Journal of Pediatric Urology (2015) 11, 356.e1–356.e5

Nadir creatinine in posterior urethral valves: How high is low enough?☆

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Keywords
Posterior urethral valves; Prognosis; Chronic renal impairment; CKD; Nadir creatinine; Valve bladder

Received 1 January 2015
Accepted 18 June 2015
Available online 30 July 2015

Summary

Introduction
Large retrospective studies of people with posterior urethral valves (PUV) have reported chronic renal insufficiency (CRI) in up to one third of the participants and end-stage renal failure in up to one quarter of them. Nadir creatinine (lowest creatinine during the first year following diagnosis) is the recognised prognostic indicator for renal outcome in PUV, the most commonly used cut-off being 1 mg/dl (88.4 umol/l).

Objective
To conduct a statistical analysis of nadir creatinine in PUV patients in order to identify the optimal cut-off level as a prognostic indicator for CRI.

Study design
Patients treated by endoscopic valve ablation at the present institution between 1993 and 2004 were reviewed. Chronic renal insufficiency was defined as CKD2 or higher.

Statistical methods included receiver operating characteristic (ROC) curve analysis, Fisher exact test and diagnostic utility tests. Statistical significance was defined as $P < 0.05$.

Results and discussion
Nadir creatinine was identified in 96 patients. The median follow-up was 9.4 (IQR 7.0, 13.4) years. A total of 29 (30.2%) patients developed CRI, with nine (9.4%) reaching end-stage renal failure. On ROC analysis, Nadir creatinine was highly prognostic for future CRI, with an Area Under the Curve of 0.887 ($P < 0.001$). Renal insufficiency occurred in all 10 (100%) patients with nadir creatinine >88.4 umol/l compared with 19 of 86 (22.2%) patients with lower nadir creatinine ($P < 0.001$). As a test for future CRI, a nadir creatinine cut-off of 88.4 umol/l gave a specificity of 100%, but poor sensitivity of 34.5%.

Lowering the cut-off to 75 umol/l resulted in improvement in all diagnostic utility tests (Table). All 14 (100%) patients with nadir creatinine >75 umol/l developed CRI, compared with 15 of 82 (18.3%) patients with lower nadir creatinine ($P < 0.001$). Sensitivity only approached 95% at 35 umol/l, at which level specificity was low (Table). Two out of 36 (5.6%) patients with nadir creatinine <35 umol/l developed CRI.

Multivariate analysis found recurrent UTI (OR 4.733; CI 1.297–17.280) and nadir creatinine >75 umol/l (OR 48.988; CI 4.9–490.11) to be independent risk factors for progression to CRI.

Using cut-off values of 35 umol/l and 75 umol/l, patients can be stratified into low-, intermediate- and high-risk groups, with development of CRI in 5.3%, 28.3% and 100%, respectively ($P <0.001$). The stage of CKD was higher in higher risk groups.

Conclusion
Patients with nadir creatinine >75 umol/l (0.85 mg/dl) should be considered at high risk for CRI, while patients with nadir creatinine ≤35 umol/l (0.4 mg/dl) should be considered low risk. Patients with nadir creatinine between these two values have an intermediate risk of CRI.

Table Diagnostic utility tests for identified nadir creatinine cut-off levels.

Nadir creatinine cut-off (μmol/L)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
88.4	34.5	100	100	78.8
75	48.3	100	100	81.7
35	93.1	50.7	45	94.4

☆ Presented at the Fall Congress of Pediatric Urology, Miami, October 2014.

http://dx.doi.org/10.1016/j.jpurol.2015.06.008

Introduction

Posterior urethral valves (PUV) account for almost 17% of children with end-stage renal failure (ESRF) [1]. Large retrospective studies have reported chronic renal insufficiency (CRI) to occur in up to one third, and ESRF to occur in up to one quarter of PUV patients [2,3]. Bladder function can also be affected in PUV patients, resulting in the so-called 'valve bladder syndrome'. Bladder dysfunction patterns include detrusor over activity, hypocompliance, poor emptying and myogenic failure [4,5].

Nadir creatinine (lowest creatinine during the first year following diagnosis) is the recognised prognostic indicator for renal outcome in posterior urethral valves [2,6,7]. A cut-off value of 1 mg/dl (88.4 umol/l) as a risk factor for development of chronic renal insufficiency (CRI) has traditionally been used without scientific validation [2,6,7]. The present study conducted a statistical analysis of nadir creatinine in PUV patients in order to identify the optimal cut-off level as a prognostic indicator for CRI and validated nadir creatinine against other prognostic indicators of renal outcome by multivariate analysis.

Materials and methods

Medical records for patients treated by endoscopic valve ablation at the present institution between 1993 and 2004 were reviewed. The prognostic indicators that were analysed included: age at drainage; abnormal antenatal ultrasound; oligohydramnios; presence of a 'pop-off' mechanism (ascites, urinoma or unilateral reflux); history of recurrent (>3) UTI; and nadir creatinine. Other data collected included demographics, bladder function and current renal function. The lowest serum creatinine during the first 12 months following initial bladder drainage was recorded in umol/l (as provided by the laboratory). The Schwartz formula was used to calculate eGFR in order to determine CKD stage at follow-up. Chronic renal insufficiency was defined as CKD2 or higher according to Kidney Disease Outcomes Quality Initiative guidelines [8].

Statistical analysis was conducted using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago). Correlation between prognostic indicators and renal functional outcome was studied using Pearson correlation. Multivariate analysis was performed by binary logistic regression. Univariate analysis of prognostic indicators and outcomes in test groups were analysed by Fisher exact test. Receiver operating characteristic (ROC) curve analysis was used to demonstrate test significance and to identify optimal cut-off criterion of nadir creatinine as a prognostic indicator. Statistical significance was defined as $P < 0.05$.

Table 1 Pearson correlation analysis of risk factors for development of CRI.

Prognostic indicator	Pearson correlation	*P*-value
Age at diagnosis	0.007	0.95
Pop-off mechanism	−0.118	0.29
Recurrent UTI	0.257	0.02
Abnormal antenatal USS	−0.086	0.44
Oligohydramnios	0.165	0.14
Nadir creatinine	0.531	<0.01

Results

A total of 129 patients were identified. Of these, progress notes were available for 120 patients. Seventeen patients had insufficient creatinine results available to determine nadir creatinine. A further seven patients were not followed for longer than 12 months and were therefore excluded. Nadir creatinine was recorded in 96 patients. The median age at diagnosis was 8 days (IQR 1,105). The median follow-up was 9.4 years (IQR 7.0, 13.4).

Recorded nadir creatinine ranged from 20 to 237 umol/l. A total of 29 (30.2%) patients developed CRI, with ESRF developing in nine (9.4%). A scatter plot of CKD stage developed versus nadir creatinine is included in Fig. 1.

Complete data for multivariate analysis was available in 82 patients. Univariate analysis by Pearson correlation found a statistically significant positive correlation between development of CRI and both recurrent UTI ($P = 0.02$) and nadir creatinine ($P = 0.01$). Age at diagnosis, presence of a pop-off mechanism, abnormal antenatal USS and oligohydramnios did not correlate with development of CRI (Table 1).

Analysis of nadir creatinine as a test for future CRI by receiver operating characteristic (ROC) analysis demonstrated a high diagnostic accuracy with AUC of 0.887 ($P < 0.001$) (Fig. 2).

Renal insufficiency occurred in all 10 (100%) patients with nadir creatinine >88.4 umol/l compared with 19 of the

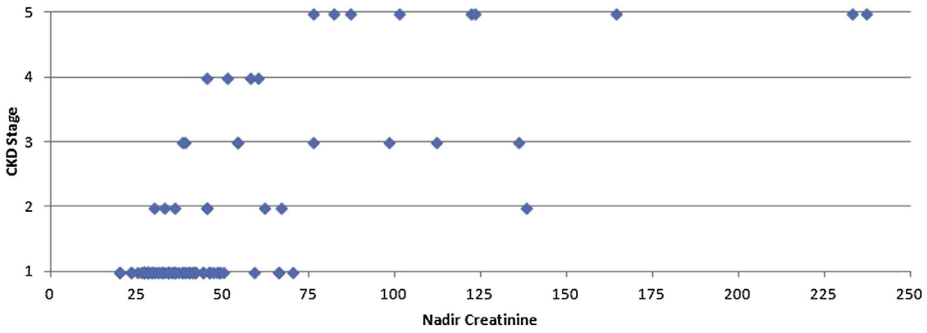

Figure 1 Scatter plot CKD stage versus nadir creatinine.