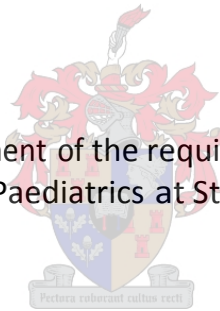


FACTORS PREDICTING THE LONG-TERM RENAL FUNCTION IN BOYS PRESENTING WITH POSTERIOR URETHRAL VALVES AT TYGERBERG CHILDREN'S HOSPITAL, SOUTH AFRICA – A TEN YEAR STUDY

By

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Thesis presented in partial fulfilment of the requirements for the degree Master of
Medicine degree in Paediatrics at Stellenbosch University



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Short title

Prognostic factors in boys with posterior urethral valves

Keywords

Posterior urethral valves; Prognostic factors; Creatinine; Renal failure

Abbreviations and acronyms

PUV = posterior urethral valves; COPUM = congenital obstructing posterior urethral membrane; CKD = chronic kidney disease; ESRD = end-stage renal disease; VUR = vesicoureteric reflux; MCUG = micturating cystourethrogram; UTI = urinary tract infection; CMD = corticomedullary differentiation; eGFR = estimated glomerular filtration rate; NKF-K/DOQI = National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; ROC = receiver operating characteristic; AUC = area under the curve; IQR = inter-quartile range

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Declaration

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April 2014

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ABSTRACT

SETTING

Tertiary children's hospital, Cape Town, South Africa.

OBJECTIVES

The aim of this study was to determine long-term renal function in boys presenting with posterior urethral valves at Tygerberg Children's Hospital and to determine the prognostic value of certain clinical, biochemical and radiological variables

DESIGN

Retrospective, descriptive study of boys diagnosed and treated with posterior urethral valves at Tygerberg Children's Hospital between 2001 and 2011.

RESULTS

Between 2001 and 2011, 47 cases of posterior urethral valves were diagnosed and treated at our institution. Thirteen patients were excluded from this study. Seven (20,6%) were diagnosed antenatally and 27 (79,4%) presented postnatally. Mean age at presentation was 13,9 months (median 2; range 0-74). The most common postnatal presentation was urinary tract infection (51,9%). Mean follow-up was 54,2 months (median 47,5; range 12-133). A total of 13 boys (38,2%) progressed to chronic renal failure or end-stage renal disease. Initial and nadir serum creatinine, poor corticomedullary differentiation and moderate-severe hydronephrosis were significant predictors of final renal function ($p < 0,050$). Patient age at presentation, type of primary surgical intervention, increased renal echogenicity, bladder wall thickness, the presence of vesicoureteric reflux (no matter what the laterality or severity), severe bladder dysfunction and initial or breakthrough urinary tract infection had no significant impact on future renal function. Receiver operating characteristic curve analysis confirmed that boys with an initial serum creatinine $\geq 145 \mu\text{mol/L}$ and a nadir serum creatinine $\geq 62 \mu\text{mol/L}$ were at highest risk to develop chronic renal insufficiency (area under the curve 0,8 and 0,9, respectively).

CONCLUSION

More than a third of boys (38,2%) developed chronic renal failure or end-stage renal disease at the end of follow-up. Our data confirmed the high prognostic value of initial and nadir serum creatinine. Optimal threshold levels for initial and nadir serum creatinine to predict final renal function were $145 \mu\text{mol/L}$ and $62 \mu\text{mol/L}$, respectively. Similarly, poor corticomedullary differentiation and moderate-severe hydronephrosis on initial kidney ultrasound were significant indicators of poor renal prognosis. Although all patients with posterior urethral valves should be counselled on potential renal morbidity, children with risk factors warrant closer monitoring.

OPSOMMING

OMGEWING

Tersiêre kinders hospitaal, Kaapstad, Suid-Afrika.

DOELWITTE

Die doel van hierdie studie was om langtermyn nierfunksie te bepaal in seuns wat gediagnoseer is met posterior uretrale kleppe by Tygerberg-kinders hospitaal. Die prognostiese waarde van sekere kliniese, biochemiese en radiologiese veranderlikes is ook ondersoek.

STUDIE ONTWERP

Retrospektiewe, beskrywende studie van seuns wat tussen 2001 en 2011 by Tygerberg-kinders hospitaal gepresenteer het met posterior uretrale kleppe.

RESULTATE

Tussen 2001 en 2011 is 47 gevalle van posterior uretrale kleppe gediagnoseer en behandel by ons instelling. Dertien pasiënte is uitgesluit van hierdie studie. Sewe (20,6%) is met voorgeboorte sonar gediagnoseer en 27 (79,4%) het ná geboorte gepresenteer. Die gemiddelde ouderdom by diagnose was 13,9 maande (mediaan 2; reeks 0-74). Urieweginfeksie was die mees algemene metode waarmee postnatale pasiënte gepresenteer het (51,9%). Die gemiddelde opvolgperiode was 54,2 maande (mediaan 47,5; reeks 12-133). Dertien seuns (38,2%) het chroniese nierversaking of eind-stadium nierversaking ontwikkel. Aanvanklike en nadir serumkreatinien, swak kortiko-medullêre differensiasie en matig-erge hidronefrose was beduidende voorspellers van finale nierfunksie ($p < 0,050$). Pasiënt ouderdom met diagnose, tipe chirurgiese ingryping, verhoogde niereggogenisiteit, blaaswanddikte, vesikoureteriese refluks, blaasdisfunksie en aanvanklike of deurbraak urieweginfeksies het geen beduidende impak op toekomstige nierfunksie gehad nie. Seuns met 'n aanvanklike serumkreatinien $\geq 145 \mu\text{mol/L}$ en 'n nadir serumkreatinien $\geq 62 \mu\text{mol/L}$ het die grootste risiko om chroniese nierversaking te ontwikkel, soos bevestig met 'n ROC-ontleding (AUC 0,8 en 0,9, onderskeidelik).

GEVOLGTREKKING

Meer as 'n derde van die pasiënte (38,2%) het chroniese nierversaking of eind-stadium nierversaking ontwikkel. Ons data bevestig die prognostiese waarde van aanvanklike en nadir serumkreatinienvlakke. Die optimale drempelwaardes vir die aanvanklike en nadir serumkreatinien om finale nierfunksie te voorspel was $145 \mu\text{mol/L}$ en $62 \mu\text{mol/L}$, onderskeidelik. Swak kortiko-medullêre differensiasie en matig-erge hidronefrose op die aanvanklike niersonar was ook beduidende aanwysers van toekomstige nierfunksie. Alhoewel alle pasiënte met posterior uretrale kleppe berading moet ontvang oor potensiële niermorbiditeit, regverdig seuns met risikofaktore noukeurige monitering.

INTRODUCTION

BACKGROUND

The World Health Organisation has indicated that it is necessary to evaluate the potential burden of congenital disorders in every country, with a view to introducing preventive measures at the appropriate time. As infectious diseases and malnutrition are brought under control in developing countries, congenital anomalies will assume a greater importance as a cause of morbidity and mortality among infants and children, as has been the case in the developed world¹.

Posterior urethral valves (PUV) are the most common cause of congenital obstruction in the lower urinary tract², with an estimated incidence of 1:5000-8000 live male births³. The incidence of this condition in the African population is unknown⁴. Young et al first described PUV in 1919 as valve-like folds in the lumen of the posterior urethra⁵. PUV are formed in the fourth gestational week as the mesonephric ducts fuse with the developing cloaca (the site of the future verumontanum). When the insertion of the mesonephric ducts into the cloaca are anomalous or too anterior, normal migration of the ducts are impeded, and the ducts fuse anteriorly resulting in the formation of abnormal folds⁴. Young's initial classification was recently challenged by Dewan et al after studying un-instrumented posterior urethra in patients with PUV. They propose that, instead of a true valve, a persistent oblique membrane associated with the verumontanum is ruptured either antenatally or due to postnatal instrumentation to form a valve-like structure^{6,7}. This new concept of a congenital obstructing posterior urethral membrane (COPUM) has not yet been widely adopted into clinical practice.

Despite advances in the medical and surgical management of PUV, 13-64% of boys still develop chronic kidney disease (CKD) or end-stage renal disease (ESRD) during long-term follow-up⁸. The impact of CKD and ESRD due to PUV are enormous not only in terms of well-being of the boys affected but also the cost of renal replacement therapy to their families and the health system⁹.

LITERATURE REVIEW

There is a paucity of research on renal morbidity in boys with PUV in Sub-Saharan Africa. Although prognostic factors affecting final renal outcome in PUV have been identified and researched in a number of studies^{2,3,8-15,17-24}, this research has rarely been extended to the South African population.

Several factors have a significant impact on outcome, such as age at presentation, type of surgery, initial and nadir serum creatinine, certain sonographic parameters on initial abdominal ultrasound, the presence of vesicoureteric reflux (VUR) on initial micturating cystourethrogram (MCUG), bladder dysfunction after the age of 60

months and initial or recurrent urinary tract infections (UTI's)^{2,3,8-15,17-24}. There is no agree in the literature as to the value of these prognostic factors.

Age at presentation

There is significant controversy regarding timing of diagnosis of PUV and its impact on final renal outcome¹⁰. Some authors believe that early presentation of PUV is associated with a poor renal outcome^{10,11}. They suggest that more severely obstructed patients are detected earlier. Ansari et al, however, showed that patients with PUV presenting after 2 years of age should be treated with caution because these patients are at a higher risk of developing chronic renal insufficiency¹². El-Ghoneimi et al failed to demonstrate that long-term renal outcome is different between boys with PUV detected on antenatal ultrasound and those who presented postnatally¹³.

Primary surgical intervention

Reinberg et al suggests that the progression of renal failure is independent of the type of primary surgical treatment¹⁴. Valve ablation and vesicostomy are equally effective¹⁵. Primary valve ablation remains the mainstay of surgical treatment for PUV, although a vesicostomy or upper urinary tract diversion will be considered where the resection of valves are technically difficult (as in premature babies), when the upper urinary tracts are severely compromised or in infants with on-going urinary infection¹⁶.

Initial serum creatinine

A clear prognostic relation between initial (preoperative) serum creatinine and future renal function is well described^{17,18}. Sarhan et al showed that an initial serum creatinine of more than 1mg/dL (88,5µmol/L) correlates significantly with poor renal outcome in boys with PUV¹⁸.

Nadir serum creatinine

The nadir serum creatinine is defined as the lowest creatinine attained in the first year after initial surgical intervention. A higher serum creatinine after bladder drainage is associated with a decreased glomerular filtration rate (GFR) later in life^{17,18}. Ansari et al and Sarhan et al reported that a nadir serum creatinine of greater than 1mg/dL (88,5µmol/L) is one of the main factors predictive of progression to CKD and ESRD^{9,18}.

Initial renal-bladder ultrasound

Certain sonographic findings on initial renal-bladder ultrasound can be suggestive of PUV. Echogenic renal parenchymal changes and pathological corticomedullary differentiation (CMD) have been previously described as insensitive prognostic markers for chronic renal disease¹⁹. Pohl et al, however, found that increased renal parenchymal echogenicity (compared to the liver or spleen) and a loss of CMD

correlate significantly with long-term renal function²⁰. Engel et al demonstrated that the presence of preoperative bilateral hydronephrosis and increased hydronephrosis severity are useful parameters for identifying patients at highest risk of renal deterioration². Pohl et al also looked at pathological bladder configuration as a prognostic indicator for CKD. Although 94% of the boys showed a trabeculated bladder wall (with or without diverticulae) on the initial sonar, this was not predictive of poor renal outcome²⁰.

Initial micturating cystourethrogram

The initial MCUG is performed to confirm the diagnosis of PUV and to detect the presence of VUR. Urinary reflux in patients with PUV is secondary and found in approximately 50% of cases^{16,20,21}. Some studies agree that high grade, bilateral VUR is associated with increased renal morbidity^{2,3,9,11}, while other authors have found no significant difference between VUR (no matter what the laterality or severity) and long-term renal outcome^{10,18,20,21}.

Bladder dysfunction

Bladder outlet obstruction leads to muscular hypertrophy of the bladder wall. These changes may cause an overactive and non-compliant bladder that may persist after surgery. The reported incidence of voiding dysfunction after surgery is as high as 75%²². Severe bladder dysfunction, especially if daytime continence has not been achieved by 60 months of age, is associated with CKD and ESRD^{9,11,23}.

Urinary tract infection

Boys with valves often present with an UTI or have recurrent UTI's (even after surgery). Infection is the result of urinary stasis due to the presence of VUR, persistent hydroureteronephrosis, inefficient bladder emptying and/or persistent bladder outlet obstruction⁴. UTI's resulting in renal scarring has thought to be an important risk factor for CKD. Akdogan et al, however, reported that the presence of UTI's before treatment was not a significant cause of long-term renal morbidity²⁴. Although Pohl et al showed that suffering from more than 3 febrile UTI's after surgery was associated with poor renal outcome²⁰, most publications did not find a significant relation between breakthrough UTI's and long-term renal insufficiency^{8,9}.

AIM

The aim of this study was to determine long-term renal function in boys presenting with posterior urethral valves at Tygerberg Children's Hospital and to determine the prognostic value of certain clinical, biochemical and radiological variables.

METHODOLOGY

After obtaining approval from the Stellenbosch University Health Research Ethics Committee (protocol number S12/07/203), we retrospectively reviewed the medical records of all boys diagnosed with PUV at Tygerberg Children's Hospital between January 2001 and December 2011.

Our study population was retrieved from the paediatric nephrology clinic. This clinic serves both medically and surgically treated patients and thus functions as a central referral area for all paediatric nephrology cases.

Patients lost to follow-up, or where the follow-up period was less than 12 months after surgery, did not take part in this study. Boys who died during the study period, or where an additional urological anomaly was present and not directly attributed to PUV, were also excluded.

The folders of all study patients were reviewed for preoperative evaluation, surgical intervention and postoperative course.

At the preoperative evaluation, age at presentation, the presenting complaint and the first available serum creatinine (in $\mu\text{mol/L}$) were noted. We reviewed several sonographic parameters on the first renal-bladder ultrasound, including renal parenchymal echogenicity, CMD, bladder wall thickening and the presence, laterality and severity of hydronephrosis. Hydronephrosis severity was categorised by the worse of the 2 sides, if bilateral. Mild hydronephrosis included Society of Fetal Urology grades 1 and 2, and moderate-severe hydronephrosis included Society of Fetal Urology grades 3 and 4²⁵. The upper urinary tract was further assessed for the presence, laterality and severity of VUR on initial MCUG. Reflux severity was categorised by the worse of the 2 sides, if bilateral. Non-dilating VUR included International Reflux Study grades I and II, and dilating VUR included International Reflux Study grades III to V²⁶. Still images were reported by a single experienced sonographer where formal reports were not available.

Initial surgical management consisted of primary valve ablation, vesicostomy or upper urinary tract diversion (pyelostomy or ureterostomy), dependent on the patient's clinical state.

Regular follow-up was done by clinical examination, urine culture, serum creatinine and estimated glomerular filtration rate (eGFR). The nadir serum creatinine, defined as the lowest serum creatinine within the first year after initial surgery, was recorded. Boys older than 60 months at the last follow-up were evaluated for severe bladder dysfunction (defined as having one or more of the following: daytime incontinence, chronic use of anticholinergics, self-intermittent catheterisation or

bladder dysfunction diagnosed by formal urodynamic studies). The number of UTI's since initial surgery, proven on a sterile collected urine specimen with leukocytes more than $10/\text{mm}^3$ and/or bacterial growth were noted.

Renal function at the last follow-up visit was determined by calculating the eGFR using the modified Schwartz formula ($\text{eGFR} = (k \times l) \div \text{sCr}$; where $k = 38,5$ for all age groups, l = patient height in cm and sCr = serum creatinine in $\mu\text{mol/L}$, measured by the Jaffe method)²⁷. Final renal function was then categorised according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines for chronic kidney disease in children and adolescents²⁸ (Table 1).

Table 1: NKF-K/DOQI classification of the stages of CKD

Stage	GFR	Description
1	≥ 90	Kidney damage with normal or increased GFR
2	60-89	Kidney damage with mild reduction of GFR
3	30-59	Moderate reduction of GFR
4	15-29	Severe reduction of GFR
5	<15 (or dialysis)	Kidney failure (ESRD)

To study the prognosis of long-term renal outcome, the cohort was divided into two groups: group A, comprising of boys with a normal or moderately impaired (NKF-K/DOQI stage 1-2) renal function and group B, comprising of boys with chronic renal failure or ESRD (NKF-K/DOQI stage 3-5 or receiving renal replacement therapy).

Both groups were analysed for statistical differences in certain prognostic variables related to final renal function including: age at presentation, primary surgical intervention, serum creatinine (initial and nadir), initial sonographic findings, VUR on initial MCUG, bladder dysfunction and the presence of UTI's.

All data collected was entered into a Microsoft ExcelTM spread sheet. Statistic Aver 10 (2012)TM was used to analyse all data. Descriptive data was analysed by using means and standard deviations. Continuous and categorical data were analysed as counts and percentages. Continuous responses were compared with the presence or absence of chronic renal failure by using the Mann-Whitney U test. The Pearson's Chi-squared test was applied to compare categorical responses. Probability values of less than 0.050 (two-sided) were regarded as statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal cut-off points of initial and nadir serum creatinine in the prediction of renal failure from the area under the curve (AUC).

RESULTS

Between January 2001 and December 2011, 47 cases of PUV were diagnosed and treated at Tygerberg Children's Hospital. We excluded 13 patients from this study. Eight were lost to follow-up, 2 had a follow-up period of less than 12 months after initial surgery, 2 died of sepsis and 1 patient was diagnosed with prune belly syndrome (Table 2).

Table 2: Patients excluded

	Total	%
Lost to follow-up	8	61,5
Follow-up period < 12 months	2	15,4
Died	2	15,4
Additional urological anomaly	1	7,7
Total	13	100

Thirty-four patients were retrospectively enrolled. Seven (20,6%) were diagnosed by means of antenatal ultrasound at a mean gestational age of 29 weeks (range 19-34). Twenty-seven boys (79,4%) presented postnatally.

The most common postnatal presentation was UTI (51,9%), followed by poor stream (14,8%) and an abdominal mass (14,8%). Other modes of presentation were anuria, seizures and vomiting (Table 3).

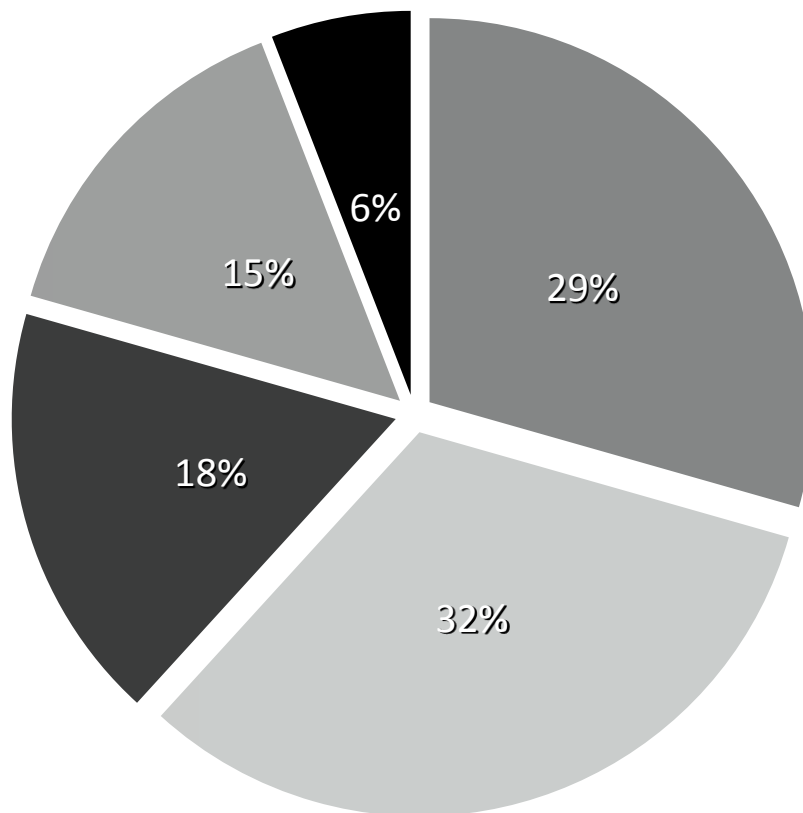
Table 3: Postnatal presentation

	Total	%
UTI	14	51,9
Poor stream	4	14,8
Abdominal mass	4	14,8
Anuria	1	3,7
Seizures	2	7,4
Vomiting	2	7,4
Total	27	100

The follow-up period was 12 to 133 months (median 47,5; mean 54,2). Chronic renal failure or ESRD (NKF-K/DOQI stage 3-5) developed at the end of follow-up in 13 patients (38,2%), of whom 2 (5,9%) required renal replacement therapy (dialysis 1, transplant 1). Twenty-one patients (61,8%) were classified as having a favourable long-term renal function (Figure 1).

Figure 1: Final renal function according to NKF-K/DOQI staging

■ Normal or Stage 1 ■ Stage 2 ■ Stage 3 ■ Stage 4 ■ Stage 5



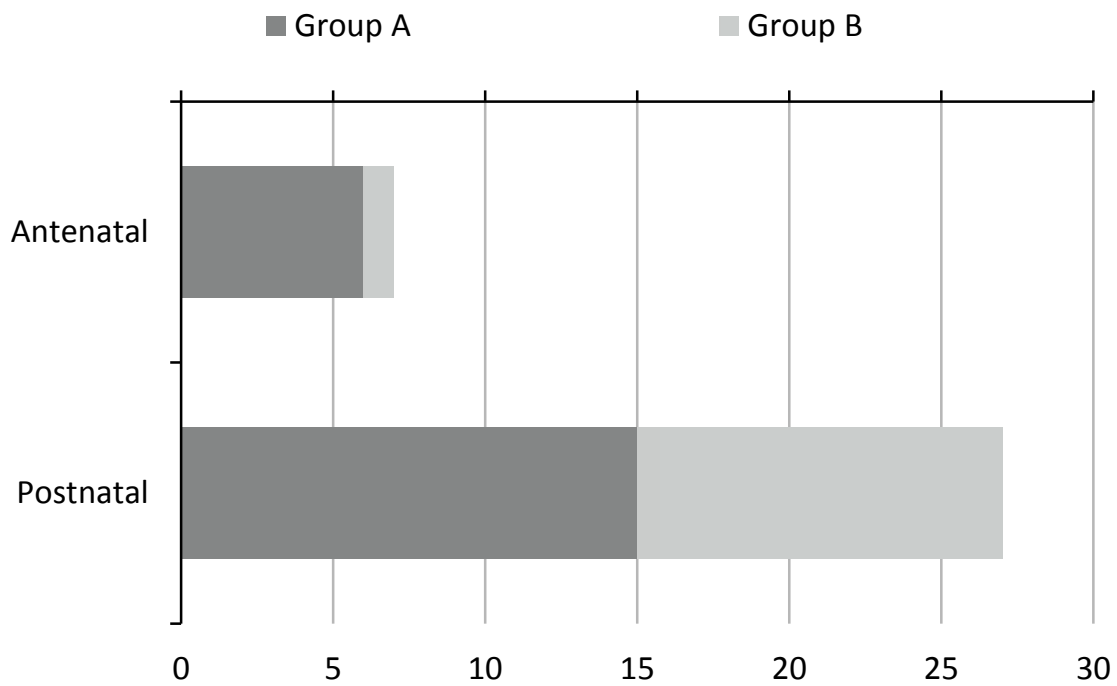
Age at presentation

The mean age at presentation was 13,9 months (median 2; range 0-74). Boys in group A presented at a mean age of 10,2 months (inter-quartile range (IQR) 0-13). Patients in group B presented at a mean age of 19,7 months (IQR 0-27).

In group A, 8 patients presented in the first month of life (including 6 diagnosed antenatally), while 7 patients presented between the age of 1 and 12 months. Six boys presented after the age of 12 months.

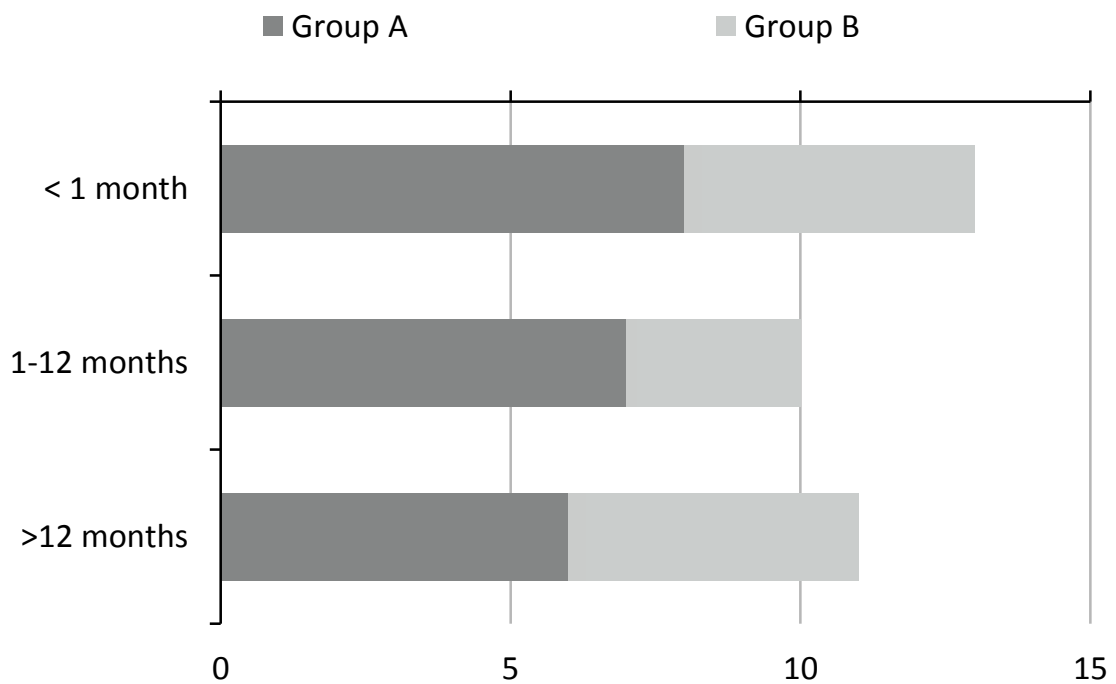
In group B, 5 patients presented in the first month of life (including 1 diagnosed antenatally), while 3 patients presented between the age of 1 and 12 months. Five boys presented after the age of 12 months (Figure 2 and 3).

Figure 2: Antenatal vs postnatal diagnosis



Antenatal vs postnatal diagnosis had no significant impact on future renal function ($p=0,210$).

Figure 3: Age at presentation (<1 month vs 1-12 months vs >12 months)



Age at presentation (<1 month vs 1-12 months vs >12 months) was not predictive of progression to chronic renal failure ($p=0,767$).

Primary surgical intervention

Primary valve ablation was performed in 16 cases (47,1%). Fifteen patients (44,1%) underwent open vesicostomy and 3 (8,8%) had upper urinary tract diversions. Table 4 lists type of surgery as per group A and B.

Table 4: Initial surgical intervention

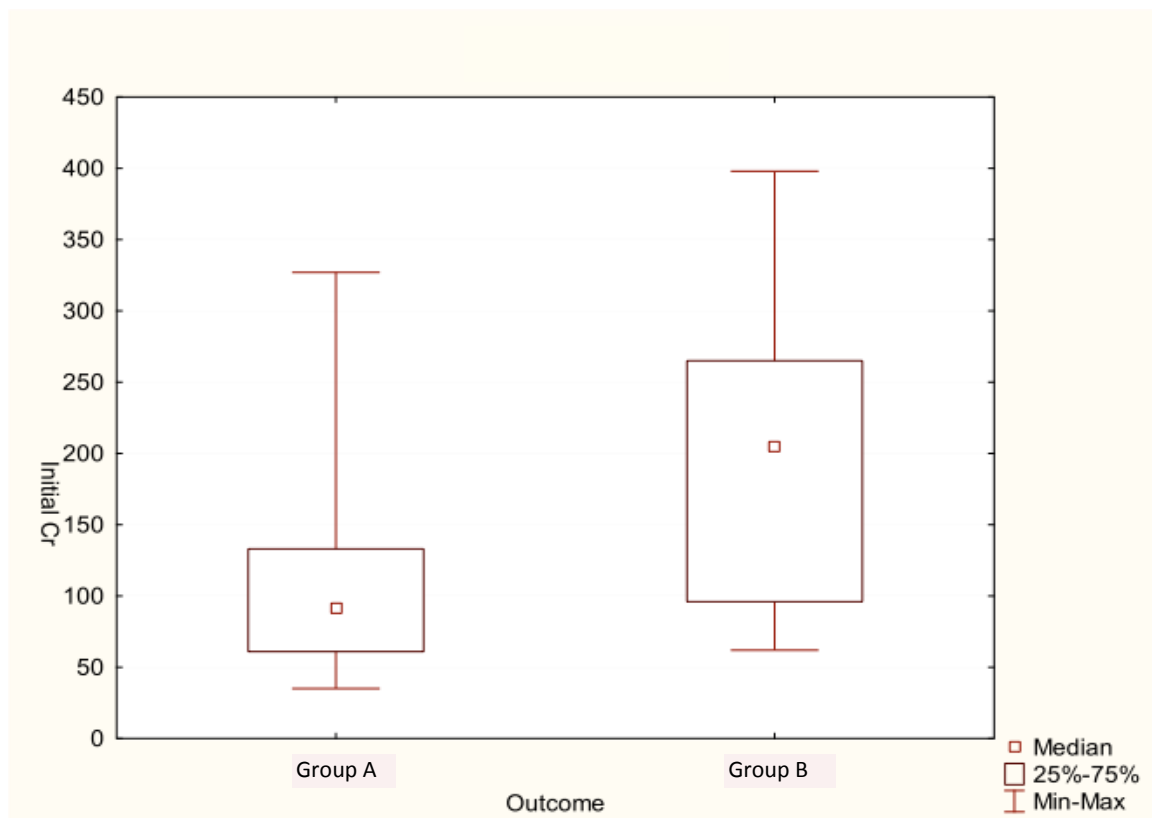
	Group A	Group B	Total
Valve ablation	12	4	16
Vesicostomy	9	6	15
Upper tract diversion	0	3	3
Total	21	13	34

The progression to chronic renal insufficiency was independent of the type of primary surgical treatment, even if we exclude the small number of patients who underwent upper urinary tract diversion ($p=0,458$).

Initial serum creatinine

The mean serum creatinine at admission for group A was $118,9\mu\text{mol/L}$ (median 91; range 35-327) and $210,1\mu\text{mol/L}$ (median 205; range 62-398) for group B (Figure 4).

Figure 4: Boxplot by group for initial serum creatinine



When serum creatinine was $\leq 88,5\mu\text{mol/L}$ before surgery, chronic renal insufficiency developed in 2 of 12 boys (16,7%), while it developed in 11 of 22 (50%) who presented with a serum creatinine $>88,5\mu\text{mol/L}$ (Table 5).

Table 5: Initial serum creatinine

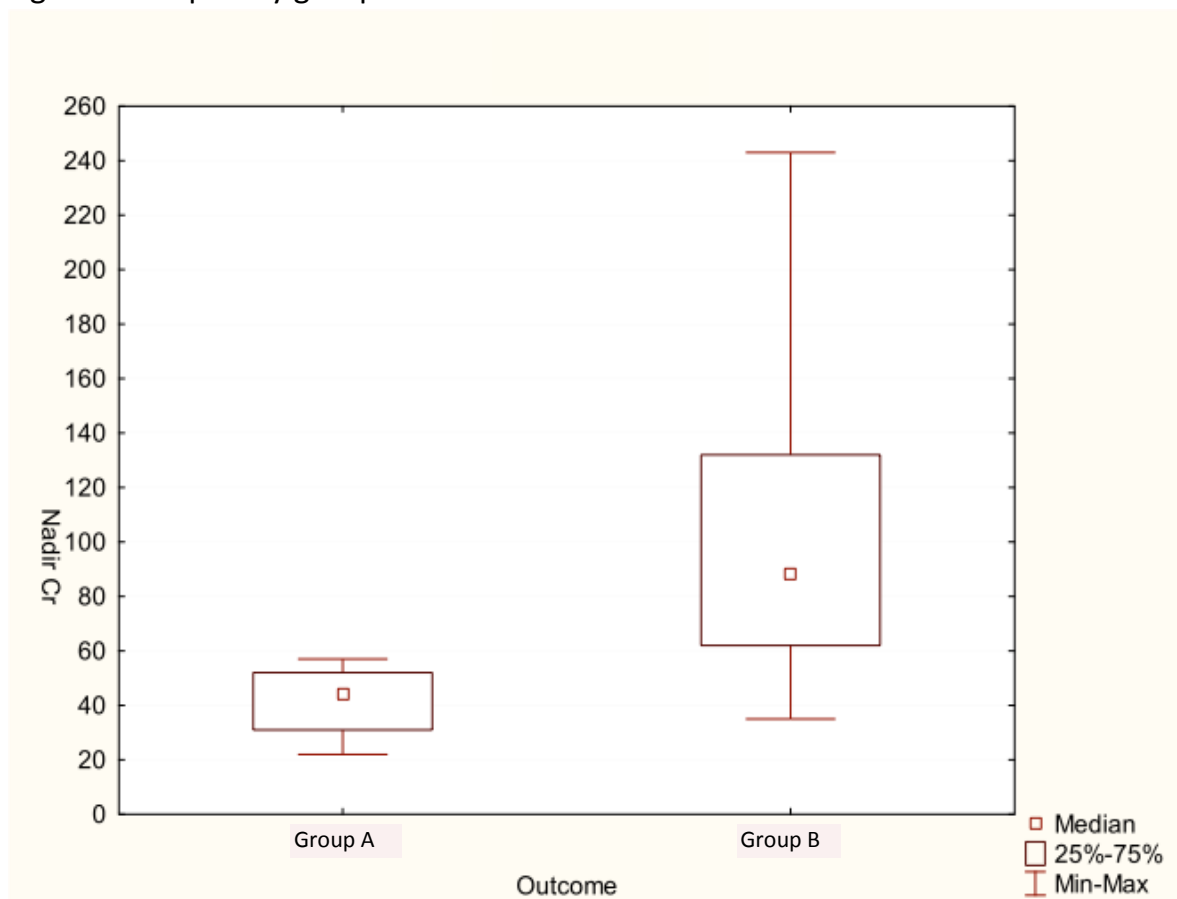
	Group A	Group B	Total
Initial creatinine $\leq 88,5\mu\text{mol/L}$	10	2	12
Initial creatinine $> 88,5\mu\text{mol/L}$	11	11	22
Total	21	13	34

Our results were not statistically significant when we used a serum creatinine cut-off point of $88,5\mu\text{mol/L}$ to predict final renal function ($p=0,075$). However, the results of a Mann-Whitney U test showed that initial serum creatinine was related to future renal outcome in our population ($p=0,013$). A ROC analysis determined that in our study the optimal cut-off point for initial serum creatinine was $145\mu\text{mol/L}$ to preclude chronic renal failure ($\text{AUC}=0,8$).

Nadir serum creatinine

The mean nadir serum creatinine for group A was $40,4\mu\text{mol/L}$ (median 44; range 22-57) and $100,6\mu\text{mol/L}$ (median 88; range 35-243) for group B (Figure 5).

Figure 5: Boxplot by group for nadir serum creatinine



When nadir serum creatinine was $\leq 88,5\mu\text{mol/L}$, chronic renal insufficiency developed in 7 of 28 boys (25%), while it developed in all boys with a nadir serum creatinine $>88,5\mu\text{mol/L}$ (Table 6).

Table 6: Nadir serum creatinine

	Group A	Group B	Total
Nadir creatinine $\leq 88,5$	21	7	28
Nadir creatinine $> 88,5$	0	6	6
Total	21	13	34

Our results were statistically significant when we used a nadir serum creatinine cut-off point of $88,5\mu\text{mol/L}$ to predict final renal function ($p=0,001$). A ROC analysis further determined that the optimal cut-off point for nadir serum creatinine to preclude chronic renal failure in our population was $62\mu\text{mol/L}$ ($\text{AUC}=0,9$).

Renal parenchymal echogenicity

On preoperative imaging, increased renal parenchymal echogenicity was found in 17 patients (50%). This indicator was present in 8 (38,1%) of the children in group A and in 9 (69,2%) of the children in group B (Table 7).

Table 7: Renal parenchymal echogenicity

	Group A	Group B	Total
Increased echogenicity	8	9	17
Normal echogenicity	13	4	17
Total	21	13	34

The difference between the two groups was statistically insignificant ($p=0,157$).

Renal corticomedullary differentiation

Twenty-two boys (64,7%) were identified as having poor CMD based on initial renal ultrasound findings, 10 (47,6%) from group A and 12 (92,3%) from group B (Table 8).

Table 8: Renal corticomedullary differentiation

	Group A	Group B	Total
Poor CMD	10	12	22
Good CMD	11	1	12
Total	21	13	34

Poor CMD on preoperative kidney sonar was significantly associated with progression to chronic renal failure ($p=0,011$).

Hydronephrosis

At the first visit, dilation of the renal collecting system was seen in 33 patients (97,1%); unilateral in 2 and bilateral in 31. Hydronephrosis severity was graded as mild in 7 boys (21,2%) and moderate-severe in 26 boys (78,8%). The incidence of grade 3 and 4 hydronephrosis was higher in group B (12 patients; 100%) than in group A (14 patients; 66,7%). Table 9 lists hydronephrosis severity as per group A and B.

Table 9: Hydronephrosis severity

	Group A	Group B	Total
Mild	7	0	7
Moderate-severe	14	12	26
Total	21	12	33

Moderate-severe hydronephrosis on preoperative ultrasound was a significant predictor of poor renal outcome ($p=0,032$).

Bladder configuration

A thickened bladder wall on initial bladder sonar was diagnosed in 31 patients (91,2%). Only 3 boys (all from group A) showed a normal bladder configuration (Table 10).

Table 10: Bladder configuration

	Group A	Group B	Total
Thick walled	18	13	31
Normal	3	0	3
Total	21	13	34

A pathological bladder configuration on preoperative bladder ultrasound had no significant impact on future renal function ($p=0,270$).

Initial micturating cystourethrogram

Initial MCUG revealed that 13 patients (38,2%) had VUR of whom 9 had unilateral and 4 had bilateral reflux. VUR severity was graded as non-dilating in 1 boy (7,7%) and dilating in 12 boys (92,3%). Nine patients (42,9%) from group A and 4 patients (30,8%) from group B were diagnosed with reflux (Table 11).

Table 11: Vesicoureteric reflux

	Group A	Group B	Total
Present	9	4	13
Absent	12	9	21
Total	21	13	34

We did not identify any significant difference in the rates of chronic renal failure in the group with VUR vs no VUR ($p=0,718$), unilateral vs bilateral VUR ($p=0,496$) or non-dilating vs dilating VUR ($p=0,628$).

Bladder dysfunction

Of the 19 boys who were older than 60 months of age at the last follow-up, 13 (68,4%) had severe bladder dysfunction according to our case definition. All 13 patients had daytime urinary incontinence, 8 of them received oxybutynin and 2 performed self-intermittent catheterisation. Vesical dysfunction was objectively confirmed by urodynamic studies in 3 boys.

Table 12: Severe bladder dysfunction in boys >60 months

	Group A	Group B	Total
Present	7	6	13
Absent	6	0	6
Total	13	6	19

Renal failure developed in none of the continent boys and in 6 of the 13 (46,2%) with vesical dysfunction (Table 12). Severe bladder dysfunction was not a significant predictor of final renal function ($p=0,109$).

Urinary tract infection

Fourteen boys presented preoperatively with an UTI: 10 (47,6%) from group A and 4 (30,8%) from group B (Table 13).

Table 13: Mode of presentation

	Group A	Group B	Total
UTI on presentation	10	4	14
Other mode of presentation	11	9	20
Total	21	13	34

There was no significant difference in long-term renal morbidity between patients presenting with an UTI and boys who had another mode of presentation, including those who were diagnosed antenatally ($p=0,332$).

The mean number of UTI's after initial surgery was 2,9 (median 2; range 0-14). A total of 8 patients had more than 3 breakthrough UTI's: 6 (28,6%) from group A and 2 (15,4%) from group B (Table 14).

Table 14: Number of recurrent UTI's after initial surgery

	Group A	Group B	Total
0 – 3	15	11	26
> 3	6	2	8
Total	21	13	34

We did not find a significant relation between breakthrough UTI's (0-3 vs >3) and long-term renal insufficiency ($p=0,444$).

DISCUSSION

The short-term outcome for boys with PUV has markedly improved in recent years but the long-term outcome in terms of renal function remains a matter of great concern. Despite advances in the medical and surgical management of PUV, 13-64% of boys still have chronic renal insufficiency at long-term follow-up^{8,11}. The incidence of chronic renal failure and ESRD in our series is 38,2% and did not differ from those in other studies.

Various factors have been studied to predict long-term renal function in patients with PUV. These factors are: age at presentation, type of primary surgical management, initial and nadir serum creatinine, abnormal renal parenchyma and bladder wall thickness on initial ultrasound, the presence of gross hydronephrosis and VUR, bladder dysfunction and initial or recurrent UTI's^{2,3,8-15,17-24}.

Age at presentation has been propagated as a prognostic factor. Some authors have reported that the younger the age at presentation the poorer the outcome will be^{10,11}. Contrary to this, others believe that late presentation is associated with a higher risk of developing chronic renal insufficiency¹². Moreover, Engel et al noted no difference in final renal function whether boys presented antenatally or postnatally². In our series, children with a poor renal outcome presented later (mean age 19,7 months) than children with a favourable prognosis (mean age 10,2 months). Although the incidence of chronic renal failure in patients who presented postnatally was higher than in those who were diagnosed antenatally (44,4% vs 14,3%), the difference was not statistically significant. We also could not demonstrate any significant difference in renal outcome between boys who presented at less than 1 month as compared to those presenting at 1-12 months or older than 12 months. Our findings were similar to those previously reported^{2,9,18}.

The progression of renal failure is independent of the type of primary surgical management, whether it is valve ablation, vesicostomy or upper urinary tract diversion¹⁴⁻¹⁶. In our study, the number of boys who received primary ablation was similar to those who had a vesicostomy with delayed valve ablation (47,1% vs 44,1%). When the 3 patients who had upper urinary tract diversions were excluded, valve ablation was not found to be significantly superior to vesicostomy in preserving renal function. The high primary vesicostomy rate at our institution could possibly be explained by a shortage of appropriate surgical equipment.

Sarhan et al noted a clear relationship between initial serum creatinine and future renal function, with an initial serum creatinine of more than 1mg/dL (88,5µmol/L) significantly correlating with poor renal outcome^{17,18}. In this series, the mean serum creatinine at presentation was significantly higher in boys with poor renal outcome than in those without renal impairment (210,1µmol/L vs 118,9µmol/L; p=0,013).

Although the incidence of chronic renal failure was higher when the preoperative serum creatinine was $>88,5\mu\text{mol/L}$ (50% vs 16,7%), the difference between the 2 groups was not statistically significant. We determined by means of a ROC analysis that our optimal initial serum creatinine threshold was $145\mu\text{mol/L}$ to predict final renal function. The difference between our creatinine threshold and the reported value of 1mg/dL ($88,5\mu\text{mol/L}$) may be attributed to our small sample size and short follow-up period.

Nadir serum creatinine has emerged as a reliable predictor of future renal function^{17,18}. Two recent reports concluded that a nadir serum creatinine of $\leq 1\text{mg/dL}$ ($88,5\mu\text{mol/L}$) had a more beneficial course in terms of final renal function^{9,18}. In our population, the mean nadir serum creatinine was significantly lower in patients without chronic renal insufficiency than in those with kidney failure at last follow-up ($40,4\mu\text{mol/L}$ vs $100,6\mu\text{mol/L}$; $p=0,000$). Moreover, a nadir serum creatinine $>88,5\mu\text{mol/L}$ was strongly associated with a higher incidence of future renal impairment ($p=0,001$). Our results coincide with those reported by Sarhan et al and Ansari et al. The ideal cut-off point for nadir serum creatinine to avoid future renal failure in our population ($62\mu\text{mol/L}$) was determined by means of a ROC analysis. Although nearer to the reported threshold of 1mg/dL ($88,5\mu\text{mol/L}$), this difference may once again be due to our sample size and follow-up period.

Recent data suggest that the initial renal ultrasound may be useful to identify those patients at highest risk for renal function deterioration. Abnormal renal parenchyma, in terms of increased echogenicity and loss of CMD, correlates well with a declining eGFR later in life²⁰. In this study, increased renal parenchymal echogenicity was detected in 17 patients (50%), including 9 (52,9%) in whom kidney failure developed. The difference between the 2 groups was statistically insignificant and might be explained by the dependence of this study on ultrasound reports done by different operators. The incidence of chronic renal insufficiency in boys with poor CMD was significantly higher than in those with good CMD (54,5% vs 8,3%; $p=0,011$), confirming the results of previously published data.

Authors suggest that bilateral hydronephrosis and increased hydronephrosis severity are associated with progression to CKD². In our series, the majority of patients presented with bilateral, moderate-severe hydronephrosis ($n=25/33$). The incidence of grade 3 and 4 hydronephrosis was higher in boys with chronic renal failure compared to those without (100% vs 66,7%) and was a significant predictor of poor renal outcome ($p=0,032$). This data correlates well with findings reported by Engel et al.

Pohl et al looked at pathological bladder configuration as a prognostic indicator for CKD²⁰. Similar to their study, 91,2% of our boys showed a thickened bladder wall on the initial sonar, but results were not statistically predictive of poor renal outcome.

VUR is found in approximately 50% of patients diagnosed with PUV^{16,20,21}. Some groups consider that high grade, bilateral reflux significantly correlates with renal prognosis^{2,3,9,11}. Others have found no relationship between unilateral or bilateral VUR and renal function^{10,18,20,21}. In our study, 38,2% of children had VUR on initial MCUG. The majority of boys had unilateral, dilating reflux (n=8/13). We failed to identify any significant difference in the rates of chronic renal failure in those with VUR vs no VUR (30,8% vs 42,9%), unilateral vs bilateral VUR (22,2% vs 50%) or in those with dilating vs non-dilating VUR (33,3% vs 0%), affirming the outcome of most published articles.

Severe bladder dysfunction has been associated with CKD and ESRD^{9,11,23}. Nearly 75% of children with PUV have voiding dysfunction in spite of adequate surgical management²². Parkhouse et al showed that 46% of patients (over 60 months of age) with daytime incontinence developed renal failure, compared to 4% of those who were continent¹¹. In our series the incidence of severe bladder dysfunction was 68,4%. Six boys (46,2%) who had daytime incontinence developed renal failure, while none (0%) of the continent boys did. However, the presence or absence of severe bladder dysfunction did not predict final renal function. Our high rate of vesical dysfunction and the difference in statistical significance can be attributed to the following: our small sample of boys over the age of 60 months and our limited access to formal urodynamic studies.

The presence of an UTI at diagnosis was thought to be one of the prognostic factors in boys with PUV²⁴. Fourteen (41,2%) of the 34 patients presented with an UTI. However, the risk to develop renal failure at the end of follow-up was the same in those who presented with an UTI when compared to those who had another mode of presentation. These findings are in agreement with Akdogan et al who suggest that ultimate renal function is more dependent on other factors than the presence of an UTI at diagnosis²⁴.

Recurrent UTI's after initial surgery can lead to irreversible renal damage⁴. Pohl et al showed that suffering from more than 3 UTI's after bladder decompression is significantly associated with poor renal outcome²⁰. Most publications, however, did not find a significant relation between breakthrough UTI's and long-term renal function^{8,9}. Our study concurs with the latter that recurrent UTI's is not a significant contributing factor for CKD progression.

This study has some limitations. In common with other rare disease, establishing a large enough database of cases with PUV is difficult which limits the statistical analysis. This was further complicated by the large number of patients lost to follow-up, limiting our sample size even further. In addition, the retrospective nature of data collection has led to possible selection bias. The mean patient age at presentation was high with only a small number of cases diagnosed antenatally. This

delay in diagnosis could be attributed to the poor access to health and the limitations of the present health care system. The prevalence of CKD is dependent on the length of the follow-up period as renal function may only deteriorate during the pubertal growth spurt. Our follow-up period was relatively short with most boys being of pre-pubertal age when final renal function was calculated. Image-based selection bias possibly influenced the outcome of radiological variables as real-time images could not be viewed where formal reports were not available.

CONCLUSION

Obstruction due to PUV remains a significant cause of renal morbidity and mortality in males^{4,9}. By identifying prognostic factors that are associated with chronic renal impairment in our setting will help us plan treatment protocols, guide parent counselling and distribute limited resources.

The majority of patients presented postnatally with an UTI. More than a third of boys (38,2%) developed chronic renal failure or ESRD at the end of follow-up. Our data confirmed the high prognostic value of initial and nadir serum creatinine. Optimal threshold levels for initial and nadir serum creatinine to predict final renal outcome were 145µmol/L and 62µmol/L, respectively. Also, poor CMD and moderate-severe hydronephrosis on initial kidney ultrasound were significant indicators of poor renal prognosis.

By extending our study period we can improve the validity of our results by increasing sample size and follow-up period.

An increasing number of patients with PUV are diagnosed prenatally and/or treated primarily with valve ablation at our institution. Further research is necessary to see how this will impact long-term renal function.

Although all patients with PUV should be counselled on potential renal morbidity, children with risk factors warrant closer monitoring.

CONFLICT OF INTEREST

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