

Original Article

A novel comprehensive predictive model for obstructive pyonephrosis patients with upper urinary tract stones

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Abstract: Background: Calculous pyonephrosis tended not to be accurately diagnosed before operations. It is mostly confirmed during percutaneous nephrolithotripsy or percutaneous nephrostomy. We aimed to evaluate the risk factors for predicting obstructive pyonephrosis patients with upper urinary tract stones. Methods: Clinical data of 322 patients with upper urinary tract stones and obstructive hydronephrosis were retrospectively searched and analyzed in our study. The patients were divided into two groups; pyonephrosis and non-pyonephrosis groups. Both disease related factors and infection-associated indicators were analyzed. Univariate and multivariate logistic analyses were performed on preoperative variables. Accordingly, ROC curves were drawn, and a novel comprehensive model was constructed to predict the pyonephrosis. Outcomes: Compared to the non-pyonephrosis group, patients in the pyonephrosis group showed statistical differences in sex, urinary tract infection (UTI) within 3 months, stone density, computerized tomography (CT) value of hydronephrosis, serum creatinine, hydronephrosis, contralateral kidney severe hydronephrosis or atrophy, preoperative white blood cells, neutrophils, serum C-reactive protein, urine leukocyte, nitrite, and urine culture revealed statistical difference ($P<0.05$). Univariate analysis showed that there were significant differences for sex, UTI history, degree of hydronephrosis, contralateral severe hydronephrosis or atrophy, serum creatinine, and CT value of hydronephrosis ($P<0.001$). Multivariate analysis demonstrated several independent risk factors for pyonephrosis, including degree of hydronephrosis ($P=0.02$), CT value of hydronephrosis ($P=0.001$), urine leukocyte ($P=0.002$), urine culture ($P=0.001$) and blood neutrophils ($P=0.009$). Based on these risk factors, we constructed a novel comprehensive model and confirmed it was an effective method to predict pyonephrosis (AUC, 0.970). Bootstrapped calibration curves showed no untoward deviation in both training and validation dataset (mean absolute error of 0.027, 0.036). Conclusions: Hydronephrosis, CT value of hydronephrosis, blood neutrophils, urine leukocyte, and urine culture were independent risk factors to predict pyonephrosis. The novel comprehensive model was found to be an effective method to predict pyonephrosis and needed to be further confirmed in prospective studies.

Keywords: Calculous pyonephrosis, hydronephrosis, risk factors, predict

Introduction

Upper urinary tract stones obstruction resulting in hydronephrosis or even renal pyonephrosis is not uncommon in urology. Pyonephrosis referred to the purulent exudate accumulation in the renal collection system, which could be secondary to infection with hydronephrosis or develop from pyelonephritis [1]. Obstructive pyonephrosis accounted for 3.2% of upper urinary stones in patients [2]. Studies had indicated that the incidence of systemic response inflammatory syndrome (SIRS) after percutaneous nephrolithotripsy (PCNL) was nearly 21% in patients with non-acute stage pyonephrosis [3].

Currently, primary drainage (nephrostomy or retrograde ureteral intubation) followed by secondary surgery, was the principle of pyonephrosis treatment. The final diagnosis depended on the discovery of pyogenic fluids during puncture and drainage of the affected kidney. Different researchers had tried ultrasound [1], computerized tomography (CT), and even Magnetic Resonance Imaging (MRI) for preoperative prediction of pyonephrosis [4-6].

The application of the reported previous clinical methods had certain limitations and could not achieve higher prediction efficacy. Moreover, the imaging findings of pyonephrosis were not utterly consistent due to the different degrees

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of hydronephrosis and infection. In this study, we aimed to evaluate the risk factors for predicting obstructive pyonephrosis patients with upper urinary tract stones.

Methods

Data collection

The clinical data of patients with calculous pyonephrosis in our hospital in recent years, from March 2013 to March 2018, were retrospectively analyzed. From that data, 76 cases were included in the observation group. The control group consisted of 246 non-pyonephrosis patients who received ureteroscopic lithotripsy or PCNL for obstructive upper urinary tract stones. We studied and summarized the preoperative clinical data of all enrolled patients, including basic demographic data, clinical symptoms, duration of symptoms, the recent history of urinary tract infections, coexisting chronic diseases, basic characteristics of stones, and characteristics of affected contralateral kidneys. Diagnosis of hydronephrosis was classified as mild, moderate, and severe by ultrasound, according to Noble's classification [7]. Relevant laboratory examination data of the patients was collected and compared, such as the level of preoperative white blood cells (WBC), neutrophils, serum C-reactive protein (CRP), urine leukocyte, urine nitrite, and urine culture results. Urine cultures with a single microorganism growth of $\geq 10^5$ colony-forming units (CFU)/mL for a sterile midstream urine sample and $\geq 10^4$ CFU/mL for a catheterized sample were considered positive results [8]. CT values (Hounsfield units (HU)) were obtained and calculated automatically from picture archiving and communication systems (PACS) [4]. The collection and calibration of the information were done in collaboration with two independent researchers.

Inclusion and exclusion criteria

In the preliminary screening, cases with significant missing data were excluded. Specific inclusion and exclusion criteria for the pyonephrosis group were as follows. Inclusion criteria: (1) adult patients aged at least 18 years; (2) complete surgical or surgical drainage data related to the hospital stay; and (3) pus or purulent aggregates found during intraoperative or surgical drainage (PCN or retrograde ureteral intubation). Exclusion criteria: (1) patients who had

undergone nephrostomy or retrograde ureteral intubation before admission; (2) patients who have made an appointment for this pyogenic nephrectomy; (3) patients who have recently received endoscopic surgery to confirm abscess kidney and prepare for secondary surgery to treat residual stone; (4) no urological ultrasound or CT scan in our hospital; and (5) had identified perirenal abscess or retroperitoneal abscess.

Criteria for inclusion in the control group: (1) patients with upper urinary calculi who planned to receive PCNL or ureteroscopic lithotripsy in the same period; and (2) patients with hydronephrosis seen by plain CT scan or urinary system ultrasound. Exclusion criteria: (1) patients with previous diagnosis of pyonephrosis; and (2) patients with a history of repeated urological surgery in recent 6 months.

Diagnosis of calculous pyonephrosis

There were two main elements in the diagnosis of calculous pyonephrosis. The first element was the upper urinary tract calculi. All the enrolled subjects had different degrees of the renal pelvis, calices and/or ureteral calculi, which were confirmed by a non-enhanced CT scan. The second element was the presence of pus or purulent aggregated in the renal collection system. Patients with serious complications such as perirenal abscess and pyothorax were not included in the study.

The definitive diagnosis of pyonephrosis was based on the amount of pus of varying thicknesses seen by the naked eye during endoscopic surgery or surgical drainage (percutaneous nephrostomy or retrograde ureteral intubation), which was known as the "gold standard". These patients were later treated with percutaneous nephrolithotomy or transurethral ureteroscope lithotripsy.

Statistical analysis

All the statistical tests involved in this paper were analyzed by SPSS version 22.0 (IBM Corp., New York, NY) statistical software. Measurement data were verified by t-test (normal distribution, homogeneity of variance), and Mann-Witney test (non-normal distribution). The counting data were processed by the chi-square test or Fisher's exact test. Statistical signifi-

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Table 1. Preliminary analysis of variables before operation

	Pyonephrosis group (N=76)	Non-pyonephrosis group (N=246)	p value
Age (yrs)	48.6±13.4	51.7±11.6	0.054
Sex (Male/Female)	24/52	169/77	<0.001*
UTI within 3 months (n)			<0.001*
YES	50	26	
NO	26	220	
Duration of symptoms (days)	28 (11-110)	23 (8-98)	0.149
Hyperuricemia (n/N)	26/76	96/246	0.45
Coexisting chronic diseases (n/N)			
Hypertension	25/76	82/246	0.943
Diabetes	8/76	21/246	0.596
Hepatitis	14/76	36/246	0.426
HBV	14	32	
HCV	0	4	
Stone size (mm)	17.3±10.2	15.2±9.5	0.103
Stone density (HU)	1325.6±444.9	1192.5±335.8	0.007*
CT value of hydronephrosis (HU)	14.5 (11.1-22.0)	6.4 (2.0-12.7)	<0.001*
Staghorn calculi (n/N)	5/76	28/246	0.322
Serum creatinine (umol/L)	181±188 (70-195)	108±58 (73-125)	<0.001*
Hydronephrosis	70	208	<0.001*
Mild	12	162	
Moderate	20	22	
Severe	38	24	
SHACK (n/N)	26/76	18/246	<0.001*
Congenital renal malformation (n/N)	3/76	14/246	0.764

The interval in the parenthesis is interquartile range and the number before each parenthesis is the median value. yrs, years; UTI, urinary tract infection; HBV, hepatitis B virus; HCV, hepatitis C virus; HU, Hounsfield unit; SHACK, Severe hydronephrosis or atrophy of Contralateral kidney; Range, interquartile spacing; *P<0.05.

cance was defined as $P<0.05$. Preoperative related clinical information was analyzed by univariate logistic analysis. The degree of hydronephrosis and the urine culture results were assigned as dichotomous variables. Further, variables with statistical differences were analyzed by multivariate logistic regression. Independent risk factors were screened out. Using each independent risk factor as the diagnostic variable, receiver operating characteristic (ROC) curves were drawn. The sensitivity, specificity, as well as accuracy of each diagnostic test were calculated. A new comprehensive model was performed to predict pyonephrosis. According to the ratio of 70:30, the overall data was randomly divided into test dataset and validation dataset. Further, calibration curves were plotted and decision curve analyses (DCAs) were conducted to determine the net benefits by using the R software v.3 (<http://www.R-project.org>).

Results

Primary analysis of preoperative indicators between the two groups

All 322 obstructive hydronephrosis patients with upper urinary tract stones were divided into the observation group (76 pyonephrosis patients) and the control group (246 non-pyonephrosis patients). The preliminary analysis showed no significant difference in symptom duration, the incidence of coexisting chronic diseases, stone size, and kidney malformation. However, there were significant statistical differences in stone density ($P=0.007$), gender composition, history of UTI in recent 3 months, serum creatinine, degree of hydronephrosis, incidence of severe hydronephrosis or atrophy of the contralateral kidney (SHACK), and CT value of hydronephrosis ($P<0.001$) (**Table 1**; **Figure 1**).

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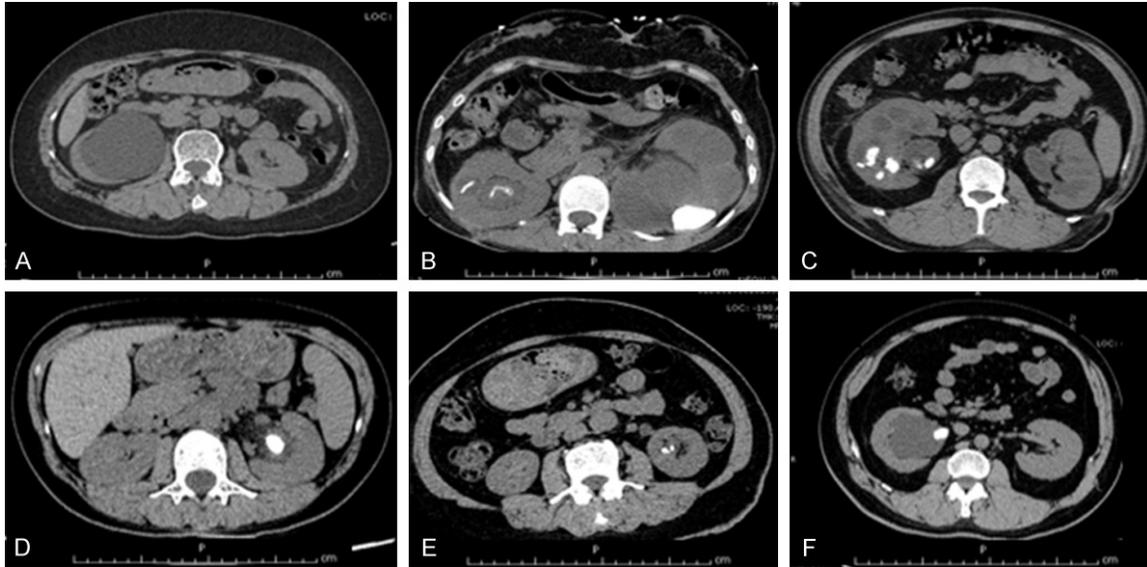


Figure 1. Preoperative axial CT images of 3 different patients in pyonephrosis and non-pyonephrosis group. A-C. Axial CT images of different patients in pyonephrosis group; D-F. Axial CT images of different patients in non-pyonephrosis group.

Table 2. Preliminary analysis of variables for infection-related indicators

Variables	Pyonephrosis group (76)	Non-pyonephrosis group (246)	p-value
WBC (*10 ⁹ /L)	9.92 (7.19-15.60)	6.02 (5.08-7.41)	<0.001 ^a
Neutrophils (*10 ⁹ /L)	7.11 (5.28-12.87)	3.49 (2.83-4.44)	<0.001 ^a
Serum CRP (mg/L)	73.7 (41.9-131.6)	2.7 (1.1-6.8)	<0.001 ^a
Urine leukocyte (/ul)	227.7 (60.9-3403.9)	76.2 (27.4-189.2)	0.001 ^a
Urinary nitrite			0.002 ^b
Positive	17	24	
Negative	55	218	
Urine culture			<0.001 ^b
Positive	34	26	
Negative	31	214	

The interval in the parenthesis is interquartile range and the number before each parenthesis is the median value. ^aMann-Whitney test. ^bChi-squared test. WBC, white blood cells; CRP, c-reactive protein.

In addition, we compared infection-related laboratory indicators between the two groups and found that the positive rate of nitrite in mid-stream urine in the observation group was higher than that in the control group ($P=0.002$). Before the operation, there were significant statistical differences in the WBC count ($P<0.001$), neutrophils count ($P<0.001$), serum CRP ($P<0.001$), urine leukocyte ($P<0.001$), and positive rates of 48-hour urine culture ($P<0.001$) between the two groups (Table 2).

Univariate and multivariate analysis of the risk factors for pyonephrosis

The univariate analysis supported statistical significance in sex, UTI within 3 months, CT value of hydronephrosis, serum creatinine, hydronephrosis, SHACK, preoperative WBC, neutrophils, serum C-reactive protein, urine leukocyte, nitrite, and urine culture ($P<0.05$), except stone density ($P=0.078$). Then, these 11 preoperative observation indicators were included in multivariate logistic regression analysis. Finally, 5 independent risk factors were screened out, including

degree of hydronephrosis ($P=0.02$), preoperative blood neutrophils ($P=0.009$), CT value of hydronephrosis ($P=0.001$), urine leukocytes ($P=0.002$), and urine culture ($P=0.001$) (Table 3).

ROC curves and the novel predictive model for pyonephrosis

Different ROC curves with the corresponding accuracy were constructed, which contained

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Table 3. Univariate and multivariate analysis of significant factors for predicting pyonephrosis before operation

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (yr)	0.980 (0.960-1.000)	0.06		
Sex (ref: female)	0.210 (0.121-0.366)	<0.001***	0.439 (0.091-2.113)	0.305
Duration of symptom (day)	1.000 (1.000-1.000)	0.305		
UTI within 3 months	16.272 (8.716-30.38)	<0.001***	0.550 (0.091-3.320)	0.514
Previous urological surgery (n)	1.255 (0.977-1.613)	0.076		
Hypertension (n/N)	0.980 (0.567-1.694)	0.943		
Diabetes (n/N)	1.261 (0.534-2.974)	0.597		
Hepatitis (n/N)	1.317 (0.668-2.598)	0.427		
Hyperuricemia (n/N)	1.231 (0.718-2.109)	0.450		
Stone size (mm)	1.021 (0.996-1.047)	0.105		
Staghorn calculi (n/N)	0.548 (0.204-1.473)	0.233		
Stone density (HU)	1.001 (1.000-1.002)	0.078		
Hydronephrosis (ref: mild and moderate)	9.104 (4.829-17.164)	<0.001***	7.233 (1.374-38.092)	0.020
Contralateral severe hydronephrosis or atrophy (n/N)	6.587 (3.356-12.929)	<0.001***	8.539 (0.987-73.885)	0.051
Congenital renal malformation (ref: normal)	0.681 (0.190-2.436)	0.555		
CT value of Hydronephrosis (HU)	1.157 (1.111-1.204)	<0.001***	1.312 (1.125-1.529)	0.001
Preop-serum creatinine (umol/l)	1.005 (1.003-1.008)	<0.001***	0.990 (0.976-1.004)	0.159
Preop-neutrophils# (*10 ⁹ /L)	1.832 (1.550-2.167)	<0.001***	2.162 (1.211-3.859)	0.009
Preop-serum CRP (mg/L)	1.040 (1.029-1.050)	<0.001***	1.009 (0.996-1.022)	0.186
Preop-urine leukocyte	1.001 (1.000-1.001)	<0.001***	1.001 (1.000-1.001)	0.002
Preop-urinary nitrite (ref: negative)	2.808 (1.411-5.587)	0.003	0.128 (0.012-1.321)	0.084
Preop-urine culture (ref: negative)	9.027 (4.786-17.026)	<0.001***	149.435 (8.126-2747.977)	0.001

HU, Hounsfield unit; Preop-, Preoperational; #, multicollinearity; OR, Odds ratio; CI., Confidence intervals; ***P<0.001.

the degree of hydronephrosis (AUC=0.714), preoperative blood neutrophils (AUC=0.856), HU of hydronephrosis (AUC=0.801), urine Leukocyte (AUC=0.695), and urine culture (AUC=0.707). Multivariate logistic analysis was used to obtain the independent risk factor coefficients. The prediction model equation was calculated as follows: $Y=K1 \times 1 + K2 \times 2 + K3 \times 3 + K4 \times 4 + K5 \times 5$ (Y: model score; K1, 1.979; K2, 0.271; K3, 0.771; K4, 0.001; K5, 5.007; $\times 1$, degree of hydronephrosis; $\times 2$, HU of hydronephrosis; $\times 3$, blood neutrophils count ($\times 10^9/L$), $\times 4$, urine leukocyte (n/ul), $\times 5$, urine culture). Finally, the model score which combined with these risk factors achieved a higher diagnostic accuracy with an area under the curve (AUC) of 0.970 (0.952-0.987, 95% CI (confidential interval)) (Figure 2; Table 4). Moreover, bootstrapped calibration curve in both training (N=225) and validation dataset (N=97) showed no untoward deviation of predicted risk from observed risk of pyonephrosis, with a mean absolute error of 0.027 and 0.036, respectively. The clinical net benefit results were achieved by performing the decision curve analyses (DCAs), harbouring net benefits with threshold probability range

from 0 to 0.94 in training dataset and 0 to 0.81 in validation dataset (Figure 3).

Discussion

Recent studies suggested that pyonephrosis caused by stone obstruction accounts for 77% of all causes. Other causes include stenosis, papillary necrosis, and obstruction of the ureteropelvic transition [9]. In our study, we aimed to evaluate the risk factors for predicting obstructive pyonephrosis patients with upper urinary tract stones. We identified several independent predictors, and for the first time, built a novel model to predict pyonephrosis.

To date, different researchers have tried to predict the presence of pyonephrosis by using ultrasound, CT, and MRI scans. By studying dogs, the researchers found that the purulent kidneys in ultrasound images had two characteristics: scattered or filled with echoes from the collecting system of the kidney. A liquid fragment formed by layered purulent exudates. Ismail et. al. believed that the pyonephrosis predicted by Hounsfield unit (HU) was a positive cut-off value of 0, with high sensitivity and

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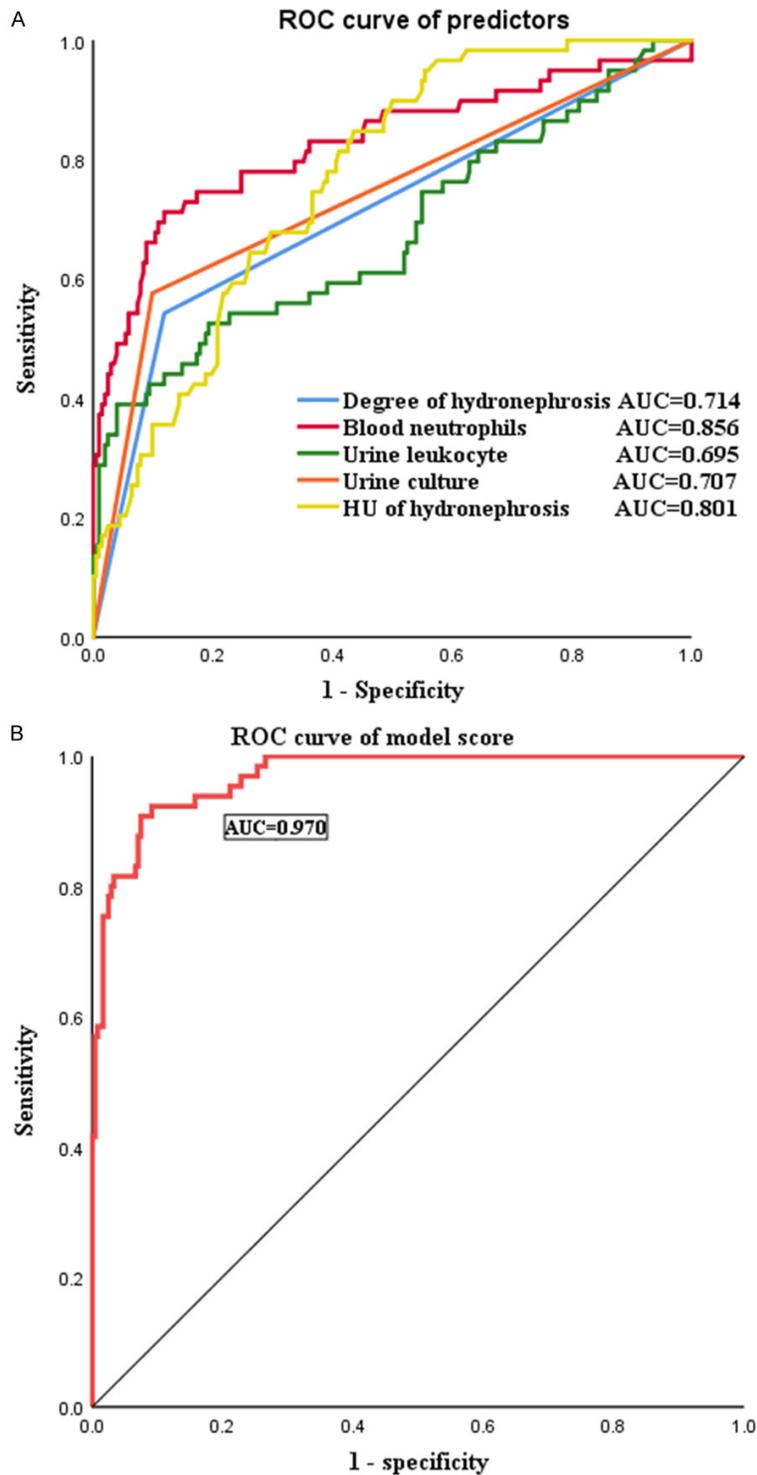


Figure 2. Comparing ROC curve of predictors and prediction model for pyonephrosis. A. ROC curves of independent risk factors; B. ROC curve of a novel prediction model.

specificity [4]. However, Emrah et. al. believed that the CT value of the patients with pyonephrosis was significantly higher than that of patients

with hydronephrosis. The average value of the pyonephrosis was 13.51 [5]. Although these methods had a certain value in the diagnosis of pyonephrosis, they failed to combine more relevant indicators to guide the preoperative prediction of pyonephrosis to a greater extent. In our study, five independent risk factors, including hydronephrosis degree, preoperative urine leukocyte cells, and urine culture results, CT value of hydronephrosis, and preoperative blood neutrophils count were screened out by multivariate logistic regression analysis. A novel comprehensive model was built to predict pyonephrosis, with sensitivity and specificity up to 98% and 81.6%, respectively.

It had been certified that age was a risk factor for recurrent urinary tract infections (UTIs) [10]. However, there was no difference in age between the two groups. Interestingly, women in the pyonephrosis group were older in our study. Moreover, the observation group had a higher proportion of female patients. This was consistent with previous literature studies, that elderly women were a risk factor for urinary tract infection [11].

Hydronephrosis was often accompanied by obstructive stone. In order to reduce data bias, all matched patients in the control group had different degrees of hydronephrosis. Patients without hydronephrosis were excluded. The results of the the urinary ultrasound examination were further confirmed by preoperative non-enhanced CT scan which had a higher rate of distal ureteral calculi detection compared with KUB/ultrasound [12]. Patients with

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Table 4. Comparing ROC curve of significant predictors for pyonephrosis

	AUC	95% CI	Sensitivity (%)	Specificity	Accuracy (%)
Degree of hydronephrosis	0.714	0.637-0.791	54.3	88.5	79.9
Blood neutrophils	0.856	0.799-0.914	47.4	97.2	85.4
Urine leukocyte	0.695	0.622-0.768	26.3	99.2	82.0
Urine culture	0.707	0.628-0.787	52.3	89.2	81.3
HU of hydronephrosis	0.801	0.749-0.853	35.5	93.1	79.5
Model score	0.970	0.952-0.987	75.4	97.9	93.1

HU, Hounsfield; AUC, area under the curve; 95% CI, 95% confidential interquartile; Model score, a new prediction model for pyonephrosis based on statistical significant variables in multivariate logistic regression analysis.

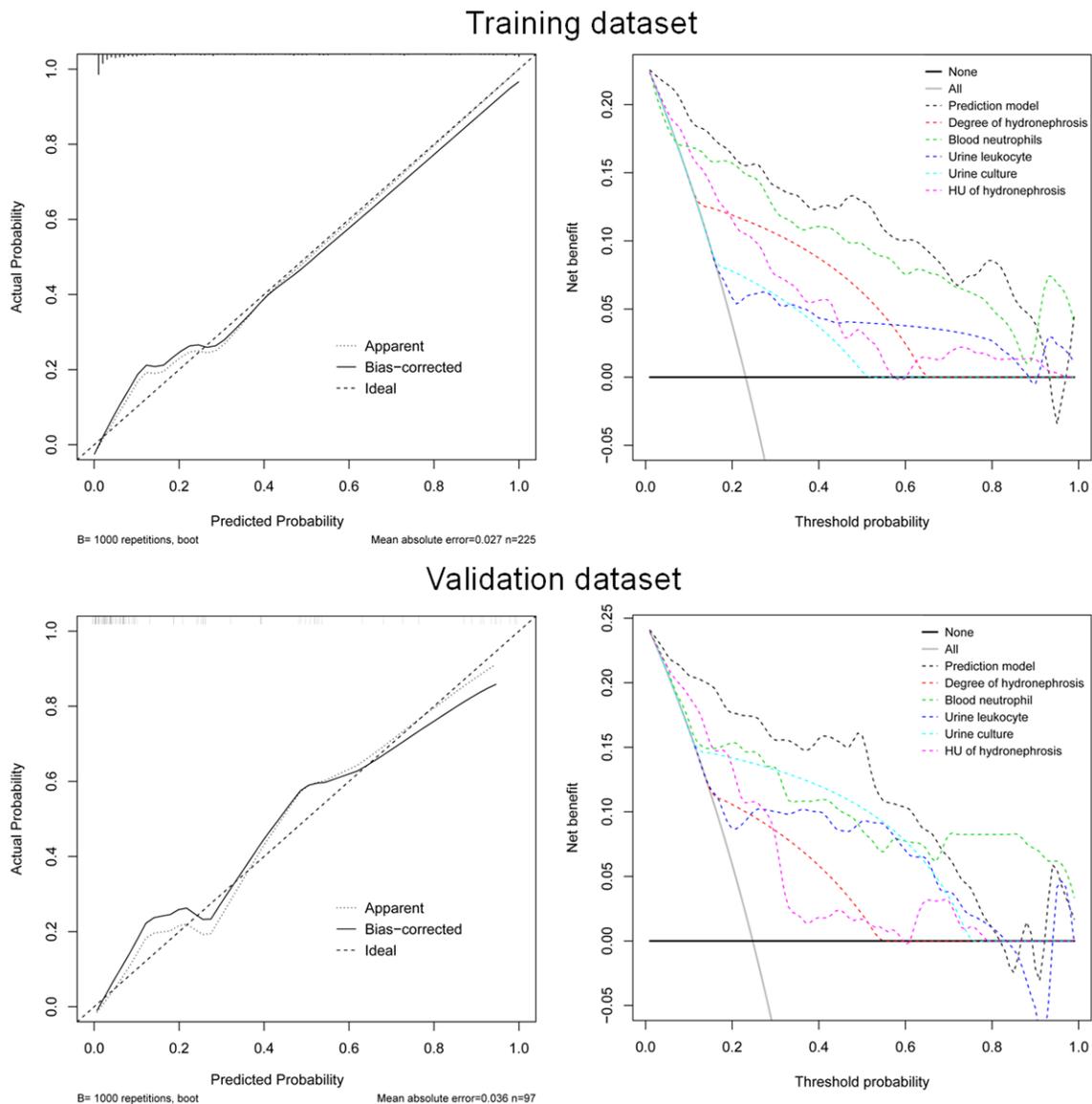


Figure 3. Calibration curves and decision curve analyses (DCAs) for the prediction model. Notes: < Calibration curves of the prediction model on the left in each “Training/Validation set” > The x-axis means the predicted risk of pyonephrosis; The y-axis represents the definitive diagnosed pyonephrosis. The solid line represents the prediction performance of the model. A higher degree of closeness to the ideal line indicates higher predictive ability. < Decision curve analyses of the prediction model on the right in each “Training/Validation set” > The x-axis means the threshold probability; The y-axis represents the clinical net benefit. The thick/thin solid line shows that no/all patients are pyonephrosis. The prediction model apparently adds more benefit than intervention-none and intervention-all group.

severe hydronephrosis increased significantly in the observation group, considering that it was associated with long-term obstruction. The progressive aggravation of hydronephrosis caused by unrelieved obstruction resulted in further impairment of renal function, which was confirmed by the high serum creatinine value in the observation group. It was noted that in univariate analysis, the proportion of severe hydronephrosis or atrophy of the contralateral kidney in patients with obstructive pyonephrosis was significantly higher than that in the control group. We thought that these might be attributed to the following two reasons. First, some patients had neurogenic bladder lesions and bacteria-holding urine reflux leading to contralateral ureteral inflammatory stricture. Second, contralateral ureter itself existed malformation, such as distortion and stenosis. Our hypothesis was supported by the fact that 3 patients had a history of urodynamic diagnosis of obstructive bladder and some patients had undergone surgical treatment for contralateral ureteral stenosis. The mean CT value of hydronephrosis in the pyonephrosis group and the non-pyonephrosis group were 13.8 and 7.0, respectively, which was consistent with the study of Emrah Yuruk [5]. Also, this was consistent with a higher density of viscous pus than sterile urine. The multivariate logistic analysis further proved that it could be performed as an independent risk factor for pyonephrosis.

It had been verified that *Escherichia coli* was often the leading group of pathogenic bacteria due to retrograde infections. In addition, special bacterial (*E.hirae* [13], *S.typhisuis* [14], etc.), tuberculosis, and fungal infections had been reported [15, 16]. Moreover, a history of urinary tract infection in the last 3 months was indeed higher in the observation group. Obviously, the preoperative urine leukocyte count of patients with pyonephrosis was higher than that of the non-pyonephrosis group. The positive rate of urine culture was 49.3% in pyonephrosis group, far higher than that of the control group. The presence of bacteriuria was connected with the degree of pyuria [17]. Preoperative urine culture was used to predict pyonephrosis, which was similar to the prediction of SIRS after PCNL [18]. In view of the fact that the number of preoperative urine culture tests in our enrolled patients varied from 1-3 times and the presence of complete ureteral obstruction in some patients, the true positive rate of

urine culture would be higher [9]. Among the positive bacteria, gram-negative bacteria accounted for 84%. The appearance of nitrite was thought to be the result of gram-negative bacillus infection. Mammals lack specific and effective nitrate reductase enzymes, while bacteria can promote the urine protein product nitrate to nitrite conversion, so the patients in pyonephrosis group had a higher positive rate of urine nitrite [19]. WBC count and neutrophils count could be increased to different degrees in patients with bacterial infectious diseases. Neutrophils were the primary cellular component of the host immune system and served as the primary mediator of innate immune defenses against invading microorganisms [20]. In this study, there was a significant difference between the pyonephrosis and the non-pyonephrosis group for WBC and neutrophils. Correspondingly, C-reactive protein (CRP) was included in our study due to its significant increase in bacterial infectious diseases. It was found that the cutoff value of 3.0 mg/dl of CRP combined with the cutoff value of 100 mm of erythrocyte sedimentation rate could significantly improve the diagnostic performance of infectious hydronephrosis and non-infectious hydronephrosis [21]. The univariate analysis confirmed significant statistical differences between the two groups in our study.

Although the area under the curve (AUC) from 0.695 to 0.856 was obtained by drawing ROC with any of the 5 independent risk factors selected from multivariate logistic regression analysis, the efficacy of the diagnostic test could be significantly improved by using model score (combining the 5 risk factors) (AUC= 0.970).

Indeed, our study also had some limitations, including inherent defects of a retrospective study. The sample size of the observation group was not large enough. In addition, we did not incorporate the procalcitonin into the study due to incomplete clinical data of it. However, this study contributed to our understanding of pyonephrosis prediction. This is the first time, that we know of, using a novel model to comprehensively predict pyonephrosis.

Conclusion

Our study showed that the degree of hydronephrosis, CT value of hydronephrosis, blood neu-

trophils, urine leukocyte, and urine culture were independent risk factors for the prediction of pyonephrosis. Most importantly, based on these risk factors, we constructed a novel comprehensive model and confirmed it was an effective method to predict pyonephrosis.

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Disclosure of conflict of interest

None.

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