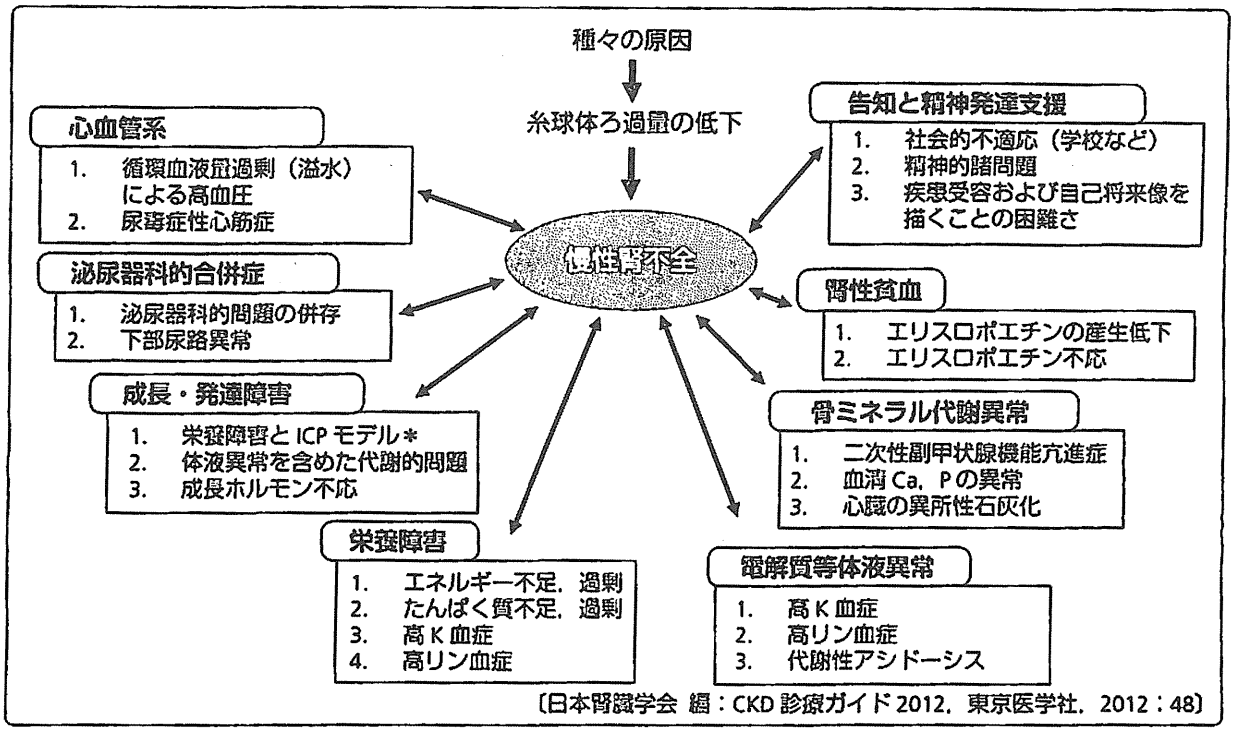

〔日本腎臓学会 編：CKD診療ガイド2012，東京医学社，2012：48〕

図1 小児慢性腎不全の合併症

＊ Karlbergは，小児の縦断的成長を数学的にモデル化，Infancy(乳幼児期)・Childhood(小児期)・Puberty(思春期)の3つの成分に分けるICPモデルを提唱，小児期は成長ホルモン，思春期には性ホルモンが重要であるが，乳幼児期の成長については栄養が重要であるとした．

ない．

- 小児の血圧の基準値の年齢による違い．
  基準値はQ71表参照．
- 移行(transition)への配慮．
  移行とは，慢性疾患を持った思春期や若年成人を小児医療施設から成人医療施設に向けて目的をもって計画的に移動させることをいう．移行の失敗は患者の治療不適応に繋がり不可逆的障害を残すこともあるので，そのプログラムは疾患の始まりから前もって計画的に始められる必要がある．子ども達が自尊心を確立し自己決定できる自立／自律した大人になることを目標に，専門的な医療やケアを意図的・計画的に提供しなくてはならない．
- 小児に対するACE-I(アンジオテンシン変換酵素阻害薬)やARB（アンジオテンシン受容体拮抗薬)の腎保護効果の有効性の有無．
  有効である可能性は高いが証拠はまだない．

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（上村 治）

Q20 小児のCKD患者の動向はどのようになっていますか？

A 日本の小児CKD患者の疫学研究により，生後3か月～15歳の日本の小児における透析前のCKDステージ3～5の有病率が29.5例/100万であることがわかりました．実際の日本全国の症例数は447例(回収率77.7%)で，そのうち405例(90.6%)は非糸球体疾患で，しかも278例(68.6%)は先天性腎尿路疾患(CAKUT)でした．

日本の小児CKD患者の疫学研究

小児CKDの疫学研究は，アジアでは初めてで，これまでは西欧諸国の報告[1-3]のみであった．これらの研究では，血清クレアチニン値による推算GFR(eGFR)によってステージ分類されており，古いシュワルツの式がGFRを推定するために使用されている．しかし，最近血清クレアチニン(Cr)測定の多くがヤッフェ法から酵素法を使用するようになったので，シュワルツの式は新たに作り変えられた[4]．しかし，これらは欧米人の式であり，日本人の小児でシュワルツの式を使用する場合，GFRを過大評価する可能性があり，また12歳以上に同一の式を使うことにも問題がある[5]．

日本人小児に固有のeGFRはまだなく(ほぼ完成しているが疫学研究をやる時点ではまだなかった)，われわれが独自に確立した血清Cr基準値を利用して腎機能を評価しCKDステージ分類を行った(Q3参照)．小児のCKDの定義上の最大の問題点は，腎機能の成熟にある．GFRは新生児期に成人の20～30%程度からはじまり，2歳までに成人値に達すると考えられている[6,7]．小児と思春CKDについての臨床診療ガイドライン[8]が2003年にNKF KDOQIから示され，成人同様に定義された．このガイドラインでは，腎機能の生理的未成熟の理由から5段階のCKDステージ分類の適応は2歳以上に限るべきとしている．しかし，2歳未満の乳幼児についても同様に分類できることが望ましい．KDOQIのCKDについての臨床診療ガイドラインでは[9]，GFR 60 mL/分/1.73 m^2 をloss of half(腎機能が正常の半分)と考えていることが明らかである．本来の理念を利用して2歳未満の乳幼児についても分類すべきであり，正常者の腎機能の代表値(中央値または平均値)の半分を切ればステージ3(1/4を切ればステージ4，1/8を切ればステージ5)と考えて定義可能であるとした．

この方法で日本人小児のCKDを診断しステージ分類した．生後3か月から15歳の日本人小児のCKDは，調査回収率77.7%で総数447例であり，そのうち405例(90.6%)は非糸球体疾患で，しかも278例(68.6%)は先天性腎尿路疾患(CAKUT)であった．原疾患の詳細な内訳は表1の通りである．つまり，腎機能が半分以下の小児CKD患者の多くはCAKUTを原因としており，いわゆる慢性糸球体腎炎はごく少数であった．また，全体の70.7%はステージ3，23.3%はステージ4，6.0%はステージ5であった．

またこの疫学研究で，透析前のCKDステージ3～5の有病率は29.5例/100万日本人小児であると推定された．これは，ItalKid[1]とREPIR II Projects[2](それぞれ74.7例，71.1例/100

表1 3か月から15歳の日本人小児のCKDステージ3～5患者447例の原疾患(代表的なものに限る)

疾患	非糸球体性	糸球体性	分類不能
	N＝405(90.6%)	N＝38(8.5%)	N＝4(0.9%)
先天性腎尿路疾患	278	−	−
周産期障害	37	−	−
多発性嚢胞腎	21	−	−
ネフロン癆	20	−	−
アルポート症候群	−	10	−
巣状糸球体硬化	−	9	−
慢性糸球体腎炎	−	8	−
先天性ネフローゼ症候群	−	3	−

〔日本小児腎臓病学会・小児 CKD 対策委員会〕

万小児)で報告されたものより低かった．ただし対象が，ItalKid は eGFR ＜ 75 mL/分/1.73 m^2 の 20 歳未満の小児で，REPIR II は 19 歳未満の小児 CKD ステージ 2～5(ステージ 2 が 42% 含まれる)であるという点で異なり，REPIR II で CKD ステージ 3～5 を計算すると有病率は 41.2 例/100 万小児となることもあわせて考えると，大きな違いはないように思える．

日本の小児 CKD 疫学研究では，糸球体疾患は非常に少なく，なかでも慢性糸球体腎炎はわずか 8 例のみであった．また別に 1998 年に実行された小児 ESKD 患者の日本のレジストリにおいて，IgA 腎症はわずか 3% であった[10]．これらの慢性糸球体腎炎が CKD や ESKD の原疾患として少ないのは 1974 年にはじまった腎臓病学校検診の効果であるとも考えられる．今後は CAKUT に対する対策の充実が望まれる．

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Original Article

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Pre-dialysis chronic kidney disease in children: results of a nationwide survey in Japan

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Abstract

Background. Chronic kidney disease (CKD) in children is a progressive and intractable condition that may severely impair the child's growth, development and quality of life. Epidemiological information on pediatric CKD, particularly in Asians, is scant.

Methods. We conducted a nationwide survey of Japanese children aged 3 months to 15 years with pre-dialysis CKD to examine the prevalence of pediatric CKD in Japan. CKD was classified according to newly established criteria derived from reference serum creatinine levels in Japanese children. Surveys were sent to 1190 institutions across Japan to report on cases of pediatric CKD managed as of 1 April 2010.

Results. A total of 925 institutions (77.7%) responded. Information on 447 children was collected. When subdivided according to our diagnostic criteria, 70.5% of children had stage 3 CKD, 23.9% stage 4 and 5.6% stage 5. The estimated prevalence of Japanese children with CKD was 2.95 cases/100 000 children. Of 407 CKD cases with non-glomerular disease, 278 (68.3%) had congenital anomalies of the kidney and urinary tract (CAKUT). The newly established criteria showed good validity compared with existing criteria, including the abbreviated Schwartz equation.

Conclusions. Findings from the first nationwide survey of pre-dialysis CKD in Asian children indicate that the prevalence of stage 3–5 CKD in children in Japan aged 3 months to 15 years is 2.95 cases/100 000 children. Most children with CKD presented with non-glomerular disease, most frequently CAKUT. Improved management of CAKUT, including renoprotective treatment and urological intervention, is required.

Keywords: adolescent; child; creatinine; epidemiology; Japan; kidney diseases; preschool

Introduction

Chronic kidney disease (CKD) in children is a progressive and intractable condition, with devastating effects on the patient's growth, development and quality of life. If left untreated, pediatric CKD eventually progresses to end-stage renal disease (ESRD), which requires long-term dialysis or repeated renal transplantation. The mortality rate for children with ESRD on dialysis is estimated to be 30–150 times that of the general pediatric population [1, 2]. Therefore, it is particularly important to detect CKD as early as possible, possibly by applying simple but accurate screening of at-risk children. Early identification of these children can then allow the physician to promptly introduce appropriate therapy that can prevent or slow the progression of CKD to ESRD, reducing the incidence of stage 5 CKD and to control comorbidity.

Epidemiological information on CKD in children is currently limited, but this sort of information is necessary to understand the extent of the problem, to identify populations at risk and to determine the efficacy of current therapeutic interventions. Although several studies have described the epidemiology of pre-dialysis CKD in children in Western countries [3–10], very few have focused on Asian children. It is also important to consider that there may be differences in the epidemiology of CKD among countries that may be due to racial differences, variations in screening methods among medical

Table 1. Diagnostic criteria for stage 3–5 chronic kidney disease based on reference serum creatinine levels (mg/dL) of Japanese children aged 3 months to 11 years

Age	2.5th percentile	50th percentile	97.5th percentile	CKD stage 3	CKD stage 4	CKD stage 5
<2 years						
3–5 months	0.14	0.20	0.26	0.41–0.80	0.81–1.60	≥1.61
6–8 months	0.14	0.22	0.31	0.43–0.84	0.85–1.68	≥1.69
9–11 months	0.14	0.22	0.34	0.47–0.92	0.93–1.84	≥1.85
1 year	0.16	0.23	0.24	0.47–0.92	0.93–1.84	≥1.85
2–12 (years)						
2	0.17	0.24	0.37	0.49–0.96	0.97–1.92	≥1.93
3	0.21	0.27	0.37	0.55–1.08	1.09–2.16	≥2.17
4	0.20	0.30	0.40	0.61–1.20	1.21–2.40	≥2.41
5	0.25	0.34	0.45	0.69–1.36	1.37–2.72	≥2.73
6	0.25	0.34	0.48	0.69–1.36	1.37–2.72	≥2.73
7	0.28	0.37	0.49	0.75–1.48	1.49–2.96	≥2.97
8	0.29	0.40	0.53	0.81–1.60	1.61–3.20	≥3.21
9	0.34	0.41	0.51	0.83–1.64	1.65–3.28	≥3.29
10	0.30	0.41	0.57	0.81–1.60	1.61–3.20	≥3.21
11	0.35	0.45	0.58	0.91–1.80	1.81–3.60	≥3.61

Values were matched for age alone. Values for the 2.5, 50 and 97.5th percentiles are as presented in Uemura *et al.* [11]. Table reproduced with the permission of the Japanese Society of Nephrology.

institutions and differences in in-school screening programs. To address this problem of limited information in Asian children and to assist subsequent population-based surveys, we previously determined reference serum creatinine (SCr) levels in Japanese children [11].

Our first objective in this study was to determine the prevalence of pre-dialysis CKD in a cross-sectional, nationwide survey of Japanese children aged 3 months to 15 years with pre-dialysis CKD. Stage 3–5 CKD was detected and classified using newly established criteria derived from normal SCr levels of age- and sex-matched Japanese children. Because CKD is defined as a GFR of <60 mL/min/1.73 m^2 (less than half of normal GFR) in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [12, 13] and the Kidney Disease: Improving Global Outcomes (KDIGO) position statement [14] (corresponding to stage 3 or worse), we focused on patients meeting this criterion and who had not yet received dialysis or renal transplantation. Our second objective was to determine the etiology of CKD as well as the method of detection of CKD and the treatment modalities used in routine clinical practice in Japan.

Materials and methods

Establishment of new diagnostic criteria for CKD in children

The new diagnostic criteria for stage 3–5 CKD were based on previously established reference SCr levels of Japanese children [11]. Briefly, in that study, body length and SCr levels were determined in 1151 healthy children aged 1 month to 18 years who presented at the facilities of the Committee of Measures for Pediatric CKD and Tokyo Health Service Association between 2008 and 2009. Reference intervals of SCr against age were calculated in children aged 3 months to 11 years, and those against age and sex were calculated in children aged 12–16 years.

According to the K/DOQI guidelines [12, 13] and KDIGO position statement [14] for CKD, 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), whereas normal GFR was considered to be ~120 mL/min/1.73 m^2. Given that the GFR is inversely proportional to SCr for a given body type and age [15], we classified stage 3–5 CKD as SCr more than twice, four times and eight times, the median normal SCr levels matched for age alone in children aged 3 months to 11 years (Table 1), or matched for age and sex in children aged 12–16 years (Table 2).

Table 2. Diagnostic criteria for stage 3–5 chronic kidney disease based on reference serum creatinine levels (mg/dL) of Japanese male and female children aged 12–15 years

	2.5th percentile	50th percentile	97.5th percentile	CKD stage 3	CKD stage 4	CKD stage 5
Males (years)						
12	0.40	0.53	0.61	1.07–2.12	2.13–4.24	≥4.25
13	0.42	0.59	0.80	1.19–2.36	2.37–4.72	≥4.73
14	0.54	0.65	0.96	1.31–2.60	2.61–5.20	≥5.21
15	0.48	0.68	0.93	1.37–2.72	2.73–5.44	≥5.45
Females (years)						
12	0.40	0.52	0.66	1.05–2.08	2.09–4.16	≥4.17
13	0.41	0.53	0.69	1.07–2.12	2.13–4.24	≥4.25
14	0.46	0.58	0.71	1.17–2.32	2.33–4.64	≥4.65
15	0.47	0.56	0.72	1.13–2.24	2.25–4.48	≥4.49

Values were matched for age and sex. Values for the 2.5, 50 and 97.5th percentiles are as presented in Uemura *et al.* [11]. Table reproduced with the permission of the Japanese Society of Nephrology

Study design and population

This was a cross-sectional, nationwide, population-based survey conducted by the Pediatric CKD Study Group in Japan in conjunction with the Committee of Measures for Pediatric CKD of the Japanese Society of Pediatric Nephrology (JSPN). Two surveys were sent in August 2010 to a total of 1190 institutions in Japan, including all institutions that are members of the JSPN, all university and children's hospitals and all general hospitals with >200 beds, inviting them to report cases of pediatric CKD that were managed as of 1 April 2010. We selected these types of hospital because children with apparent CKD were usually referred to institutions meeting one of these criteria. The deadlines for the first and second surveys were October 2010 and November 2010, respectively.

The first questionnaire was designed to record the presence and approximate number of children with stage 3–5 CKD in each institution. The second questionnaire recorded data for each case, including age, date of birth, sex, height, SCr level, primary renal diagnosis and associated diseases, method of detection, co-morbidities and prescribed

treatment. For the purpose of this survey, only data recorded within 6 months of 1 April 2010 were included. The patient's age was calculated from the date of birth and the date of each measurement. This questionnaire also recorded information for each institution, including the SCr assay method used and prescribed treatment strategies. The respondents were asked to search their medical records for patients with a confirmed diagnosis of CKD or for patients with an abnormal SCr.

The inclusion criteria were as follows: (i) children with CKD aged 3 months to 15 years at the time of 1 April 2010; (ii) stage 3–5 CKD, as determined by the newly established diagnostic criteria and (iii) no prior treatment with dialysis or renal transplantation. Only cases with renal failure that had lasted for >3 months were included and cases with transient increases in creatinine were excluded.

The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki, and with the 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 536.5 (95% CI: 493.2–579.8) as of 1 April 2010. On the basis of this, the prevalence of stage 3–5 CKD was calculated to be 2.95 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.

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 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 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.

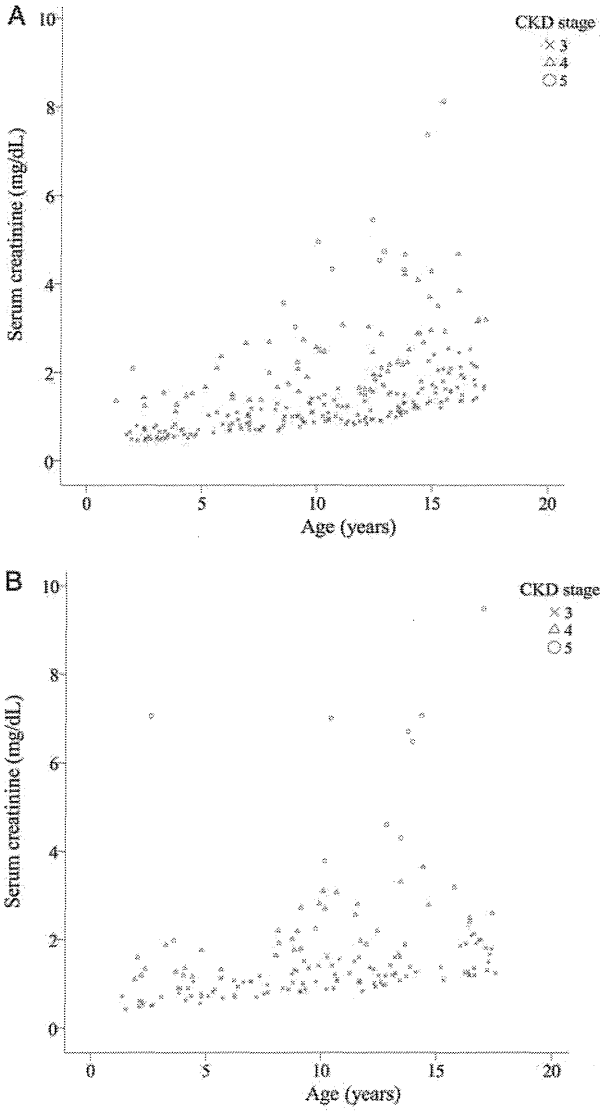


Fig. 1. Serum creatinine levels according to age and CKD stage. Actual serum creatinine levels according to age and CKD stage are plotted separately for males (**A**) and females (**B**).

The diseases included syndromal stigmata [$n = 46$ (10.3%)], 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.

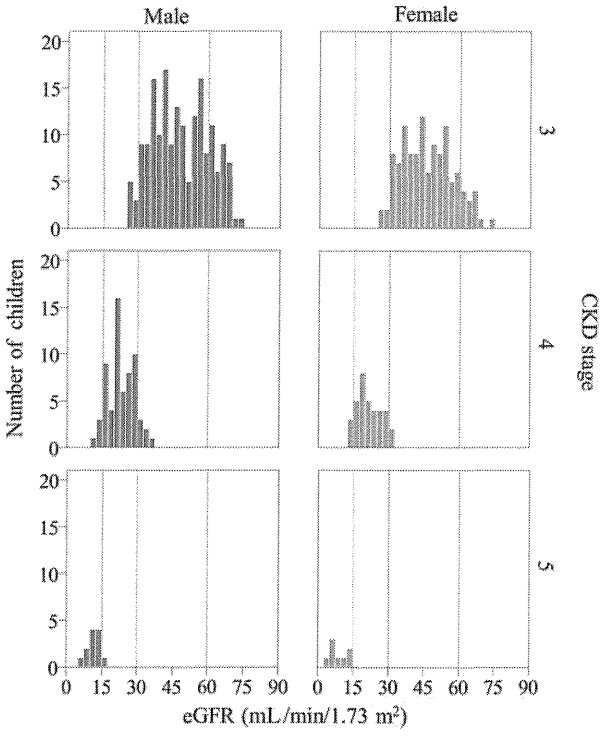
Treatment modalities for pediatric CKD

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 2.95 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 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



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%)

Fig. 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* (%).

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 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 2.95 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

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%) *n* (%)	Glomerular kidney disease ($n=35$, 7.8%) *n* (%)	Unclassified ($n=5$, 1.1%) *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.

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, including (i) genetic differences that affect the distribution of 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].

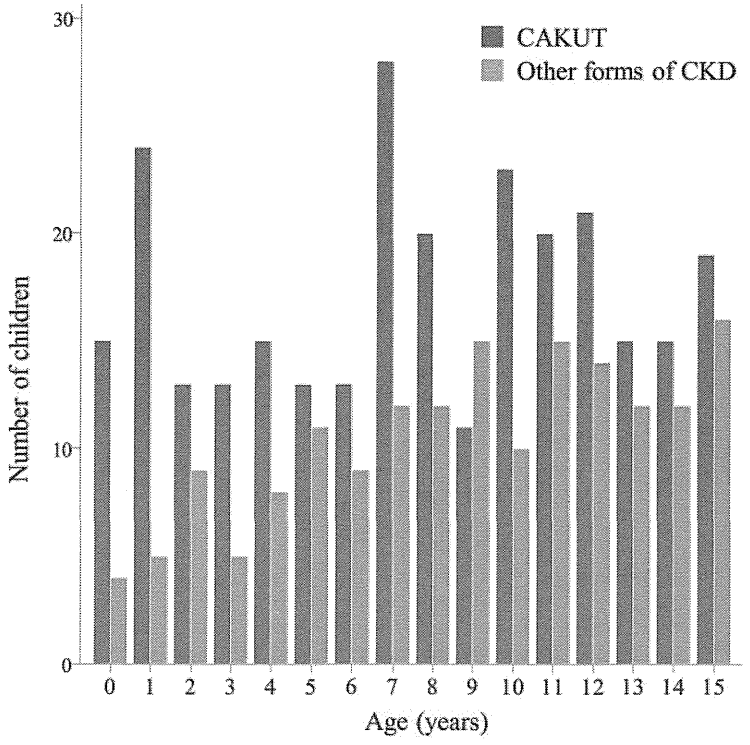
Despite the lower prevalence of CKD in our study compared with European cohorts, we believe that our data accurately represent the current situation in Japan because 1190 institutes, including all institutes belonging to the JSPN, were included in the survey and there was a very high response rate (77.7%). 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 595.7 children rather than the 536.5 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-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 investigation of 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 were generally similar (Table 6), 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



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	13	19	278
Other forms of CKD[b]	4	5	9	5	8	11	9	12	12	15	10	15	14	12	12	16	169

Fig. 3. Age distribution of children with stage 3–5 CKD in Japan. Children with CAKUT are shown in red bars, while those with other forms of CKD are shown in blue bars. 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)[a]. Number of children with CAKUT or other forms of CKD reported in the survey[b].

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

Screening method	CAKUT (n = 278)	Other forms of CKD (n = 169)		Other forms of CKD (n = 169)	Age at which CKD 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.

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

	CAKUT ($n=278$) n (%)	Other forms of CKD ($n=169$) n (%)	All patients ($n=447$) 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.

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 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 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 2.95 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. None declared.

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ORIGINAL ARTICLE

Measurements of serum cystatin C concentrations underestimate renal dysfunction in pediatric patients with chronic kidney disease

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Abstract
Background In our clinical experience, cystatin C (CysC) concentrations are not as high as expected in patients with chronic kidney disease (CKD) and high-stage renal dysfunction. We therefore investigated whether measurements of serum CysC result in an underestimation of renal dysfunction in pediatric patients with CKD.
Methods Glomerular filtration rate (GFR) was estimated from serum creatinine (Cr) concentration, using the equation Cr-GFR (%) = [0.30 × body length (m)/serum Cr] × 100; and from serum CysC concentration, using the equation Cys-GFR (%) = (0.70/serum CysC) × 100. We investigated the relationship between GFR estimated by these 2 equations. Patients aged 2–12 years were assorted into 5 groups, based on GFR-Cr categories of <12.5, ≥12.5 to <25, ≥25 to <50, ≥50 to <75, and ≥75%, and GFR-CysC/GFR-Cr ratios were compared in these 5 groups.
Results The median GFR-CysC/GFR-Cr ratio in groups of patients with GFR-Cr of <12.5, ≥12.5 to <25, ≥25 to <50, ≥50 to <75, and ≥75% were 2.28, 1.48, 1.22, 1.18 and 0.98, respectively, with statistically significant differences between any two groups ($p < 0.001$).
Conclusion Measurements of serum CysC concentrations lead to underestimation of renal dysfunction in pediatric patients with CKD.

Keywords Serum cystatin C level · Pediatric chronic kidney disease · CKD · Renal dysfunction

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Introduction

Glomerular filtration rate (GFR) reflects kidney function, and is measured by renal clearance techniques. Inulin clearance is the gold standard for evaluating kidney function, but it cannot be measured easily. Therefore, various other methods are used to determine kidney function.

We previously observed a significant positive correlation between serum creatinine (Cr) concentration and body length in children aged 1–12 years, with body length (m) × 0.30 yielding a value similar to the reference serum Cr concentration [1]. An equation for estimated GFR (eGFR) has been used to assess the relationships among body length, glomerular filtration rate (GFR), and serum Cr concentration, using the equation eGFR (ml/min/1.73 m^2) = κ × body length (cm)/serum Cr value (mg/dl) [2], where the constant κ was assumed to be unvaried in children aged 2–12 years. This equation indicates that at constant body length, GFR is in reciprocal proportion to serum Cr concentration. Serum Cr concentration can be determined as body length (m) × 0.30 if GFR is 100%, therefore eGFR (%) = [0.30 × body length (m)/serum Cr] × 100.

We have also found that reference serum cystatin C (CysC) concentrations gradually decrease during the year after birth, with slightly higher concentrations in 1 year olds (0.76 ± 0.10 mg/L) than in children aged ≥2 years (0.70 ± 0.09 mg/L), and serum CysC concentrations are

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relatively constant in children aged ≥2 years [3]. The reciprocal of CysC concentration may therefore correlate with GFR as well or better than the reciprocal of serum Cr [4]. Thus, eGFR may be derived from serum CysC concentration using the equation eGFR (%) = (0.70/serum CysC) × 100. In our clinical experience, however, CysC levels are not as high as expected in chronic kidney disease (CKD) patients with high-stage renal dysfunction. We therefore investigated whether measurements of serum CysC concentrations result in an underestimation of renal dysfunction in pediatric CKD patients.

Materials and methods

We included a total of 199 children (114 males and 85 females), aged 2–12 years, who had been admitted to or attended the outpatient clinic of Aichi Children's Health and Medical Center between December 2003 and February 2008 for CKD, but had not undergone dialysis or renal transplantation.

Patients from whom consent was not received for inclusion of specimens in a clinical report were excluded. Data on serum Cr values, serum CysC values, and body length measured in daily laboratory tests were reviewed.

Serum Cr concentrations were determined by an enzymatic method, using a Hitachi 7170S automated analyzer (Hitachi High-Technologies Corp.) with Accuras Auto antibody (Shino-Test Corp.). The coefficients of inter- and intra-assay variance were satisfactory (1.31 and 1.80%, respectively).

Serum CysC concentrations were also determined using the Hitachi 7170S automated analyzer and a latex agglutination turbidimetric method (Mitsubishi Chemical Medience Corp.). The coefficients of inter- and intra-assay variance were satisfactory (1.14 and 1.25%, respectively).

We utilized two equations for eGFR [1–4]. In children aged 1–12 years, body length (m) × 0.30 yielded a value similar to the reference serum Cr concentration measured enzymatically [1]. Since the reciprocal of serum Cr correlated with GFR [2, 5, 6], we utilized an equation for eGFR derived from serum Cr

$$\text{Cr - GFR}\ (\%) = [0.30 \times \text{body length (m)}/\text{serum Cr}] \times 100.$$

We also found that normal children aged ≥2 years have relatively constant serum CysC concentrations (0.70 ± 0.09 mg/L) [3]. Since the reciprocal of CysC correlated with GFR [4], we utilized an equation for eGFR derived from serum CysC

$$\text{Cys - GFR}\ (\%) = (0.70/\ \text{serum CysC}) \times 100.$$

The relationship between values obtained from these two equations was plotted by scattergram. Patients were assorted into five CKD stage groups by Cr-GFR, i.e., Cr-GFR <12.5, ≥12.5 to <25, ≥25 to <50, ≥50 to <75, and ≥75%, thought to be approximately equal to an international CKD stage classification, and the GFR-CysC/GFR-Cr ratio was compared among these 5 groups.

Spearman's rank correlation and Mann–Whitney's U test were used for statistical comparisons, and $p < 0.01$ was regarded as statistically significant.

Results

The demographic and clinical characteristics, including any underlying illnesses, of the patients are shown in Table 1. The correlation between GFR-Cr and GFR-CysC in all subjects was compared with a line with a slope of 1.0 that passed through the origin (Fig. 1). In CKD patients with high-stage renal dysfunction, the GFR-CysC levels were generally higher than this line. We therefore compared GFR-CysC/GFR-Cr ratios in five groups of patients at different CKD stages, as assessed by GFR-Cr percentages (Table 2). We found that the median GFR-CysC/GFR-Cr in pediatric patients with GFR-Cr <12.5, ≥12.5 to <25, ≥25 to 50, ≥50 to <75, and ≥75% were 2.28, 1.48, 1.22, 1.18 and 0.98, respectively, with significant differences between any two groups ($p < 0.001$). The

Table 1 Patient characteristics

	Total (n = 199)
Male, n (%)	114 (60.0)
Age (years), median (range)	7 (2–12)
Underlying illness, n (%)	
Vesicoureteral reflux	27 (13.6)
Renal hypoplasia/dysplasia	23 (11.6)
Hydronephrosis	17 (8.5)
Minimal change nephritic syndrome	16 (8.0)
Nephritis	14 (7.0)
IgA nephropathy	11 (5.5)
Neurogenic bladder	9 (4.5)
Reflux nephropathy	9 (4.5)
Megaureter	8 (4.0)
Focal segmental glomerulosclerosis	7 (3.5)
Alport's syndrome	6 (3.0)
Hematuria syndrome	4 (2.0)
Henoch–Schönlein purpura nephritis	4 (2.0)
Autosomal recessive polycystic kidney disease	3 (1.5)
Branchio-oto-renal syndrome	3 (1.5)
Membranoproliferative glomerulonephritis	3 (1.5)
Membranous nephropathy	2 (1.0)
Nephronophthisis	2 (1.0)
Others	31 (15.6)

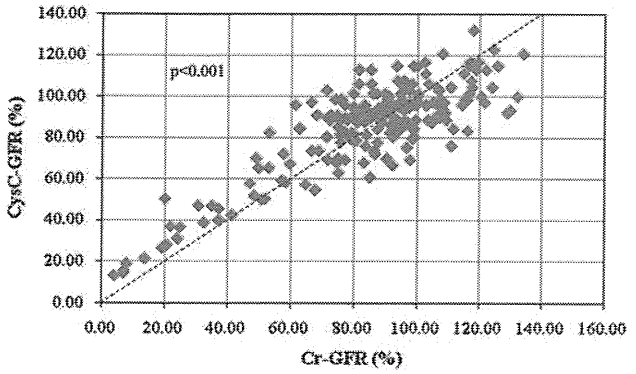

Fig. 1 Correlation between GFR-Cr and GFR-CysC in all subjects. The *dashed line* represents a line with a gradient of 1.0 passing through the origin

Table 2 GFR-CysC/GFR-Cr in five CKD stage groups by GFR-Cr categories

GFR-Cr	*n*	Median (GFR-CysC/GFR-Cr)
<12.5%	4	2.28
≥12.5 and <25%	7	1.48
≥25 and <50%	10	1.22
≥50 and <75%	28	1.18
≥75%	150	0.98

Significant difference between any two groups ($p < 0.001$)

relationships between GFR-Cr strata and GFR-CysC/GFR-Cr are shown in box-and-whisker plots in Fig. 2. The boxes are drawn around the quartile values, and the whiskers extend from each quartile to the smallest and largest observed values. The GFR-CysC/GFR-Cr ratio exceeded 1.0 more often in CKD patients with high-stage renal dysfunction.

Discussion

True measurements of GFR using the inulin clearance method are impractical as a regular monitoring tool. This method is complicated, requiring timed urine collections and frequent blood samplings. It is difficult to obtain timed urine collections from young children because of the physiological immaturity of their bladder function, and this method is even more difficult in children with bladder dysfunction. Therefore, easy, reproducible and precise surrogate methods are needed to measure GFR.

It is necessary to set standard serum Cr and CysC measurements for the medical care of pediatric CKD patients. We previously reported a significant positive correlation between serum Cr concentration and body length in children aged 1–12 years, showing that body

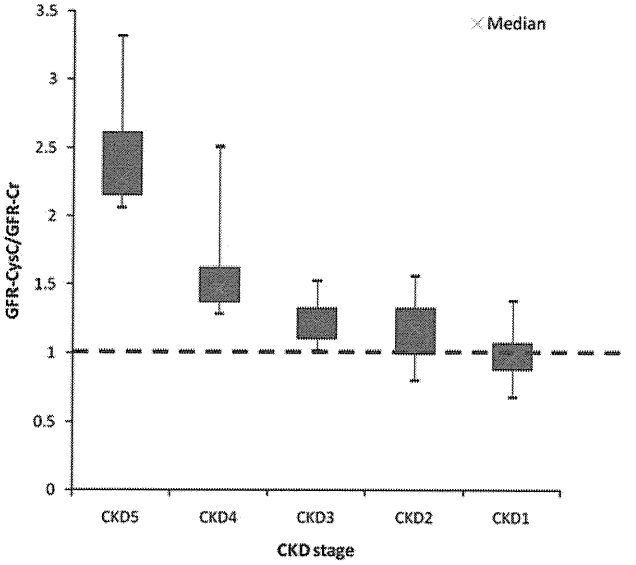

Fig. 2 Relationships between GFR-Cr strata and GFR-CysC/GFR-Cr. *Box-and-whisker* plots of the relationships between GFR-Cr strata and GFR-CysC/GFR-Cr, with significant differences between any two groups ($p < 0.001$). The *boxes* are drawn around the quartile values, and the *whiskers* extend from each quartile to the smallest and largest observed values

length (m) × 0.30 yielded a value similar to the reference serum Cr [1]. In addition, we reported that reference serum CysC concentrations gradually decrease during the year after birth, with slightly higher concentrations in 1 year old children (0.76 ± 0.10 mg/L) than in children aged ≥2 years (0.70 ± 0.09 mg/L) [3].

Although the correlation between reciprocal serum CysC concentration and GFR was reported equivalent to the correlation between serum Cr and GFR, we observed clinically that CysC concentrations were not as high as expected in CKD patients with high-stage renal dysfunction. We therefore determined whether measurements of serum CysC concentrations underestimate renal dysfunction in pediatric CKD patients.

Since the reciprocal of serum Cr has been found to correlate with GFR [2, 5, 6], we defined Cr-GFR (%) as [0.30 × body length (m)/serum Cr] × 100 in children aged 1–12 years. If we assume that the reciprocal of CysC is correlated with GFR, we could define Cys-GFR (%) as (0.70/serum CysC) × 100 at the age of 2 years or over. We compared these two estimated GFR equations by scattergram and by examining the GFR-CysC/GFR-Cr ratio in five groups of patients with CKD stages defined by GFR-Cr. We found that the GFR-CysC/GFR-Cr ratio exceeded 1.0 more often in CKD patients with high-stage renal dysfunction and that there were significant differences between any two groups. If we assume a simple reciprocal relationship between CysC and GFR, serum CysC concentrations lead to underestimations of renal

dysfunction compared with serum Cr in pediatric patients with CKD. At present, the reasons that serum CysC concentrations levels are not as high as expected in CKD patients with high-stage renal dysfunction are unclear. It has been reported that elevation of the serum CysC level slowed down for high-stage adult CKD patients. The existence of non-renal clearance of CysC is indicated and the magnitude is about 20 ml/min/1.73 m^2 in humans [7], which may explain the results in this study.

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ORIGINAL ARTICLE

Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children: a multicenter study

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Abstract
Background Enzymatic methods have recently been used to measure creatinine (Cr) instead of the Jaffe method. Therefore, it is necessary to determine the reference serum Cr value for these enzymatic methods to evaluate renal function in Japanese children.
Methods To determine reference values of serum Cr in Japanese children, 1151 children (517 male, 634 female) aged between 1 month and 18 years had their serum Cr values measured by an enzymatic method. To be included in the study the children had to be without kidney disease, urogenital disease, infectious disease, inflammatory disease, dehydration, muscular disease, anomaly syndrome, cardiovascular disease, malignant disease, hypertension, liver or pancreas disease, or pregnancy.
Results The medians of reference values increased gradually with age, i.e., 0.30 mg/dl at 4 years old and 0.41 mg/dl at 10 years old. In adolescence, they increased significantly more rapidly in males than in females. We found a linear regression equation capable of estimating the reference value of serum Cr in children aged 2–11 years, and quintic regression equations capable of estimating the reference values of serum Cr in male and female children of all ages.
Conclusion The reference serum Cr levels determined by an enzymatic method related to age, gender, and body length, and our linear and polynomial equations showing the relationship between body length and serum Cr level will be applicable for screening of renal function in Asian as well as Japanese children.

Keywords Reference serum creatinine level · Japanese children · Enzymatic method · Body length · eGFR

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Introduction

Serum creatinine (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 relationship between body length, glomerular filtration rate (GFR), and serum Cr level as estimated GFR (eGFR; ml/min/1.73 m^2) $=\kappa \times$ body length (cm)/serum Cr value (mg/dl). The coefficient κ 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 [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 Jaffe method to measure Cr; however, enzymatic methods have recently been used to measure Cr, making the above formula no longer applicable. In 2009, the updated Schwartz formula was reported as follows: eGFR (ml/min/1.73 m^2) $= 0.413 \times$ body length (cm)/serum Cr value (mg/dl) by enzymatic Cr determination in children 7.7–14.3 years old [5].

It would be beneficial to obtain a reference serum Cr value by an enzymatic method in Japanese children according to sex and age for renal function evaluation in routine practice. We also attempted to derive a formula to estimate reference serum Cr values in Japanese children as a function of body length, based on the Schwartz formula: i.e., normal serum Cr value (mg/dl) = $k \times$ body length (m) in subjects aged 2–11 years, and to derive polynomial formulae to estimate reference serum Cr values as functions of body length in males and females between 1 month and 18 years old.

Materials and methods

A total of 1151 children (517 male and 634 female) between the ages of 1 month and 18 years presenting at the facilities of the members for the Committee of Measures for Pediatric Chronic Kidney Disease (CKD) and Tokyo Health Service Association between 2008 and 2009 were included in the study. The children had to be without kidney disease, urogenital disease, infectious disease, inflammatory disease, dehydration, muscular disease, anomaly syndrome, malignant disease, hypertension, cardiovascular disease, liver or pancreas disease, or pregnancy. The study was approved by the local ethics boards, and written informed consent was obtained from the parents of each subject.

Data regarding serum Cr values and body lengths measured at the same time were reviewed.

With the exception of 1 male and 2 females at the age of 1 month, and 1 male and 1 female at the age of 18 years, the subjects were divided into the following groups based on age: $\geq$3 to <6 months ($n = 18$; 16 male, 2 female), $\geq$ 6 to < 9 months old ($n = 19$; 15 male, 4 female), $\geq$ 9 months to <1 year old ($n = 31$; 17 male, 14 female), 1 year old ($n = 70$; 33 male, 37 female), 2 years old ($n = 73$; 40 male, 33 female), 3 years old ($n = 88$; 48 male, 40 female), 4 years old ($n = 81$; 43 male, 38 female), 5 years old ($n = 96$; 47 male, 49 female), 6 years old ($n = 102$; 43 male, 59 female), 7 years old ($n = 85$; 38 male, 47 female), 8 years old ($n = 56$; 18 male, 38 female), 9 years old ($n = 36$; 18 male, 18 female), 10 years old ($n = 44$; 12 male, 32 female), 11 years old ($n = 58$; 19 male, 39 female), 12 years old ($n = 69$; 15 male, 54 female), 13 years old ($n = 68$; 30 male, 38 female), 14 years old ($n = 57$; 17 male, 40 female), 15 years old ($n = 37$; 15 male, 22 female), and 16 years old ($n = 57$; 30 male, 27 female). Reference intervals (2.5 percentile and 97.5 percentile) of serum Cr against age were calculated in children between the age of 3 months and 11 years, and against sex and age between 12 and 16 years old. In addition, reference intervals for serum Cr were calculated in children relative to body length every 10 cm. In subjects aged 2–11 years, the relationship between body length and serum Cr level was determined by linear regression analysis according to the report of Uemura [6]. In all subjects, the relationship between body length and serum Cr level was determined by polynomial regression analysis in males and females, respectively. We expressed reference serum Cr level as a quintic equation of body length. In mathematics, a quintic equation is a polynomial equation of degree 5. We chose a quintic equation as a polynomial expression of theoretical changes in serum Cr level with growth in childhood. Age-related changes in serum Cr level have 4 phases with growth where the level decreases gradually up to around 1 year while renal function is developing, increases gradually before puberty while muscle mass is increasing, increases markedly according to the rapid increase in muscle mass in adolescence, and plateaus in adulthood. Therefore, we speculated that there were 4 inflection points in the developmental curve of reference serum Cr level.

Serum samples were stored at −70°C until serum Cr was measured at SRL Inc (Tokyo, Japan). The serum level of Cr was determined by an enzymatic method using a Bio Majesty automated analyzer (JCA-BM8060; JEOL Ltd, Tokyo, Japan) with Pureauto S CRE-L (Sekisui Medical Co., Ltd, Tokyo, Japan). The coefficient of variation was satisfactory (2.08%).

All analyses were conducted using Microsoft Excel 2007 and a statistical software package (JMP 8; SAS Institute Inc, Cary, NC, USA). We conducted linear and polynomial regression analyses to evaluate factors influencing Cr levels. We used Wilcoxon analysis to compare differences in serum Cr levels between the sexes. In all analyses, $P < 0.01$ was taken to indicate statistical significance.

Results

We examined the correlations between serum Cr concentration and age in all subjects divided according to sex (Fig. 1). Scattergrams showed that reference serum Cr concentrations increased gradually with age, and the increase was more marked in males than females in adolescence. We reviewed the median, 2.5 percentile, and 97.5 percentile of serum Cr reference value in each age group regardless of sex between 3 months and 11 years, because no significant differences were found between males and females in these age groups (Table 1). The median of the reference value increased gradually with age, i.e., 0.30 mg/dl at 4 years old and 0.41 mg/dl at 10 years old. In addition, we reviewed serum Cr reference value equally between 12 and 16 years old in males and females

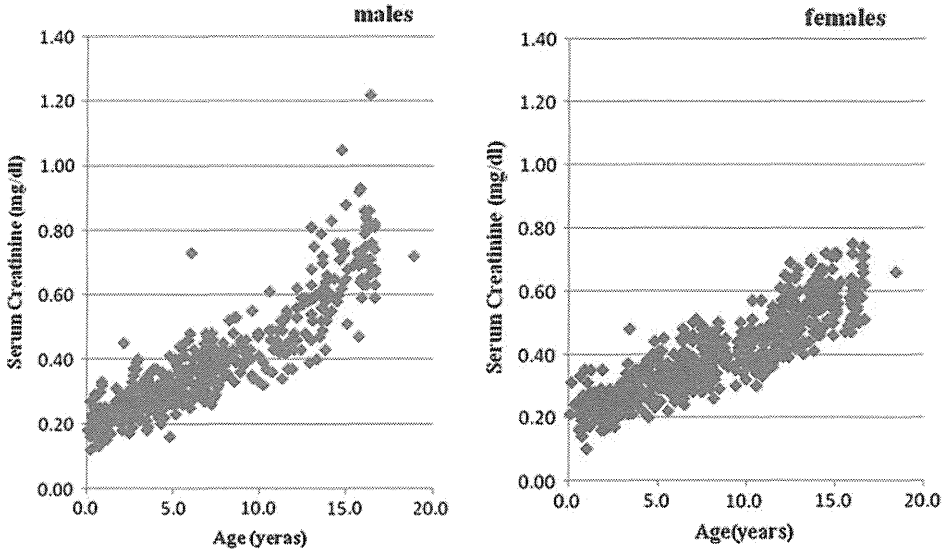

Fig. 1 Correlations between serum Cr concentration and age in all subjects divided according to sex. These scattergrams show that reference serum Cr concentration gradually increases with age, and the increase is more marked in males than females in adolescence

Table 1 Median, 2.5 percentile, and 97.5 percentile of serum Cr reference value in each age group regardless of sex between 3 months and 11 years old

Age	*N*	2.5%	50.0%	97.5%
3–5 months	18	0.14	0.20	0.26
6–8 months	19	0.14	0.22	0.31
9–11 months	31	0.14	0.22	0.34
1 year	70	0.16	0.23	0.32
2 years	73	0.17	0.24	0.37
3 years	88	0.21	0.27	0.37
4 years	81	0.20	0.30	0.40
5 years	96	0.25	0.34	0.45
6 years	102	0.25	0.34	0.48
7 years	85	0.28	0.37	0.49
8 years	56	0.29	0.40	0.53
9 years	36	0.34	0.41	0.51
10 years	44	0.30	0.41	0.57
11 years	58	0.35	0.45	0.58

(Table 2). The median reference value in males was almost equal to that in females at the age of 12 years; however, the median reference value in males increased rapidly, and became significantly different from that in females at 16 years old (0.73 mg/dl and 0.59 mg/dl, respectively, $P < 0.0001$).

We reviewed the median, 2.5 percentile, and 97.5 percentile of serum Cr reference values in each body length group in males and females (Table 3). We again found that the median reference values were higher in males than in females >160 cm in body length.

The correlations between serum Cr value and body length were determined in subjects aged 2–11 years. The regression equation was $y = 0.34x$–0.044, and that passing through the origin was $y = 0.30x$. A significant positive correlation was observed in 717 children aged 2–11 years, with a correlation coefficient of 0.732 (Fig. 2, $P < 0.001$).

Table 2 Median, 2.5 percentile, and 97.5 percentile of reference serum Cr value between 12- and 16-year-old males and females

Sex	Males				Females			
Age (years)	*n*	2.5%	50.0%	97.5%	*n*	2.5%	50.0%	97.5%
12	15	0.40	0.53	0.61	54	0.40	0.52	0.66
13	30	0.42	0.59	0.80	38	0.41	0.53	0.69
14	17	0.54	0.65	0.96	40	0.46	0.58	0.71
15	15	0.48	0.68	0.93	22	0.47	0.56	0.72
16	30	0.62	0.73	0.96	27	0.51	0.59	0.74

In all subjects, the relationships between body length and serum Cr level were determined by polynomial regression analysis in males and females, and reference serum Cr level was expressed as a quintic equation of body length (Figs. 3, 4). The regression equations were $y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$ in 516 males, and $y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$ in 630 females. Significant correlations were observed in males with a correlation coefficient of 0.908 (Fig. 3, $P < 0.001$), and in females with a correlation coefficient of 0.879 (Fig. 4, $P < 0.001$).

Discussion

GFR is used to assess kidney function, and is measured by renal clearance techniques. Inulin clearance is the gold standard for evaluation of kidney function, but cannot be measured easily. Therefore, various methods to determine GFR have been used. One method involves monitoring

Table 3 Median, 2.5 percentile, and 97.5 percentile of reference serum Cr value in each body length group in males and females

Sex	Males				Females			
Body length (cm)	*n*	2.5%	50.0%	97.5%	*n*	2.5%	50.0%	97.5%
<70	30	0.13	0.20	0.29	9	0.14	0.23	0.25
≥70 to <80	33	0.15	0.22	0.34	34	0.15	0.23	0.35
≥80 to <90	44	0.18	0.23	0.35	44	0.17	0.24	0.29
≥90 to <100	58	0.19	0.27	0.38	49	0.20	0.27	0.37
≥100 to <110	67	0.20	0.30	0.42	72	0.24	0.32	0.42
≥110 to <120	77	0.26	0.36	0.47	102	0.25	0.34	0.46
≥120 to <130	45	0.28	0.40	0.53	50	0.28	0.39	0.49
≥130 to <140	31	0.33	0.41	0.54	34	0.31	0.42	0.52
≥140 to <150	25	0.34	0.49	0.61	55	0.31	0.45	0.64
≥150 to <160	30	0.41	0.56	0.93	132	0.39	0.55	0.72
≥160 to <170 (≥160 in females)	48	0.46	0.67	0.86	49	0.47	0.58	0.68
≥ 170	28	0.57	0.72	1.02				

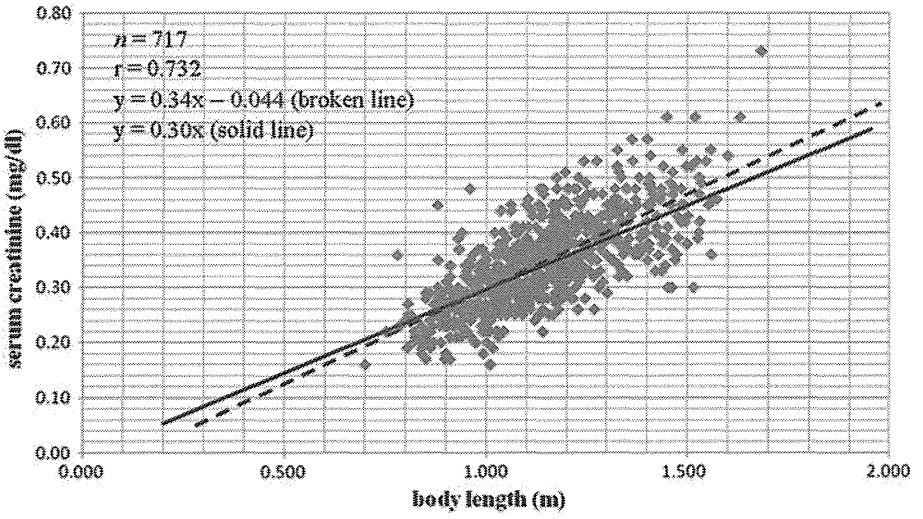

Fig. 2 Correlations between serum Cr values and body length (2–11 years). The regression equation was $y = 0.34x–0.044$, and that passing through the origin was $y = 0.30x$. A significant positive correlation was observed in 717 children aged 2–11 years, with a correlation coefficient of 0.732 ($P < 0.001$)

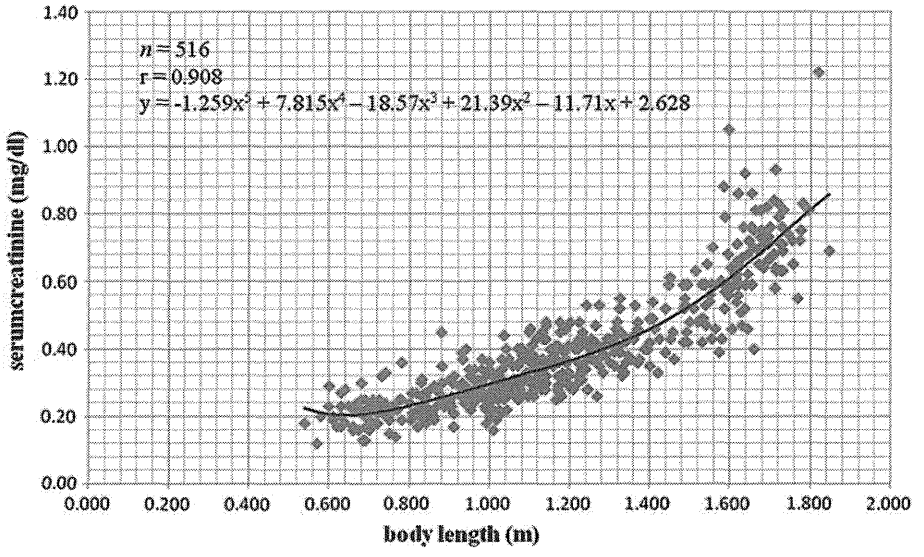

Fig. 3 Correlations between serum Cr value and body length (males, 3 months–18 years). A significant correlation between serum Cr value and body length was determined by polynomial regression analysis in males, and reference serum Cr level was expressed as a quintic equation of body length