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Original Article

ORIGINAL ARTICLE

A clinical predictive model of renal injury in children with isolated antenatal hydronephrosis

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ABSTRACT

Background. Antenatal hydronephrosis (ANH) affects ∼1–5% of pregnancies. The aim of this study was to develop a clinical prediction model of renal injury in a large cohort of infants with isolated ANH.

Methods. This is a longitudinal cohort study of 447 infants with ANH admitted since birth between 1989 and 2015 at a tertiary care center. The primary endpoint was time until the occurrence of a composite event of renal injury, which includes proteinuria, hypertension and chronic kidney disease (CKD). A predictive model was developed using a Cox proportional hazards model and evaluated by *C*-statistics.

Results. Renal pelvic dilatation (RPD) was classified into two groups [Grades 1–2 ($n = 255$) versus Grades 3–4 ($n = 192$)]. The median follow-up time was 6.4 years (interquartile range 2.8–12.5). Thirteen patients (2.9%) developed proteinuria, 6 (1.3%) hypertension and 14 (3.1%) CKD Stage 2. All events occurred in patients with RPD Grades 3–4. After adjustment, three covariables remained as predictors of the composite event: creatinine {hazard ratio [HR] 1.27, [95% confidence interval (CI) 1.05–1.56]}, renal parenchyma thickness at birth [HR 0.78(95% CI 0.625–0.991)] and recurrent urinary tract infections [HR 4.52 (95% CI 1.49–13.6)]. The probability of renal injury at 15 years of age was estimated as 0, 15 and 24% for patients assigned to the low-risk, medium-risk and high-risk groups, respectively ($P < 0.001$).

Conclusion. Our findings indicate an uneventful clinical course for patients with Society for Fetal Urology (SFU) Grades 1–2 ANH. Conversely, for infants with SFU Grades 3–4 ANH, our prediction model enabled the identification of a subgroup of patients with increased risk of renal injury over time.

Keywords: antenatal hydronephrosis, chronic kidney disease, clinical prediction model, hypertension, proteinuria, renal injury, urinary tract infection

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INTRODUCTION

Antenatal hydronephrosis (ANH) is a known surrogate marker of congenital anomalies of the kidney and urinary tract (CAKUT) and affects ~1–5% of pregnancies [1, 2]. In spite of continuous advances in the understanding of its etiopathogenesis and clinical course, there are still many controversies regarding the clinical significance and management of infants with ANH [3–7]. Postnatal management of ANH is a challenge and clinical protocols vary considerably regarding the follow-up evaluation of infants with ANH. There is also a lack of agreement on how best to monitor and how long these children should be followed [8–10]. In addition, before the Society for Fetal Urology (SFU) guidelines, there was no uniformity in the definition and grading of urinary tract dilation both in the prenatal and postnatal periods [11–13]. Information about the clinical course of ANH and the identification of risk factors for renal injury may contribute to early recognition of patients at risk and to the formulation of management strategies.

In a previous retrospective cohort study including 822 patients with prenatally diagnosed CAKUT, we showed that the risk of chronic kidney disease (CKD) was greater in patients with ANH associated with alterations of the urinary tract, including megaureter and oligohydramnios [14]. We have recently developed clinical prediction models of renal injury and CKD in infants with congenital solitary functioning kidney and posterior urethral valves [15, 16]. With the purpose of enhancing the comprehension of the CAKUT spectrum, in this study we focused our analysis on infants with isolated ANH, i.e. without clinically manifest CAKUT, with the aim of evaluating the clinical outcomes and developing a clinical prediction model of renal injury in this selected homogeneous population.

MATERIALS AND METHODS

Patients

The study group comprised 447 infants diagnosed with isolated ANH who were prospectively followed at the Pediatric Nephrourology Unit (Belo Horizonte, Brazil) between 1989 and 2015. Isolated ANH was defined by the absence of other alterations in the urinary tract on perinatal ultrasonography (US), including megaureter, megacystis, cystic kidneys and oligohydramnios. Renal pelvic dilatation (RPD) was assessed by measurement of the anteroposterior renal pelvis diameter (APRPD) *in utero* and the inclusion criterion was an isolated RPD ≥5 mm on antenatal US at the third trimester of gestation [11, 12]. RPD was classified according to the SFU grading system into two groups (Grades 1–2 versus Grades 3–4) [17]. The study group began as 459 patients; 12 patients were excluded due to loss of postnatal follow-up, resulting in a final cohort of 447.

Baseline data (at birth)

The first postnatal renal US was performed at a median time of 14 days of life [interquartile range (IQR) 9–21] by the same trained examiner using a standardized method [18, 19]. After the initial renal US, patients underwent urinary tract imaging workup according to a systematic protocol described elsewhere [20]. A voiding cystourethrogram (VCUG) was performed for a selected subgroup of patients according to criteria previously described [21]. Renal scintigraphy was performed after 3 months of life in patients with RPD >10 mm [7]. Antibiotic prophylaxis was started at the first postnatal day and maintained according to the magnitude of RPD. The median time of antibacterial prophylaxis for SFU Group 1–2 was 18 months (IQR 10–28) and for SFU Group 3–4 was 41 months (IQR 21–52).

Follow-up protocol

After initial evaluation, clinical, laboratory and renal US assessments were carried out periodically at 6-month intervals. Plasma creatinine concentration was determined at baseline and yearly thereafter. Glomerular filtration rate (GFR) was estimated by the conventional Schwartz formula [22] or by the modified Schwartz formula [23], according to the creatinine measurement method. Blood pressure was measured according to the recommendations of updated guidelines [24]. Proteinuria was assessed yearly by measurement of the protein:creatinine ratio or albumin:creatinine ratio in a spot morning urine sample [25]. Postnatal renal US was performed by the same trained examiner using a standard method [18, 19]. The anteroposterior, transverse and longitudinal renal diameters were systematically measured, as was maximum thickness of the renal parenchyma [26]. The longitudinal renal and renal pelvic diameters were measured in the coronal plane and the anteroposterior and transverse diameters and maximum thickness of the renal parenchyma were measured in the axial plane [27]. Kidney volume was calculated in cubic centimeters using the equation of an ellipsoid: volume (cm^3) = 0.523 × length (mm) × width (mm) × depth (mm) [28]. For patients with unilateral dilatation, the affected unit was considered for analysis, whereas for patients with bilateral dilatation, only the unit with higher RPD was included.

Outcomes

A composite endpoint of renal injury events included hypertension, proteinuria and reduced GFR. The primary endpoint for this study was time until the first occurrence of any of the components of the composite event.

Outcomes and covariables definitions

CKD was defined as a GFR <90 mL/min/1.73 m^2 in two consecutive exams with an interval of at least 3 months [29]. This criterion was used for children >2 years at the end of the follow-up. For children <2 years of age, we used appropriate age-specific reference values [30]. Reference values and definitions of normal blood pressure were based on updated guidelines [24]. Proteinuria was defined as a protein:creatinine ratio >0.5 mg/mg for children <2 years of age, >0.2 mg/mg for children >2 years of age or as a urine albumin:creatinine ratio >30 mg/g [25]. Urinary tract infection (UTI) was defined as growth of at least 100 000 cfu/mL in urine obtained by bag or from a midstream sample, with fever (≥38.0°C) and/or urinary symptoms. For analysis, severe bilateral alteration was considered as the presence of severe hydronephrosis or renal hypoplasia on the contralateral unit.

Statistical analysis

The nonparametric values are expressed as the median and IQR and parametric values as the mean and standard deviation as appropriate. Survival analyses were performed by the Kaplan–Meier (KM) method and Cox proportional hazards model to evaluate time until the occurrence of the event. For KM analysis, the optimal cutoff point for continuous variables was determined by the receiver operating characteristics curve using the Youden index [31]. Differences between dichotomous variables were assessed by the two-sided log-rank test [32]. A Cox

Table 1. Baseline characteristics of infants with prenatally detected isolated ANH according to the SFU grading system (*N* = 447)

Variables	SFU 1–2 (*n* = 255)	SFU 3–4 (*n* = 192)	P-value
Gender, *n* (%)			
Male	188 (73.7)	128 (66.7)	0.11
Female	67 (26.3)	64 (33.3)	
Birthweight, *n* (%)			
<2500 g	22 (8.6)	17 (8.9)	0.99
>2500 g	223 (91.4)	175 (91.1)	
Birth length (cm), median (IQR)	48.5 (47.0–50.0)	50.0 (48.0–51.0)	<0.001
Prematurity (<37 weeks), *n* (%)			
Present	13 (5.1)	7 (3.6)	0.49
Absent	242 (94.9)	185 (96.4)	
Laterality, *n* (%)			
Unilateral	133 (52.2)	123 (64.1)	0.012
Bilateral	122 (47.8)	69 (35.9)	
APRPD (mm), median (IQR)	7.9 (6.5–9.6)	28 (22.0–34.2)	<0.001
Renal length (mm), median (IQR)	50.3 (47.7–53.5)	68.2 (59.7–79.9)	<0.001
Renal volume (cm^3), median (IQR)	19.2 (15.8–23.3)	52.3 (34.0–82.3)	<0.001
RPT (mm), median (IQR)	11.3 (10.0–12.4)	8.9 (7.8–9.7)	<0.001
Creatinine (mg/dL), median (IQR)	0.30 (0.26–0.31)	0.40 (0.30–0.56)	<0.001

Table 2. Clinical outcomes in infants with prenatally detected isolated ANH according to the SFU grading system (*N* = 447)

Variables	SFU 1–2 (*n* = 255)	SFU 3–4 (*n* = 192)	P-value
Age (months), median (IQR)	56.4 (16.7–71.8)	100.2 (45.4–155)	<0.001
Creatinine (mg/dL), median (IQR)	0.35 (0.30–0.41)	0.51 (0.40–0.65)	<0.001
Surgical intervention, *n* (%)			
No	255 (100.0)	127 (66)	<0.001
Yes	0 (0.00)	65 (34)	
UTI, *n* (%)			
Present	24 (9.4)	65 (33.8)	<0.001
Absent	231 (90.6)	127 (66.2)	
Proteinuria, *n* (%)			
Present	NR	13 (6.8)	NR
Absent	NR	179 (93.2)	
Hypertension, *n* (%)			
Present	0 (0.00)	6 (3.0)	<0.001
Absent	255 (100.0)	186 (97.0)	
CKD, *n* (%)			
Present	0 (0.00)	14 (7.30)	<0.001
Absent	255 (100.0)	178 (92.7)	
Composite event, *n* (%)			
Present	0 (0.00)	23 (12.0)	<0.001
Absent	255 (100.0)	169 (88.0)	

NR, not recorded.

proportional hazards model was applied to identify variables that were independently associated with the occurrence of the event. Variables selected for multivariable analyses were used to build a final model after discarding any violation of proportionality assumptions or possible interactions [32, 33].

A prognostic model was then constructed from these data by dividing each β coefficient in the final multivariable model with significant risk factors by the lowest β coefficient. The β coefficients were used for factor weighting; points were assigned to each independent prognostic factor, their coefficients being rounded to the nearest integer [34]. Finally, a prognostic score was calculated for each patient by summing up the points. The prognostic score derived was then grouped into three categories (low, medium and high risk). We assessed the accuracy of the derived model by looking at the components of accuracy, discrimination and calibration [34–36]. Discrimination was evaluated on the basis of 2, 5 and 10 years of follow-up using the C-statistic [37]. Calibration was assessed graphically by a KM plot for patients in different risk groups (low, medium and high) [38]. To adjust for overfitting and overoptimistic performance of the model, we performed an internal validation with a bootstrapping technique [37]. In each bootstrap sample, the entire modeling process was repeated, resulting in shrinkage of the regression coefficients when applicable [39]. All reported P-values are two-sided and P-values <0.05 were considered to represent a statistically significant difference for all analyses, including interaction terms.

Ethical aspects

The study was approved by the ethics committee of Federal University of Minas Gerais.

RESULTS

Among 447 infants with ANH included in the analysis, 147 (32.9%) had SFU Grade 1, 108 (24.2%) Grade 2, 72 (16.1%) Grade 3 and 120 (26.8%) Grade 4. Baseline clinical characteristics stratified according to SFU classification (SFU 1–2 versus SFU 3–4) are summarized in Table 1. All patients were enrolled within the first month of life. Twenty-five patients (13.7%) were diagnosed with severe bilateral alteration (>15 mm). Renal US measurements, including RPD, renal length and volume were significantly greater among patients with SFU 3–4 ($P < 0.001$). Conversely, renal parenchyma thickness (RPT) at birth was significantly less for the group with severe dilatation ($P < 0.001$).

Surgical interventions

A total of 127 patients (28.4%) underwent surgical procedures. The most common surgical intervention was pyeloplasty for 107 patients with ureteropelvic junction obstruction. The median age at surgical intervention was 13.4 months (IQR 4.8–55.6).

Clinical course. The median follow-up time was 6.4 years (IQR 2.8–12.5); 243 patients (54.5%) were followed up for >5 years and 89 (20%) for >10 years.

Renal injury

Of 447 patients included in the analysis, 13 (2.9%) exhibited persistent mild proteinuria, 6 (1.3%) had hypertension, 14 (3%) developed CKD Stage 2 and 23 (5%) had the composite outcome. Table 2 summarizes the clinical outcomes according to the SFU classification. The risk of the composite event was estimated by survival analysis as ∼7% at 10 years of age for patients with SFU Grades 3–4. There were no renal injury events among patients with SFU Grades 1–2 ($P = 0.004$). Figure 1 illustrates the

probability of the incidence of the composite event according to the SFU grade.

During follow-up, UTI occurred in 89 (20%) children. Sixty-seven children (15%) had one episode of UTI and 22 (2.2%) had two or more episodes. By KM survival analysis, the cumulative incidence of UTI was estimated as 5% at 6 months and 15% at 24 months of age. Females had a greater risk of UTI than males (log-rank = 5.7, P = 0.016). Patients with SFU Grades 3–4 had a significantly higher risk of UTI as compared with patients with SFU Grades 1–2 (log-rank = 3.1, P < 0.001).

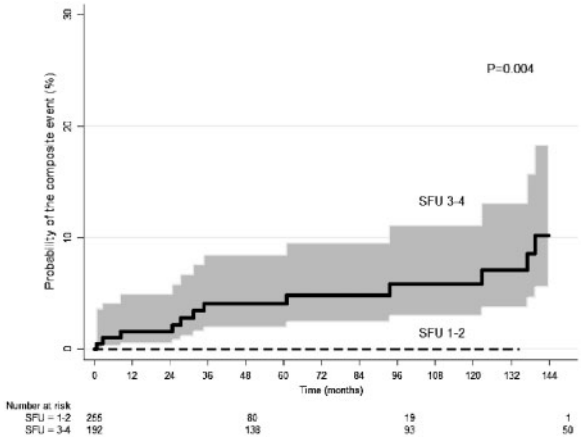

FIGURE 1: KM survival curves reveal the probability of renal injury according to the SFU classification. The shaded areas represent 95% CIs. The number of patients at risk is shown below the x-axis.

Table 3 summarizes the results of the univariate analysis of possible risk factors for renal injury. There was no significant difference in the occurrence of renal injury with regard to gender, low birthweight, period of admission and laterality. In contrast, birth length, prematurity, severe bilateral alteration, occurrence of UTI, initial RPD, recurrent UTI, serum creatinine and RPT at birth were associated with renal injury (Table 3). The optimal cutoff points for baseline creatinine and RPT were 0.45 mg/dL and 8.7 mm, respectively. The area under the curve was 0.86 [95% confidence interval (CI) 0.82–0.89] for baseline creatinine and 0.92 (95% CI 0.88–0.94) for the RPT (Figure 2A and B).

After adjustment by the Cox regression model stratified by the SFU grade, three variables remained as independent predictors of the composite event: baseline serum creatinine, recurrent UTI and RPT at birth (Table 4). The probability of the composite event according to the presence of recurrent UTI, baseline creatinine (cutoff 0.45 mg/dL) and RPT (cutoff 8.7 mm) is illustrated in Figure 3A–C. A prognostic weighting was derived for each variable by dividing each β coefficient by the lowest β. The shrinkage factor obtained from bootstrap results was 0.8919 (Table 4). Finally, a prognostic risk score was calculated as the sum of weightings of these variables. A risk score was calculated for each patient by adding up these points. The risk score ranged from 0 to 12.5 points (median 2 points). The accuracy of the score applied to the sample was consistently high through time, with a mean *C*-statistic of 0.938 (95% CI 0.910–0.960), 0.885

Table 3. HRs and respective 95% CIs for predictors of renal injury among patients with isolated ANH

Predictive factors	Proteinuria	Hypertension	CKD	Composite event
Gender	1.57	2.21	0.48	0.66
(male versus female)	(0.49–4.8)	(0.44–10.9)	(0.10–2.2)	(0.24–1.8)
Low birthweight	0.94	2.61	2.06	0.78
(<2500 g versus >2500 g)	(0.12–7.3)	(0.29–23.6)	(0.24–17.2)	(0.10–5.9)
Prematurity	2.97	7.54	8.74	2.81
(present versus absent)	(0.37–22.9)	(0.83–48.3)	(0.90–84.1)	(0.35–22.2)
Birth length (cm)	1, 07	0.86	0.76*	0.97
(continuous variable)	(0.85–1.35)	(0.64–1.150	(0.64–0.92)	(0.81–1.17)
Period of admission	0.91	0.77	0.67	0.86
(before 2000 versus after 2000)	(0.25–3.8)	(0.13–4.7)	(0.12–3.6)	(0.28–2.6)
Laterality	0.73	3.19	1.71	0.92
(unilateral versus bilateral)	(0.22–2.49)	(0.58–17.5)	(0.51–5.7)	(0.38–2.2)
Severe bilateral lesion	4.38*	6.64*	3.17	1.69
(present versus absent)	(1.3–14.7)	(1.26–34.8)	(0.94–10.4)	(0.58–4.9)
UTI	2.21	4.8	1.29	1.04
(present versus absent)	(0.74–6.7)	(0.87–26.9)	(0.42–4.0)	(0.42–2.6)
Recurrent UTI	10.9**	35.3**	12.6*	7.5**
(present versus absent)	(3.4–34.8)	(5.92–58.4)	(2.8–57.2)	(2.6–21.7)
APRPD (mm)	1.03*	1.02	1.01	1.02
(continuous variable)	(1.01–1.06)	(0.97–1.06)	(0.98–1.05)	(0.99–1.04)
Renal length (mm)	1.02*	1.008	1.009	1.01
(continuous variable)	(1.01–1.04)	(0.96–1.05)	(0.97–1.03)	(0.99–1.03)
Renal volume (cm^3)	1.005	1.00	1.005	1.004
(continuous variable)	(0.99–1.01)	(0.97–1.01)	(0.99–1.01)	(0.99–1.01)
Renal parenchyma	0.63**	0.72	0.79	0.68**
(continuous variable)	(0.48–0.81)	(0.48–1.02)	(0.59–1.05)	(0.55–0.84)
Baseline creatinine	1.47**	1.73*	1.67*	1.47**
(continuous variable)	(1.22–1.81)	(1.26–2.4)	(1.3–2.14)	(1.22–1.78)

*P < 0.05, **P < 0.001.

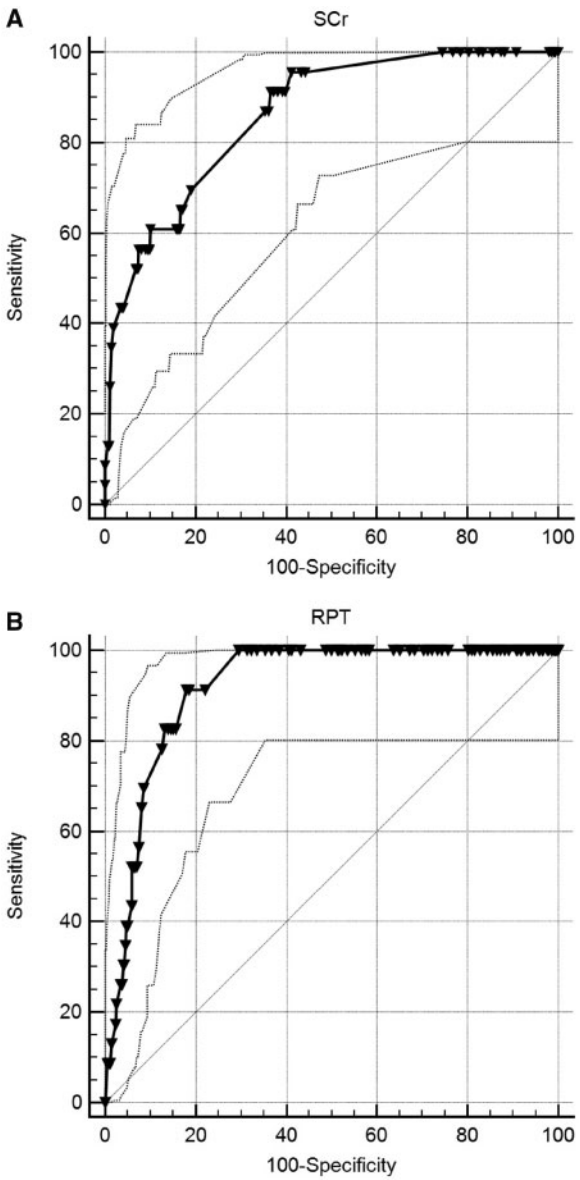

FIGURE 2: Receiver operating characteristics curves estimated for evaluating the capacity of discrimination of continuous variables to predict the composite event. (A) Baseline creatinine. (B) RPT at birth. The dotted lines represent 95% CIs.

(95% CI 0.834–0.925) and 0.867 (95% CI 0.782–0.928) for the follow-up periods of 2, 5 and 10 years, respectively. Finally, the prognostic score was divided into three risk categories for renal injury: low risk [≤2 points, 261 infants (58.4%)], medium risk [3–5 points, 152 infants (34%)] and high risk [>5 points, 34 infants (7.6%)]. The probability of renal injury at 15 years of age was estimated as 0, 15 and 24% for patients assigned to the low-, medium- and high-risk groups, respectively ($P < 0.001$; Figure 4).

DISCUSSION

In this longitudinal cohort study, we evaluated long-term clinical outcomes in infants with isolated ANH from a single tertiary care center. Our findings show that the clinical course is strongly associated with the magnitude of RPD. Patients with SFU Grades 1–2 presented with well-preserved renal function

Table 4. Risk factors associated with renal injury after adjustment by the Cox regression model and respective weighting points used in the risk score

Variables	Coefficient[a]	HR (95% CI)	P-value	Points[b]
Baseline creatinine (mg/dL)	0.216	1.27 (1.05–1.56)	0.014	
0.10–0.37				0
0.38–0.65				1
0.66–0.93				2
≥0.94				3
Parenchyma thickness (mm)	−0.190	0.787 (0.625–0.991)	0.042	
16.5–14.0				0
13.9–11.4				1
11.3–8.80				2
≤8.70				3.5
Recurrent UTI (0/1 versus ≥2)	1.343	4.52 (1.49–13.6)	0.007	6

[a]Shrunk coefficients using the shrinkage estimator obtained from bootstrap results.
[b]Score: low risk (≤2 points), medium risk (3–5 points) and high risk (>5 points).

and rare episodes of UTI during the follow-up. Conversely, the risk of renal injury in patients with severe ANH (SFU Grades 3–4) increased over time. Of particular interest, we developed a clinical predictive model that predicts with good accuracy the occurrence of renal injury among infants with isolated ANH. In this clinical prediction model, baseline creatinine, recurrent UTI and RPT at birth were identified as independent predictors of renal injury during follow-up.

There is a paucity of long-term follow-up studies including a representative sample of infants with isolated ANH. In our analysis, we decided to include a composite event of well-recognized factors associated with impairment of renal function, namely proteinuria, hypertension and early stage CKD [40–46]. First, our findings corroborated that the SFU grading discriminates the clinical outcomes of infants with ANH. In agreement with a recent survey, patients with SFU Grades 1–2 had an uneventful clinical evolution without renal injury [47]. Conversely, patients with SFU Grades 3–4 had a steadily increasing risk of renal injury. In unadjusted analysis, prematurity, birth length, serum creatinine >0.45 mg/dL, occurrence of UTI and severe bilateral dilatation were associated with some of the components of the composite event. After adjustment, recurrent UTI, higher baseline creatinine levels and thinner RPT were each independently associated with renal injury. If these results are confirmed in future studies, the presence of these factors may allow clinicians to readily identify infants with ANH who might require closer follow-up and surveillance.

We believe that our study is the first to show a possible role of recurrent episodes of UTI for an adverse clinical outcome in patients with ANH. In our series, about a third of patients had at least one episode of UTI and 22 (5%) had two or more episodes. The incidence of renal injury was ∼5 times greater among patients with recurrent UTI, even after adjustment for other covariates. Some studies have suggested that prenatal screening has the potential to decrease UTI in infants by early use of antibiotic prophylaxis [48]. However, other studies have shown the failure of prophylaxis to prevent UTI in some infants with ANH [49, 50]. Interestingly, Braga et al. [51] showed that infants with high-grade hydroureteronephrosis had significantly higher febrile UTI rates in a large series of infants with ANH. Of note,

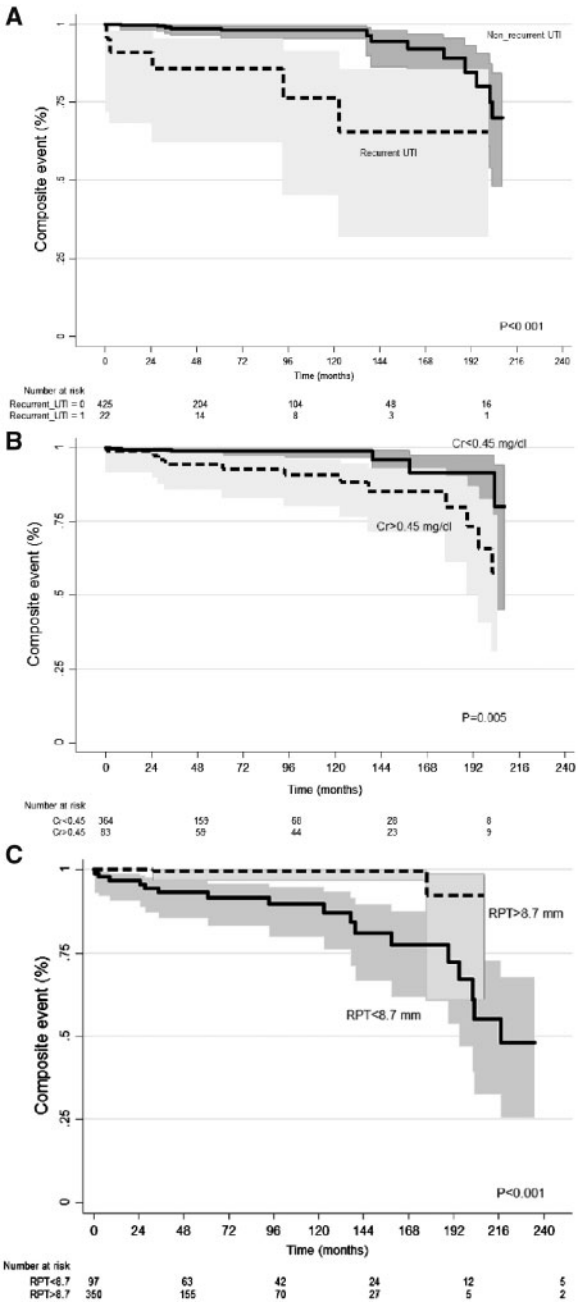

FIGURE 3: KM survival curves reveal the probability of renal injury according to the occurrence of (**A**) recurrent UTI, (**B**) baseline creatinine >0.45 mg/dL and (**C**) RPT <8.7 mm. The shaded areas represent 95% CIs. The number of patients at risk is shown below the x-axis.

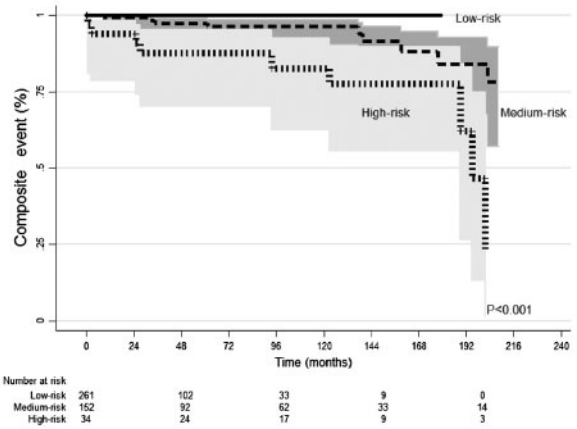

FIGURE 4: KM estimates for overall survival without renal injury by risk category ($N = 447$). The shaded areas represent 95% CIs. The number of patients at risk is shown below the x-axis.

our findings suggest that repeated episodes of UTI might play a role as a risk factor for renal injury. Nevertheless, further studies are necessary to evaluate whether prophylactic antibiotics might prevent renal injury in patients with ANH.

Our study has some limitations and several clinical and methodologic considerations should be taken into account in evaluating our findings. First, from the clinical point of view, VCUG was not uniformly performed across the entire period of the study for patients with mild RPD. Therefore the presence of low-grade VUR might have been underestimated in this subgroup of patients. Nevertheless, mild vesicoureteral reflux (VUR) was not associated with frequent UTI relapses or with renal parenchyma damage [49, 52, 53]. Thus the omission of some cases of mild VUR had a negligible impact on our results. Similarly, renal scintigraphy and systematic assessment for proteinuria were carried out only in patients with severe RPD. Unfortunately, more suitable markers to estimate GFR and to search for early renal injury such as cystatin C or β-trace protein were not available for systematic assessment in our cohort. This fact hampered a more robust analysis of the risk factors for renal injury. From a methodological point of view, we have not validated the risk prediction instrument in an independent cohort. External validation is an important component in the development of clinical predictive models because accurate predictions in the patients that were used to develop a model are not a guarantee for good predictions in a new set of patients [54]. On the other hand, we believe that the most original aspect of our study was the systematic analysis of clinical outcomes in this homogeneous group of infants. To the best of our knowledge, our study is the first to estimate renal survival and related outcomes in a large series of isolated ANH. The prospective follow-up, large sample size and consistent management by the same medical team should have minimized the inherent biases of a single-center cohort study.

In summary, the findings of this cohort study have shown an overall low risk of renal injury for most infants with isolated ANH. Patients with SFU Grades 1–2 had rare episodes of UTI and did not develop any signs of renal injury over a median follow-up period of 6 years. Conversely, patients with SFU Grades 3–4 had an increased risk for renal injury by exhibiting proteinuria, hypertension and impairment of renal function. Independent risk factors for renal injury beyond the SFU grade included increased plasma levels of creatinine at baseline, decreased thickness of renal parenchyma at the first postnatal US, and recurrent UTI episodes during follow-up. If confirmed in future studies, infants with higher SFU grades and any of these risk factors may benefit from closer surveillance during long-term follow-up.

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CONFLICT OF INTEREST STATEMENT

None declared.

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