Posterior urethral valves: risk factors of progression to end-stage chronic renal disease after 10 years of follow-up

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Abstract

Objective. To determine risk factors (RF) of progression to end-stage chronic renal disease (ESCRD) and the need for renal replacement therapy (RRT) in patients with posterior urethral valve (PUV).

Materials and methods. A retrospective case and control study of patients diagnosed with PUV in the 1995-2023 period was carried out. Two study groups were created – RRT vs. no-RRT. Clinical, laboratory, and radiological variables were collected. A bivariate analysis and a binary logistic regression were conducted to detect RFs of the need for RRT.

Results. 127 patients were included, 12.% of whom had undergone RRT (n=20). Mean follow-up was 9.87 years. Mean age at clinical onset was younger in the RRT group (3 months vs. 1.23 years; p=0.010). Pathological prenatal ultrasonography (p<0.001), increased Nadir creatinine levels (p<0.001) and maximum creatinine levels in the first year of life (p<0.001), and onset with acute renal insufficiency (p=0.03) were more frequent in the RRT group. Increased creatinine levels in the first week of life (OR: 4.74) and younger age at clinical onset (OR: 1.2) were the only independent RFs to predict the need for RRT. Diagnostic-therapeutic delay and the presence of UTIs during follow-up are not predictive of the risk of final RRT.

Conclusions. In PUV children, renal functional reserve at birth is the only ESCRD risk predictor. Early clinical onset implies a higher risk of RRT.

Key Words: Urethral obstruction; Renal insufficiency, chronic; Urologic diseases; Case-control studies.

Valvas de uretra posterior: factores de riesgo de progresión hasta la enfermedad renal crónica terminal tras 10 años de seguimiento

Resumen

Introducción. Determinar factores de riesgo (FR) de progresión a enfermedad renal crónica terminal (ERCT) y necesidad de terapia renal sustitutiva (TRS) en pacientes afectos de valvas de uretra posterior (VUP).

Material y métodos. Estudio de casos y controles retrospectivo, de pacientes diagnosticados de VUP en el período (1995-2023). Creamos dos grupos a estudio: si-TRS *versus* no-TRS. Recogimos variables clínicas, analíticas y radiológicas. Realizamos un análisis bivariante y una regresión logística binaria con la finalidad de detectar FR de necesidad de TRS.

Resultados. Incluimos 127 pacientes, con 12,% de TRS (n=20). El seguimiento medio fue de 9,87 años. La media de edad en el debut clínico fue inferior en el grupo si-TRS (3meses versus 1,23 años; p=0,010). La ecografía prenatal patológica (p<0,001), la Cr Nadir (p<0,001) y Cr máxima 1º año de vida (p<0,001) elevadas y el debut con insuficiencia renal aguda (p=0,03), fueron más frecuentes en si-TRS. El aumento de Cr la primera semana de vida (OR=4,74) y la menor edad en el debut clínico de los pacientes (OR=1,2) fueron los únicos FR independientes para predecir necesidad de TRS. El retraso diagnóstico-terapéutico y la presencia de ITUs durante el seguimiento no predicen riesgo de TRS final.

Conclusiones. En niños con VUP, la reserva renal funcional al nacimiento es el único predictor de riesgo de ERCT. El debut clínico precoz condiciona mayor riesgo de TRS.

Palabras Clave: Estenosis uretral posterior; Enfermedad renal en etapa terminal; Enfermedades urológicas; Estudio caso-control.

INTRODUCTION

Posterior urethral valves (PUVs) are the most frequent cause of lower urinary tract obstruction in pediatric male patients[1,2]. This abnormality emerges in an early stage of gestation, causing an increase in urinary tract pressure, hypertrophy, and bladder wall deformation. If the obstruction reaches the upper urinary tract, it can exert pressure

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on the renal pelvis, thus reducing parenchymal thickness during nephrogenesis, which induces various degrees of renal dysplasia[3]. According to the recent literature, 20%-65% of PUV infants can develop chronic renal disease (CRD), and approximately 8%-21% progress to end-stage chronic renal disease (ESCRD)[4,5].

Endoscopic PUV resection is the baseline treatment in most patients. More rarely, early temporary urinary diversion is required. However, in spite of the advances made in terms of surgical techniques and early diagnosis, the progression of renal prognosis has been limited over time[6,7].

Various prognostic factors have been analyzed both pre- and postnatally to identify the PUV children with a higher risk of progression to ESCRD and the need for dialysis or renal transplantation. The predictive factors reported in the literature include NADIR creatinine levels in the first year of life, ultrasound renal volume, and certain urinary markers[8-13].

Even though PUVs are a well-known disease with a significant impact on mid- and long-term renal prognosis, there are few solid literature references regarding the predictive factors of CRD development. Therefore, our objective was to assess potential risk factors of progression to ESCRD and the need for renal replacement therapy (RRT) in PUV patients.

MATERIALS AND METHODS

An observational, analytical, retrospective case and control study was carried out. All patients diagnosed with PUV and subject to active follow-up in our institution from 1995 to 2023 were included. All medical records were retrospectively reviewed. Demographic (date of birth, personal and family history, among others), clinical (perinatal data, symptoms, surgical variables, complications, radiological and laboratory data, among others), and long-term follow-up (date of CRD onset, need for RRT, type of RRT, among others) variables were collected.

Patients were divided into two comparative groups, according to the need for RRT anytime during follow-up (case group: RRT) vs. no need for RRT (control group: no-RRT).

The study was approved by the relevant regional ethics committee. Given its anonymous and retrospective nature (including patients from many years back), informed consent was not gathered from participants or their relatives. Patients with incomplete medical records or with follow-up loss were excluded. Patients with comorbidities (digestive, cardiac) or other associated congenital urological abnormalities were included in the analysis.

Age at diagnosis and age at clinical presentation were differentiated. The **age at diagnosis** variable was defined as the time at which PUV-confirming urethrocystography or cystoscopy had been conducted. In case urinary diversion (either surgical or through a bladder probe) had been performed before cystoscopy, the date at which diversion had been carried out was used as the date of diagnosis. The **age at clinical presentation** variable was defined as the time at which urinary symptoms had started, or a laboratory or radiological finding suggestive of PUV had emerged. In case of abnormal prenatal ultrasonography, the clinical presentation date was defined as the date of birth.

The **diagnostic delay** (qualitative: yes/no) variable was considered to be present when time from age at clinical presentation to age at diagnosis was ≥ 4 months. Given the lack of literature references, the 4-month diagnostic delay cut-off point was statistically calculated as p75 of the diagnostic delay in our series.

The **follow-up time** variable was defined as the time from the date of diagnosis to that of the last check-up.

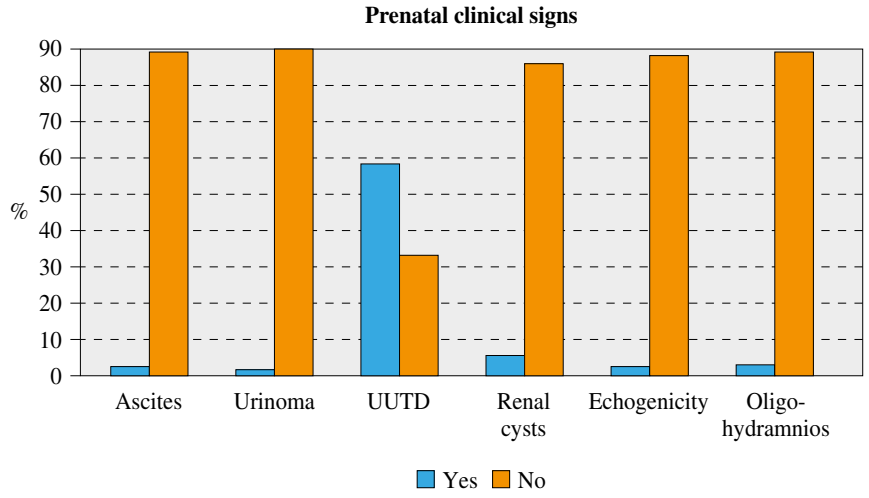
Prenatal ultrasonography was considered to be abnormal in the presence of unilateral or bilateral urinary tract dilatation (according to the UTD classification system criteria[14]), or in the presence of Keyhole bladder, urinoma, oligohydramnios, urinary ascites, renal cysts, and/or renal dysplasia. The presence of postnatal radiological findings such as upper urinary tract dilatation[14], unilateral or bilateral vesicoureteral reflux (VUR) according to the International Grading System for VUR[15], megaureter (> 7 mm), trabeculated bladder, persistent urachus, and giant bladder diverticulum (> 1/3 of bladder volume) was considered to be suggestive of PUV.

UTI was defined as the presence of fever associated with a probe-collected urinary culture (UC) of more than 100,000 CFU. Acute renal insufficiency was defined according to the European Renal Best Practice modified KDIGO (Kidney Disease: Improving Global Outcomes) criteria[16]. Lower urinary tract symptoms (LUTS) were defined as the presence of urinary incontinence around 5 years of age, weak urine stream, acute urine retention, urinary frequency, urinary urgency, abdominal straining during voiding, and/or repeated epididymitis.

Regarding the laboratory parameters of renal function, the highest creatinine levels recorded in the first week of life, in the first year of life, and throughout follow-up were collected. Creatinine levels recorded in the first 48 hours postnatally –which may be distorted by maternal creatinine– and creatinine levels in the presence of acute renal insufficiency were excluded. NADIR creatinine and urea levels, defined as the lowest in the first year of life, were also gathered.

Blood pressure was considered to be high when above p95[17], and albuminuria was considered to be present according to the reference laboratory thresholds (0-30 mg/dL). Renal replacement therapy onset date was defined as the time of hemodialysis/peritoneal dialysis initiation, or the date of early renal transplantation.

Calculations were performed using the IBM SSPS® statistical software (version 28). In the statistical analysis,



UUTD: upper urinary tract dilatation.

Figure 1. Prevalence of prenatal ultrasonography abnormalities in PUV patients.

the lacking data was omitted. A descriptive analysis of the variables collected in the study was first conducted. Quantitative variables were expressed as median and range, whereas qualitative variables were reported as absolute value and percentage. A bivariate analysis of all variables collected was subsequently carried out between the RRT and no-RRT groups. The mean values of quantitative variables were compared by means of Student's t-test or Mann-Whitney U test according to normality following the Kolmogorov-Smirnov test. When more than two categories were compared, the ANOVA test or the Kruskal-Wallis test were employed. The association of qualitative variables was estimated using the Chi-squared test or Fisher's exact test. The bivariate analysis helped identify those variables that could potentially be related to a higher risk of need for RRT. Finally, a multivariate analysis –with the significant variables achieved in the bivariate analysis, as well as those regarded as clinically relevant by the authors– was carried out, while looking for independent risk factors of the need for RRT during follow-up.

RESULTS

The study sample consisted of 127 PUV patients, 15% of whom (20 patients) required RRT (67% dialysis and 33% early renal transplantation). Mean follow-up was 9.87 years.

At diagnosis, 35 patients were infants (mean age: 3 months; range: 0-1.9 years) and the remaining 89 were >2 years old (mean age: 7.3 years; range: 2-13.7 years).

Clinical presentation was prenatal in 66.1% of the cases (84 patients), and postnatal in the remaining 44.7% (39 patients). Of the patients with postnatal clinical presentation, the latter was early (before 2 years of age) in 19, and late (after 2 years of age) in 20.

Mean age at sign or symptom presentation was 1.13 years (range: 0-11 years), and mean age at diagnosis was 2.2 years (range: 0-13.7 years). In 44 patients (34.6%), there was at least a 4-month diagnostic delay from sign or symptom onset to confirmation.

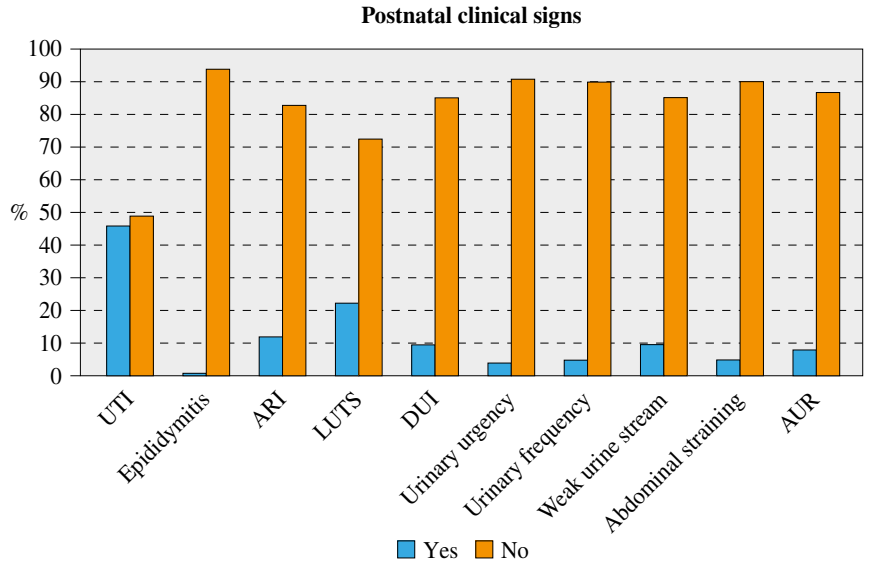
The distribution of prenatally detected ultrasound data is featured in Figure 1. The predominant sign was upper urinary tract dilatation (58.3% of the series).

62.2% of the patients (79) had postnatal symptoms secondary and previous to urological disease (Fig. 2). 47.2% of the children had VUR at baseline cystography, and 34.6% had trabeculated bladder.

The most frequent baseline surgery was endoscopic resection (116 patients, 91.3%) vs. surgical urinary diversion (9 patients, 7.1%). After baseline endoscopic surgery, 11 extra patients underwent diversion (11/116). In total, 20 patients underwent diversion anytime during follow-up (15.7% of the series).

The patients who required RRT during follow-up had a higher prevalence of severe clinical signs at prenatal ultrasonography, except for the presence of prenatal UTD, which was not associated with a higher risk of RRT ($p=0.295$). Early abnormal prenatal ultrasonography (in the second pregnancy trimester) was associated with a higher risk of RRT ($p\leq 0.005$) (Table 1).

In addition, the younger age at clinical presentation was, the higher risk of need for RRT was observed in the follow-up period (mean age at clinical presentation in the no-RRT group = 1.23 years vs. 0.31 years in the RRT group) ($p=0.010$). Neither age at diagnosis nor diagnostic delay were associated with a higher risk of need for RRT during follow-up (Table 1).



UTI: urinary tract infection; ARI: acute renal insufficiency; LUTS: lower urinary tract symptoms, including daytime urinary incontinence, urinary urgency, urinary frequency, weak urine stream, abdominal straining when urinating, and acute urine retention; DUI: daytime urinary incontinence; AUR: acute urine retention.

Figure 2. Prevalence of postnatal symptoms in PUV patients.

Table 1. Bivariate analysis of potential risk factors of need for RRT in PUV patients.

		no-RRT	*RRT*	*Total*	*p*
Age at diagnosis (years)		2.34 (3.72)	1.84 (3.65)	2.29 (3.68)	0.627
Age at presentation (years)		1.23 (2.76)	0.31 (0.87)	1.13 (2.59)	**0.010**
Diagnosis	Prenatal	84.9% (45)	15.1% (8)	53 (100%)	0.719
	Early	86.5% (32)	13.5% (5)	37 (100%)	
	Late	90.9% (30)	9.1% (3)	33 (100%)	
Presentation	Prenatal	84.5% (71)	15.5% (13)	84 (100%)	0.475
	Early	88.9% (16)	11.1% (2)	18 (100%)	
	Late	94.7% (18)	5.3% (1)	19 (100%)	
Infant at diagnosis	No	86.4% (76)	13.6% (12)	88 (100%)	0.468
	Yes	91.2% (31)	8.8% (3)	34 (100%)	
Infant at presentation	No	90.9% (20)	9.1% (2)	22 (100%)	0.517
	Yes	85.7% (84)	14.3% (14)	98 (100%)	
Diagnostic delay (4 months)	No	85.5% (65)	14.5% (11)	76 (100%)	0.414
	Yes	90.7% (39)	9.3% (4)	43 (100%)	
Prenatal ascites	No	91% (101)	9% (10)	111 (100%)	
	Yes	100% (3)	0 (0%)	3 (100%)	
Prenatal keyhole bladder	No	93.1% (94)	6.9% (7)	101 (100%)	0.05
	Yes	76.9% (10)	23.1% (3)	13 (100%)	
Prenatal urinoma	No	92.5% (99)	7.5% (8)	107 (100%)	0.013
	Yes	60% (3)	40% (2)	5 (100%)	
Prenatal UUTD	No	95% (38)	5% (2)	40 (100%)	0.295
	Yes	89.2% (66)	10.8% (8)	74 (100%)	
Prenatal cysts	No	93.5% (100)	6.5% (7)	107 (100%)	**0.001**
	Yes	57.1% (4)	42.9% (3)	7 (100%)	

(Continues)

Table 1. *(Continued)* **Bivariate analysis of potential risk factors of need for RRT in PUV patients.**

		TRS no	*TRS Yes*	*Total*	*p*
Prenatal dysplasia	No	92.7% (102)	7.3% (8)	110 (100%)	**<0.001**
	Yes	33.3% (1)	66.7% (2)	3 (100%)	
Oligohydramnios	No	93.3% (92)	6.1% (6)	98 (100%)	**0.009**
	Yes	73.3% (11)	26.7% (4)	15 (100%)	
Prenatal treatment	No	91.9% (102)	8.1% (9)	111 (100%)	**0.005**
	Yes	50% (2)	50% (2)	4 (100%)	
Diagnosis trimester	No diagnosis	94.7% (36)	5.3% (2)	38 (100%)	**0.005**
	2nd	73.9% (17)	26.1% (6)	23 (100%)	
	3rd	100% (23)	0% (0)	23 (100%)	
Postnatal symptoms	No	95.1% (39)	4.9% (2)	41 (100%)	0.120
	Yes	85.7% (66)	14.3% (11)	77 (100%)	
Postnatal UTIs	No	93.4% (57)	6.6% (4)	61 (100%)	0.109
	Yes	84.2% (48)	15.8% (9)	57 (100%)	
ARI	No	92.2% (95)	7.8% (8)	103 (100%)	**0.003**
	Yes	66.7% (10)	33.3% (5)	15 (100%)	
LUTS	No	87.9% (80)	12.1% (11)	91 (100%)	0.495
	Yes	92.6% (25)	7.4% (2)	27 (100%)	
VUR	No	97.6% (40)	2.4% (1)	41 (100%)	0.05
	Yes	86.7% (52)	13.3% (8)	60 (100%)	
IV-V unilateral VUR	No	89.8% (79)	10.2% (9)	88 (100%)	0.356
	Yes	95.8% (23)	4.2% (1)	24 (100%)	
Pop-off	No	91.9% (68)	8.1% (6)	74 (100%)	0.671
	Yes	89.5% (34)	10.5% (4)	38 (100%)	
Nadir Cr (mg/dl)		0.34 (0.20)	1.49 (1.01)	0.43 (0.43)	**<0.001**
Nadir Urea (mg/dl)		16.64 (10.33)	27 (14.43)	17.52 (10.90)	0.388
Maximum Cr 1st week (mg/dl)		1.35 (0.92)	3.53 (1.75)	1.58 (1.22)	**<0.001**
Maximum Cr 1st year (mg/dl)		0.947 (0.81)	4.37 (2.04)	1.19 (1.30)	**<0.001**
Maximum urea 1st year (mg/dl)		40.82 (28.21)	112 (68.39)	45.45 (36.13)	**0.032**
Scar at DMSA	No	96.9% (31)	3.1% (1)	32 (100%)	0.329
	Yes	100% (30)	0% (0)	30 (100%)	

RRT: renal replacement therapy; UUTD: upper urinary tract dilatation; ARI = acute renal insufficiency; LUTS: lower urinary tract symptoms; VUR: vesicoureteral reflux; Cr: creatinine.

The presence of UTIs and/or LUTS was not a risk factor of need for RRT during follow-up, contrarily to the patients who had ARI at onset (no RRT: 33.3% vs. RRT: 66.7%, p<0.05) or VUR at baseline SVCU (no RRT: 13.3% vs. RRT: 86.7%, p<0.05). Both increased NADIR creatinine levels and maximum creatinine levels in the first week and the first year of life were associated with the need for RRT during follow-up in a statistically significant manner (Table 1).

In the multivariate analysis, creatinine levels in the first week of life and age at clinical onset were the only independent risk factors of need for RRT in the follow-up period. Every 1-unit increase in creatinine levels during the first week of life was associated with a 4.74-fold rise in the risk of progressing to RRT [OR= 4.75; 95%CI (1.446;15.590); p= 0.01]. Every 1-year decrease in age at clinical onset was associated with a 1.2-fold rise in the risk of need for RRT [OR= 1.26; 95%CI (1.071;15.418), p= 0.004]. The presence of VUR at onset tended to be an independent risk factor of RRT, but without statistical significance [OR= 11.9; 95%CI 0.993;151.23), p= 0.05].

DISCUSSION

The risk factors associated with developing ESCRD in the mid- and long-term have been discussed in many PUV studies. However, numerous controversies persist in this field. Increased NADIR creatinine levels in the first year of

life have been acknowledged as an independent risk factor of developing ESCRD in PUV children[8]. However, other factors such as age at symptom onset, age at diagnosis, recurrent urinary infections, and the presence or absence of pop-off phenomena, among others, remain uncertain and open to discussion.

Access to and quality of prenatal ultrasonography used to be poorer in the past, which meant PUV patients were usually diagnosed within the context of repeated UTIs, voiding dysfunction, or CRD. Consequently, early presentation used to be regarded as an unfavorable prognostic factor suggestive of severe obstruction, whereas late presentation used to be considered indicative of less severe obstruction, with little clinical importance and better long-term progression. Subsequently, various authors argued that prenatal detection and early treatment could improve renal prognosis[18-22]. However, the relationship between early and late diagnosis and its impact on renal functionality in PUV children remains controversial today. Bomalaski et al. found no correlation between patient age and CRD severity[18]. In addition, Yadav et al. could not prove that prenatal diagnosis reduces progression to CRD or the need for RRT in the long-term vs. postnatal presentation patients[19]. On the other hand, Ansari et al. found a higher prevalence of CRD in patients diagnosed at >2 years of age[20].

Ansari et al. suggest that the "diagnostic delay" and "late presentation" terms should be differentiated. According to them, the former may be due to lack of experience in PUV diagnosis or late medical care, when patients may have been experiencing symptoms for a given period of time[20]. In this respect, our study is the first to define these concepts, by differentiating age at the first clinical manifestation suggestive of PUV from age at diagnostic confirmation, and defining diagnostic delay as the time from one event to the other. Our results showed that the earlier clinical onset occurs, the higher the risk of developing ESCRD will be. This means that every 1-year decrease in the occurrence of the first radiological sign or symptom is associated with a 1.2-fold rise in the risk of need for RRT in the mid- and long-term. And contrary to what one might expect, neither age at diagnostic confirmation nor diagnostic-therapeutic delay are associated with a higher risk of unfavorable renal prognosis.

Along these lines, patients with early abnormal prenatal ultrasonography (2nd vs. 3rd trimester) and/or with severe ultrasound signs had a higher risk of renal failure and need for RRT in the follow-up period. Once again, the younger age at onset is, the more likely it is for renal function to be impacted. However, consistent with the literature, fetal therapy was not demonstrated to protect renal function in the long-term.

Some authors posit that some urinary tract pressure relief mechanisms might protect the function of one or both kidneys (pop-off phenomena). It has been hypothesized that the presence of high-grade unilateral VUR protects the function of the non-dysplastic contralateral kidney, and that urinary extravasation or the presence of a giant diverticulum protects the function of both[24,25]. In the recent literature, these pressure relief mechanisms have not been demonstrated to protect renal function in the long-term[25]. Even if this was not the primary objective of this study, our results go along the same lines.

Regarding the analysis of postnatal clinical signs, and contrarily to multiple studies, neither the presence of UTI at onset nor renal scars at DMSA were associated with a higher risk of renal failure throughout follow-up. Huang et al. found that patients with repeated UTIs undergo more rapid renal deterioration[9]. However, in the bibliographic review conducted, no recent literature references analyzing these variables with >10-year follow-up means were found. In our study, only the presence of VUR –which has been widely described in the literature as a risk factor of poor renal prognosis– and a history of ARI at onset were associated with a higher risk of renal failure in the long-term. This could stem from the fact patients with severe valvular disease have a lower renal functional reserve, which could lead to a greater tendency to acute failure in the presence of external aggressions and the lower urinary tract obstruction inherent to the disease.

As for renal function laboratory markers, our results are consistent with the literature. Today, NADIR creatinine levels are the best prognostic factor of long-term renal function in PUV patients[8]. However, in our study, it is worth noting that maximum creatinine levels in the first week of life –excluding the first 48 hours– were a more reliable predictor of long-term renal failure, which is a major development. Similarly to the presence of ARI at onset, it could be associated with reduced functional reserve, which makes patients more fragile to aggression in the neonatal period.

One of the main limitations of our study lies in its retrospective nature. However, since PUV has a low prevalence, this type of design is the most convenient, and for a number of reasons. Indeed, identifying a significant amount of cases can be challenging, and retrospective studies allow time and resources to be saved. They also grant access to historical data, which facilitates the assessment of past cases and disease-related risk factors.

In conclusion, in our study, the only independent risk factors of the need for RRT in PUV children were young age at clinical onset and increased creatinine levels in the first week of life. Therefore, renal functional reserve at birth is seemingly the only predictor of ESCRD in the long-term.

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