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Diagnostic efficacy and influence factors of urinary protein/creatinine ratio replacing 24-h urine protein as an evaluator of proteinuria in children

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Abstract

Purpose The aim was to investigate the diagnostic efficacy of urinary protein/creatinine ratio (UPCR) and factors influencing its substitutability of 24-h urine protein (24hUP) in children with proteinuria.

Methods A total of 356 children were recruited, including 149 with non-nephrotic-range proteinuria and 207 with nephrotic-range proteinuria which were further divided into Henoch–Schönlein purpura nephritis (HSPN), lupus nephritis (LN), and primary nephrotic syndrome (PNS). The urine protein and creatinine were measured by routine methods. Bland–Altman analysis was used to test the agreement. Spearman correlation was performed to evaluate the relevance. The receiver operating characteristic curve was used to analyze the diagnostic efficacy of UPCR.

Results Bland–Altman analysis showed there was an excellent agreement between UPCR and 24hUP in each group. Correlations between UPCR and 24hUP were strong in 356 children ($r=0.869$) and in the non-nephrotic-range proteinuria group ($r=0.806$), but moderate in nephrotic-range proteinuria group ($r=0.586$). With the increase of nephrotic-range proteinuria, the correlations between UPCR and 24hUP were decreased further, however, after UPCR was adjusted by 24-h urine creatinine (24hUCr), the correlation coefficient was improved ($r=0.682$). In three subgroups with nephrotic-range proteinuria, high correlation coefficient ($r=0.731$) was observed in HSPN, but not in LN ($r=0.552$) and PNS ($r=0.563$). The sensitivity and specificity of UPCR for diagnosing nephrotic-range proteinuria were 89.9 % and 92.2%.

Conclusions UPCR is competent in evaluating proteinuria. The degree of proteinuria, 24hUCr and the underlying pathological types of renal disease may be the important influencing factors in the correlation between UPCR and 24hUP in children with nephrotic-range proteinuria.

Keywords Urinary protein/creatinine ratio · Nephrotic-range proteinuria · 24-h urine protein · Children

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Introduction

Proteinuria is a well-known biological marker used for the diagnosis, evaluation efficacy and prognostic assessment of kidney disease [1, 2]. Accurate quantification of proteinuria is important not only for diagnostic purposes, but also for the management of kidney diseases [3]. Twenty-four-hour urine protein (24hUP) is regarded as the gold standard for the diagnosis of pathological proteinuria [4]. However, the collection of 24-h urine is cumbersome and time-consuming for infants and outpatients. The concentration of urine, the addition of preservatives and sampling differences can all likely lead to the inaccurate results [5, 6]. It has been shown that 24-h urine retention error is as high as 12–35% in pediatric patients [7]. For progressive kidney disease, measuring urinary protein/creatinine ratio (UPCR) offers more advantages over measuring total proteinuria for its convenience and rapidity. The American Kidney Disease Outcome Quality Initiative also proposes that UPCR can replace 24hUP to detect and monitor proteinuria [8], and UPCR ≥ 200 mg/mmol is considered as the diagnostic threshold for nephrotic-range proteinuria [9]. The usage of UPCR to estimate daily urine protein excretion is prevalent, such as type II diabetes [10], eclampsia [11], cancer [12], chronic kidney disease [13], hypertensive nephropathy [14] and lupus nephritis (LN) [4]. However, in a study of chronic kidney disease, Nayak et al. [15] reported that there was a weak correlation ($r = 0.35$) between UPCR and 24hUP at nephrotic-range proteinuria. Our previous research [16] has shown a moderate correlation ($r = 0.638$, $P < 0.001$) between UPCR and 24hUP in children with nephrotic-range proteinuria. Therefore, whether UPCR can predict 24hUP in nephrotic-range proteinuria or not still needs further investigation. Gender, age, body mass index, renal function and podocytopathy have been reported to affect urinary protein excretion [17, 18]. Twenty-four-hour urine creatinine (24hUCr) is also variable depending on age, gender and body weight [19]. However, the influencing factors of the correlation between UPCR and 24hUP in children with nephrotic-range proteinuria need to be verified. In the present study, the specificity and sensitivity of UPCR ≥ 200 mg/mmol as a diagnostic threshold for nephrotic-range proteinuria in children will also be investigated.

Materials and methods

Patient selection

The present study was done on 356 children who admitted to our hospital from March 2015 to August 2019, including 233 boys and 133 girls, aged between 1 and 18 years old. Among 356 patients, 132 cases had Henoch–Schönlein purpura nephritis (HSPN), 18 cases had LN, and 206 cases had primary nephrotic syndrome (PNS). Participants showed different degrees of proteinuria: 24hUP > 4 and ≤ 40 mg/m^2/h are defined as the non-nephrotic-range proteinuria, and 24hUP ≥ 40 mg/m^2/h is defined as nephrotic-range proteinuria [9]. First, 207 children with nephrotic-range proteinuria were divided into two subgroups. Among them, 24hUP in 76 /207 children were between 40 to 80 mg/m^2/h, and 131/207 children were greater than 80 mg/m^2/h. Second, 207 children with nephrotic-range proteinuria were also divided into three subgroups, 51/207 cases had Henoch–Schönlein purpura nephritis, 11/207 cases had LN, and 145/207 cases had PNS. The histopathological changes of HSPN were divided into six levels according to the International Study of Kidney Disease in Children (ISKDC) [20]. The pathological classification of PNS was based on the pathological classification criteria of glomerulopathy established by the World Health Organization in 1995. An estimated glomerular filtration rate (eGFR) was calculated with the updated Schwartz equation [21]. The diuretic was not used within 3 days before urine collection. The study protocol was approved by the institutional review board at the First Affiliated Hospital of Henan University of Chinese Medicine, with exemption from the informed consent.

The detection of urinary protein and urine creatinine

Spot urine was collected on the first day's morning after admission to the detection of UPCR, and the 24-h urine collection starting from the second voiding in the morning to the last void at the end of the 24 h period for the detection of 24hUP and 24hUCr. Measurements of all urine specimens were performed with the ES480 autoanalyzer (E-LAB Biological Science and Technology Company, Nanjing, China) in our laboratory. The urine protein level was measured by total protein UC FS (DiaSys Diagnostics Systems, Shanghai, China) based on the pyrogallol red-molybdate method, and urine creatinine was detected by creatinine reagent kit based on sarcosine oxidase method (Yijie Bio, Ningbo, China). High and low quality controls were tested separately; $\bar{x}$ mean ± 2 standard deviation (SD) was taken as warning line and $\bar{x}$ mean ± 3 SD as the control line, to ensure that 95% of quality control results falls within the range of $\bar{x}$ mean ± 2 SD.

Statistical analysis

Data was expressed as means (standard deviation) or median and interquartile range, and analyzed by SPSS23.0

and Medcalc statistical software. Bland–Altman analysis was conducted to test the agreement. Spearman correlation analysis was performed to assess the relationship. Receiver operating characteristics (ROC) curve was used to assess the diagnostic utility of UPCR in predicting nephrotic-range proteinuria. Differences were considered to be significant when the P value was < 0.05.

Results

Study participants and baseline characteristics

Among 356 patients, 149 cases had non-nephrotic-range proteinuria and 207 cases were nephrotic-range proteinuria. Clinical characteristics and laboratory test results of different groups were shown in Table 1. Additionally, there were 19 children with abnormal kidney function. The eGFR < 90 ml/min/1.73 m^2 was tested in 6 children with non-nephrotic-range proteinuria, and in 13 children with nephrotic-range proteinuria respectively.

The agreement between UPCR and 24hUP

Bland Altman analysis was conducted to determine the limits of agreement. In the overall study population, there were 95.79% spots in the 95% confidence intervals of UPCR and 24hUP (Fig. 1A); in non-nephrotic-range proteinuria patients, there were 96.63% in the 95% confidence intervals (Fig. 1B); and in nephrotic-range proteinuria patients, there were 97.58% in the 95% confidence intervals (Fig. 1C). Therefore, a high agreement was considered between UPCR and 24hUP.

Table 1 Clinical characteristics and laboratory test results of different groups

Variables	Total patients Median (IQR)	Non-nephrotic-range proteinuria Median (IQR)	Nephrotic-range proteinuria Median (IQR)
Number of patients	356	149	207
Age (years)	8.50 ± 3.91	9.15 ± 3.70	8.02 ± 3.99
Sex (male:female)	233:133	86:63	137:70
Weight (kg)	31.05 ± 14.35	32.69 ± 13.80	29.86 ± 14.66
BUN (mmol/l)	3.75 (2.96, 4.65)	3.75 (3.09, 4.40)	3.76 (2.89, 4.94)
Scr (mg/dl)	0.35 (0.28, 0.45)	0.37 (0.30, 0.45)	0.34 (0.28, 0.44)
eGFR (ml/min/1.73m^2)	147.13 (120.03, 175.91)	147.47 (123.11, 177.01)	146.07 (117.92, 175.73)
UPCR (mg/mmol)	227.97 (51.66, 479.62)	45.61 (16.49, 104.60)	397.48 (254.56, 643.41)
24hUP(mg/m^2/h)	53.30 (19.30, 124.29)	14.19 (6.92, 25.38)	108.83 (66.06, 159.53)
24hUCr (mg/24/h)	585.29 (369.84, 863.80)	698.96 (418.47, 1008.29)	532.70 (351.74, 799.62)

eGFR estimated Glomerular filtration rate, *UPCR* urinary protein/creatinine ratio, *24hUP* twenty-four-hour urine protein, *24hUCr* twenty-four-hour urinary creatinine

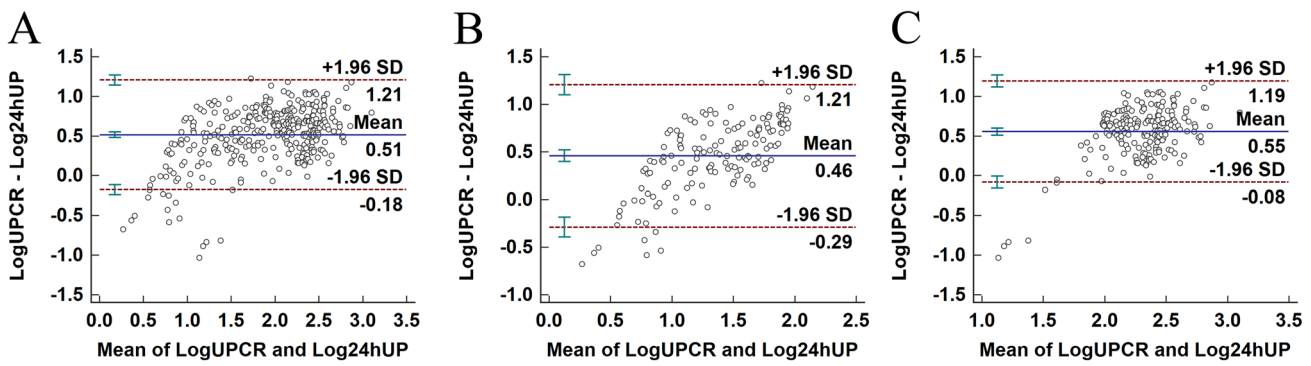

Fig. 1 Scatterplot of the agreement between UPCR and 24hUP. Bland–Altman analysis comparing UPCR and 24hUP in 356 children with renal disease (**A**), in 149 children with non-nephrotic-range proteinuria (**B**) and in 207 children with nephrotic-range proteinuria (**C**). All values are log10 transformed. UPCR, urinary protein/creatinine ratio; 24hUP, twenty-four-hour urine protein

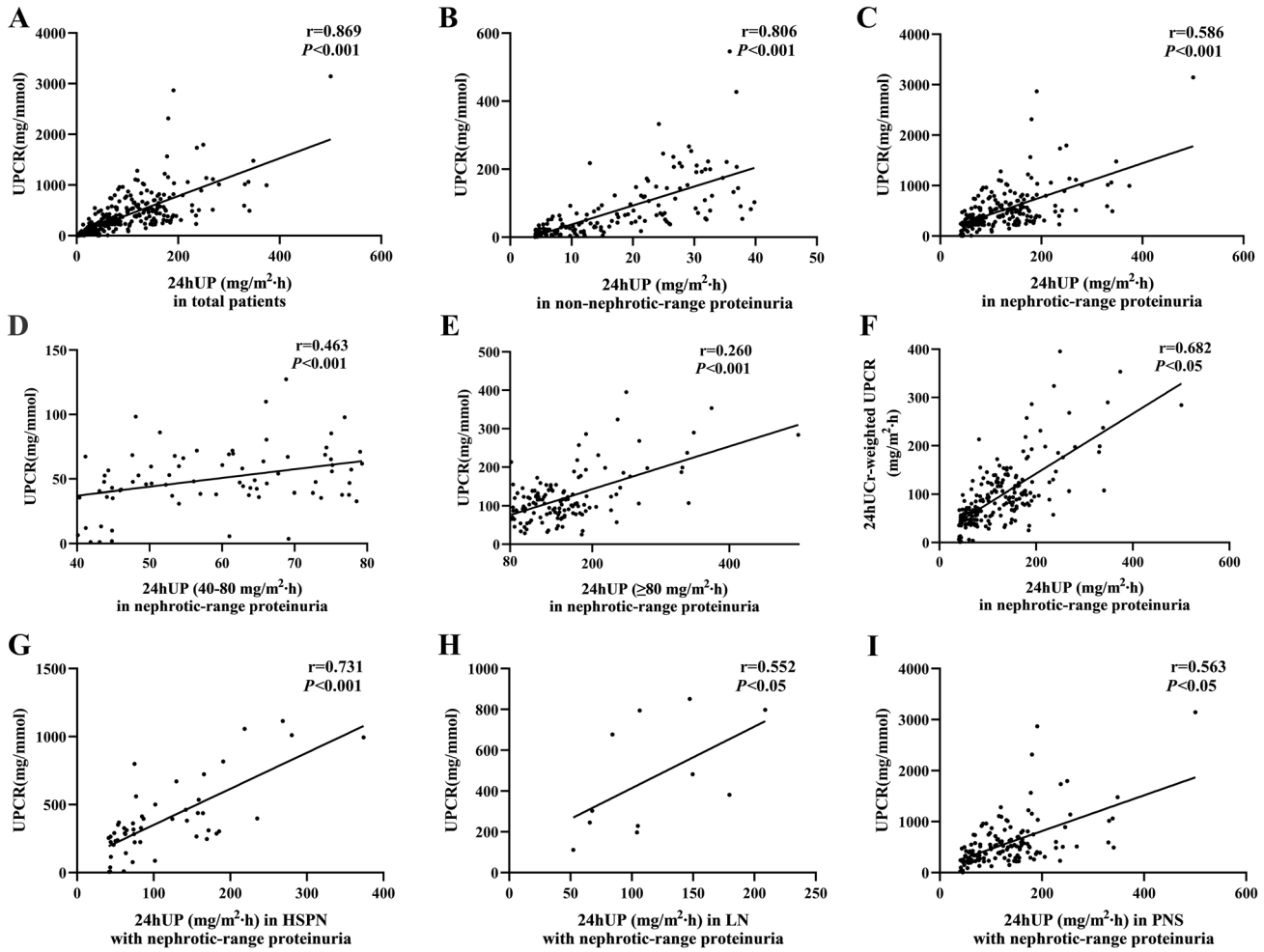

Fig. 2 Scatterplot of the correlation between UPCR and 24hUP. The correlation between UPCR and 24hUP in 356 children with renal disease (**A**), in 149 children with non-nephrotic-range proteinuria (**B**), in 207 children with nephrotic-range proteinuria (**C**), in 76 children with nephrotic-range proteinuria (24hUP = 40–80 mg/m^2/h) (**D**), and in 131 children with nephrotic-range proteinuria (24hUP ≥ 80 mg/m^2/h) (**E**). The correlation between 24hUCr-weighted UPCR and 24hUP in 207 children with nephrotic-range proteinuria (**F**). The correlation between UPCR and 24hUP in HSPN with nephrotic-range proteinuria (**G**), in LN with nephrotic-range proteinuria (**H**), in PNS with nephrotic-range proteinuria (**I**). *UPCR* urinary protein/creatinine ratio, *24hUP* twenty-four-hour urine protein, *HSPN* Henoch–Schönlein purpura nephritis, *LN* lupus nephritis, *PNS* primary nephrotic syndrome. 24hUCr-weighted UPCR was equal to UPCR by multiplying the measured 24hUCr

The correlation between UPCR and 24hUP in each group

The Spearman correlation between UPCR and 24hUP in total patients and non-nephrotic-range proteinuria were strong ($r = 0.869$, $r = 0.806$), (Fig. 2A, B), but moderate in nephrotic-range proteinuria children ($r = 0.586$) (Fig. 2C). In nephrotic-range proteinuria children, the further grouping studies showed that the Spearman correlation coefficient between UPCR and 24hUP (40–80 mg/m^2/h) was 0.463 (Fig. 2D), and 0.260 between UPCR and 24hUP (≥ 80 mg/m^2/h) (Fig. 2E).

Influencing factors of the correlation between UPCR and 24hUP

To explore whether daily urinary creatinine excretion affects the correlation between UPCR and 24hUP or not, UPCR was adjusted by 24hUCr, which varied with age, sex and body weight. The Spearman correlation between the 24hUCr-weighted UPCR (UPCR by multiplying the measured 24hUCr) and 24hUP were improved in total patients ($r = 0.894$), non-nephrotic-range proteinuria group ($r = 0.812$), and especially in nephrotic-range proteinuria group ($r = 0.682$) (Fig. 2F).

When 207 children with nephrotic-range proteinuria were divided into three subgroups, the correlations between UPCR and 24hUP was high in 50/207 children with HSPN ($r=0.731$, $P<0.05$) (Fig. 2G), but moderate in 11/207 children with LN ($r=0.552$, $P<0.05$) and 145/207 children with PNS ($r=0.563$, $P<0.05$) (Fig. 2H, I).

Verification of the diagnostic efficacy of UPCR ≥ 200 mg/mmol for nephrotic-range proteinuria

Taking 24hUP ≥ 40 mg/m^2/h as the diagnostic criteria of nephrotic-range proteinuria, the area under ROC curve was 0.96 ($P<0.001$), the sensitivity and specificity of UPCR at 200 mg/mmol were 89.9 and 92.2% respectively (Fig. 3). Therefore, the diagnostic efficacy of UPCR ≥ 200 mg/mmol for nephrotic-range proteinuria was equivalent to that of 24hUP ≥ 40 mg/m^2/h.

Discussion

The present study has shown there was a good agreement between UPCR and 24hUP using Bland Altman analysis, which is in accordance with other investigations [3, 22]. Chen [23] observed there was a good agreement between UPCR and 24hUP when proteinuria below 3 g/day, while high variability occurrence with proteinuria > 3 g/day. Our data indicated that the correlations between UPCR and 24hUP were strong ($r=0.869$, 0.806) in all the 356 hospitalized children with renal disease and 149/356 children with non-nephrotic-range proteinuria. This finding was supported by many other studies [3, 22, 24, 25]. For instance, Hogan et al. [25] reported that random UPCR could reliably be used to predict 24hUP between 0.5 to 10 g/day in adults. Kobayashi et al.[22] also found a high correlation between UPCR and 24hUP in IgA nephropathy ($r=0.86$). Moreover, the European Alliance Against Rheumatism recommends that UPCR can be used to assess the urinary protein excretion in children with LN [26]. However, the correlation between UPCR and 24hUP was not always satisfactory in patients with nephrotic-range proteinuria. Our previous research ($r=0.638$) [16] and the present study ($r=0.586$) have both indicated there was a moderate correlation between UPCR and 24hUP in children with nephrotic-range proteinuria. With the increase of nephrotic-range proteinuria, the present study also showed a decreased correlation between UPCR and 24hUP. Jorge et al. [4] did a study on 322 adults' LN, and observed a poor correlation ($r=0.3$) between UPCR and 24hUP (0.5–1.99 g/day), a moderate correlation ($r=0.6$) with 24hUP ≥ 2 g/day. In a study of 116 adults with different pathologic nephropathy, patients were divided into three groups according to the 24hUP (< 1.0 g/day, 1.0–3.5 g/day, > 3.5 g/day), the correlation coefficients between UPCR and 24hUP were 0.2943, 0.3585, and 0.3908, respectively [19]. Therefore, the degree of urine protein excretion may be an important factor affecting the correlation between UPCR and 24hUP.

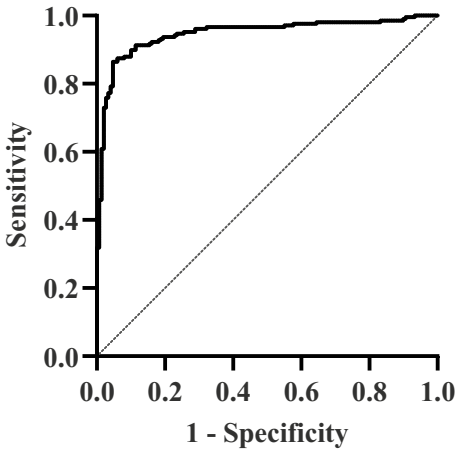

Fig. 3 ROC curve of UPCR for nephrotic-range proteinuria

As we have already know, the urinary creatinine excretion is relatively stable throughout the day, however, it varies with age, sex and weight. Our data showed that the correlations between UPCR and 24hUP were improved significantly in nephrotic-range proteinuria group after UPCR was adjusted by 24hUCr. A clinical investigation in 442 children with 24hUP ≤ 4 and > 4 mg/m^2/h were also showed there was an improved correlation between 24hUCr-weighted UPCR and 24hUP [3]. The adjustment of UPCR using equations of estimated 24hUCr to improve correlation with 24hUP were also available in several studies [3, 27]. These lead us to conclude that the 24hUCr could be a significant factor influencing the correlation between UPCR and 24hUP.

When it came to certain renal disease, our study has shown there was a strong correlation ($r=0.731$) between UPCR and 24hUP in HSPN children with nephrotic-range proteinuria, but a moderate correlation in LN ($r=0.552$) and PNS ($r=0.563$) groups. Zhang et al. [28] conducted a study on 90 patients with biopsy-proven LN, which were divided into three groups according to their scores of activity index (AI): low AI group (0–8), middle AI group (9–16), and high AI group (17–24), the correlation coefficients between UPCR and 24hUP in three groups were 0.825, 0.567, 0.686, respectively. Guedes [29] investigated 53 adults with LN, and found the correlation was moderate for proteinuria under 500 mg/day ($r=0.471$), whereas almost did not exist in a range between 500 and 1000 mg/day ($r=-0.106$), yet high in proteinuria range > 1000 mg/day ($r=0.917$). Medina-Rosas [30] also showed that UPCR did not have sufficient accuracy compared with 24hUP for evaluating the improvement and deterioration of LN. In addition, the present study

has observed there was a moderate correlation ($r = 0.565$) in PNS. Singh [31] reported a strong correlation between UPCR and 24hUP ($r = 0.833$) in 40 children with clinical suspicion of nephrotic syndrome. Kobayashi [22] observed there were different correlations between UPCR and 24hUP in various pathological types: the correlation was strong in IgA nephropathy, but not in MCD and MN. These conflicting results have suggested that UPCR may sometimes not be a good predictor of 24hUP in LN and PNS patients with nephrotic-range proteinuria. The following facts may contribute to explain this phenomenon. First, the decreased glomerular filtration rate or renal tubules reabsorption dysfunction may cause the abnormal excretion of urinary creatinine and protein in patients with nephrotic-range proteinuria [18]. Second, the loss of nephron mass may also cause hyperfiltration that results in more proteinuria [32]. Third, persistent proteinuria is postulated to initiate a detrimental cycle of proteinuria-induced tubulointerstitial and glomerular damage, which in turn can exacerbate the proteinuria. Fourth, the heterogeneous of renal tissue lesions differ in acute and chronic phases enrolled in different studies may be the reason for the inconsistent correlation in LN. PNS also has various pathological types, accompanied by different degrees of proteinuria. Therefore, the underlying pathological types of renal disease may be the critical factors that affect the correlation between UPCR and 24hUP.

As a diagnostic threshold for nephrotic-range proteinuria, UPCR ≥ 200 mg/mmol was suggested by Kidney Disease: Improving Global Outcomes (KDIGO) [9]. However, the diagnostic efficacy of the criteria in nephrotic-range proteinuria in children was barely verified in large-scale clinical studies. In this study, we mapped the ROC curve based on the data of 356 patients with proteinuria. When 24hUP ≥ 40 mg/m^2/h was set as the diagnostic criterion for nephrotic-range proteinuria, the area under ROC curve was 0.96. Meanwhile, the sensitivity and specificity of UPCR (cut-off value at 200 mg/mmol) were 89.9 and 92.2%, respectively. Thus, these data supported UPCR ≥ 200 mg/mmol recommended by the KDIGO guideline as the diagnostic cut-off point for the nephrotic-range proteinuria in children. The random UPCR has the diagnostic efficacy of monitoring nephrotic-range proteinuria.

In conclusion, UPCR and 24hUP had excellent agreement in all the groups. The correlations in all 356 patients and non-nephrotic-range proteinuria groups were strong, but moderate in nephrotic-range proteinuria group. The degree of proteinuria, 24hUCr and underlying pathological types of renal disease may be the critical factors that affect the correlation between UPCR and 24hUP. Even if the diagnostic efficacy of UPCR ≥ 200 mg/mmol is comparable with 24hUP ≥ 40 mg/m^2/h as a diagnostic threshold for nephrotic-range proteinuria in children, it is still necessary to use 24hUP as gold standard for determining treatment strategy in children with nephrotic-range proteinuria, especially in LN or PNS. Limitations of the present study were that the effect of drugs on the correlation between UPCR and 24hUP was not included and the LN cohort in nephrotic-range proteinuria group was small.

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Author contributions PZ conducted the research, interpreted the results of the analysis, made figures, and wrote the paper; YH is the lead as well as corresponding author who conceived of and supervised the project, interpreted the results of the analysis, made figures, and wrote the paper; SY was responsible for the data integrity and analysis; XY, JL discussed the draft; YZ, XM, LB provided significant inputs for data collection; WZ, XR, YY, XZ and TY provided guidance and critically reviewed the manuscript; all authors read and commented on the manuscript.

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Declarations

Conflict of interest No conflicts of interest (financial or otherwise) are declared by the authors.

Ethical approval This study was performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was approved by the institutional review board at the First Affiliated Hospital of Henan University of Chinese Medicine. Waiver of patient consent was approved for this retrospective medical records review.

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