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

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ABSTRACT

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

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

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

Chronic kidney disease (CKD) in children is a progressive and intractable disease [1]. In the CKD in Children study, children with a glomerular filtration rate (GFR) of <30 mL/min/1.73 m² showed significant growth failure and other clinically important disorders compared with children with a higher GFR (≥50 mL/min/1.73 m²), and experienced greater progressive changes in their GFR [2]. The mortality rate in children with end-stage kidney disease (ESKD) is also quite high, and was reported to be 98.8/1000 person-years among children who started dialysis between 1990 and 2010 in the USA [3].

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

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

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

MATERIALS AND METHODS

Study design and population

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

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

CKD stage was assessed as previously described [9, 18]. Stages 3, 4 and 5 CKD were defined as SCr levels more than twice, four times and eight times, respectively, the median normal levels in age- and sex-matched Japanese children. In our previous report [9], we validated these reference levels by applying the abbreviated Schwartz equation [19], with Stages 3, 4 and 5 CKD being classified as GFR 30–59, 15–29 and <15 mL/min/1.73 m², respectively (<1/2, <1/4 and <1/8 of normal GFR, respectively), defined according to established guidelines [20–22]. All of the participating institutions reported using enzyme immunoassays to measure SCr. Heavy proteinuria was defined as urine protein/creatinine ratio >2.0 g/g urine

Keywords: Asia, child, chronic kidney disease, end-stage kidney disease, prognosis
Table 1. Patient characteristics according to CKD stage

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>All patients</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>447</td>
<td>315</td>
<td>107</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.6 ± 4.5</td>
<td>8.6 ± 4.6</td>
<td>8.4 ± 4.2</td>
<td>9.9 ± 4.5</td>
<td>0.321</td>
</tr>
<tr>
<td>Sex, male/female (n)</td>
<td>272/175</td>
<td>192/123</td>
<td>67/40</td>
<td>13/12</td>
<td>0.618</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.6 ± 1.2</td>
<td>1.1 ± 0.4</td>
<td>2.2 ± 0.8</td>
<td>5.3 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>119.6 ± 27.8</td>
<td>120.5 ± 28.1</td>
<td>117.1 ± 26.9</td>
<td>118.1 ± 28.9</td>
<td>0.547</td>
</tr>
<tr>
<td>Height (SD)</td>
<td>–1.5 ± 1.8</td>
<td>–1.3 ± 1.5</td>
<td>–1.8 ± 2.1</td>
<td>–2.8 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>35.5 ± 18.7</td>
<td>28.3 ± 9.7</td>
<td>48.4 ± 18.1</td>
<td>74.9 ± 31.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cystatin-C (mg/L)</td>
<td>2.1 ± 0.8</td>
<td>1.9 ± 0.5</td>
<td>3.1 ± 1.0</td>
<td>4.1 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR abbreviated (mL/min/1.73 m²)</td>
<td>39.6 ± 15.9</td>
<td>47.3 ± 11.4</td>
<td>22.6 ± 5.3</td>
<td>10.4 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR complete (mL/min/1.73 m²)</td>
<td>39.9 ± 12.4</td>
<td>43.9 ± 10.0</td>
<td>24.7 ± 5.2</td>
<td>13.5 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± standard deviation. CKD, chronic kidney disease; SDS, standard deviation score; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

*Abbreviated Schwartz equation [19], eGFR = 41.3 [height (m)/Scr (mg/dL)].

†Complete Schwartz equation [19], eGFR = 39.1 [height (m)/cystatin C (mg/L)]0.516[1.8/cystatin C (mg/L)]0.294 × [30/BUN (mg/dL)]0.169 [1.099]male [(height (m)/1.4]0.188.

P-values were determined by analysis of variance for all variables except sex, which was analyzed by the χ² test.

creatinine. The patients were divided into three age groups for males (<2, ≥2 to <10.8 and ≥10.8 years) and females (<2, ≥2 to <10.0 and ≥10.0 years), where 10.8 and 10.0 years correspond to the mean age of Japanese males and females, respectively, at the start of puberty [23]. Hypertension was defined as systolic blood pressure >95th percentile [24]. The study was conducted in accordance with the principles of the Declaration of Helsinki and the ethical guidelines issued by the Ministry of Health, Labour and Welfare, Japan. The study was approved by a central ethics board at Tokyo Metropolitan Children’s Medical Center (approval number: 23–49). Because data were reported using patient medical records, informed consent was not obtained in accordance with the above guidelines.

Statistical analysis

The primary outcome was the progression of CKD to ESKD. The cumulative proportion of progression was estimated by the Kaplan–Meier method, where death was also considered as an event. The day on which SCR was measured was closest to 1 April 2010 was used as the starting point (i.e. T = 0 years). Cox’s proportional hazard regression model was used to identify possible predictors of CKD progression by calculating hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were carried out using SAS system version 9 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient characteristics

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

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

Progression to ESKD and renal replacement therapy

Table 2 shows the patient outcomes during this survey. Overall, 52 patients progressed to ESKD during the follow-up period (median follow-up period (interquartile range) 1.49 years (1.16–1.64 years); Stage 3, n = 9; Stage 4, n = 29; Stage 5, n = 14). Of these, 1/9 patients in Stage 3, 21/29 patients in Stage 4 and 8/14 in Stage 5 had CAKUT. Five deaths (sepsis in two; acute encephalitis, graft versus host disease and acute heart failure and pulmonary edema caused by advanced uremia in one each) occurred during the study period, of which four occurred before and one occurred after progression to ESKD. The detailed characteristics of patients with progression to ESKD or who died are presented in Table 3. The
Table 3. Characteristics of patients who progressed to ESKD or who died

<table>
<thead>
<tr>
<th>CKD stage in 2010(^a)</th>
<th>Age in 2010 (years)</th>
<th>Sex</th>
<th>Primary etiology</th>
<th>Method of detecting CKD</th>
<th>Recognizable syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.6</td>
<td>Male</td>
<td>Unknown</td>
<td>Urinary tract infection</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>4</td>
<td>3.4</td>
<td>Male</td>
<td>Cortical necrosis (perinatal period)</td>
<td>Blood analysis in the neonatal period, asphyxia, neonatal shock</td>
<td>—</td>
</tr>
<tr>
<td>4 Deaths</td>
<td>0.7</td>
<td>Male</td>
<td>CAKUT without obstructions</td>
<td>Fetal ultrasonography/ultrasonography in the neonatal period</td>
<td>—</td>
</tr>
<tr>
<td>after ESKD</td>
<td>8.3</td>
<td>Male</td>
<td>Drug induced</td>
<td>Detected during the management of other diseases(e.g. heart disease)</td>
<td>—</td>
</tr>
<tr>
<td>4 Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>13.5</td>
<td>Female</td>
<td>CAKUT without obstructions</td>
<td>Failure to thrive, weight loss and general fatigue</td>
<td>—</td>
</tr>
</tbody>
</table>

Progression to ESKD

<table>
<thead>
<tr>
<th>CKD stage in 2010(^a)</th>
<th>Age in 2010 (years)</th>
<th>Sex</th>
<th>Primary etiology</th>
<th>Method of detecting CKD</th>
<th>Recognizable syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (n = 9)</td>
<td>9.8 ± 4.9</td>
<td>6 males 3 females</td>
<td>CAKUT without obstructions (1); chronic glomerulonephritis (2); congenital nephrotic syndrome (1); focal segmental glomerulosclerosis (2); nephronophthisis (1); other inherited kidney damage (2)</td>
<td>Analysis by chance (4); annual urinalysis at school (3); blood analysis in the neonatal period, asphyxia, neonatal shock (1); fetal ultrasonography/ultrasonography in the neonatal period (1)</td>
<td>Bardet–Beadle syndrome (1); Lowe syndrome (1)</td>
</tr>
<tr>
<td>4 (n = 28)</td>
<td>9.5 ± 4.7</td>
<td>15 males 13 females</td>
<td>CAKUT with obstructions (4); CAKUT without obstructions (17); congenital nephrotic syndrome (1); hemolytic uremic syndrome (1); nephronophthisis (3); neurogenic bladder (1); other inherited kidney damage (1)</td>
<td>Analysis by chance (6); annual urinalysis at school (2); blood analysis in the neonatal period, asphyxia, neonatal shock (4); dysuria, including neurogenic bladder and nocturia (1); failure to thrive, weight loss and general fatigue (3); fetal ultrasonography/ultrasonography in the neonatal period (6); symptoms of glomerulonephritis (edema, oliguria or gross hematuria (1); unknown (1); urinalysis at 3 years (2); urinary tract infection (2)</td>
<td>15q syndrome (1); chromosomal anomalies (1); Ellis–van Creveld syndrome (1); Prune belly syndrome (1); renal coloboma syndrome (1)</td>
</tr>
<tr>
<td>5 (n = 14)</td>
<td>9.9 ± 1.2</td>
<td>9 males 5 females</td>
<td>CAKUT with obstructions (1); CAKUT without obstructions (7); cortical necrosis (perinatal period) (3); nephronophthisis (1); polycystic kidney disease (2)</td>
<td>Analysis by chance (2); annual urinalysis at school (2); blood analysis in the neonatal period, asphyxia, neonatal shock (1); failure to thrive, weight loss and general fatigue (2); fetal ultrasonography/ultrasonography in the neonatal period (5); unknown (1); urinary tract infection (1)</td>
<td>—</td>
</tr>
</tbody>
</table>

CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; ESKD, end-stage kidney disease. Values in parentheses indicate the number of patients. Age is shown as the mean ± SD.

\(^a\)Data are presented for individual patients (deaths) or groups by CKD stage (alive).
The most common chronic renal replacement therapy in children with ESKD was peritoneal dialysis, which was used in 27 children, followed by preemptive kidney transplantation in 16 patients (Table 2).

Factors associated with CKD progression

CKD progression was defined as ESKD or death occurring during follow-up. Table 4 shows the factors that were independently associated with CKD progression, as determined using Cox’s proportional hazards model. As shown in this table, CKD stage and heavy proteinuria were significantly associated with disease progression. Age of <2 years and age at or above the start of puberty were significantly associated with increased risk of disease progression. In contrast, sex, the presence of a recognizable syndrome, disease (CAKUT or other disease), preterm delivery (<37 weeks), hypertension (systolic blood pressure >95th percentile) [24] and the use of antihypertensive drugs were not associated with disease progression. The results did not change when we included the duration of disease instead of age or eGFR calculated using the abbreviated Schwartz equation instead of CKD stage, or if deaths were censored instead of being included as an event (data not shown).

Kaplan–Meier analysis for the time to ESKD or death (included as an event) is presented in Figure 1. Among 429/447 children with available data, the survival rates at 1 year were 98.3, 80.0 and 40.9% in children with Stage 3, 4 and 5 CKD, respectively. The Kaplan–Meier plot and survival rates were almost identical when deaths were censored instead of being included as an event; the survival rates at 1 year were 98.3, 80.9 and 43.1% in children with Stage 3, 4 and 5 CKD, respectively.
a sizeable proportion (12.5%) of children progressed from Stage 3 to 5 CKD to ESKD during the follow-up period (median 1.49 years). In addition, children with advanced stage CKD (4/5) are at particularly high risk of progressing to ESKD, irrespective of the primary etiologies of CKD. Furthermore, as in the study by Sanna-Cherchi et al [26], we found that proteinuria was a risk factor for progression to ESKD. We also found that age <2 years and age at or above the start of puberty were significantly associated with increased risk of progressing to ESKD relative to the risk in patients aged 2 to the start of puberty (10.8 years in males and 10.0 years in females). These results may reflect the risk of disease progression in very young patients with severe congenital complications and that disease progression may be more pronounced in puberty.

The CKD in Children cohort study in the USA [5, 6], as well as studies performed in France [15], Sweden [14], Italy [11] and Australia/New Zealand [25], consistently reported that many children with CKD ultimately require renal replacement therapies. However, renal transplantation was reported to achieve better long-term outcomes and reduce the mortality rate compared with dialysis in children with ESKD [25]. Although the most common modality (51.9%) of renal replacement therapies was peritoneal dialysis in our cohort, ∼30% of children with ESKD received preemptive kidney transplantation, reflecting the current trends in Japan. The superiority and clinical benefits of preemptive kidney transplantation relative to dialysis should be confirmed in future studies.

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

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

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

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

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

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