BJU Int 2022; **130:** 350–356 doi:10.1111/bju.15708

Original Article

BJUI
BJU International

Pre-versus postnatal presentation of posterior urethral valves: a multi-institutional experience

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Objective

To compare the outcomes of pre- vs postnatally diagnosed posterior urethral valves (PUV) at two large paediatric centres in North America to ascertain if the prenatal diagnosis of PUV is associated with better outcomes.

Patients and Methods

All boys with PUV were identified at two large paediatric institutions in North America between 2000 and 2020 (The Hospital for Sick Children [SickKids, SK] and Children's Hospital of Philadelphia [CHOP]). Baseline characteristics and outcome measures were compared between those diagnosed pre- vs postnatally. Main outcomes of interest included progression of chronic kidney disease (CKD), the need for renal replacement therapy (RRT), and bladder function compromise, as determined by need for clean intermittent catheterisation (CIC). Time-to-event analyses were completed when possible.

Results

During the study period, 152 boys with PUV were treated at the SK (39% prenatal) and 216 were treated at the CHOP (71% prenatal). At the SK, there was no difference between the pre- and postnatal groups in the proportion of boys who required RRT, progressed to CKD Stage ≥3, or who were managed with CIC when comparing the timing of diagnosis. The time to event for RRT and CIC was significantly younger for prenatally detected PUV. At the CHOP, significantly more prenatal boys required RRT; however, there was no significant difference in the age this outcome was reached. The proportion of boys managed with CIC was not different but the time to event was significantly earlier in the prenatal group.

Conclusion

This study represents the largest multi-institutional series of boys with PUV and failed to identify any difference in the outcomes of pre- vs postnatal detection of PUV. A multidisciplinary approach with standardisation of the treatment pathways will help in understanding the true impact of prenatal/early detection on outcomes of PUV.

Keywords

prenatal diagnosis, postnatal detection, posterior urethral valves, lower urinary tract obstruction, end-stage renal disease, renal replacement therapy, #Urology, #PedUro

Introduction

Posterior urethral valves (PUV) represent the most common aetiology for lower urinary tract obstruction in boys, reported in up to two to three in 10 000 live births [1]. PUV is a chronic condition, with as many as 50% of boys having persistent incontinence with bladder dysfunction persisting into adulthood, and up to 40% requiring medications or clean intermittent catheterisation (CIC) to help with bladder emptying [2,3]. Close observation and optimised management are important to preserve renal reserve; however, up to 30% of boys with PUV will ultimately require renal replacement therapy (RRT; i.e. dialysis or renal transplantation) in their lifetime [4].

PUV may be detected on prenatal ultrasonography (US) in the first or second trimester. A subgroup of patients with severe forms of obstruction may undergo fetal procedures such as vesico-amniotic shunting [5,6]. However, it is unclear if prenatal detection (± fetal intervention) is beneficial in delaying or preventing detrimental long-term outcomes when compared to postnatal presentation. Some studies conclude that a prenatal diagnosis is associated with poorer prognosis [4,7], while others have demonstrated that prenatal diagnosis has superior renal outcomes [8,9]. Several studies evaluating the same outcomes have found no difference between pre- and postnatal diagnosis, including progression to chronic kidney disease (CKD) and end-stage renal disease (ESRD) [10,11]. All the PUV studies in the literature are retrospective in nature and span across a time that saw continuous evolution in the diagnosis and management of PUV. In addition, many do not include prenatal US findings, time to CKD and RRT, data on CIC, which makes interpretation not only difficult but also less reliable. Hence, a systematic review and meta-analysis may fail to assess the outcomes of PUV adequately.

The aim of this study was to review the experience of two large paediatric centres in management of boys with PUV, comparing the outcomes of pre- and postnatally diagnosed patients.

Patients and Methods

Data Collection

The charts of boys with PUV aged 0–18 years from 2000 to 2020 were reviewed following ethics board approval at two institutions: the Hospital for Sick Children (SickKids, SK) Research Ethics Board identification number (ID): 1000053438; and the Children's Hospital of Philadelphia (CHOP) Institutional Review Board ID: 17–014098. The SK is a tertiary paediatric referral and transplant centre in Ontario, Canada; and the CHOP is a tertiary paediatric referral and transplant centre in Pennsylvania, United States. The following variables were collected: pre- vs postnatal presentation, prenatal US findings, age at postnatal presentation, presence of VUR, type of initial surgical management, anticholinergic use, α-blocker use, development of UTIs (after stopping antibiotic prophylaxis), creation of catheterisable channels, CIC, declining eGFR, progression to ESRD, and the need for RRT. The eGFR was calculated using the Schwartz formula [12]. CKD Stage 3 was defined as an eGFR of <60 mL/min/1.73 m^2 and ESRD was defined as an eGFR of <15 mL/min/1.73 m^2. The indications for CIC were incomplete bladder emptying, recurrent UTIs, and risk of upper tract deterioration due to high intravesical pressure for those who were investigated with urodynamic studies. A representative clinical pathway for management of PUV is presented in Fig. 1 and Fig. 2.

Statistical Analysis

Demographic characteristics were presented as median (interquartile range [IQR]) for continuous variables and counts/percentages for categorical variables. Categorical variables were compared using chi-square and Fisher's exact test. Continuous variables were compared using Mann–Whitney *U*-test. Time-to-event analyses were carried out using Kaplan–Meier curves and log-rank tests for each institution. The tests were two-sided and $P < 0.05$ was considered statistically significant. Data were analysed using the Statistical Package for the Social Sciences (SPSS®), version 23.0 (IBM Corp., Armonk, NY, USA).

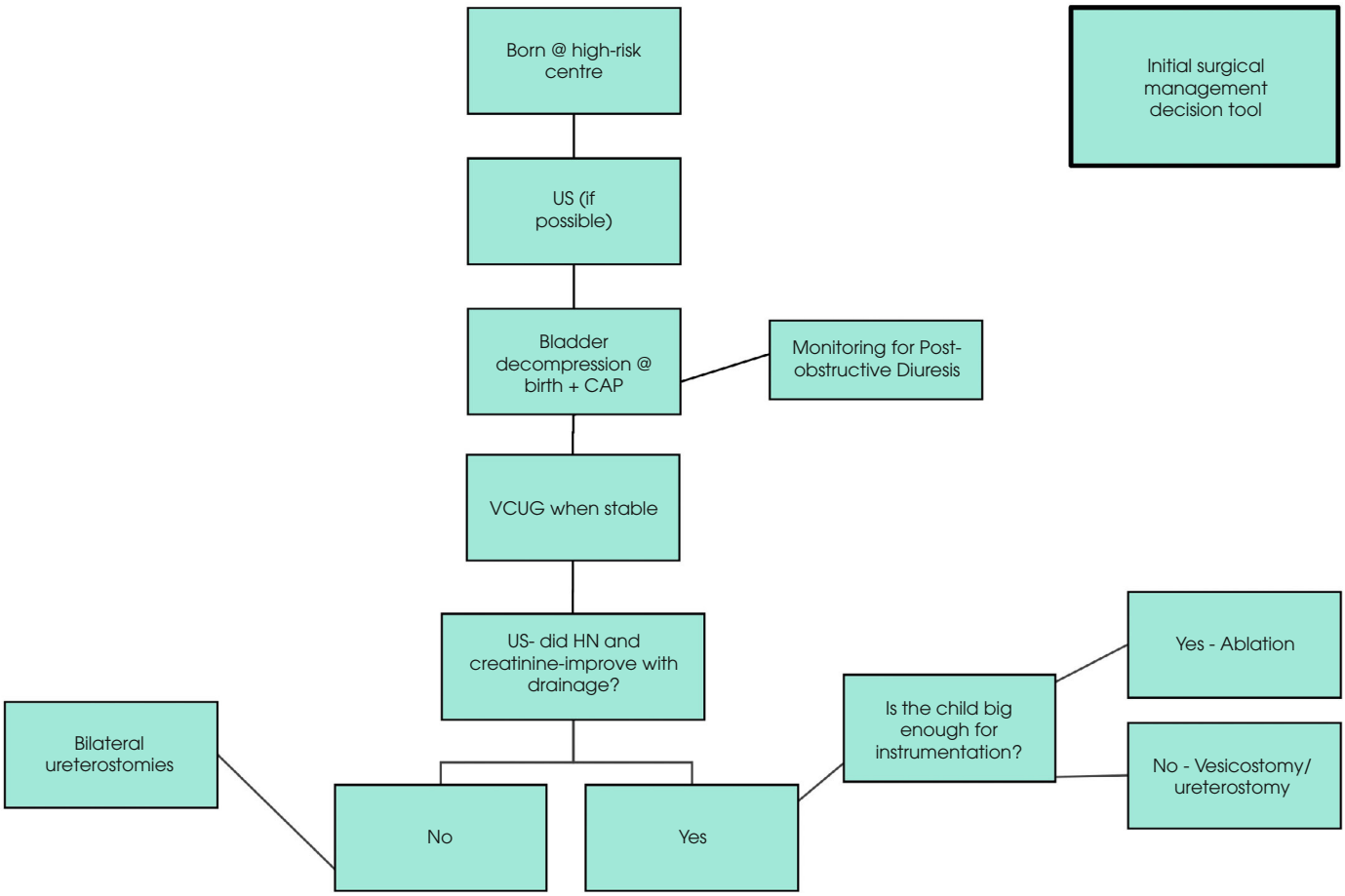
Results

SickKids

A total of 152 boys with PUV were contributed by the SK, the median (IQR) age at presentation was 14 (3–108) days, and the proportion of prenatal detection was 59/152 (39%). Initial surgical management was in the form of valve ablation in 131 (86%) boys, while 16 (11%) were managed with an initial vesicostomy, five with a higher diversion (3%), and 11 (8%) required a diversion procedure after valve ablation. CIC was initiated in 40 (26%) boys at a median (IQR) age of 4.4 (2–8) years and 23 (15%) underwent a Mitrofanoff procedure. The reasons for initiating CIC (some patients had more than one indication) were worsening hydronephrosis (HN; 35%), recurrent UTIs (5%), deteriorating renal function (53%), and poor bladder emptying (45%). The median (IQR) follow-up was 6.5 (3–12) years. Kidney function data were available for 84% of the patients (Table 1).

When comparing pre- to postnatal presentation, we found no significant difference in the proportion of patients who required RRT (11/59 [19%] prenatal vs 11/93 [12%] postnatal presentation), proportion of patients with VUR, who progressed to CIC and who were started on anticholinergic and/or α-blocker medications. The mean time to UTI was

Fig. 1 Proposed initial surgical management decision tool. CAP, continuous antibiotic prophylaxis; VCUG, voiding cystourethrogram.



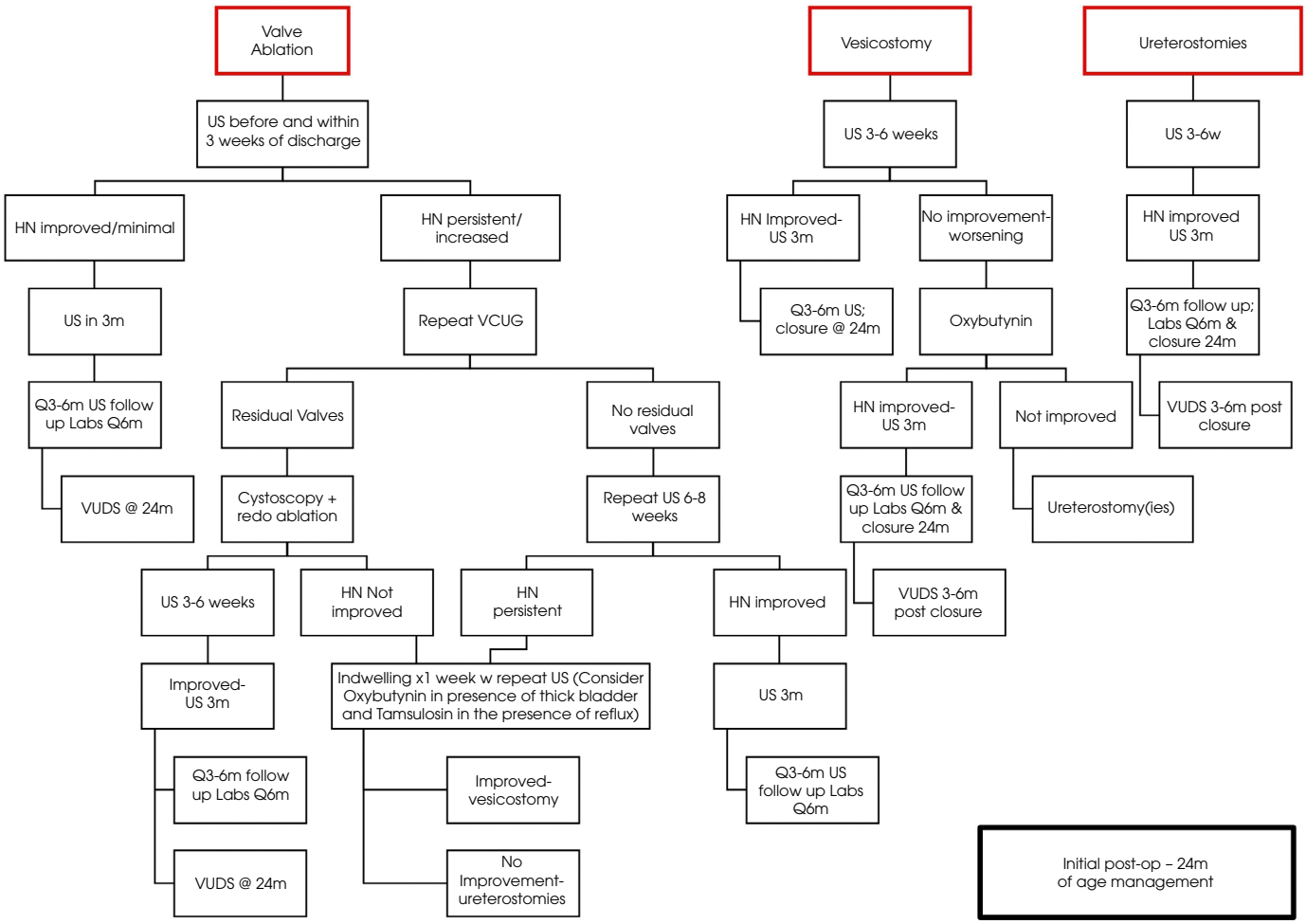
1.9 years in the prenatal group vs 2.8 years in the postnatal group (P = 0.363). Regarding timing of RRT, patients in the prenatal group were significantly younger, with a mean (IQR) age of 1 (5) year vs 8 (7) years (P = 0.016) in the postnatal group. (Table 2; Fig. 3). We found no difference between the groups in the CKD stage at first visit or last follow-up. The mean eGFR at last follow-up was significantly higher in postnatally diagnosed patients with a mean (SD) eGFR of 87.1 (36.8) vs 79.2 (36.3) mL/min/1.73 m^2 (P = 0.047) in the prenatal group. CKD progression occurred at a later age in the postnatal group, at a median (IQR) of 13.8 (10–18) vs 6.2 (3–9) years in the prenatal group, and CKD developed in six of 59 (10.1%) boys in the prenatal group vs six of 93 (6.5%) in the postnatal group (P = 0.048).

The CHOP

The CHOP contributed 216 boys, the median (IQR) age at presentation was 2 (0–83) days and 153/216 (71%) were prenatally detected. The initial surgery was valve ablation in 189 (88%) boys, 17 (8%) were managed with a vesicostomy, and 15 (7%) required a vesicostomy after initial valve ablation. In 10 boys the type of initial surgery was unknown. CIC was required in 29 (13%) boys at a mean (IQR) age of 3.9 (1–10) years, and 7 (3%) underwent a Mitrofanoff procedure. The median (IQR) follow-up was 6 (2–11) years. The kidney function data are presented in Table 1.

When comparing pre- to postnatal presentation, there was a significant difference in proportion of patients who required RRT in the prenatal group (21/153 [14%]) compared to the postnatal group (two of 63 [3%]; P = 0.016). As in the SK, there was no difference in the proportion of patients with VUR, who progressed to CIC or who were started on anticholinergics. The mean time to UTI was 2.4 years in the prenatal group vs 2.3 years in the postnatal group (P = 0.824). The age at CIC initiation was significantly younger in prenatally diagnosed patients, at a median (IQR) of 3 (1–7) vs 9.8 (5–12) years (P = 0.032). Time to RRT was shorter in the prenatal group, with a median (IQR) age of 1.6 (1–8) years vs 3.4 (N/A) years in the postnatal group, but this was not significant (P = 0.870) (Table 2; Fig. 3).

Fig. 2 Proposed postoperative management decision tool (0–24 months). VCUG, voiding cystourethrogram; VUDS, video-urodynamics.



Discussion

Progression to CKD and need for RRT are important outcomes of PUV, because up to one third will eventually progress to ESRD [4]. There was no difference between groups in progression to CKD at both institutions. At the SK, there was no difference in the need for RRT between the pre- and postnatal groups. On the other hand, there was a difference in the proportion of patients from the CHOP who required RRT in the prenatal compared to the postnatal group. This may be due to predominance of prenatally diagnosed patients at this site (71%). Differences in the relative proportion of prenatal diagnosis across the centres hampers direct comparison of the outcomes, particularly for the variables that evolve over time. These trends are reflected in the literature, as well and underline the importance of a standardised protocol for prenatal diagnosis and postnatal management. When time-to-event analysis was calculated, the age at initiation of RRT was younger in the prenatal group (although significant only for the SK).

The institutional data on CIC had rates varying from 13% to 26%; however, there was no difference in the proportion of patients in pre- vs postnatal groups. We found the same to be true when we reviewed those patients managed with a catheterisable channel. The time to CIC was available only for institutional data and as expected, CIC was initiated earlier in the prenatal group. α-blocker use was only captured at the SK and was similar for both groups but initiated earlier in the prenatal group. We acknowledge that the decision to start a child on CIC, initiate medications or offer a catheterisable channel is provider-dependent and multifactorial, which makes it variable and unpredictable.

Prenatal diagnosis of PUV results in a shift in the management of this population from treating symptomatic presentation, such as sepsis in infants, to proactive bladder decompression at birth and early surgical intervention to relieve the obstruction. Selective fetal interventions, such as vesico-amniotic shunting, for more severe cases may be offered [5,6], which are thought to preserve renal reserve and

Table 1 Comparison of renal function outcomes between pre- and postnatally diagnosed PUV at the SK and CHOP.

Variable		SK			CHOP		
		Prenatal (*n* = 59)	Postnatal (*n* = 93)	*P*	Prenatal (*n* = 153)	Postnatal (*n* = 63)	*P*
CKD* at first visit, *n* (%)	Stage 1	21 (35.6)	38 (40.9)	0.432	28 (18.3)	21 (33.3)	0.032
	Stage 2	14 (23.7)	28 (30.1)		13 (8.5)	11 (17.5)	
	Stage 3A	5 (8.5)	4 (4.3)		9 (5.9)	8 (12.7)	
	Stage 3B	2 (3.4)	1 (1.1)		15 (9.8)	3 (4.8)	
	Stage 4	4 (6.8)	6 (6.5)		35 (22.8)	4 (6.3)	
	Stage 5	3 (5.1)	4 (4.3)		29 (19.0)	6 (9.5)	
	Unknown	10 (16.9)	12 (12.9)		24 (15.7)	10 (15.9)	
CKD* at last follow-up, *n* (%)	Stage 1	25 (42.4)	49 (52.7)	0.497	39 (25.5)	13 (20.6)	0.068
	Stage 2	5 (8.5)	15 (16.1)		21 (13.7)	8 (12.7)	
	Stage 3A	5 (8.5)	3 (3.2)		6 (3.9)	2 (3.2)	
	Stage 3B	2 (3.4)	2 (2.1)		10 (6.5)	0 (0)	
	Stage 4	5 (8.5)	2 (2.1)		9 (5.9)	3 (4.8)	
	Stage 5	6 (10.2)	9 (9.7)		10 (6.5)	2 (3.2)	
	Unknown	11 (18.6)	13 (14.0)		58 (37.9)	35 (55.5)	
First visit Mean (SD) eGFR, mL/min/1.73 m^2		79.2 (36.3)	87.1 (36.8)	0.235	48.5 (41.0)	77.6 (48.4)	<0.001
Last follow-up Mean (SD) eGFR, mL/min/1.73 m^2		76.6 (42.6)	92.3 (42.9)	0.047	77.2 (47.3)	88.0 (50.3)	0.318
Progressive renal dysfunction†, *n* (%)		11 (18.6)	13 (14.0)	0.497	17 (11.1)	9 (14.2)	0.499

**CKD defined as CKD Stage 3A or higher (eGFR <60 mL/min/1.73 m^2). †Progressive renal dysfunction defined as up-staging of CKD stage by filtration rate.*

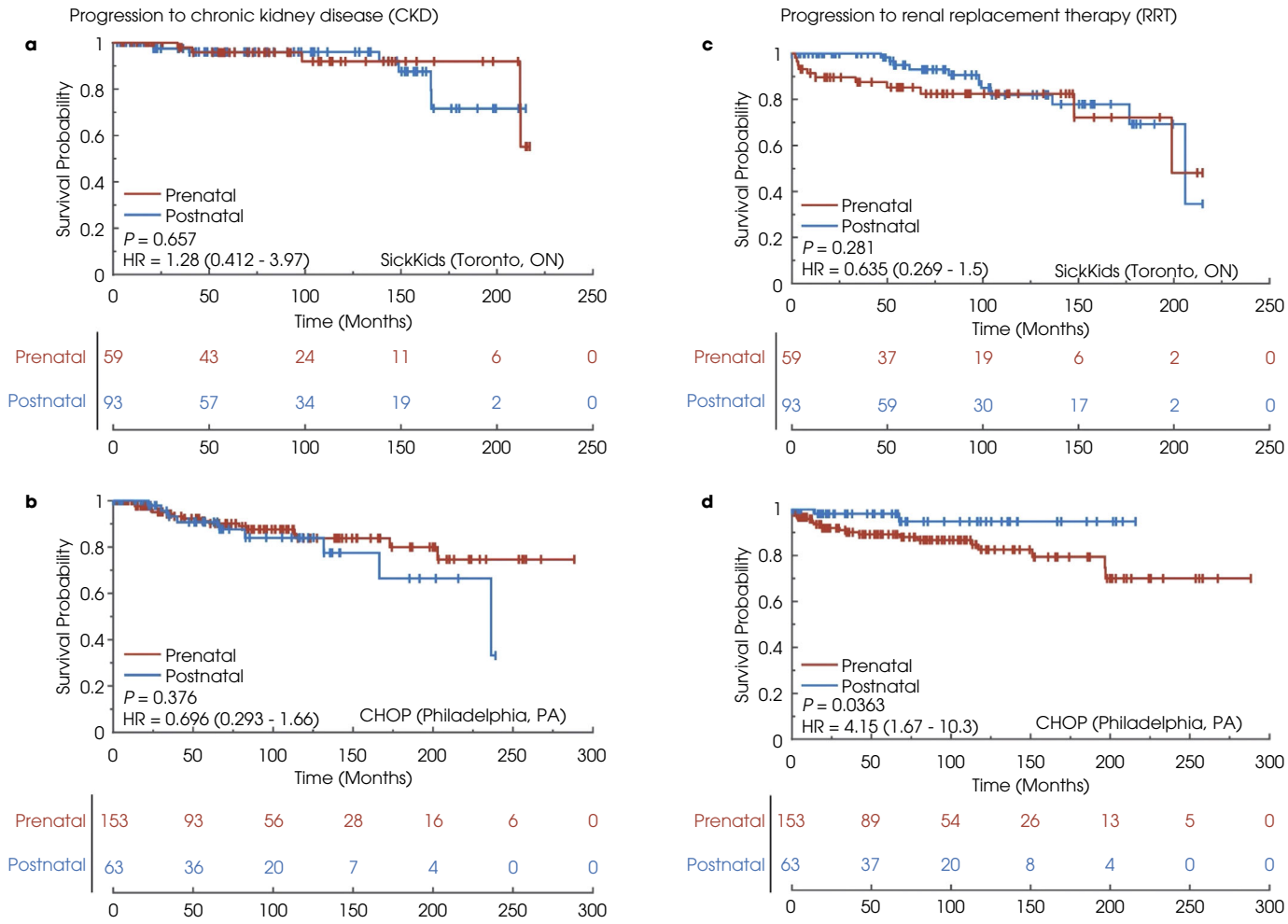
Table 2 Comparison of outcomes between pre- and postnatal presentation of PUV at the SK and CHOP.

Variable	SK			CHOP		
	Prenatal (*n* = 59)	Postnatal (*n* = 93)	*P*	Prenatal (*n* = 153)	Postnatal (*n* = 63)	*P*
Age at presentation, days, median (IQR)	4 (1–9)	44 (11–337)	**<0.01**	1 (0–4)	190 (31–730)	**<0.01**
Dialysis, *n* (%)	7 (12)	5 (5)	0.148	19 (12)	1 (2)	**0.015**
Age dialysis started, years, median (IQR)	0.3 (0–1)	7 (4–10)	**0.010**	2.5 (0–10)	1.2*	1.00
Transplant, *n* (%)	10 (17)	10 (11)	0.271	12 (8)	1 (2)	0.079
Age of transplant, median (IQR), years	3.9 (3–8)	7.5 (5–13)	0.052	5.7 (5–10)	5.6*	1.00
RRT, *n* (%)	11 (19)	11 (12)	0.244	21 (14)	2 (3)	**0.016**
Age at RRT, years, median (IQR)	1 (0–6)	8 (8–13)	**0.028**	1.6 (1–8)	3.4*	0.870
CKD progression, *n* (%)	6 (10)	6 (7)	0.539	17 (11)	9 (14)	0.499
Age at CKD progression, years, median (IQR)	13.8 (10–18)	6.2 (3–9)	**0.048**	3.6 (2–8)	6.1 (4–14)	0.234
Anticholinergic use, *n* (%)	20 (34)	25 (27)	0.356	64 (42)	21 (22)	0.245
Age anticholinergic started, years, median (IQR)	2 (0–6)	1.7 (0–6)	0.762	0.8 (0–4)	0.7 (0–3)	0.950
α-blocker, *n* (%)	27 (47)	36 (39)	0.370	–	–	–
Age α-blocker started, years, median (IQR)	3.3 (1–5)	6 (4–10)	**0.004**	–	–	–
VUR, *n* (%)	39 (70)	52 (57)	0.130	77 (56)	28 (54)	0.809
CIC, *n* (%)	19 (32)	21 (23)	0.203	21 (14)	8 (13)	0.841
Age CIC started, years, median (IQR)	3.2 (1–6)	6.5 (4–10)	**0.020**	3 (1–7)	9.8 (5–12)	**0.032**
Mitrofanoff, *n* (%)	11 (19)	12 (13)	0.414	4 (3)	3 (5)	0.486
Age at Mitrofanoff, years, median (IQR)	4.3 (3–7)	7 (4–12)	0.110	6.1 (4–8)	7.7 (4–13)	0.629
UTIs, *n* (%)	32 (54)	54 (58)	0.643	59 (39)	31 (49)	0.149
Follow-up time, years, median (IQR)	6.8 (3–12)	6.1 (2–12)	0.451	6.7 (2–11)	5.2 (2–10)	0.288

**IQR is not applicable because there were only two patients. Statistically significant values denoted in bold.*

bladder function, but evidence for this is limited [13]. However, offering early interventions, whether *in utero* or postnatally may allow for preservation of the renal reserve and bladder function they have for as long as possible. In contrast, the boys presenting postnatally may have less severe obstruction, with greater renal reserve and better bladder function, which slowly deteriorates until they reach the point of becoming symptomatic. This hypothesis may explain why the proportion of boys from both groups who experience important outcomes appears to be the same. Prenatal diagnosis therefore may lead to systematic differences and bias impacting the prognosis of boys with PUV.

Fig. 3 Kaplan–Meier curves comparing the progression to CKD between the pre- and postnatal groups at the (**a**) SK and (**b**) CHOP. Kaplan–Meier curves comparing the progression to RRT between the pre- and postnatal groups at the (**c**) SK and (**d**) CHOP.



Another important consideration is that it might not be the timing of presentation but the optimisation of care, particularly early in life, that may improve long-term outcomes. Perhaps lowering the threshold for fetal intervention to minimise the effort of the bladder to empty may lessen the extent of bladder dysfunction and progression to myogenic failure later in life, and ultimately help to preserve overall renal function for longer. Considering post-ablation diversion for infants with persistent HN may also help to preserve renal function and delay outcomes that may be inevitable. Due to the variability in management between centres and providers, a multicentre standardised care pathway for these patients may help to improve these long-term outcomes.

While we believe there is value in the present study, we acknowledge there are limitations. Most importantly, the mean follow-up period of up to 6–7 years in the institutional data is not sufficient to cover the spectrum of PUV, which evolves throughout the first two decades of life. With longer follow-up, more patients may progress to ESRD [9]. Further, the number of patients in the pre- and postnatal groups were very different across the two institutions. The use of an α-blocker was reported only at the SK and not the CHOP. However, despite these limitations, our study adds value to the current body of literature. We have included data from two large, paediatric academic North American centres with large sample sizes of a relatively rare condition, making this review one of the largest in contemporary literature that targets the important question of outcomes of pre- vs postnatal presentation of PUV.

What still remains to be explored especially through prospective studies is the role of new biomarkers in assessment of renal function in boys with PUV. Serum creatinine remains by far the most common surrogate of the renal function, but it is known to be less sensitive than the reference methods such as inulin clearance. Further, it is

affected by maternal creatinine levels in the neonatal period, so early estimation of GFR using creatinine is inaccurate. Cystatin C is independent of age and muscle mass and may be promising in this age group. However, it is not yet validated for practice particularly for preterm infants in whom it may be able to screen acute renal insufficiency but not predict the exact level of GFR [14]. It is possible that a combination of biomarkers and physical/physiological characteristics of patients may be necessary for accurate prediction of GFR in young boys with PUV.

Conclusion

In this study, through the analysis of data from two large paediatric centres in North America, we found that prenatal diagnosis of PUV does not appear to improve long-term outcomes of these patients. However, this may represent oversimplification of analysis given the inherent heterogeneity in the retrospective institutional datasets. Regardless, optimising management early on and creation of standardised management pathway could potentially help to improve long-term outcomes, although the current evidence falls short of such affirmation or otherwise.

Acknowledgements

None.

Ethics Approval

The study was approved by the Research Ethics Committee of the SK and CHOP.

Conflict of Interest

The authors have no conflict of interests to declare.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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Abbreviations: CHOP, Children's Hospital of Philadelphia; CIC, clean intermittent catheterisation; CKD, chronic kidney disease; HN, hydronephrosis; ESRD, end-stage renal disease; ID, identification number; IQR, interquartile range; PUV, posterior urethral valves; RRT, renal replacement therapy; SK, Hospital for Sick Children (SickKids); US, ultrasonography.