ethical guidelines for epidemiological studies issued by the Ministry of Health, Labour and Welfare in Japan. The study was approved by the JSPN ethics board and a central ethics board (the institution of the Principal Investigator, KI) before study commencement. Because, data were reported retrospectively using patient charts, informed consent was not obtained in accordance with the above guidelines.

Statistical analyses

Estimation of the number of patients with stage 3–5 CKD in Japan from the reported number of patients in our survey was conducted as follows. The estimates were derived as the reported number divided by the response rate. Because the response rate tends to be lower in institutions with fewer patients, simple estimates can overestimate the true prevalence. Therefore, the reported patients were stratified according to institution type (i.e. university hospital, children's hospital and general hospital) and the number of beds (<200, 200–500 and ≥500), based on the assumption that the response rate is independent of the number of patients in each stratified category [16]. Then, the number of reported patients in each category was divided by the response rate and summed to calculate the total estimated number of patients in Japan. The total estimated number of patients was divided by the size of the population at risk in Japan reported by the Statistics Bureau of the Ministry of Internal Affairs and Communications of Japan (http://www.stat.go.jp/english/index.htm) to calculate the prevalence as of 1 April 2010. Weighted κ with 95% confidence interval (CI) was calculated to compare the CKD classification used here with the abbreviated Schwartz equation. All statistical analyses were carried out using SAS system version 9 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Subject characteristics

A total of 925 of 1190 institutions (77.7%) responded to the first questionnaire. A total of 479 children were identified in the second questionnaire. Of these, 447 children (272 males and 175 females) with stage 3–5 CKD who had not been treated with dialysis/renal transplantation fulfilled the eligibility criteria and were included in this study. Their characteristics are summarized in Table 3. Most of the children (315; 70.5%) had stage 3 CKD, whereas 107 (23.9%) had stage 4 and 25 (5.6%) had stage 5. The number of Japanese children with stage 3–5 CKD was estimated to be 542.5 (95% CI: 497.5–587.5) as of 1 April 2010. On the basis of this, the prevalence of stage 3–5 CKD was calculated to be 2.98 cases/100 000 Japanese children aged 3 months to 15 years. Figure 1 shows the SCr values for males and females according to CKD stage. All of the responding institutions used enzyme immunoassays to determine SCr levels for the assessment of CKD stage; none used other methods, such as the Jaffe method.

Figure 2 shows the frequencies of CKD stage according to the estimated GFR (eGFR) of 412 children in whom height was measured. Stage 3–5 CKD was classified using our diagnostic criteria derived from SCr levels of age- and sex-matched Japanese children, while the eGFR was determined using the abbreviated Schwartz equation, which was recently revised from the original Schwartz equation [17]. This figure also shows the distribution of children classified in each CKD stage determined using both methods. These data indicate that the distribution of CKD stages determined using population-based reference values is comparable with the distribution derived using a method based on the abbreviated Schwartz

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Table 3. Patient characteristics according to chronic kidney disease stage

	All subjects	Stage 3	Stage 4	Stage 5
n	447	315	107	25
Age (years)	8.7 ± 4.5	8.7 ± 4.6	8.5 ± 4.3	10.0 ± 4.5
Serum creatinine (mg/dL)	1.6 ± 1.2	1.1 ± 0.4	2.2 ± 0.8	5.3 ± 2.0
Height (cm)	119.8 ± 28.9	121.1 ± 28.7	118.8 ± 27.4	107.8 ± 35.6
Height SDS[a]	−1.6 ± 1.8	−1.3 ± 1.5	−2.2 ± 2	−3.5 ± 3
BUN (mg/dL)	35.6 ± 18.8	28.4 ± 9.8	48.6 ± 18.2	74.9 ± 31.5
CysC (mg/L)	2.1 ± 0.8	1.9 ± 0.5	3.1 ± 1.0	4.1 ± 0.9
eGFR–abbreviated (mL/min/1.73 m^2)[b]	39.5 ± 16	47.2 ± 11.2	22.6 ± 5.5	9.6 ± 3.2
eGFR–complete (mL/min/1.73 m^2)[c]	39.6 ± 12.3	43.7 ± 9.7	24.9 ± 5.3	11.6 ± 4.1

Values are means ± standard deviation.
SDS, standard deviation score; BUN, blood urea nitrogen; CysC, cystatin C.
[a]Height SDS was calculated using data recorded by the Japanese Society for Pediatric Endocrinology in 2000 (http://jspe.umin.jp/ipp_taikaku.htm).
[b]Determined using the abbreviated Schwartz equation.
[c]Determined using the complete Schwartz equation.

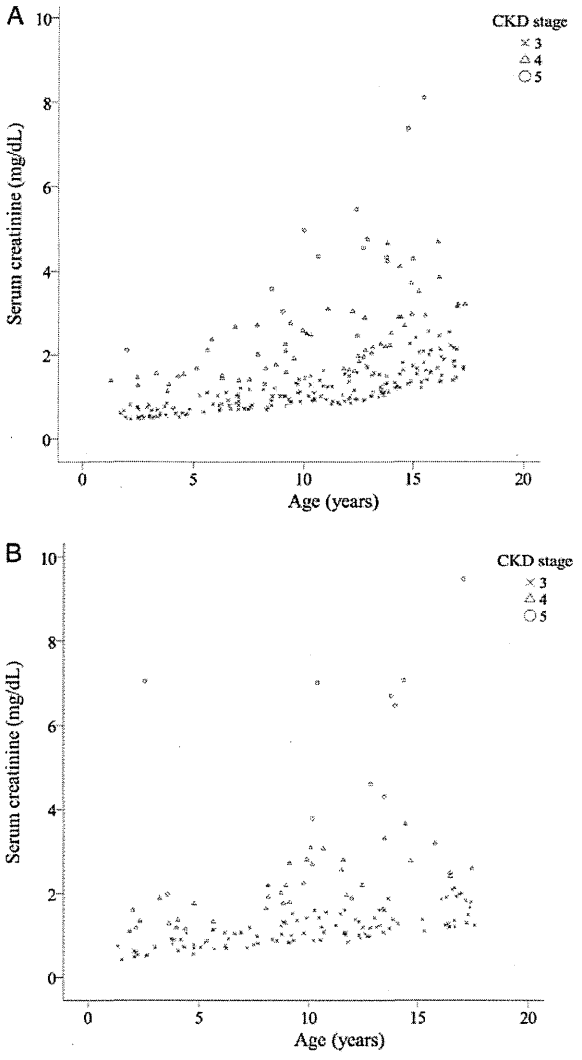


FIGURE 1. Serum creatinine levels according to age and CKD stage. Actual serum creatinine levels according to age and CKD stage are plotted separately for males (**A**) and females (**B**).

equation. The weighted κ-value for this comparison was 0.71 (95% CI: 0.65–0.77). For 198 children with cystatin C data, similar distributions were obtained when we compared our new classification with the complete Schwartz equation, which requires cystatin C-values [17] (data not shown).

Primary etiologies of pediatric CKD in Japan

The primary etiologies of CKD in the study population are presented in Table 4. Non-glomerular disease (407/447; 91.1%) was the most common primary cause of CKD, whereas glomerular disease accounted for 7.8% (35/447) of all cases.

Among those with non-glomerular diseases, 278 (68.3%) children had congenital anomalies of the kidney and urinary tract (CAKUT), of which 60 (21.6% of those with CAKUT) had obstructive urological malformations comprising posterior urethral valve, stricture of the urethra, hydronephrosis, hydroureter and cloacal anomaly (Table 4). The three most common causes of glomerular diseases were Alport's syndrome, focal segmental glomerulosclerosis and chronic glomerulonephritis ($n = 8$ each). No children presented with definitively diagnosed IgA nephropathy. Figure 3 shows the distribution of CAKUT and non-CAKUT diseases by age.

The diseases included recognizable syndrome [$n = 46$ (10.3%)] as follows: Down syndrome (OMIN, #190685, $n = 6$); VATER association (#192350, $n = 4$); Kabuki syndrome (#147920); Wolf–Hirschhorn syndrome (#194190) and Townes–Brocks syndrome (#107480, $n = 3$ each); prune belly syndrome (#100100) and branchio-oto-renal syndrome (#113650, 2 each) and others.

Methods of detecting Stage 3–5 CKD

Table 5 summarizes the methods and reasons for the detection of children with stage 3–5 CKD. Table 5 also presents the age at diagnosis for each of the methods. Fetal and perinatal ultrasonography was the most common method, followed by analysis by chance and urinary tract infection. As might be expected, CKD was generally detected at an earlier age in children with CAKUT than in children with other forms of CKD, particularly for analysis by chance (3.9 versus 5.8 years), urinary tract infection (0.7 versus 1.8 years) and failure to thrive (0.3 versus 2.2 years). Annual urinalysis at school detected CKD in 27 children (9.7%; median age, 8.9 years) with CAKUT and 12 children (7.1%; median age, 8.3 years) with other forms of CKD.

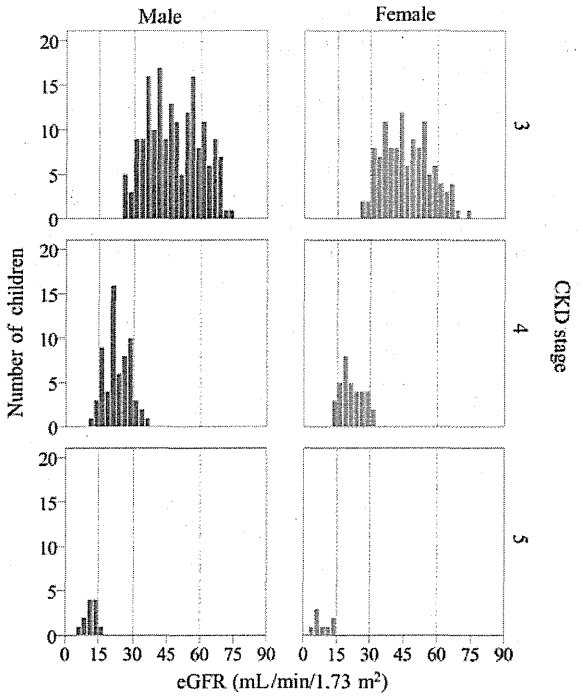
Treatment modalities for pediatric CKD

The treatment modalities for all patients included in this survey, and for patients with CAKUT and those with other forms of CKD, are summarized in Table 6. The most common treatments for CAKUT were angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) which were used in approximately one-quarter of the patients. Both ARBs and ACEIs together were used in 11 and 23 patients with CAKUT and other forms of CKD, respectively (data not shown). Carbon adsorbents (e.g. AST-120), which are approved as renoprotective agents adsorbing uremic toxins in the gastrointestinal tract [18] and calcium antagonists, were used in 13.0 and 7.2% of patients, respectively.

DISCUSSION

Our findings revealed that the prevalence of stage 3–5 CKD in children in Japan aged 3 months to 15 years is 2.98 cases/100 000 children. Out of 447 CKD cases surveyed, 407 (91.1%) had non-glomerular disease; among them, 278 (68.3%) had CAKUT. To our knowledge, this is the first cross-sectional, nationwide, population-based survey of children with pre-dialysis CKD in Asia. Several reports to date have described the epidemiology of pre-dialysis CKD in children; however, these studies were restricted to Western countries [3–10].

SCr levels were frequently used to estimate the GFR and screen for CKD. The original Schwartz equation has been used extensively in clinical practice for estimating the GFR in children, where GFR (mL/min/1.73 m^2) = age-dependent



Our classification	CKD classification determined using the abbreviated Schwartz equation				
	2	3	4	5	Total
Males					
3	35 (19.7%)	135 (75.8%)	8 (4.5%)	0 (0.0%)	178 (100.0%)
4	0 (0.0%)	6 (9.5%)	53 (84.1%)	4 (6.3%)	63 (100.0%)
5	0 (0.0%)	0 (0.0%)	1 (8.3%)	11 (91.7%)	12 (100.0%)
Females					
3	13 (11.2%)	99 (85.3%)	4 (3.4%)	0 (0.0%)	116 (100.0%)
4	0 (0.0%)	2 (5.7%)	30 (85.7%)	3 (8.6%)	35 (100.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (100.0%)	8 (100.0%)

FIGURE 2. Distribution of CKD stage in males and females. Stage 3–5 CKD was classified using our newly established diagnostic criteria derived from normal SCr levels of age- and sex-matched Japanese children. The eGFR was determined using the abbreviated Schwartz equation [17]. Stage 3–5 CKD was classified as GFR 30–59, 15–29 and <15 mL/min/1.73 m^2, respectively (<1/2, <1/4 and <1/8 of normal GFR, respectively). Only subjects in whom height was measured were included in this analysis. Values in the table are *n* (%).

coefficient $\kappa \times$ height (cm)/SCr (mg/dL) [15]. This equation was recently modified because of the increasing use of enzymatic methods to determine SCr levels, replacing the Jaffe method [17]. However, there are some possible limitations of the original Schwartz equation. First, it requires the patient's height, which is not always measured in routine clinical practice. Secondly, the GFR was reported to be lower in Asian adults than in Caucasians [19], which may have led us to overestimate the GFR when using the Schwartz equation in Asian children. To overcome these perceived limitations, several research groups have sought to establish reference levels in large populations of children [11, 20], which may be more practical and relevant for screening purposes in a specific country. Accordingly, in our present study, we evaluated renal function by comparison with established reference values [11]. In this way, CKD was determined based on SCr, rather than relying on equations adjusted for height and mathematical constants. As a result, children aged <2 years, to whom the normal CKD classification could not be applied, could be included. Similarly, Pottel *et al.* [20] proposed and validated a height-independent, population-normalized equation derived from the patient's SCr and the median SCr for age-matched healthy children. Based on their results, population-based reference levels for renal function and CKD may provide a valid approach to determine CKD stage for screening purposes, as in the present study. Indeed, our newly established CKD classification showed good validity compared with the abbreviated and complete Schwartz equations.

To classify stage 3–5 CKD, we used new diagnostic criteria based on previously determined SCr reference levels in age- and sex-matched Japanese children [11]. In that study, SCr was determined using enzymatic methods; in our current study, the participating institutes only used the enzymatic method to determine SCr. Therefore, our current results are

Table 4. Primary etiologies of stage 3–5 chronic kidney disease in Japanese children aged 3 months to 15 years

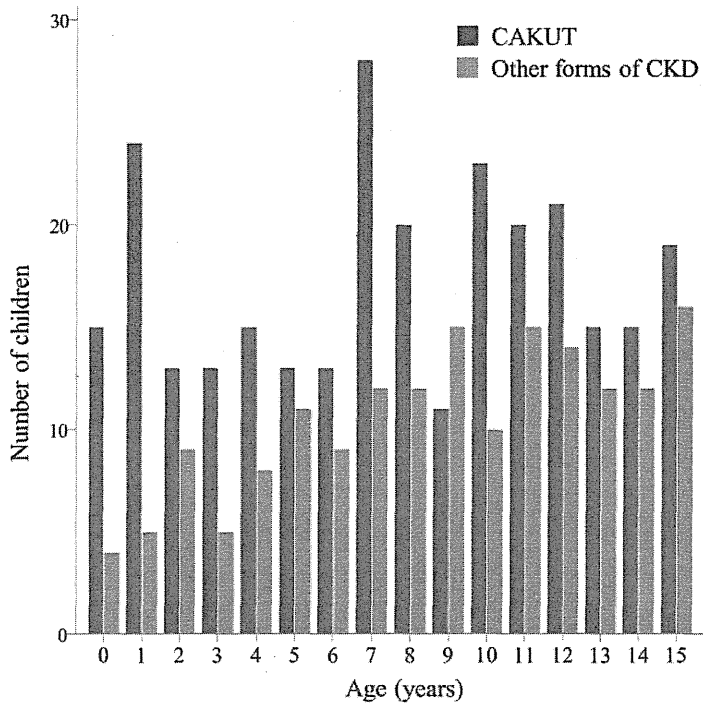
Primary disease	Non-glomerular kidney disease (n = 407, 91.1%)	Glomerular kidney disease (n = 35, 7.8%)	Unclassified (n = 5, 1.1%)
	n (%)	n (%)	n (%)
CAKUT	278 (68.3)	0 (0.0)	0 (0.0)
CAKUT with obstructive urological malformations[a]	60 (21.6)	0 (0.0)	0 (0.0)
CAKUT without obstructive urological malformations	218 (78.4)	0 (0.0)	0 (0.0)
Cortical necrosis (perinatal period)	40 (9.8)	0 (0.0)	0 (0.0)
Polycystic kidney disease	20 (4.9)	0 (0.0)	0 (0.0)
Nephronophthisis	19 (4.7)	0 (0.0)	0 (0.0)
Drug induced	17 (4.2)	0 (0.0)	1 (20.0)
Other inherited kidney damage	10 (2.5)	1 (2.9)	0 (0.0)
Acute kidney injury	10 (2.5)	0 (0.0)	0 (0.0)
Neurogenic bladder	6 (1.5)	0 (0.0)	0 (0.0)
Other non-inheritable character	4 (1.0)	2 (5.7)	0 (0.0)
Alport's syndrome	0 (0)	8 (22.9)	0 (0.0)
Cystinosis	1 (0.2)	0 (0.0)	0 (0.0)
Wilms tumor	1 (0.2)	0 (0.0)	0 (0.0)
Chronic tubulointerstitial nephritis	1 (0.2)	0 (0.0)	0 (0.0)
Focal segmental glomerulosclerosis	0 (0.0)	8 (22.9)	0 (0.0)
Chronic glomerulonephritis	0 (0.0)	8 (22.9)	0 (0.0)
Congenital nephrotic syndrome	0 (0.0)	3 (8.6)	0 (0.0)
Hemolytic uremic syndrome	0 (0.0)	3 (8.6)	0 (0.0)
Systemic lupus erythematosus	0 (0.0)	2 (5.7)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	4 (80.0)

[a]Posterior urethral valve, stricture of the urethra, hydronephrosis, hydroureter, and cloacal anomaly.

not subject to confounding because of the use of multiple assay types.

The prevalence of pre-dialysis stage 3–5 CKD was estimated to be 2.98 cases/100 000 Japanese children, which was lower than that reported in the ItalKid and REPIR II Projects (7.47 and 7.106 cases/100 000 children, respectively). The reason for this lower prevalence of CKD in Japan in comparison with Western countries is unclear, but differences in the age of the cohort and the method of case definition may account for some of the difference. For example, the ItalKid Project [3] included children aged <20 years, used the original Schwartz equation to determine GFR and included children with eGFR <75 mL/min/1.73 m^2. Similarly, the REPIR II study [4] included children aged <19 years with stage 2 CKD, which accounted for 42% of their cases. Nevertheless, the estimated prevalence of stage 3–5 CKD in Spain, based on data from the REPIR II study, is 4.12 cases per 100 000 children (7.106 × 58%), which is slightly higher than that estimated in our study. The low frequency of pre-dialysis CKD in our study is consistent with the low frequency of children with ESRD in Japan [7].

A number of factors, such as differences in racial and ethnic distributions, primary cause of CKD and quality of medical care, may contribute to the difference in reported prevalence estimates between Japan and Western countries. Additionally, the prevalence of obstructive uropathy is low in Japan, being detected in just 21.6% of patients with CAKUT; by contrast, in Western countries, obstructive uropathy accounts for many cases of non-glomerular disease in children with CKD [21, 22]. Several factors may explain the differences in the prevalence of CAKUT with obstructive uropathy, including (i) genetic differences that affect the distribution of



Age	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Population (thousands)[a]	1,078	1,092	1,084	1,072	1,050	1,088	1,111	1,145	1,160	1,180	1,179	1,193	1,188	1,183	1,206	1,208	18,217
CAKUT[b]	15	24	13	13	15	13	13	28	20	11	23	20	21	15	15	19	278
Other forms of CKD[b]	4	5	9	5	8	11	9	12	12	15	10	15	14	12	12	16	169

FIGURE 3. Age distribution of children with stage 3–5 CKD in Japan. Children with CAKUT are shown in dark gray bars, while those with other forms of CKD are shown in light gray bars. [a]Total numbers of children of each age in Japan derived from national census data (1 April 2010) published by the Statistics Bureau of Ministry of Internal Affairs and Communications in Japan (http://www.stat.go.jp/english/index.htm). [b]Number of children with CAKUT or other forms of CKD reported in the survey. CKD, chronic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract.

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obstructive diseases (e.g. prune-belly syndrome) and (ii) the diagnosis of these congenital diseases may be difficult, resulting in underestimation of obstructive uropathies. However, despite the lower frequency of obstructive uropathy in Japan, appropriate urological interventions are still an indispensable part of the management of children with CKD, because they are one of very few treatments that can change the outcome of CKD [23].

Despite the lower prevalence of CKD in our study compared with European cohorts, we believe that our data accurately represent the current situation in Japan because 1190 institutes, including all institutes belonging to the JSPN, were included in the survey and there was a very high response rate (77.7%). We also stratified institutions by hospital type and the number of beds to improve the accuracy of the estimated prevalence. Because the response rate tended to be lower for institutions with fewer patients, estimates of CKD prevalence that do not take strata (hospital size and type) into account are possibly overestimates. For example, a simple estimate without stratification in the present study would have been 599.0 children rather than the 542.5 estimated with strata taken into account. Thus, the stratified estimation method should correct for a bias between response rates and hospital type/size. Nevertheless, it is possible that some patients with stage 3–5 CKD were treated at other types of institutions not included in this survey.

The majority of Japanese children with CKD presented with non-glomerular disease. CAKUT was the primary cause of CKD (i.e. 62.2% of all CKD cases). This observation was expected. Unlike in adults, in whom diabetes and hypertension are the primary cause of CKD, congenital causes are responsible for majority of pediatric CKD cases [1, 7]. The prevalence of CAKUT in our study is also consistent with that reported in the ItalKid and REPIR II studies (67.5 and 59%, respectively) [3, 4].

Interestingly, there were very few cases of glomerular disease, such as focal segmental glomerulosclerosis, and no confirmed cases of IgA nephropathy (one case was suspected, but diagnosis was not confirmed). In a Japanese registry of pediatric ESRD patients conducted in 1998, 19% of patients had focal segmental glomerulosclerosis and 3% had IgA nephropathy [24]. The present analysis is likely to have underestimated the prevalence of these diseases for several reasons. First, these diseases progress more rapidly than non-

Table 5. Method of detection of Stage 3–5 CKD

Screening method	CAKUT (n = 278)	Age at which CKD was detected (years)		Other formsof CKD (n = 169)	Age at whichCKD was detected (years)	
	n (%)	Median	IQR	n (%)	Median	IQR
Fetal ultrasonography/ultrasonography in the neonatal period	88 (31.7)	0.0	0.0–0.0	19 (11.2)	0.0	0.0–0.0
Analysis by chance	38 (13.7)	3.9	1.2–6.1	32 (18.9)	5.8	1.7–9.4
Urinary tract infection	38 (13.7)	0.7	0.3–2.0	4 (2.4)	1.8	0.3–3.6
Annual urinalysis at school	27 (9.7)	8.9	7.0–10.3	12 (7.1)	8.3	7.1–10.9
Blood analysis in the neonatal period, asphyxia, neonatal shock and other events	25 (9.0)	0.0	0.0–0.1	31 (18.3)	0.0	0.0–0.0
Failure to thrive, weight loss and general fatigue	25 (9.0)	0.3	0.1–1.0	7 (4.1)	2.2	0.2–12.3
Urinalysis at 3 years	9 (3.2)	3.2	3.0–3.4	7 (4.1)	3.1	3.0–3.6
Routine health check (infants/toddlers)	7 (2.5)	0.3	0.1–1.7	4 (2.4)	2.8	0.4–5.1
Symptoms of glomerulonephritis (edema, oliguria or gross hematuria)	5 (1.8)	3.8	1.0–5.0	13 (7.7)	5.3	2.7–8.7
Analysis because of anomalies and syndromal stigmata	3 (1.1)	0.0	0.0–0.1	1 (0.6)	1.7	1.7–1.7
Detected during the management of other diseases(e.g. heart disease and malignancy)	2 (0.7)	5.3	5.3–5.3	18 (10.7)	3.2	0.2–8.2
Dysuria, including neurogenic bladder and nocturia	2 (0.7)	4.9	4.9–4.9	4 (2.4)	5.7	1.2–9.5
Analysis because of family history	0 (0.0)	—	—	3 (1.8)	6.2	4.5–9.7
Sepsis	0 (0.0)	—	—	3 (1.8)	0.0	0.0–0.1
Others	0 (0.0)	—	—	2 (1.2)	2.2	0.8–3.7
Unknown (not available)	9 (3.2)	—	—	9 (5.3)	—	—

CKD, chronic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract.

glomerular diseases and could have been missed in the survey. Secondly, we restricted our analysis to those aged <16 years, but chronic glomerulonephritis frequently affects patients aged 16–20 years. Furthermore, these diseases respond well to novel treatment regimens that are well established in Japan, including combination therapy for IgA nephropathy [25] and cyclosporine in combination with steroids for steroid-resistant nephrotic syndrome, including focal segmental glomerulosclerosis [26].

Fetal/neonatal ultrasonography was the most frequently used method to detect CAKUT, followed by blood analyses by chance and urinary tract infection. Only 27 children with CAKUT and 12 with other forms of CKD were detected following annual urinalysis at school. Patients with CKD, particularly children with CAKUT, do not necessarily show abnormal urinalysis, and are missed by the screening. It is also possible that CKD (particularly non-CAKUT forms of CKD) could be detected in the earlier stages (earlier than stage 3) and patients could then receive appropriate intervention to treat the underlying disease. The treatment strategies for CAKUT and other forms of CKD in each institution were generally similar, although the responding institutions more often reported using carbon absorbents for CAKUT and ACEIs in other forms of CKD (data not shown).

Some limitations of the study merit consideration. First, only 77.7% of the surveyed institutions responded to the questionnaire, which may limit the accuracy of the estimate. Secondly, although the classification system used for CKD staging in the present study was based on reference SCr levels determined via enzymatic methods from Japanese children, these diagnostic criteria have not been validated globally and other reference values would be needed for other populations. Height could have also been determined to estimate GFR via the Schwartz equation; however, because the GFR is inversely

Table 6. Treatment strategies for CAKUT and other forms of CKD for individual patients

	CAKUT (n = 278)	Other forms of CKD (n = 169)	All patients (n = 447)
	n (%)	n (%)	n (%)
ARBs			
No	201 (72.3)	115 (68.0)	316 (70.7)
Yes	74 (26.6)	53 (31.4)	127 (28.4)
NA	3 (1.1)	1 (0.6)	4 (0.9)
ACEIs			
No	209 (75.2)	108 (63.9)	317 (70.9)
Yes	66 (23.7)	60 (35.5)	126 (28.2)
NA	3 (1.1)	1 (0.6)	4 (0.9)
Carbon absorbents			
No	237 (85.3)	144 (85.2)	381 (85.2)
Yes	34 (12.2)	24 (14.2)	58 (13.0)
NA	7 (2.5)	1 (0.6)	8 (1.8)
Calcium antagonists			
No	264 (94.9)	147 (87.0)	411 (91.9)
Yes	11 (4.0)	21 (12.4)	32 (7.2)
NA	3 (1.1)	1 (0.6)	4 (0.9)

CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; NA, not available.

proportional to SCr in age- and sex-matched individuals, and because we used age- and sex-matched reference SCr levels established in a previous study with 1151 children, our measurements should be accurate enough and more practical for screening purposes. Indeed, our CKD staging showed good agreement with CKD staging based on the abbreviated Schwartz equation (Figure 2). Because, our CKD staging method is based on the SCr level, CKD may be missed in children with small muscle mass, such as those with spina bifida, neuromuscular disease and short stature.

To our knowledge, this is the first nationwide, population-based survey of children with pre-dialysis CKD in Asia and applied reference levels for CKD derived from a large cohort of Japanese children. This method showed good agreement with the abbreviated Schwartz equation and is practical for screening purposes, including children aged <2 years, as current methods are not appropriate for estimating CKD in this age group. The estimated prevalence of stage 3–5 CKD in Japan was 2.98 cases/100 000 children, which is lower than that in Western countries. Most cases presented with non-glomerular disease, and CAKUT was the most common cause of CKD. Improved management of CAKUT in children with CKD, including renoprotective treatment and urological interventions, is required. We are planning randomized and longitudinal studies to improve the management of pediatric CKD, and better understand its long-term prognosis.

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CONFLICT OF INTEREST STATEMENT

Kenji Ishikura has received travel expense from Asahi Kasei Pharma and lecture fee and travel expense from Novartis Pharma.

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Original Article

Progression to end-stage kidney disease in Japanese children with chronic kidney disease: results of a nationwide prospective cohort study

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ORIGINAL ARTICLE

ABSTRACT

Background. The risk of progressing to end-stage kidney disease (ESKD) and factors associated with progression in children with chronic kidney disease (CKD) are unclear, especially in Asian children.

Methods. We started a nationwide, prospective cohort study of 447 Japanese children with pre-dialysis CKD in 2010, with follow-up in 2011. Progression to ESKD was analyzed by Kaplan–Meier analysis according to CKD stage. Cox regression analysis was used to identify risk factors for progression.

Results. Data were analyzed for 429/447 children. Five patients died, of which four died before progression to ESKD. Fifty-two patients progressed to ESKD (median follow-up 1.49 years), including 9/315 patients with stage 3 CKD, 29/107 with Stage 4 CKD and 14/25 with Stage 5 CKD. One-year renal survival rates were 98.3, 80.0 and 40.9%, for Stages 3, 4 and 5 CKD, respectively. Risk factors for progression to ESKD included CKD stage [versus Stage 3; Stage 4: hazard ratio (HR) 11.12, 95% confidence interval (CI) 4.22–29.28, $P < 0.001$; Stage 5: HR 26.95, 95% CI 7.71–94.17, $P < 0.001$], heavy proteinuria (>2.0 g/g urine creatinine; HR 7.56, 95% CI 3.22–17.77, $P < 0.001$) and age (< 2 years: HR 9.06; 95% CI 2.29–35.84, $P = 0.002$; after starting puberty: HR 4.88; 95% CI 1.85–12.85, $P = 0.001$).

Conclusions. In this cohort, 12.5% of children with pre-dialysis CKD progressed to ESKD with a median-follow-up of 1.49 years. Children with advanced (Stage 4/5) CKD were particularly likely to progress. To our knowledge, this is the first, nationwide, prospective cohort study of children with pre-dialysis CKD in Asia.

Keywords: Asia, child, chronic kidney disease, end-stage kidney disease, prognosis

INTRODUCTION

Chronic kidney disease (CKD) in children is a progressive and intractable disease [1]. In the CKD in Children study, children with a glomerular filtration rate (GFR) of <30 mL/min/1.73 m^2

showed significant growth failure and other clinically important disorders compared with children with a higher GFR (≥50 mL/min/1.73 m^2), and experienced greater progressive changes in their GFR [2]. The mortality rate in children with end-stage kidney disease (ESKD) is also quite high, and was reported to be 98.8/1000 person-years among children who started dialysis between 1990 and 2010 in the USA [3].

The prevalence of CKD in children/adolescents varies considerably among studies and countries [4–10]. Furthermore, the incidence of Stage 2–5 CKD in children was reported to range from 7.7 to 12.1 per million [6], based on data reported in six countries (Italy [11], Belgium [12], Spain [13], Sweden [14], France [15] and Turkey [16]). The broad range in the incidence of CKD was at least partly due to differences in the clinical definition of CKD used in each study. The differences in study design and possible differences in CKD characteristics among ethnic groups also mean it is difficult to compare the prevalence of CKD and ESKD among studies, or estimate the prevalence of severe kidney disease worldwide or in specific populations lacking current data. Furthermore, while the prevalence of CKD in adults is steadily increasing in many countries [8], the current situation in children is less clear, particularly in Asian children.

It was also suggested that the rate of decline in renal function in Japanese adults appears to be slow compared with that in other countries, and that hypertension, proteinuria and low GFR were significant risk factors for a faster decline of GFR in Japanese adults [17]. However, no studies have examined the decline in renal function in Japanese children with CKD, or sought to identify risk factors for progression to ESKD.

To address these issues and to help us to better understand the current status of CKD in Japan, we implemented a nationwide, prospective cohort study of pre-dialysis CKD in Japanese children [9], the first such study in Asia. We previously reported that the prevalence of Stage 3–5 CKD was 2.98 cases/100 000 children, and that most children with CKD presented with non-glomerular disease, including congenital anomalies of the kidney and urinary tract (CAKUT). As the original results were derived from a cross-sectional analysis, we could not determine the rate of disease progression in these patients at that time. Therefore, as planned, we conducted a follow-up survey to determine the rate of disease progression in these patients. From this context, the aims of the present analyses were (1) to investigate the progression of CKD to ESKD or death and (2) to identify factors associated with disease progression.

MATERIALS AND METHODS

Study design and population

The study design and patient population are described in more detail in our original report [9]. Briefly, we sent two surveys in August 2010 to 1190 institutions (all members of the Japanese Society for Pediatric Nephrology, all university and children's hospitals, and all general hospitals with >200 beds) in Japan inviting them to report on cases of pediatric CKD managed as of 1 April 2010. The first survey documented the number of children with Stage 3–5 CKD in each institution. The respondents were asked to search their medical records to determine the numbers of patients with a confirmed diagnosis of CKD, or patients with abnormal serum creatinine (SCr) values. In the second survey, the respondents were asked to record the clinical characteristics of each patient. A total of 925/1190 institutions (77.7%) responded to the first questionnaire. In the second questionnaire, the participating institutions provided data for 479 children. Of these, 447 children who met the following criteria were evaluable: (i) children with CKD aged 3 months to 15 years as of 1 April 2010; (ii) presence of Stage 3–5 CKD; (iii) no history of chronic dialysis or renal transplantation; (iv) renal failure lasting >3 months (cases with transient increases in SCr were excluded).

In September 2011, surveys were conducted for the 113 medical institutions that provided data for the cohort of children ($n = 447$) established in our original report [9]. The deadline for responding to this survey was November 2011. Data were provided for 429/447 children in the follow-up survey. The survey asked clinicians to record patient characteristics [e.g. height, weight, blood pressure, cardiac function and blood and urine parameters, including urine protein/creatinine ratio (g/g urine creatinine)], outcomes (start of dialysis, kidney transplantation and death), CKD complications, disease type and neonatal data (birth weight, gestational age and presence of asphyxia), as of 1 November 2011. All surveys were to be returned using provided envelopes and data entry was conducted by the data center.

CKD stage was assessed as previously described [9, 18]. Stages 3, 4 and 5 CKD were defined as SCr levels more than twice, four times and eight times, respectively, the median normal levels in age- and sex-matched Japanese children. In our previous report [9], we validated these reference levels by applying the abbreviated Schwartz equation [19], with Stages 3, 4 and 5 CKD being classified as GFR 30–59, 15–29 and <15 mL/min/1.73 m^2, respectively (<1/2, <1/4 and <1/8 of normal GFR, respectively), defined according to established guidelines [20–22]. All of the participating institutions reported using enzyme immunoassays to measure SCr. Heavy proteinuria was defined as urine protein/creatinine ratio >2.0 g/g urine creatinine. The patients were divided into three age groups for males (<2, ≥2 to <10.8 and ≥10.8 years) and females (<2, ≥2 to <10.0 and ≥10.0 years), where 10.8 and 10.0 years correspond to the mean age of Japanese males and females, respectively, at the start of puberty [23]. Hypertension was defined as systolic blood pressure >95th percentile [24].

The study was conducted in accordance with the principles of the Declaration of Helsinki and the ethical guidelines issued by the Ministry of Health, Labour and Welfare, Japan. The study was approved by a central ethics board at Tokyo Metropolitan Children's Medical Center (approval number: 23–49). Because data were reported using patient medical records, informed consent was not obtained in accordance with the above guidelines.

Statistical analysis

The primary outcome was the progression of CKD to ESKD. The cumulative proportion of progression was estimated by the Kaplan–Meier method, where death was also

Table 1. Patient characteristics according to CKD stage

	All patients	Stage 3	Stage 4	Stage 5	P-value*
n	447	315	107	25	
Age (years)	8.6 ± 4.5	8.6 ± 4.6	8.4 ± 4.2	9.9 ± 4.5	0.321
Sex, male/female (*n*)	272/175	192/123	67/40	13/12	0.618
Serum creatinine (mg/dL)	1.6 ± 1.2	1.1 ± 0.4	2.2 ± 0.8	5.3 ± 2.0	<0.001
Height (cm)	119.6 ± 27.8	120.5 ± 28.1	117.1 ± 26.9	118.1 ± 28.9	0.547
Height (SD)	−1.5 ± 1.8	−1.3 ± 1.5	−1.8 ± 2.1	−2.8 ± 3.2	<0.001
BUN (mg/dL)	35.5 ± 18.7	28.3 ± 9.7	48.4 ± 18.1	74.9 ± 31.5	<0.001
Cystatin-C (mg/L)	2.1 ± 0.8	1.9 ± 0.5	3.1 ± 1.0	4.1 ± 0.9	<0.001
eGFR abbreviated (mL/min/1.73 m^2)[a]	39.6 ± 15.9	47.3 ± 11.4	22.6 ± 5.3	10.4 ± 3.3	<0.001
eGFR complete (mL/min/1.73 m^2) [b]	39.9 ± 12.4	43.9 ± 10.0	24.7 ± 5.2	13.5 ± 4.0	<0.001

Values are means ± standard deviation. CKD, chronic kidney disease; SDS, standard deviation score; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.
[a]Abbreviated Schwartz equation [19], eGFR = 41.3 [height (m)/SCr (mg/dL)].
[b]Complete Schwartz equation [19], eGFR = 39.1 [height (m)/Scr (mg/dL)]$^{0.516}$[1.8/cystatin C (mg/L)]$^{0.294}$ × [30/BUN (mg/dL)]$^{0.169}$ [1.099]^{male} [height (m)/1.4]$^{0.188}$.
*P-values were determined by analysis of variance for all variables except sex, which was analyzed by the χ^2 test.

considered as an event. The day on which SCr was measured that was closest to 1 April 2010 was used as the starting point (i.e. T = 0 years). Cox's proportional hazard regression model was used to identify possible predictors of CKD progression by calculating hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were carried out using SAS system version 9 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient characteristics

The characteristics of the patients, as of 1 April 2010, are summarized in Table 1. Of the 447 children in this cohort, 405 were of Asian ethnicity and 3 were of another ethnicity; ethnicity was not reported by the institution for the remaining 39 children.

As would be expected, SCr, blood urea nitrogen and cystatin C levels increased significantly with increasing CKD stage, consistent with reductions in eGFR, as determined with the abbreviated and complete Schwartz equations [19]. Children with Stage 5 CKD tended to be older than children with Stage 3/4 CKD.

Progression to ESKD and renal replacement therapy

Table 2 shows the patient outcomes during this survey. Overall, 52 patients progressed to ESKD during the follow-up period [median follow-up period (interquartile range) 1.49 years (1.16–1.64 years); Stage 3, $n = 9$; Stage 4, $n = 29$; Stage 5, $n = 14$]. Of these, 1/9 patients in Stage 3, 21/29 patients in Stage 4 and 8/14 in Stage 5 had CAKUT. Five deaths (sepsis in two; acute encephalitis, graft versus host disease and acute heart failure and pulmonary edema caused by advanced uremia in one each) occurred during the study period, of which four occurred before and one occurred after progression to ESKD. The detailed characteristics of patients with progression to ESKD or who died are presented in Table 3. The Kaplan–Meier analysis for the time to ESKD or death (included as an event) is presented in Figure 1. Among 429/447 children with available data, the survival rates at 1 year were 98.3, 80.0 and 40.9% in children with Stage 3, 4 and 5 CKD, respectively. The Kaplan–Meier plot and survival rates were almost identical when deaths were censored instead of being included as an event; the survival rates at 1 year were 98.3, 80.9 and 43.1% in children with Stage 3, 4 and 5 CKD, respectively.

Table 2. Outcomes and renal replacement therapies according to CKD stage

	All patients	Stage 3	Stage 4	Stage 5
n	447	315	107	25
Data not provided by the participating institution	18	11	4	3
Death before progression to ESKD	4	1	2	1
ESKD	52[a]	9	29[a]	14
Renal replacement therapies				
PD	27	6	15	6
Preemptive kidney transplantation	16	1	11	4
Kidney transplantation after PD	3	0	1	2
HD	4[a]	2	1[a]	1
PD after HD	2	0	1	1
Change in CKD stage (excluding death before progressing to ESKD)				
To Stage 2		43	1	0
To Stage 3		210	6	0
To Stage 4		40	56	1
To Stage 5 (5D)		10 (9)	38 (29)	20 (14)

CKD, chronic kidney disease; ESKD, end-stage kidney disease; PD, peritoneal dialysis; HD, hemodialysis.
[a]Includes one death.

The most common chronic renal replacement therapy in children with ESKD was peritoneal dialysis, which was used in 27 children, followed by preemptive kidney transplantation in 16 patients (Table 2).

During the follow-up period, 40 and 10 of 315 children with Stage 3 CKD progressed to Stage 4 and Stage 5 (Stage 5D in 9/10 patients) CKD, respectively, while 38/107 patients with Stage 4 CKD progressed to Stage 5 (Stage 5D in 29/38 patients).

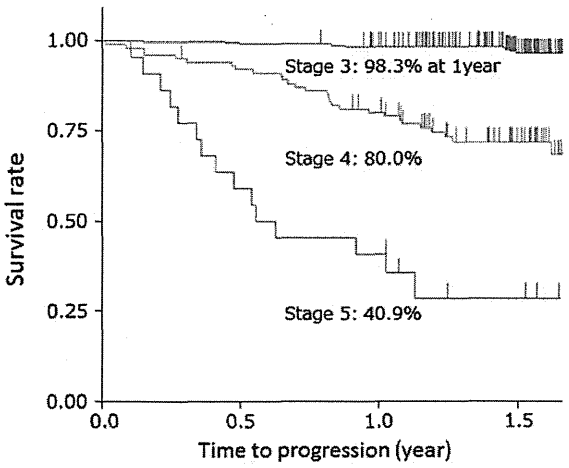
Factors associated with CKD progression

CKD progression was defined as ESKD or death occurring during follow-up. Table 4 shows the factors that were

Table 3. Characteristics of patients who progressed to ESKD or who died

CKD stage in 2010[a]	Age in 2010 (years)	Sex	Primary etiology	Method of detecting CKD	Recognizable syndrome
Deaths					
3	3.6	Male	Unknown	Urinary tract infection	Down syndrome
4	3.4	Male	Cortical necrosis (perinatal period)	Blood analysis in the neonatal period, asphyxia, neonatal shock	—
4	0.7	Male	CAKUT without obstructions	Fetal ultrasonography/ultrasonography in the neonatal period	—
4 Deaths after ESKD	8.3	Male	Drug induced	Detected during the management of other diseases(e.g. heart disease)	—
5	13.5	Female	CAKUT without obstructions	Failure to thrive, weight loss and general fatigue	—
Progression to ESKD					
3 ($n = 9$)	9.8 ± 4.9	6 males 3 females	CAKUT without obstructions (1); chronic glomerulonephritis (2); congenital nephrotic syndrome (1); focal segmental glomerulosclerosis (2); nephronophthisis (1); other inherited kidney damage (2)	Analysis by chance (4); annual urinalysis at school (3); blood analysis in the neonatal period, asphyxia, neonatal shock (1); fetal ultrasonography/ultrasonography in the neonatal period (1)	Bardet–Beadle syndrome (1); Lowe syndrome (1)
4 ($n = 28$)	9.5 ± 4.7	15 males 13 females	CAKUT with obstructions (4); CAKUT without obstructions (17); congenital nephrotic syndrome (1); hemolytic uremic syndrome (1); nephronophthisis (3); neurogenic bladder (1); other inherited kidney damage (1)	Analysis by chance (6); annual urinalysis at school (2); blood analysis in the neonatal period, asphyxia, neonatal shock (4); dysuria, including neurogenic bladder and nocturia (1); failure to thrive, weight loss and general fatigue (3); fetal ultrasonography/ultrasonography in the neonatal period (6); symptoms of glomerulonephritis (edema, oliguria or gross hematuria (1); unknown (1); urinalysis at 3 years (2); urinary tract infection (2))	15q syndrome (1); chromosomal anomalies (1); Ellis–van Creveld syndrome (1); Prune belly syndrome (1); renal coloboma syndrome (1)
5 ($n = 14$)	9.9 ± 1.2	9 males 5 females	CAKUT with obstructions (1); CAKUT without obstructions (7); cortical necrosis (perinatal period) (3); nephronophthisis (1); polycystic kidney disease (2)	Analysis by chance (2); annual urinalysis at school (2); blood analysis in the neonatal period, asphyxia, neonatal shock (1); failure to thrive, weight loss and general fatigue (2); fetal ultrasonography/ultrasonography in the neonatal period (5); unknown (1); urinary tract infection (1)	—

CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; ESKD, end-stage kidney disease. Values in parentheses indicate the number of patients. Age is shown as the mean ± SD.
[a]Data are presented for individual patients (deaths) or groups by CKD stage (alive).



Number of participants remaining

Stage 3	315	296	287	178
Stage 4	107	92	78	41
Stage 5	25	13	9	3

FIGURE 1. Kaplan–Meier plot showing time to ESKD according to CKD stage. $T = 0$ years was defined as the day on which serum creatinine was measured that was closest to 1 April 2010. The 1-year survival rates are shown for each stage.

Table 4. Risk factors for ESKD (Cox regression model)

Variable	HR	95% CI	P-value
Sex			
Female	1.56	0.67–3.62	0.306
Male	1.00	—	—
Age			
Age <2 years (versus 2 years to the start of puberty)[a]	9.06	2.29–35.84	0.002
After puberty (versus 2 years to the start of puberty)[a]	4.88	1.85–12.85	0.001
Recognizable syndrome[b]	2.54	0.75–8.58	0.133
CKD stage			
CKD Stage 4 (versus Stage 3)	11.12	4.22–29.28	<0.001
CKD Stage 5 (versus Stage 3)	26.95	7.71–94.17	<0.001
CAKUT	0.60	0.25–1.47	0.261
Preterm delivery (<37 weeks)	1.33	0.50–3.53	0.562
Heavy proteinuria[c]	7.56	3.22–17.77	<0.001
Hypertension[d]	0.53	0.19–1.46	0.219
Use of antihypertensive drugs	1.08	0.42–2.75	0.874

ESKD, end-stage kidney disease; HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract.
[a]Age at the start of puberty was defined as 10.8 years for males and 10.0 years for females [23].
[b]Recognizable syndromes included Down syndrome, Kabuki syndrome, Townes–Brocks syndrome, VATER association, prune belly syndrome, Wolf–Hirschhorn syndrome and branchio-oto-renal syndrome, among others.
[c]Urine protein/creatinine ratio >2.0 g/g urine creatinine.
[d]Systolic blood pressure >95th percentile.

independently associated with CKD progression, as determined using Cox's proportional hazards model. As shown in this table, CKD stage and heavy proteinuria were significantly associated with disease progression. Age of <2 years and age at or above the start of puberty were significantly associated with increased risk of disease progression. In contrast, sex, the presence of a recognizable syndrome, disease (CAKUT or other disease), preterm delivery (<37 weeks), hypertension (systolic blood pressure >95th percentile) [24] and the use of antihypertensive drugs were not associated with disease progression. The results did not change when we included the duration of disease instead of age or eGFR calculated using the abbreviated Schwartz equation instead of CKD stage, or if deaths were censored instead of being included as an event (data not shown).

DISCUSSION

The main findings of this prospective cohort study in Japanese children with CKD Stages 3–5 are that (i) the prognosis of CKD in children is poor, as disease progression to a higher CKD stage or ESKD occurred in a sizeable number of children, particularly those with advanced (Stages 4/5) CKD, and (ii) advanced CKD stage and heavy proteinuria were independently associated with progression to ESKD. Age of <2 years and age at or above the start of puberty (≥10.8 years in males and ≥10.0 years in females) were also significantly associated with increased risk of disease progression. To our knowledge, this is the first nationwide, prospective cohort study of children with pre-dialysis CKD to examine the risk for progression to ESKD in Asia.

The present results are broadly consistent with those reported elsewhere, showing the poor outcomes of CKD in children [1, 3–6, 11, 12, 14–16, 25]. In a retrospective analysis of 176 children with dysplastic kidneys and ≥5 years of follow-up, Gonzalez Celedon *et al.* [1] reported that there was an early improvement in renal function, which lasted until ~3.2 years of age, and was followed thereafter by maintained or deteriorating renal function, particularly after 7 and 11 years of age. They reported that hypertension, albuminuria, number of febrile urinary tract infections, eGFR at onset and puberty were significantly associated with disease progression. Sanna-Cherchi *et al.* [26] reported that the prognosis of CAKUT was also poor, as 58/312 patients required dialysis by 30 years of age. Elevated SCr and proteinuria were associated with worse outcomes, as were specific disorders (solitary kidney, posterior urethral valves and vesicoureteral reflux). In the present study, a sizeable proportion (12.5%) of children progressed from Stage 3 to 5 CKD to ESKD during the follow-up period (median 1.49 years). In addition, children with advanced stage CKD (4/5) are at particularly high risk of progressing to ESKD, irrespective of the primary etiologies of CKD. Furthermore, as in the study by Sanna-Cherchi *et al* [26], we found that proteinuria was a risk factor for progression to ESKD. We also found that age <2 years and age at or above the start of puberty were significantly associated with increased risk of progressing to ESKD relative to the risk in patients aged 2 to the start of puberty (10.8 years in males and 10.0 years in females). These results may reflect the risk of disease progression in very young patients with severe congenital complications and that disease progression may be more pronounced in puberty.

The CKD in Children cohort study in the USA [5, 6], as well as studies performed in France [15], Sweden [14], Italy [11] and Australia/New Zealand [25], consistently reported that many children with CKD ultimately require renal replacement

therapies. However, renal transplantation was reported to achieve better long-term outcomes and reduce the mortality rate compared with dialysis in children with ESKD [25]. Although the most common modality (51.9%) of renal replacement therapies was peritoneal dialysis in our cohort, ~30% of children with ESKD received preemptive kidney transplantation, reflecting the current trends in Japan. The superiority and clinical benefits of preemptive kidney transplantation relative to dialysis should be confirmed in future studies.

The present study and the studies described above have consistently shown that heavy proteinuria is independently associated with CKD progression. Prior studies have also indicated that antihypertensive drugs, particularly angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), help to delay or prevent the progression to ESKD in children [27, 28]. These drugs not only lower blood pressure, but also have antiproteinuric, antifibrotic and anti-inflammatory properties. In the present study, 28.4 and 28.2% of patients were prescribed an ARB or ACEI, respectively, and 7.2% were prescribed a calcium channel blocker [9]. In contrast, the use of an antihypertensive drug and hypertension *per se* were not associated with progression to CKD in our cohort study. In the ItalKid project, also an observational study, the use of an ACEI did not significantly modify the progressive course of hypodysplastic nephropathy in children [29]. Therefore, in children with CKD, the effects of antihypertensive drugs, particularly ACEIs and ARBs, on modifying disease progression shown in adults need to be verified in future studies. We are now conducting a randomized controlled trial to prospectively examine the renoprotective effects of ARBs to address this issue (UMIN ID: UMIN000006917, http://indice.umin.ac.jp).

The strengths of this study are that the cohort was representative of children with CKD throughout Japan, as the information was obtained from ~80% of the institutions that manage children with CKD at the time of establishment of the cohort, and the follow-up rate of this cohort was 96%.

Some limitations also warrant mention. We classified CKD using reference SCr levels determined enzymatically in Japanese children. These diagnostic criteria have not been validated globally and so the criteria may not be appropriate for other populations, particularly non-Asian children. However, as described in our prior report [9], this approach was necessary because of potential limitations of using the Schwartz equation in Japanese children or for screening purposes, where SCr is available, but height is not. The duration of follow-up, ~1.5 years, is also relatively short in the context of CKD progression. The pubertal stage of patients was not assessed in this study. Therefore, to estimate the effects of puberty on disease progression, we stratified the patients according to the mean age of Japanese children at the start of puberty (10.8 years in males and 10.0 years in females [23]) in lieu of the actual pubertal stage.

In conclusion, this nationwide, prospective cohort study showed that 12.5% of children with pre-dialysis CKD (stages 3–5) ultimately progressed to ESKD in the follow-up period (median 1.49 years). In particular, children with Stage 4 or 5 were at very high risk of progression to ESKD. Heavy proteinuria was also significantly associated with progression to ESKD. A longer follow-up of this cohort is currently underway to explore outcomes of these children beyond adolescence and into adulthood.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format. Kenji Ishikura has received lecture fees and travel expenses from Novartis Pharma and Asahi Kasei Pharma. Osamu Uemura has received lecture 370 fees and travel expenses from Asahi Kasei Pharma and Siemens Group in Japan. Yuko Hamasaki has received research grants from Novartis Pharma, and lecture fees from Novartis Pharma, Astellas Pharma, and Pfizer Japan. Ryojiro Tanaka has received lecture fees from Pfizer Japan. Koichi Na-375 kanishi has received lecture fees from Novartis Pharma, Asahi Kasei Pharma, and Astellas Pharma. Masataka Honda has received lecture fees from Novartis Pharma and Asahi Kasei Pharma.

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ORIGINAL ARTICLE

Creatinine-based equation to estimate the glomerular filtration rate in Japanese children and adolescents with chronic kidney disease

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Abstract
Background Renal inulin clearance is the gold standard for evaluation of kidney function, but cannot be measured easily in children. Therefore, we utilize the serum creatinine (Cr)-based estimated GFR (eGFR) measuring serum Cr by the enzymatic method, and we have reported simple serum Cr-based eGFR in Japanese children aged between 2 and 11 years old. Furthermore, we should use serum Cr-based eGFR in Japanese adolescents as well as children with chronic kidney disease for evaluation of renal function.
Methods The inulin clearance and serum Cr level determined by an enzymatic method were measured in 131 pediatric chronic kidney disease (CKD) patients between the ages of 2 and 18 years old with no underlying disease affecting renal function except CKD to determine the serum Cr-based eGFR in Japanese children and adolescents.
Results We offer the complex estimated GFR equation using polynomial formulae for reference serum creatinine levels with body length in Japanese children except infants, resulting in the following equation:

$$\text{eGFR} = 110.2 \times (\text{reference serum Cr}/\text{patient's serum Cr}) + 2.93$$

Reference serum Cr levels (y) are shown by the following two equations of body length (x):

$$\text{Males}: \quad y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$$

$$\text{Females}: \quad y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$$

Conclusion The new polynomial eGFR formula showing the relationship with body length and serum Cr level may be applicable for clinical screening of renal function in

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Japanese children and adolescents aged between 2 and 18 years.

Keywords Estimate glomerular filtration rate · Japanese children and adolescents · Creatinine-based equation · Chronic kidney disease

Introduction

Using renal inulin clearance to measure the glomerular filtration rate (GFR) directly is compromised by problems of collecting urine samples in children, and we should utilize the serum creatinine (Cr)-based estimated GFR (eGFR). Serum Cr levels are generally proportional to muscle mass and inversely proportional to renal function. Therefore, they are lower in infancy, and increase gradually with growth. Schwartz et al. [1] expressed the relations between body length, GFR, and serum Cr level as estimated GFR (eGFR; ml/min/1.73 m^2) = k × body length (cm)/serum Cr level (mg/dl). The coefficient k is 0.33 in preterm infants under 1 year old, 0.45 in full-term infants under 1 year old, 0.55 in children 2–12 years old, and 0.55 and 0.70 in females and males over 12 years old, respectively [1–4].

This formula is clinically useful as it allows estimation of the normal serum Cr level from the patient's body length. This equation utilizes the Jaffé method to measure Cr. However, enzymatic methods have recently been used to measure Cr, rendering the above formula no longer applicable. In 2009, the updated Schwartz formulae were reported as follows: eGFR (ml/min/1.73 m^2) = 0.413 × body length (cm)/serum Cr level (mg/dl) and eGFR (ml/min/1.73 m^2) = 39.1 × [body length (m)/s-Cr (mg/dl)]$^{0.516}$ × [1.8/cystatin C (mg/l)]$^{0.294}$ × [30/BUN (mg/dl)]$^{0.169}$ × [1.099]^{male} × [body length (m)]/1.4]$^{0.188}$ by enzymatic Cr determination in children 1–16 years old [5].

We doubt whether the new Schwartz equations can be used to estimate the GFR in Japanese children with chronic kidney disease (CKD), because there are differences in renal function and muscle mass between Japanese and American individuals. In addition, it is inconclusive whether one common "bedside" linear equation can be used in children from 1 to 16 years old, including the period of adolescence. Therefore, we attempted to derive formulae to estimate the glomerular filtration rate by enzymatic Cr determination in Japanese children with CKD.

We have determined reference serum Cr levels by an enzymatic method related to age, gender, and body length, and linear and polynomial equations showing the relationship between body length and the serum Cr level for screening of renal function in Japanese children [6, 7]. We intended to develop creatinine-based estimated GFR equations using these linear and polynomial equations, with serum creatinine levels being inversely proportional to renal function.

Initially, we developed an estimated GFR equation for Japanese children aged between 2 and 11 years old whose reference serum creatinine levels were thought to be proportional to body length as follows: eGFR (ml/min/1.73 m^2) = 0.35 × body length (cm)/serum Cr level (mg/dl) [8]. Here, we present a complex estimated GFR equation using polynomial formulae for reference serum creatinine levels with body length in Japanese children aged between 2 and 18 years old, i.e., all children and adolescents except infants.

Materials and methods

Study population

A total of 174 children (113 males and 61 females) between the ages of 1 month and 18 years old presenting at the facilities of the members for the Committee of Measures for Pediatric Chronic Kidney Disease (CKD) between 2008 and 2011 with chronic kidney disease were included. Nevertheless, excluding the cases we describe in detail later, a total of 131 patients (84 males and 47 females) were included in formulating the new eGFR. The study was approved by the local ethics boards of each institution, and written informed consent was obtained from the parents of each subject. The ethics committee approval number in Aichi Children's Health and Medical Center is 200810.

GFR and serum Cr measurements

Data regarding serum Cr levels, renal inulin clearance (Cin), and body length measured at the same time were reviewed. The glomerular filtration rate (GFR) was measured with inulin [9, 10]. Cin was measured from samples taken twice over 2 h under fasting and hydrated conditions by the continuous infusion method (Fig. 1). The children were fasted overnight and were allowed only water after waking up in the morning. First, they received an intravenous Ringer's solution load of 20 ml/kg body weight for 30 min to obtain good diuresis, followed by a load of 5 ml/kg/h until testing was completed. From 30 min after water loading, inulin was given intravenously in a priming dose of 40 mg/kg body weight for 30 min calculated to achieve an extracellular fluid (ECF) level of 20 mg/dl. After the priming dose, inulin was administered at a rate calculated to maintain a constant level in the blood [10]. For this purpose, the rate of inulin infusion must equal that of loss in the urine. To calculate inulin loss, GFR was estimated from serum creatinine by the old Schwartz

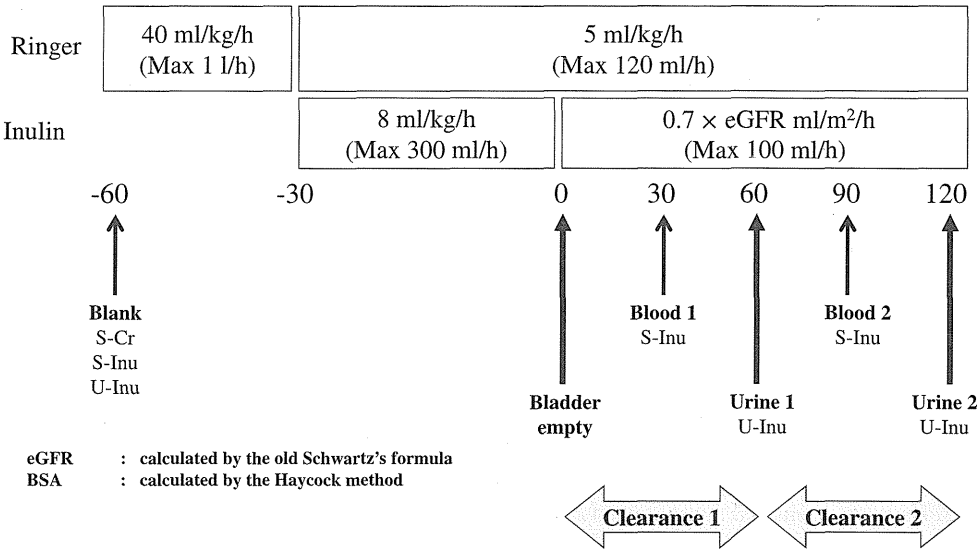

Fig. 1 Inulin clearance method standardized according to the Committee of Measures for Pediatric CKD. Inulin was given intravenously to achieve extracellular fluid levels of 20 mg/dl in testing. For this purpose, the rates of inulin infusion must equal the rates of loss in the urine, which were calculated using the Schwartz formulae based on the serum creatinine level

formulae [1–5]. Therefore, the patients received an inulin load of 0.7 × eGFR ml/m^2/h with calculation of body surface area by the Haycock method [11]. Urine samples were collected in two periods of 1 h each, and blood samples were obtained twice from an indwelling cannula in the middle of urine collection. We collected urine samples of children under 6 years old or with bladder dysfunction by indwelling catheters.

Serum samples were stored at −70 °C until serum Cr was measured by SRL, Inc. (Tokyo, Japan). The serum Cr level was determined by an enzymatic method using a Bio Majesty automated analyzer (JCA-BM8060; JEOL Ltd., Tokyo, Japan) with Pure Auto S CRE-L (Sekisui Medical Co., Ltd., Tokyo, Japan). The coefficient of variation was satisfactory (2.08 %). This method utilizes National Institute of Standards and Technology (NIST) Standard Reference Material 914a as calibration standards similar to isotope dilution mass spectroscopy (IDMS). Urine and serum samples were stored at 4 °C until urine and serum inulin were measured by SRL, Inc. The urine and serum levels of inulin were determined by an enzymatic method using an automated analyzer (Hitachi 7170; Hitachi Ltd., Tokyo, Japan) with Dia-color-inulin (Toyobo Co., Ltd., Tokyo, Japan). The coefficient of variation was satisfactory (<15 %).

Estimated GFR based on serum Cr

In Japanese children and adolescents, the reference serum Cr level (y) was expressed as a quintic equation of body length (x), and the regression equations were $y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$ in males and $y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$ in females [6]. As the reciprocal of serum Cr is generally correlated with GFR [1–5, 12], we utilized the equation for eGFR derived from serum Cr, eGFR (%) = (reference serum Cr/patient's serum Cr) × 100. Therefore, we derived the following two equations:

$$\text{Males} < 19 \text{ years old: eGFR (\%)} = [(-1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628)/\text{patient's serum Cr}] \times 100$$

$$\text{Females} < 19 \text{ years old: eGFR (\%)} = [(-4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778)/\text{patient's s serum Cr}] \times 100$$

With this report [6], we intend to develop the GFR (ml/min/1.73 m^2) estimation expression for Japanese children by examining relations of GFR (ml/min/1.73 m^2) and reference serum Cr/patient's serum Cr.

Exclusion criteria and cases excluded

In this study, the exclusion criteria were as follows: (1) severe obstructive uropathy; (2) infection during treatment; (3) inflammatory disease; (4) dehydration; (5) myopathy; (6) severe cardiac, hepatic, or pancreatic disease; (7) pregnancy or the possibility of pregnancy; (8) nursing; and (9) refusal or inability to give informed consent. Infants under 2 years old were excluded because of low GFR compared with adults [13]. Three cases (one case with no serum creatinine data and two cases with myopathy) were excluded because of violation of the protocol. In this study, doses of intravenously administered inulin were decided as blood concentrations were constant during testing by calculating the estimated GFR by the old Schwartz' formula. Therefore, cases in which the ratios of urine inulin excretion and intravenous inulin administration were <0.5 or >1.5 were excluded from

this study because this may have been due to failure to collect all urine. Pediatric patients with chronic kidney disease causing hyperfiltration such as diabetic nephropathy are rare, and we are interested in determining the eGFR of cases with GFR <120 ml/min/1.73 m^2. Therefore, we excluded cases with GFR >150 ml/min/1.73 m^2.

Statistical analyses

All analyses were conducted using Microsoft Excel 2010 and the JMP 10 statistical software package (SAS Institute Inc, Cary, NC, USA). Linear regression analyses were performed to evaluate relations between the ratios of patient's serum Cr/reference serum Cr and Cin in males and females. Differences in the bias (absolute value) of eGFRs were evaluated using paired *t* tests, and differences in accuracy (i.e., P_{30}) were evaluated using χ^2 tests, similar to the method of Horio et al. [14]. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Characteristics of the study population

Of the 174 children studied, 8 patients under 2 years old, 3 with violation of protocol, 27 whose ratios of urine inulin excretion and intravenous inulin administration were <0.5 or >1.5, and 5 with GFR >150 ml/min/1.73 m^2 were excluded from the study. Therefore, a total of 131 cases (84 males and 47 females) were included in this study (Table 1); 64 % were male, 41 % had congenital anomalies of the kidney and urinary tract (CAKUT), 5 % were posttransplant patients, and only 4 % had chronic glomerulonephritis. The median age was 10.8 years old, median height was 134.5 cm, and median weight was 30.9 kg. The median values of serum Cr, average inulin GFR, and maximum inulin GFR were 0.66 mg/dl, 66.6 ml/min/1.73 m^2, and 71.8 ml/min/1.73 m^2, respectively. As urine collection was suspected to become insufficient in children, we decided to use the maximum inulin GFR in the present study.

Serum Cr-based eGFR formula in pediatric CKD patients aged between 2 and 18 years old

Figure 2 shows scatter plots of maximum inulin GFR versus reference serum Cr/patient's serum Cr ratio in pediatric CKD patients aged between 2 and 18 years old, resulting in the following equation:

Table 1 Characteristics of 131 children included in this study

Characteristics	Median (IQR)	*n*
Total		131
Age (years)	10.8 (7.5–13.9)	
<6		17
≥6 and <12		59
≥12		55
Gender		
Male		84
Female		47
Renal abnormality		
Congenital anomalies of the kidney and urinary tract		54
Reflux nephropathy		15
Idiopathic nephrotic syndrome		13
Renal transplant		7
Chronic glomerulonephritis		5
Nephronophthisis		5
Neurogenic bladder		4
Polycystic kidney disease		3
Alport's syndrome		3
Miscellaneous		22
Height (cm) (years)	134.5 (112.6–152.2)	
<6	98.4 (91.6–110.0)	
≥6 and <12	122.4 (110.6–132.0)	
≥12	154.2 (145.4–162.8)	
Weight (kg) (yeras)	30.9 (19.6–41.9)	
<6	15.4 (12.3–17.7)	
≥6 and <12	24.6 (18.8–28.9)	
≥12	45.3 (37.9–50.7)	
BSA (m^2) (years)	1.04 (0.79–1.32)	
<6	0.65 (0.55–0.74)	
≥6 and <12	0.91 (0.76–1.03)	
≥12	1.38 (1.23–1.51)	
Serum creatinine (mg/dl) (years)	0.66 (0.51–0.90)	
<6	0.56 (0.38–0.66)	
≥6 and <12	0.69 (0.43–0.74)	
≥12	0.97 (0.63–1.05)	
Average inulin GFR (ml/min/1.73 m^2) (years)	66.6 (46.5–93.5)	
<6	58.8 (40.6–73.0)	
≥6 and <12	74.6 (50.0–95.5)	
≥12	71.7 (52.4–91.9)	
Maximum inulin GFR (ml/min/1.73 m^2) (years)	71.8 (53.0–97.4)	
<6	63.9 (46.0–74.4)	
≥6 and <12	80.0 (55.5–106.5)	
≥12	77.0 (53.9–93.6)	

IQR interquartile range

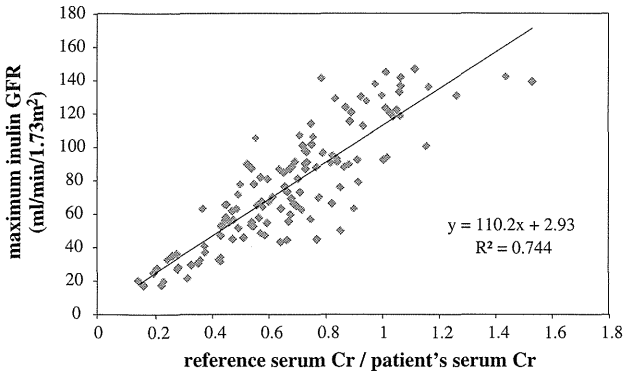

Fig. 2 Analysis of reference serum Cr/patient's serum Cr and maximum inulin GFR in pediatric CKD patients aged between 2 and 18 years old. The regression equation was $y = 110.2x + 2.93$. A significant positive correlation was observed in children with CKD aged between 2 and 18 years old, with a correlation coefficient of 0.863

$$\text{eGFR} = 110.2 \times (\text{reference serum Cr/patient's serum Cr}) + 2.93$$

Reference serum Cr levels (y) are shown by the following two equations of body length (x):

$$\text{Males}: \quad y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.9x^2 - 11.71x + 2.628$$

$$\text{Female}: \quad y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$$

Correlation between two serum Cr-based eGFR formulae in pediatric CKD patients aged between 2 and 11 years old

We developed an estimated GFR equation for use in Japanese CKD patients aged between 2 and 11 years old as follows: eGFR (ml/min/1.73 m^2) = 0.35 × body length (cm)/serum Cr level (mg/dl) [6].

We compared our new formula with the formula in CKD patients of this age group. Figure 3 shows the correlation between these two serum Cr-based eGFR formulae in these patients. The eGFR using a quintic equation of body length (y) is shown as the eGFR using a linear equation of the body length (x) as follows: $y = 0.98x + 1.63$. In contrast, in CKD patients aged between 12 and 18 years old, the relation were shown as follows: $y = 1.06x + 6.56$.

Thus, the eGFR values derived from the two equations showed a good degree of accordance in Japanese CKD patients aged between 2 and 11 years old.

Comparison of performance of our new eGFR formula and the other eGFR formulae including the updated Schwartz formula

We used a diagnostic test design to compare our new polynominal eGFR formula, our simple linear formula previously reported in CEN [8], and the original [1–4] and updated [5] Schwartz's formula in all 131 subjects and each age category, such as <12, and ≥12 years old; these are listed in Table 2. The new polynomial formula had significantly less bias than other eGFRs ($P < 0.001$). Accuracy was not significantly different between our simple linear formula and our polynomial formula, but significantly different between the two Schwartz's formulae and our polynomial formula. Root mean square error (RMSE) was lower for our new polynomial formula than for other eGFRs stratified by glomerular filtration rate measured by the inulin clearance method mGFR in all 131 subjects. In particular, Fig. 4 showed the RMSE between measured maximum inulin GFR and estimated GFR obtained using our polynomial formula in CKD patients aged between 2 and 16 years old was lower than the estimated GFR obtained using the updated Schwartz formula (17.2 vs. 18.3, respectively). The reason why we analyzed patients aged 2–16 years old was a limitation in updated Schwartz formula.

Discussion

The glomerular filtration rate is used to assess kidney function and is measured by monitoring renal clearance. Inulin clearance is the gold standard for evaluation of kidney function, but cannot be measured easily. Therefore, various methods have been used to determine GFR. The estimated GFR [eGFR (ml/min/1.73 m^2) = k × body length (cm)/serum Cr level (mg/dl)] determined by the Jaffé method devised by Schwartz has been used clinically [1]. Recently, however, enzymatic methods have been used to measure Cr rather than the Jaffé method, so it is not possible to use the formula in this form. Therefore, it was necessary to reevaluate the value of the coefficient k in the formula. Recently, Zappitelli et al. [15] revised the Schwartz formula relating the eGFR to the serum creatinine level determined enzymatically and reported that the value of k in the Schwartz equation decreased from 0.55 to 0.47 for children and adolescent girls. Schwartz et al. reported the updated formula, the so-called "bedside" version, as eGFR = 0.413 × body length (cm)/serum Cr level (mg/dl) by the enzymatic method showing a 25 % reduction in value of k from the previous value of 0.55 generated from Jaffé-based serum Cr measurements and eGFR (ml/min/1.73 m^2) = 39.1 × [body length (m)/s − Cr (mg/dl)]$^{0.516}$ × [1.8/cystatin C (mg/l)]$^{0.294}$ × [30/BUN (mg/dl)]$^{0.169}$ × [1.099]^{male} × [body length (m)]/1.4]$^{0.188}$ by enzymatic Cr determination in children 1–16 years old [5]. This was defined in a population of American children with chronic kidney disease, enriched for those with obstructive uropathy. They concluded that the formula can be used in children 1–16 years old.