Journal of Pediatric Urology (2023) **19**, 778.e1–778.e8

Supranormal differential renal function on MAG3 scan in children with ureteropelvic junction obstruction – Prevalence and pyeloplasty during follow-up

Sanni Värelä [a,b,*], Christoffer Jakobsson [a], Eva Persson [c], Anna Börjesson [a,d], Lars Hagander [a,d], Martin Salö [a,d]

[a]Department of Clinical Sciences, Pediatrics, Lund University, Lund, Sweden

[b]Department of Surgery, Skåne University Hospital, Malmö, Sweden

[c]Department of Clinical Physiology and Nuclear Medicine, Skåne University Hospital, Lund, Sweden

[d]Department of Pediatric Surgery, Skåne University Hospital, Lund, Sweden

* Correspondence to: Sanni Värelä, Lasarettgatan 40, Lund, 22145, Sweden, Tel.: +46736225940
sanni.varela@med.lu.se (S. Värelä)

Keywords
Hydronephrosis; Supranormal differential renal function; Pyeloplasty

Received 17 January 2023
Revised 31 July 2023
Accepted 8 August 2023
Available online 18 August 2023

Summary

Background
Children with suspected ureteropelvic junction obstruction (UPJO) may present with a paradoxical ipsilateral supranormal differential renal function (snDRF) on ^{99m}Technetium mercaptoacetyltriglycine scintigraphy (MAG3 scan).

Objective
The aim was to investigate the prevalence of snDRF, the risk of pyeloplasty among children with UPJO and snDRF, and to explore the experience of snDRF among international pediatric urologists.

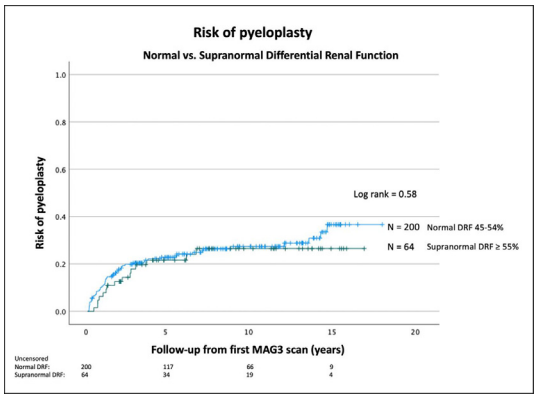
Methods
A retrospective cohort study of children with suspected unilateral UPJO who underwent MAG3 scan at four hospitals in Sweden between 2005 and 2020. SnDRF was defined as DRF ≥55%. Normal DRF was defined as DRF 45–54%. Primary outcome was risk of pyeloplasty. Indications for pyeloplasty were loss of >10%-points of differential renal function (DRF), ipsilateral DRF <40%, or symptomatic UPJO. Logistic and cox regressions were performed in univariate and multivariable analyses, adjusting for age, gender, year, laterality, antenatal hydronephrosis, anterior-posterior diameter (APD), and kidney size. An international questionnaire regarding the management of snDRF was developed and distributed to pediatric urologists.

Results
The prevalence of snDRF was 19%. SnDRF was more common in boys, children with antenatal hydronephrosis, children undergoing their first MAG3 scan at a younger age, and in the left kidney. After further exclusion of 70 children with DRF <45%, a total of 264 were included for longitudinal follow-up of median 6.6 (IQR 2.5–11.5) years. SnDRF was not associated with increased risk of pyeloplasty (adjusted OR 0.98 (95% CI 0.41–2.33), p = 0.96, and adjusted HR 1.00 (95% CI 0.53–1.91), p = 0.99) or time to pyeloplasty (1.1 years vs. 1.6 years, p = 0.40). Among the 79 surveyed pediatric urologists, a majority would not change clinical UPJO-management based on the presence or absence of ipsilateral snDRF.

Discussion
There are only a few studies considering the need of pyeloplasty based on the presence of snDRF and this is the first survey among pediatric urologists on its management. With more included patients than previous studies, this study showed a snDRF prevalence of 19%, congruent with the findings of others. The underlying cause of snDRF is debated, but it cannot solely be explained as an artifact of hydronephrotic kidneys. Further studies on the clinical implications of snDRF are warranted, since DRF influences the decision to operate.

Conclusion
A fifth of all children with suspected UPJO presented with ipsilateral snDRF on initial MAG3 scan, and snDRF was not associated with a greater risk of pyeloplasty. Supported by a large group of international pediatric urology colleagues, this study concludes that the same clinical follow-up and management apply, regardless of presence of snDRF.

https://doi.org/10.1016/j.jpurol.2023.08.006



Summary figure 1

Introduction

Ureteropelvic junction obstruction (UPJO) is considered the most common pathologic cause of congenital hydronephrosis, with an estimated prevalence of 1 in 750—1500 live births [1]. Apart from renal ultrasound (US), the diagnostic modality of choice for suspected UPJO is ^{99m}mtechnetium mercaptoacetyltriglycine scintigraphy (MAG3 scan), also known as renography. A MAG3 scan provides information about the drainage from the kidney and the differential renal function (DRF), by dynamic imaging of the kidneys and urinary tract [1,2]. Dismembered Anderson-Hynes pyeloplasty is the standard treatment for UPJO and indications often include pain, infection, DRF $<$40%, progressive anterior posterior diameter (APD), renal atrophy, and/or a $>$10%-points deterioration of DRF during follow-up [3—5].

Paradoxically, some children undergoing MAG3 scan for suspected UPJO present with a high DRF, or a supranormal DRF (snDRF), in the hydronephrotic kidney compared to the contralateral non-hydronephrotic side [6—8]. The threshold definition of snDRF varies in the literature, with definitions ranging from $>$50% to $\geq$55% on the ipsilateral side of UPJO. This contributes to a variation of reported prevalences of snDRF, ranging from 4 to 28% [7,9—11]. It is also debated whether the snDRF represent a true supranormal function or simply an artifact of the examination [7,8]. Further, the prognostic significance of snDRF remains unclear, since snDRF may decrease during follow-up and eventually lead to pyeloplasty [6]. Today there is no consensus on the prevalence of snDRF in these children, and to what extent the finding should affect clinical management and the risk of requiring or delaying pyeloplasty.

Consequently, the aim of this retrospective cohort study was to determine the prevalence of snDRF on MAG3 scan in children with suspected unilateral UPJO and determine the risk of pyeloplasty among these children. Our hypothesis was that snDRF is common and that it carries a higher risk of pyeloplasty compared to normal DRF. The aim was also to explore the experience among international pediatric urologists regarding the clinical management of children with supranormal DRF.

Material and methods

This study was approved by the Swedish Ethical Review Authority (DNR no 2021—02840).

Study design

This was a retrospective cohort study of data collected from a prospectively collected digital database of children who underwent a MAG3 scan between January 2005 and December 2020 at four pediatric hospitals in southern Sweden sharing the same electronical medical records platform. The study period was chosen to allow all included children at least two years of follow-up. In addition, an international digital survey was distributed among pediatric urologists between July 2022 and October 2022.

Inclusion and exclusion criteria

All patients under 15 years of age who underwent a MAG3 scan were included in the cohort study. Excluded from the study were patients with vesicoureteral reflux (VUR), bilateral hydronephrosis, single kidney, horseshoe kidney, duplex anomalies, distal ureteric obstruction, neurogenic bladder, multicystic kidney disease, as well as children without confirmed hydronephrosis on US or with missing data on MAG3 scans (Appendix Fig. 1). Patients with persistent ipsilateral DRF $<$45% were included in the evaluation of the prevalence of snDRF and were then excluded from follow-up analysis. All patients who met the inclusion criteria were included and no sample size calculation or power analysis were carried out.

Diagnostic imaging and follow-up

Over the 15-year study period, there were slight variations regarding timing of diagnostic modalities in the work-up protocols between pediatric nephrologist at different hospitals, but the decision to operate was consistently concentrated to just one pediatric surgical hospital. Gener-

ally, US was performed every year (stable APD) to every second year (decreasing APD or stable APD over two consecutive years). US scans were performed by pediatric radiologists or by radiologists specialized in ultrasonography. MAG3 was performed at the time of diagnosis and was followed by at least one repeat MAG3 scan. Postoperative MAG3 scans were performed at 3, and 12 months after pyeloplasty.

DRF was assessed by MAG3 scans interpreted by clinical physiologists using the same evaluation method at all four participating hospitals. All patients included in the study were followed longitudinally to detect deterioration of renal function on repeat MAG3 scans. DRF and presence of high-grade obstruction of the hydronephrotic kidney were collected from the result of MAG3 scans. To validate the DRF measurements, 10 randomly selected MAG3 scans with snDRF were reviewed by a clinical physiologist and MAG3 miscalculations were ruled out. Renal US data included in this study were collected from the US scans performed within six months and closest to the MAG3 scan of interest.

Exposure and independent variables

Study participants were categorized based on presence of snDRF in the hydronephrotic kidney at any MAG3 scan. SnDRF was defined as DRF $\geq$55% on any of the initial MAG3 scans and some patients with snDRF could therefore display normal or sub-normal DRF during follow-up and at the time of pyeloplasty. Independent variables and potential confounders were gender, age at the first MAG3-scan, year of first MAG3, laterality, prenatal hydronephrosis, median anterior posterior diameter (APD), and median kidney size on serial US.

Primary and secondary outcome

Primary outcome was pyeloplasty. The indications for pyeloplasty in patients included in this study were DRF impairment on MAG3 scan (>10%-points function loss during active follow-up, or ipsilateral DRF <40%) or symptomatic UPJO (e.g., pain or recurrent upper urinary tract infection). Isolated dilatation-increase on serial renal US, isolated large anterior posterior diameter (APD) measurements, or isolated obstructive drainage pattern on MAG3 scan without loss of function, were not considered sufficient independent indications for pyeloplasty but sometimes contributed to the decision to operate. Patients with UPJO requiring surgery underwent pyeloplasty at the pediatric urological tertiary center, one of the four participating hospitals. Follow-up time was from the first MAG3 scan, either to the day pyeloplasty was performed, the day the child turned 15 years, or to the day of medical chart review. Information whether patients underwent pyeloplasty after 15 years of age was not obtained. Secondary outcomes were loss of DRF >10%-points during follow-up and presence of symptoms during follow-up.

Statistics

Continuous data are presented as median (IQR; interquartile range) and categorical data as absolute numbers and percentages, n (%). To test for differences between quantitative data, two-tailed Mann–Whitney U-test was used. Chi-square test was used to test for differences in categorical data. Risk of pyeloplasty between exposures was presented in Kaplan Meier curves and differences were assessed with log-rank test, and with univariate and multivariable logistic and Cox regressions, presented as odds ratio (OR) and hazard ratios (HR) with 95% confidence intervals (95% CI). Sensitivity analyzes were performed for the logistic regression by using different cut-offs for snDRF. A p-value of <0.05 was considered significant. IBM SPSS Statistics for Mac Version 28 (IBM, Armonk, New York, USA) was used for all statistical analyzes.

Survey

The questionnaire was created by the authors based on clinical experience, and was further validated in consultation with a few pediatric urologists at our centre. An invitation to participate was handed out personally at two conferences in pediatric urology, or by email from a mailing list to pediatric urologists between June and October 2022. The questionnaire was created in RedCap, surveying the pediatric urologists' perception of snDRF, their level of experience, and clinical management of children with snDRF (link to online survey in Appendix). The answers were anonymous and directly entered to the online database of RedCap. A reminder was sent out to participants who had not responded a few weeks prior to closure of the survey. The survey did not allow comparison of characteristics between responders and non-responders.

Results

A total of 1180 children underwent a MAG3 scan between January 2005 and December 2020. After the exclusion of 846 patients, a total of 334 children remained (Appendix Figure A). The prevalence of snDRF was 19.2% and 76.6% of these children had the highest DRF on their initial MAG3 scan. Patient characteristics are listed in Table 1. Comparison between children with snDRF and normal or low DRF is presented in Appendix Table A. After further exclusion of 70 children with stable DRF <45%, a total of 264 were finally included for longitudinal follow-up (Appendix Figure A). The median follow-up time was 6.6 (IQR 2.5–11.5) years.

Compared to children with normal DRF, children with snDRF were more commonly male, younger at their first MAG3 scan, and had a higher rate of antenatal diagnosis of hydronephrosis, and more often a hydronephrotic left kidney. No differences were seen between the groups regarding kidney size or APD (Table 2).

Deterioration of DRF (10%-points or more) was more common during follow-up in patients with snDRF compared to children with normal DRF (14.1% vs 3.5%, p = 0.002). Overall, 23.4% (n = 15) of children with snDRF eventually underwent pyeloplasty, compared with 27.0% (n = 54) of children with a normal DRF (p = 0.57). There was no difference in time to pyeloplasty among children undergoing pyeloplasty between children presenting with snDRF versus normal DRF (1.1 years vs. 1.6 years, p = 0.40). A total of 77% (n = 49) children with snDRF did not undergo pyeloplasty, and one of these children had loss of renal function during follow-up. Of these 49 children, 78%

Table 1 Patient characteristics of 334 children who underwent MAG3 scan for suspected unilateral ureteropelvic junction obstruction.

	Total N = 334 (%)
Sex (boys)	230 (68.9)
Age at first MAG3 (years)	0.6 (0.2–5.6)
Antenatal hydronephrosis	211 (63.2)
Symptoms	
Infection	45 (13.5)
Pain	60 (18.0)
Both infection and pain	6 (1.8)
No symptoms	193 (57.7)
Missing	30 (9.0)
Laterality (right)	120 (35.9)
Pyeloplasty	116 (34.7)
APD on US (mm)	17 (10–25)
Kidney size on US (mm)	79 (68–95)
Supranormal DRF	64 (19.2)

Values presented as the absolute number and percentage of patients, n (%), and median (IQR; interquartile range); DRF: differential renal function.
APD: anteroposterior diameter; MAG3: Tc99m mercaptoacetyltriglycine.
US: ultrasound.

(n = 38) presented with snDRF on their initial MAG3 scan of which 34% normalized in DRF during follow-up. No differences were seen between groups regarding symptoms (Table 2).

The risk of pyeloplasty was first assessed using logistic regression. SnDRF was neither associated with increased risk of pyeloplasty in the crude (OR 0.83 (95% CI 0.43–1.60) p = 0.57), nor in the adjusted analysis (aOR 0.98 (95% CI 0.41–2.33), p = 0.96) (Appendix Table B). These results remained in the sensitivity analysis with different cut-offs for snDRF (Appendix Table C). The risk of a future pyeloplasty was decreased by antenatal hydronephrosis (aOR 0.23 (95% CI 0.08–0.66), p = 0.006) and increased by an elevated APD (aOR 1.12 per mm increase (95% CI 1.06–1.19), p < 0.001) (Appendix Table B). The risk of pyeloplasty was then assessed using survival analysis, and there was similarly no difference in the risk of pyeloplasty over time between children presenting with snDRF versus normal DRF (p = 0.58) (Fig. 1) (unadjusted HR 0.85 (95% CI 0.48–1.51), p = 0.58 and adjusted HR 1.00 (95% CI 0.53–1.91), p = 0.99) (Table 3). Among the children with snDRF who underwent pyeloplasty, 20% had persistent snDRF postoperatively and 80% had normalized DRF. Among the children with preoperative normal DRF, 12% increased to snDRF postoperatively. There was no difference in postoperative change in DRF between children with preoperative snDRF compared to children with preoperative normal DRF (1.7 vs. 2.8 percentage points of DRF (p = 0.09)).

The survey was distributed to 225 pediatric urologists from all over the world and 79/225 (35%) from 18 different countries participated. Their clinical experience in the field of pediatric urology was median 15.5 (IQR 6.5–25) years and they had performed a median of 125 (IQR 35–200) pyeloplasties in their career.

Table 2 Comparison of patients with ipsilateral normal and supranormal differential renal function (DRF) in 264 children who underwent MAG3 scan for unilateral ureteropelvic junction obstruction.

	Normal DRF (45–54%) N = 200	Supranormal DRF (≥55%) N = 64	p-value
Sex (boys)	132 (66.0)	54 (84.4)	**0.005**[b]
Age at first MAG3 (years)	0.7 (0.3–4.7)	0.3 (0.1–1.2)	**0.001**[a]
Antenatal hydronephrosis	130 (65.0)	49 (76.6)	**0.04**[b]
Laterality (right)	74 (37.0)	11 (17.2)	**0.003**[b]
Median APD on US (mm)	15 (10–23)	18 (13–24)	0.13[a]
Median kidney size on US (mm)	78 (65–90)	80 (70–95)	0.48[a]
Risk of pyeloplasty	54 (27.0%)	15 (23.4%)	0.57[b]
Time to pyeloplasty (years)	1.1 (0.4–3.4)	1.6 (0.7–2.9)	0.40[a]
Symptoms			0.62[b]
Infection	25 (12.5)	6 (9.4)	
Pain	32 (16.0)	6 (9.4)	
Both infection and pain	4 (2.0)	1 (1.6)	
No symptoms	124 (62.0)	45 (70.3)	
Missing	15 (7.5)	6 (9.4)	
≥10%-points deterioration on MAG3 scan	7 (3.5)	9 (14.1)	**0.002**[b]
Missing	95 (47.5)	17 (26.6)	
High-grade obstruction on MAG3 scan	30 (15.0)	14 (21.9)	0.20[b]
Missing	7 (3.5)	11 (17.1)	

Values presented as the absolute number and percentage of patients, n (%), and median (IQR; interquartile range). Bold means the p-value is significant (<0.05); APD: anteroposterior diameter, MAG3: Tc99m mercaptoacetyltriglycine, DRF: differential renal function, US: ultrasound.
Bold means the p-value is significant (<0.05).
[a] Mann-Whitney test.
[b] Chi-square test.

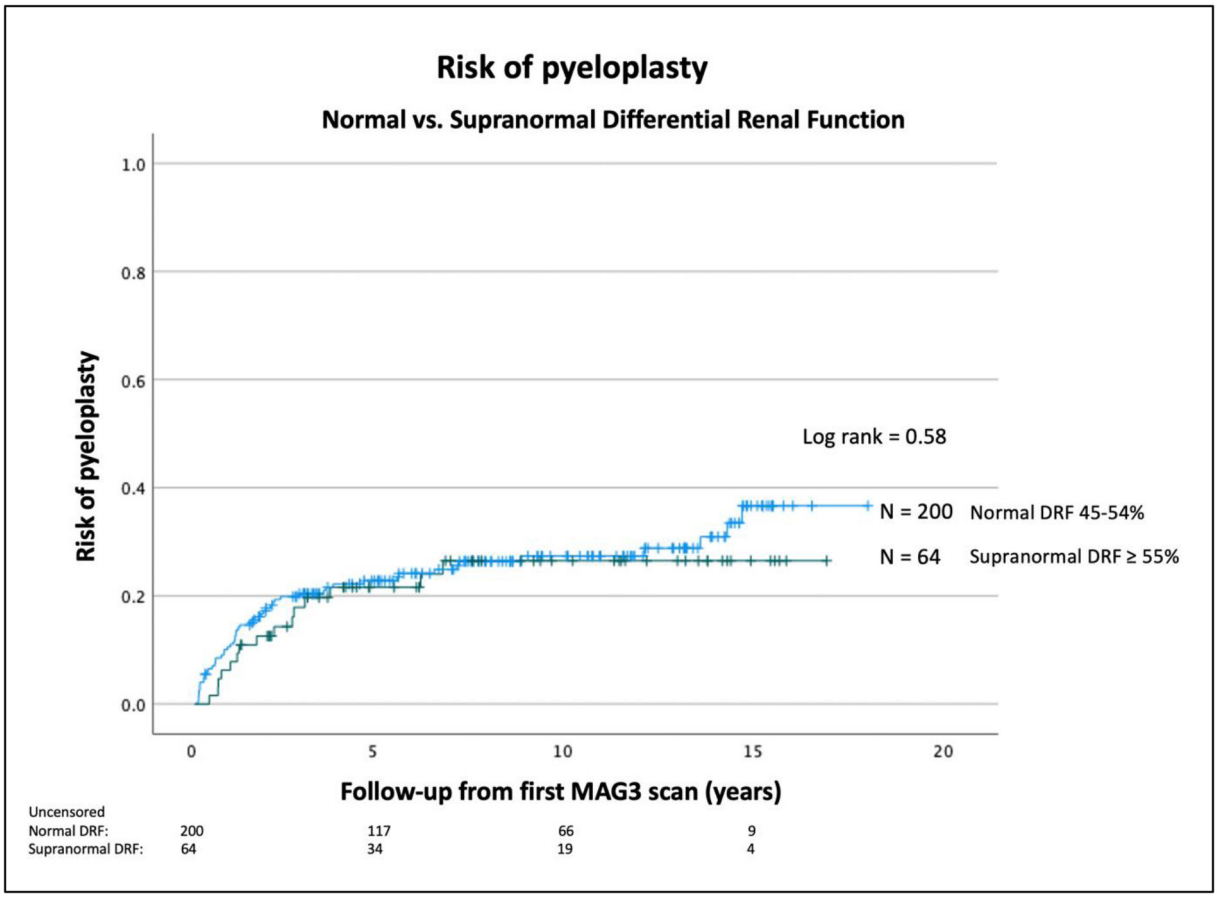


Fig. 1 Kaplan Meier curve with comparison of risk of pyeloplasty between children with normal and supranormal differential renal function on MAG3 scan. Log-rank test, p = 0.58; DRF: differential renal function; MAG3: Tc99m mercaptoacetyltriglycine.

DRF of 55% (IQR 55—58) or more on MAG3 scan was considered 'supranormal' in an ipsilateral hydronephrotic kidney, and 91% of the responders had experience of children presenting ipsilateral DRF ≥55% in the hydronephrotic kidney with suspected UPJO. Regarding the clinical follow-up, 25% found it to be more difficult to plan the follow-up if a child presented ipsilateral snDRF, and 19% would change the follow-up based on the presence of snDRF, mainly by planning a closer follow-up. The questionnaire included a case, where a 7-year-old asymptomatic child with suspected UPJO and unilateral hydronephrosis (APD 2 cm and SFU grade III) presented with snDRF. In this case, the responders would plan a follow-up MAG3 scan in median 6 (IQR 6—12) months. A total of 75% of the responders shared their thoughts of the possible underlying cause of snDRF in a hydronephrotic kidney with UPJO, presenting a variety of responses (Appendix Table D).

Discussion

In this study of 334 children who underwent MAG3 scan for suspected unilateral UPJO, the prevalence of supranormal DRF (snDRF) was 19%. The risk of future pyeloplasty did not statistically differ between children with snDRF compared to normal DRF on MAG3 scan, and neither did the timing of surgery. Patients with snDRF were more often male, generally younger, and had a higher rate of antenatal hydronephrosis; but did not have more severe hydronephrosis compared to patients with normal DRF. Children with snDRF had higher DRF at pyeloplasty compared to children with normal DRF.

The international survey performed in this study confirms that the current understanding of the clinical significance of a snDRF on MAG3 scan is open to discussion. While several studies have investigated the postoperative course of ipsilateral snDRF after pyeloplasty [6,9,12,13], there are few studies considering the need of pyeloplasty based on presence of snDRF. While this study does not specifically investigate the etiology of snDRF, our findings suggest a similar clinical course between children with normal DRF and children with snDRF, since there was no difference in risk of pyeloplasty, time to pyeloplasty, or in symptomatic presentation between the groups.

The definition of snDRF varies between different studies, resulting in variation of the prevalence between studies. With more included patients than previous similar studies, this study showed a prevalence of 19%, supporting the findings of Rickard et al. [9] using the same definition of snDRF (≥55%). We chose a relatively high percentage as definition of snDRF, given the margin of error of estimates due to factors affecting the calculations from a MAG3 scan [14,15]. Further adding to the ambiguity, other studies have

Table 3 Univariable and multivariable cox regression analysis for the risk of pyeloplasty over time among 264 children who underwent MAG3 scan for suspected ureteropelvic junction obstruction.

Risk of pyeloplasty over time				
	HR (95% CI)	p-value	aHR (95% CI) p-value	
SnDRF (Yes)	0.85 (0.48–1.51)	0.58	1.00 (0.53–1.91)	0.99
Sex (boys)	0.61 (0.38–1.00)	0.05	1.66 (0.91–3.02)	0.10
Age at first MAG3 (years)	1.02 (1.00–1.03)	**0.04**	1.00 (0.97–1.04)	0.97
Year of first MAG3	1.03 (0.98–1.08)	0.33	1.11 (1.04–1.18)	**0.002**
Antenatal hydronephrosis	0.28 (0.17–0.45)	**<0.001**	0.33 (0.18–0.61)	**<0.001**
Laterality (right)	0.92 (0.56–1.52)	0.74	1.32 (0.71–2.45)	0.39
Median APD on US (mm)	1.07 (1.05–1.10)	**<0.001**	1.08 (1.05–1.12)	**<0.001**
Median kidney size on US (mm)	1.04 (1.03–1.06)	**<0.001**	1.02 (1.00–1.04)	**0.04**

aHR: adjusted hazard ratio, CI: Confidence interval; SnDRF: supranormal differential renal function.
MAG3: Tc99m MAG3: mercaptoacetyltriglycine; APD: anteroposterior diameter.
US: ultrasound; HR: hazards ratio; CI: confidence interval.
Bold means the p-value is significant (<0.05).

proposed that a snDRF in neonates and young children might in fact be much less prevalent than reported due to age-related variation and limitations in radiologic techniques [16].

The underlying cause of snDRF is debated, whether it is a true supranormal function or a technical artifact, e.g. due to a more hydronephrotic kidney [17,18]. Gluckman et al. [11] conclude that snDRF in most cases is caused by a technical problem and Inanir et al. [7] propose it is at least in part technical in origin. Further, Maenhout et al. [18] state that snDRF is related to borderline hypofunctioning of the contralateral kidney. On the contrary, several studies conclude that snDRF is a true hyperfunction of the kidney [8,19], demonstrating a relationship between degree of hydronephrosis, APD, and snDRF, which may be partially explained by volume asymmetry, according to Sanavi et al. [17]. This was further explored in an experimental study by Pippi Salle et al. where experimental findings lend evidence to that artifactual snDRF observed during MAG3 scans of large hydronephrotic kidneys actually exist [20]. Our results indicate that snDRF does not represent an artifact of a large hydronephrotic kidney, since we did not find an association between snDRF and APD or kidney size. We conclude that snDRF is a complex multifactorial phenomenon.

All things considered, 25% of the responders thought it was more difficult to plan the clinical follow-up if ipsilateral snDRF was present. Our retrospective study showed no clinically significant difference in risk of pyeloplasty, symptomatic presentation, presence of high-grade obstruction or time to pyeloplasty between groups. These findings suggest that patients with snDRF do not significantly differ regarding future risk of pyeloplasty or clinical presentation compared to patients with normal DRF. On the contrary, deterioration of 10%-points or more in DRF was noted more often in patients with snDRF. Deterioration of >10%-points in DRF on serial MAG3 in children with snDRF has been an indication for pyeloplasty in our institution and thus for the patients included in our study. Today we do not know the natural history of snDRF, and we lack knowledge of the true explanation of snDRF. However, if snDRF turns out to be an actual artifact or that snDRF rather normalize than deteriorate below 40%, this could imply that patients with initial snDRF and subsequent apparent deterioration of DRF risk undergoing pyeloplasty unnecessarily, without a true deterioration of DRF and that a decrease of >10%-points of DRF therefore no longer should be considered an indication for surgery among these patients. In addition, snDRF was more common in younger patients and usually detected solely on the initial MAG3. Patients with snDRF who were treated conservatively resolved in DRF in 34% of the cases. There is a possibility that snDRF is an unspecific finding in younger children and that clinicians may disregard snDRF in young children who present with this finding on the initial MAG3 scan.

Normalization of snDRF without pyeloplasty has previously been shown to a higher degree in younger patients [6,21,22]. This is in line with the results of our study, where younger age and antenatal hydronephrosis were associated with snDRF and where snDRF itself did not indicate an increased risk of pyeloplasty. There was no difference in postoperative change in DRF between children with snDRF and normal DRF, indicating a similar postoperative result between the two groups, with normalization of DRF.

Decision-making for pyeloplasty cannot solely be based on DRF on MAG3 scan and more research is warranted, to divulge the true cause and significance of ipsilateral snDRF. We would not recommend to routinely perform a DMSA, because of additional radiation and because it does not provide dynamic information on the drainage from the kidneys. Yücel et al. [23] added a new perspective when they recently found that urinary biomarkers could identify the need for pyeloplasty in patients with snDRF, before deterioration of renal function. It is plausible that the results of this study would have been improved by a prospective study design, or by limiting the age of patient presentation or standardizing the follow-up period. It would be interesting to study if it is necessary to operate on children with snDRF based on subsequent 10%-point loss of DRF. Does the DRF remain normal, or does it continue to deteriorate in these children? We would welcome a future study investigating the possibility to disregard this indication of pyeloplasty among children with snDRF. This study is focusing on the interpretation of snDRF in clinical practice, and does not evaluate the methodology of a MAG3 scans per

se. However, there is always an intra- and intervariability during the evaluation of MAG3 and there are several technical artifacts that may cause snDRF, such as activity in the liver or spleen, movement during the image acquisition, delineation of background region of interest (ROI), or incorrect calculation of DRF. Consequently, we believe that deterioration of snDRF to normal DRF can be accepted and without being an indication for pyeloplasty, unless it is accompanied by another existing indication. Further, the DRF must always be interpreted together with the drainage curve, and with the degree of dilatation on ultrasound. To conclude, our recommendation is that the same clinical follow-up and management apply, regardless of presence of snDRF. Our recommendation is to not operate children with snDRF solely based on deterioration of 10%-points during follow-up, if DRF stays normal, the child is asymptomatic and if APD remains stable on US.

A limitation of this study is its retrospective design. Furthermore, since the US scans included in this study were performed within 6 months of the MAG3 scan of interest, differences could possibly have been found if all US scans were performed at the time of the MAG3 scan of interest. Moreover, investigations and diagnostics were performed at different years of age and stages of disease, including children with different etiology of the disease. However, we tried to adjust for this by the inclusion of age and year of MAG3 scan in the multivariable analysis and by performing a cox-regression. In addition, a few MAG3 scans were reviewed and validated, without detecting any miscalculation. The variable snDRF was dichotomized as children were categorized as either of normal or supranormal renal function, thereby not taking the full degree of snDRF into account, and hence possibly somewhat reducing the statistical power. A possible difference might have been found if another definition of snDRF had been used, but the adjusted sensitivity analyzes did not show any difference when using $>$53% as a cut-off. Our definition was based on most previous studies, also using the cut-off value of DRF $\geq$55%.

Responders were required to estimate percentages in the questionnaire, and it might have been difficult to know the percentage of patients presenting DRF $\geq$55%, without checking their own data. There is always a risk of response bias since it was not possible to compare characteristics of responders to non-responders. It is challenging to isolate and investigate the clinical management of patients with snDRF in the format of a questionnaire, since there are multiple factors other than DRF affecting the decision of surgery. In addition, indications for pyeloplasty may vary between centers. We conclude that snDRF is an intriguing phenomenon and that there is a need of prospective studies to come closer to the clinical significance of snDRF.

Conclusion

One out of five children with suspected UPJO present with ipsilateral supranormal DRF (snDRF) on MAG3 scan. Pediatric urologists usually consider a DRF of 55% or more to be 'supranormal'. Presence of snDRF was not associated with increased risk of pyeloplasty or time to pyeloplasty. The explanation behind snDRF is still not fully understood but it cannot solely be explained as an artifact of hydronephrotic kidneys. Supported by a large group of international pediatric urology colleagues, this study concludes that the same clinical follow-up and management apply, regardless of presence of snDRF.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

References

[1] Hashim H, Woodhouse CR. Ureteropelvic junction obstruction. Eur Urol Suppl 2012;11(2):25—32.
[2] Bubeck B, Brandau W, Weber E, Kälble T, Parekh N, Georgi P. Pharmacokinetics of technetium-99m-MAG3 in humans. J Nucl Med 1990;31(8):1285—93.
[3] Lowe FC, Marshall FF. Ureteropelvic junction obstruction in adults. Urology 1984;23(4):331—5.
[4] Wang Y, Puri P, Hassan J, Miyakita H, Reen D. Abnormal innervation and altered nerve growth factor messenger ribonucleic acid expression in ureteropelvic junction obstruction. J Urol 1995;154(2):679—83.
[5] Maizels M, Stephens F. Valves of the ureter as a cause of primary obstruction of the ureter: anatomic, embryologic and clinical aspects. J Urol 1980;123(5):742—7.
[6] Cho SY, Kim IS, Lee S-B, Choi H, Park K. Nature and fate of supranormal differential renal function: lessons from long-term follow-up after pyeloplasty. Urology 2013;81(1):163—7.
[7] Inanir S, Biyikli N, Noshari O, Caliskan B, Tugtepe H, Erdil TY, et al. Contradictory supranormal function in hydronephrotic kidneys: fact or artifact on pediatric MAG-3 renal scans? Clin Nucl Med 2005;30(2):91—6.
[8] Martín-Solé O, Soria-Gondek A, Pérez-Bertólez S, Paredes P, Tarrado X, García-Aparicio L. Value of supranormal function on 99mTc-mercaptoacetyltriglycine renal scan in paediatric patients with obstructive hydronephrosis. BJU Int 2019;124(5):842—8.
[9] Rickard M, Braga LH, Gandhi S, Oliveria J-P, Demaria J, Lorenzo AJ. Comparative outcome analysis of children who underwent pyeloplasty for ureteropelvic junction obstruction associated with or without supranormal differential renal function. Urology 2017;99:210—4.
[10] Capolicchio G, Jednak R, Dinh L, Pippi Salle JL, Brzezinski A, Houle A-M. Supranormal renographic differential renal function in congenital hydronephrosis: fact, not artifact. J Urol 1999;161(4):1290—4.
[11] Gluckman GR, Baskin LS, Bogaert GA, Mevorach RA, Hattner RS, Kogan BA. Contradictory renal function measured with mercaptoacetyltriglycine diuretic renography in unilateral hydronephrosis. J Urol 1995;154(4):1486—90.
[12] Nordenström J, Koutozi G, Holmdahl G, Abrahamsson K, Sixt R, Sjöström S. Changes in differential renal function after pyeloplasty in infants and children. J Pediatr Urol 2020;16(3):329.
[13] Song C, Park H, Park S, Moon KH, Kim KS. The change in renal function in the supranormal hydronephrotic kidney after pyeloplasty. BJU Int 2007;99(6):1483—6.

[14] Nykanen AO, Rautio PJ, Aarnio JV, Heikkinen JO. Multicenter evaluation of renography with an automated physical phantom. Nucl Med Commun 2014;35(9):977—84.
[15] Brolin G, Edenbrandt L, Granerus G, Olsson A, Afzelius D, Gustafsson A, et al. The accuracy of quantitative parameters in (99m) Tc-MAG3 dynamic renography: a national audit based on virtual image data. Clin Physiol Funct Imag 2016;36(2):146—54.
[16] Ozcan Z, Anderson PJ, Gordon I. Robustness of estimation of differential renal function in infants and children with unilateral prenatal diagnosis of a hydronephrotic kidney on dynamic renography: how real is the supranormal kidney? Eur J Nucl Med Mol Imag 2006;33(6):738—44.
[17] Sanavi C, Dacher JN, Caudron J, Dolores M, Liard A, Vivier PH. Supranormal differential renal function in unilateral hydronephrotic kidney: insights from functional MR urography. J Magn Reson Imag 2014;40(3):577—82.
[18] Maenhout A, Ham H, Ismaili K, Hall M, Dierckx R, Piepsz A. Supranormal renal function in unilateral hydronephrosis: does it represent true hyperfunction? Pediatr Nephrol 2005;20(12):1762—5.
[19] Oh S-J, Moon DH, Kang W, Park YS, Park T, Kim KS. Supranormal differential renal function is real but may be pathological: assessment by 99mtechnetium mercaptoacetyltriglycine renal scan of congenital unilateral hydronephrosis. J Urol 2001;165(6 Part 2):2300—4.
[20] Pippi Salle JL, Cook A, Papanikolaou F, Bagli D, Breen SL, Charron M, et al. The importance of obtaining conjugate views on renographic evaluation of large hydronephrotic kidneys: an in vitro and ex vivo analysis. J Urol 2008;180(4):1559—65.
[21] Dowling KJ, Harmon EP, Ortenberg J, Polanco E, Evans BB. Ureteropelvic junction obstruction: the effect of pyeloplasty on renal function. J Urol 1988;140(5):1227—30.
[22] Tapia J, Gonzalez R. Pyeloplasty improves renal function and somatic growth in children with ureteropelvic junction obstruction. J Urol 1995;154(1):218—22.
[23] Yücel ÖB, Dönmez M, Küçükgergin C, Ziylan O, Seçkin Ş, Oktar T. Urinary biomarkers can identify the need for pyeloplasty in presence of supranormal differential renal function in antenatally diagnosed unilateral hydronephrosis. J Pediatr Urol 2022 Feb;18(1):6—12.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2023.08.006.