Acta Med. Okayama, 2022
Vol. 76, No. 1, pp. 41–49

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Urinary Protein-to-creatinine Ratios Predict Recurrence in Pediatric and Young Adult Cases of Minimal Change Nephrotic Syndrome

Hiroyuki Miyahara[a]*, Takayuki Miyai[a,b], Kunihiko Aya[a,c], and Hirokazu Tsukahara[d]

Department of Pediatrics, [a]Okayama University Hospital, [d]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan,
[b]Department of Pediatrics, Japanese Red Cross Okayama Hospital, Okayama 700-8607, Japan,
[c]Department of Pediatrics, Kurashiki Central Hospital, Kurashiki, Okayama 710-8602, Japan

High-dose steroids are required for the treatment of minimal change nephrotic syndrome (MCNS), especially for episodes of recurrence. Predicting and avoiding recurrence can help reduce the steroid dose, but prediction is currently difficult. We herein examined whether changes in laboratory data, especially the urinary protein-to-creatinine ratio (UTP/UCr), can predict clinical recurrence. We also assessed differences in clinical features between children and young adults. We included 36 patients with MCNS; for each case, we retrospectively studied laboratory data during stable remission and pre-recurrence, with the "stable" period defined as all but the 6 weeks before recurrence, and pre-recurrence defined as the 4 ± 2 weeks before recurrence. UTP/UCr, serum albumin, *etc*. were measured every 5 years during stable periods. We divided patients into cohorts by age at recurrence, < 15 years and ≥ 15 years, and compared stable and pre-recurrence values for the two groups. UTP/UCr values during stable periods tended to be higher in younger patients. UTP/UCr and serum albumin showed statistically significant changes during pre-recurrence periods, but only in those aged ≥ 15 years. Thus, clinical features of recurrence differed depending on age. Signs of recurrence can be confirmed via UTP/UCr or serum albumin several weeks before recurrence in patients ≥ 15 years.

Key words: minimal change nephrotic syndrome, recurrence, urinary protein to creatinine ratio

Massive proteinuria accompanied by hypoalbuminemia is a clinical feature of nephrotic syndrome (NS) [1]. Minimal change NS (MCNS) is the most common type of NS among children; it occurs suddenly, and then remits, but often recurs during the clinical course [2]. The standard treatment for recurrence is high-dose steroids, a treatment with various potential adverse side effects; hence, recurrence must be avoided as much as possible [1]. Although predicting recurrence using laboratory data may help in prevention, relevant data are lacking, and current knowledge cannot predict recurrences sufficiently early. Thus, we focused on whether changes in quantitative factors such as the urinary protein-to-creatinine ratio (UTP/UCr) can be predictive of recurrence in MCNS patients as urine chemistry is routinely monitored in these patients [1].

It is known that MCNS is one of the major types of adult-onset NS; furthermore, some cases with childhood-onset MCNS carry over into adulthood [3-5]. Although there may be some differences in clinical features between pediatric and adult MCNS patients, adequate investigations have not been made thus far. In particular, age-based differences in laboratory data need clarification.

Received March 31, 2021; accepted August 19, 2021.
*Corresponding author. Phone: +81-86-235-7249; Fax: +81-86-221-4745
E-mail: pjb80lgi@okayama-u.ac.jp (H. Miyahara)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

In this study, we investigated laboratory data during remission of MCNS cases, and changes in these data before recurrence. The data we examined included UTP/UCr, and we compared these data by age group, mainly in children and young adults.

Methods

We retrospectively reviewed clinical records and investigated cases with NS followed in the Department of Pediatrics at Okayama University Hospital, Japan, from May 2005 to December 2019. We excluded cases without laboratory data during remission, cases without recurrence, or those diagnosed by renal biopsy as types of NS other than MCNS.

As we wanted to address the importance of slight increases in UTP/UCr during the clinical course of MCNS patients, we defined complete remission when UTP/UCr decreased to ≤ 0.15 g/g·Cr after initial presentation or recurrence. Recurrence was defined as proteinuria > 40 mg/h/m^2, proteinuria > 50 mg/kg/day, dipstick test +++ for 3 consecutive days or UTP/UCr > 2 g/g·Cr after having been in remission according to the criteria of Kidney Disease Improving Global Outcomes (KDIGO). Recurrence was also defined according to the individual physician's judgment. To investigate changes in laboratory data examined several weeks before recurrence, we also defined the period of remission from induction to the 6 weeks before recurrence as the "stable" period, and the period 4 ± 2 weeks before recurrence as the "pre-recurrence" period.

To identify patient characteristics, we examined sex, age at the start and at the end of hospital observation, age at recurrence, number of recurrences, and duration of observation period. We examined the following laboratory data: UTP/UCr and daily urinary protein in urine tests, and total cholesterol (TCH), triglycerides (TG), and albumin in serum tests. When urinary protein was lower than the detection sensitivity, we defined UTP/UCr as zero. We examined mean prednisone (mPSL) and cyclosporine A (CyA) doses per day during the laboratory data examination. We graphed all UTP/UCr data in the stable and pre-recurrence periods for all patients by histogram.

To elucidate differences depending on age, we examined UTP/UCr during the stable periods in 5-year intervals. Based on this data, significant differences were found between ages 0-4 and 5-9 years ($p < 0.001$), 5-9 and 10-14 years ($p < 0.001$), and 10-14 and 15-19 years ($p = 0.004$), but no statistical differences were found between ages 15-19 and 20-24 years ($p = 0.57$); UTP/UCr reached a plateau at approximately 15 years of age. Based on this data, we divided our patients into two groups: those aged < 15 years and those aged ≥ 15 years. We graphed all UTP/UCr data in the stable and pre-recurrence periods for the two groups using a histogram. Furthermore, in these two groups, we selected only those patients for whom laboratory data of both the stable and pre-recurrence periods were available. We investigated medians of the laboratory data for all patients in each age group in the two age groups. Using these data, we compared laboratory data of the stable and pre-recurrence periods of the two age groups via tables and box plots.

Statistical analysis. We used the Mann–Whitney *U* test to compare numerical variables and the Wilcoxon signed-rank test to compare two related values of laboratory data. We defined $p < 0.05$ as statistically significant. We used R commander (version 2.3-0) software based on R version 3.3.2.

This study was approved by the Medicine Ethics Committee of Okayama University Hospital (approval number K2006-038). All patients and/or their parents were informed about the study and given the option to refuse participation.

Results

Study population. A total of 61 cases diagnosed as NS were reviewed. Two cases were diagnosed as focal segmental glomerular sclerosis and membranous nephropathy, respectively. In two cases of MCNS, no UTP/UCr data during remission were available at our hospital as the patients were transferred to other hospitals after short-term treatment. Twenty-one patients did not experience recurrence during treatment in our hospital. After exclusions, a total of 36 MCNS cases confirmed by renal biopsy or strongly suspected as MCNS based on their clinical features were included in our study.

Patient characteristics. Table 1A shows the characteristics of the patients in this study. Twenty-one patients (58%) were male. The median ages at the start and at the end of the observation period were 8 and 14 years, respectively. The median number of recurrences was 2. We summarized all laboratory data during the

stable or pre-recurrence periods for all cases, and we also summarized UTP/UCr data for those aged <15 years and those aged ≥15 years at recurrence (Table 1B). Statistical significance was found between disease stages for UTP/UCr, daily urinary protein, TCH, albumin, and mPSL and CyA doses. PSL doses were higher during pre-recurrence periods, and CyA doses were higher during stable periods. Although no obvious difference was found in UTP/UCr values between the stable and pre-recurrence periods for patients <15 years old, statistically significant differences were found for patients ≥15 years old.

UTP/UCr during stable and pre-recurrence periods. All data regarding UTP/UCr findings of the 36 cases during the stable and pre-recurrence periods are shown in Table 1B and depicted in Fig. 1 via histograms. A comparison of these two histograms shows that the values of UTP/UCr in pre-recurrence periods were somewhat higher, although UTP/UCr values were mostly within the normal range (≤0.15 g/g·Cr) during both periods.

UTP/UCr values every 5 years and comparison of UTP/UCr and daily urinary protein between patients <15 and those ≥15 years old. Fig. 2A shows UTP/UCr values during stable periods taken every 5 years. In younger children, UTP/UCr values tended to be higher

Table 1A Patients' characteristics

Parameter	Median (min~max), or n (%)
Sex, male (%)	21 (58)
Age at the start of treatment (years)	8 (1~19)
Age at the end of the observation (years)	14 (3~34)
Age at recurrence (years)	14 (1~24)
Number of recurrences	2 (1~18)
Observation period (years)	5 (1~17)

Table 1B Laboratory data parameters for the stable and pre-recurrence periods

Parameter	Stable periods		Pre-recurrence periods		*p*-value
	N	Median (min~max)	n	Median (min~max)	
UTP/UCr (g/g·Cr)	1,103	0.06 (0~1.2)	155	0.07 (0~1.3)	0.0018**
UTP/UCr (g/g·Cr) <15 years old	669	0.067 (0~0.80)	94	0.061 (0~0.70)	0.84
UTP/UCr (g/g·Cr) ≥15 years old	434	0.050 (0~1.2)	61	0.092 (0~1.3)	<0.001**
Daily urinary protein (g/day)	25	0.043 (0.009~0.22)	25	0.072 (0.015~0.16)	0.036*
TCH (mg/dL)	692	189 (92~660)	94	215 (141~506)	<0.001**
TG (mg/dL)	483	101 (25~1,261)	60	111 (45~352)	0.098
Albumin (g/dL)	780	4.2 (1.7~5.2)	106	3.9 (1.6~4.8)	<0.001**
mPSL (mg/day)	1,130	7.5 (0~70)	170	15 (0~80)	<0.001**
CyA (mg/day)	1,081	110 (0~220)	169	85 (0~220)	0.023*

**$p<0.01$.
*$p<0.05$.
P-values are for Mann–Whitney *U* test.
UTP/UCr, urinary protein-to-creatinine ratio; TCH, total cholesterol; TG, triglyceride; mPSL, mean prednisone; CyA, cyclosporine A.

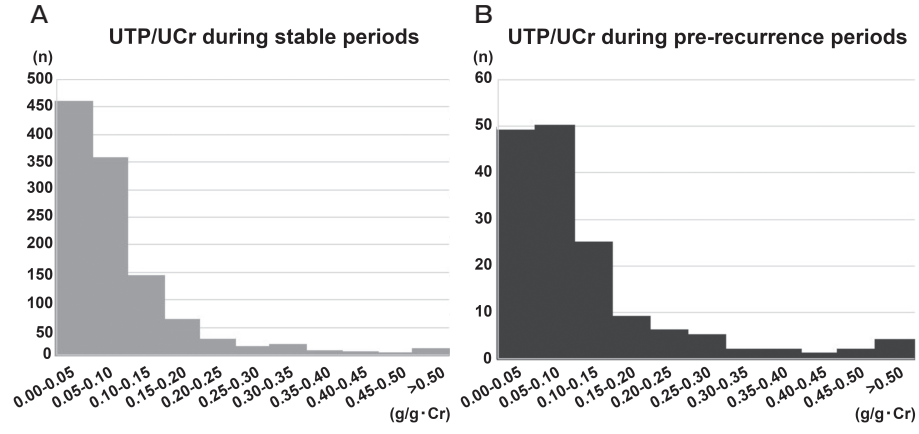

Fig. 1 UTP/UCr values during the stable and pre-recurrence periods. (**A**) Most UTP/UCr values were much lower than 0.15 g/g・Cr during stable periods. (**B**) Relatively higher UTP/UCr values were frequently found during pre-recurrence periods compared with stable periods.
UTP/UCr, urinary protein-to-creatinine ratio.

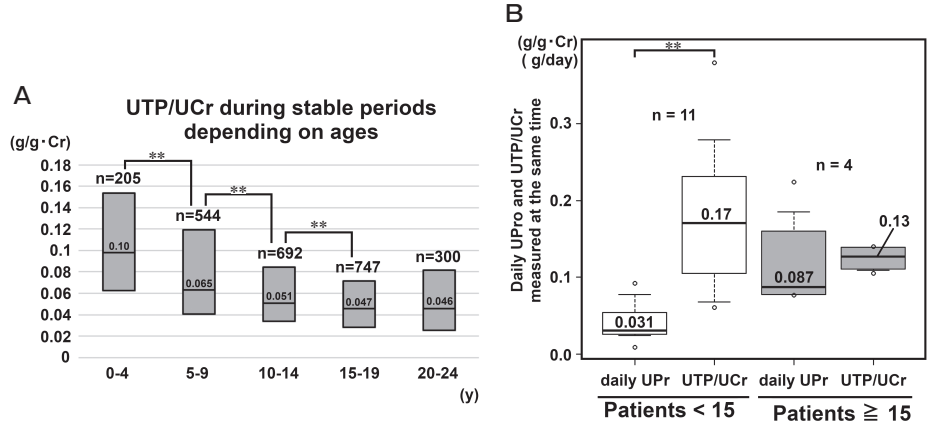

Fig. 2 (**A**) UTP/UCr values taken every five years during stable periods. The respective graphs indicate values from the 25th to 75th percentile and medians. UTP/UCr tended to have higher values in younger patients. After the age of 15 years, UTP/UCr medians become stable. (**B**) Daily urinary protein (g/day) and UTP/UCr (g/g・Cr) values during stable periods were compared in patients < 15 and ≥ 15 years old. UTP/UCr values were significantly higher in relation to daily urinary protein values in patients < 15 years old ($p < 0.001$). $^{**}p < 0.01$.
UTP/UCr, urinary protein-to-creatinine ratio; UPr, urinary protein.

than those in older children. The outcomes of our data analysis show that the values of UTP/UCr gradually declined and reached a plateau at approximately 15 years of age. As mentioned earlier, we categorized our cases into two groups according to this data to clarify the differences in clinical features between children and young adults. Fig. 2B shows that UTP/UCr observed in the cases < 15 years old overestimated daily urinary protein ($p < 0.001$).

UTP/UCr of patients < 15 versus those ≥ 15 years old. All UTP/UCr values in the stable or pre-recurrence periods of the two groups shown in Table 1B were used to create histograms (Fig. 3). For patients < 15 years old, no obvious change was found in the distribution of UTP/UCr values between the stable and pre-recurrence periods (Fig. 3A, B). The overall UTP/UCr values tended to be lower during stable periods and higher during pre-recurrence periods for patients ≥ 15

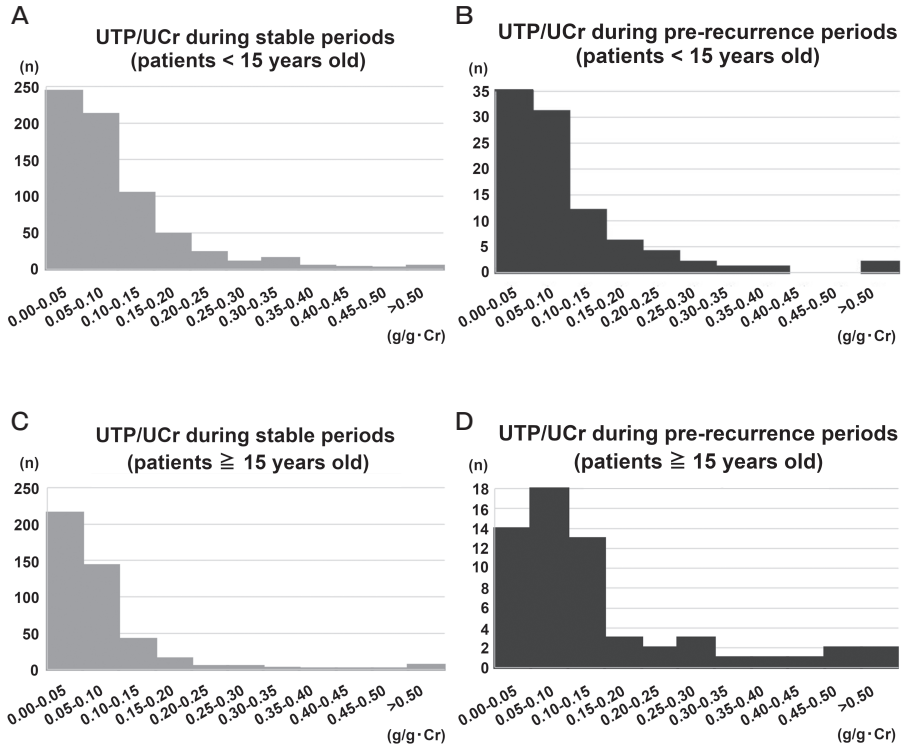

Fig. 3 UTP/UCr values during stable and pre-recurrence periods for patients < 15 and ≥ 15 years old. (**A**, **C**) UTP/UCr values during stable periods in patients ≥ 15 years old were lower than those in patients < 15 years old. (**A**, **B**) No obvious change was found in UTP/UCr distributions between the stable and pre-recurrence periods in patients < 15 years old. (**B**, **D**) UTP/UCr values in pre-recurrence periods tended to be higher in patients ≥ 15 years old than in those < 15 years old.
UTP/UCr, urinary protein-to-creatinine ratio.

years old in comparison to those of patients aged < 15 years. These histograms also indicate that when UTP/UCr was within the normal range (≤ 0.15 g/g・Cr), stable periods were expected rather than pre-recurrence periods in both age groups (Fig. 3).

Because the number of examinations varied widely among the cases, we compared our cases using medians during both the stable and pre-recurrence periods in the two age groups. Table 2 summarizes the laboratory data collected for patients who were examined during both stable and pre-recurrence periods. During the pre-recurrence periods, an increase in UTP/UCr and a decrease in serum albumin were found only in patients ≥ 15 years of age ($p = 0.006$ and $p = 0.009$, respectively) (Table 2). No statistical significance was found in mPSL or CyA doses between the two periods in the two age groups. Based on the data in Table 2, the distributions of UTP/UCr and serum albumin values during the stable and pre-recurrence periods of the two groups were represented using box-and-whisker plots. These box plots indicate obvious differences in the values of UTP/UCr and serum albumin only in patients ≥ 15 years of age (Fig. 4).

Recurrences and slight proteinuria. Although a slight increase in UTP/UCr was found during pre-recurrence periods in patients ≥ 15 years of age, most of these UTP/UCr values were within the normal range (UTP/UCr ≤ 0.15 g/g・Cr). When UTP/UCr was within the normal range via only a single examination, a stable period was predicted rather than the pre-recurrence period from the outcome of Fig. 3, and it was difficult to predict recurrences. Therefore, we additionally investigated the possibility of recurrence after slight proteinuria was found. We generated a receiver-operating characteristic (ROC) curve to determine the area under the curve (AUC) and cut-off value of UTP/UCr for predicting MCNS recurrence (Fig. 5). ROC analysis revealed that although AUC was only 0.661 for patients ≥ 15 years old, the specificity for the UTP/UCr cut-off value (0.324 g/g・Cr) was 0.769, which is relatively high.

Table 2 Laboratory data for patients less than 15 years old and patients 15 years or older with both stable and pre-recurrence periods

Parameter	Age group	n	Stable periods	Pre-recurrence periods	*p*-value
			Median (min~max)	Median (min~max)	
UTP/UCr, (g/g·Cr)	<15	18	0.06 (0.04~0.16)	0.06 (0.02~0.7)	0.5
	≥15	10	0.04 (0.02~0.08)	0.10 (0.05~0.24)	0.006**
TCH, (mg/dL)	<15	11	210 (165~264)	202 (169~305)	0.52
	≥15	9	202 (150~239)	216 (165~235)	0.29
TG, (mg/dL)	<15	9	111 (62~190)	110 (86~197)	1
	≥15	9	88 (73~138)	102 (63~154)	0.055
Albumin, (g/dL)	<15	12	4.0 (3.7~4.3)	3.9 (3.2~4.3)	0.4
	≥15	10	4.4 (3.7~4.6)	4.0 (3.2~4.5)	0.009**
mPSL, (mg/day)	<15	18	7.9 (0~40)	8.8 (0~80)	0.86
	≥15	10	5 (0~10)	5 (1.25~40)	0.4
CyA, (mg/day)	<15	18	12.5 (0~220)	0 (0~200)	1
	≥15	10	130 (50~180)	115 (30~180)	0.14

**$p<0.01$.
P-values are for Wilcoxon signed-rank test.
UTP/UCr, urinary protein-to-creatinine ratio; TCH, total cholesterol; TG, triglyceride; mPSL, mean prednisone; CyA, cyclosporine A.

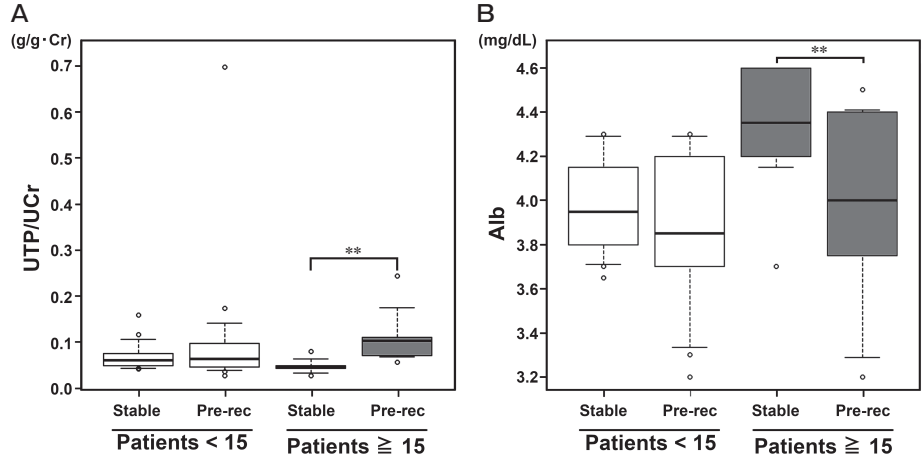

Fig. 4 Box-and-whisker plots of UTP/UCr and serum albumin values of cases examined during stable and pre-recurrence periods. (A) While no obvious change in UTP/UCr between the stable and pre-recurrence periods was found in patients <15 years old, pre-recurrence periods showed higher UTP/UCr compared to those in stable periods in patients ≥15 years old ($p=0.006$). (B) Data for serum albumin values showed a similar tendency as UTP/UCr, in that differences between the stable and pre-recurrence periods could only be seen in patients ≥15 years old ($p=0.009$). **$p<0.01$.
UTP/UCr, urinary protein-to-creatinine ratio; Alb, albumin; Stable, stable periods; Pre-rec, pre-recurrence periods; Patients <15, Patients <15 years old; Patients ≥15, Patients ≥15 years old.

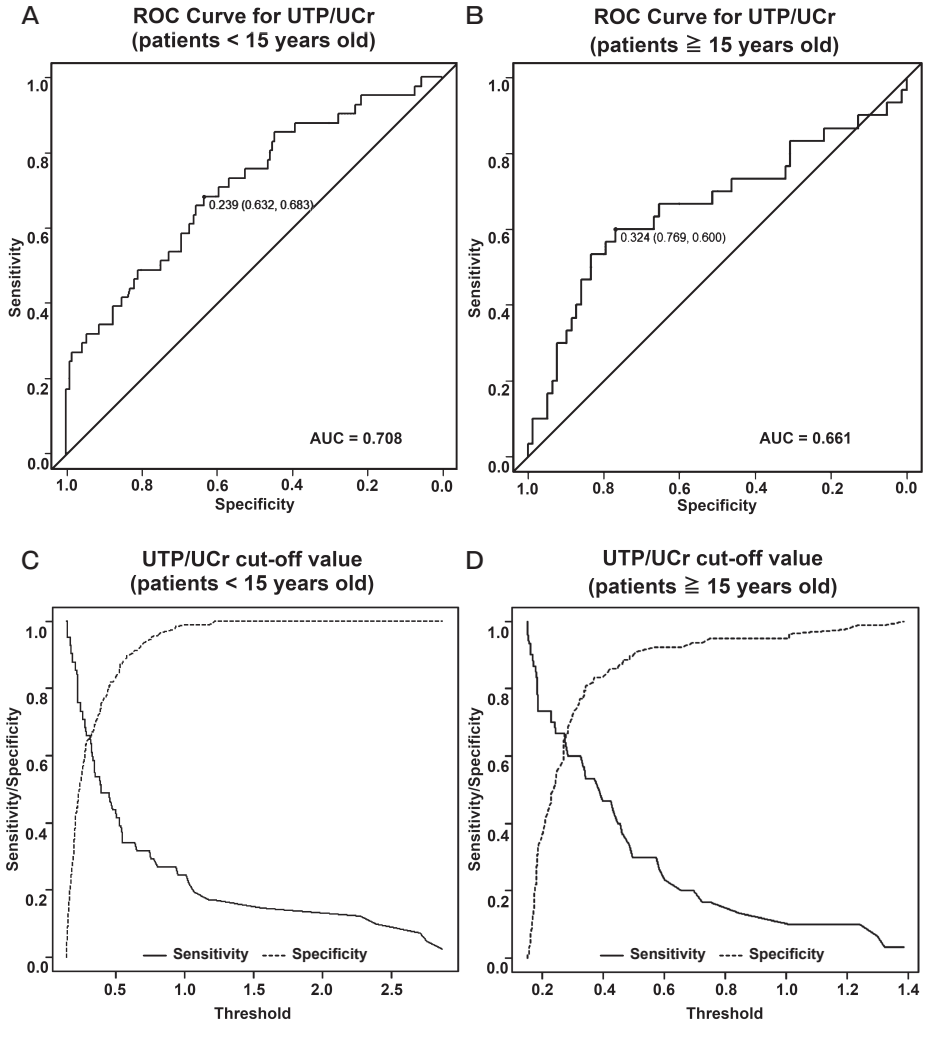

Fig. 5 Risk of recurrence evaluated when slightly elevated proteinuria (UTP/UCr >0.15g/g·Cr) was found. (**A**, **B**) ROC curves revealed an AUC of 0.708 and 95% CI of 0.616–0.8 for cases <15 years old and an AUC of 0.661 and 95% CI of 0.532–0.79 for cases ≥15 years old. (**C**, **D**) Cut-off value curves revealed UTP/UCr cut-off values of 0.324 and 0.239 g/g·Cr for cases ≥15 years and <15 years, respectively. The cutoff for cases ≥15 years had greater specificity (0.769) than that for cases <15 years (0.632). Sensitivity was 0.600 and 0.683, respectively.
UTP/UCr, urinary protein-to-creatinine ratio; ROC, receiver-operating characteristic; AUC, area under the curve; CI, confidence interval.

Discussion

In this study, differences in clinical features were found between patients <15 and ≥15 years of age, and signs of MCNS recurrence were found several weeks before recurrence in patients ≥15 years old.

Similar to adult MCNS cases, UTP/UCr is often evaluated instead of 24-hour protein in urine for child patients [6,7]. However, it is not well known whether UTP/UCr can reflect daily urinary protein excretion as well in pediatric cases as it does in adult cases. From previous reports of daily urinary protein excretion, it is known that urinary protein excretion in healthy children increases with age [8,9] and that daily urinary protein excretion in most adults is <0.1 g/day [10]. Evaluated simultaneously, UTP/UCr values were significantly higher than daily urinary protein levels among patients <15 years old, although no significant difference between UTP/UCr values and daily urinary protein levels was found in patients ≥15 years old.

Thus, the higher UTP/UCr observed in children may result in an overestimation of daily protein excretion in urine compared with adults. However, it is not known whether this outcome reflects UTP/UCr in healthy children or not.

Although prediction of MCNS subtypes, such as steroid sensitivity, steroid resistance, or frequently relapsing NS, has been discussed [11-13], no study to date has reported the predictive factors of recurrence in the short term. Regarding the relationship between laboratory data and MCNS recurrence, changes in UTP/UCr values during remission have not been examined to date. It has been reported that hyperlipidemia, in particular a high TCH level, was a risk factor for recurrence in pediatric cases of MCNS [14]. In our study, a significant difference was found in all TCH data between the stable and pre-recurrence periods (Table 1B), but the median TCH for cases examined both during the stable periods and the pre-recurrence periods revealed no significant difference between the <15 and ≥15-year-old cohorts (Table 2). Thus, although TCH might change before recurrence, further discussions are required. Though it has been reported that patients with serum albumin levels >3.5 g/dL have a decreased risk of NS recurrence provoked by membranous nephropathy [15], no study so far has examined whether serum albumin can be a predictive factor of recurrence in MCNS cases. The results of our study imply that signs of recurrence can be found in patients ≥15 years of age several weeks before the recurrence itself, and that changes in UTP/UCr or serum albumin data can be useful for predicting recurrence in MCNS cases.

We first examined UTP/UCr values during the stable and pre-recurrence periods, stratified by patient age. Our study shows that it is difficult to predict recurrences of MCNS using a single test that shows high-normal UTP/UCr: the risk of recurrence is considered relatively low when UTP/UCr values are within the normal range, even in patients ≥15 years of age. Impending recurrence may be considered in patients ≥15 years old when UTP/UCr values or daily urinary tests measured using dip sticks show slight worsening and this worsening is sustained over time. Further studies are required to precisely detect early signs of recurrence.

We performed ROC analysis to study the risk of recurrence when slight proteinuria is found, and the results showed that although AUC values for both age groups were low, the UTP/UCr cut-off value (0.324 g/g·Cr) for cases ≥15 years old had higher specificity (0.769) than the cut-off value (0.239 g/g·Cr) for cases <15 years old (specificity, 0.632). Reasons for proteinuria with UTP/UCr >0.3 g/g·Cr other than recurrence in patients ≥15 years old were viral infection and contamination with sperm; therefore, such conditions should be ruled out in these patients before determining recurrence when UTP/UCr >0.3 g/g·Cr. Further studies are required regarding the ideal management of slight proteinuria during the clinical course of MCNS patients, especially in those who are 15 years or older.

Our study had some limitations. First, this was a retrospective study with a non-uniform definition of recurrence, as cases could be diagnosed as recurrence by attending physicians before meeting the criteria of KDIGO. Second, the number of examinations varied widely among cases. Third, laboratory data for patients ≤5 years old or ≥20 years old were relatively few. However, we think the data on the natural course of MCNS patients at our hospital were meaningful.

In conclusion, the clinical features of MCNS cases differed depending on patient age. Slight changes in UTP/UCr or serum albumin can be found several weeks before MCNS recurrence in patients ≥15 years of age.

Acknowledgments. We are grateful to all the staff of Okayama University Hospital who were involved in patient care and labwork relating to this study. We would like to thank Editage (www.editage.com) and KN International for the English language editing.

References

1. Niaudet P and Boyer O: Idiopathic Nephrotic Syndrome in Children: Clinical Aspects; in Pediatr Nephrol, Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F and Goldstein SL eds, Springer Berlin Heidelberg, Berlin, Heidelberg (2016) pp839–882.
2. Eddy AA and Symons JM: Nephrotic syndrome in childhood. Lancet (2003) 362: 629–639.
3. Trompeter RS, Lloyd BW, Hicks J, White RH and Cameron JS: Long-term outcome for children with minimal-change nephrotic syndrome. Lancet (1985) 1: 368–370.
4. Wynn SR, Stickler GB and Burke EC: Long-term prognosis for children with nephrotic syndrome. Clin Pediatr (Phila) (1988) 27: 63–68.
5. Broyer M, Meyrier A, Niaudet P and Habib R: Minimal changes and focal segmental glomerular sclerosis; in Oxford Textbook of Clinical Nephrology, Cameron S, Davison A, GrünfeldJP, Kerr D and Ritz E eds, Oxford University Press, Oxford (1992) pp298–339.
6. Tsai WS, Tsau YK, Chen CH and Sheu JN: Correlation between

total urinary protein quantitation and random urine sample protein/creatinine ratio in children. J Formos Med Assoc (1991) 90: 760–763.
7. Ginsberg JM, Chang BS, Matarese RA and Garella S: Use of single voided urine samples to estimate quantitative proteinuria. N Engl J Med (1983) 309: 1543–1546.
8. Yang C, Kaushal V, Shah SV and Kaushal GP: Autophagy is associated with apoptosis in cisplatin injury to renal tubular epithelial cells. Am J Physiol Renal Physiol (2008) 294: F777–787.
9. Mori Y, Hiraoka M, Suganuma N, Tsukahara H, Yoshida H and Mayumi M: Urinary creatinine excretion and protein/creatinine ratios vary by body size and gender in children. Pediatr Nephrol (2006) 21: 683–687.
10. Nicholl DD, Hemmelgarn BR, Turin TC, MacRae JM, Muruve DA, Sola DY and Ahmed SB: Increased urinary protein excretion in the "normal" range is associated with increased renin-angiotensin system activity. Am J Physiol Renal Physiol (2012) 302: F526–532.
11. Rheault MN and Gbadegesin RA: The Genetics of Nephrotic Syndrome. J Pediatr Genet (2016) 5: 15–24.
12. Jellouli M, Brika M, Abidi K, Ferjani M, Naija O, Hammi Y and Gargah T: Nephrotic syndrome in children: risk factors for steroid dependence. Tunis Med (2016) 94: 401–405.
13. Mishra K, Kanwal SK, Sajjan SV, Bhaskar V and Rath B: Predictors of poor outcome in children with steroid sensitive nephrotic syndrome. Nefrologia (2018) 38: 420–424.
14. Mahmud S, Jahan S and Hossain MM: Hyperlipidemia in childhood idiopathic nephrotic syndrome during initial remission and relapse. Mymensingh Med J (2011) 20: 402–406.
15. Lee T, Chung Y, Poulton CJ, Derebail VK, Hogan SL, Reich HN, Falk RJ and Nachman PH: Serum Albumin at Partial Remission Predicts Outcomes in Membranous Nephropathy. Kidney Int Rep (2020) 5: 706–717.