Original Article

Semiquantitative analysis of power doppler ultrasonography versus Tc-99m DMSA scintigraphy in diagnostic and severity assessment of acute childhood pyelonephritis

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Background: This study aimed to compare the diagnostic and predictive value of power Doppler ultrasonography (PDU) with Tc-99m dimercaptosuccinic acid (DMSA) renal scintigraphy in pediatric acute pyelonephritis (APN) using a semiquantitative analysis system.

Methods: A total of 92 children and infants (184 kidneys) were hospitalized with possible APN. All children were examined by PDU and DMSA scintigraphy within 72 hours of admission. An empiric 9-point semiquantitative analysis system was used to sort kidneys into four grades (grade 0–III). Patients with several episodes of APN and congenital structural anomalies were excluded.

Results: Of 184 kidneys, we found 68 abnormal (grade I–III) and 116 normal (Grade 0) with DMSA scintigraphy, and 84 abnormal and 100 normal with PDU. In all, 23 kidneys were shown to be diseased by PDU but normal on DMSA scintigraphy while 7 kidneys showed the opposite trend. The sensitivity and specificity of PDU for diagnosing APN was 89.7% and 80.2%, respectively ($P<0.05$). In children older than 6 months, the sensitivity was higher (92%, $P<0.05$) than that in children younger than 6 months (87%, $P<0.05$). A moderate agreement (41%, $P<0.05$) on grade was found between the two methods.

Conclusions: With the help of a semiquantitative analysis system, PDU can obviate the use of DMSA scintigraphy in children older than 6 months for APN diagnosis.

Keywords: Power Doppler ultrasonography (PDU); Tc-99m dimercaptosuccinic acid renal scintigraphy (Tc-99m DMSA renal scintigraphy); acute pyelonephritis (APN); semiquantitative analysis system

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Introduction

Febrile urinary tract infection (UTI) is the second most common infectious disease in infants and children and the most common disease in children under the age of two (1). About 50–90% children with febrile UTI have renal parenchyma involvement which indicates acute pyelonephritis (APN). Without prompt diagnosis and treatment, 40–60% of children with this condition will develop permanent renal scarring with sequelae of hypertension and renal failure (2). The diagnosis of APN is initially made through urinalysis and the presence of clinical symptoms, which makes it hard to differentiate it from lower UTI (3). Therefore, a fast and accurate diagnosis is required.

According to the literature, Tc-99m dimercaptosuccinic acid (DMSA) renal scintigraphy is the most reliable diagnostic tool for suspected APN, and it is able to evaluate the degree of renal parenchymal involvement (4-6). However, DMSA scintigraphy has the disadvantages of ionizing radiation exposure, invasiveness, and relatively high cost, rendering it unappealing to children and parents (7). The recent development of power Doppler ultrasonography (PDU) shows encouraging results in diagnosing APN, with a reported accuracy of 89% (7-10). With additional advantages of being radiation-free, convenient, and low cost, PDU may be a new tool in APN diagnosis (7-10). However, experiments in clinic and on piglet models revealed the lower accuracy of PDU compared with DMSA scintigraphy (11-13).

Thus, the purpose of this study was to assess the diagnostic and predictive value of PDU for APN in children, with the help of a new semiquantitative system, and to determine whether PDU may supersede Tc-99m DMSA in renal scintigraphy.

We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/tp-20-59).

Methods

Clinical and biologic findings

From December 2016 to April 2017, we evaluated 92 infants and children (36 girls and 56 boys; aged 36 days to 10 years; mean age 18.0±2.8 months) who were admitted to the Pediatric Nephrology Department with potential APN. The retrospective trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of The Second Affiliated Hospital of Wenzhou Medical University (No. L-2019-08), and informed consent was given by all the patients and/or their guardians. The inclusion criteria were as follows: (I) age between 1 week and 16 years (inclusive); (II) clinical diagnosis of APN including (i) fever >38.5 ℃ or localized symptoms of APN, (ii) pyuria or a positive urine culture (>10 white blood cells per cubic millimeter and bacteriuria to the extent of 10^4 colony-forming units per milliliter) (14,15); (III) children and parents' consent to accept both PDU and Tc-99m DMSA renal scintigraphy. Exclusion criteria included several previous episodes of APN and congenital structural anomalies of the urinary system. All children underwent a standardized clinical examination including abdominal and lumbar fossa palpation, temperature and blood pressure measurement, standardized blood studies including C-reactive protein (CRP), differential blood count, iconography, renal function, and liver function analysis. A midstream urine sample was taken for N-acetylglucosaminidase (NAG), β2-microglobulin (β2-MG), dipstick analysis, and culturing. Clinical examination results, urine samples and blood samples were collected on admission before commencing usual intravenous antibiotic treatment, and PDU and Tc-99m DMSA renal scintigraphy were performed within 72 hours of admission. Young, uncooperative patients were duly sedated before examination.

DMSA

Tc-99m DMSA renal scintigraphy was performed using the standard protocol (16). In brief, a dose of 3.7 MBq/kg (0.1 mCi/kg) Tc-99m DMSA was intravenously injected, and 2–4 h later, images were obtained in the planar anterior, posterior, and right and left posterior oblique using an Orbiter Siemens gamma camera with a low-energy high-resolution parallel-hole collimator. Images were obtained for 300,000–500,000 counts on a 256×256 matrix format. International Radionuclide Nephrourology Group (IRN) consensus criteria were used for interpretation of DMSA scintigraphy results. To standardize the interpretation, an empiric 9-point semiquantitative analysis that evaluated the lesion size and radioactivity of each kidney was performed. The kidneys were divided into three zones (the upper pole, midzone, and lower pole), and the radioactive uptake of each zone was scored from 0 (no uptake) to 3 (normal uptake). The sum of the zone scores was considered the total score of each kidney. An 8–9 score was considered grade 0 (normal), a 6–7 score was considered grade I (mildly abnormal), a 4–5 score was considered grade II (moderately abnormal), and a 0–3 score was considered grade III (severely abnormal) (17,18).

Two expert senior physicians who were blinded to the other examination results and clinical information analyzed all the images. If disagreements occurred, a final diagnosis was made after discussion.

PDU

Grey-scale ultrasonography and PDU were performed using the Esaote MyLab Class C with variable-frequency

Table 1 Comparative results of Tc-99m DMSA scintigraphy and power Doppler sonography in 184 kidneys

Tc-99m DMSA Scintigraphy (kidneys)	Grade 0	Grade I	Grade II	Grade III	Total
Grade 0	93	13	8	2	116
Grade I	3	11	5	8	27
Grade II	4	12	7	2	25
Grade III	0	6	2	8	16
Total	100	42	22	20	184

DMSA, dimercaptosuccinic acid; Grade 0, normal; Grade I–III, abnormal.

(2.5–4.0 MHz) curved transducers in prone and supine positions for both axial and longitudinal scans. Grey-scale ultrasonography of the kidneys was performed to exclude structural urinary tract anomalies and to evaluate size, echogenicity, and stasis. The parameters of PDU were individualized for each kidney in every patient for the optimized visualization of the parenchymal perfusion map. To standardize the interpretation, the same 9-point semiquantitative analysis was performed. Briefly, each kidney was divided into three zones, and the perfusion of each zone was scored from 0 (no perfusion) to 3 (normal perfusion). A grade 0, I, II, or III was determined by a total score of 8–9, 6–7, 4–5, and 0–3 in each kidney, respectively. Grade 0 indicated a normal kidney, and grades I–III indicated the respective degrees of abnormality.

Two expert senior physicians who were blinded to the results of the other imaging examinations and clinical information analyzed all the images. If disagreements occurred, a final diagnosis was made after discussion. To compare the scintigraphic and sonographic images, the grades of each kidney were evaluated.

Statistics

Statistical analysis was performed on all 92 children comprising 184 kidneys. Inter-rater agreement between PDU and DMSA scintigraphy was assessed by calculation of the kappa coefficient (Ko) and with the χ^2 test using SPSS 19.0 software. Based on Ko values, the strength of agreement was classified as very good (81–100%), good (61–80%), moderate (41–60%), fair (21–40%), and poor (<20%) (8). The diagnostic values (sensitivity, specificity, predictive values, and accuracy) of PDU were assessed with contingency tables. A P value ≤0.05 was considered significant.

Results

Comparison of characteristics and biologic findings in children

All 92 children met the diagnostic criteria of febrile APN. Among them, 52 (56.5%) were abnormal (grade I–III) on DMSA scintigraphy, and 58 (63.0%) were abnormal on PDU. Based on urine analysis, 83 patients (90.2%) had increased neutrophil esterase in urine, 30 patients (32.6%) had positive urinary nitrite, 24 patients (26.1%) had elevated urine NAG, and 19 patients (20.7%) had increased urine β2-MG. Blood analysis revealed high CRP (≥20 mg/L) and elevated white blood cell count in 76 (82.6%) and 79 patients (85.9%) respectively. None of the patients had abnormal renal function, albumin, or blood electrolytes. Urinary grey-scale ultrasonography revealed renal cortical echo changes in 5 patients (5.4%), kidney enlargement in 33 patients (35.9%), and kidney atrophy in 2 patients (2.2%). The positive rate of grey-scale ultrasonography was 40.2%.

Semiquantitative analysis of PDU and DMSA and their comparison

PDU and DMSA scintigraphy were performed successfully on all 184 kidneys. In all, 68 kidneys appeared abnormal on DMSA scintigraphy, of which 61 showed the same on PDU (*Table 1*, *Figures 1*,*2*). Meanwhile, 116 kidneys presented normal (grade 0) on DMSA scintigraphy, and 93 of them appeared the same on PDU. Thus, PDU showed a sensitivity of 89.7%, a specificity of 80.2%, and an accuracy of 83.7% (P<0.05). Positive and negative predictive values of PDU were 72.6% and 93.0% respectively (P<0.05).

To determine whether the grade detected by PDU accorded with DMSA scintigraphy, we ran a Ko analysis

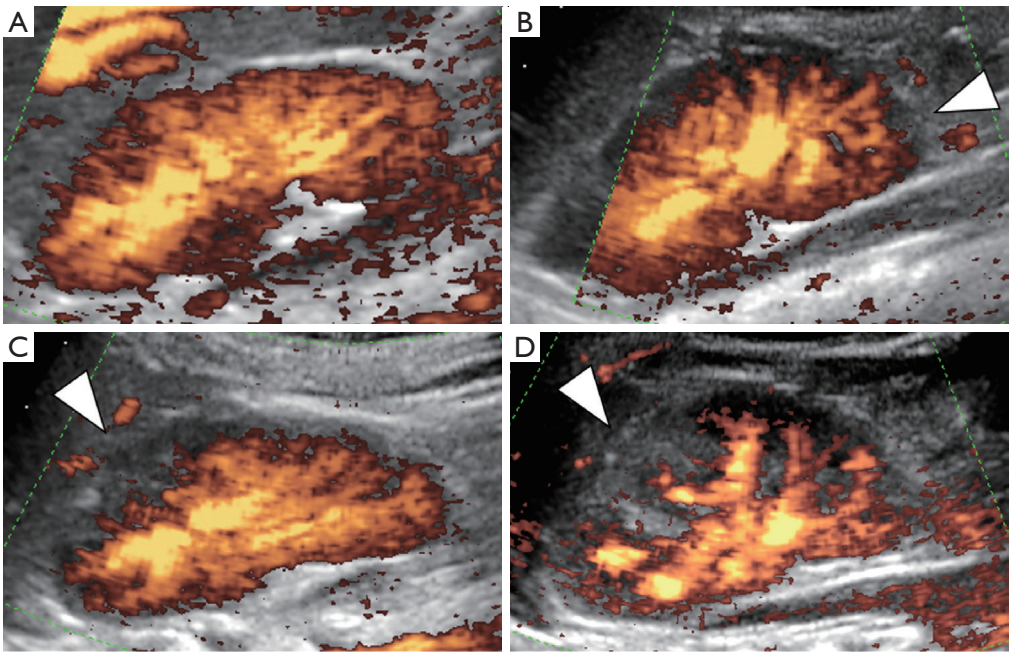

Figure 1 Examples for different scores in kidney zones for PDU in children. (A) A PDU score of 3 in the upper pole, midzone, and lower pole in a 7-month-old boy's right kidney; the grade of this kidney was 0. (B) A PDU score of 2 in the lower pole of a 9-month-old boy's left kidney; the grade of this kidney was 0, as no other hypoperfusion lesion was found. (C) Scores of 1, 3, and 2 in the upper pole, midzone and lower pole of right kidney, respectively, were detected in a 2-year-old girl; the grade of this kidney was I. (D) Scores of 0, 1, and 1 were measured in the upper pole, midzone, lower pole of a 2-year-old boy's left kidney in sequence; the grade of this kidney was III. Obvious hypoperfusion lesions are marked with triangles.

which uncovered a moderate strength of agreement (41%, P<0.05).

Semiquantitative analysis of PDU and DMSA with different age

Children were divided into two groups: under 6 months (inclusive, group 1) and over 6 months (group 2), with 102 and 82 kidneys in each group respectively (*Table 2*). In group 1, 58 kidneys appeared normal on both PDU and DMSA scintigraphy while 27 kidneys appeared abnormal. In group 2, 35 kidneys revealed normal while 34 revealed abnormal on both DMSA scan and PDU detection. Thus, the sensitivity, specificity, accuracy, and positive and negative predictive values were 87.1%, 81.7%, 83.3%, 67.5%, and 93.5% for group 1 (P<0.05), and 91.9%, 77.8%, 84.1%, 77.3%, and 92.1% for group 2 (P<0.05).

To determine whether the consistency of grade was related to age, Ko analysis was conducted, with the results showing a fair strength of agreement between PDU and DMSA scintigraphy for group 1 (38%, P<0.05) and a moderate one for group 2 (43%, P<0.05).

Discussion

APN is an infection involving the renal parenchyma and is considered to be one of the most serious bacterial illnesses of childhood. About 40–60% of APN children will develop renal scarring and a possible long-term morbidity of hypertension and renal failure (2,3). The clinical diagnosis of APN is mainly based on symptoms, signs, and laboratory results. However, the symptoms are often vague and influenced by the child's age, inflammatory immune response, and the virulence of the organism (3). In very young infants (<2–3 months), there can be non-specific symptoms (slow weight gain, drowsiness etc.) which further confound diagnosis. Children with ambiguous symptoms have been reported to be at higher risk of complications, such as sepsis and meningitis (3). These facts emphasize the importance of rapid and accurate diagnosis of APN.

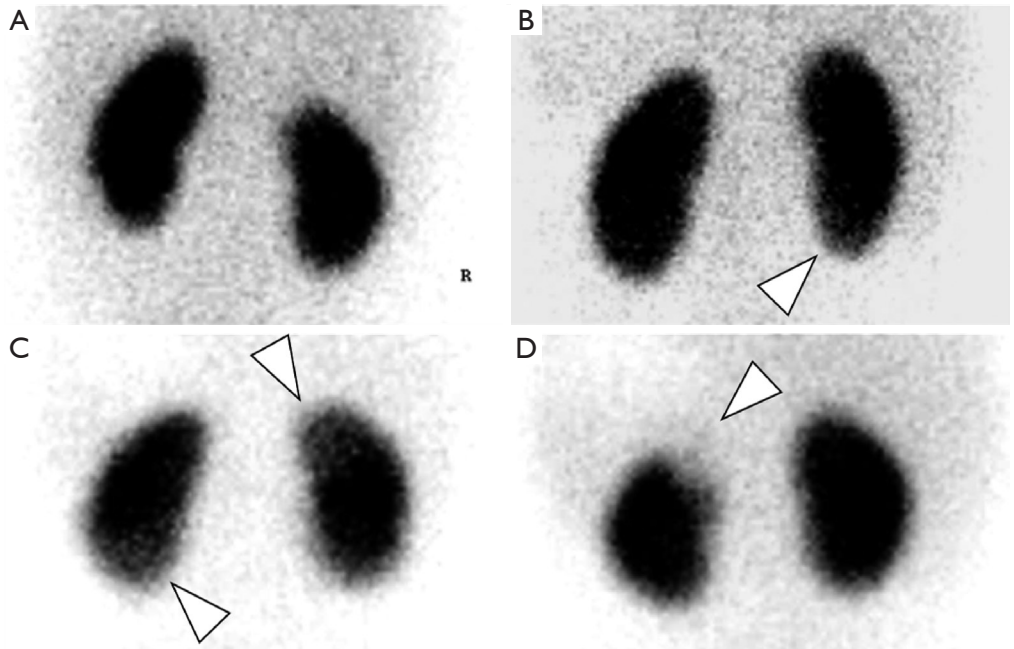

Figure 2 Examples of different scores in kidney zones on Tc-99m DMSA scintigraphy in children (posterior view). (A) An 8-year-old girl with a score of 3 in each kidney zone as revealed by DMSA scintigraphy; the grade for both kidneys was 0. (B) A score of 2 was found in the lower pole of left kidney in a 5-month-old boy with a score of 3 in the other zones; the grade for both kidneys was 0. (C) DMSA scintigraphy of a 4-month-old boy revealed a score of 1 in both the lower pole of the right kidney and the upper pole of the left kidney, while a score of 2 was found in the lower pole of left kidney; the grade for both kidneys was I. (D) A score of 0, 3, 3 was measured in the upper pole, midzone and lower pole of the right kidney of a 3-month-old boy, with no lesion detected of the left kidney; the grades for his right and left kidney were I and 0, respectively. Obvious hypoperfusion lesions are marked with triangles.

Table 2 Comparative results of Tc-99m DMSA scintigraphy and power Doppler sonography (kidneys) in different age groups

Tc-99m DMSA scintigraphy (kidneys)	Group 1 (age ≤6 months)				Group 2 (age >6 months)			
	Grade 0	Grade I	Grade II	Grade III	Grade 0	Grade I	Grade II	Grade III
Grade 0	58	8	4	1	35	5	4	1
Grade I	1	4	1	8	2	7	4	0
Grade II	3	5	3	1	1	7	4	1
Grade III	0	0	2	3	0	6	0	5

DMSA, dimercaptosuccinic acid; Grade 0, normal; Grade I–III, abnormal.

Blood and urine samples are collected when UTI is suspected. The literature shows that the elevation of CRP levels and white blood cell count can imply the presence of renal involvement, but their sensitivity and specificity are vague (3,19). Positive urinary leukocyte esterase and nitrite result from the presence of white blood cells in urine and bacteriuria and may be related to UTI. Their combination may even be more helpful in diagnosing APN than when each is used alone, but their ability to diagnose bacteriuria is significantly less reliable in younger children (20-22). Renal damage may cause NAG and β2-MG excretion in urine (17,23). Studies show that detecting these factors can enable the early diagnosis of APN in children (23). However, urine NAG excretion normalizes rapidly during APN, resulting in low sensitivity (17,24), while urinary β2-MG often tests normal in the earlier stages of renal injury (23). In

accordance with the relevant literature, our data confirmed a positive rate of 82.6% in CRP, 85.9% in white blood cell count, 90.2% in urine leukocyte esterase, 32.6% in urine nitrite, 26.1% in urine NAG, and 20.7% urine β2-MG. With the abnormal rate of 63.0% on DMSA scintigraphy in our study, those examinations can rarely permit a diagnostic value for APN.

Changes in APN kidneys appeared on gray-scale ultrasonic imaging, and included increased renal size, mass, and triangular or renal sinus hyperechogenicity (15). These features are related to renal swelling and loss of corticomedullary differentiation (8). In recent studies using DMSA scintigraphy as the gold standard, the sensitivity of grey-scale ultrasonography was shown to be inferior to that of DMSA and Doppler ultrasonography for the diagnosis of APN (15,25). Mitra's study revealed a positive rate of 40% for patients on grey scale ultrasonography, which was lower than that on DMSA (56%) and PDU (50%) (7). In our study, we found cortical echo changes in 5.4% of patients, renomegaly in 35.9%, and kidney atrophy in 2.2%. A positive rate of 40.2% presents a lower diagnostic value of grey-scale ultrasonography than DMSA (56.5%) and PDU (63.0%).

Many imaging techniques have been compared for their ability to diagnose APN in the pediatric population. Their theoretical basis mainly relies on observation of reduced renal blood flow, which is attributed to intravascular granulocyte aggregation, edema, and dysregulated transport to the intratubular neutrophils. In sequelae, arteriolar or capillary occlusion, toxic enzymes, or superoxide production and accumulation occur (26). Tc-99m DMSA renal scintigraphy is considered the gold standard for the confirmation of APN (14,27) with a 91% and 99% sensitivity and specificity, having been reported, respectively (4). The invasiveness of the procedure, ionizing radiation exposure, and cost limit its appeal to children and parents. Meanwhile, normal DMSA findings cannot fully exclude APN (10), and its false-positive findings can lead to the misdiagnosis of APN. Furthermore, the results from DMSA scintigraphy are hard to quantify, and the photopenic lesion area or change in radioactivity cannot be accurately assessed. Researchers have exhaustively attempted to resolve this problem: Chiou introduced an empiric-threshold method for volume determination while Linne and Hitzel conducted score systems to measure the volume of an APN focus and calculate the degree of DMSA uptake defect (17,18). These attempts were unsuccessful, and a new imaging method is urgently required.

PDU is a relatively new, non-invasive technique for renal vascular visualization that does not involve exposure to radiation. Mixed results have emerged across studies, while here, a promising diagnostic value was noted due to high sensitivity (89%) and specificity (92.3%) (7,9). Data from 57 children with a mean age of 5 years showed a sensitivity of 80% and a specificity of 81% (15). However, lower sensitivity was found in Bukov's (74%) and Stogianni's (73.8%) data (8,10). Experiments using a pig model also demonstrated a low sensitivity (56.6%) of PDU compared with DMSA scintigraphy (92.1% sensitivity) (11,12). We made a seriously study of them, and found the PDU results had been calculated qualitatively, which may have led to its determination of low sensitivity and specificity (8,10-12). Despite this, PDU has shown some success in revealing lesions that remained invisible on DMSA scintigraphy (10), which may give credibility to its diagnostic value. Thus, we synthesized the scoring systems of DMSA scintigraphy (17,18), and were first to introduce a 9-point semiquantitative analysis system in PDU in order to produce a more reliable and accurate diagnostic result. Meanwhile, we classified kidneys into four grades to assess the severity of APN and predict its development. The diagnostic ability and consistency of both methods were compared to discern whether PDU could replace DMSA scintigraphy.

With the new semiquantitative analysis system, our data confirmed a high sensitivity (89.7%) and specificity (80.2%) of PDU which correlated well with the results of other experimental research (7,9,10). We had only 7 (of 184) false-negative findings (4 in group 1 and 3 in group 2), all from the upper and lower pole of the kidney. This may be explained by the partial venous congestion caused by edema, difficulty in differentiating normal from increased flow, and the absence of a hepatic acoustic window in the upper pole of the left kidney (7,10). Furthermore, the normal heterogeneity of DMSA uptake within the renal cortex might mimic areas of abnormally decreased uptake (10). The 23 false-positive results (13 in group 1 and 10 in group 2) might be explained by technical artifacts, rib artifacts, respiratory motion, or intestinal gas (10). However, with the P value below 0.05, we could not verify whether PDU could supersede DMSA scintigraphy in diagnosing APN.

To further assess the value of PDU for detecting APN and to clarify the consistency between the two methods, grouping and Ko analysis were performed. We divided

children into two groups: younger than 6 months (inclusive, group 1) and older than 6 months (group 2). The sensitivity and specificity for group 1 were 87.1% and 81.7% (P<0.05), respectively, and 91.9% and 77.8% for group 2, respectively (P<0.05), indicating that the diagnostic value of PDU increased with age. This might be due to age-related kidney development and a different pathophysiology in those younger than 6 months (3,15). Furthermore, the more pronounced respiratory motion of younger children might have compromised the reliability of PDU in APN diagnosis. A moderate level of agreement (41%, P<0.05) between PDU and DMSA scintigraphy in distinguishing the grade was observed in our study, and fair and moderate agreement was found for group 1 (38%, P<0.05) and group 2 (43%, P<0.05), respectively. These results agreed with our data above. Thus, we can conclude that PDU has the potential to obviate DMSA scintigraphy in children older than 6 months for APN diagnosis.

With the result that lesions detected by ultrasonography might remain invisible on DMSA scintigraphy, we found that the severity detected with PDU was consistent with that of DMSA scintigraphy to some degree (15). Published studies have shown that abnormal findings of DMSA scintigraphy regarding APN in children indicated a high risk of renal scarring, and renal scarring was a precipitator of decline in renal function (1,15). Besides this, the extent of DMSA uptake defect was found to correlate with clinical significance and the need for continuous prophylaxis (10,17). Indeed, if treatment is not started within the first week, there would be no difference in the prognosis (27). Roupakias and Yuan-Yow's study uncovered a correlation between the likelihood of renal scarring and the size and area of renal parenchymal involvement (1,27). Since the grade in our research depended mainly on hypoperfusion or defect area and severity, we can deduce that the PDU grade can predict the prospect of the development of APN, especially for children older than 6 months.

Our study had some limitations: (I) we used a relatively small sample size combined with a wide age range (36 days to 10 years), which might have introduced sample selection bias; (II) there were no pathological results for each kidney, and since imaging technology was subjective, the diagnostic bias could not be avoided; (III) we did not re-examine patients 6 or 12 months after their discharge to assess the relationship between PDU grade and prognosis. Therefore, adequate follow-up, including PDU and DMSA scintigraphy to assess renal scarring, should be considered for future studies.

Conclusions

With the help of a semiquantitative analysis system, we can conclude that PDU presents a promising alternative for diagnosing APN in children, especially those older than 6 months. However, because of the false-positive results and moderate agreement, PDU may over diagnose or misjudge the development of APN, to an extent. The predictive value of PDU should increase with the technical advancement of the equipment and the accumulation of radiologist experience.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-59). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional board of The Second Affiliated Hospital of Wenzhou Medical University (No. L-2019-08), and informed consent given by all patients and/or their guardians.

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