Clinical and Experimental Nephrology
https://doi.org/10.1007/s10157-022-02205-0

ORIGINAL ARTICLE

Ultrasonographic reference values and a simple yet practical formula for estimating average kidney length in Japanese children

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Received: 2 August 2021 / Accepted: 22 February 2022

Abstract

Background The assessment of kidney size is essential for treating kidney disease. However, there are no reliable and sufficiently robust ultrasonographic reference values or prediction formulas for kidney length in Japanese children, based on a sufficient number of participants.

Methods We retrospectively analyzed kidney measurements by ultrasonography in children aged 18 years or younger from eight facilities throughout Japan between January 1991 and September 2018. Detailed reference values were developed by aggregating the left and right kidneys of boys and girls separately. Simple and practical reference values were developed by combining all the data from left and right kidneys and boys and girls. The estimation formulas for the average value and lower limit of the normal range for kidney length were developed based on regression analysis.

Results Based on the aggregated kidney length data of 1984 participants (3968 kidneys), detailed reference values and simple reference values for kidney length were determined. From the regression analysis, the formula for calculating the average kidney length was generated as "kidney length (cm) = body height (m) × 5 + 2", and that for predicting the lower limit of normal kidney length in children under 130 cm was calculated as "lower limit (cm) = 0.85 × [body height (m) × 5 + 2]".

Conclusion Detailed ultrasonographic reference values of kidney length for Japanese children and simple reference values and estimation formulas for daily practice have been established.

Keywords Kidney length · Ultrasonography · Pediatric nephrology · Chronic kidney disease · Reference value · Prediction formula

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Published online: 16 April 2022

Introduction

Assessing kidney size is essential for treating children with kidney disease. Many kidney diseases are accompanied by changes in the morphology and size of the kidneys, and the relationship between kidney function and size in children has been shown in previous reports [1, 2]. Evaluating kidney size can also provide important insight for the diagnosis and management of chronic kidney disease. Congenital anomalies of the kidney and urinary tract in children, especially hypoplastic or dysplastic kidneys, can be determined by data like kidney size.

Ultrasonography is the most common diagnostic imaging method used to investigate kidneys and urinary tracts and can provide information on kidney size in children [3]. A reliable ultrasonographic reference value is crucial for assessing kidney size. Although some reports provided reference values for normal kidney measurements in children by ultrasonography [3–6], most of them were not reliable due to relatively small sample sizes. Therefore, it is vital to establish robust reference values for normal kidney size in children based on a large dataset. Additionally, determining a formula that could easily estimate average and lower limits of normal kidney length would be useful in clinical practice.

This study aimed to define detailed ultrasonographic reference values for kidney length in healthy Japanese children. We also tried to establish simple reference values of kidney length for daily practice and a simple yet practical formula that could estimate the normal lower limit of kidney length in children.

Materials and methods

Study design and data collection

In this observational retrospective study, we reviewed the medical records of pediatric participants aged 18 years or younger who underwent ultrasonography at each institution (Table 1) between January 1991 and September 2018. The inclusion criteria were as follows: (1) patients with asymptomatic hematuria, benign familial hematuria, or monosymptomatic nocturnal enuresis based on the main diagnosis at the time of ultrasonography; (2) children who underwent ultrasonography during an infant medical examination and were assumed to have normal kidneys and urinary tracts. We included participants with differences of 1 cm or more in kidney length between the left and right kidneys if there were no obvious abnormalities in morphology, internal structure, or echo intensity. We also included patients with mild hydronephrosis defined as grade 1 by the Society for Fetal Urology classification (SFU) based on the report which showed that the length of kidneys with SFU grade 1 hydronephrosis is almost equal to that of kidneys with SFU grade 0 [7].

The exclusion criteria were as follows: (1) patients with kidney or urological disorders (excluding asymptomatic hematuria, benign familial hematuria, and monosymptomatic nocturnal enuresis); (2) abnormal ultrasonography findings such as hydronephrosis with SFU grade 2 or higher, kidney cysts, horseshoe kidney, double pelvis, single kidney, and abnormal echo intensity; (3) patients with infectious or inflammatory diseases; (4) malformation syndrome including chromosomal abnormalities; (5) patients with a history of malignancy; (6) hypertensive patients requiring treatment; (7) patients with heart/liver/pancreatic disease requiring treatment; (8) women who were pregnant or could become pregnant; (9) participants considered inappropriate by the authors.

We obtained the following data from medical records retrospectively: date of birth, sex, date of ultrasonography examinations, kidney length (maximum longitudinal diameter) of the right and left kidneys measured by ultrasonography, body height, and body weight at the time of ultrasonography (if there was no data available on the day of ultrasonography, measurements within three months before and after the date of ultrasonography were accepted), body position at the time of ultrasonography, gestational age, birth body weight, and the presence or absence of SFU grade 1 hydronephrosis.

In this study, we only used data collected from ultrasonography results prepared by pediatric nephrologists, radiologists, and medical sonographers proficient in pediatric kidney ultrasonography. The type of ultrasound machine system, ultrasonic probe, and acoustic operating frequency were not specified.

Reference values of kidney length for ultrasonography

Reference values of kidney length for ultrasonography for each age and body height were calculated from the collected data. Values by age were summarized as follows: every 3 months for 1 year, every 6 months between 1 and 2 years, and every year between 2 and 18 years old. Values of body height were summarized for each 10 cm body height (50 to 59.9 cm, 60 to 69.9 cm, etc.). Then, we calculated the mean ± 2 standard deviations (SD) for each age and body height group. Detailed reference value tables were created and organized separately by sex, and by right or left kidneys. Simple and practical reference value tables for daily clinical use were developed by combining all the data regardless of sex or kidney position.

Table 1 Clinical characteristics of participants and data-providing facilities

Age (years) ($n=1984$)	8.0(4.3)
Sex	
Male	889 (44.8%)
Female	1095 (55.2%)
Body height (cm) ($n=1771$)	124.9 (27.8)
Body weight (kg) ($n=1783$)	28.1(14.5)
Gestational age (week) ($n=698$)	38.9(1.7)
Birth weight (g) ($n=1115$)	3037.1(432.4)
SFU grade	
Grade 0	1660 (83.7%)
Grade 1	303 (15.2%)
No data	21 (1.1%)
Position ($n=3968$ kidneys)[a]	
Prone	2844 (71.7%)
Supine	1039 (26.2%)
Lateral position	73 (1.8%)
Sitting position	10 (0.3%)
No data	2 (0.05%)
The facility that provided the data for this study[b]	
Aichi Children's Health and Medical Center	
Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital	
Kitasato University School of Medicine	
National Center for Child Health and Development	
National Hospital Organization Chibahigashi National Hospital	
Shiga University of Medical Science	
Toho University Faculty of Medicine	
Tokyo Metropolitan Children's Medical Center	

Data are presented as mean (SD) or *n* (%)

SFU Society for fetal urology

[a]The result is shown by the number of kidneys because there are cases in which the left and right kidneys were measured in different positions

[b]Facility names are listed in alphabetical order

Formula for estimating kidney length by ultrasonography

Linear regression analysis was used to create a prediction formula for kidney length based on age or body height.

A simple and practical formula for estimating kidney length by ultrasonography

A simple formula for predicting kidney length for daily clinical use was developed based on the regression formula using the combined data of all participants. To simplify the formula, we rounded off to the first decimal place for each term of the regression formula.

A simple formula for estimating the lower limit of normal kidney length for children by ultrasonography

A formula for estimating the lower limit of normal kidney length was developed using the prediction formula for kidney length. We set the lower limit of kidney length as "mean—2 SD" and converted it to "mean × (1–2 SD/mean)" so that it could be expressed by a single equation using a coefficient and calculated "2 SD/mean" from the collected data of age or body height groups with 100 or more participants. While using this formula for screening, we adopted the rounded down values as the "2 SD/mean" so that participants with borderline values could be detected as requiring

attention. To evaluate the performance of this prediction formula, we examined the rate of participants who were below the lower limit based on the lower limit value calculated from the formula. This evaluation was performed for all participants younger than 10 years of age, which is equivalent to approximately 130 cm or less in height; where kidney size is considered to be a more important indicator of congenital kidney disease than it is in older children.

Difference in measured values at each facility

When comparing values by institution, we considered the issue of legitimacy when using a small amount of data for regression analysis, and therefore only examined institutions that reported more than 100 cases.

Differences in measured values according to sex, kidney position, and body position

To examine the differences in kidney length according to sex, kidney position, and body position during ultrasonography, each regression line corresponding to body height and kidney length was compared to its 95% confidence intervals in all participants.

Statistical analysis

Statistical analyses were performed using SPSS® version 26 (IBM, Chicago, USA), to clarify descriptive statistics and linear regression analysis.

Results

Characteristics of the study population (Table 1)

The data of 1997 participants were obtained from eight facilities throughout Japan. Of these, 1984 children; 889 boys and 1095 girls, who fulfilled the eligibility criteria, were included (Fig. 1). However, since height data were missing in 213 cases, 1771 (89.3%) cases were included for regression with height.

Reference values of kidney length by ultrasonography

Tables 2 and 3 show the detailed reference values for kidney length ± 2 SD for each age and body height group. Since there was only one patient (two kidneys) with a body height less than 50 cm, they were excluded from Table 3. Tables 4 and 5 show the simple reference values for kidney length, regardless of sex or kidney position, for each age and body height group.

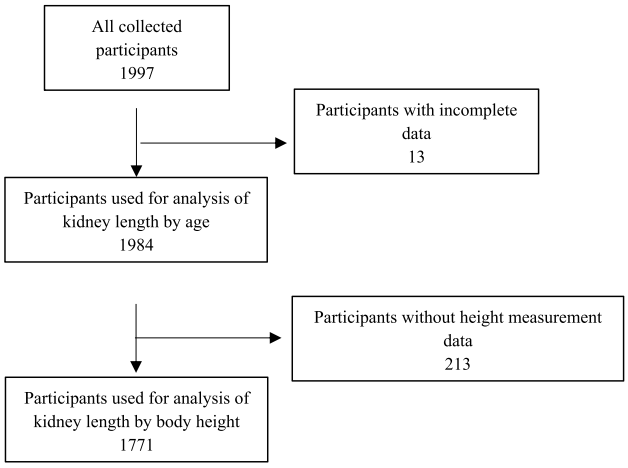

Fig. 1 Participant selection flow chart

Formula for estimating kidney length by ultrasonography

As shown in Supplementary Fig. S1, the reference values of kidney length for each height were almost completely linear when plotted on the height-length graph, while those for each age formed a curve. From this, we decided to use height data for the prediction formula of kidney length.

The kidney lengths measured by ultrasonography by body height for 1771 participants (3542 kidneys) and their regression lines are shown in Fig. 2. The regression formula and coefficient of determination of kidney length (cm) and body height (cm) for all participants combined was $y = 0.496x + 2.0836$ ($R^2 = 0.8234$).

A simple yet practical formula for estimating average kidney length by ultrasonography

Based on the regression equation for all participants mentioned above, each term was rounded off to the first decimal place and as a result, we set a simple and practical formula for estimating the average value of kidney length by body height as "body height (m) × 5 + 2". Supplementary Fig. S2 shows the measured ultrasonographic values of kidney length by body height, their regression line, and a straight line indicating the results of the estimated average values of kidney length calculated by this formula.

A simple formula for estimating the lower limit of normal kidney length for children by ultrasonography

Table 6 shows the results of the "2 SD/mean" reference values for each height group. The calculated average value for "2 SD/mean" values from the data with a sufficient

Table 2 Detailed reference values of kidney length by ultrasonography according to age

Age	(m/y)	Kidney length (cm)													
		Boys							Girls						
		Right kidney				Left kidney			Right kidney				Left kidney		
		n	Mean	Mean +2sd	Mean -2sd	Mean	Mean +2sd	Mean -2sd	*n*	Mean	Mean +2sd	Mean -2sd	Mean	Mean +2sd	Mean -2sd
0–2	(m)	21	5.0	6.2	3.8	5.1	6.0	4.2	7	4.9	6.0	3.7	5.2	6.5	3.9
3–5		25	5.5	6.6	4.4	5.6	6.6	4.6	6	4.9	6.5	3.3	5.3	7.1	3.6
6–8		17	5.4	6.7	4.1	5.8	7.0	4.5	4	5.2	7.4	3.0	5.5	7.0	4.1
9–11		17	5.5	6.7	4.3	5.8	6.6	4.9	9	5.7	6.8	4.6	6.0	7.2	4.7
12–17		23	5.8	6.5	5.2	6.0	7.0	4.9	13	5.7	6.8	4.6	6.1	7.1	5.0
18–23		12	5.9	7.1	4.7	6.4	7.5	5.3	6	6.3	7.3	5.3	6.4	7.8	4.9
2	(y)	20	6.5	7.5	5.5	6.7	7.6	5.8	26	6.4	7.4	5.4	6.6	7.4	5.7
3		108	6.6	7.7	5.6	6.9	8.0	5.8	174	6.7	7.8	5.6	6.9	8.0	5.8
4		44	7.1	8.3	5.9	7.3	8.9	5.7	65	7.0	8.2	5.9	7.2	8.5	6.0
5		46	7.4	8.6	6.3	7.6	8.9	6.4	46	7.5	8.7	6.3	7.5	8.8	6.1
6		78	7.7	9.0	6.4	7.8	9.2	6.4	86	7.8	9.0	6.6	7.9	9.3	6.5
7		65	7.9	9.3	6.6	8.1	9.7	6.5	96	8.0	9.3	6.7	8.1	9.6	6.6
8		59	8.1	9.3	6.9	8.3	9.6	6.9	81	8.3	9.7	7.0	8.5	9.9	7.0
9		43	8.3	9.5	7.0	8.5	9.8	7.3	66	8.2	9.7	6.8	8.5	10.1	6.8
10		45	8.7	10.0	7.4	9.0	10.3	7.7	74	9.0	10.5	7.6	9.2	10.7	7.7
11		46	9.2	10.6	7.8	9.3	10.9	7.7	94	9.4	10.9	8.0	9.5	10.9	8.1
12		72	9.6	11.6	7.7	9.7	11.6	7.8	85	9.7	11.2	8.2	9.9	11.5	8.3
13		55	10.2	11.9	8.5	10.4	11.9	9.0	71	9.9	11.5	8.3	10.0	11.5	8.4
14		55	10.0	11.4	8.6	10.2	11.8	8.6	60	10.0	11.3	8.6	10.2	11.6	8.7
15		30	10.4	12.3	8.5	10.5	12.3	8.6	17	10.0	11.6	8.5	10.2	11.5	8.8
16		4	10.4	12.6	8.3	10.3	12.8	7.8	4	10.2	12.3	8.2	10.5	14.2	6.7
17		2	11.0	11.1	11.0	11.3	11.6	11.0	2	10.1	10.1	10.1	10.6	11.0	10.1
18		2	10.2	10.3	10.0	10.3	10.4	10.3	3	9.8	10.4	9.2	10.2	12.1	8.3

SD standard deviation, *m* months, *y* years

number of participants of 100 or more was 0.156, and the rounded down value of 0.15 was applied to "mean × (1–2 SD / mean)". As a result, the formula for calculating the value of the lower limit of kidney length was set as "mean × 0.85" i.e. "0.85 × [body height (m) × 5 + 2]".

The number and rate of participants whose actual kidney lengths were shorter than the lower limit by this formula is shown in Table 6. When the formula was applied to all cases or cases with a height of 130 cm or less, the rate of cases judged to be below the normal range was approximately 2.1% and 2.3%, respectively. The rate of being below the lower limit of the normal range tended to be small in participants with a body height of 140 cm or more. Figure 3 shows the measured kidney length by height, the estimated normal values of kidney length by height, and the lower limit of the normal range by this formula for children with body height up to 130 cm.

Difference in measured values for each facility

Figure 4 shows the measured values for five facilities, which reported more than 100 cases. As shown in the figure, there were differences in the measured values depending on the facility.

Differences in measured values according to sex, kidney position, and body position

The regression lines, regression formulas, and coefficients of determination for boys and girls, for right and left kidneys, and for each body position are shown in Supplementary Fig. S3 and S4. The regression lines for body height and kidney length in all participants along with their 95% confidence intervals are also shown in Supplementary Fig. S5 and S6. Each regression line was within a narrow range, but some

Table 3 Detailed reference values of kidney length by ultrasonography according to body height

Body height (cm)	Kidney length (cm)													
	Boys							Girls						
	Right kidney				Left kidney			Right kidney				Left kidney		
	n	Mean	Mean +2sd	Mean -2sd	Mean	Mean +2sd	Mean -2sd	*n*	Mean	Mean +2sd	Mean -2sd	Mean	Mean +2sd	Mean -2sd
50–59.9	12	5.0	6.4	3.5	5.0	5.9	4.2	6	4.6	5.4	3.9	4.9	5.3	4.6
60–69.9	20	5.3	6.4	4.3	5.5	6.5	4.5	11	5.3	6.9	3.6	5.4	6.2	4.5
70–79.9	27	5.7	6.9	4.6	5.9	7.0	4.7	18	5.9	6.9	4.9	6.2	7.0	5.4
80–89.9	25	6.3	7.5	5.2	6.6	7.5	5.7	40	6.4	7.5	5.2	6.5	7.3	5.6
90–99.9	90	6.6	7.7	5.5	6.9	7.9	5.8	170	6.7	7.7	5.8	6.9	8.0	5.8
100–109.9	64	7.2	8.2	6.1	7.4	8.7	6.0	80	7.3	8.5	6.1	7.4	8.8	6.1
110–119.9	93	7.7	9.0	6.5	7.8	9.1	6.5	116	7.8	8.9	6.7	7.8	9.2	6.5
120–129.9	85	8.1	9.3	6.9	8.2	9.5	6.9	128	8.2	9.2	7.1	8.3	9.4	7.2
130–139.9	77	8.5	9.7	7.2	8.8	10.1	7.5	98	8.6	10.2	7.1	8.7	10.3	7.1
140–149.9	46	9.2	10.7	7.7	9.3	10.8	7.8	130	9.3	10.4	8.1	9.4	10.9	7.9
150–159.9	71	9.5	11.1	8.0	9.8	11.5	8.1	166	9.9	11.1	8.6	10.0	11.3	8.7
160–169.9	93	10.1	11.4	8.7	10.3	11.7	8.9	58	10.2	11.9	8.6	10.3	12.0	8.6
170–179.9	40	10.6	11.9	9.3	10.6	11.9	9.3							
180–189.9	5	11.4	14.3	8.4	11.4	12.8	10.1							

SD standard deviation

segments of the lines were found to deviate from the 95% confidence intervals.

Discussion

In this study, we developed the ultrasonographic reference values for kidney length in Japanese children based on the data of 1984 participants (3968 kidneys) from eight facilities throughout Japan. Detailed and simple reference value tables by age and by height were prepared; the detailed tables were shown separately by sex, and by right or left position, and the simple tables were shown regardless of sex or position. Additionally, we developed an estimation formula for kidney length by ultrasonography. The regression equation of kidney length (cm) and body height (cm) was "$y = 0.0496x + 2.0836$ ($R^2 = 0.8234$)". Based on these results, we proposed the following simple and practical estimation formulas: "the estimated average kidney length (cm) = body height (m) × 5 + 2" for all children, and "the estimated lower limit of normal kidney length (cm) = 0.85 × [body height (m) × 5 + 2]" for children up to 130 cm tall. These are the first reference values created with a sufficiently large number of participants, and simple reference values and estimating formulas are expected to be widely utilized in daily clinical practice.

Reliable reference values for clinical use should be based on the data of a sufficient number of participants. However, most previous reports on ultrasonographic reference values of kidney length in children were based on the data of approximately 200 to 1000 participants, and the number of participants per age group was small [3, 4, 6]. Our reference values, especially the simple ones, were considered more reliable than previously reported values because they were based on a much larger number of participants for each age and height group.

The clinical reference values should be applicable to a variety of situations at multiple institutions. Most previous reports of kidney size by ultrasonography in children were based on measurements performed by a limited number of examiners on the same ultrasonography device in the same body position and in a single facility [5]. However, it has not been fully verified whether these values can be applied when other examiners use different models at other facilities or with different body positions. The data we used to create reference values in this study were obtained from multiple examiners at eight facilities throughout Japan using different ultrasonography systems. We also did not limit the body position at the time of ultrasonography. Previous reports have shown that kidney length differs depending on the body position during ultrasonography [8]. Although we could not analyze kidney length in the lateral and sitting positions due to the insufficient number of participants, we did find that the difference between the supine and prone positions was small and practically negligible (Supplementary Fig. S4 and S6). Therefore, our results can be considered to be more

Table 4 Simple and practical reference values of kidney length by ultrasonography for practical clinical use by age

Age	(m/y)	*n*	kidney length (cm)		
			mean	mean +2SD	mean -2SD
0–2	(m)	56	5.0	6.1	3.9
3–5		62	5.4	6.7	4.2
6–8		42	5.5	6.9	4.2
9–11		52	5.7	6.8	4.6
12–17		72	5.9	6.9	4.9
18–23		36	6.2	7.4	5.0
2	(y)	92	6.5	7.5	5.6
3		564	6.8	7.9	5.7
4		218	7.2	8.5	5.8
5		184	7.5	8.7	6.3
6		328	7.8	9.1	6.5
7		322	8.0	9.5	6.6
8		280	8.3	9.7	7.0
9		218	8.4	9.8	6.9
10		238	9.0	10.5	7.6
11		280	9.4	10.9	7.9
12		314	9.7	11.5	8.0
13		252	10.1	11.7	8.5
14		230	10.1	11.6	8.6
15		94	10.3	12.0	8.6
16		16	10.4	12.8	7.9
17		8	10.7	11.7	9.8
18		10	10.1	11.1	9.1

SD standard deviation, *m* months, *y* years

Table 5 Simple and practical reference values of kidney length by ultrasonography for practical clinical use by body height

Body height (cm)	*n*	kidney length (cm)		
		Mean	Mean +2SD	Mean -2SD
50–59.9	36	4.9	5.9	3.9
60–69.9	62	5.4	6.5	4.3
70–79.9	90	5.9	7.0	4.8
80–89.9	130	6.4	7.4	5.4
90–99.9	520	6.8	7.8	5.7
100–109.9	288	7.3	8.6	6.1
110–119.9	418	7.8	9.0	6.5
120–129.9	426	8.2	9.4	7.0
130–139.9	350	8.6	10.1	7.2
140–149.9	352	9.3	10.7	7.9
150–159.9	474	9.9	11.3	8.4
160–169.9	302	10.2	11.7	8.7
170–179.9	82	10.6	12.0	9.2
180–189.9	10	11.4	13.6	9.2

SD standard deviation

widely applicable than previously reported findings and may be specifically used for measurements in the prone and supine positions.

There may be differences in kidney length depending on gestational age and birth weight [9]. Given that considerable data on gestational age or birth weight were lacking among the participants included in this study (Table 1), it should be noted that our results include findings of cases wherein where we could not clearly ascertain preterm birth and/or of participants with a low birth weight history. As a reference, data on kidney length in participants with clear data on gestational age and body weight at birth are shown in Supplementary Fig. S7.

Simple reference values can be more useful for daily clinical use than detailed ones. However, the creation of simple reference values by combining the data of both left and right kidneys could be considered controversial, because the length of the left kidney has been reported to be slightly longer than the right kidney in previous studies [6, 10]. In this study, slight but significant differences in length were also observed between the left and right kidney, and between boys and girls (Fig. 2, Supplementary Fig. S1, S3, and S5). However, these differences were considered minor enough to be practically insignificant in daily clinical practice. Therefore, we thought that the simple reference values that we developed by combining all the data can be applied to daily clinical practice regardless of sex and kidney position.

A simple predictive formula that can easily estimate normal kidney length at the bedside would be highly useful in clinical practice. Several formulas for predicting the normal length of kidneys in children based on age and/or body height have been shown in previous reports (Supplementary Table S1) [3–6, 10–13]. However, these formulas were relatively complicated for daily use at the bedside. Therefore, we tried to create a simpler estimation formula. Of the formulas shown in Supplementary Table S1, there were similarities between the formulas of Kim et al. [11] and our own. This could be due to the fact that both sets of formulas were based on data from East Asian children.

Whether age or body height is more appropriate as a parameter for estimating kidney length has not been sufficiently investigated. One previous study reported a simple formula that used age data to predict normal kidney length in children [6]. However, in our data on kidney length, the relationship with body height was almost linear, while the relationship with age was a curve similar to a growth curve. Furthermore, although there was almost no difference in kidney length by body height between boys and girls, kidney length tended to differ by age between boys and girls after puberty (Supplementary Fig. S1). Therefore, we considered body height a more appropriate measure than age to establish a single, simple, and practical predictive formula. For these reasons, based on the regression equation of body height

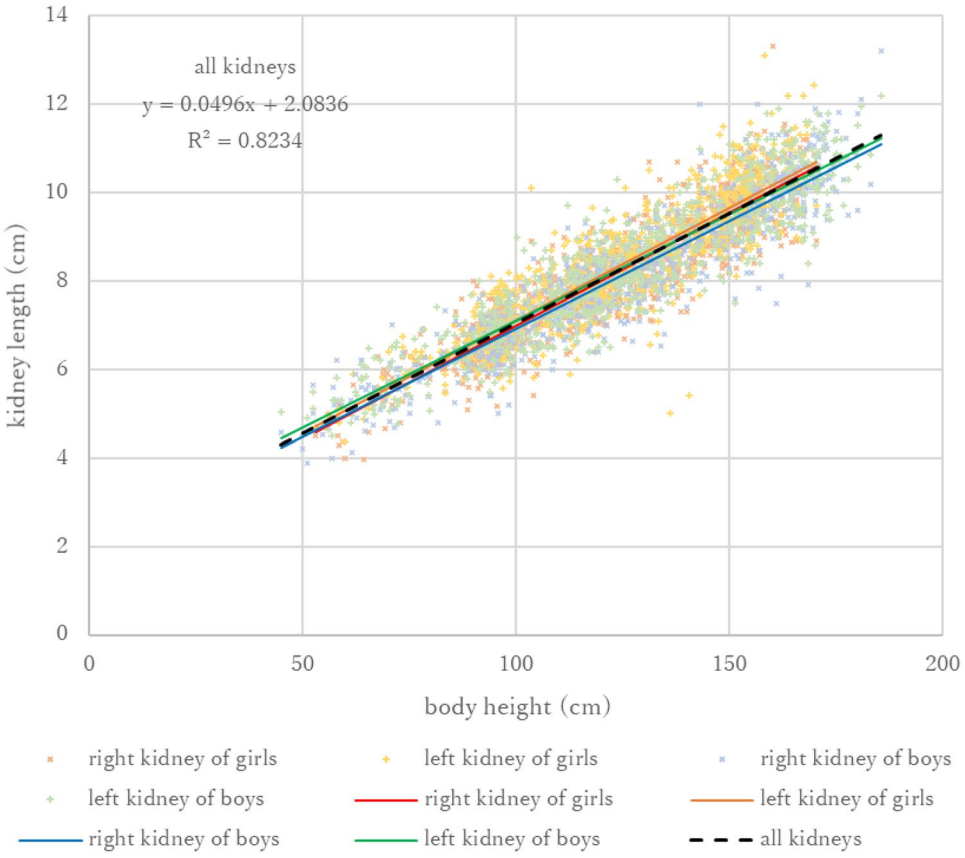

Fig. 2 Kidney length by ultrasonography of right (light red cross) and left (light orange cross) kidneys of girls and those of right (light blue cross) and left (light green cross) kidneys of boys according to body height. Colored solid lines show each regression line, and the thick black dashed line indicates the regression line for all participants

Table 6 The 2 SD and "2 SD/mean" reference values for each height group, and the number and rate of subjects whose actual kidney length were judged shorter than the lower limit by the formula "estimated kidney length by body height × (1–0.15) (cm)"

Body height (cm)	*n*	2SD (cm)	2SD/mean	Number and rate of subjects lower than the value of "estimated kidney length by body height × (1–0.15) (cm)"	
				n (kidney)	Rate (%)
50–59.9	36	1.01	0.20	1	2.8
60–69.9	62	1.12	0.21	3	4.8
70–79.9	90	1.09	0.18	3	3.3
80–89.9	130	1.03	0.16	4	3.1
90–99.9	520	1.05	0.15	9	1.7
100–109.9	288	1.27	0.17	9	3.1
110–119.9	418	1.24	0.16	11	2.6
120–129.9	426	1.16	0.14	6	1.4
130–139.9	350	1.46	0.17	13	3.7
140–149.9	352	1.40	0.15	5	1.4
150–159.9	474	1.43	0.14	6	1.3
160–169.9	302	1.51	0.15	4	1.3
170–179.9	82	1.36	0.13	2	2.4
180–189.9	10	2.16	0.19	0	0.0

SD standard deviation

and kidney length from our results, we propose "estimated average kidney length (cm) = body height (m) × 5 + 2" as a simple prediction formula. Using this formula, the estimated average kidney length can be easily calculated at the bedside regardless of sex and kidney position.

The normal range of kidney length is as important as the average value, and it would be highly useful if the lower limit of normal kidney length can be easily clarified at the bedside. Therefore, we suggest that "0.85 × the estimated average value of kidney length (cm)." could be used as the prediction formula for estimating the lower limit of kidney length.

However, when this formula was applied to participants with a body height of 140 cm or more, the rate of being judged below the lower limit was low (Table 6); hence, it was considered inappropriate to apply this formula to taller participants. In contrast, when this formula was applied to those with a body height of 130 cm or less, which corresponds to under 10 years of age, 2.3% were judged to be below the normal range (Table 6); therefore, it was considered appropriate for this prediction formula to be used for children with a body height of 130 cm or less.

There are some limitations to this study. First, we included patients with asymptomatic hematuria, benign familial hematuria, and monosymptomatic nocturnal

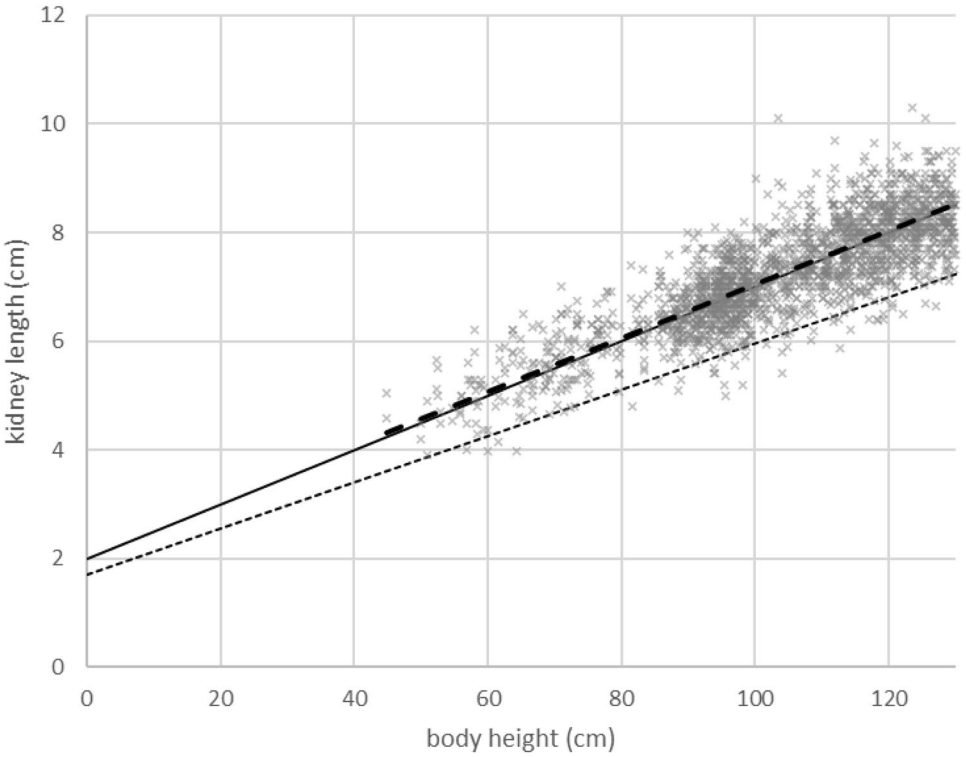

Fig. 3 The measured values of kidney length by height by ultrasonography, their regression line (thick dashed line), and the estimated normal values of kidney length (solid line). The straight dotted line shows the lower limit of the normal range by this calculation formula (dotted line). Body height is shown in meters up to 1.3 m

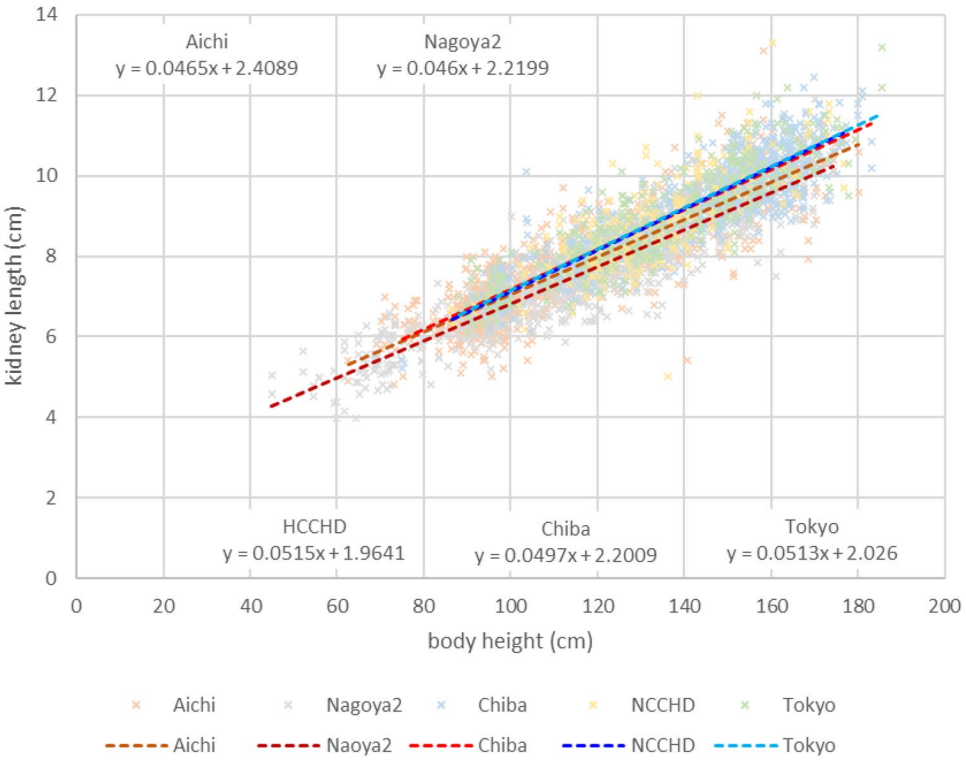

Fig. 4 Kidney length by ultrasonography by body height for five facilities, which reported more than 100 cases. Aichi: Aichi Children's Health and Medical Center, Nagoya2: Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Chiba: National Hospital Organization Chiba-higashi National Hospital, NCCHD: National Center for Child Health and Development, Tokyo: Tokyo Metropolitan Children's Medical Center

enuresis, in addition to healthy children who underwent ultrasonography during physical examination. Strictly speaking, these patients may not be considered healthy. However, we only excluded children with diseases that might affect kidney size. Second, some cases reported as SFU grade 1 were not described as bilateral or unilateral; therefore, the

actual number of kidneys with SFU grade 1 was unknown. Third, the number of participants varied depending on the age and body height categories. For example, the number of 3-years-old children included was extremely large compared to other age groups; both younger and older, due to the medical examination required of 3-years-old children in Japan. Since the number of participants under 2 and over 16 years was insufficient, as well as those with body height less than 60 cm or over 180 cm, the reference values for kidney length in these age and body height groups were unreliable. Finally, we conducted research by collecting data measured by multiple examiners using different types of ultrasound machine systems at multiple facilities throughout Japan. The technical quality of each examiner who performed ultrasonography was guaranteed based on the study method that specified the qualification of the examiner. However, the differences in the measurement values due to technical skill variations of each examiner and ultrasound machine system distinctions were not examined.

Conclusions

Ultrasonographic reference values and simple prediction formulas for normal kidney length in healthy Japanese children under 18 years were developed in this study. These reference values and prediction formulas can be applied in any facility regardless of sex, kidney position, presence of SFU grade 1 hydronephrosis, and body position at the time of ultrasonography. We propose "the estimated average kidney length (cm) = body height (m) × 5 + 2" as a simple and practical calculation formula for predicting normal kidney length in children under 18 years. We also propose the formula "the estimated lower limit of normal kidney length (cm) = 0.85 × [body height (m) × 5 + 2]" to estimate the lower limit of normal kidney length for children up to 130 cm tall.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10157-022-02205-0.

Author contributions NF, OU, and KI contributed to the study's conception and design. Data acquisition was performed by NF, RH, CM, TS, YH, KN, KI, and YG. Data analysis was performed by NF, OU, TK, and YG. All authors read and approved the final manuscript.

Funding This work was funded by childhood-onset, rare and intractable kidney diseases in Japan, research on rare and intractable diseases, Health, Labour and Welfare Sciences Research Grants (20FC1028).

Declarations

Conflict of interest The authors have declared that no conflicts of interest exist.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the first author's facility (approval number 2018097) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The Institutional Review Board waived the requirement for informed consent due to the retrospective nature of this study.

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Pediatric Nephrology (2023) 38:1057–1066
https://doi.org/10.1007/s00467-022-05703-1

ORIGINAL ARTICLE

Early predictive factors for progression to kidney failure in infants with severe congenital anomalies of the kidney and urinary tract

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Received: 6 March 2022 / Revised: 23 July 2022 / Accepted: 25 July 2022 / Published online: 11 August 2022

Abstract

Background Severe congenital anomalies of the kidney and urinary tract (CAKUT) progress to infantile kidney failure with replacement therapy (KFRT). Although prompt and precise prediction of kidney outcomes is important, early predictive factors for its progression remain incompletely defined.

Methods This retrospective cohort study included patients with CAKUT treated at 12 centers between 2009 and 2020. Patients with a maximum serum creatinine level ≤ 1.0 mg/dL during the first 3 days, patients who died of respiratory failure during the neonatal period, patients who progressed to KFRT within the first 3 days, and patients lacking sufficient data were excluded.

Results Of 2187 patients with CAKUT, 92 were finally analyzed. Twenty-five patients (27%) progressed to KFRT and 24 (26%) had stage 3–5 chronic kidney disease without replacement therapy during the median observation period of 52.0 (interquartile range, 22.0–87.8) months. Among these, 22 (24%) progressed to infantile KFRT. The kidney survival rate during the infantile period was significantly lower in patients with a maximum serum creatinine level during the first 3 days (Cr-day3-max) ≥ 2.5 mg/dL (21.8%) compared with those with a Cr-day3-max < 2.5 mg/dL (95.2%) (log-rank, $P < 0.001$). Multivariate analysis demonstrated Cr-day3-max ($P < 0.001$) and oligohydramnios ($P = 0.025$) were associated with higher risk of infantile KFRT. Eighty-two patients (89%) were alive at the last follow-up.

Conclusions Neonatal kidney function, including Cr-day3-max, was associated with kidney outcomes in patients with severe CAKUT. Aggressive therapy for severe CAKUT may have good long-term life outcomes through infantile dialysis and kidney transplantation.

Keywords Chronic kidney disease · Dialysis · Kidney transplantation · Children · Congenital anomalies of the kidney and urinary tract · Infants

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) comprise a broad range of congenital disorders, including hypoplastic kidney, dysplastic kidney, kidney agenesis, posterior urethral valves, and congenital obstructive uropathy [1, 2]. Although the severity of these diseases can range from normal kidney function to neonatal or infantile kidney failure with replacement therapy (KFRT), CAKUT in children is the most common cause of chronic kidney disease (CKD) and KFRT [3–5].

Patients with CAKUT and complicated kidney dysfunction during the neonatal period may require dialysis and systemic management, including respiratory support, circulation management, and/or electrocyte management from an early age [6, 7]. Although the management of neonates and infants with kidney failure remains challenging and demanding, even in pediatric nephrology centers, the mortality rate has improved significantly in recent decades in line with advancements in dialysis technology and clinical expertise

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[6, 8]. Accordingly, early prediction of the timing and indications for dialysis initiation in infants with kidney failure is important for making an appropriate decision regarding early patient transfer to a treatment center, safe initiation of dialysis, and provision of an appropriate explanation to the family. Moreover, it may lead to an improvement in the life prognosis. In a previous birth cohort, further kidney prognosis was predicted by neonatal kidney function. However, the outcome in that study was progression to KFRT and CKD at the time of the last follow-up, and the timing of the evaluated outcome was different for each patient [7]. The early predictive factors for the progression of CAKUT to infantile and neonatal KFRT remain to be clarified in a large study cohort.

We therefore initiated a multicenter study to investigate the kidney outcomes and associated risk factors of KFRT during the neonatal or infantile period in patients with severe CAKUT.

Materials and methods

Study design, site, and participants

This retrospective cohort study included patients who developed CAKUT with kidney dysfunction at birth between January 1, 2009, and August 31, 2020. Twelve pediatric nephrology centers that deliver infantile dialysis treatment in Japan submitted data to this study, including six university hospitals, three children's hospitals, and three local hospitals. Inclusion criteria included patients diagnosed with hypoplastic kidney, dysplastic kidney, including multicystic dysplastic kidney, kidney agenesis, and urinary tract obstruction. Patients with hydronephrosis alone or reflux nephropathy alone were excluded. Patients with a maximum serum creatinine (SCr) level ≤ 1.0 mg/dL during the first 3 days, patients who died of respiratory failure within the neonatal period, patients who progressed to KFRT within the first 3 days, and patients who lacked sufficient data on SCr levels during the first 3 days were also excluded. We explored which factors predicted infantile KFRT in the early stages of disease.

Data collection

Anonymized data were extracted remotely from the 12 centers using the hospitals' patient administration systems. We identified subjects by querying each hospital's electronic medical record system for the insurance-related disease. Patients who satisfied the inclusion criteria after subsequent medical record review were included in the study. The following data were collected from the medical records to determine the clinical courses of the patients: sex, birth information, oligohydramnios, primary kidney diagnosis and associated diseases, including syndrome/genetic diagnosis, lower urinary tract function, extrarenal congenital complications, other complications, neonatal complications, laboratory data, treatment, including kidney replacement therapy, time to KFRT, kidney outcome, death, and follow-up duration. Laboratory data included all SCr levels during the neonatal period.

Outcome

The primary endpoint was infantile KFRT. The secondary endpoint was neonatal KFRT and progression to CKD. Infantile KFRT was defined as the need to start kidney replacement therapy within the infantile period. Non-kidney failure (non-KF) included patients who did not progress to KFRT until the last follow-up. Older KFRT included patients who progressed to KFRT after the first year of life. According to the Kidney Disease Improving Global Outcome guidelines for CKD in 2012, CKD stages 1–5 were classified as a glomerular filtration rate (GFR) of > 90, 60–90, 30–59, 15–29, and < 15 mL/min/1.73 m^2, respectively [9].

Definitions

CAKUT was diagnosed using combined data from kidney ultrasonography, kidney scintigraphy, and/or voiding cystourethrography carried out by nephrologists at each institution. Voiding cystourethrography was only performed in a selected subgroup of patients. Syndromic CAKUT was defined as CAKUT with congenital extrarenal complications.

Patients with kidney failure included those with kidney-associated death without initiation of dialysis. The estimated GFR (eGFR) was calculated in Japanese children with CKD using the creatinine-based equation [10, 11] and was then used for the staging of CKD. Neonatal acute kidney injury (AKI) was defined as an increase in SCr > 0.3 mg/dL or SCr $> 150\%$ from previous trough value [12] and an elevation of SCr with obvious triggers, such as infection, dehydration, hypoxic injury, or nephrotoxic drugs, unexplained by the natural history of progression to kidney failure on CAKUT by pediatric nephrologists. Bilateral kidney lesions included bilateral hypoplastic kidney/dysplastic kidneys, including MCDK, bilateral kidney agenesis, kidney agenesis and opposite hypoplastic kidney/dysplastic kidney including MCDK, and bilateral hypoplastic kidney/dysplastic kidneys secondary to posterior urethral valves and urinary tract obstruction.

We defined Cr-day3-max as the maximum SCr level during the first 3 days. SCr was measured by an enzymatic method. Infantile dialysis was prescribed for patients with inadequate nutrition, uncontrollable metabolic acidosis and electrolyte abnormalities, and fluid overload [6]. Low eGFR alone was not an indication for dialysis. In the observation

period, there was no change in the methods used to measure SCr or indications for dialysis.

Statistical analysis

Continuous variables were expressed as the median with interquartile range (IQR) and categorical variables were expressed as the number (%). Normally distributed continuous variables were compared using the *t*-test and non-normally distributed variables were compared using the Mann–Whitney *U*-test. Categorical variables were compared by χ^2 test. Infantile and neonatal kidney survival were analyzed by the Kaplan–Meier method to evaluate the time until occurrence of outcome. Differences between groups were compared using the log-rank test. Risk factors for infantile KFRT were determined by multivariate analysis using a Cox proportional hazard regression model. Cr-day3-max, oligohydramnios, gestational age, bilateral kidney lesions, and neonatal AKI were adjusted as risk factors.

A two-sided P value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using the JMP software package for Macintosh, 14.2 (SAS Institute Japan, Tokyo, Japan).

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour, and Welfare, Japan. The study protocol was approved by the institutional ethics committee of the National Center for Child Health and Development (approval no. 2020–169). Study approval with agreement for data was shared among each institution's ethics committee. In agreement with the above-mentioned guidelines, informed consent was not required for participation in the study.

Results

Patient characteristics

During the study period, 2187 patients with CAKUT treated at 12 centers fulfilled the inclusion criteria. Of these, 2083 patients with a maximum SCr level ≤ 1.0 mg/dL during the first 3 days, 6 patients who died of respiratory failure within the neonatal period, 2 patients who progressed to KFRT within the first 3 days, and 4 patients who lacked data on SCr levels during the first 3 days were excluded from the study. The final analyses included 92 patients (56 male, 36 female).

Table 1 summarizes the clinical characteristics of the study cohort. Briefly, approximately 50% were low birth weight infants, including five and two with very low birth weight and extremely low birth weight, respectively. The most common primary diagnosis of CAKUT was bilateral hypoplastic/dysplastic kidneys. Bilateral kidney lesions were observed in 61 patients (66%) and unilateral lesions in 31 patients (34%). Twenty-nine patients (32%) had identified syndromes associated with CAKUT. Oligohydramnios was reported in 29 patients (32%). Lower tract obstruction was treated before the initiation of dialysis in all affected patients.

Bilateral kidney lesions ($P < 0.001$), oligohydramnios ($P < 0.001$), neonatal AKI ($P = 0.042$), neonatal infection ($P = 0.002$), neonatal ventilator use ($P < 0.001$), and neonatal inotrope use ($P = 0.005$) were significantly related to infantile KFRT (Table 1). Oligohydramnios was the most common in bilateral hypoplastic/dysplastic kidneys ($n = 12$), followed by posterior urethral valves ($n = 5$), and MCDK and opposite hypoplastic/dysplastic kidney ($n = 4$). Of 29 patients with oligohydramnios, 26 (90.0%) had bilateral kidney lesions, 10 (34.5%) were complicated with neonatal infections, 15 (51.7%) required neonatal ventilator, and 23 (79.3%) required inotrope. Of 63 patients without oligohydramnios, 35 (55.6%) had bilateral kidney lesions ($P = 0.002$), 7 (11.1%) were complicated with neonatal infections ($P = 0.018$), 13 (20.6%) required neonatal ventilator ($P = 0.004$), and 21 (33.3%) required inotrope ($P < 0.001$).

KFRT

Of the 92 patients, 25 (27%) progressed to KFRT during the observation period. Of these, 22 (24%) progressed to KFRT during the infantile period, including 10 patients (11%) who progressed during the neonatal period. The remaining three patients progressed to KFRT after the first year of life.

Kidney outcome at last follow-up

Of the 70 patients who did not progress to KFRT during the infantile period, 17 (24%) had stage 1 CKD, 26 (37%) had stage 2 CKD, 16 (23%) had stage 3 CKD, six (9%) had stage 4 CKD, two (3%) had stage 5 CKD without replacement therapy, and three (4%) had progressed to KFRT at the time of the last follow-up with a median observation period of 48.0 months (IQR 20.5–89.0 months). Three patients progressed to KFRT in 12, 52, and 67 months, respectively. Consequently, 25 patients (27%) progressed to KFRT and 24 patients (26%) had stage 3–5 CKD without replacement therapy at the time of the last follow-up with a median observation period of 52.0 months (IQR 22.0–87.8 months) (Fig. 1). The observation period for 12 patients in the non-KF/older KFRT group was < 1 year. Of the remaining 80 patients, 25 (31%) progressed to KFRT and 19 (24%) progressed to stage 3–5 CKD without kidney replacement therapy. These ratios

Table 1 Clinical characteristics of 92 patients with CAKUT and comparisons between patients with and without infantile KFRT

	All subjects ($n=92$)	Infantile KFRT ($n=22$)	Non-KF/older KFRT ($n=70$)	P value
Male	56 (61%)	14 (64%)	42 (60%)	0.760
Gestational age (weeks)	37 (35–39)	37 (35–38)	37 (36–39)	0.233
< 37	32 (35%)	9 (41%)	23 (33%)	
37–42	59 (64%)	13 (59%)	46 (66%)	
42 <	1 (1%)	0 (0%)	1 (1%)	
Birth weight (g)	2509 (2119–2982)	2389 (2154–2723)	2523 (2060–3046)	0.552
< 1000	2 (2%)	0 (0%)	2 (3%)	
1000–1499	5 (6%)	1 (5%)	4 (6%)	
1500–2499	38 (41%)	12 (55%)	26 (37%)	
2500–3999	47 (51%)	9 (41%)	38 (54%)	
4000 <	0 (0%)	0 (0%)	0 (0%)	
Maternal SCr value	0.51 (0.43–0.57)[a]	0.48 (0.40–0.52)[b]	0.53 (0.45–0.59)[c]	0.015
Primary kidney diagnosis				
Bilateral hypo/dys	36 (39%)	9 (41%)	27 (39%)	
Unilateral hypo/dys	10 (11%)	0 (0%)	10 (14%)	
Bilateral kidney agenesis	1 (1%)	1 (5%)	0 (0%)	
Unilateral kidney agenesis	6 (7%)	0 (0%)	6 (9%)	
Kidney agenesis and opposite hypo/dys	1 (1%)	1 (5%)	0 (0%)	
Bilateral MCDK	2 (2%)	2 (9%)	0 (0%)	
MCDK and opposite kidney agenesis	1 (1%)	1 (5%)	0 (0%)	
MCDK and opposite hypo/dys	9 (10%)	3 (14%)	6 (9%)	
Unilateral MCDK	15 (16%)	0 (0%)	15 (21%)	
PUV	9 (10%)	4 (18%)	5 (7%)	
Urinary tract obstruction	2 (2%)	1 (5%)	1 (1%)	
Kidney lesion				
Bilateral	61 (66%)	22 (100%)	39 (56%)	< 0.001
Unilateral	31 (34%)	0 (0%)	31 (44%)	< 0.001
Syndromic CAKUT	29 (32%)	4 (18%)	25 (36%)	0.123
VACTERL association	6 (7%)	1 (5%)	5 (7%)	
4p deletion	4 (4%)	0 (0%)	4 (6%)	
*HNF1*β mutation	4 (4%)	0 (0%)	4 (6%)	
BOR syndrome	2 (2%)	1 (5%)	1 (1%)	
Trisomy 21 (Down syndrome)	2 (2%)	0 (0%)	2 (3%)	
Kabuki syndrome	2 (2%)	0 (0%)	2 (3%)	
PAX2 mutation	1 (1%)	1 (5%)	0 (0%)	
17q12 deletion	1 (1%)	1 (5%)	0 (0%)	
Trisomy 18	1 (1%)	0 (0%)	1 (1%)	
Noonan syndrome	1 (1%)	0 (0%)	1 (1%)	
Monosomy 9p	1 (1%)	0 (0%)	1 (1%)	
6q25.2 deletion	1 (1%)	0 (0%)	1 (1%)	
1q duplication	1 (1%)	0 (0%)	1 (1%)	
2p deletion	1 (1%)	0 (0%)	1 (1%)	
14 Robertsonian translocation	1 (1%)	0 (0%)	1 (1%)	
Oligohydramnios	29 (32%)	18 (82%)	11 (16%)	< 0.001
Neonatal complications				
AKI	13 (14%)	6 (27%)	7 (10%)	0.042
Infections	17 (18%)	9 (41%)	8 (11%)	0.002

Table 1 (continued)

	All subjects ($n=92$)	Infantile KFRT ($n=22$)	Non-KF/older KFRT ($n=70$)	P value
Neonatal treatments				
Ventilator	44 (49%)	21 (95%)	23 (33%)	<0.001
Inotrope	28 (30%)	12 (55%)	16 (23%)	0.005
Observation period (months)	52.0 (22.0–87.8)	53.5 (19.0–85.8)	48.0 (20.5–89)	0.752

Values are expressed as the number (%) and median (interquartile range)

[a]Measured in 54 cases; [b]measured in 15 cases; [c]measured in 39 cases

AKI, acute kidney injury; *BOR*, branchio-oto-renal; *CAKUT*, congenital anomalies of kidney and urinary tract; *Hypo/dys*, hypoplastic kidney/dysplastic kidney; *KFRT*, kidney failure with replacement therapy; *MCDK*, multicystic dysplastic kidney; *PUV*, posterior urethral valves; *SCr*, serum creatinine; *VACTERL*, vertebral, ano-rectal, cardiac, tracheo-esophageal, renal, and limb

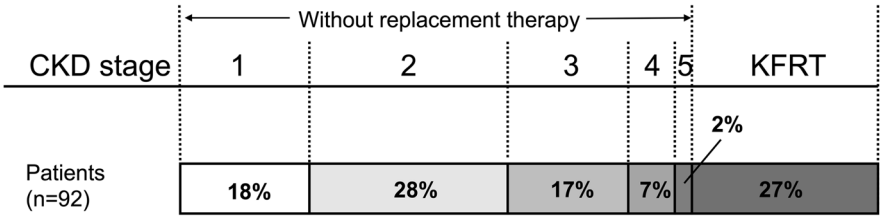

Fig. 1 Kidney outcome at last follow-up. CKD, chronic kidney disease; KFRT, kidney failure with replacement therapy

were similar to the analysis of 92 patients, including 12 with an observation period < 1 year.

Transplantation

During the study period, 11 patients (44%) received kidney transplants at a median age of 54.0 (IQR, 37.0–62.0) months, including two (8%) who received pre-emptive kidney transplantation at 52 and 67 months, respectively.

Death

Ten patients (11%) died during the study period, with a median age at death of 10.0 (IQR, 0.8–44.0) months. The causes of death in the infantile KFRT group were kidney failure without initiation of dialysis in three patients, and sepsis, encapsulating peritoneal sclerosis, and interstitial lung disease in one patient each. The causes of death in the non-KF/older KFRT group were sepsis, respiratory failure after Glenn anastomosis, pneumonia, and sudden death in one patient each.

Identifying suitable neonatal SCr data to predict infantile KFRT

The peak SCr and each maximum SCr level during the first 1 to 7 days were significantly higher in the infantile KFRT group than in the non-KF/older KFRT group (Supplemental Figure). However, because the SCr cannot predict KFRT progression before reaching its peak, it is necessary to evaluate predictive factors before the progression to KFRT. In this study, five cases progressed to KFRT within the first 7 days of life and five cases progressed to KFRT before reaching the peak SCr. Moreover, it was important to determine the indications for dialysis initiation as early as possible. Of note, Cr-day3-max was a more effective prognostic factor for infantile KFRT than Cr-day1-max and Cr-day2-max. Therefore, we selected Cr-day3-max as a predictive factor for infantile KFRT in this study.

Predictors of infantile and neonatal KFRT

The median Cr-day3-max was significantly higher in the infantile KFRT group (3.23 (IQR, 2.87–3.88) mg/dL) compared with the non-KF/older KFRT group (1.30 (IQR, 1.08–1.84) mg/dL) ($P<0.001$). Multivariable Cox proportional hazard analyses identified higher Cr-day3-max ($P<0.001$) and oligohydramnios ($P=0.025$) as factors associated with higher risk of infantile KFRT (Table 2). The Kaplan–Meier curves for times from birth to progression to

Table 2 Multivariable Cox proportional hazard analyses for infantile KFRT

Factors	Multivariate analysis		
	HR	95% CI	P value
Gestational age	0.85	0.62–1.17	0.304
Oligohydramnios	4.51	1.2–16.92	0.025
Cr-day3-max	6.46	3.22–14.1	<0.001
Bilateral kidney lesions	1.52	0.19–12.32	0.697
Neonatal AKI	1.12	0.35–3.63	0.846

AKI, acute kidney injury; *Cr-day3-max*, maximum SCr level during the first 3 days; *KFRT*, kidney failure with replacement therapy

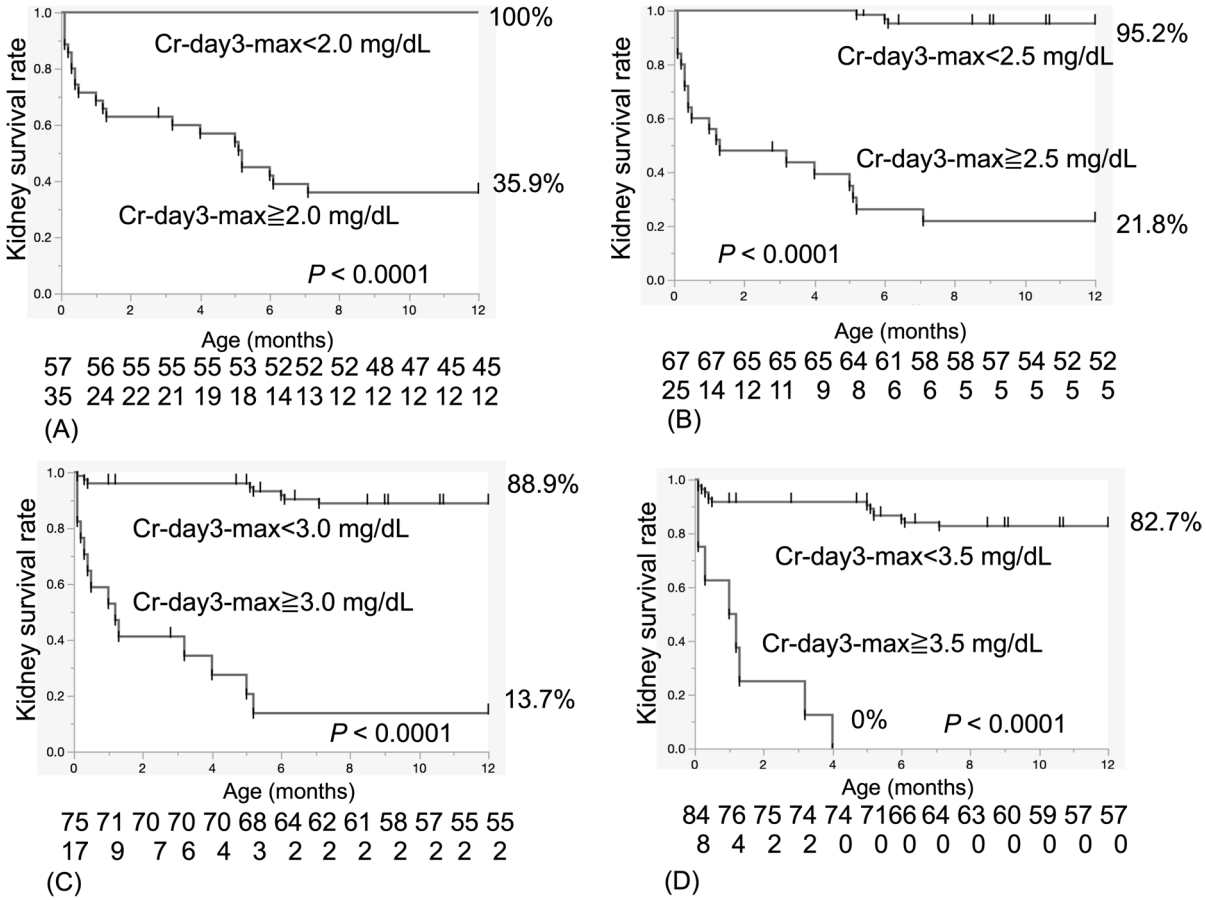

Fig. 2 Kaplan–Meier curves for time to progression from birth to infantile KFRT according to (**A**) Cr-day2.0-max, (**B**) Cr-day2.5-max, (**C**) Cr-day3.0-max, and (**D**) Cr-day3.5-max. Cr-day3-max, maximum serum creatinine level during the first 3 days; KFRT, kidney failure with replacement therapy

infantile KFRT and neonatal KFRT according to cutoff values of the Cr-day3-max are shown in Figs. 2 and 3, respectively. All cutoff values of Cr-day3-max were significant risk factors for neonatal and infantile KFRT.

Discussion

In this multicenter retrospective cohort study, we evaluated the kidney outcomes and associated early predictive factors of infantile KFRT in children with severe CAKUT. Twenty-two of 92 patients (24%) progressed to infantile KFRT. Multivariate analysis identified higher Cr-day3-max and oligohydramnios as significant risk factors for infantile KFRT after adjusting for other risk factors, including gestational age, bilateral kidney lesions, and neonatal AKI. The prompt and precise prediction of the timing and indications for dialysis initiation in infants with severe CAKUT can improve their prognosis.

During the study period, 22 patients (24%) progressed to KFRT within the first year of life, including 10 (11%) who progressed during the neonatal period. CAKUT generally has an insidious progression time to KFRT, with most cases progressing after school age and adolescence in some large cohort studies [13–16]. However, the present study showed that severe CAKUT with kidney dysfunction during the neonatal period progressed rapidly to KFRT. Nevertheless, 82 (89%) patients remained alive in the present study, and 11 patients (44%) who progressed to KFRT had received transplants at the last follow-up. These results suggested that the long-term outcomes could be favorable following appropriate treatment, even in patients with severe CAKUT.

More prompt and precise prediction of the timing and indications for dialysis initiation in infants with severe CAKUT is required. Although progression to KFRT should be predicted as soon as possible, we selected Cr-day3-max, rather than Cr-day1-max or Cr-day-2-max, as a prognostic indicator for KFRT in the present study. This was because Cr-day3-max showed more significant differences between the two groups than Cr-day1-max and Cr-day2-max, even though all of the *P*-values were < 0.001. Furthermore, Cr-day1-max and Cr-day-2-max may have been more affected

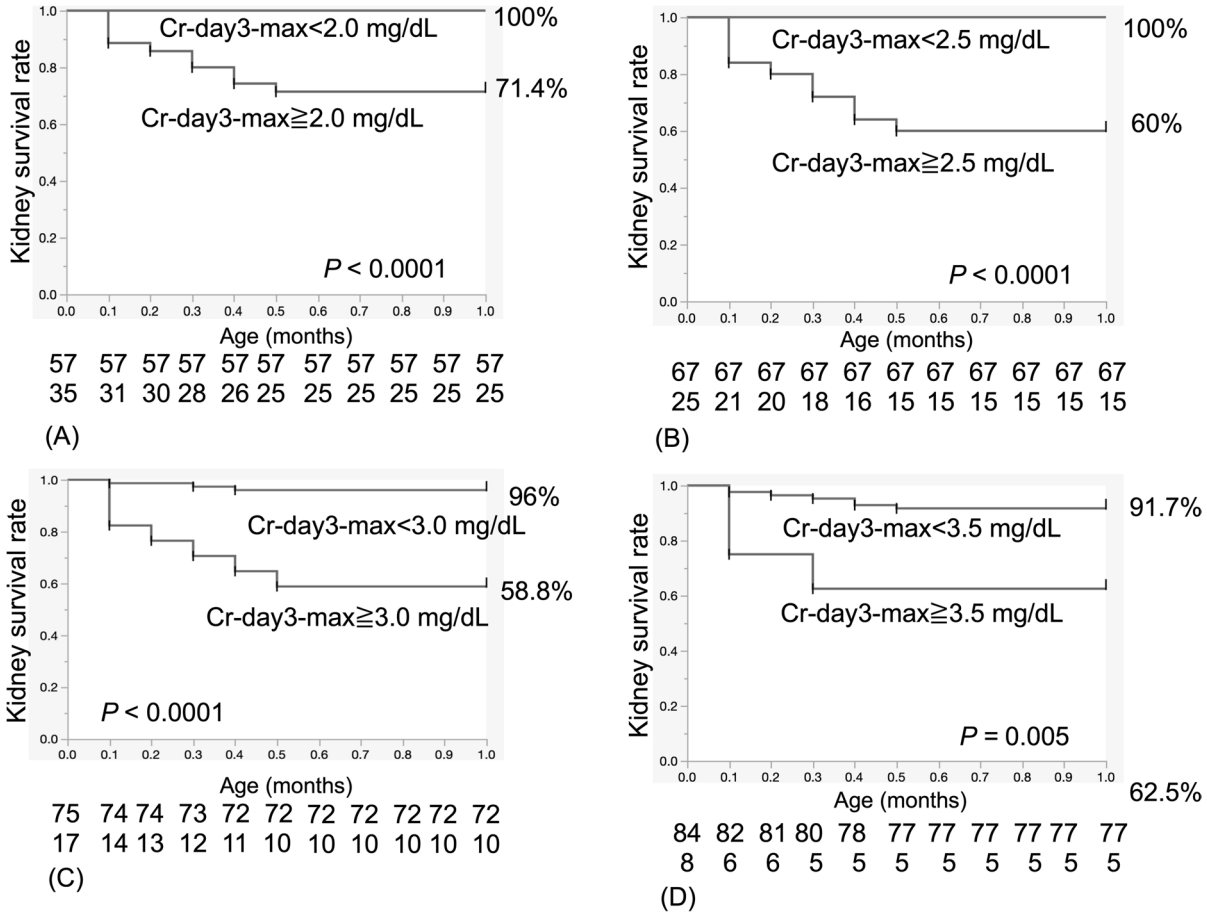

Fig. 3 Kaplan–Meier curves for time to progression to neonatal KFRT from birth according to (**A**) Cr-day2.0-max, (**B**) Cr-day2.5-max, (**C**) Cr-day3.0-max, (**D**) and Cr-day3.5-max. Cr-day3-max, maximum serum creatinine level during the first 3 days; KFRT, kidney failure with replacement therapy

by contamination with maternal SCr and less affected by an increase in SCr than Cr-day3-max. Although it is not a relatively large cohort study, Cox proportional hazard regression analysis accordingly identified a higher Cr-day3-max and oligohydramnios as factors significantly associated with infantile KFRT risk in the present study. The significance remained for all cutoff values of Cr-day3-max. Considering that a cutoff value associated with a kidney survival rate > 95% is useful, we determined that Cr-day3-max cutoff values of 2.5 mg/dL and 3.0 mg/dL were likely to be suitable for assessing the risks of infantile KFRT and neonatal KFRT, respectively. Katsoufis et al. reported that a neonatal cystatin C level ≥ 3.0 mg/dL and peak SCr (maximum increase in SCr after birth) ≥ 2.0 mg/dL predicted progression to KFRT up to an average age of 6.1 ± 2.8 years [7]. This was consistent with the current results in that kidney function during the neonatal period can predict future kidney outcomes. CAKUT is characterized by microscopic abnormalities, including decreased numbers of nephrons, and geographic disorganization of nephron elements. Therefore, neonatal SCr can estimate kidney reserves [17]. This might explain why a higher Cr-day3-max was associated with infantile kidney outcomes. The cutoff value for SCr in the present study was higher than that in the previous study, which may reflect differences in outcomes between KFRT at the last follow-up and infantile KFRT. Although cystatin C might be a predictive factor, unfortunately, it was not available because of a lack of data and different timings of measurements in our multicenter retrospective study.

The univariate analysis identified the ratios of bilateral kidney lesions, oligohydramnios, neonatal ventilator use, neonatal inotrope use, neonatal AKI, and neonatal infection as significantly higher in the infantile KFRT group. Hypoxia and ischemia with ventilator use and inotrope use would have had some influence on the progression to infantile KFRT. However, because these factors were significantly relevant confounding factors with oligohydramnios, we did not add neonatal ventilator use, neonatal inotrope use, and neonatal infection into the multivariate logistic analysis. Bilateral kidney lesions are a risk factor for kidney failure in patients

with CAKUT [18, 19]. In particular, the Potter sequence, which leads to fetal oligohydramnios and fatal respiratory distress related to pulmonary hypoplasia within an hour of birth, was the most critical CAKUT [20, 21]. We speculated that neonatal ventilator and inotrope use were associated with these fatal states because of their association with fetal oligohydramnios. Kidney outcomes were generally good if compensatory hypertrophy of the contralateral kidney was present [19], and no patients with unilateral kidney lesions progressed to KFRT in the present study. However, predicting compensatory hypertrophy in the neonatal period is not easy.

The present study had several limitations. First, SCr was not measured every day in some patients because of the retrospective study design. However, the timing of SCr measurements was determined by neonatology and pediatric nephrology experts, and SCr was measured in all patients other than one patient in the infantile KFRT group every day during the first 3 days. One patient in the infantile KFRT group had two measurements of SCr during the first 3 days. In the non-KF/older KFRT group, 3, 3, and 64 patients had one, two, or more than three measurements of SCr, respectively, during the first 3 days. Second, the diagnosis of AKI based on CAKUT during the neonatal period was very difficult and was based on an elevation of SCr unexplained by the natural history of progression to kidney failure on CAKUT with obvious triggers such as infection, dehydration, and nephrotoxic drugs by pediatric nephrologists. Moreover, the influence of AKI after the neonatal period was not fully considered in the present study. Third, the baseline SCr value differed between full-term and small preterm newborns. However, gestational age was not associated with a risk of infantile KFRT by multivariable Cox proportional hazard analyses. Fourth, although the criteria for the indication of dialysis induction were consistent at all facilities, the detailed judgement for starting dialysis differed between each pediatric nephrologist. However, we think that KFRT is the most important hard endpoint. Fifth, patients with a maximum SCr level of 1.0 mg/dL or lower during the first 3 days were excluded. However, we do not consider this a serious problem because none of the patients with SCr levels between 1.0 and 2.0 mg/dL progressed to infantile KFRT. Sixth, cystatin C data were not available for this multicenter retrospective study.

In conclusion, patients with CAKUT who had severe kidney dysfunction during the neonatal period had poor kidney outcomes. Additionally, kidney function during the neonatal period was associated with infantile KFRT. The prompt and precise prediction of kidney outcomes in infants with severe CAKUT can guide the need for dialysis and management to preserve and promote residual kidney function.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-022-05703-1.

Acknowledgements The authors would like to thank Dr. Naoya Morisada for conducting the genetic diagnosis; Drs. Hitoshi Yoda, Norio Mizukaki, and Mai Kubota for providing clinical data; and Dr. Shuichi Ito for their overall contributions to the study. The authors also thank the medical editors from the Division of Education for Clinical Research at the National Center for Child Health and Development for editing a draft of this manuscript. We also thank Susan Furness, PhD, and J. Ludovic Croxford, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Author contribution KN prepared the first draft of the manuscript, oversaw the data collection, and performed the data analysis as the primary investigator. RHar, MY, YO, KM, YG, TKi, DH, YH, NF, TU, TN, TI, and RHam performed the research, and edited and reviewed the manuscript. TKa designed the study, analyzed the data, and revised the manuscript for important intellectual content. KK conducted the statistical analysis. OU supervised and designed the study and critically revised the manuscript. KI designed the study, critically revised the manuscript for important intellectual content, and oversaw the work as the corresponding author. All authors contributed to the study conception and design and approved the final manuscript.

Funding This work was funded by childhood-onset, rare, and intractable kidney diseases in Japan, research on rare and intractable diseases, Health, Labour and Welfare Sciences Research Grants (20FC1028).

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval The study protocol was approved by the institutional ethics committee of the National Center for Child Health and Development (approval no. 2020–169). Study approval with agreement for data was shared among each institution's ethics committee.

Informed consent Informed consent for participating in this study was not required in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour, and Welfare. Consent for publication was waived in accordance with the guidelines.

Competing interests Kenji Ishikura has received research funding from the Asahi Kasei Pharma Corporation, Novartis International AG, Japan Blood Products Organization, Teijin Pharma Limited, JCR Pharmaceuticals Co., Ltd., Chugai Pharmaceutical Co., Ltd., Zenyaku Kogyo Co., Ltd., Otsuka Pharmaceutical Co. Ltd., Shionogi Co., Ltd., and The Morinaga Foundation for Health & Nutrition; and lecture fees from Asahi Kasei Pharma Corporation, Novartis International AG, Chugai Pharmaceutical Co., Ltd., Zenyaku Kogyo Co., Ltd., Otsuka Pharmaceutical Co. Ltd., Teijin Pharma Limited, Astellas Pharma Inc., Sanofi S.A., Pfizer Inc., AstraZeneca plc, and Miyarisan Pharmaceutical Co. Yusuke Okuda has received research funding from JSPS Kakenhi. Yuko Hamasaki has received lecture fees from Torii Pharmaceutical Co., Ltd and Pfizer Inc. Koichi Kamei has received research funding from the Terumo Foundation for Life Sciences and Arts, Public Foundation of Vaccination Research Center, and Taiju Life Social Welfare Foundation; donations from Chugai Pharmaceutical Co. Ltd., Astellas Pharma Inc., Ono Pharmaceutical Co., Teijin Pharma Ltd., Shionogi Co. Ltd., and Otsuka Pharmaceutical Co. Ltd.; and lecture fees from Tanabe Mitsubishi Pharma, Baxter Ltd., and Zenyaku Kogyo Co. Ltd. Other authors have no potential conflicts of interests to disclose.

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