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ORIGINAL ARTICLE

KIDNEY OUTCOMES IN CHILDREN WITH POSTERIOR URETHRAL VALVES

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ABSTRACT

Background: Posterior urethral valves (PUV) affect 1 in 5,000 live male births, with 8–21% progressing to end-stage kidney disease (ESKD) within ten years. Early predictors of adverse kidney outcomes in PUV are poorly defined.

Methods: A retrospective cohort study was conducted on children who underwent PUV ablation at a single center from January 2015 to June 2022. Patients with less than six months of follow-up were excluded. The primary outcome was a composite of low estimated glomerular filtration rate (eGFR) for age or the need for kidney replacement therapy (KRT).

Results: Among 41 patients, 24 (59%) were diagnosed prenatally, and 14 (34%) were referred from other countries. Prenatally diagnosed patients were more likely to be born preterm (50% vs. 12%, p = 0.006) and had higher baseline serum creatinine (0.66 [IQR 0.49-2.45] vs. 0.52 [IQR 0.44-0.54] mg/dL; p = 0.036). Over a median follow-up of 3.1 years, 13 patients (32%) met the primary outcome, including three requiring peritoneal dialysis, all born preterm. Logistic regression analyses, adjusted for age at last follow-up, identified prenatal diagnosis (OR 7.49; 95% CI 1.18-47.56; p = 0.033), prematurity (OR 18.59; 95% CI 2.63-131.50; p = 0.003), and high pre-ablation serum creatinine (OR 5.88; 95% CI 1.19-28.97; p = 0.029) as significant predictors of adverse outcomes.

Conclusion: Nearly one-third of the cohort experienced a decline in eGFR or required KRT. Prenatal diagnosis, prematurity, and elevated preablation serum creatinine were significant predictors of adverse kidney outcomes in children with PUV.

Introduction

Posterior urethral valves (PUV) are a congenital anomaly of the urinary tract found exclusively in male patients, with an incidence of approximately 1 in 5,000 live male births.^{1,2} These membranous folds within the posterior urethra obstruct urine flow, potentially

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ABBREVIATIONS:

CKD - Chronic kidney disease CI - Confidence interval ESKD – End-stage kidney disease eGFR - Estimated glomerular filtration rate IQR – Interquartile range KRT - Kidney replacement therapy OR – Odds ratio PALOP - Portuguese-speaking African countries PUV – Posterior urethral valves SD – Standard deviations ULN – upper limit of normal UTD – urinary tract dilatation UTI - urinary tract infection VUR – Vesicoureteral reflux

leading to severe complications. Although the precise embryological mechanism underlying PUV remains unclear, it likely involves disruptions in the development of the male urethra during fetal growth.³

As the most severe form of pediatric obstructive uropathy, PUV is a leading cause of chronic kidney disease (CKD) in children. Up to 65% of affected individuals develop CKD, with 8–21% progressing to end-stage kidney disease (ESKD) by the age of ten.^{4,5} This underscores the importance of identifying early predictive factors for adverse kidney outcomes.

CKD in PUV is driven by a combination of congenital kidney dysplasia and acquired kidney injury, often resulting from poor bladder function and infections. Bladder dysfunction contributes to urinary stasis and progressive renal parenchymal damage.⁶ Prenatal ultrasound findings, such as severe bilateral hydronephrosis, oligohydramnios, or features suggestive of kidney dysplasia, particularly when identified before 24 weeks of gestation, are associated with an increased risk of perinatal mortality and CKD.^{7,8}

This study aims to investigate predictors of kidney outcomes in children with PUV, focusing on markers that can inform risk stratification and guide clinical management. By understanding these factors more comprehensively, we aim to improve kidney outcomes in children with PUV through targeted interventions and personalized care strategies.

Methods

Study design and population

This retrospective, single-center cohort study was conducted at a level III care university hospital. All patients aged 0-18 years diagnosed with posterior urethral valves (PUV) who underwent ablation at our center between January 1, 2015, and June 30, 2022 were eligible for inclusion. Patients with less than six months of follow-up were excluded.

Data analyzed

Data were collected through a review of electronic medical records. Key patient information included country of birth, gestational age, birth weight, need for neonatal resuscitation, and comorbidities. The timing of diagnosis (prenatal or postnatal), findings leading to a prenatal diagnosis, and clinical presentation of postnatally diagnosed cases were documented. Initial postnatal ultrasound findings and results from preoperative cystography (e.g., vesicoureteral reflux and post-void residual volume) were analyzed.

Management data included the age at first urethral catheterization, age at endoscopic PUV ablation, and any interventions performed before or at the time of PUV ablation (e.g., vesicostomy or high diversion). Postablation interventions, such as endoscopic re-ablation of residual PUV, were also recorded.

Perioperative PUV ablation metrics included maximum serum creatinine levels before surgery, nadir creatinine levels within the first week after ablation, and preand postoperative estimated glomerular filtration rate (eGFR).

The primary outcome was a composite of low eGFR for age or the need for kidney replacement therapy (KRT). Low eGFR for age was defined as eGFR <90 mL/ min/1.73m² for children older than two years and eGFR below two standard deviations (SD) below the mean for children under two years, calculated using the bedside serum creatinine Schwartz formula.

Other outcomes assessed included the presence of vesicoureteral reflux (VUR), post-void residual volume, and significant renal scarring on dimercaptosuccinic acid (DMSA) renal scintigraphy.

Statistical methods

Continuous variables were summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the distribution of the data. Categorical variables were reported as frequencies and percentages.

Comparisons between groups were made using independent t-tests for normally distributed continuous variables, and Mann-Whitney U tests for non-normally distributed continuous variables. For categorical variables, Chi-square tests or Fisher's exact tests were applied as appropriate.

Univariate logistic regression analyses were conducted to identify predictors of adverse kidney outcomes. These analyses were subsequently adjusted for age at the last follow-up visit. A multivariate logistic regression model, including all significant predictors identified in univariate analyses and adjusted for age at the last follow-up, was also performed. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for all regression models. A two-tailed p-value of <0.05 was considered statistically significant.

All statistical analyses were performed using Stata® version 14.0 (StataCorp).

Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. As a retrospective observational study using anonymized data collected as part of routine clinical care, it was exempt from formal ethical approval. Informed consent was not required due to the retrospective nature of the data collection and the anonymization of patient information. All data were handled and analyzed in compliance with data protection regulations to safeguard confidentiality and privacy.

Results

We identified 45 patients who underwent PUV ablation at the study institution between January 1, 2015, and June 30, 2022. After excluding four patients with a follow-up period of less than six months, the final cohort consisted of 41 patients. Most patients were diagnosed prenatally (54%), and the majority (66%) were from Portugal. Fourteen patients (34%) were born prematurely, and four (10%) required neonatal resuscitation. In addition to prematurity, relevant comorbidities were identified in 10 patients (24%), including sickle cell disease (6), trisomy 21 (2), nephroblastoma (1), and ureterocele with ureteral duplication (1). Regarding the timing of diagnosis, the median gestational age at the first abnormal prenatal scan for patients with a prenatal diagnosis of PUV was 29 (IQR 22-34) weeks, with a range from 12 to 36 weeks. For patients diagnosed postnatally, the median age at diagnosis ranged from 0 days to 9 years, with a median of 3.84 months (IQR 11.00 days to 4.71 years). Overall, the median peak serum creatinine before ablation was 0.54 (IQR 0.46-1.03; range 0.37-6.27) mg/dL (Table 1).

Table 1. Demographic and clinical characteristics of the study population.

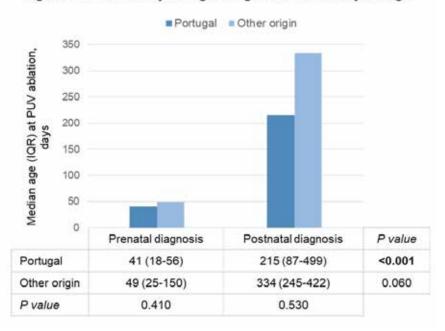
| Characteristics | N = 41 |
|--|-------------------|
| Timing of diagnosis, n (%) | |
| Prenatal diagnosis | 24 (59) |
| Postnatal diagnosis | 17 (41) |
| Country of origin, n (%) | |
| Portugal | 27 (66) |
| PALOP | 12 (29) |
| Brazil | 2 (5) |
| Birth gestational age (weeks), median (IQR) | 38 (36–39) |
| Birth weight (grams), median (IQR) | 3007 (2515-3480) |
| Need for neonatal resuscitation, n (%) | 4 (10) |
| Prematurity, n (%) | 14 (34) |
| Comorbidities excluding prematurity, n (%) | 10 (24) |
| Peak serum creatinine before PUV ablation (mg/dL), median (IQR) | 0.54 (0.46-1.03) |
| Gestational age at first abnormal prenatal scan in patients with prenatal diagnosis of PUV (weeks), median (IQR) | 28.5 (21.5-33.5) |
| Age at diagnosis in patients diagnosed postnatally (months), median (IQR) | 3.80 (0.36-56.52) |

IQR – interquartile range; PALOP – Portuguese-speaking African countries.

| | All (N = 41) | Prenatal diagnosis (N = 24) | Postnatal diagnosis (N = 17) | P value |
|--|-----------------------|-----------------------------------|------------------------------------|---------|
| PRIMARY OUTCOME* | 13 (32) | 10 (42) | 3 (18) | 0.024 |
| SECONDARY OUTCOMES | | | | |
| eGFR below expected for age, n (%)* | 10 (24) | 8 (33) | 3 (18) | 0.014 |
| Kidney replacement therapy, n (%) | 3 (7) | 2 (8) | 0 | 0.210 |
| eGFR at last follow-up visit (mL/min/1.73 m2), median (IQR)* | 95.4 (79.2- 115.1) | 80.0 (36.0- 97.0) | 101.0 (90.0- 126.0) | 0.014 |
| Nadir serum creatinine (mg/dL), median (IQR) | 0.48 (0.42- 0.73) | 0.57 (0.40- 1.18) | 0.46 (0.42- 0.57) | 0.340 |
| Nadir serum creatinine >1 mg/dL, n (%) | 6 (15) | 5 (21) | 1 (6) | 0.150 |
| VUR in the first post ablation cystography, n (%) | 15 (37) | 7 (29) | 8 (47) | 0.160 |
| Bilateral VUR | 7 (17) | 6 (25) | 1 (6) | 0.060 |
| Post voiding residue | 2 (5) | 2 (8) | 0 (0) | 0.140 |
| Any degree of renal scarring in the last available scintigraphy, n (%) | 11 (27) | 6 (25) | 5 (29) | 0.300 |
| Bilateral renal scarring | 9 (22) | 5 (21) | 4 (24) | 0.500 |
| Relative renal function =40% | 10 (24) | 6 (25) | 4 (24) | 0.120 |

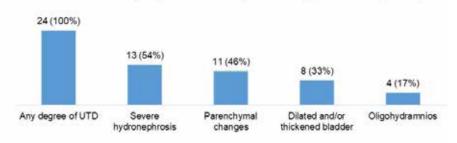
eGFR – estimated glomerular filtration rate; IQR – interquartile range; KRT – kidney replacement therapy; PUV - posterior urethral valves; VUR - vesicoureteral reflux.

Figure 1. Clinical presentation by the timing of diagnosis. A. Prenatal scan findings in patients with a prenatal diagnosis of PUV. B. Clinical presentation in patients with a postnatal diagnosis of PUV. PUV – posterior urethral valves; UTD – urinary tract dilatation; UTI – urinary tract infection.

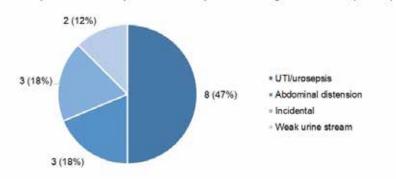


Age at PUV ablation by timing of diagnosis and country of origin

A. Prenatal scan findings in patients with a prenatal diagnosis of PUV (N = 24)



B. Clinical presentation in patients with a postnatal diagnosis of PUV (N = 17)



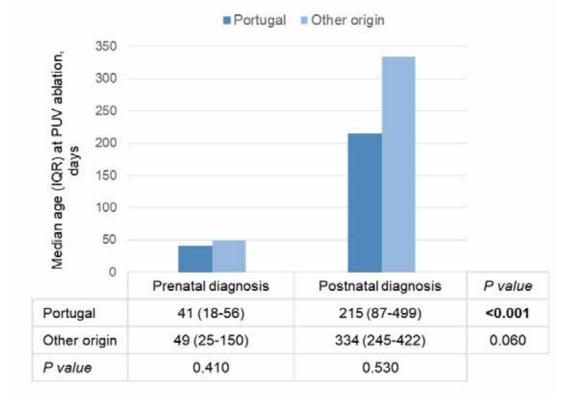
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Clinical presentation based on the timing of diagnosis is illustrated in Figure 1. Among the 24 (59%) children diagnosed prenatally, 13 (54%) presented with severe hydronephrosis, 11 (46%) showed kidney parenchymal changes, and 4 (17%) were diagnosed with oligohydramnios on prenatal ultrasound scans. The majority of the 17 (41%) children diagnosed postnatally were symptomatic. The most common indications for imaging were urinary tract infection or urosepsis (8, 47%), followed by abdominal distention (3, 18%) and weak urine stream (2, 12%). Notably, three children (18%) had PUV discovered incidentally during an ultrasound performed for other reasons.

A comparison of clinical patient characteristics and interventions based on the timing of PUV diagnosis is shown in Table 2. Patients with a prenatal diagnosis were more frequently born preterm (12 [50%] versus 2 [12%]; p = 0.006), had higher peak serum creatinine before PUV ablation (0.66 [IQR 0.49–2.45] versus 0.52 [IQR 0.44–0.54] mg/dL; p = 0.036), and were more likely to have a dilated posterior urethra on postnatal ultrasound scans (12 [50%] versus 3 [18%]; p = 0.041).

Notably, during the study period, the median age at PUV ablation varied widely based on the timing of diagnosis and country of origin (Figure 2). Overall, patients with a prenatal diagnosis underwent PUV ablation at a younger age than those with a postnatal diagnosis (45 [IQR 24-62] days versus 9 [IQR 3.25-16.07] months; p < 0.001). Additionally, patients born in Portugal tended to undergo ablation at a younger age than those referred from other countries. Initial management included immediate bladder drainage for all patients via a feeding tube or Foley catheter upon suspicion or confirmation of PUV. As expected, patients diagnosed prenatally underwent their first urethral catheter placement at a significantly younger age than those diagnosed postnatally (0 [IQR 0-5] versus 82 [IQR 15-123] days; p <0.001). Prior to April 2021, when the hospital acquired a neonatal resectoscope, patients were gradually catheterized with progressively larger catheters until they could tolerate a 9 Fr catheter, after which they proceeded to PUV ablation with the smallest available resectoscope at the time. Since April 2021, the median age at primary PUV ablation for the three term-born patients with a prenatal diagnosis from Portugal has been reduced to 7 days.

Figure 2. Age (in days) at PUV ablation by timing of diagnosis and country of origin. IQR – interquartile range; PUV – posterior urethral valves. Note: Since the acquisition of a neonatal resectoscope in April 2021, the median age at primary PUV ablation for the three patients with a prenatal diagnosis born at term in Portugal was 7 days.



Age at PUV ablation by timing of diagnosis and country of origin

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| | All (N = 41) | Prenatal diagnosis (N = 24) | Postnatal diagnosis (N = 17) | P value |
|--|-----------------------|-----------------------------------|------------------------------------|---------|
| PRIMARY OUTCOME* | 13 (32) | 10 (42) | 3 (18) | 0.024 |
| SECONDARY OUTCOMES | | | | |
| eGFR below expected for age, n (%)* | 10 (24) | 8 (33) | 3 (18) | 0.014 |
| Kidney replacement therapy, n (%) | 3 (7) | 2 (8) | 0 | 0.210 |
| eGFR at last follow-up visit (mL/min/1.73 m2), median (IQR)* | 95.4 (79.2- 115.1) | 80.0 (36.0- 97.0) | 101.0 (90.0- 126.0) | 0.014 |
| Nadir serum creatinine (mg/dL), median (IQR) | 0.48 (0.42- 0.73) | 0.57 (0.40- 1.18) | 0.46 (0.42- 0.57) | 0.340 |
| Nadir serum creatinine >1 mg/dL, n (%) | 6 (15) | 5 (21) | 1 (6) | 0.150 |
| VUR in the first post ablation cystography, n (%) | 15 (37) | 7 (29) | 8 (47) | 0.160 |
| Bilateral VUR | 7 (17) | 6 (25) | 1 (6) | 0.060 |
| Post voiding residue | 2 (5) | 2 (8) | 0 (0) | 0.140 |
| Any degree of renal scarring in the last available scintigraphy, n (%) | 11 (27) | 6 (25) | 5 (29) | 0.300 |
| Bilateral renal scarring | 9 (22) | 5 (21) | 4 (24) | 0.500 |
| Relative renal function =40% | 10 (24) | 6 (25) | 4 (24) | 0.120 |

*excluding patients on KRT for the eGFR calculation.

eGFR – estimated glomerular filtration rate; IQR – interquartile range; KRT – kidney replacement therapy; PUV – posterior urethral valves; VUR – vesicoureteral reflux.

| Table 4. Predictors of low eGFR for age or need for kidney replacement therapy in the overall cohort of children | ۱ |
|--|---|
| with PUV. | |

| | OR/coefficient | 95% CI | P value |
|--|----------------|-------------|---------|
| Unadjusted univariate regression | | | |
| Prenatal diagnosis | 6.25 | 1.14-34.12 | 0.034 |
| Prematurity | 8.63 | 1.96-37.94 | 0.004 |
| Pre-ablation serum creatinine levels above the ULN | 7.70 | 1.40-42.44 | 0.019 |
| Age-adjusted univariate regression | | | |
| Prenatal diagnosis | 7.49 | 1.18-47.56 | 0.033 |
| Prematurity | 18.59 | 2.63-131.50 | 0.003 |
| Pre-ablation serum creatinine levels above the ULN | 5.88 | 1.19-28.97 | 0.029 |
| Age-adjusted multivariate regression model | | | |
| Prenatal diagnosis | 1.29 | 0.11-15.6 | 0.842 |
| Prematurity | 3.60 | 0.26-49.1 | 0.337 |
| Pre-ablation serum creatinine levels above the ULN | 3.46 | 0.66-18.1 | 0.142 |

CI – confidence interval; OR – odds ratio; PUV – posterior urethral valves; ULN – upper limit of normal

The median follow-up duration was 3.08 years (IQR: 24.96 months to 3.99 years), and the median age at the latest follow-up was 3.1 (IQR: 2.1-4.0) years. The primary outcome was met by 13 (32%) patients in the overall cohort, with a significantly higher rate among those with a prenatal diagnosis compared to those diagnosed postnatally (10 [42%] vs. 3 [18%]; p = 0.024). Three children (7%) required peritoneal dialysis, and an additional ten (24%) had an eGFR lower than expected for their age. Notably, 10 (45%) of prenatally diagnosed children achieved the composite renal outcome, whereas only 3 (17%) of postnatally diagnosed children met the primary outcome. Among the three patients who underwent KRT, two were diagnosed prenatally, and all three were born prematurely. The maximum serum creatinine values recorded prior to PUV ablation were 1.15 mg/ dL, 4.24 mg/dL, and 6.27 mg/dL, while the nadir serum creatinine values were 0.86 mg/dL, 4.08 mg/dL, and 5.59 mg/dL, respectively. The mean eGFR at the end of follow-up, excluding patients on KRT, was 95 (IQR: 79–115) mL/min/1.73 m², which was significantly lower for patients with a prenatal diagnosis than for those diagnosed postnatally (80 [IQR: 36-97] vs. 101 [IQR: 90–126] mL/min/1.73 m²; p = 0.014). Other secondary outcomes included post-ablation vesicoureteral reflux in 15 (37%) patients, any degree of renal scarring in 11 (27%) children, and relative renal function of 40% or less in 10 (24%) patients (Table 3).

Prenatal diagnosis, prematurity, and pre-ablation serum creatinine values above the upper limit of normal were identified as predictors of low eGFR for age or the need for KRT in univariate logistic regression analyses. These predictors remained significant after adjusting for age at the last follow-up. However, none of these predictors remained significant in the multivariate model adjusted for age at the last follow-up, which included all three predictors (Table 4).

Discussion

This study aimed to assess kidney outcomes in children with PUV treated at a single institution over 7.5 years and identify predictors of poor kidney outcomes. Nearly one-third of our cohort experienced a decline in eGFR below the expected range for age or required KRT over a median follow-up of 3 years. We identified prenatal diagnosis, prematurity, and pre-ablation serum creatinine levels above the upper limit of normal as significant predictors of worse kidney outcomes. These findings are consistent with those from other published cohorts.^{9,10}

Our findings suggest a clustering of risk factors among children with worse kidney outcomes, as patients diagnosed prenatally were more likely to be born prematurely and had higher peak serum creatinine levels prior to PUV ablation compared to those diagnosed postnatally. This clustering of risk factors may have contributed to the lack of improvement in outcomes despite earlier diagnosis and intervention. As expected, prenatal diagnosis was frequently associated with severe hydronephrosis, kidney parenchymal changes, and oligohydramnios, all factors that have been identified as prenatal markers of worse longterm kidney outcomes in studies with longer followup.^{5,11} This suggests that PUV is often detected earlier

(in utero) in more severe cases. In contrast, postnatally diagnosed patients are more likely to have partial obstruction and a milder course, as evidenced by the three postnatal cases diagnosed incidentally in our cohort. One of the most significant changes in clinical practice during the study period was the acquisition of a neonatal resectoscope in April 2021, which enabled earlier PUV ablation. This advancement may improve outcomes for some children by reducing the duration of obstruction and allowing for earlier intervention. However, the overall impact on outcomes remains uncertain, and continued follow-up is essential to assess the long-term benefits of early intervention. The higher incidence of adverse kidney outcomes in the prenatal diagnosis group, despite earlier first urine drainage and PUV ablation, highlights that earlier desobstruction does not necessarily guarantee optimal outcomes.12,13,14

Among the three patients requiring peritoneal dialysis, two were diagnosed prenatally, all were born prematurely, and all had significantly elevated pre-ablation serum creatinine levels. Additionally, the nadir creatinine in the first week following PUV ablation was higher than 0.70 mg/dL for all of them, which aligns with the consistent finding in the literature that nadir creatinine is the best prognostic factor for long-term renal function in patients affected by PUV.^{5,15,16} Unfortunately, we were unable to consistently capture nadir creatinine during the first year due to shared care with local hospitals and had to limit our analysis to nadir creatinine in the first week following PUV ablation, which was consistently documented for all patients in the cohort.

While this study provides valuable insights into the factors influencing renal outcomes in children with PUV, it is limited by its retrospective design, single-center nature, relatively small sample size and short duration of follow-up. Additionally, we were unable to capture detailed data on all potential confounding factors, such as post-ablation pharmacologic management strategies, urinary tract infections, bladder dysfunction, need for clean intermittent catheterization, or other long-term complications.

In conclusion, nearly one-third of our cohort experienced a decline in eGFR below the expected range for age or required KRT over a median follow-up period of 3 years. We identified prenatal diagnosis, prematurity, and elevated pre-ablation serum creatinine as predictors of worse kidney outcomes in children with PUV. Improving outcomes for higher-risk children remains challenging, as the clustering of these risk factors may limit the potential benefits of early detection and intervention in PUV.

Compliance with Ethical Standards Funding None Conflict of Interest None

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