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ORIGINAL ARTICLE

Correlation of urine protein/creatinine ratios to 24-h urinary protein for quantitating proteinuria in children

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Abstract

Background The purpose of this study was to evaluate the correlation and consistency between urine protein/creatinine ratio (UPCR) and 24-h urine protein (24HUPr) in children, and to determine cutoff values of UPCR relative to 24HUPr at 100 mg/m^2/d (≥ 100 mg/m^2/d as pathological proteinuria) and 1000 mg/m^2/d (≥ 1000 mg/m^2/d as nephrotic-range proteinuria).

Methods Three hundred sixty-six children were enrolled, including 81 controls, 109 with Henoch-Schönlein purpura nephritis, 167 with nephrotic syndrome, 5 with IgA nephropathy, and 4 with lupus nephritis. Patients were divided into three groups: normal group; non-nephrotic-range proteinuria group; nephrotic-range proteinuria group. The cutoff values of UPCR in predicting the different levels of proteinuria were determined using ROC curve analysis.

Results UPCR was positively correlated with 24HUPr ($r = 0.915$, $p < 0.01$). Bland-Altman diagrams showed that UPCR and 24HUPr had good consistency, and > 95% spots of UPCR and 24HUPr were within 95% confidence intervals. Relative to 24HUPr at 100 mg/m^2/d, the cutoff value of UPCR (0.18 g/g Cr) had the highest sensitivity (94%) and specificity (98.8%) which is close to 0.2 g/g Cr as proposed by the American College of Rheumatology. Relative to 24HUPr at 1000 mg/m^2/d, the cutoff value of UPCR (2.09 g/g Cr) had the highest sensitivity (92.1%) and specificity (92.1%) which is close to the 2.0 g/g Cr proposed in KDIGO guidelines.

Conclusions UPCR showed strong correlation and consistency with 24HUPr for evaluating levels of proteinuria in children. UPCR < 0.2 g/g Cr can be considered a criterion for normal-range proteinuria. Instead of 24HUPr ≥ 1000 mg/m^2/d, UPCR ≥ 2.0 g/g Cr can be considered a criterion for nephrotic-range proteinuria or nephrotic syndrome in children.

Keywords 24-h proteinuria quantity · Urine protein/creatinine ratio · Correlation · Consistency · Cutoff value

Introduction

Proteinuria is the most common clinical manifestation of renal disease and an important marker of renal injury; therefore, the quantitative detection of urinary protein is of great significance for the diagnosis, treatment, and prognosis of renal diseases [1, 2]. The protein level in 24-h urine is considered as the "gold standard" for the clinical diagnosis of renal diseases in clinic. The 24-h urine protein quantity (24HUPr) ≥ 100 mg/m^2/d is defined as pathological proteinuria [3, 4], and 24HUPr ≥ 1000 mg/m^2/d represents the nephrotic-range proteinuria in children [4]. However, the 24-h urine collection is not convenient for outpatients and is subject to collection errors, which might range from 12 to 35% as reported in previous studies [5, 6]. The National Kidney Foundation recommended urine protein/creatinine ratio (UPCR) instead of the traditional 24HUPr in developing the clinical practice guidelines for chronic kidney disease in adults and children [7, 8]. Since

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then, several studies have verified that UPCR can be used to evaluate urinary protein excretion in diabetic nephropathy [9], kidney transplantation [10], lupus nephritis [11, 12], pregnancy [13], preeclampsia [14], and other glomerulopathy [15]. The above studies were conducted in adults; therefore, the purpose of this study is to evaluate the correlation and consistency between UPCR and 24HUPr in children, in order to establish the diagnostic cutoff values of UPCR in children with pathological proteinuria and nephrotic-range proteinuria.

Materials and methods

Patient selection

We reviewed the records of 285 children who were admitted to our hospital between 2016 and 2018. From among 285 patients, 109 cases were diagnosed with Henoch-Schönlein purpura nephritis, 167 cases with nephrotic syndrome, 5 cases with IgA nephropathy, and 4 cases with lupus nephritis. The clinical symptoms and laboratory results were collected retrospectively. Eighty-one normal children were used as controls.

Detection of urinary protein

Morning urine samples were collected on the first day after admission for the detection of UPCR and the 24-h urine samples were collected from 7 a.m. to 7 a.m. the following day. The urine protein and creatinine concentration of both 24-h and morning urines were determined by the Dirui CS400 autoanalyzer. The total protein of urine was quantitatively determined by phloroglucinol colorimetry and urine creatinine by enzyme colorimetry. High and low quality control products were detected in the two tests; $\bar{x} \pm 2s$ is taken as warning line and $\bar{x} \pm 3s$ as control line, to ensure that 95% of quality control results fall within the range of $\bar{x} \pm 2s$. The body surface area was calculated using the Mosteller formula: body surface area = ([height (cm) × weight (kg)]/3600)$^{0.5}$.

Statistical analysis

SPSS22.0 and MedCalc statistical software were used. Data are presented as mean ± SD or median and interquartile range (IQR). The relationship analysis was assessed with the Spearman correlation analysis coefficient. The 95% confidence interval of UPCR and 24HUPr was tested by Bland-Altman analysis. The cutoff values of UPCR in predicting non-nephrotic-range proteinuria and nephrotic-range proteinuria groups were determined using receiver operating characteristics (ROC) curves. Differences were considered significant when the p value was < 0.05.

Results

Characteristics of study population

The 366 children included in the study comprised 221 boys and 145 girls, aged between 1 and 18 years (mean, 8.27 ± 3.82 years). According to 24HUPr, 366 children were divided into three groups: (1) normal urinary protein group ($n = 81$), 24HUPr < 100 mg/m^2/d; (2) non-nephrotic-range proteinuria group ($n = 122$), 100 mg/m^2/d ≤ 24HUPr < 1000 mg/m^2/d; (3) nephrotic-range proteinuria group ($n = 163$), 24HUPr ≥ 1000 mg/m^2/d. There were no significant differences in age and sex among the different groups.

Correlation between UPCR and 24HUPr

The data of 24HUPr and UPCR were normalized by log conversion. The levels of 24HUPr and UPCR showed a strong correlation in all three groups ($r = 0.915$, $p < 0.001$), and the r values were 0.682, 0.731, and 0.638, respectively (Table 1 and Fig. 1).

Consistency between UPCR and 24HUPr

Bland-Altman diagrams were plotted with the means of log24HUPr and logUPCR as abscissa and the difference between log24HUPr and logUPCR as ordinate, as shown in Fig. 2. In 366 children, 95.90% (351/366) of the spot urines were within the 95% confidence interval (Fig. 2a). In the non-nephrotic-range proteinuria group, 95.08% (116/122) of the spot urines were within the 95% confidence interval (Fig. 2b). In the nephrotic-range proteinuria group, 95.71% (156/163) of the spot urines were within the 95% confidence interval (Fig. 2c).

Establishment of diagnostic boundary points of proteinuria and their specificity and sensitivity

Taking 24HUPr ≥ 100 mg/m^2/d as the standard for the diagnosis of proteinuria, the ROC curve of UPCR and 24HUPr was plotted with 1-specificity as abscissa and sensitivity as ordinate. As shown in Fig. 3a, the area under the curve was 0.98, and the optimal diagnostic boundary point of UPCR for proteinuria was 0.18 g/gCr with sensitivity of 94% and specificity of 98.8%. Taking 24HUPr ≥ 1000 mg/m^2/d as the standard for the diagnosis of nephrotic-range proteinuria, the area under the curve was 0.97, and the optimal diagnostic boundary point of UPCR for nephrotic-range proteinuria was 2.09 g/g Cr with sensitivity of 92.1% and specificity of 92.1% (Fig. 3b).

Table 1 Correlation of UPCR and 24HUPr of all groups and entire dataset

Groups	*n*	Diseases (no. of patients)	UPCR (g/g Cr)	24HUPr (mg/m^2/d) median (IQR)	*r*	*p*
Normal group	81	Normal (81)	0.06 [0.04, 0.08]	35.04 [23.04, 56.64]	0.682	0.00
Non-nephrotic-level proteinuria group	122	HSPN (76) NS (42) IgA nephropathy (2) Lupus nephritis (2)	0.67 [0.29, 1.52]	467.76 [281.25, 669.36]	0.731	0.00
Nephrotic-level proteinuria group	163	NS (125) HSPN (33) IgA nephropathy (3) Lupus nephritis (2)	3.95 [2.75, 5.79]	2609.28 [1602.24, 3831.6]	0.638	0.00
Total	366		2.0 0[0.13, 3.96]	900 [191.76–2447.04]	0.915	0.00

Discussion

The 2003 National Kidney Foundation guidelines in the USA indicated that UPCR could replace 24HUPr (A grade recommendation) for evaluating proteinuria [16]. However, there is still a lack of clinical data from large cohorts of children. We conducted correlation analysis of UPCR and 24HUPr in 366 children, including 81 children with normal urinary protein, 122 children with non-nephrotic-range proteinuria, and 163 children with nephrotic-range proteinuria.

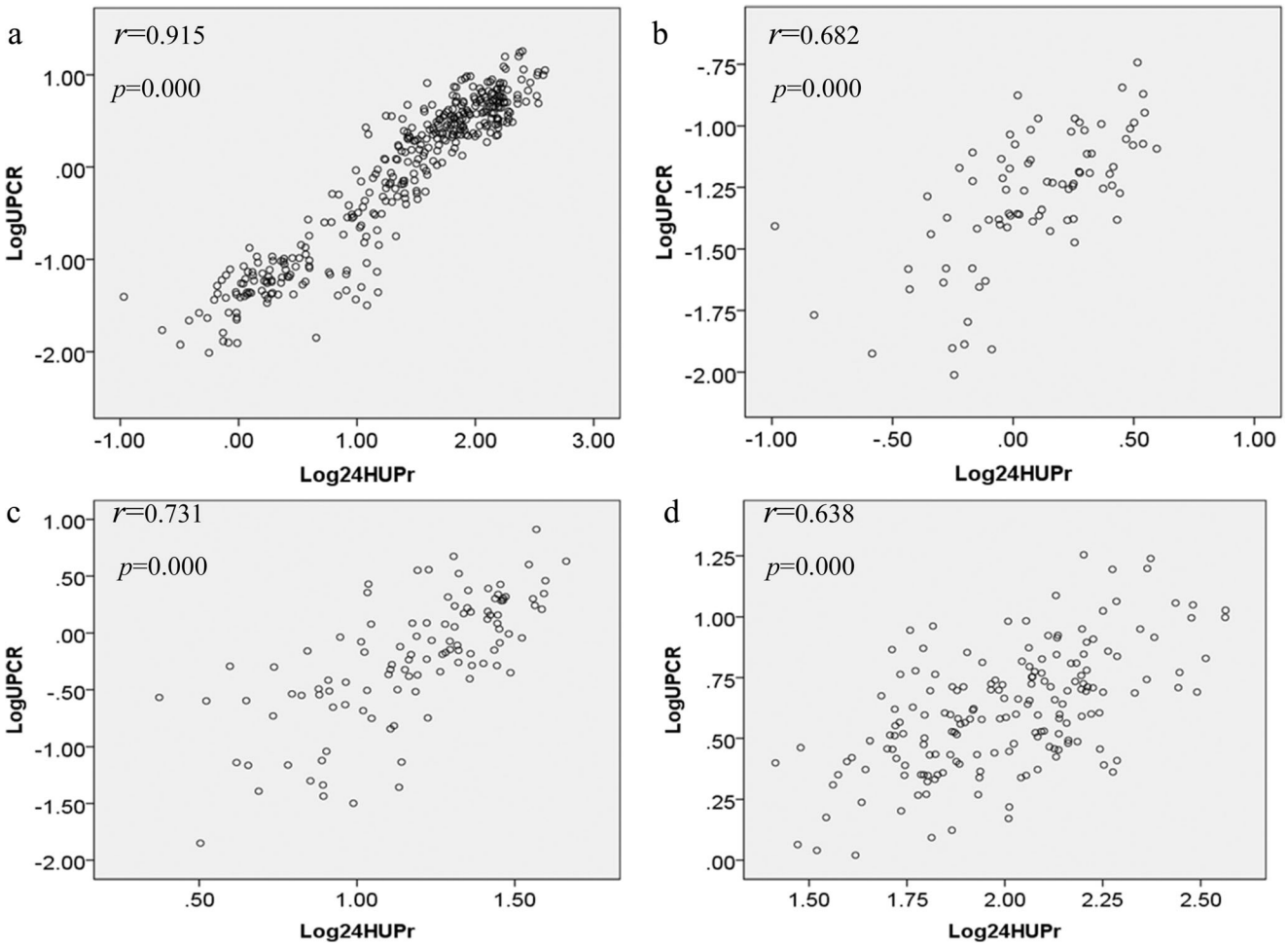

Fig. 1 Correlation between the UPCR and 24HUPr. **a** Entire dataset of 366 children. **b** Normal urinary protein group. **c** Non-nephrotic-range proteinuria group. **d** Nephrotic-range proteinuria group

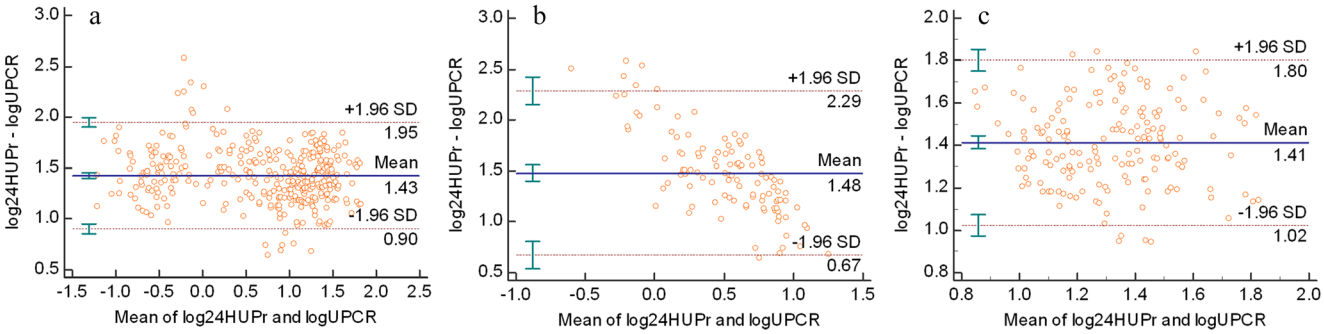

Fig. 2 Bland-Altman diagram showing UPCR is consistent with 24HUPr. **a** Entire dataset of 366 children. **b** Non-nephrotic-range proteinuria group. **c** Nephrotic-range proteinuria group

Our results showed that UPCR level correlates significantly with 24HUPr ($p < 0.01$) in all three groups, and the two methods have good consistency in evaluating proteinuria. Mustafa et al. [17] detected the proteinuria levels during different phases of nephrotic syndrome in 57 children, and showed that UPCR could replace 24HUPr to reliably assess the degree of proteinuria in children with nephrotic syndrome. Abitbol et al. [18] examined the feasibility of using UPCR in the quantitation of proteinuria in 64 children with relapsing nephrotic syndrome, and the results showed that random UPCR appeared to offer the most sensitive test for classification of proteinuria in children with nephrosis. Yang et al. [19] found that the spot UPCR multiplied by the estimated 24-h urine creatinine (Ucr) excretion {Ucr (mg/24 h) = [28 − (0.2 × age)] × weight(kg) × (0.85 if female)} improved the accuracy of prediction of the 24HUPr in children. These results suggested that UPCR could replace 24HUPr to evaluate proteinuria levels in children.

In our study, the Bland-Altman method was used to analyze the consistency between UPCR and 24HUPr. The results indicated that over 95% of the points in both groups were within the confidence intervals. The deviation of UPCR and 24HUPr was less than 5%, which was the level allowable in clinical studies. These results suggest that the two methods are consistent in evaluating different levels of proteinuria in children. However, UPCR and 24HUPr also show a certain degree of day-to-day variability [8]. The variability indicates that some patients may have poor consistency between UPCR and 24HUPr sometimes. Therefore, if the results of a single UPCR are inconsistent in clinical detection, it can be dynamically monitored to clarify the changes.

Taking 24HUPr ≥ 1000 mg/m^2/d as the diagnostic criteria of the nephrotic-range proteinuria in children in this study, the optimal diagnostic boundary point of UPCR was 2.09 g/g Cr by ROC curve, which was close to the UPCR (2 g/gCr) corresponding to nephrotic syndrome or nephrotic-range

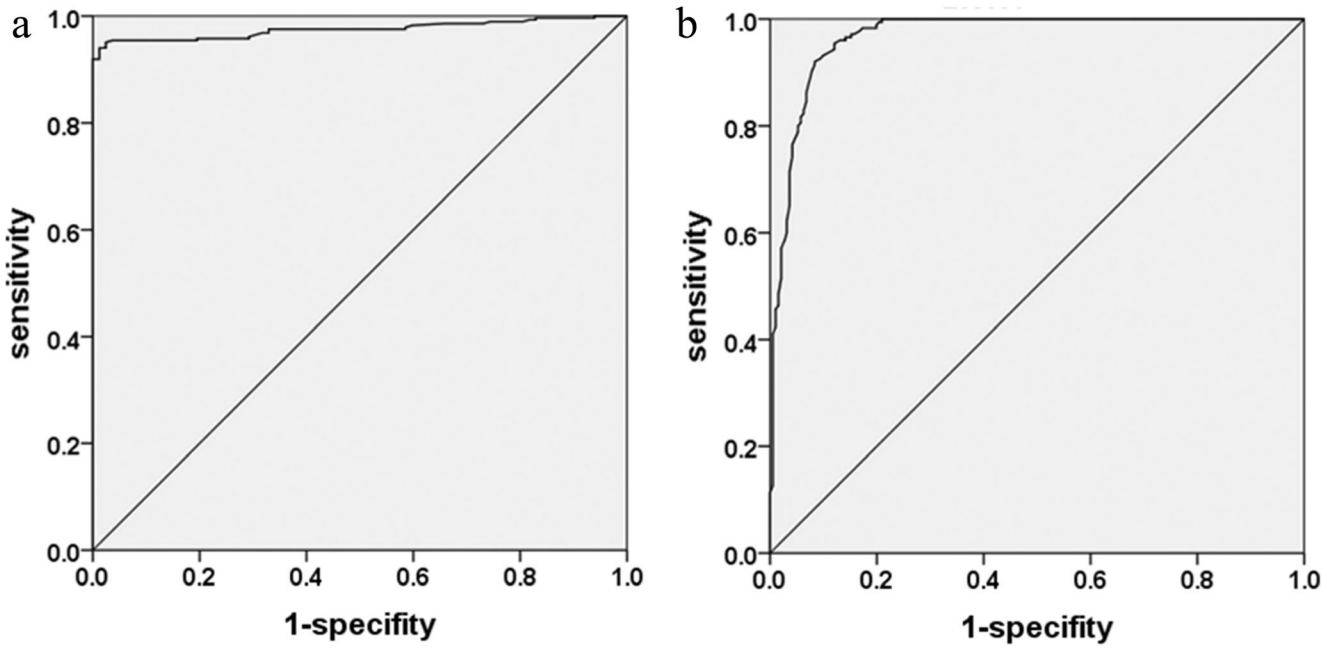

Fig. 3 ROC curve of UPCR for non-nephrotic-range proteinuria and nephrotic-range proteinuria. **a** Non-nephrotic-range proteinuria. **b** Nephrotic-range proteinuria

proteinuria as described in the 2012 KDIGO guidelines [8]. Lane et al. [20] observed 103 adult patients with nephropathy, and the results showed that the UPCR corresponding to nephrotic-range proteinuria was 2.35 g/g Cr, slightly higher than the standard proposed by the KDIGO guidelines. Based on the earlier studies on normal urinary protein excretion [21], in 2006, the kidney disease subcommittee of the American College of Rheumatology (ACR) proposed UPCR < 0.2 g/g Cr as the standard for complete remission of renal diseases [22]. Compared to 24HUPr (100 mg/m^2/d), our data demonstrate that the best diagnostic threshold of UPCR is 0.18 g/g Cr, which is close to the standard proposed by the ACR.

Sadjadi et al. [23] studied the effect of physical activity on urinary protein quantification in patients with nephropathy, and suggested that the accuracy of UPCR might be affected by the level of physical activity in patients. Because all children included in our study were hospitalized children and morning urine samples were collected and detected, physical activity was unlikely to impact the results. Lei et al. [24] showed the value of UPCR 2 h after breakfast was also correlated with 24HUPr. Yang et al. [25] found that UPCR in samples with low or high specific gravity are more likely to overestimate or underestimate actual daily urine protein amounts, respectively. These factors on urinary protein excretion should also be considered in clinical examination.

Taken together, this study demonstrates that UPCR is an accurate, reliable, and convenient method for evaluation of proteinuria in children, and can be used as a substitute for 24HUPr. Instead of 24HUPr < 100 mg/m^2/d, UPCR < 0.2 g/g Cr can be considered as an evaluation criterion of normal-range proteinuria and proteinuria returning to normal in kidney disease. Instead of 24HUPr ≥ 1000 mg/m^2/d, UPCR ≥ 2.0 g/g Cr can be considered as an evaluation criterion of nephrotic-range proteinuria or nephrotic syndrome in children.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics For this type of study, formal consent is not required.

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