ORIGINAL ARTICLE

Validation of the estimated glomerular filtration rate equation for Japanese children younger than 2 years

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Abstract

Background We have developed a simple and easy method of estimating the glomerular filtration rate (eGFR) of serum creatinine in Japanese children (eGFR$_{Uemura}$). The eGFR equation is for children aged 2–18 years. Therefore Uemura et al. developed an equation for children younger than 2 years (eGFR$_{under\ 2}$). The aim of the present study was to validate this new equation.

Methods We collected the data of 13 patients from previous studies and compared the results of eGFR$_{under\ 2}$, eGFR$_{Uemura}$, and updated eGFR developed by Schwartz (eGFR$_{Schwartz}$) with measured GFR using mean error (ME), root mean square error (RMSE), P_{30} and Bland–Altman analysis.

Results The ME of eGFR$_{under\ 2}$, eGFR$_{Uemura}$ and eGFR$_{Schwartz}$ were 2.3 ± 15.9, 7.7 ± 14.5, and 16.0 ± 18.2 ml/min/1.73m^2, respectively. The RMSEs were 15.5, 15.9, and 49.6, respectively. The P_{30} values were 76.9%, 76.9%, and 53.8%, respectively. The graph of Bland–Altman bias analysis showed fan-shape. The eGFR$_{under\ 2}$ equation was the most accurate in the three equations.

Conclusion The eGFR$_{under\ 2}$ equation was useful for Japanese children younger than 2 years.

Keywords Validation · Estimated glomerular filtration rate · Children under 2 years of age · Japanese

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Introduction

The gold standard for evaluation of renal function is inulin clearance (Cin). However, the procedure of Cin is complicated and difficult, especially in younger children and/or patients with bladder dysfunction. Therefore, various simple and easy methods to determine the estimated GFR (eGFR) have been developed. Recently, the most known equation for eGFR used in children is the updated Schwartz (eGFR$_{Schwartz}$) equation [1]. However, Uemura et al. reported that the eGFR$_{Schwartz}$ equation is not applicable for Japanese children [2]. Therefore, an original equation for eGFR (eGFR$_{Uemura}$) was developed using serum creatinine (Cr) in Japanese children [3], and its accuracy was validated [4]. However, the equation was for children aged 2–18 years. Therefore, an equation for children younger than 2 years was then developed by multiplying eGFR$_{Uemura}$ by a coefficient $(0.107 \times \ln(\text{age[month]}) + 0.656)$ [5]. In this study, we aimed to validate eGFR$_{under\ 2}$ equation.

Material and methods

Study population

We extracted the data of patients under 2 years of age from three studies. The first was 7 of 174 patients' data when the eGFR$_{Uemura}$ equation was created [3]. The second was 8 of 140 patients' data when the accuracy of the eGFR$_{Uemura}$ equation was validated [4]. The third was 1 of 59 patients' data validated the safety of Inulide® for Japanese children (in press) (Table 1). All data were collected from pediatric patients with chronic kidney disease (CKD) in clinical need of Cin. Finally, we used data from 13 patients after excluding patients (Table1).

The measured GFR (mGFR) for each patient was obtained using Cin. The procedure is described in a previous report [6]. Cin values were measured in the same way in three studies.

The calculate method of eGFR$_{under 2}$ is as follows:

1. The reference serum Cr level (ref Cr) is shown by the following two equations of body length (x):
   males: ref Cr $= -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$
   females: ref Cr $= -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$
2. Provisional GFR $= 110.2 \times$ (ref Cr/ patient's serum Cr) $+ 2.93$
3. $R = 0.107 \times \ln$ [age (months)] $+ 0.656$

4. eGFR under 2 years of age (eGFR$_{under 2}$) $= R \times$ provisional GFR

Exclusion criteria and cases excluded

The exclusion criteria were as follows:

1. Primary diseases including severe obstructive uropathy, infection during treatment, inflammatory disease, dehydration, neuromuscular disease, severe cardiac, hepatic, or pancreatic disease, and/or endocrine disease, including thyroid impairment.
2. Cases in which the ratios of inulin excretion and intravenous inulin administration were < 0.5, or > 1.5, during the measurement of Cin. We determined the dose of intravenous inulin by assuming that the blood concentration was constant during testing. Ratios of inulin excretion and intravenous inulin that were not within 0.5 and 1.5 may have been due to failure to collect all urine.
3. Cases in which the measured GFR (mGFR) was > 150 ml/min/1.73m^2; pediatric patients with CKD due to a hyperfiltration disease such as diabetic nephropathy are rare. We were only interested in cases in which GFR was < 120 ml/min/1.73m^2. Therefore, we excluded cases in which mGFR was > 150 ml/min/1.73m^2.

Statistical analysis

To validate eGFR$_{under 2}$ equation, we used four methods as follows:

1. Mean error (ME): to evaluate the mean difference between each value for eGFR and mGFR values
2. Root mean square error (RMSE): to evaluate the precision of eGFR and mGFR values.
3. P_{30} (the percentage of eGFR value within 30% of mGFR): to evaluate the accuracy of eGFR and mGFR values.
4. Bland–Altman analysis (difference versus average): to determine agreement with the estimation.

We also compared these statistical results of eGFR$_{under 2}$ equations, with the results of eGFR$_{Uemura}$, and eGFR$_{Schwartz}$.

The formula for eGFR$_{Uemura}$ equation is mentioned above in the calculation method of eGFR$_{under 2}$ from (1) to (2). First, calculate the reference Cr level as described (1), and then the eGFR$_{Uemura}$ from reference Cr and patient's serum Cr using the method described in (2).

The updated Schwartz equation is 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 aged 1–16 years [1]. Therefore, in the second analysis, the data of three patients under 1 year of age were excluded. Finally,

Table 1 Characteristics of the 13 patients included in this study

Characteristics	Median (IQR)	n
Age (months)	17.0 (10.0–20.5)	
Gender		
Male		11
Female		2
CKD stage		
Stage 1		2
Stage 2		4
Stage 3		6
Stage 4		1
Renal abnormality		
Congenital anomalies of the kidney and urinary tract		6
Solitary kidney		3
Reflux nephropathy		2
Hydronephrosis		1
Small kidney		1

CKD chronic kidney disease, *IQR* interquartile range

data from 10 patients were used for comparison between eGFR$_{under 2}$ and eGFR$_{Schwartz}$.

All analyses were performed using GraphPad Prism for Mac OS X (version 7.0).

Results

Characteristics of the study population (Table 1)

Data of 6 patients were extracted from the three studies. Data of three patients were excluded because the ratios of urinary inulin excretion to intravenous inulin administration
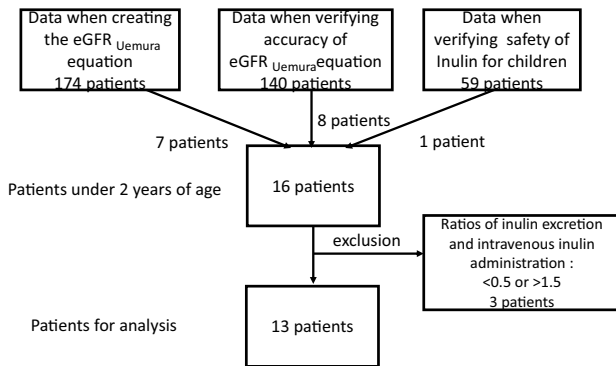

Fig. 1 Flow chart of included data

were < 0.5 or > 1.5. None of the patients were included in the 1 or 3 exclusion criteria. Finally, 13 patients' data (2 female, median 17.0 months of age [interquartile range (IQR) 10.0–20.5 months, range 1–23 months]) were used for analysis (Fig. 1). The number of chronic kidney disease (CKD) stages 1, 2, 3, 4, and 5 were 2, 4, 6, 1, and 0, respectively. The number of renal abnormalities, congenital anomalies of the kidney and urinary tract (CAKUT), solitary kidney, reflux nephropathy, hydronephrosis, and small kidney were 6, 3, 2, 1, and 1, respectively.

Result of statistical analysis

Figure 2 shows a scatter plot of mGFR versus each of the three eGFR equations. The straight line shows the equivalent values of mGFR and eGFR. The open circles represent the patient data under 1 year of age. The scatter plots of eGFR$_{under 2}$ and eGFR$_{Uemura}$ seem to be similar. Figure 3 shows the Bland–Altman plot of the difference versus the average for both mGFR and each 3 eGFR equations.

Table 2a shows the numerical values for each examination in all 13 patients. The ME values for eGFR$_{under 2}$, eGFR$_{Uemura}$, and eGFR$_{Schwartz}$ were 2.3 ± 15.9, 7.7 ± 14.5, and 16.0 ± 18.2 ml/min/1.73m^2, respectively. The RMSE values were 15.5, 15.9, and 49.6 ml/min/1.73m^2, respectively. The P_{30} values were 76.9%, 76.9%, and 53.8%, respectively. Table 2b shows the numerical values for the results of eGFR$_{under 2}$ and eGFR$_{Schwartz}$ in 10 patients aged

Fig. 2 Scatter plot of mGFR versus each 3 eGFR equations. **a** eGFR$_{under 2}$, **b** eGFR$_{Uemura}$, **c** eGFR$_{Schwartz}$. Straight line: $Y=X$, Open circle: data of children under 1-year-old
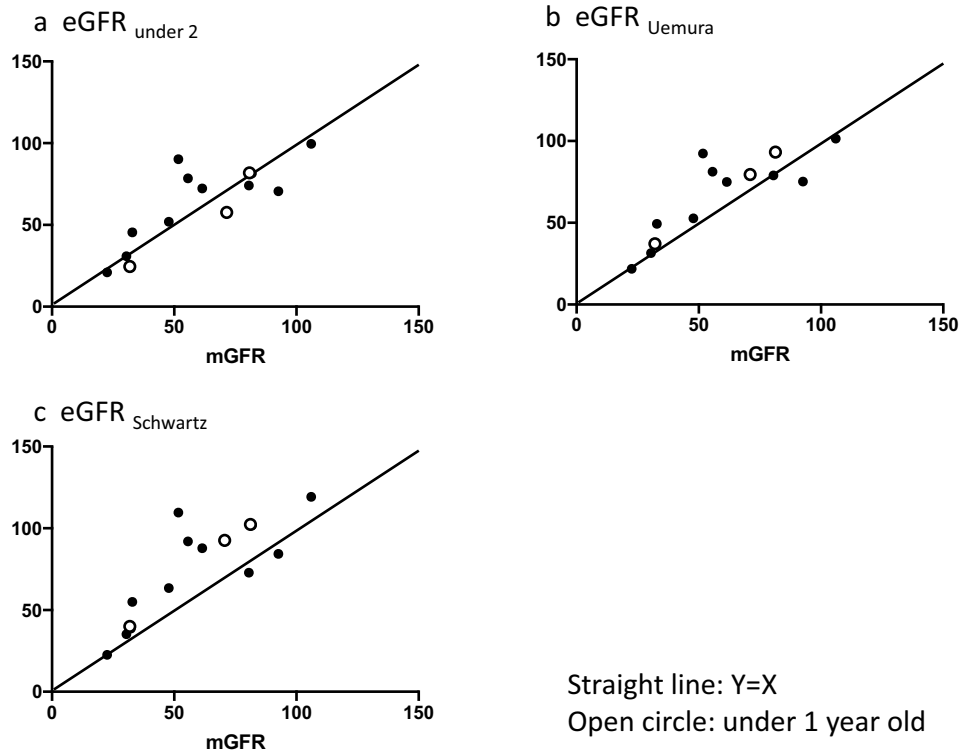
Straight line: Y=X
Open circle: under 1 year old

Fig. 3 Bland–Altman plot. Difference versus average mGFR and each 3 eGFR equations. **a** eGFR$_{under\ 2}$, **b** eGFR$_{Uemura}$, **c** eGFR$_{Schwartz}$. Open circle: data of children under 1 year old
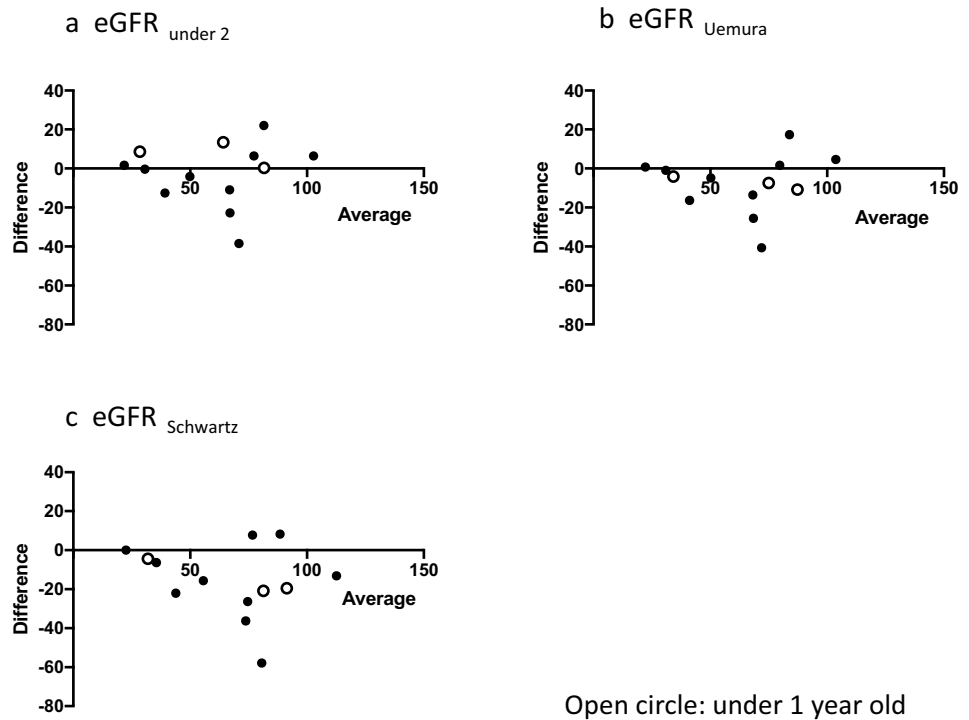
a eGFR$_{under\ 2}$

b eGFR$_{Uemura}$

c eGFR$_{Schwartz}$

Open circle: under 1 year old

Table 2 Comparison of performance using three eGFR equations, eGFR$_{under\ 2}$ equation, eGFR$_{Uemura}$ equation and eGFR$_{Schwartz}$

(a) Comparison of results with data from 13 patients

	ME (bias) (ml/min/1.73m^2) (95% CI)	RMSE (ml/min/1.73m^2)	P_{30} (%)
eGFR$_{under2}$	2.3 ± 15.9 (-7.3 to 12.0)	15.5	76.9
eGFR$_{Uemura}$	7.7 ± 14.5 (-1.0 to 16.5)	15.9	76.9
eGFR$_{Schwartz}$	16.0 ± 18.2 (5.0 to 27.0)	49.6	53.8

(b) Comparison of results of eGFR$_{under2}$ and eGFR$_{Schwartz}$ equation from 10 patients' data between the ages of 1 and 2 years

	ME (bias) (ml/min/1.73m^2) (95% CI)	RMSE (ml/min/1.73m^2)	P_{30} (%)
eGFR$_{under2}$	5.3 ± 17.0 (-6.9 to 17.4)	16.9	70.0
eGFR$_{Schwartz}$	16.0 ± 20.7 (1.2 to 30.8)	50.0	50.0

eGFR estimated glomerular filtration rate, *ME* mean error, P_{30} the percentage of eGFR value within 30% of measured GFR, *RMSE* root mean square error

between 1 and 2 years. The ME values for eGFR$_{under\ 2}$, and eGFR$_{Schwartz}$ were 5.3 ± 17.0 and 16.0 ± 20.7 ml/min/1.73m^2, respectively. The RMSE values were 16.9 and 50.0 ml/min/1.73 m^2, respectively. The P_{30} values were 70.0%, and 50.0%, respectively.

Figure 3 shows a scatter plot of the Bland–Altman analysis. In all three equations, the spread of the graph of the Bland–Altman analysis was fan-like shaped, with systematic error.

In the three equations, the values using eGFR$_{under\ 2}$ equation showed the lowest value for ME and Bland–Altman analysis, and showed the larger values for P$_{30}$ than that for eGFR$_{Schwartz}$.

Discussion

We evaluated a new eGFR equation for children under 2 years of age. Using several statistical techniques, we confirmed that the eGFR$_{under\ 2}$ equation could be useful.

For Japanese children, there are several eGFR equations with surrogate markers, serum Cr [3], cystatin C [7], and β2 microglobulin [8]. The Cr-based eGFR$_{Uemura}$ equation is the most commonly used method for children aged 2–18 years. Cystatin C and β2 microgrobulin based eGFR are not always available for retrospective epidemiologic studies or common clinical practice. Therefore, we developed

Cr-based eGFR for children younger than 2 years using eGFR$_{Uemura}$ using a coefficient. The method reported in a previous article [5] is based on the following idea. Physiologically, kidney function gradually increases from birth and reaches adult stage at the age of 2 years. Using the median normal reference values of GFR for each age (months) up to 2 years examined previously, we estimated the percentage of the normal adult GFR that corresponds to and calculated a regression curve using a logarithmic function. As a result, the coefficient was calculated as $0.107 \times \ln [age (months)] + 0.656$. The aim of this study was to evaluate the eGFR$_{under\ 2}$ equations. We compared the values of eGFR$_{under\ 2}$, eGFR$_{Uemura}$, and eGFR$_{Schwartz}$ equation using ME, RMSE, P_{30}, and Bland–Altman analysis. We divided the patients according to age: 13 patients under 2 years of age and 10 patients aged between 1 and 2 years; patient data underwent two analyses. Because eGFR$_{under\ 2}$ equation is for children under 2 years old, the eGFR$_{Uemura}$ equation is for children aged 2–18 years and eGFR$_{Schwartz}$ is for children aged 1–16 years. Therefore, in the comparison of 10 patients at the age of 1 to 2 years, we only compared eGFR$_{under\ 2}$ equation and eGFR$_{Schwartz}$. In the analysis of 13 patients, the ME value of eGFR$_{under\ 2}$ was the smallest among the three equations. The RMSE value and percent of P_{30} of eGFR$_{under\ 2}$ and eGFR$_{Uemura}$ were similar. On the other hand, the ME and RMSE values of eGFR$_{Schwartz}$ were the highest, and the percentage of P_{30} was the lowest among the three eGFR equations. In the analysis of 10 patients, the ME and RMSE values of eGFR$_{under\ 2}$ were lower than that of eGFR$_{Schwartz}$. The percentage of P_{30} of eGFR$_{under\ 2}$ was higher than that of eGFR$_{Schwartz}$.

This study has several limitations. First, the sampling data was small particular under 1 year of age. Although we collected patients' data from our three previous studies, there were only 13 among 373 patients (3.5%) under 2 years of age. Further, it is very rare to perform inulin clearance in patients under 2 years of age, thus limiting data collection. In addition to that, there were only two patients of a female under the age of two. However, since there was no gender difference in normal Cr values at younger ages [9], we believed that this result was not affected. Second, to add to the data as much as possible, we also used the patient data when creating the equation of eGFR$_{Uemura}$. Third, we did not exclude preterm infants and low birth weight infant because we had no information for them. We don't know whether the eGFR$_{under\ 2}$ equation can be applied to such cases or not.

Conclusion

We evaluated the eGFR$_{under\ 2}$ equation for Japanese children aged 2 years or less. The results suggest that eGFR$_{under\ 2}$ equation could be a useful parameter.

Declarations

References

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