Original Article

Trend of Prognostic Serum Creatinine Levels Associated with Chronic Kidney Disease in Posterior Urethral Valves: A 12-Year Review at Siriraj Hospital

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Objective: Posterior urethral valve (PUV) is the most common cause of lower urinary tract obstruction in male children. PUV has a broad spectrum of clinical presentations and can develop into renal failure at varying ages. Many previous studies reported serum creatinine to be a useful prognostic factor and a practical method for predicting long-term renal outcome, but the cut-off value is still unclear. The authors aimed to identify the optimum cut-off value of initial creatinine (iCr) as a prognostic factor for Chronic Kidney Disease (CKD), and to estimate the renal failure-free survival (RFFS) rate in PUV patients.

Materials and Methods: Male pediatric patients who were diagnosed with PUV at Siriraj Hospital (Bangkok, Thailand) from January 2005 to December 2016 were retrospectively reviewed. Statistical methods, including receiver operating characteristic (ROC) curve analysis, Kaplan-Meier method, log-rank test and Cox proportional hazards regression were used. Statistical significance was defined as $p<0.05$.

Results: Of the 69 patients identified, 41 were included. The median age at intervention was 240 days (range: 2 to 3,240). CKD was found in 48.7% at the last follow-up, the optimal cut-off value for initial creatinine associated with CKD was 0.7 mg/dL, and median renal failure-free time was 57 months. Multivariable analysis revealed initial creatinine to be the only independent predictor of longterm renal outcome in PUV patients.

Conclusion: Initial creatinine was found to be an independent predictor of long-term renal outcome in PUV patients. An initial creatinine cut-off value of 0.7 mg/dL or greater is significantly associated with high risk of developing CKD (adjusted HR: 4.4, 95% CI: 1.4 to 13.8; $p = 0.011$).

Keywords: Posterior urethral valves, PUV, Valve ablation, Initial creatinine

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Posterior urethral valve (PUV) is the most common cause of lower urinary tract obstruction in male children. The lifetime prevalence of end-stage renal disease (ESRD) in boys with PUV ranges from 20% to 50%[1]. The main treatment goal is to preserve renal and bladder function. Long-term renal outcome remains the most important determinant of quality of life[2]. The prediction of renal outcome status in children with PUV depends on multiple factors, including age at diagnosis, degree of renal dysplasia, vesicoureteral reflux, creatinine level, and bladder dysfunction[3].

Many studies described serum creatinine as being a useful prognostic factor and a relatively easy method for predicting long-term renal outcome in affected children, especially the nadir creatinine level at the 1st year of life. A nadir creatinine level less than 0.8 mg/dL appears to indicate a minimal risk, whereas a value greater than 1.2 mg/dL predicts a higher risk of developing ESRD[4]. In contrast, Bhadoo, et al[5] reported initial creatinine level to be a factor that significantly predicts the development of CKD in patients with PUV.

Regarding the use of nadir creatinine, many patients are diagnosed with PUV very early in life and clinicians have to wait until they reach 1 year of age, which is when nadir creatinine is reached. In PUV patients with late presentation, the nadir creatinine at the 1st year of life cannot be used to predict renal outcome. Enhanced understanding of the relationship between serum creatinine level and long-term renal outcome in PUV may improve treatment, outcomes of treatment, and patient survival.

The aim of this study was to identify the optimum cut-off value of initial creatinine (iCr) as a prognostic factor for CKD, to estimate the renal failure-free survival (RFFS) rate, and to identify potential risk factors associated with CKD in patients with PUV.

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Materials and Methods

All children who were diagnosed with PUV at Siriraj Hospital (Bangkok, Thailand) during January 2005 to December 2016 were retrospectively reviewed. There were 69 patients with a median age at intervention of 240 days (range: 2 to 3,240). The clinical records, radiological findings, and laboratory results were analyzed.

Pre-operative evaluation included birth weight, age at intervention, type of PUV, urinalysis, and urine culture. Serum creatinine in all patients was recorded at presentation and post-intervention (vesicostomy, valve ablation). Renal ultrasound was performed in almost all patients. Creatinine clearance (eGFR) was calculated using the Schwartz formula[6]. As the primary procedure, vesicostomy was performed in 11 patients (25%), and valve ablation was performed in 29 patients (72.5%). Most patients were followed-up every 3 to 6 months with clinical examination, urinalysis and urine culture, serum creatinine, and ultrasonography.

According to National Kidney Foundation guidelines[7], the definition of non-CKD is eGFR 60 ml/min/1.73 m^2 or greater, and the eGFR for CKD is less than 60 ml/min/1.73 m^2.

Sample size calculation

The sample size was calculated based on a study by Sarhan, et al[8] that reported a 17-year survival rate for initial creatinine and nadir creatinine ≤1 mg/dl of 40% and 36%, respectively, and a 17-year survival rate for initial creatinine and nadir creatinine >1 mg/dl of 18% and 10%, respectively. Using a type I error of 5% and power of test of 80%, a sample size of 35 patients for each group were calculated. The sample size calculation was performed using nQuery Advisor sample size software (Statistical Solutions, Ltd., Cork, Ireland).

Statistical analysis

Quantitative variables were described using median (minimum, maximum), while qualitative variables were described using frequency and percentage. Chi-square test, Yate's continuity correction or Fishers' exact test were used to compare proportions between CKD and non-CKD groups. Mann-Whitney U test was used to compare quantitative variables between groups. Receiver operating characteristic (ROC) curve analysis was used to identify the optimum cut-off level of initial creatinine as a prognostic indicator for CKD in PUV patients. Kaplan-Meier method was used to estimate renal failure-free survival time (RFFS), and log-rank test was used to compare RFFS between the CKD and non-CKD groups. Multiple Cox regression analysis was performed to identify prognostic factors independently associated with CKD in PUV patients. The results of that analysis are reported as hazard ratio (HR) and 95% confidence interval (CI) to evaluate the strength of association. Statistical significance was defined as a *p*-value less than 0.05.

Results

Forty-one of 69 patients who met the study inclusion criteria were analyzed. The median age at intervention was 240 days (range: 2 to 3,240). The median follow-up time was 48 months (range: 12 to 152). Primary endoscopic valve ablation was performed in 29 (72.5%) cases, while 11 (27.5%) cases underwent vesicostomy. Chronic kidney disease developed at the end of follow-up in 20 (48.8%) cases. Initial creatinine, nadir creatinine at 1 year of life, and hydronephrosis from ultrasonography were significant predictors of renal outcome ($p<0.05$).

After comparing the prognostic factors between the CKD group and the non-CKD group using Mann-Whitney U test, a statistically significant difference between groups was observed for 3 factors, including initial creatinine (median 1.1 vs. 0.31 mg/dL, $p<0.001$), nadir creatinine (median 0.4 vs. 0.3 mg/dL, $p<0.001$), and hydronephrosis from ultrasonography (none HN 5.6% vs. 45%, $p<0.014$), as shown in Table 1.

ROC curve analysis was used to identify the optimal cut-off value of initial creatinine for prediction of CKD. That analysis yielded an area under the curve (AUC) of 0.889 (95% CI: 0.768 to 1.000; $p<0.0001$). The results revealed the optimal cut-off value of initial creatinine to be 0.7 mg/dL. This value demonstrated high diagnostic accuracy with a sensitivity of 70% (95% CI: 48.1 to 85.5%), specificity of 85.7% (95% CI: 65.4 to 95%), and accuracy of 78% (95% CI: 63.3 to 88.0%) (Figure 1).

Patients with initial creatinine below 0.7 mg/dL developed CKD in 6 (25%) of 24 patients, whereas patients with initial creatinine of 0.7 mg/dL or greater developed CKD in 14 (82.4%) of 17 patients ($p<0.001$).

The Kaplan-Meier curve represents renal failure-free survival time (RFFS), and the results showed that 50% of patients with PUV will develop CKD within 57 months. After using initial creatinine of 0.7 mg/dL to divide patients into two groups, significantly more patients that had an initial creatinine level of 0.7 mg/dL or greater developed CKD compared to the <0.7 mg/dL group (CKD rate 76.5% vs. 25.0%, respectively; $p<0.001$), especially within the follow-up range of 4 to 18 months (Figures 2 and 3).

Multivariable Cox regression analysis was performed to identify independent prognostic factors associated with CKD in PUV patients. The factors that were included in that analysis were initial creatinine, nadir creatinine, hydronephrosis, age at intervention, and type of primary procedure. The results showed initial creatinine to be the only independent prognostic factor for CKD (adjusted HR: 4.4, 95% CI: 1.4 to 13.8; $p = 0.011$).

Discussion

Posterior urethral valve is a serious lower urinary tract obstruction that can lead to bladder dysfunction and renal deterioration. Prediction of renal outcome status in children with PUV depends on several factors, including age at diagnosis, degree of renal dysplasia, vesicoureteral reflux, bladder dysfunction, and serum creatinine level. The authors found initial creatinine to be a very important prognostic factor for predicting renal outcome after a mean follow-up of

Table 1. Demographic and clinical characteristics compared between non-CKD and CKD patients

Variables	Non-CKD (n = 21)	CKD (n = 20)	*p*-value
Age at intervention (days)	240 (2, 3,240)	270 (11, 2,880)	0.804
BW (grams)	2,760 (1,600, 3,000)	2,970 (2,300, 3,900)	0.132
Initial creatinine (mg/dL)	0.3 (0.2, 1.7)	1.1 (0.3, 2.8)	<0.001
Nadir creatinine (mg/dL)	0.3 (0.2, 0.5)	0.4 (0.2, 0.4)	<0.001
Primary procedure			0.424
Vesicostomy	4 (19.0%)	7 (35.0%)	
Valve ablation	17 (81.0%)	12 (65.0%)	
Type of PUV	(n = 19)		0.487
Type 1	18 (94.7%)	20 (100%)	
Type 3	1 (5.3%)	0 (0.0%)	
Hydronephrosis	(n = 20)	(n = 18)	0.014
None	9 (45.0%)	1 (5.6%)	
Unilateral	1 (5.0%)	4 (22.2%)	
Bilateral	10 (50.0%)	13 (72.2%)	

Data presented as median (minimum, maximum) or number and percentage
A *p*-value <0.05 indicates statistical significance
CKD = chronic kidney disease, BW = body weight, PUV = posterior urethral valve

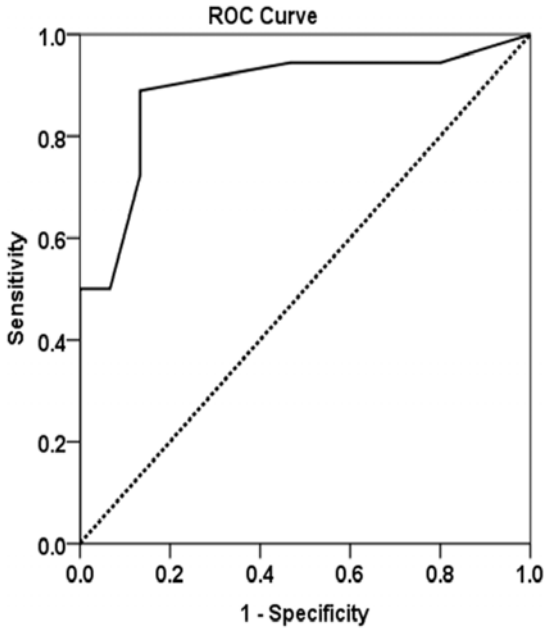

Figure 1. Receiver operating characteristic (ROC) curve analysis to identify the optimal cut-off initial creatinine to predict future CKD.

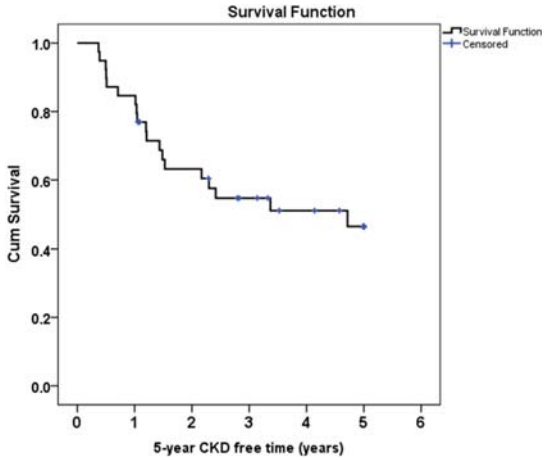

Figure 2. Kaplan Meier plot showed incidence of CKD and time to develop renal failure.

longer than 48 months. Importantly, we found the initial creatinine level to be significantly lower in non-CKD patients than in patients who developed CKD. Most of the cases diagnosed with PUV were referred to our national tertiary referral center with an indwelling catheter. Therefore, the initial creatinine value reflected a post-drainage level.

Using ROC curve analysis to identify an initial creatinine cut-off value, we found 0.7 mg/dL to be the value with the greatest sensitivity, specificity, and accuracy. About 70% of patients in the CKD group had an initial creatinine level greater than 0.7 mg/dL, while only 14.3% of patients in the non-CKD group had a level exceeding 0.7 mg/dL.

Univariate analysis using simple Cox regression analysis showed initial creatinine, nadir creatinine, and hydronephrosis from ultrasonography to be statistically significantly associated with development of CKD in PUV patient (all $p<0.05$). Age at intervention, type of primary procedure, bladder abnormalities, and VUR were not found to be correlated with the development of CKD. Multivariate analysis revealed initial creatinine to be the only factor that is independently associated with the development CKD.

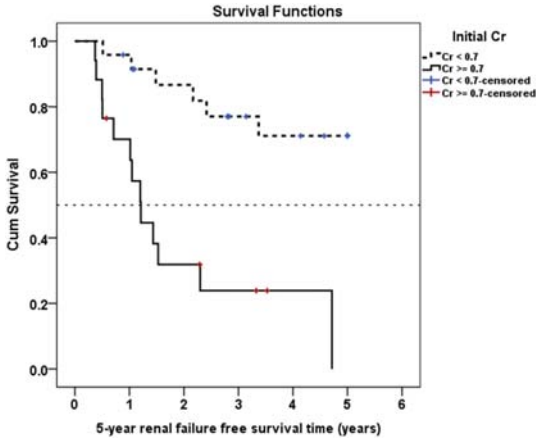

Figure 3. Kaplan Meier plot compared 5-year renal failure survival time between CKD and non-CKD group.

During the early years of the data collection period, there was no routine prenatal ultrasound in Thailand's healthcare system. Thus, some cases were delayed in diagnosis. Early identification of factors that predict long-term renal deterioration is important in children diagnosed PUV to guide therapy and to ensure that patients are adequately and appropriately counseled about their condition. In the future, PUV should be classified into different risk groups, with each having its own set of management protocols. The high-risk group would be given more aggressive management, such as the maximum dose of anticholinergic therapy, early video-urodynamic study, and/or early bladder augmentation. Finally, PUV is a disease with a wide spectrum of presentations and long-term sequelae. As such, parents should be carefully and thoroughly counseled relative to things to observe for at home, long-term outcome, and follow-up.

Limitations

The present study has some mentionable limitations. First, this was retrospective study so some patient data may have been missing or incomplete. Second, the size of the study population was relatively small. As a result, our study may have lacked sufficient power to identify all significant differences and associations. Third, the patients enrolled in the present study were from a single center. Fourth and last, our center is Thailand's largest tertiary referral hospital, which means to which the authors often have referred patients with complicated and intransigent conditions. As such, it is possible that our findings may not be generalizable to patients with the same condition in other settings.

Conclusion

The present study confirms that initial creatinine has important prognostic value, and that it is significantly associated with long-term renal function in children with PUV. Initial creatinine of 0.7 mg/dL or greater is highly specific for predicting the development of renal insufficiency, especially during the 4- to 18-month follow-up period.

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What is already known on this topic?

Posterior urethral valve is the most common cause of lower urinary tract obstruction in male children leading to renal insufficiency. From the previous studies, serum creatinine is one of the prognostic factors for predicting longterm chronic kidney disease in posterior urethral valve patient.

What this study adds?

In the present study the most important factor for predict long term chronic kidney disease was initial creatinine. The cut-off value of Initial creatinine was 0.7 mg/dL or greater considered high risk for predicting the development of renal insufficiency.

Funding disclosure

This was an unfunded study.

Potential conflicts of interest

The authors declare no conflicts of interest.

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แนวโน้มค่าการทำงานของไตที่มีความสัมพันธ์ต่อภาวะไตวายเรื้อรังในผู้ป่วยลิ้นอุดกั้นท่อปัสสาวะส่วนหลัง: รวบรวมข้อมูล 12 ปี ในโรงพยาบาลศิริราช

พันธุ์ศักดิ์ เมืองขุนรอง, ไชยยงค์ นวลยง, บรรณสิทธิ์ ไชยประสิทธิ์, ธวัชชัย มั่นคงศรีสุข, กิตติพงษ์ พินธุโสภณ

วัตถุประสงค์: โรคลิ้นอุดกั้นท่อปัสสาวะส่วนหลัง (posterior urethral valves) เป็นสาเหตุหลักที่ทำให้เกิดภาวะทางเดินปัสสาวะส่วนล่างอุดกั้นในเด็กผู้ชายโดยมีอาการแสดงได้หลายแบบ และสามารถทำให้เกิดภาวะไตวายเรื้อรังตามมาได้ มีหลายการศึกษาพบว่าค่าการทำงานของไต (creatinine) นั้นสามารถใช้ทำนายโอกาสในการเกิดไตวายเรื้อรังได้ แต่ยังไม่มีค่าตัวเลขที่ชัดเจนเพียงพอ ผู้นิพนธ์จึงตั้งใจหาค่าจุดตัดค่าของไตแรกเริ่ม (initial creatinine) ที่สามารถเป็นตัวพยากรณ์ค่าการทำงานของไตในผู้ป่วยโรคลิ้นอุดกั้นท่อปัสสาวะส่วนหลังและเปรียบเทียบระยะเวลาในการเกิดไตวายในกลุ่มที่ค่าการทำงานของไตสูงและต่ำกว่าจุดตัดด้วย

วัสดุและวิธีการ: การศึกษาย้อนหลังโดยเก็บรวบรวมข้อมูลจากเด็กที่วินิจฉัยเป็นโรคลิ้นอุดกั้นท่อปัสสาวะส่วนหลังที่รักษาในโรงพยาบาลศิริราชตั้งแต่ เดือนมกราคม พ.ศ. 2548 ถึง เดือนธันวาคม พ.ศ. 2559 โดยใช้วิธีการทางสถิติได้แก่ receiver operating characteristic (ROC) curve, Kaplan-Meier method, log rank test, multiple cox-regression analysis

ผลการศึกษา: ผู้ป่วย 41 คนผ่านเข้าเกณฑ์งานวิจัย โดยอายุของผู้ป่วยที่ได้รับการผ่าตัดเฉลี่ยอยู่ที่ 240 วัน (2 วัน ถึง 3,240 วัน) พบผู้ป่วยไตวายเรื้อรังร้อยละ 48.7 ในตอนสุดท้ายของการติดตาม, ค่าจุดตัดค่าของไตแรกเริ่ม (cut-off initial creatinine) เท่ากับ 0.7 มก.ต่อดล. พบว่าผู้ป่วยจำนวนร้อยละ 50 จะเกิดภาวะไตวายเรื้อรังที่ระยะเวลา 57 เดือน, จากการวิเคราะห์พหุตัวแปรพบว่า ค่าของไตแรกเริ่ม คือ ปัจจัยเดียวที่สัมพันธ์กับโอกาสในการเกิดไตวายเรื้อรัง

สรุป: ค่าของไตแรกเริ่ม เป็นตัวแปรที่สัมพันธ์กับโอกาสในการเกิดไตวายเรื้อรังในผู้ป่วยลิ้นอุดกั้นท่อปัสสาวะส่วนหลัง โดยค่าของไตแรกเริ่มเท่ากับ 0.7 มก.ต่อ ดล. หรือมากกว่าเป็นตัวแสดงถึงความเสี่ยงในการเกิดไตวายเรื้อรังในอนาคต