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ORIGINAL RESEARCH

The association between urodynamic findings and chronic kidney disease in children with neurogenic lower urinary tract dysfunction: A potential model for a standardised risk-based surveillance tool in South Africa

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Background: Patients with neurogenic lower urinary tract dysfunction (NLUTD) have an increased risk of chronic kidney disease (CKD). Urodynamic studies (UDS) are used to risk-stratify these patients for renal deterioration. The key study objective was to assess the association of UDS parameters with CKD and use this data to develop a risk-based surveillance tool for monitoring patients with NLUTD.

Methods: A retrospective descriptive study was conducted at two public tertiary hospitals in South Africa (SA). The study included UDS conducted between July 2013 and June 2018 on children younger than 18 years with NLUTD. Simple random sampling followed by screening to select the reports that met the criteria was done. Parameters analysed were: percentage bladder capacity (PBC), end filling pressure, compliance, detrusor activity, detrusor leak point pressure and vesicoureteral reflux (VUR). Glomerular filtration rate (GFR) was used to establish the presence of CKD.

Results: A total of 105 UDS reports of children aged 11 months to 17 years were analysed. CKD was identified in 23% of participants. Female sex and VUR were found to be associated with CKD. There was a significant difference in the mean age and mean PBC between those without and those with CKD (8 years vs 11 years and 82.04% vs 59.71%, respectively).

Conclusion: Using these local findings, the investigator developed a risk-based surveillance tool for long-term monitoring of patients with NLUTD in SA. This tool includes PBC, age, sex and VUR which had statistically significant findings. A longitudinal study is required to validate this tool.

Keywords: NLUTD, urodynamics, CKD, spina bifida, follow-up

Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) is defined by the International Continence Society (ICS) as lower urinary tract dysfunction due to disturbance of the neurological control mechanism.[1] Patients with NLUTD have an increased risk of upper tract damage[2-4] with chronic kidney disease (CKD)[2] frequency of 25%.[5,6] CKD may develop insidiously and go unrecognised in these patients, which can further progress to end-stage renal disease (ESRD).[7] This is a devastating disorder associated with cardiovascular morbidity and high mortality.[7] The impact of CKD on the quality of life of patients and their families, as well as the resources required to manage these patients, in a resource-constrained country like South Africa (SA), is concerning. Appropriate assessments should be conducted in children with NLUTD to enable upper urinary tract function preservation/improvement.[1,7] Urodynamic studies (UDS) have played a central role in risk-stratifying patients with NLUTD for renal deterioration.[1,8] The landmark study by McGuire et al., for example, introduced detrusor leak point pressure (DLPP) higher than 40 cm H_2O as an objective measure to define high risk for upper tract deterioration.[6,9] Galloway et al. formulated a hostility scoring system from 0 to 10 using the sum of five measurable UDS parameters from 0 (absence) to 2 (worst pattern). The parameters assessed were vesicoureteral reflux (VUR), neurogenic detrusor overactivity (NDO), compliance, leak point pressure and detrusor sphincter dyssynergia. A hostility score ≥ 5 was significantly related to the upper urinary tract damage ($p < 0.05$).[3] Low functional bladder capacity has also been reported to be associated with upper tract deterioration.[6] In addition, urinary tract infections are known to cause renal damage.[5,10] There is, however, limited research conducted in Africa.

The South African public healthcare system is structured into levels of care (primary, secondary and tertiary) that follow a strict referral system. Tertiary healthcare facilities receive referrals from secondary healthcare facilities and provide supervised specialist and intensive care services. Primary healthcare facilities are the first point of contact for patients and refer to secondary healthcare facilities. This study gives a local perspective on the association of UDS findings and CKD in children with NLUTD from two public tertiary hospitals in SA. The parameters analysed were percentage bladder capacity (PBC), end filling pressure (EFP), compliance (Comp), detrusor activity (DA), DLPP and VUR. Current surveillance tools are not standardised, do not give clear guidance on the surveillance of patients based on their individual risk(s) and are thus not adaptable to SA. It is intended that the findings of this study will contribute to the formulation of a standardised risk-based surveillance tool that is relevant to SA and can potentially be adapted for use in other countries.

This paper seeks to address the following research question: Can a risk-based surveillance tool using local data be developed to monitor patients with NLUTD in order to preserve/improve upper urinary tract function?

The study's aim is to assess local data on the association of urodynamic findings and CKD in children with NLUTD and present a potential model for a standardised risk-based surveillance tool for monitoring patients with NLUTD that will optimise efficient use of all levels of care in SA.

The following objectives will achieve this aim and address the research question:

i. To identify the demographic profile of the participants at two selected public tertiary hospitals in SA.
ii. To analyse the parameters of the UDS conducted on children with NLUTD.
iii. To characterise the glomerular filtration rate (GFR) of children with NLUTD.
iv. To compare participants with no CKD and those with CKD with respect to the UDS parameters.
v. To determine the association of UDS findings with CKD.

Materials and methods

This was a retrospective descriptive study. Quantitative, secondary data from UDS conducted between July 2013 and June 2018 at Steve Biko Academic Hospital (SBAH)'s Paediatric Urology department and the Red Cross Children's Hospital (RCCH) was collected. Only one data set of parameters per participant was included. In addition, voiding cystourethrogram (VCUG) and GFR previously done on participants were retrieved. The key study objective was to assess the association of CKD with specified UDS parameters. A UDS is a specialised invasive study, the UDS included in this study were performed by trained healthcare practitioners who followed standard steps to ensure uniformity. These steps are based on the International Children's Continence Society (ICCS)[11,12] guidelines.

The expected proportion of patients with NLUTD with CKD is 25%.[5] A sample of 81 patients will estimate this proportion with 95% confidence to an accuracy within 10%.

The simple random sampling model was used to select UDS reports from all UDS conducted at SBAH's Paediatric Urology department and the RCCH. From these, those conducted between July 2013 and June 2018 on children below the age of 18 were identified. Finally, screening was done to include the UDS reports conducted on children with NLUTD who met the criteria.

Inclusion criteria

- UDS conducted between July 2013 and June 2018.
- UDS reports of children below the age of 18 years.
- UDS reports of children with NLUTD.

Exclusion criteria

- UDS conducted outside the specified period.
- UDS reports of patients aged 18 years and older.
- UDS reports of patients not diagnosed with NLUTD.
- Invalid UDS.
- UDS conducted on children post renal transplant.

To establish the presence of VUR, fluoroscopy images were reviewed from the video UDS. Where standard UDS was conducted, VCUG reports were retrieved. The presence of CKD was established using GFR. Six parameters were analysed according to two groups (no CKD and CKD), these were: PBC, EFP, compliance, DA, DLPP and VUR. Percentage bladder capacity was calculated as per the ICCS terminology:[12] [bladder capacity/expected bladder capacity (EBC)] X 100. In this study, cystometric bladder capacity was used and EBC was calculated using age-appropriate formulas. The Holmdahl et al. formula[13] [EBC = 38 + age (months) x 2.5 (expressed in ml)] was used for children < 2 years and the Hjalmas formula [EBC = age (years) x 30 + 30 (expressed in ml)] for children ≥ 2 years.[14]

The presence of CKD was based on measured/estimated GFR < 60 ml/min/1.73 m² present for > 3 months, as per Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[15] A departmental protocol based on the 2001 European Association of Nuclear Medicine (EANM) guideline for GFR determination in children was used to measure GFR.[16] Where the measured GFR was not available, creatinine-based equations[16-20] were used (Schwartz equation where height measurements were available and Pottel equation where height measurements were not available).

A total of 105 UDS reports were included in the study, 93 had GFR, 82 had VCUG results and 76 participants had all parameters available (Figure 1). Notwithstanding, all 105 UDS reports were analysed in order to achieve study objectives (i) and (ii).

Parameters were assessed as set out in Table I. Methods, definitions and units in the study conformed to the standards of the ICCS.[11,12]

Prior to data collection, approval from the Human Research Ethics Committees of the University of Pretoria (Ref. 617/2018) and the University of Cape Town (Ref. 793/2018) was received. The

Table I: Parameters and categories used for analysis

Category / Parameter	Normal	Abnormal
PBC	65–150%	< 65% or > 150%
EFP*1	< 10 cmH_2O	> 30 cmH_2O
Comp	< 10 ml/cmH_2O	≥ 10 ml/cmH_2O
DA	Normoactive: No contractions during filling	Overactive: Involuntary contractions during filling
DLPP*2	No leak	Abnormal: DLPP < 40 cm H_20 Severely abnormal: DLPP ≥ 40 cmH_20
VUR	No VUR	VUR
GFR	No CKD: GFR ≥ 60 ml/min/1.73 m²	CKD: GFR < 60 ml/min/1.73 m²

PBC – percentage bladder capacity, EFP – end filling pressure, Comp – compliance, DA – detrusor activity, DLPP – detrusor leak point pressure, VUR – vesicoureteral reflux, GFR – glomerular filtration rate, CKD – chronic kidney disease
*1EFP was categorised into normal/undetermined/abnormal, but only the normal and abnormal categories are included in the table and analysed to determine the association of UDS findings with CKD. The undermined EFP data were, however, analysed to achieve study objectives (i), (ii) and (iii).
*2No leak was categorised as normal, the abnormal and severely abnormal categories were grouped together as abnormal.

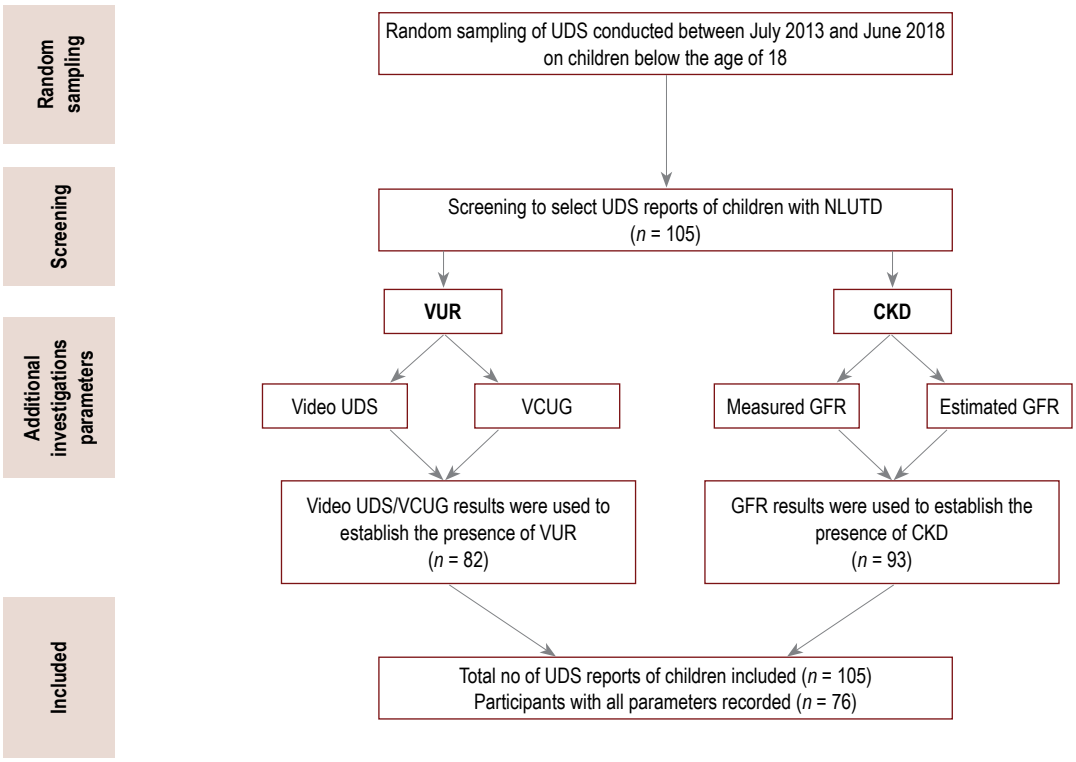

Figure 1: Enrolment flow diagram
UDS – urodynamic studies, NLUTD – neurogenic lower urinary tract dysfunction, VUR – vesicoureteral reflux, CKD – chronic kidney disease, VCUG – voiding cystourethrogram, GFR – glomerular filtration rate

study was conducted in compliance with both universities' ethics regulations.

Determinants for CKD were identified with multivariable logistic regression. Six parameters went into the logistic regression, which also included some demographic parameters as potential confounders. Data summary overall and by group (no CKD, CKD) employed descriptive statistics (mean, standard deviation [SD], median, 95% confidence interval [CI]) for continuous parameters. For discrete parameters, frequencies, percentages, cross-tables and 95% CIs were used. The proportion of children that had UDS done with CKD is reported as a percentage along with a 95% CI. Groups (no CKD; CKD) were compared with respect to individual parameters using univariable tests (chi-squared test and Fisher's exact test). Crude odds ratios (ORs) were reported along with 95% CIs. The main statistics derived for parameters analysed in the multivariable logistic regression were adjusted ORs and 95% CIs.

Results

A total of 105 UDS reports of children aged 11 months to 17 years were analysed. Of these, 50% were female (52/105) and 74% had spina bifida (78/105). CKD was found in 23% of the participants. Female sex and VUR were found to have a statistically significant association with CKD (OR 3.09 and 3.71 and *p*-values 0.03 and 0.02, respectively). There was a statistically significant difference in the mean age and mean PBC between those with no CKD and those with CKD ($p = 0.03$ for both). The mean age for participants with no CKD was 8 years and 11 (10.6) years for those with CKD. The mean PBC for participants with no CKD was 82.04% and 59.71% for those with CKD.

Table II: Mean values of the continuous parameters
Mean GFR: 101.31 ml/min/1.73 m²

Parameter	Mean (±SD)	95% CI
Age	8.46 (4.39)	(7.60 : 9.31)
PBC	79.08 (41.67)	(71.01 : 87.14)
EFP	27.69 (19.62)	(23.89 : 31.48)
Comp	15.35 (20.25)	(11.43 : 19.27)
DLPP	33.55 (17.33)	(29.07 : 38.03)
GFR	**101.31 (56.20)**	(89.74 : 112.89)

SD – standard deviation, CI – confidence interval, PBC – percentage bladder capacity, EFP – end filling pressure, Comp – compliance, DLPP – detrusor leak point pressure, GFR – glomerular filtration rate

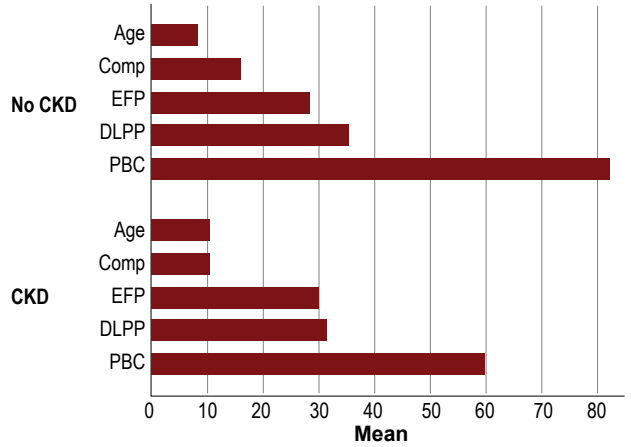

Figure 2: Comparison of GFR categories and continuous parameters. There was a significant difference in the mean PBC and mean age between those with no CKD compared with those with CKD ($p = 0.03$ for both). The mean age for participants with no CKD was 8 years and 11 (10.6) years for those with CKD. The mean PBC for participants with no CKD was 82.04% and 59.71% for those with CKD.
CKD – chronic kidney disease, Comp – compliance, EFP – end filling pressure, DLPP – detrusor leak point pressure, PBC – percentage bladder capacity

Parameter	CKD		No CKD		Odds ratio with 95% CI
	Yes	No	Yes	No	
PBC (Abn)	13	8	31	41	2.15 (0.79; 5.82)
EFP (Abn)	9	2	26	17	2.94 (0.57; 15.31)
Comp (Abn)	14	7	37	35	1.89 (0.68; 5.24)
DA (Abn)	6	15	33	39	0.47 (0.16; 1.36)
DLPP (Abn)	9	12	45	27	0.45 (0.17; 1.21)
VUR (Abn)	13	6	21	36	3.71 (1.23; 11.24)
Sex (Abn)	14	6	31	41	3.09 (1.06; 8.94)

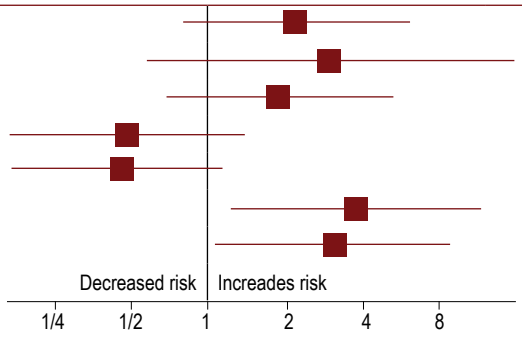

Figure 3: Association of CKD with the parameters. CKD was associated with VUR and female sex (OR 3.71 and 3.09 and *p*-values 0.02 and 0.03, respectively).
CKD – chronic kidney disease, PBC – percentage bladder capacity, EFP – end filling pressure, Comp – compliance, DA – detrusor activity, DLPP – detrusor leak point pressure, VUR – vesicoureteral reflux

The mean values for the continuous parameters are reported in Table II. The mean GFR was 101.31ml/min/1.73 m²

In the analysis of the mean DLPP, only the abnormal and severely abnormal values were included, no-leak results were not included, because when there is no leak, a DLPP value cannot be reported.

There was a significant difference in the mean PBC and mean age between those with no CKD compared with those with CKD (p = 0.03 for both). The mean age for participants with no CKD was 8 years and 11 (10.6) years for those with CKD. The mean PBC for participants with no CKD was 82.04% and 59.71% for those with CKD. Figure 2 compares the GFR of the continuous parameters in the two categories (no CKD and CKD).

CKD was associated with VUR and female sex (OR 3.71 and 3.09 and *p*-values 0.02 and 0.03, respectively) as illustrated in the forest plot (Figure 3).

The forest plot includes two sets of categories (normal/abnormal). EFP has three categories (normal/undetermined/abnormal), only the normal and abnormal categories were included. The undetermined category was not included; thus, the number of observations for EFP was 54 and not 93. No-leak was analysed as normal and abnormal and severely abnormal DLPP categories were grouped together as abnormal.

Discussion

This study showed CKD in 23% of the participants. This is consistent with the findings of the systematic review done by Veenboer et al. on the upper and lower urinary tract outcomes in adults with myelomeningocele, which showed 25% of patients had renal damage and 1.3% had ESRD.[5]

In the current study, VUR was significantly associated with CKD (OR 3.71, p = 0.02). In longitudinal studies, Mcguire et al.[9] and Galloway et al.[3] found that VUR was associated with increased risk of renal deterioration. The Galloway score includes VUR to assess bladder hostility, and was shown to have significant correlation with upper tract changes (p = 0.0001).[3]

Interestingly this study appears to be the first that found that female sex was significantly associated with CKD (OR 3.09, p = 0.03). This indicates a gap in similar studies and requires further investigation.

In this study, there was a significant difference in mean PBC between those with no CKD and those with CKD. The mean PBC for participants with no CKD was 82.04% (normal: 65–150%) and the PBC for participants with CKD was 59.71 (abnormal: < 65% or > 150%). This difference was statistically significant (p = 0.03). This indicated that participants with CKD were associated with low bladder capacity as this will result in a low PBC. The study findings of Arora et al. showed a low bladder capacity is a high-risk bladder that predisposes to renal injury.[21]

This study showed a statistically significant difference in the mean age between those with no CKD and those with CKD. The mean age for participants with no CKD was 8 years and 11 (10.6) years for those with CKD. It is noted that although the study population includes children from a wide age group (11 months to 17 years) the mean age group was 8.46 with an SD of 4.39. The mean age for children with CKD (10.6 years) falls within the mean age (±SD) for the study population; thus, the study findings can be interpreted as valid and reliable. Aora et al. demonstrated increasing age as a high-risk bladder that predisposes to renal injury in patients with myelodysplasia.[21]

Detrusor overactivity was not associated with CKD (OR 0.47). Although this was not statistically significant (p = 0.16), it is contrary to literature. Various authors have identified detrusor overactivity as a risk factor for upper tract deterioration and developing CKD.[3,5,6] The findings of the systematic review by Veenboer et al. showed detrusor overactivity as an adverse prognostic factor for the development of renal damage.[5] The current study's findings could be qualified by Galloway et al.'s reflection on the value of detrusor contractions in bladder hostility. Although detrusor overactivity is included in the five component Galloway hostility score, Galloway et al. report that the summation of the different components provides a synergistic effect greater than that of the individual components. Specifically, detrusor contractions (detrusor overactivity) on their own do not constitute a significant threat to the upper tract. Instead, Galloway et al. found that detrusor contractions are often associated with urinary leakage and the beneficial effect of bladder

emptying may offset the adverse effect on bladder pressure. They further suggested that detrusor contractility be excluded from the score because it does not add the discriminating power of the other four components.[3]

In this study, DLPP of 40 cm H_2O and above was not associated with CKD (OR 0.28). Although this finding was not statistically significant (p = 0.11), it is contrary to McGuire's pioneering work. This landmark study stated that patients with myelomeningocele and a DLPP > 40 cm H_2O were at risk of developing upper tract deterioration.[9,22] This cut-off has been traditionally accepted without a high level of evidence. Tarcan et al. reported that several of their patients with DLPPs of > 40 cm H_2O (followed over a long period) showed no deterioration in their upper tracts, while some individuals undergoing successful bladder augmentation required an artificial urinary sphincter, despite apparently good outlet resistance before surgery.[22] These authors suggested that absolute values of DLPP reported previously were unreliable because the technique lacked standardisation. The value of DLPP to predict upper urinary tract deterioration is not known precisely, and the measurement of DLPP lacks standardisation and carries pitfalls.[6,22] For example, although DLPP measurement has been recommended in neurological patients with reduced bladder compliance, some authors measure DLPP during involuntary detrusor contractions.[22] This was observed in the current study, as in some instances, DLPP were recorded

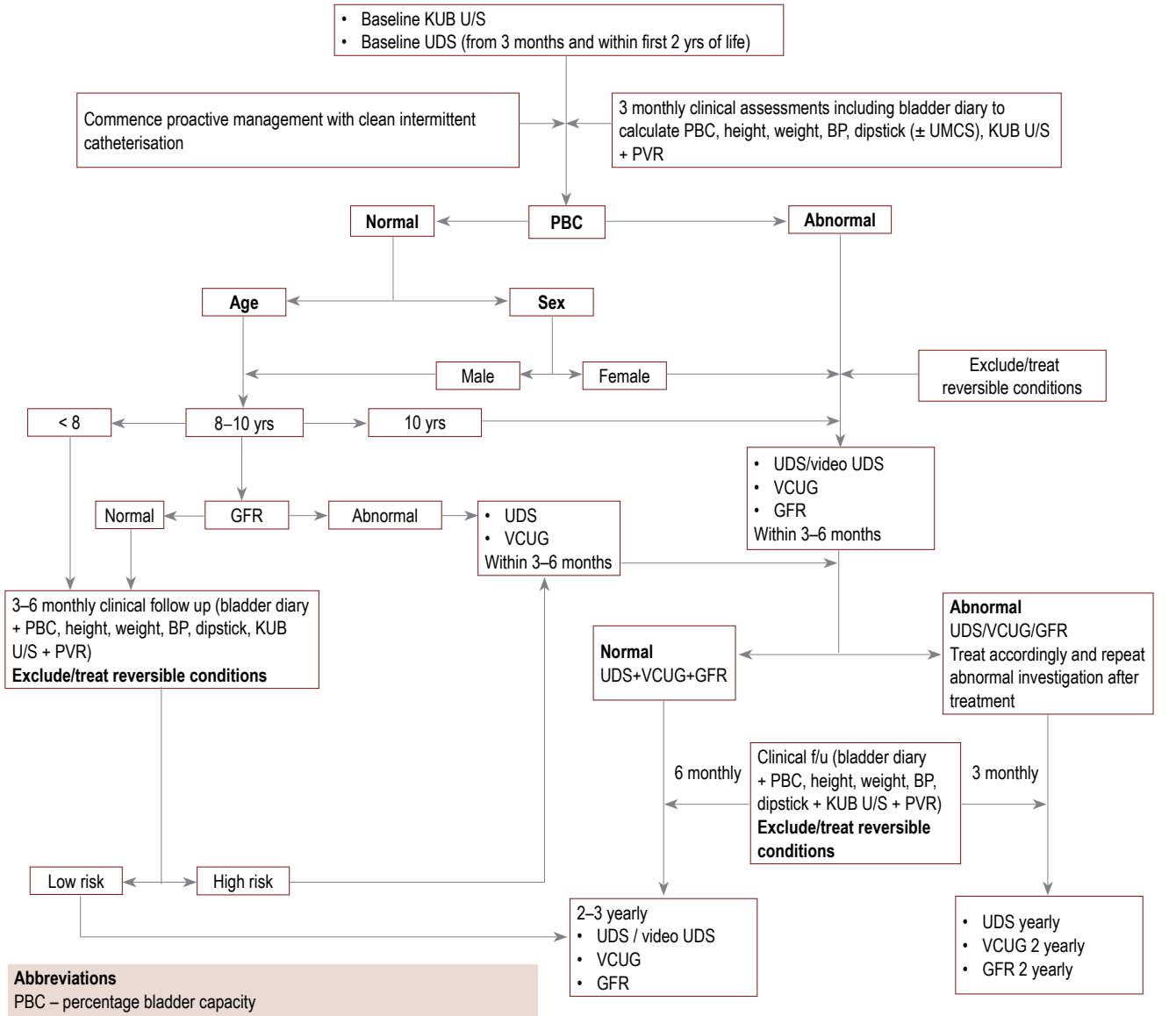

Figure 4: Morolo's PBC risk-based surveillance tool for patients with NLUTD

while the participant had an involuntary detrusor contraction. The ICS suggests that if leakage occurs with an episode of neurogenic detrusor overactivity (N-DO) any time during filling cystometry, this should be documented as N-DO LPP and not DLPP. [22] The (clinical) significance of N-DO LPP versus DLPP in NLUTD, however, has not been investigated.[22] Detrusor leak point pressure is not consistently defined throughout the literature.[6] This study's findings show that detrusor overactivity is not associated with CKD and, based on this, it is expected that participants with severely abnormal DLPP, which includes those with N-DO LPP, are also not associated with CKD.

A few limitations were noted. In particular, some of the recordings of DLPP were, in actual fact, N-DO LPP. In addition, multiple parameters were included in this study that involve different investigations (UDS, VCUG and GFR) and thus, not all the participants had all the parameters. Of the 105 participants included, 76 had all the parameters recorded. This may be related to non-standardised follow-up of patients or poor compliance to follow-up. Furthermore, only one data set of parameter per participant was collected, and as such, the study did not distinguish between congenital and acquired VUR (that developed as a consequence of NLUTD). It is worth mentioning that 22 participants were less than five years. Of these, eight had VUR, and in seven participants, no VCUG was retrieved. Notwithstanding this, VUR was found to be significantly associated with CKD in this patient population. Lastly, estimated GFR values were obtained using two different creatinine-based equations (Schwartz equation, Pottel equation) depending on the availability of height measurements. This may have impacted on the validity of the GFR values. It is recommended that all children have height measurements recorded in all their visits.

Monitoring of patients with NLUTD requires invasive investigations (UDS, VCUG and GFR). In this study, cystometric bladder capacity was used to calculate PBC, which is invasive. Maximum voided volume (MVV) measured on the frequency-volume-chart (FVC) is a non-invasive tool which is reflective of real-life, unlike the cystometric bladder capacity. This MVV is used to calculate the PBC.[12] Non-invasive assessments can become useful in guiding decisions for more invasive investigations to identify patients at risk of CKD.

Based on the findings, the investigator developed a risk-based surveillance tool to guide the long term monitoring of patients with NLUTD. This is a potential model for a standardised risk-based surveillance tool in SA with the intention to improve patient follow-up, compliance and ultimately enable upper urinary tract function preservation/improvement in these patients. In the context of SA with a structured healthcare system and limited resources (216 urologists registered in SA in 2022[23] serving a population of 60.14 million[24]), a surveillance tool that includes primarily non-invasive investigations is required to screen patients with NLUTD. This tool should stratify patients who can be monitored at primary healthcare facilities with fewer specialist visits from those who require frequent follow-up assessments with specialists at tertiary healthcare facilities. Patients can then be managed at a specific level of care depending on their risk(s), i.e. low-risk patients can be primarily managed at primary/secondary healthcare facilities with the tertiary hospitals spared for high-risk patients. In the current context of the coronavirus disease (COVID-19) pandemic and the ongoing potential risk of lockdowns, decreasing the patient burden of tertiary healthcare facilities and optimising the use of primary and secondary healthcare facilities has become even more pertinent.

Percentage bladder capacity, age and sex, which were statistically significant findings in this study, are non-invasive assessments (using MVV measured on FVC to calculate PBC) and can be determined in facilities at all levels of care. These can be used to screen patients with NLUTD to inform the individual patient's surveillance programme once the baseline assessment and investigations have been done. This will optimise the use of all levels of care and facilitate efficient utilisation of resources without compromising patient care. Morolo's PBC risk-based surveillance tool for patients with NLUTD is illustrated in Figure 4.[25]

Conclusion

Patients with NLUTD have an increased risk of upper tract deterioration with a CKD frequency of 23% in this study. In this study, VUR and female sex were associated with CKD in children with NLUTD. There is a gap in the literature on the association of female sex with CKD in the NLUTD population, which warrants further studies. Surveillance is critical in patients with NLUTD for upper urinary tract preservation/improvement and to reduce CKD. From the study findings, a risk-based surveillance tool was developed for patients with NLUTD that guides individualised investigations and optimises the use of all levels of care in SA. This tool could potentially be adapted and used in other countries. A longitudinal study is required to validate Morolo's PBC risk-based surveillance tool for patients with NLUTD.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethics approval from the Human Research Ethics Committees of the University of Pretoria (Ref. 617/2018) and the University of Cape Town (Ref. 793/2018).

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