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Diagnostic test characteristics of ultrasound-based hydronephrosis for chronic kidney disease in children and adolescents with myelomeningocele: results from the UMPIRE and NSBPR cohort studies

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Abstract

Purpose: Renal ultrasounds are performed in patients with myelomeningocele to screen for markers of kidney health, including hydronephrosis. We evaluated the diagnostic accuracy of hydronephrosis to screen for low kidney function defined by estimated glomerular filtration rate (eGFR).

Materials and Methods: We performed a retrospective cross-sectional study using data from two cohorts of children and youth with myelomeningocele. The first cohort is the Urological Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida (UMPIRE; 2016–2022), and the second from the National Spina Bifida Patient Registry (NSBPR; 2009–2021). We identified patients aged 1-to-18-years-old with available eGFR data within 6 months of an ultrasound. We excluded NSBPR patients <6-years-old to address potential duplication across cohorts. The primary outcome was $eGFR < 90 \text{ mL/min/1.73m}^2$, calculated using the bedside Schwartz formula. Hydronephrosis was dichotomized into any/none. We calculated sensitivity, specificity, positive predictive value, and negative predictive value of any hydronephrosis using eGFR as the reference standard.

Results: In UMPIRE, 221 patients were included with median age 2.4 years (IQR 1.9–3.8) and 24% having $eGFR < 90$. Any hydronephrosis versus none conferred a sensitivity/specificity/positive predictive value/negative predictive value of 25/75/24/77%, respectively. In NSBPR, 2,269 patients were included with median age 13 years (IQR 9.6–16.3) and 17% having $eGFR < 90$. Any hydronephrosis versus none conferred a sensitivity/specificity/positive predictive value/negative predictive value of 24/87/26/85%, respectively.

Conclusions: In two cohorts of children and youth with myelomeningocele, hydronephrosis conferred a sensitivity of ~25% for a creatinine-based $eGFR < 90 \text{ mL/min/1.73m}^2$. This low sensitivity suggests that hydronephrosis alone is a poor screening marker of kidney health.

Keywords

hydronephrosis; chronic kidney disease; spina bifida; myelomeningocele; spinal dysraphism

Introduction

Spina bifida (SB) is the most common, permanently disabling, congenital birth defect in the United States (US),^{1, 2} with downstream effects on multiple organ systems. Among SB phenotypes, myelomeningocele (MMC) is the most severe survivable form. At birth, most infants with SB are thought to have normal kidney health.³ However, individuals with SB reach end-stage kidney disease (ESKD) by nearly two decades younger age than individuals without SB.^{4, 5} Kidney dysfunction is therefore an acquired condition in SB that some believe occur in up to 50% of individuals by their 3rd decade of life.^{6, 7}

Measurement of kidney dysfunction varies depending on the modality used,⁸ such as imaging or laboratory testing. Renal bladder ultrasound (RUS) is often used to screen for hydronephrosis. Given how kidney function may be altered in neurogenic bladder from backpressure or vesicoureteral reflux leading to febrile urinary tract infections, hydronephrosis in the literature has often been used as a measure of kidney health as shown in a recent systematic scoping review.⁸ Laboratory-based testing for estimated glomerular filtration rate (eGFR) is commonly used to define chronic kidney disease (CKD). In the National Spina Bifida Patient Registry (NSBPR), most participating SB centers routinely used RUS, but not serum creatinine measurements,⁹ which is commonly used to calculate eGFR. RUS screening may be favored over venipuncture in children to avoid the pain and distress known to be associated with needle-related procedures.¹⁰ However, the correlation of these two modalities of kidney dysfunction have not been well-studied, which, given the bias in practice patterns towards ultrasound over serum creatinine, raises concerns of underdiagnosing CKD in the SB population when using RUS alone. In addition, differences in recommendations on serum creatinine testing by age group in the Spina Bifida Association's Guidelines for the Care of People with Spina Bifida¹¹ or on laboratory testing in general across different guidelines^{11, 12} may further cloud practice patterns of kidney surveillance with limited evidence supporting these recommendations.

Given that RUS is often considered a screening tool that triggers checking serum creatinine in both clinical practice and in the Guidelines,¹¹ we sought to determine the diagnostic test characteristics of ultrasound-based hydronephrosis for low kidney function defined by creatinine-based eGFR. Based on data suggesting that hydronephrosis is a transient finding dependent on bladder filling,¹³ we hypothesized that hydronephrosis diagnosed by screening RUS would have low sensitivity to serve as a high-yield screening tool for low eGFR.

Materials and Methods

Study Design and Patient Population

We performed a retrospective cross-sectional study using two cohorts of children and youth with SB which are funded and coordinated by the Centers for Disease Control and Prevention (CDC). The first cohort is the Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida (UMPIRE) prospective protocol project, which included data from infants with MMC enrolled from birth to 3 months old from 10 SB centers across the country.¹⁴ The second cohort is the NSBPR,¹⁵ which includes data from 37 multidisciplinary pediatric or adult clinics from 32 SB centers

in the US; patients can be enrolled at any age with any of 6 forms of SB (MMC, lipomyelomeningocele, fatty filum terminale, meningocele, split cord malformation, and terminal myelocystocele). In this study, we only included patients from NSBPR with MMC to match SB severity with the UMPIRE cohort. We used data from 2016–2022 from UMPIRE and 2009–2021 from NSBPR.

We initially included all participants aged 1 to 18 years with available eGFR data measurements within 6 months of a RUS. Because some participants are enrolled in both UMPIRE and NSBPR and because UMPIRE follows a more regimented management protocol than NSBPR, we excluded NSBPR patients less than age six years to address potential duplication between cohorts and separate results by management protocol. For UMPIRE participants, we excluded infants less than age 1 year or older than 6 years as the eGFR equation used is not validated in the former age group and the latter age group was excluded to avoid overlap with NSBPR. We also excluded participants with extreme eGFR values (i.e., $>200 \text{ mL/min/1.73m}^2$). For participants with multiple eligible data measurements, the most recent one was used in the analyses.

Informed consent was obtained from participants or parent/guardian at UMPIRE or NSBPR enrollment. Institutional Review Board approval was obtained locally from each study site.

Variables

The primary outcome of interest was low eGFR, defined as an eGFR $<90 \text{ mL/min/1.73m}^2$ using the bedside Schwartz eGFR equation,¹⁶ which incorporates serum creatinine and standing height (or recumbent length or arm-span measurements, if standing height is unavailable). An eGFR $<90 \text{ mL/min/1.73m}^2$ defines CKD Stage 2 or higher. In UMPIRE, serum creatinine is measured annually (i.e., every birthday) and at age three and 18 months.¹⁴ The NSBPR does not follow a standardized serum creatinine protocol. According to the Guidelines, serum creatinine measurement is recommended at age 3 months and annually after 6 years of age, but among children aged one to five years, serum creatinine is measured only if changes on ultrasound are noted.¹¹

Our primary exposure was hydronephrosis on RUS, which was categorized into any hydronephrosis versus no hydronephrosis using the Society for Fetal Urology (SFU) classification system¹⁷ and was self-reported from each participating center and not reviewed centrally. In UMPIRE, RUS is obtained annually (i.e., every birthday) and at three, six, and 18 months of life¹⁴ and is read using SFU classification. The NSBPR does not follow a standardized ultrasound protocol. Per the Guidelines, RUS is recommended at age 3 and 9 months, every 6 months under age 2 years old, and annually after age 2 years and as needed for recurrent urinary tract infections or bladder hostility.¹¹

Variables included age, sex, race/ethnicity, and functional lesion level.

Statistical Analysis

Study variables were summarized using medians and interquartile ranges (IQR) for continuous variables and frequency counts and percentages for categorical variables. To test the difference in baseline variables between UMPIRE and NSBPR, we used **Fisher's**

exact tests, Chi-squared tests and Wilcoxon rank-sum tests. We calculated diagnostic test characteristics¹⁸ using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence intervals (CI).

We performed two sensitivity analyses. First, we redefined our exposure as high-grade hydronephrosis (i.e., SFU grade 3–4) versus low-grade or no hydronephrosis (i.e., SFU grade 0–2), using the same outcome of eGFR <90 mL/min/1.73m². Second, we redefined our outcome as eGFR <60 mL/min/1.73m², which defines CKD Stage 3 or higher, and kept the exposure as any hydronephrosis versus no hydronephrosis. All data analyses were performed using SAS 9.4 software with a two-tailed alpha of 0.05.

Results

In UMPIRE, a total of 221 participants were included (Figure 1). The median age of the cohort was age 2.4 years (interquartile range [IQR] 1.9–3.8), 53% were male, 63% were Non-Hispanic white, and 9% had thoracic level lesions (Table 1). The median time between RUS and serum creatinine was 0 months (IQR 0–6). A quarter (25%) of participants were determined to have any hydronephrosis, and nearly a quarter (24%) had eGFR <90 mL/min/1.73m². In NSBPR, a total of 2,269 participants with MMC were included (Figure 2). The median age of the cohort was age 13 years (IQR 9.6–16.3), 50% were male, 54% were Non-Hispanic white, and 15% had thoracic level lesions. The median time between RUS and serum creatinine was 0 months (IQR 0–3). Fewer participants (15%) had any hydronephrosis and 17% had eGFR <90 mL/min/1.73m².

Primary outcome

In UMPIRE, for the primary outcome of low eGFR, any hydronephrosis versus none resulted in a sensitivity, specificity, PPV, NPV of 25%, 75%, 24%, and 77%, respectively (Table 2). In NSBPR, any hydronephrosis versus none conferred a sensitivity, specificity, PPV, NPV of 24%, 87%, 26%, and 85%, respectively.

Sensitivity analyses

When assessing high grade hydronephrosis, in UMPIRE, high-grade versus non-high-grade hydronephrosis conferred a sensitivity, specificity, PPV, NPV of 6%, 92%, 19%, and 76%, respectively (Table 3). In NSBPR, high-grade versus non-high-grade hydronephrosis conferred a sensitivity, specificity, PPV, NPV of 11%, 97%, 43%, 85%, respectively.

When assessing CKD Stage 3 or higher, in UMPIRE, there were too few outcome events to perform the analysis (Table 4). In NSBPR, any hydronephrosis versus none conferred a sensitivity, specificity, PPV, NPV of 51%, 86%, 10%, 98%, respectively.

Discussion

In SB, kidney health is an essential, life-long health concern. In the current study, we compared a commonly used imaging test for kidney health, hydronephrosis on RUS, against a commonly used laboratory test for kidney health, creatinine-based eGFR. These tests reflect common practice patterns across many urologists and centers who care for

patients with SB, with RUS used more often than serum creatinine testing in childhood but not necessarily in adults.^{9, 19} We found that ultrasound-based hydronephrosis had poor sensitivity for CKD based on creatinine-based eGFR. Our results indicate that RUS alone is a poor screening marker of kidney health and should be combined with routine serum testing.

Aside from our findings, RUS offers many advantages over routine serum testing that otherwise would strengthen its case as an ideal screening test. RUS is non-invasive and safe with minimal morbidity to the patient, is nearly ubiquitous across most pediatric centers, and is relatively easy to perform with trained technicians. In contrast, venipuncture can be quite distressing for both the child and caregiver.²⁰ Although attention in more recent years has been placed on effective pain management strategies during needle-related procedures,²¹ significant needle fear can persist into adulthood and negatively affect medical adherence.¹⁰

As per the Spina Bifida Association Guidelines, serial RUS are recommended in SB to monitor for bladder or kidney dysfunction.¹¹ An example of the former is that detection of hydronephrosis could prompt a urodynamics study to assess for elevated bladder storage pressures or vesicoureteral reflux. For kidney health, however, the Guidelines recommend obtaining serum creatinine testing only if there is a change in the upper urinary tract for certain age groups (i.e., 1–5 years old).¹¹ Our study results, and those from prior literature, do not support this latter recommendation. Indeed, our study results support recommendations from other guidelines, such as the European Association of Urology Paediatric Urology Guidelines, that recommend annual laboratory testing.¹²

The major, critical limitation of using hydronephrosis alone is its poor sensitivity for CKD. An ideal screening test would achieve close to 100% sensitivity, meaning there are zero to very few false negatives or false reassurances that there is no CKD. In our current study, we found a sensitivity of 25% in the UMPIRE cohort (who are 1–5 years old) and 24% in the NSBPR cohort for a creatinine-based eGFR <90 mL/min/1.73m². Another interpretation is that patients who have CKD will have ~75% chance of having no hydronephrosis on RUS. Prior retrospective work from a single institution using more conservative, Cystatin-C-based eGFR calculations found similarly poor sensitivity of ultrasound-based hydronephrosis for CKD.²² We suspect that a combination of the transient nature of hydronephrosis (i.e., dependency on bladder fullness at time of RUS¹³) and the greater physiologic renal reserve found in younger children may drive our findings, as supported by our sensitivity analysis using high-grade hydronephrosis that found similar results. It is important to note that while creatinine values may be abnormal in settings of dehydration or infection, most values in UMPIRE are collected during ambulatory clinic visits and not from inpatient hospitalizations.

Although ultrasound-based hydronephrosis alone is a poor screening marker, we are not advocating that hydronephrosis should not be checked routinely. Our results found specificities of 75–87% in the UMPIRE and NSBPR cohorts, meaning that 75–87% of patients without CKD will test negative for concurrent hydronephrosis. Another interpretation is that patients who do not have CKD will have 13–25% chance of having hydronephrosis on RUS. Given that hydronephrosis could also trigger bladder function

evaluation with urodynamics, RUS maintains a vital role in urologic screening in SB. We are suggesting that, for kidney health, routine serum testing be combined with routine imaging testing, as parallel testing (versus serial testing) increases overall sensitivity.

One other study finding warrants further discussion. We noted a significant difference in prevalence of eGFR <90 mL/min/1.73m² between the UMPIRE and NSBPR cohorts, with a higher prevalence in the former (24% versus 17%). This finding may be due in part to detection bias from the more regimented and standardized follow-up protocol of the UMPIRE cohort when compared to the non-standardized follow-up protocol within the NSBPR cohort. There are also likely more NSBPR participants, being older, who underwent bladder reconstructive surgery, which may help mitigate kidney dysfunction. Further, as shown in the study flowcharts of the Figures, many more NSBPR participants were excluded than UMPIRE participants. This selection bias may also have contributed to the difference in CKD prevalence between cohorts. However, separation of the UMPIRE and NSBPR groups by age was necessary to ensure separation of a strict surveillance protocol for kidney health from a non-protocolized surveillance strategy.

Our study results should be interpreted in context of its strengths and limitations. Given the wide clinical spectrum and heterogeneity of SB, we restricted our study population to individuals with MMC, which is the most severe survivable form of SB. We examined the two largest SB registries in North America, both of which are multi-centered, reflect the clinical spectrum of MMC, and likely reflect different management paradigms of individuals with MMC. Lastly, we analyzed our results with two different sensitivity analyses with similar, robust results about the poor sensitivity of hydronephrosis.

Our study has limitations. As the reference in the current study for determining diagnostic test characteristics, creatinine-based eGFR was used, which has well-known unreliability and variability and is not the gold standard used for measuring true GFR (which is urinary inulin clearance or iothexol plasma clearance).^{23, 24} However, increasing the uptake of gold standard testing faces barriers including prolonged duration of the test and the requirement of intravenous catheters. Use of recumbent length or arm-span as a proxy for standing height may provide bias for eGFR calculations, though multiple studies in healthy volunteers show very high correlations between arm-span and height with small differences.²⁵ Similarly, though the Schwartz eGFR equation was developed in a cohort of children as young as 1-year-old, GFR in children does not approach typical adult levels until age 1.5-to-2-years-old, which may bias results.²⁶ However, ~75% of the UMPIRE cohort was >2 years old, so results are unlikely to change substantially. Cystatin-C may be a more reliable marker for CKD than serum creatinine,²⁷ but since serum creatinine is used more commonly in practice than serum cystatin-C,¹⁹ and since the Guidelines mention serum creatinine specifically,¹¹ our study design reflects contemporaneous clinical practice patterns and guideline recommendations. Additionally, since low muscle mass in youth with MMC may cause creatinine-based eGFR to be overestimated, a low creatinine-based eGFR likely signifies an even lower actual GFR. We did not adjust for bladder fullness at time of RUS, which may impact degree of hydronephrosis,¹³ though we suspect a single cross-sectional timepoint to hold minimal value and more chronic bladder fullness to be more meaningful. Our study evaluated only hydronephrosis as an RUS outcome, when other

outcomes such as thinned cortex, dysplasia, or hyperechogenicity may also be concerning findings for CKD, but were not captured in UMPIRE and NSBPR. We did not evaluate nuclear medicine scans nor urine studies such as microalbuminuria, but these were not the focus of our current study and may be a part of future directions, along with prospective studies to validate our findings. Our study results may have limited generalizability, given that we assessed only patients with MMC and at NSBPR and UMPIRE clinic sites, which may not be representative of the larger pediatric SB population in the US. Lastly, our study identified relatively few outcome events for eGFR <60 mL/min/1.73m², which limits the power of our analyses for more severe CKD.

Conclusions

In conclusion, in our study of two large SB cohorts in the US, ultrasound-based hydronephrosis has poor diagnostic sensitivity for low eGFR based on serum creatinine. Our findings indicate that RUS alone is a poor screening marker of kidney health and should be combined with routine serum testing of at least serum creatinine. Current CKD screening protocols in people with spina bifida should include at least annual serum laboratory testing in addition to annual RUS.

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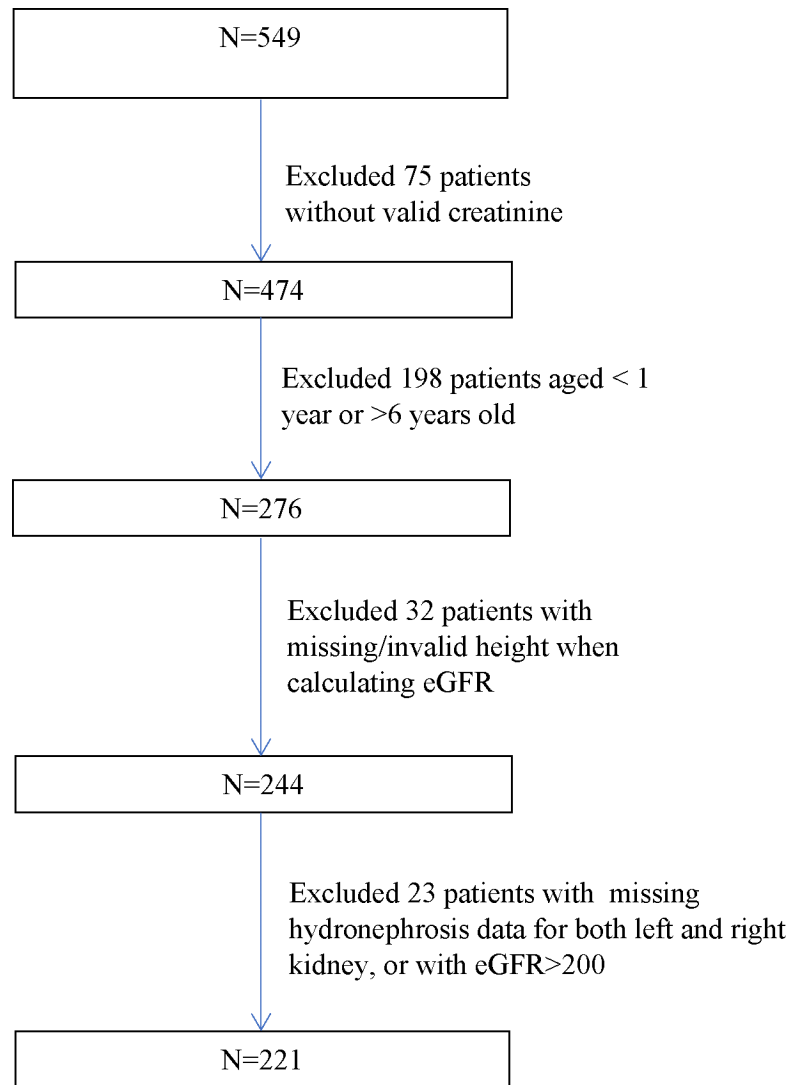


Figure 1.
Study flowchart for eligibility criteria from UMPIRE 2016–2022

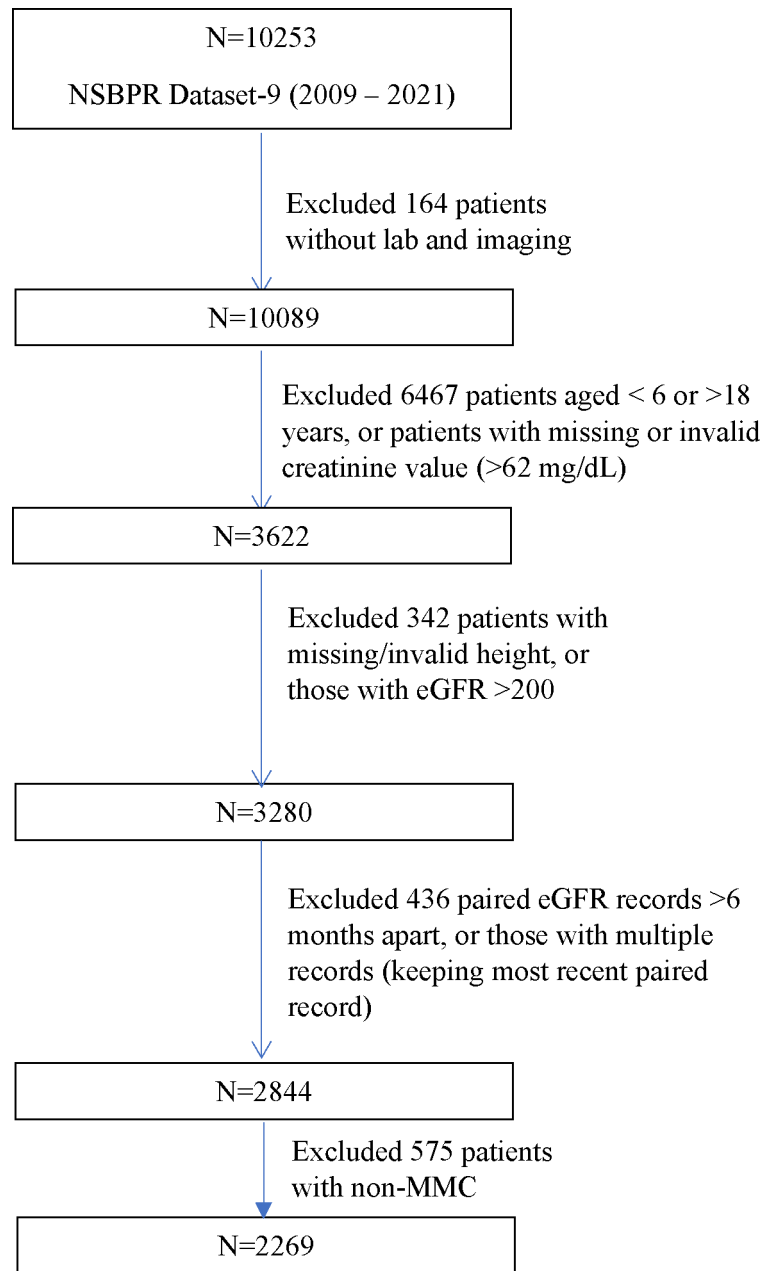


Figure 2.
Study flowchart for eligibility criteria from NSBPR 2009–2021

Table 1.

Characteristics of study cohorts, UMPIRE 2016–2022 and NSBPR 2009–2021, MMC diagnosis.

Variables	UMPIRE	NSBPR	p-value
N	221	2269	
Age, years			<0.001 ^a
Median (IQR)	2.4 (1.9–3.8)	13.0 (9.6–16.3)	
Sex, n (%)			0.48 ^b
Male	117 (52.9)	1144 (50.4)	
Female	104 (47.1)	1125 (49.6)	
Race/ethnicity, n (%)			0.02 ^c
NH white	140 (63.3)	1230 (54.4)	
NH black	25 (11.3)	226 (10.0)	
Hispanic/Latino	43 (19.5)	640 (28.3)	
Other	13 (5.9)	167 (7.4)	
Functional level of lesion, n (%)			<0.001 ^c
Thoracic	20 (9.1)	342 (15.1)	
High-Lumbar	15 (6.8)	226 (10.0)	
Mid-Lumbar	78 (35.3)	862 (38.0)	
Low-Lumbar	57 (25.8)	363 (16.0)	
Sacral	51 (23.1)	476 (21.0)	
Any hydronephrosis, n (%)	55 (24.9)	336 (14.8)	<0.001 ^b
High-grade hydronephrosis, n (%)	16 (7.2)	99 (4.4)	0.06 ^b
eGFR, mL/min/1.73m ²			0.61 ^a
Median (IQR)	125 (93.4–146.9)	122 (100–150)	
eGFR <90 mL/min/1.73m ² , n (%)	52 (23.5)	378 (16.7)	0.01 ^b
eGFR <60 mL/min/1.73m ² , n (%)	6 (2.7)	63 (2.8)	1.00 ^b

Abbreviations: eGFR = estimated glomerular filtration rate; MMC = myelomeningocele; NSBPR = National Spina Bifida Patient Registry; UMPIRE = Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida

^aWilcoxon rank-sum test

^bFisher's exact test

^cChi-squared test

Table 2.

Diagnostic test characteristics of any hydronephrosis versus none for eGFR <90 mL/min/1.73m², UMPIRE 2016–2022 and NSBPR 2009–2021.

Any hydronephrosis	eGFR<90, n (%)	eGFR≥90, n (%)	Diagnostic test characteristic	Value in UMPIRE (95% CI)	Value in NSBPR (95% CI)
UMPIRE – yes	13 (24)	42 (76)	Sensitivity	25 (13, 37)	24 (19, 28)
UMPIRE – no	39 (23)	127 (77)	Specificity	75 (69, 82)	87 (85, 88)
NSBPR – yes	89 (26)	247 (74)	Positive predictive value	24 (12, 35)	26 (22, 32)
NSBPR – no	289 (15)	1644 (85)	Negative predictive value	77 (70, 83)	85 (83, 87)

Abbreviations: CI = confidence interval; NSBPR = National Spina Bifida Patient Registry; UMPIRE = Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida

Table 3.

Sensitivity analysis 1: Diagnostic test characteristics of high-grade hydronephrosis versus low-grade or none for eGFR <90 mL/min/1.73m², UMPIRE 2016–2022 and NSBPR 2009–2021.

High-grade hydronephrosis	eGFR<90, n (%)	eGFR≥90, n (%)	Diagnostic test characteristic	Value in UMPIRE (95% CI)	Value in NSBPR (95% CI)
UMPIRE – yes	3 (19)	13 (81)	Sensitivity	6 (0, 12)	11 (8, 15)
UMPIRE – no	49 (24)	156 (76)	Specificity	92 (88, 96)	97 (96, 98)
NSBPR – yes	43 (43)	56 (57)	Positive predictive value	19 (0, 38)	43 (34, 54)
NSBPR – no	335 (15)	1835 (85)	Negative predictive value	76 (70, 82)	85 (83, 86)

Abbreviations: CI = confidence interval; NSBPR = National Spina Bifida Patient Registry; UMPIRE = Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida

Table 4.

Sensitivity analysis 2: Diagnostic test characteristics of any hydronephrosis versus none for eGFR <60 mL/min/1.73m², NSBPR 2009–2021.*

Any hydronephrosis	eGFR<60, n (%)	eGFR≥60, n (%)	Diagnostic test characteristic	Value in NSBPR (95% CI)
NSBPR – yes	32 (10)	304 (90)	Sensitivity	51 (38, 63)
			Specificity	86 (85, 88)
NSBPR – no	31 (2)	1902 (98)	Positive predictive value	10 (6, 13)
			Negative predictive value	98 (98, 99)

* UMPIRE diagnostic test characteristics not determined due to small sample size; Abbreviations: CI = confidence interval; NSBPR = National Spina Bifida Patient Registry; UMPIRE = Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida