	0.40		
Haematuria	16	7	0.062		
Fever	11	51	< 0.001		
Dysuria	15	22	0.11		
Rigors	4	26	< 0.001		
Renal angle tenderness	6	39	< 0.001		
Biochemical Abnormalities					
Elevated uric acid	37	34	0.458		
Elevated potassium	9	10	0.804		
Elevated blood urea nitrogen	19	31	0.027		
Elevated creatinine	24	38	0.015		
Elevated white cell count (> 12 x 10 <sup>6</sup> )	13	36	0.141		
Positive urine culture for bacteraemia					
No growth	64	44			
Escherichia coli	4	6			
Klebsiella pneumoniae	2	4			
Extended Spectrum Beta Lactamase	1	9	0.004		
Candida	1	2			
Acinetobacter	0	1			
Serratia marcescens	0	1			
Imaging Findings					
Number of calculi (single / multiple)	40/32	25/42	0.031		
Size of calculi > 2 cm	11	21	0.014		
Staghorn calculi present	7	23	< 0.001		
Number of renal calices involved (0/1/2/3)	35/28/8/1	30/25/10/2	0.818		
Lower calyx involvement	29	26	0.859		
Grade of hydronephrosis					
None or mild	44 (61.1%)	22 (32.8%)	0.001		
Moderate or severe	28 (38.9%)	45 (67.2%)	0.001		

#### Table 3 Variables used for logistic multivariate regression

Model	x <sup>2</sup> statistics (df)	Sig. p value
(Constant)	0.000 (1)	0.997
Sex	0.418 (1)	0.518
Past history of urinary tract infections	0.000 (1)	0.997
Diabetes mellitus	5.131 (1)	0.024
Chronic kidney disease	0.745 (1)	0.388
Non-functioning kidney on admission	5.396 (1)	0.020
Anatomic variations of kidney	0.000 (1)	0.999
Previous urological intervention	1.269 (1)	0.260
Positive urine culture for bacteraemia	2.163(1)	0.141
Number of calculi	2.310 (1)	0.129
Size of calculi > 2 cm	0.759 (1)	0.384
Staghorn calculi present	4.108 (1)	0.043
Grade of hydronephrosis	6.143 (1)	0.013
Dependent variable: Development of pyonephrosis Adjusted R square – 0.700		

pyelonephritis or presence of renal calculi, the latter of which can entail pyonephrosis. The literature regarding other potential symptoms remains otherwise limited. It is to be noted that, while seen very often in pyonephrosis, pyuria can be a nonspecific finding.<sup>12</sup>

Several other studies have explored the effects of comorbidities in pyonephrosis. Up to 20% of patients suffering from gout go on to develop nephrolithiasis, which can then in turn precipitate pyonephrosis.<sup>14</sup> Poorly-controlled diabetes mellitus, non-functioning kidney and anatomic variations of the kidney such as pelvic kidney or horseshoe kidney were noted to be risk factors for pyonephrosis[3,12,15]. In addition, an important cause of pyonephrosis is obstruction, which can be accounted for by urinary tract infections, metastatic tumours and as a post-operative complication of previous urological surgery.<sup>12</sup> There is currently limited literature on how chronic kidney disease is related to pyonephrosis. Our study showed that, of the co-morbidities, only diabetes mellitus and nonfunctioning kidney on admission showed statistically significant associations with pyonephrosis. History of urinary tract infections did not prove to be statistically significant on multivariate analysis. We suspect this may because urinary tract infections mainly affect the lower urinary tract.

Raised uric acid levels are a notable feature of gout, of which up to 20% of patients eventually develop nephrolithiasis, which itself is implicated in the pathophysiology of pyonephrosis. In addition, while not directly markers of kidney function, potassium is often affected in kidney disease.<sup>14</sup> Leucocytosis may be a feature of pyonephrosis, however a study by Erol et al proposes that leucocytosis is one of the signs which may not be present in up to 30% of cases.<sup>12</sup> In our study, none of these biochemical markers showed statistically significant associations with pyonephrosis.

Gram-negative bacilli account for most suppurative bacterial infections affecting the urinary tract, with E coli being the most common isolated pathogen in pyonephrosis.<sup>16,17</sup> Other infectious causes of pyonephrosis include fungal infections and tuberculosis. In addition, a study by Picozzi et al demonstrated Extended-Spectrum Beta-Lactamase (ESBL) producing E coli as accounting for 14.3% (7/49) of patients admitted for upper urinary tract infections, with all 7 of these patients developing pyonephrosis and sepsis.<sup>18</sup> Similar findings were noted in our study, including how most cases with positive urine cultures for bacteraemia showed gram-negative bacilli – including Escherichia coli and Klebsiella Pneumoniae – as well as how most cases of ESBL affected the pyonephrosis group. Compared to the non-pyonephrosis group, the pyonephrosis group had the most cases of bacteraemia caused by atypical microorganisms resistant to antibiotics including ESBL, a case of Ampicillin-C-beta-lactamase-producing Klebsiella pneumoniae, and the gram-negative bacilli Acinetobacter and Serratia marcescens. However while positive urine culture for bacteraemia showed univariate significance, it was not found to show a statistically significant association with pyonephrosis on multivariate analysis in our study.

Of the obstructive causes leading to pyonephrosis, renal calculi play an important part with up to 75% of these stones being staghorn calculi.<sup>12</sup> In addition, Patodia et al found that staghorn calculi, as well as the number – but not the size – of renal calculi, were statistically significant in renal calculi patients with pyonephrosis compared to renal calculi patients without pyonephrosis on logistic multivariate analysis.<sup>3</sup> In our own study, staghorn calculi, the number, and the size of renal calculi each showed univariate significance with pyonephrosis. This is likely due to large stones and multiple calculi causing urinary retention and damaging renal parenchyma. Of these factors, however, only staghorn calculi was noted to be statistically significant on multivariate analysis in our study.

The location of the renal stone within the calyx of the kidney holds important clinical significance in and of itself. Management of calculi in the lower pole of the kidney have been found to be particularly challenging both with extracorporeal shock wave lithotripsy and retrograde intra-renal surgery compared to the upper or middle poles of the kidney.<sup>19</sup> Based on our study, however, neither lower calyx involvement nor involvement of multiple renal calyces demonstrated any statistically significant association with pyonephrosis.

The severity of hydronephrosis was noted to be a predictor of pyonephrosis in our study. This is consistent with the findings of Patodia et al<sup>3</sup>, who also demonstrated that patients with pyonephrosis tended to have a more severe hydronephrosis, as well as by Boeri et al<sup>3</sup>, who identified the severity of hydronephrosis as being an independent predicting factor for pyonephrosis.

In terms of management, out of 67 pyonephrosis patients, 30 had retrograde stenting, 29 had antegrade stenting with nephrostomy and 2 patients

## **SUMMARY BOX**

What is already known about this subject:

- Pyonephrosis is associated with high mortality
- Currently there is limited data on prevalence of pyonephrosis
- There is also limited data on predictive risk factors for pyonephrosis

## What are the new findings:

- Our study demonstrates a prevalence of 120 patients across 11 years for pyonephrosis out of which 100 patients (83.3%) were renal calculus patients who developed pyonephrosis.
- We have also identified several factors showing statistically significant associations with the development of pyonephrosis. These include diabetes mellitus (p = 0.024), non-functioning kidney on admission (p = 0.020), presence of staghorn calculi (p = 0.043) and moderate or severe hydronephrosis (p = 0.013).
- In terms of complications post procedure, out of 61 patients who underwent intervention included sepsis in 14.8% (9/61) patients, perforation in 2 cases, and gross haematuria in 3 cases.
- In terms of long-term outcome, 2 patients died from urosepsis secondary to pyonephrosis, 66.1% (43/65) patients had acute kidney on acute presentation (AKI) which resolved, and 12.3% (8/65) developed AKI and progressed to chronic kidney disease (CKD). 24.6% (16/65) did not have AKI.

had antegrade stenting following failed retrograde stenting. 4 patients were treated conservatively due being unfit for operation. They were treated with high dose antibiotics and 2 patients presented too late and passed away.

The indications for nephrostomy as intervention instead of retrograde ureteric stenting in HUSM included patient not being fit for retrograde pyelography and stenting, failed retrograde ureteric stenting due to technical issues or lack of available expertise.

In terms of complications post procedure, out of 61 patients who underwent intervention included sepsis in 14.8% (9/61) patients, perforation in 2 cases, and gross haematuria in 3 cases.

Post intervention, symptoms improved within 24 hours for 54.1% (33/61) patients, within 48hrs for 26.2% (16/61) patients and only 13.1% (8/61) took more than 48hrs.

In terms of long-term outcome, 2 patients died from urosepsis secondary to pyonephrosis, 66.1% (43/65) patients had acute kidney on acute presentation (AKI) which resolved, and 12.3% (8/65) developed AKI and progressed to chronic kidney disease (CKD). 24.6% (16/65) did not have AKI.

#### CONCLUSION

Our study demonstrates a prevalence of 120 patients (35.5%) across 11 years for pyonephrosis out of which 100 patients (83.3%) were renal calculus patients who developed pyonephrosis. We have also identified several factors showing statistically significant associations with the development of pyonephrosis. These include diabetes mellitus, nonfunctioning kidney on admission, presence of staghorn calculi and moderate ог severe hydronephrosis. Other factors which demonstrated statistical significance on univariate analysis but not on multivariate analysis include sex, history of urinary tract infections, chronic kidney disease, anatomic variations of kidney, previous urological intervention, positive urine culture for bacteremia, number of calculi and large size of renal calculi. In terms of longterm outcome, 3.1% (2/65) patients passed away from urosepsis secondary to pyonephrosis and 12.3% (8/65) developed AKI and progressed to chronic kidney disease (CKD).

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