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Diagnostic Test Characteristics of Ultrasound-Based Hydronephrosis in Identifying Low Kidney Function in Young Patients with Spina Bifida: A Retrospective Cohort Study

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Abstract

Purpose: Kidney dysfunction in spina bifida (SB) is usually detected by low estimated glomerular filtration rate (eGFR) or ultrasound-based hydronephrosis. We assessed the diagnostic test characteristics of hydronephrosis for detecting low eGFR, hypothesizing that hydronephrosis has low sensitivity compared to Cystatin-C-based eGFR.

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Materials and Methods: We conducted a single-center, retrospective cohort study, including patients with SB from 2012–2017 with two kidneys and complete data needed to calculate eGFR via multiple pediatric (age 1–17.9 years) or adult (age ≥18 years) estimating equations. We evaluated the association of hydronephrosis status (highgrade, low-grade, or none) with eGFR, adjusting for small kidney size and scarring, and calculated diagnostic test characteristics of hydronephrosis for low eGFR.

Results: We analyzed 247 patients (176 children and 71 adults). Mean (standard deviation) age was 13.7 (6.6) years; 81% had myelomeningocele. Hydronephrosis (77% low-grade) was found in 35/176 children and 18/71 adults. Hydronephrosis was associated with low eGFR in stepwise fashion, independent of kidney size and scarring. However, across Cystatin-C-based pediatric equations, any hydronephrosis (compared to none) had 23–48% sensitivity and high-grade hydronephrosis (compared to none or low-grade) had 4–15% sensitivity for eGFR<90 mL/min/1.73m^2, which remained unchanged after excluding small kidneys and scarring. Across Cystatin-C-based adult equations, any and high-grade hydronephrosis had 55–75% and 40–100% sensitivity, respectively, for eGFR<90 mL/min/1.73m^2, though with wide confidence intervals. Specificity was higher with high-grade versus any hydronephrosis. Sensitivities were higher for eGFR<60 mL/min/1.73m^2.

Conclusions: Hydronephrosis was associated with low eGFR but had poor sensitivity for Cystatin-C-based eGFR<90 mL/min/1.73m^2, especially among children with SB.

Keywords

Hydronephrosis; ultrasound; sensitivity; kidney function; chronic kidney disease; spina bifida; spina dysraphism

Introduction

In patients born with spina bifida (SB), preservation of kidney health is a lifelong clinical objective that is especially prioritized during childhood when the kidneys are still growing. The natural history of kidney health in SB suggests most newborns with SB have normal baseline imaging characteristics and urinary tract anatomy.[1] Despite this, an estimated 25–50% of patients with SB will develop chronic kidney disease (CKD) by their twenties due to progressive neurogenic bladder dysfunction.[2, 3] If impaired kidney health is diagnosed early, existing interventions, including initiation of clean intermittent catheterization, anticholinergic pharmacotherapy, or surgical augmentation cystoplasty, may delay or prevent the onset of CKD in patients with SB.

Kidney health in SB is usually assessed through laboratory tests, such as serum creatinine or cystatin-C, which are used to calculate estimated glomerular filtration rate (eGFR), or through imaging tests, such as renal ultrasound (RUS), which can identify radiologic abnormalities including hydronephrosis, small size, or scarring. An increasingly recognized obstacle to CKD detection through laboratory tests is the potential unreliability of commonly-used eGFR estimating equations among patients with SB.[4] Thus, hydronephrosis may often be used alone and is even recommended in SB guidelines as the initial marker of kidney function deterioration, with follow-up laboratory testing suggested if hydronephrosis

is detected.[5] However, low eGFR may occur in the absence of hydronephrosis, as hydronephrosis may be transient and hydronephrosis and low eGFR may be asymptomatic. Patients who are screened with only serial RUS and without serial laboratory tests therefore may face risk of undiagnosed CKD.

In this study, we examined the cross-sectional associations between hydronephrosis and eGFR and determined the diagnostic test characteristics of ultrasound-based hydronephrosis for low eGFR. We hypothesized that hydronephrosis would have low sensitivity as a screening test for low eGFR, particularly with cystatin-C-based eGFR as the index test.

Materials and Methods

Study Design and Population

A retrospective cohort study of children (ages 1–17.9 years) and adults (≥18 years) was conducted using data gathered from 2012–2017 at a large multi-disciplinary SB clinic at a free-standing children's hospital. Patients with at least one set of full data needed to calculate eGFR, including age, race, sex, height, serum creatinine, serum cystatin-C (Cys-C), and serum blood urea nitrogen (BUN), and who had a corresponding RUS within 6 months of the laboratory data were included. For patients in whom standing height or length could not be obtained, arm span as measured from the back, fingertip to fingertip, with arms parallel to the ground, was used as a surrogate for height. Patients who did not have all measurements, were <1-year-old because of rapidly-changing eGFR, were on renal replacement therapy, or had a solitary kidney were excluded.

The institutional review board approved this study as part of a larger prospective study, for which informed consent was obtained from all participants. The STARD reporting criteria were followed.[6]

Outcomes and Exposures

The primary outcome was eGFR. In children and adults, 4 and 3 different eGFR equations, respectively, were used to calculate eGFR, incorporating creatinine-only, Cys-C-only, or both. The pediatric equations included the creatinine-only Schwartz "bedside" equation,[7] the Cys-C-only Schwartz equation,[8] the creatinine-and-Cys-C-containing Schwartz Chronic Kidney Disease in Children cohort study (CKiD) equation,[8] and the creatinine-and-Cys-C-containing Zappitelli equation with modifier term for SB.[9] The adult equations included the Chronic Kidney Disease Epidemiology cohort study (CKD-EPI) creatinine-only equation,[10] the CKD-EPI Cys-C equation,[11] and the CKD-EPI creatinine and Cys-C equation.[11]

The primary exposure was presence of hydronephrosis as defined by the Society for Fetal Urology (SFU) classification system.[12] Hydronephrosis grade was recorded from radiology reports if explicitly mentioned by SFU classification; otherwise, images were directly reviewed by the first author (DIC) and an SFU grade was assigned. Hydronephrosis status was divided into none, low-grade (SFU Grade 1–2), and high-grade (SFU Grade 3–4).

Covariates

Additional variables were age at eGFR measurement (centered on date of laboratory values), sex, ambulatory status, spina bifida type (myelomeningocele versus non-myelomeningocele), dependency on clean intermittent catheterization, and prior bladder augmentation. Ambulatory status was a binary covariate based on the Hoffer classification,[13] with community ambulators classified as ambulatory and all other groups as non-ambulatory.

Additional RUS findings were small kidney size and kidney scarring, both recorded from the radiology report. A small kidney was defined as <2 standard deviations below the mean for age, using a spina bifida-specific kidney size nomogram.[14] Horseshoe kidneys precluded accurate measurement of kidney length and therefore were excluded from kidney size analyses.

Statistical Analysis

Summary statistics described all variables within each age-specific cohort. Medians and interquartile ranges (IQRs) summarized eGFR for each estimating equation, stratified by hydronephrosis status. Frequencies and percentages summarized CKD stage classification by estimating equation and hydronephrosis status, with eGFR<60 and <90 mL/min/1.73m^2 corresponding to at least CKD Stages 3 and 2, respectively. We used multivariable linear regression models to assess associations between hydronephrosis status and eGFR following adjustment for small kidney size and scarring.

Overall diagnostic test characteristics of any hydronephrosis (compared to none), including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and their 95% confidence intervals (CI), were calculated as a screening tool for detecting low eGFR, defined as eGFR<90 and eGFR<60 mL/min/1.73m^2, irrespective of small kidneys or scarring.

In two sensitivity analyses, diagnostic test characteristics were repeated for hydronephrosis reclassified as high-grade (compared to low-grade or none), and again for high-grade (compared to low-grade or none) after excluding patients with small kidneys or scarring.

All analyses were performed with SAS version 9 (SAS Institute, Inc., Cary, NC, USA), and all statistical tests assumed a two-sided type one error rate of 0.05. No corrections were made for multiple comparisons.

Results

Cohort Characteristics

A total of 247 patients with two kidneys met eligibility criteria, including 176 children and 71 adults. Mean (standard deviation) age was 13.7 (6.6) years, 57% were female, and 32% were non-ambulatory. 81% had myelomeningocele, 83% were dependent on clean intermittent catheterization, and 18% had prior bladder augmentation. Cohort characteristics by age group are shown in Table 1. The median (IQR) days between eGFR and RUS dates

were 0 (0–19). Hydronephrosis was found in 35 of 176 children (19%) and 18 of 71 adults (25%). Of these 53 patients with hydronephrosis, 12 (23%) had high-grade hydronephrosis.

Association Between Hydronephrosis and Low eGFR

Across pediatric equations, eGFR<90 mL/min/1.73m^2 was found in 2–66%, 10–83%, and 33–100% of children with no, low-grade, and high-grade hydronephrosis, respectively (Table 2). An eGFR<60 mL/min/1.73m^2 was found in 0–6%, 3–24%, and 17–50% of children with no, low-grade, and high-grade hydronephrosis, respectively. Across adult equations, eGFR<90 mL/min/1.73m^2 was found in 0–9%, 8–25%, and 17–50% of adults with no, low-grade, and high-grade hydronephrosis, respectively. An eGFR<60 mL/min/1.73m^2 was found in 0%, 0–8%, and 0–17% of adults with no, low-grade, and high-grade hydronephrosis, respectively.

Multivariable linear regression models, adjusted for small kidney size and scarring, showed a consistent dose-dependent association between hydronephrosis status and eGFR for all pediatric equations and adult equations, regardless of whether incorporating creatinine-only, Cys-C-only, or both (Table 3). The effect on eGFR was greater (i.e., more negative) for high-grade hydronephrosis compared to no hydronephrosis, than for low-grade hydronephrosis compared to no hydronephrosis.

Diagnostic Test Characteristics of Hydronephrosis for Low eGFR

Diagnostic test characteristics of any hydronephrosis (compared to none) identifying eGFR<90 and <60 mL/min/1.73m^2 are shown in Table 4. Among children, for eGFR<90 mL/min/1.73m^2, hydronephrosis had sensitivity ranging from 23–62%, but only 23–48% when considering only Cys-C-based eGFR calculations. For eGFR<60 mL/min/1.73m^2, hydronephrosis had sensitivity ranging from 53–100% for children, including using Cys-C-based eGFR, albeit with very large 95% confidence intervals. Among adults, for eGFR<90 mL/min/1.73m^2, hydronephrosis had sensitivity ranging from 55–100% (55–75% for Cys-C-based eGFR); for eGFR<60 mL/min/1.73m^2, hydronephrosis had 100% sensitivity, albeit with very large 95% confidence intervals.

The sensitivity of high-grade hydronephrosis (compared to low-grade or none) for detecting low eGFR was even lower, for both children and adults, albeit with larger 95% CI due to smaller sample size (Tables 5 and 6). Among all participants, high-grade hydronephrosis had sensitivity for detecting eGFR<90 mL/min/1.73m^2 ranging 4–25% overall (4–15% for Cys-C-based eGFR) for children and 27–50% overall and for Cys-C-based eGFR for adults (Table 5). Among patients without small kidneys or scarring, high-grade hydronephrosis had similar results for children (3–17% for Cys-C-based eGFR), with higher sensitivities for adults (Table 6). Specificity did increase for high-grade hydronephrosis compared to any hydronephrosis for low eGFR, for both children and adults (Tables 4–6).

Discussion

In our cohort, we found that any hydronephrosis had 23–48% sensitivity among children for eGFR<90 mL/min/1.73m^2 when using Cys-C-based equations. When stratified by high-grade hydronephrosis (compared to low-grade or none), sensitivity dropped even lower to 4–

15% by Cys-C-based equations, which remained unchanged (3–17% sensitivity) after excluding small kidneys and kidney scarring. Another interpretation is that up to two-thirds of children without hydronephrosis on RUS could have eGFR<90 mL/min/1.73m^2. Although a significant association was found between having hydronephrosis and low eGFR, the relatively poor sensitivity and high false negative rate of hydronephrosis suggest that RUS-based hydronephrosis alone is not a reliable screening tool to detect mild-to-moderate CKD.

In patients with SB, kidney health is strongly influenced by the pathophysiology of neurogenic bladder dysfunction. Chronically elevated bladder pressures, vesicoureteral reflux, or recurrent urinary tract infections have been found to be significantly associated with hydronephrosis or renal scarring in patients with SB.[15–17] Supporting this pathophysiology, the classic study on elevated detrusor leak point pressure during urodynamics used hydronephrosis as a clinical outcome and not eGFR or other laboratory-based marker of global kidney function.[18] Since this landmark study, other studies on urodynamic findings have similarly used hydronephrosis as a clinical outcome.[19] These studies support using hydronephrosis as a proxy for worse kidney function.

In our study, we found that having hydronephrosis, compared to no hydronephrosis, was significantly associated with a step-wise, dose-dependent decrease in eGFR, with larger decreases in eGFR for more severe hydronephrosis. Prior studies assessing the association between eGFR and hydronephrosis among patients with SB are limited, but their results are consistent. A study of 40 patients (mean age 10.8 years) with neurogenic bladder noted a significant association between hydronephrosis and lower eGFR, calculated using Cys-C-only equations.[20] A recent conference abstract examined 95 patients with SB (mean age 3 years) and found a significant association between hydronephrosis and creatinine-based eGFR <70 mL/min/1.73m^2.[21]

Perhaps in recognition of the biologic plausibility and the significant associations found between hydronephrosis and impaired kidney function, imaging-based surveillance for CKD is espoused by guidelines on management of neurogenic bladder.[5, 22–27] Most guidelines recommend periodic kidney imaging from every 6 months[23] for high-risk patients to every 3 years for adults with SB.[27] Some guidelines completely omit routine laboratory testing[27] and rely only on routine kidney imaging.

These imaging-only guidelines, however, are potentially misleading given our main findings, especially if RUS is used primarily for detection of hydronephrosis. As an ideal screening test should have close to 100% sensitivity, and should detect an early-enough phase of disease when intervention has maximal benefit, hydronephrosis does not meet these criteria. We found that, across all patients, any hydronephrosis had 23–48% sensitivity, and high-grade hydronephrosis 4–15% sensitivity, in children for detecting eGFR<90 mL/min/1.73m^2. Even after excluding small kidneys and scarring, high-grade hydronephrosis still had poor sensitivity (3–17%) for detecting eGFR<90 mL/min/1.73m^2. Although with very wide 95% confidence intervals due to few individuals with advanced CKD in our study sample, the sensitivities of hydronephrosis were higher for eGFR<60 mL/min/1.73m^2. However, in this eGFR range, CKD is already advanced, suggesting that hydronephrosis

alone as a screening tool may not detect CKD progression until kidney dysfunction is already moderate-to-severe and therefore possibly more irreversible. We did find higher sensitivities among adults compared to children, which may reflect more of systematic differences in performance of eGFR equations by using adult equations instead of pediatric equations,[28] though more research is required. Notably, and as can be expected, specificity for low eGFR did increase with high-grade hydronephrosis compared to any hydronephrosis, meaning finding high-grade hydronephrosis can be useful for ruling in patients with low eGFR.

Given the pathophysiology of how bladder dysfunction affects kidney health, we hypothesize that low eGFR can occur without hydronephrosis through three potential mechanisms. First, hydronephrosis may be transient and reflect bladder filling. It is possible that true, chronic hydronephrosis is rare, particularly given the added likelihood that an intervention is performed for hydronephrosis before the next RUS, such as instituting clean intermittent bladder catheterization. Second, low eGFR may reflect injured nephrons that resulted from another cause, such as kidney scarring or small kidneys, which can be seen on RUS. Unfortunately, RUS has poor sensitivity for renal scarring compared to DMSA scans.[29] However, after excluding small kidneys and scarring, we still found very poor sensitivity (3–17%) for high-grade hydronephrosis among children. Third, low eGFR may result from chronic bladder pressures that are elevated enough to injure nephrons but not high enough to cause gross hydronephrosis. Future linkage of urodynamic data is needed to confirm this hypothesis.

Our study has limitations. We acknowledge the limitations of contemporary pediatric eGFR estimating equations. We and others have shown that pediatric eGFR estimating equations, which were mostly derived in children without SB and may have less accuracy at higher eGFR values, have high variability and unreliability when applied to children with SB.[4] The list of eGFR equations is not exhaustive and no measured GFR is available as a gold standard. As such, the possibility exists that current eGFR equations and hydronephrosis are both poor assessment tools for kidney function in patients with SB. The study design is retrospective in nature, meaning selection biases and unmeasured confounding are possible. We did not have a high number of patients with hydronephrosis, which precluded adjustment for multiple covariates. RUS results were not read by a centralized, blinded radiologist. The RUS findings are not exhaustive for each patient and were selected based on temporal timing with laboratory testing for eGFR data. Clinical interventions between clinic visits were not captured. Lastly, our study is based on a single institution, limiting potential generalizability to other SB clinics.

Despite these limitations, our study also has certain strengths. We present a large study population of children and adults with creatinine and Cys-C data and contemporaneous RUS findings. We included all commonly-used pediatric and adult equations espoused by the National Kidney Foundation and equations that may be more applicable to the SB population, such as the modified Zappitelli equation. The included equations cover creatinine-only, Cys-C-only, and combination equations. We performed a sensitivity analysis that excluded small kidneys and kidney scarring. Lastly, our study population had cohort

characteristics similar to that of the multi-institutional National Spina Bifida Patient Registry.[30]

In conclusion, we showed that a large proportion of patients with SB, particularly children, may have impaired kidney function without hydronephrosis on RUS. Hydronephrosis was associated with low eGFR, but even high-grade hydronephrosis had poor sensitivity (4–15%) in children to detect low Cys-C-based eGFR<90 mL/min/1.73m^2. Even after excluding small kidneys and scarring, high-grade hydronephrosis continued to have poor sensitivity (3–17%). We recommend adherence to clinical guidelines that more explicitly recommend routine laboratory testing in addition to routine imaging for patients with SB. Current CKD detection tools used in routine screening are unreliable in patients with SB, and better tools are needed. Until newer, SB-specific, and more accurate eGFR estimating equations or tools are developed, we recommend adding a screening Cys-C-based eGFR to screening RUS or using gold-standard methods to determine true GFR.

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References

1. Tanaka ST, Paramsothy P, Thibadeau J et al.: Baseline Urinary Tract Imaging in Infants Enrolled in the UMPIRE Protocol for Children with Spina Bifida. J Urol, 201: 1193, 2019 [PubMed: 30730412]
2. Malakounides G, Lee F, Murphy F et al.: Single centre experience: long term outcomes in spina bifida patients. J Pediatr Urol, 9: 585, 2013 [PubMed: 23602844]
3. Veenboer PW, Bosch JL, van Asbeck FW et al.: Upper and lower urinary tract outcomes in adult myelomeningocele patients: a systematic review. PLoS One, 7: e48399, 2012 [PubMed: 23119003]
4. Chu DI, Balmert LC, Arkin CM et al.: Estimated kidney function in children and young adults with spina bifida: A retrospective cohort study. Neurourol Urodyn, 2019
5. Association SB: Guidelines for the Care of People with Spina Bifida, 4th ed, 2018
6. Bossuyt PM, Reitsma JB, Bruns DE et al.: STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ, 351: h5527, 2015 [PubMed: 26511519]
7. Schwartz GJ, Munoz A, Schneider MF et al.: New equations to estimate GFR in children with CKD. J Am Soc Nephrol, 20: 629, 2009 [PubMed: 19158356]
8. Schwartz GJ, Schneider MF, Maier PS et al.: Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int, 82: 445, 2012 [PubMed: 22622496]
9. Zappitelli M, Parvex P, Joseph L et al.: Derivation and validation of cystatin C-based prediction equations for GFR in children. Am J Kidney Dis, 48: 221, 2006 [PubMed: 16860187]
10. Levey AS, Stevens LA, Schmid CH et al.: A new equation to estimate glomerular filtration rate. Ann Intern Med, 150: 604, 2009 [PubMed: 19414839]
11. Inker LA, Schmid CH, Tighiouart H et al.: Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med, 367: 20, 2012 [PubMed: 22762315]
12. Fernbach SK, Maizels M, Conway JJ: Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol, 23: 478, 1993 [PubMed: 8255658]

13. Hoffer MM, Feiwell E, Perry R et al.: Functional ambulation in patients with myelomeningocele. J Bone Joint Surg Am, 55: 137, 1973 [PubMed: 4570891]
14. Sutherland RW, Wiener JS, Roth DR et al.: A renal size nomogram for the patient with myelomeningocele. J Urol, 158: 1265, 1997 [PubMed: 9258191]
15. DeLair SM, Eandi J, White MJ et al.: Renal cortical deterioration in children with spinal dysraphism: analysis of risk factors. J Spinal Cord Med, 30 Suppl 1: S30, 2007 [PubMed: 17874684]
16. Timberlake MD, Jacobs MA, Kern AJ et al.: Streamlining risk stratification in infants and young children with spinal dysraphism: Vesicoureteral reflux and/or bladder trabeculations outperforms other urodynamic findings for predicting adverse outcomes. J Pediatr Urol, 14: 319 e1, 2018 [PubMed: 30253979]
17. Ma Y, Li B, Wang L et al.: The predictive factors of hydronephrosis in patients with spina bifida: reports from China. Int Urol Nephrol, 45: 687, 2013 [PubMed: 23483305]
18. McGuire EJ, Woodside JR, Borden TA et al.: Prognostic value of urodynamic testing in myelodysplastic patients. J Urol, 126: 205, 1981 [PubMed: 7196460]
19. Musco S, Padilla-Fernandez B, Del Popolo G et al.: Value of urodynamic findings in predicting upper urinary tract damage in neuro-urological patients: A systematic review. Neurourol Urodyn, 37: 1522, 2018 [PubMed: 29392753]
20. Millner RO, Preece J, Salvator A et al.: Albuminuria in Pediatric Neurogenic Bladder: Identifying an Earlier Marker of Renal Disease. Urology, 133: 199, 2019 [PubMed: 31454657]
21. Kang C, De S, Adams MC et al.: Estimated Glomerular Filtration Rate and Renal Ultrasound Findings are Associated in Spina Bifida Patients. In: Societies for Pediatric Urology. Chicago, IL, 2019
22. Blok B, Padilla-Fernández B, Pannek J et al.: EAU Guidelines on Neuro-Urology 2018. In: European Association of Urology Guidelines. 2018 Edition. Arnhem, The Netherlands: European Association of Urology Guidelines Office, vol. presented at the EAU Annual Congress Copenhagen 2018, 2018
23. Groen J, Pannek J, Castro Diaz D et al.: Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. Eur Urol, 69: 324, 2016 [PubMed: 26304502]
24. NICE: Urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological disease, 2012
25. Radmayr C, Bogaert G, Dogan HS et al.: EAU Guidelines on Paediatric Urology 2018. In: European Association of Urology Guidelines. 2018 Edition. Arnhem, The Netherlands: European Association of Urology Guidelines Office, vol. presented at the EAU Annual Congress Copenhagen 2018, 2018
26. Kavanagh A, Baverstock R, Campeau L et al.: Canadian Urological Association guideline: Diagnosis, management, and surveillance of neurogenic lower urinary tract dysfunction - Full text. Can Urol Assoc J, 13: E157, 2019 [PubMed: 30763235]
27. Bauer SB, Austin PF, Rawashdeh YF et al.: International Children's Continence Society's recommendations for initial diagnostic evaluation and follow-up in congenital neuropathic bladder and bowel dysfunction in children. Neurourol Urodyn, 31: 610, 2012 [PubMed: 22532312]
28. Chu DIB,L; Arkin C; Meyer T; Rosoklija I; Bowen D; Hodgkins K; Cheng E; Isakova T;, Yerkes E: Variability in Kidney Function Estimates in Emerging Adults with Spina Bifida: Implications for Transitional Care. Presented at the American Urological Association, Chicago, IL, 2019
29. Finkelstein JB, Rague JT, Chow J et al.: Accuracy of Ultrasound in Identifying Renal Scarring as Compared to DMSA Scan. Urology, 138: 134, 2020 [PubMed: 32004557]
30. Sawin KJ, Liu T, Ward E et al.: The National Spina Bifida Patient Registry: profile of a large cohort of participants from the first 10 clinics. J Pediatr, 166: 444, 2015 [PubMed: 25444012]

Table 1.

Overall cohort and kidney characteristics on ultrasound by age group.

Characteristic	Pediatric group (n=176)	Adult group (n=71)
Age, years, median (IQR)	10.4 (6.8, 14.1)	21.8 (19.9, 23.6)
Female sex, n (%)	102 (58%)	40 (56%)
Non-ambulatory, n (%)	56 (32%)	23 (32%)
Spina Bifida type, n (%)		
Myelomeningocele	141 (80%)	59 (83%)
Non-myelomeningocele	36 (20%)	12 (17%)
Dependent on CIC, n (%)	143 (81%)	63 (89%)
Prior bladder augmentation, n (%)	34 (19%)	10 (14%)
Hydronephrosis grade, n (%)		
None	141 (80%)	53 (75%)
Low-grade (SFU Grade 1–2)	29 (16%)	12 (17%)
High-grade (SFU Grade 3–4)	6 (3%)	6 (8%)
Kidney size, n (%) *		
Unilateral small	19 (11%)	10 (14%)
Bilateral small	4 (2%)	1 (1%)
Kidney scar on ultrasound, n (%)		
Unilateral scar	11 (6%)	6 (8%)
Bilateral scar	1 (1%)	3 (4%)

IQR = interquartile range; CIC = clean intermittent catheterization; SFU = Society for Fetal Urology

* n=4 patients (3 pediatric, 1 adult) with horseshoe kidneys precluding kidney size measurements were excluded; small kidney was defined as <2 standard deviations below mean kidney length for age.

Table 2.

Estimated glomerular filtration rate values (eGFR) stratified by age, 3-level hydronephrosis status, and estimating equation.

Equation name	Cr, CysC, Both	No hydronephrosis			Low-grade hydronephrosis			High-grade hydronephrosis		
		Median (IQR) eGFR, in units	eGFR <60 units No. (%)	eGFR <90 units No. (%)	Median (IQR) eGFR, in units	eGFR <60 units No. (%)	eGFR <90 units No. (%)	Median (IQR) eGFR, in units	eGFR <60 units No. (%)	eGFR <90 units No. (%)
Pediatric (n=176)		**n=141**			**n=29**			**n=6**		
Schwartz	Cr	148 (128, 168)	0	3 (2%)	130 (109, 155)	1 (3%)	3 (10%)	92 (68, 140)	1 (17%)	2 (33%)
Schwartz	CysC	88 (83, 100)	0	74 (52%)	80 (67, 89)	4 (14%)	24 (83%)	63 (50, 78)	3 (50%)	6 (100%)
CKiD	Cr + CysC	112 (103, 123)	0	14 (10%)	98 (88, 108)	1 (3%)	9 (31%)	71 (55, 90)	2 (33%)	4 (67%)
Zappitelli	Cr + CysC	84 (72, 94)	8 (6%)	93 (66%)	78 (62, 85)	7 (24%)	23 (79%)	64 (59, 69)	2 (33%)	5 (83%)
Adult (n=71)		**n=53**			**n=12**			**n=6**		
CKD-EPI	Cr	141 (130, 150)	0	0 (0%)	137 (127, 146)	0	1 (8%)	127 (107, 138)	0	1 (17%)
CKD-EPI	CysC	118 (100, 125)	0	5 (9%)	116 (97, 123)	1 (8%)	3 (25%)	86 (71, 109)	1 (17%)	3 (50%)
CKD-EPI	Cr + CysC	131 (120, 142)	0	1 (2%)	128 (109, 137)	1 (8%)	1 (8%)	106 (89, 129)	0	2 (33%)

Cr = creatinine; CysC = cystatin-C; CKiD = Chronic Kidney Disease in Children cohort; FAS = Full Age Spectrum; CKD-EPI = Chronic Kidney Disease Epidemiology cohort; IQR = interquartile range; eGFR = estimated glomerular filtration rate; OR = odds ratio; CI = confidence interval; eGFR “unit” = mL/min/1.73m^2

Table 3.

Associations between three-level hydronephrosis status (i.e., none, low-grade, high-grade hydronephrosis) and eGFR, assessed using multivariable linear regression models, adjusted for small kidneys and kidney scarring (n=4 with horseshoe kidneys precluding measurement of kidney size were excluded).

Equation name	Cr, CysC, or both	No. Patients	High-grade or low-grade hydronephrosis (vs none)	beta (95% CI) (mL/min/1.73m^2)
Pediatric (n=173)				
Schwartz	Cr	6	High-grade	−53 (−89, −16)
		28	Low-grade	−10 (−29, 9)
Schwartz	CysC	6	High-grade	−25 (−40, −10)
		28	Low-grade	−12 (−20, −4)
CKiD	Cr + CysC	6	High-grade	−38 (−55, −23)
		28	Low-grade	−12 (−20, −4)
Zappitelli	Cr + CysC	6	High-grade	−17 (−33, −2)
		28	Low-grade	−7 (−15, 0.8)
Adult (n=70)				
CKD-EPI	Cr	5	High-grade	−20 (−39, −1)
		12	Low-grade	−9 (−22, 4)
CKD-EPI	CysC	5	High-grade	−22 (−40, −4)
		12	Low-grade	−4 (−17, 8)
CKD-EPI	Cr + CysC	5	High-grade	−23 (−41, −4)
		12	Low-grade	−6 (−20, 7)

Cr = creatinine; CysC = cystatin-C; CKiD = Chronic Kidney Disease in Children cohort; CKD-EPI = Chronic Kidney Disease Epidemiology cohort; IQR = interquartile range; eGFR = estimated glomerular filtration rate; CI = confidence interval

Table 4.

Diagnostic test characteristics of any hydronephrosis identifying eGFR<90 mL/min/1.73m^2 and eGFR<60 mL/min/1.73m^2 with 95% Confidence Intervals.

Equation name	Cr, Cys-C, or both	Sensitivity	Specificity	PPV	NPV
For eGFR <90 mL/min/1.73m^2					
Pediatric (n=176)					
Schwartz	Cr	62% (24–91)	82% (75–88)	14% (5–30)	98% (94–100)
Schwartz	Cys-C	29% (20–39)	93% (85–98)	86% (70–95)	48% (39–56)
CKiD	Cr + Cys-C	48% (29–68)	85% (79–91)	37% (21–55)	90% (84–94)
Zappitelli	Cr + Cys-C	23% (16–32)	87% (76–95)	80% (63–92)	34% (26–42)
Adult (n=71)					
CKD-EPI	Cr	100% (16–100)	77% (65–86)	11% (1–35)	100% (93–100)
CKD-EPI	Cys-C	55% (23–83)	80% (68–89)	33% (13–59)	91% (79–97)
CKD-EPI	Cr + Cys-C	75% (19–99)	78% (66–87)	17% (4–41)	98% (90–100)
For eGFR <60 mL/min/1.73m^2					
Pediatric (n=176)					
Schwartz	Cr	100% (16–100)	81% (74–87)	6% (1–19)	100% (97–100)
Schwartz	Cys-C	100% (59–100)	83% (77–89)	20% (8–37)	100% (97–100)
CKiD	Cr + Cys-C	100% (29–100)	82% (75–87)	9% (2–23)	100% (97–100)
Zappitelli	Cr + Cys-C	53% (28–77)	84% (77–89)	26% (12–43)	94% (89–98)
Adult (n=71)					
CKD-EPI	Cr	*	75% (63–84)	0% (0–19)	100% (93–100)
CKD-EPI	Cys-C	100% (16–100)	77% (65–86)	11% (1–35)	100% (93–100)
CKD-EPI	Cr + Cys-C	100% (2–100)	76% (64–85)	6% (0–27)	100% (93–100)

* not able to calculate

Cr = creatinine; Cys-C = cystatin-C; CKiD = Chronic Kidney Disease in Children cohort; CKD-EPI = Chronic Kidney Disease Epidemiology cohort; eGFR = estimated glomerular filtration rate; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value

Table 5.

Diagnostic test characteristics of high-grade hydronephrosis (compared to no or low-grade hydronephrosis) identifying eGFR<90 mL/min/1.73m^2 and eGFR<60 mL/min/1.73m^2 with 95% Confidence Intervals.

Equation name	Cr, Cys-C, or both	Sensitivity	Specificity	PPV	NPV
For eGFR <90 mL/min/1.73m^2					
Pediatric (n=176)					
Schwartz	Cr	25% (3–65)	98% (94–99)	33% (4–78)	96% (92–99)
Schwartz	Cys-C	6% (2–12)	100% (95–100)	100% (54–100)	42% (35–50)
CKiD	Cr + Cys-C	15% (4–34)	99% (95–100)	67% (22–96)	86% (80–91)
Zappitelli	Cr + Cys-C	4% (1–9)	98% (90–100)	83% (36–100)	32% (25–39)
Adult (n=71)					
CKD-EPI	Cr	50% (1–99)	93% (84–98)	17% (0–64)	98% (92–100)
CKD-EPI	Cys-C	27% (6–61)	95% (86–99)	50% (12–88)	88% (77–95)
CKD-EPI	Cr + Cys-C	50% (7–93)	94% (85–98)	33% (4–78)	97% (89–100)
For eGFR <60 mL/min/1.73m^2					
Pediatric (n=176)					
Schwartz	Cr	50% (1–99)	97% (93–99)	17% (0–64)	99% (97–100)
Schwartz	Cys-C	43% (10–82)	98% (95–100)	50% (12–88)	98% (94–99)
CKiD	Cr + Cys-C	67% (9–99)	98% (94–99)	33% (4–78)	99% (97–100)
Zappitelli	Cr + Cys-C	12% (1–36)	97% (94–99)	33% (4–78)	91% (86–95)
Adult (n=71)					
CKD-EPI	Cr	*	92% (83–97)	0% (0–46)	100% (94–100)
CKD-EPI	Cys-C	50% (1–99)	93% (84–98)	17% (0–64)	98% (92–100)
CKD-EPI	Cr + Cys-C	0% (0–97)	91% (82–97)	0% (0–46)	98% (92–100)

* not able to calculate

Cr = creatinine; Cys-C = cystatin-C; CKiD = Chronic Kidney Disease in Children cohort; CKD-EPI = Chronic Kidney Disease Epidemiology cohort; eGFR = estimated glomerular filtration rate; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value

Table 6.

Diagnostic test characteristics of high-grade hydronephrosis (compared to no or low-grade hydronephrosis) identifying eGFR<90 mL/min/1.73m^2 and eGFR<60 mL/min/1.73m^2 with 95% Confidence Intervals, excluding patients with small kidneys or with kidney scarring on ultrasound.

Equation name	Cr, Cys-C, or both	Sensitivity	Specificity	PPV	NPV
For eGFR <90 mL/min/1.73m^2					
Pediatric (n=142)					
Schwartz	Cr	33% (1–91)	99% (95–100)	33% (1–91)	99% (95–100)
Schwartz	Cys-C	4% (1–11)	100% (94–100)	100% (29–100)	46% (38–55)
CKiD	Cr + Cys-C	17% (2–48)	99% (96–100)	67% (9–99)	93% (87–96)
Zappitelli	Cr + Cys-C	3% (1–9)	100% (92–100)	100% (29–100)	33% (25–42)
Adult (n=53)					
CKD-EPI	Cr	100% (2–100)	94% (84–99)	25% (1–81)	100% (93–100)
CKD-EPI	Cys-C	40% (5–85)	96% (86–99)	50% (7–93)	94% (83–99)
CKD-EPI	Cr + Cys-C	100% (16–100)	96% (87–100)	50% (7–93)	100% (93–100)
For eGFR <60 mL/min/1.73m^2					
Pediatric (n=142)					
Schwartz	Cr	0% (0–97)	98% (94–100)	0% (0–71)	99% (96–100)
Schwartz	Cys-C	50% (1–99)	99% (95–100)	33% (1–91)	99% (96–100)
CKiD	Cr + Cys-C	50% (1–99)	99% (95–100)	33% (1–91)	99% (96–100)
Zappitelli	Cr + Cys-C	9% (0–41)	98% (95–100)	33% (1–91)	93% (87–96)
Adult (n=53)					
CKD-EPI	Cr	*	92% (82–98)	0% (0–60)	100% (93–100)
CKD-EPI	Cys-C	100% (2–100)	94% (84–99)	25% (1–81)	100% (93–100)
CKD-EPI	Cr + Cys-C	*	92% (82–98)	0% (0–60)	100% (93–100)

* not able to calculate

Cr = creatinine; Cys-C = cystatin-C; CKiD = Chronic Kidney Disease in Children cohort; CKD-EPI = Chronic Kidney Disease Epidemiology cohort; eGFR = estimated glomerular filtration rate; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value