의학석사 학위논문

# 소아에서 $^{51}$Cr-EDTA 사구체 여과율 측정에 사용되는 1회 채혈 방법들의 정확도 비교 평가

# A comparison of the accuracy of different single plasma sample methods for measuring glomerular filtration rate using $^{51}$Cr-EDTA in children

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이 논문을 의학석사 학위 논문으로 제출함

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## Abstract

### Purpose

Among the different methods of measuring glomerular filtration rate (GFR) using $^{51}$Cr-ethylenediaminetetraacetic acid clearance, the two-plasma-sample method (TPSM) is widely used, and highly accurate. The single-plasma-sample method (SPSM) is occasionally used for simplicity, at the expense of accuracy. This study was performed to investigate the correlation and to compare the accuracy, of six known SPSMs in pediatric patients in reference to TPSM.

### Methods

We retrospectively reviewed 122 pediatric cases (65 boys, age 7.3 ± 4.6 years) and analyzed 307 GFR measurements. SPSMs included Groth & Aasted at 120 min, Ham at 120 min, Christensen & Groth at 120 and 240 min, Jacobsson at 120 and 240 min. Reference GFR ($GFR_{ref}$) was defined using TPSM GFR corrected by the Jodal and Brochner-Mortensen equation. $GFR_{ref}$ < 30 mL/min/1.73 m$^2$ were excluded. The standard error of the estimate (SEE) and the number of cases with differences > 10% ($N_{10\%}$) were used to evaluate accuracy.

### Results

SPSMs generally correlated well with $GFR_{ref}$ (r=0.92 ~ 0.99) and were relatively accurate (SEE=9.26 ~15.60). Groth & Aasted showed the smallest SEE, while Jacobsson at 240 min showed the smallest $N_{10\%}$ for all $GFR_{ref}$ ranges. As for decreased $GFR_{ref}$, Ham was most accurate followed by Jacobsson at 240 min.

### Conclusions

Jacobsson at 240 min provided good accuracy in all $GFR_{ref}$ ranges and was well correlated with TPSM. Jacobsson at 240 min might be the most appropriate method to substitute for TPSM in pediatric patients. Ham could be an alternative in patients with impaired renal function.

**Key Words:** Glomerular filtration rate; children; single plasma sample method; $^{51}$Cr-EDTA;

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## Introduction

The glomerular filtration rate (GFR) is widely used to evaluate renal diseases [1, 2] and to monitor kidney function when using nephrotoxic drugs, such as chemotherapeutic or immunosuppressive drugs [3]. GFR measurement methods based on serum creatinine or cystatin C are simple but their accuracy is not always reliable [4]. The GFR measurement method based on renal clearance during a continuous infusion of inulin is known to be the most accurate method but it is too complex to be performed in clinical practice. Thus, more simplified GFR measurement methods using multiple-plasma-samples after a single intravenous injection of radionuclides, such as $^{51}$Cr ethylenediaminetetraacetic acid ($^{51}$Cr-EDTA) or $^{99m}$Tc diethylenetriaminepentaacetic acid ($^{99m}$Tc-DTPA) have replaced the inulin infusion method [5-7]. However, multiple-plasma-sample methods (MPSM) are still too complicated to be routinely used in clinical practice.

With regards to simplicity, the two-plasma-sample method (TPSM) literally requires only two plasma samplings and it is widely used in practice. However, in some cases, such as pediatric patients, patients in extremely poor medical condition, or minimally cooperative patients, it is not always easy to obtain two plasma samples. A more simplified method is the single-plasma-sample method (SPSM). SPSMs use empirical equations involving volumes of distribution and plasma clearances [8]. While SPSM is simple and convenient [6, 9-11], its accuracy raises concerns [5, 6, 12]. There are not many studies on the accuracy of SPSM compared to TPSM. The aims of this study were 1) to investigate the correlation and 2) to compare the accuracy, of six known SPSMs in children, using the TPSM as a reference.

## Materials and methods

### Subjects

We retrospectively reviewed the medical records of 122 consecutive children who were referred for measurements of GFR between July 2015 (when we started to create the GFR database) and August 2017. The inclusion criteria were as follows: (1) patients aged 6 months to 15 years, (2) patients whose 1st blood samples were obtained between 110 and 130 min after a radiotracer injection [10], and (3) patients whose 2nd blood samples were obtained more than 180 min after a radiotracer injection [5, 13]. The exclusion criteria were as follows: (1) patients who had a history of an administration of radioactive material within one week of the GFR measurement [8], and (2) patients whose reference GFR was below 30 mL/min/1.73 $m^2$ because SPSMs are known to be inaccurate with GFR less than 30 mL/min/1.73 $m^2$ [11, 14-17]. Serum creatinine levels and estimated GFRs using cystatin C were recorded. This study was approved by our Institutional Review Board (IRB no. 2017-1843) and informed consents were waived.

### Procedure

Prior to the injection of $^{51}$Cr-EDTA (GE healthcare Ltd., Amersham, Buchinghamshire, UK) in each patient, we made a standard by taking a 1 mL of aliquot of the $^{51}$Cr-EDTA solution from the syringe, transferring it to a volumetric flask, and diluting it to a total volume of 200 mL. Fifty to eighty μCi (1.85-2.96 MBq) of $^{51}$Cr-EDTA were injected through an indwelling butterfly needle, which was immediately flushed with 4 mL of normal saline. Next, patency of the vein was assured by injection of 5 mL of normal saline before the $^{51}$Cr-EDTA injection. Each patient was instructed to be sufficiently hydrated prior to the study, and patient movements were not restricted [18, 19]. The syringe was weighed before and after drawing the standard dose in order to calculate the standard mass. The syringe was weighed again after injecting the $^{51}$Cr-EDTA into the patient to calculate injection mass.

Two blood samples of at least 5 mL each were taken from the contralateral arm, and ejected into EDTA anticoagulant tubes at 120 and 240 min after the radiotracer injection [8]. Sampling times were

recorded.

Each blood sample was centrifuged for 4 min at 1753 g, and then 1 mL of the plasma sample was taken from each centrifuged tube. The activity of the standard, and the 120 and 240 min plasma samples (1 mL each) were counted to an average of 10,000 counts [8] in a well-type scintillation counter (Packard Cobra II E5003, GMI, Ramsey, MN).

## Calculation of GFR

*Reference two plasma sample method*

The reference GFR ($GFR_{ref}$) was determined by a slope-intercept GFR model, corrected by Jodal and Brochner-Mortensen (JBM) equation (Appendix 1), using two plasma samples collected at 120 min and 240 min after the injection of $^{51}$Cr-EDTA.

*Single plasma sample methods*

The estimated GFR ($GFR_{est}$) was calculated using six methods; 1) Groth & Aasted's method at 120 min (G&A) [20], 2) Ham's method at 120 min (Ham) [10], 3) Christensen & Groth's method at 120 min (C&G120) [21], 4) Christensen & Groth's method at 240 min (C&G240), 5) Jacobsson's method at 120 min (Jacobsson120) [22] and 6) Jacobsson's method at 240 min (Jacobsson240) (Appendix 2-5).

*Normalization of GFR*

Body surface area (BSA) was calculated by Haycock's equation [23]:

$$BSA\ (m^2) = 0.024265 \times Height^{0.3964}\ (cm) \times Weight^{0.5378}\ (kg)$$

All of the GFR values were normalized for a standard body surface area of 1.73 $m^2$.

## Statistical analysis

Commercially available software, SPSS for Windows (version 21.0; IBM, Chicago, IL, USA), was used for the statistical analyses. A linear regression analysis between $GFR_{ref}$ and $GFR_{est}$ calculated

from SPSMs was performed. The correlation between $GFR_{ref}$ and $GFR_{est}$ was evaluated using the Pearson correlation (r). A Bland-Altman analysis plotting the percentage difference between $GFR_{ref}$ and $GFR_{est}$ against $GFR_{ref}$ was drawn [24, 25].

Standard error of the estimates (SEE) between $GFR_{ref}$ and $GFR_{est}$ [10, 11, 26-28] was calculated as shown:

$$SEE=\sqrt{\frac{\sum_1^n(GFR_{ref}-GFR_{est})^2}{n}}$$

The cases where the difference between $GFR_{est}$ and $GFR_{ref}$ was > 10% when referring to $GFR_{ref}$ ($N_{10\%}$) were used to evaluate the accuracy of $GFR_{est}$ [29].

## Results

### Patient characteristics

A total of 122 children (65 boys and 57 girls, mean age 7.3 ± 4.6 years) were included and 307 GFR measurements were analyzed in this study. The number of patients who underwent GFR measurement once, twice, three times, four times, five times, six times, seven times, eight times and nine times was 45, 32, 15, 13, 8, 5, 2, 1 and 1, respectively. The baseline characteristics of the patients according to $GFR_{ref}$ are summarized in Table 1. The reasons for the GFR measurements were: to monitor kidney function during chemotherapy (n=220), to evaluate kidney function before the use nephrotoxic drugs (n=72), before nephrectomy (n=1) and a suspicion of renal disease (n=6).

### Correlation and accuracy of estimated GFR

$GFR_{est}$ calculated from the different SPSMs generally correlated well with $GFR_{ref}$ (r=0.92 ~ 0.99) while all SPSMs overestimated GFR. SPSMs were relatively accurate (SEE=9.26 ~ 15.60) (Table 2, Fig.2), however, the accuracy of each SPSM was different according to the range of $GFR_{ref}$ (Table 2 and 3). For whole ranges of $GFR_{ref}$, G&A showed the smallest SEE (SEE=9.26 mL/min/1.73 $m^2$, $N_{10\%}$=119 (39%)) while Jacobsson240 showed the smallest $N_{10\%}$ (SEE=10.54 mL/min/1.73 $m^2$, $N_{10\%}$=80 (26%)). Jacobsson240 provided good accuracy in all $GFR_{ref}$ ranges, whereas G&A was less accurate in cases of decreased $GFR_{ref}$ ($30 \leq GFR_{ref} < 90$ mL/min/1.73 $m^2$). For $30 \leq GFR_{ref} < 90$ mL/min/1.73 $m^2$ (decreased renal function [30]), Ham was the most accurate method (SEE=4.46 mL/min/1.73 $m^2$, $N_{10\%}$=10 (10%)) followed by Jacobsson240 (SEE=6.24 mL/min/1.73 $m^2$, $N_{10\%}$=19 (18%)).

For $60 \leq GFR_{ref} < 90$ mL/min/1.73 $m^2$ (mildly decreased renal function [30]), Ham was the most accurate (SEE=3.46 mL/min/1.73 $m^2$, $N_{10\%}$=3 (4%)). For $30 \leq GFR_{ref} < 60$ mL/min/1.73 $m^2$ (moderately decreased renal function [30]), Jacobsson240 was the most accurate (SEE=3.55 mL/min/1.73 $m^2$, $N_{10\%}$=3 (14%)).

In the Bland-Altman analysis, $GFR_{est}$ calculated from SPSMs tended to be overestimated when compared with $GFR_{ref}$ (Fig. 3). For whole ranges of $GFR_{ref}$, Jacobsson240 showed the smallest mean difference (2.28%) and G&A showed the smallest standard deviation (SD) (9.17%). For $30 \leq GFR_{ref} <$ 90 mL/min/1.73 $m^2$, Jacobsson240 showed the smallest mean difference (0.71%) while C&G120

showed the smallest SD (3.88%). For $30 \leq GFR_{ref} < 90$ mL/min/1.73 $m^2$, Ham showed the smallest mean difference (4.35%) while Jacobsson240 showed the smallest SD (6.35%). For $60 \leq GFR_{ref} < 90$ mL/min/1.73 $m^2$ (mildly decreased renal function), C&G240 showed the smallest mean difference (3.73%) while Jacobsson240 showed the smallest SD (5.86%). For $60 \leq GFR_{ref} < 90$ mL/min/1.73 $m^2$, Ham showed second smallest mean difference (2.92%) and the smallest SD (3.42%).

Among SPSMs at 120 min, G&A showed smallest SEE (SEE=9.26 mL/min/1.73 $m^2$, $N_{10\%}$=119 (39%)) while Ham had smallest $N_{10\%}$ (SEE=15.6 mL/min/1.73 $m^2$, $N_{10\%}$=104 (34%)) for whole range of $GFR_{ref}$. Ham was most accurate (SEE=4.46 mL/min/1.73 $m^2$, $N_{10\%}$=10 (10%)) for $30 \leq GFR_{ref} < 90$ mL/min/1.73 $m^2$, while the accuracy decreased for $GFR_{ref} > 90$ mL/min/1.73 $m^2$. In contrast, G&A was most accurate (SEE=9.33 mL/min/1.73 $m^2$, $N_{10\%}$=58 (29%)) for $GFR_{ref} > 90$ mL/min/1.73 $m^2$, while it was less accurate for $30 \leq GFR_{ref} < 90$ mL/min/1.73 $m^2$.

## Discussion

In this study, we evaluated the accuracy of SPSMs and its correlation with reference to TPSM in pediatric patients with a broad range of renal functions. All SPSMs were well correlated with TPSM, although all SPSMs tended to overestimate the GFR. In patients with unknown renal function, the Jacobsson240 would be the best method to replace TPSM because it was accurate across a wide range of $GFR_{ref.}$ Of note, Ham was the most accurate SPSM for patients with decreased renal function, although Ham overestimated GFR when $GFR_{ref} > 90$ mL/min/1.73 $m^2$. This suggests that Ham would be a good alternative for TPSM in patients with a suspected decrease in renal function.

There have been some studies that directly compared the different SPSMs in children [12, 31, 32]. Henriksen *et al.* [12] assessed GFRs in 75 children (age 1/2-13 years), comparing the G&A's method at 60, 90 and 120 min and the Ham's method at 120 min with using a 2-exponential curve fitting of 10, 20, 30, 60, 90 and 120 min samples. They reported that the accuracy of both the G&A's and Ham's methods was excellent in majority (about 85%) of the children, and the differences in the samples between 60, 90 and 120 min was not important for the G&A's method. However, they could not explain why these two methods were less accurate in a small fraction (about 15%) of the children. Itoh *et al.*[31] assessed GFR in 14 patients (age 3-19 years) and compared the G&A's method at 90 and 120 min, the Ham's method at 120 min; the C&G's method at 90, 120 and 150 min, the Jacobsson's method at 90, 120, and 150 min and the Itoh's method at 90, 120 and 150 min using a 2-exponential curve fitting of 5, 15, 60, 90, 120 150 and 180 min samples. They reported that the C&G and Jacobsson's methods designed for adults were more accurate than the G&A's and Ham's methods designed for children, even if they could not justify their results theoretically. They concluded that C&G and the Jacobsson's methods designed for adults could be applied to children, which is in partial concordance with our results. These two studies used GFR calculated from a 2-exponential curve fitting using multiple plasma samples as the reference, while we used the GFR calculated from the TPSM as the reference. However, we corrected the slope-intercept GFR using the JBM equation [26, 29]. In addition, the number of patients included in this study was larger than in previous studies, which might make up for the use of TPSM as the reference.

The principle of SPSMs is to relate radionuclide clearance and volumes of distribution at certain time points. As those equations are empirical models derived from different populations, ages, renal

functions and under different experimental conditions with respect to sampling times and references, those equations are not universal and require careful interpretation. The Groth & Aasted's method was derived from 130 children (aged 1 to 13 years) using a 120-min sample after a $^{51}$Cr-EDTA injection, using a 2-exponential curve fitting with 5 samples. In that study, the GFRs of 19 children were less than 80 mL/min/1.73 m$^2$ and the GFRs of 5 children were less than 50 mL/min/1.73 m$^2$ [20]. However, in our study the GFRs of 65 children were less than 80 mL/min/1.73 m$^2$ and the GFRs of 11 children were less than 50 mL/min/1.73 m$^2$. As SPSMs are essentially based on an empirical relationship between volumes of distribution and plasma clearances, the small number of GFRs < 90 mL/min/1.73 m$^2$ used to derive the equation may be one of the reasons why SPSMs did not work well for $30 \leq GFR_{ref} < 90$, but did work well for $GFR_{ref} \geq 90$ mL/min/1.73 m$^2$ in our study. Additionally, G&A tended to overestimate GFR and this result is consistent with the result of the Henriksen et al. [12]. Ham's method, mentioned in the European Association of Nuclear Medicine guidelines [5, 33] for GFR determination in children, was derived from 80 children (age < 15 years) using a 120 min sample after $^{51}$Cr-EDTA injection. The reference method was a 1-exponential curve fitting 2 samples between 120 and 240 min with a composite correction constant of 0.85. The C&G's method was derived from 45 patients using samples drawn at $180 \leq t \leq 300$ after $^{99m}$Tc-DTPA injection [21]. The reference method was a 2-exponential curve fitting 16 samples. C&G120 and the reference method revealed a good correlation, but the slope of the regression line between the C&G120 and the reference method was far different from the value of 1 (1.29). On the other hand, the slope of the regression line between C&G240 and the reference method was nearly 1 (1.00). This result may support the suggestion that C&G's method should only be used with the sample drawn at $180 \leq t \leq 300$. Jacobsson's method was originally derived from 39 patients using samples drawn between 240 and 300 min after a $^{99m}$Tc-DTPA injection. The reference method was a 1-exponential curve fitting 4 samples between 240 and 300 min using the Brochner-Mortensen equation for correction. Regarding the optimal sampling time, a 240 min sample would be more appropriate than a 120 min sample for Jacobsson's method because Jacobsson240 was more accurate than Jacobsson120. We used $^{51}$Cr-EDTA instead of $^{99m}$Tc-DTPA, the radionuclide originally used to derive C&G's and Jacobsson's equations. It is well known that the volume of distribution is dependent on the type of radiotracer, and the use of different radiotracers, $^{51}$Cr-EDTA in our case will affect the accuracy of the method. However, the error would not be significant since the $GFR_{est}$ calculated from both methods is

insensitive to the precise value of the volume of distribution [22] and the volume of distribution is included in both the numerator and the denominator.

In the current study, according to the linear regression analysis between $GFR_{ref}$ and $GFR_{est}$ (Table 2), the slope of the $GFR_{est}$ calculated from Ham is larger than 1 (1.5), and that calculated from Jacobsson240 is smaller than 1 (0.69) for $GFR_{ref}$ > 90 mL/min/1.73 $m^2$. Ham's method used a slope-intercept GFR corrected by a Chantler approximation with a correction constant of 0.85 as the reference while Jacobsson's method used a slope-intercept GFR corrected by the Brochner-Mortensen equation as the reference. Fleming reported that the Chantler approximation overestimates GFR over 100 mL/min/1.73 $m^2$ [34], while the Brochner-Mortensen equation underestimates GFR over 180 mL/min/1.73 $m^2$ [26, 34]. The regression lines of the scatter plots between $GFR_{ref}$ and $GFR_{est}$ calculated from Ham and Jacobsson240 are similar to the graphs of the slope-intercept GFRs corrected by the Chantler approximation and the Brochner-Mortensen equation referring to the true GFR, respectively. This may explain why Ham tended to overestimate GFR much more than other SPSMs for GFR>90 mL/min/1.73 $m^2$, and the difference becomes larger as the $GFR_{ref}$ increases.

There is an outlier shown in Figs. 2 and 3 which is presented as a closed square. This patient was referred for GFR measurement based on a suspicion of acute renal failure, and her medical records and clinical course supported the presumed diagnosis. The patient's $GFR_{ref}$ was 35.05 mL/min/1.73 $m^2$ but Ham (60.13 mL/min/1.73 $m^2$, 71.56%), G&A (64.46 mL/min/1.73 $m^2$, 83.93%), C&G120 (50.06 mL/min/1.73 $m^2$, 42.84%) and Jacobsson120 (60.65 mL/min/1.73 $m^2$, 73.05%) all overestimated the $GFR_{est}$ in this patient. C&G240 (39.91 mL/min/1.73 $m^2$, 13.88%) and Jacobsson240 (43.26 mL/min/1.73 $m^2$, 23.43%) also overestimated the GFR but the errors were much smaller than those of the SPSMs using the 120 min sample. These results are consistent with previous reports of the improved accuracy of $GFR_{est}$ with increased sampling times with respect to results obtained from C&G's and Jacobsson's methods [11, 21, 22]. Jacobsson's method is quite insensitive to the variation of the patient's volume of distribution [22].

This study has several limitations. First, we used the slope-intercept technique which is a 1-exponential curve fitting two plasma samples instead of a 2-exponential curve fitting multiple plasma samples to determine the $GFR_{ref}$. The slope-intercept technique ignores the faster part of the plasma concentration curve and only uses the slower part of the plasma concentration curve to determine GFR. This simplification resulted in an overestimation of GFR and therefore, various correction methods

were developed. We corrected the slope-intercept GFR using the JBM equation instead of the Brochner-Mortensen equation to minimize errors [26, 29]. Second, we used samples at only two time points. More appropriate sampling times may exist, however, only 120 and 240 min samples were available because of the retrospective nature of this study.

## Conclusion

Jacobsson240 showed a good accuracy in all $GFR_{ref}$ ranges and was well correlated with TPSM. Jacobsson240 might be the most appropriate method to substitute for TPSM in pediatric patients. The Ham's method could be an alternative for patients with impaired renal function.

## Appendix

1. Slope-intercept GFR corrected by Jodal and Brochner-Mortensen equation (reference GFR) [26]

Reference GFR = $SI\text{-}GFR_{cor} / (1+0.00185 \times BSA^{-0.3} \times SI\text{-}GFR_{cor}^2)$ (mL/min/1.73 $m^2$)

$SI\text{-}GFR_{cor} = SI\text{-}GFR \times (1.73/BSA\ m^2)$

$SI\text{-}GFR = (w_i \times s \times 200/w_s) \times (\ln(C_1/C_2)/dt) \times (C_2^{(t1/dt)}/C_1^{(t2/dt)})$

$w_i$: injection mass (g)

$w_s$: standard mass (g)

$t_1$: 1st plasma sample time (min)

$t_2$: 2nd plasma sample time (min)

$dt = t_2 - t_1$

s: standard count (cpm/mL)

$C_1$: 1st plasma sample count (cpm/mL)

$C_2$: 2nd plasma sample count (cpm/mL)

BSA: body surface area ($m^2$)

2. Groth and Aasted's method [20]

Cl (mL/min/1.73 $m^2$) = A + BX

$A = -553.124 \ln(t) + 3236.76$

$B = 72.295 \ln(t) - 425.4$

$X = \ln\{C(t) \times BSA \times 10^7/ID\}$

t: sample time (90~120 min)

C(t): sample activity at time = t (min) (cpm/mL)

ID: injected dose (g)

Reference method of plasma clearance: 2-exponential curve fitting 5 samples at 5, 15, 60, 90 and 120 min after the injection of $^{51}$Cr-EDTA

3. Ham's method [6, 10]

Cl (mL/min) = $2.602V_{120} - 0.273$

$V_{120} = ID/C_{120}$ (L)

$C_{120} = A(t) \times e^{(0.008)(t-120)}$

t: sample time (100~130 min)

A(t): actual radioactivity at sample time = t

$C_{120}$: radioactivity corresponding to sample time = t (cpm/mL)

$V_{120}$: volume of distribution at sample time = t

Reference method of plasma clearance: 1-exponential curve fitting 2 samples between 2 and 4 hour after the injection of $^{51}$Cr-EDTA with composite correction constant of 0.85

4. Christensen & Groth's method [6, 21, 35]

Cl (mL/min) = -b + $\sqrt{(b^2 - 4ac)/2a}$

a = 0.0000017 $t^2$ - 0.0012 t

b= -0.000775 $t^2$ + 1.31 t

c = ECV × ln(ECV/V(t))

ECV: extracellular volume = 8116.6 BSA - 28.2

V(t): volume of distribution = ID/C(t) (mL)

t: sample time (180~300 min)

BSA: body surface area ($m^2$)

ID: injected dose

Reference method of plasma clearance: 2-exponential curve fitting 16 samples from 0 to 300 min after the injection of $^{99m}$Tc-DTPA

5. Jacobsson's method [22]

Cl (mL/min) = ln(V(t)/V') / (t/V' + 0.0016)

V(t): volume of distribution at sample time = t

ID: injected dose

C(t): plasma radioactivity at sample time = t (cpm/mL)

V' = 0.246 BW

BW: body weight (g)

t: sample time (min)

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**Table 1**. Baseline patient characteristics according to the range of glomerular filtration rate (GFR)

| Characteristics | Total | $30 \leq GFR_{ref} < 60$ (ml/min/1.73 $m^2$) | $60 \leq GFR_{ref} < 90$ (ml/min/1.73 $m^2$) | $90 \leq GFR_{ref}$ (ml/min/1.73 $m^2$) |
|---|---|---|---|---|
| No. of patients | 122 | 17 | 50 | 94 |
| Sex (male : female) | 65 : 57 | 6 : 11 | 27 : 23 | 51 : 43 |
| No. of GFR measurements | 307 | 22 | 82 | 203 |
| Age < 2 years | 48 | 7 | 15 | 26 |
| 2 ≤ Age < 5 years | 75 | 3 | 25 | 47 |
| 5 ≤ Age < 10 years | 86 | 6 | 21 | 59 |
| 10 ≤ Age < 15 years | 98 | 6 | 21 | 71 |
| Age (years) | 7.3 ± 4.6 | 6.5 ± 5.2 | 6.5 ± 4.6 | 7.7 ± 4.5 |
| Height (cm) | 119.2 ± 30.6 | 108.5 ± 34.7 | 114.0 ± 31.3 | 122.4 ± 29.5 |
| Weight (kg) | 27.4 ± 18.2 | 23.2 ± 18.5 | 25.5 ± 19.4 | 28.7 ± 17.6 |
| BSA ($m^2$) | 0.9 ± 0.4 | 0.8 ± 0.5 | 0.9 ± 0.4 | 1.0 ± 0.4 |
| Serum creatinine (mg/dL) | 0.41 ± 0.18 | 0.65 ± 0.31 | 0.44 ± 0.20 | 0.37 ± 0.13 |

Continuous values are in mean value ± SD

$GFR_{ref}$: the reference GFR

**Table 2.** Linear regression and correlation analysis of the GFR estimates ($GFR_{est}$) by single-plasma-sample methods (SPSMs) against the reference GFR ($GFR_{ref}$).

| $GFR_{ref}$ (mL/min/1.73 $m^2$) | Method | Correlation analysis | | Linear regression equation | |
|---|---|---|---|---|---|
| | | [a] r | SEE | slope | intercept |
| $30 \leq GFR_{ref}$ (n=307) | G&A | 0.98 | 9.26 | 0.94 | 13.63 |
| | Ham | 0.98 | 15.60 | 1.32 | -21.94 |
| | C&G120 | 0.99 | 11.75 | 1.29 | -21.41 |
| | C&G240 | 0.93 | 15.55 | 1.00 | 10.65 |
| | Jacobsson120 | 0.97 | 11.26 | 1.02 | 6.74 |
| | Jacobsson240 | 0.92 | 10.54 | 0.84 | 16.74 |
| $30 \leq GFR_{ref} < 90$ (n=104) | G&A | 0.97 | 9.12 | 1.09 | 1.64 |
| | Ham | 0.97 | 4.46 | 0.96 | 5.45 |
| | C&G120 | 0.97 | 7.72 | 1.40 | -30.25 |
| | C&G240 | 0.95 | 11.63 | 1.32 | -13.97 |
| | Jacobsson120 | 0.88 | 11.25 | 1.14 | -2.87 |
| | Jacobsson240 | 0.95 | 6.24 | 1.06 | -0.58 |
| $30 \leq GFR_{ref} < 60$ (n=22) | G&A | 0.73 | 9.38 | 1.03 | 4.14 |
| | Ham | 0.70 | 7.03 | 0.65 | 21.45 |
| | C&G120 | 0.72 | 14.38 | 1.28 | -24.64 |
| | C&G240 | 0.94 | 5.31 | 1.40 | -17.52 |
| | Jacobsson120 | 0.60 | 12.36 | 1.15 | -3.51 |
| | Jacobsson240 | 0.96 | 3.55 | 1.02 | 1.58 |
| $0 \leq GFR_{ref} < 90$ (n=84) | G&A | 0.97 | 9.05 | 1.08 | 2.62 |
| | Ham | 0.97 | 3.46 | 1.08 | -4.19 |
| | C&G120 | 0.98 | 4.48 | 1.40 | -30.59 |
| | C&G240 | 0.87 | 12.80 | 1.36 | -17.70 |
| | Jacobsson120 | 0.80 | 10.93 | 1.15 | -3.82 |
| | Jacobsson240 | 0.87 | 6.78 | 1.09 | -2.46 |
| $90 \leq GFR_{ref}$ (n=203) | G&A | 0.97 | 9.33 | 0.83 | 26.82 |
| | Ham | 0.97 | 18.92 | 1.50 | -44.03 |
| | C&G120 | 0.99 | 13.35 | 1.21 | -11.82 |
| | C&G240 | 0.82 | 17.22 | 0.80 | 35.33 |
| | Jacobsson120 | 0.97 | 11.26 | 0.92 | 19.39 |
| | Jacobsson240 | 0.80 | 12.17 | 0.69 | 35.17 |

SEE standard error of the estimate

[a]r: correlation coefficient

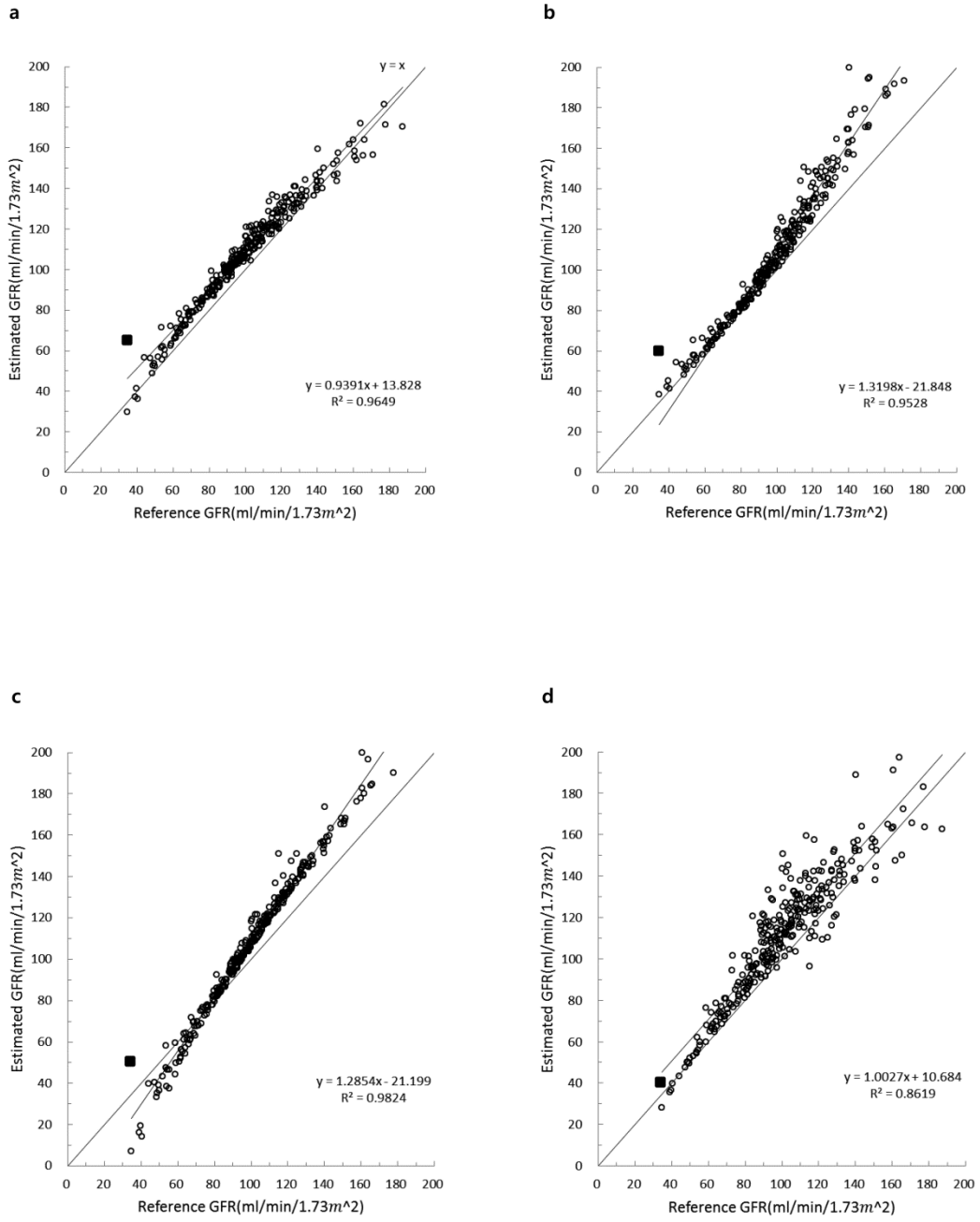
**Table 3.** Bland-Altman's analysis of the GFR difference % between the estimated GFR ($GFR_{est}$) and the reference GFR ($GFR_{ref}$)

| GFR (mL/min/1.73 $m^2$) | Method | $\frac{(\text{Estimated GFR} - \text{Reference GFR})}{\text{Reference GFR}}$ (%) | | | [a] $N_{10\%}$ |
|---|---|---|---|---|---|
| | | mean | SD | 95% CI | |
| $30 \leq GFR_{ref}$ (n=307) | G&A | 8.58 | 7.04 | -5.22, 22.39 | 119 (39%) |
| | Ham | 8.80 | 8.72 | -8.29, 25.89 | 104 (34%) |
| | C&G120 | 5.13 | 12.05 | -18.48, 28.75 | 128 (42%) |
| | C&G240 | 11.35 | 10.64 | -9.51, 32.21 | 163 (53%) |
| | Jacobsson120 | 9.28 | 9.77 | -9.88, 28.44 | 179 (58%) |
| | Jacobsson240 | 2.28 | 9.17 | -15.70, 20.26 | 80 (26%) |
| $30 \leq GFR_{ref} < 90$ (n=104) | G&A | 11.39 | 9.31 | -6.85, 29.64 | 61 (59%) |
| | Ham | 4.35 | 8.07 | -11.46, 20.16 | 10 (10%) |
| | C&G120 | -4.68 | 15.96 | -35.96, 26.61 | 29 (28%) |
| | C&G240 | 11.02 | 9.87 | -8.32, 30.36 | 49 (47%) |
| | Jacobsson120 | 9.52 | 15.38 | -20.63, 39.67 | 83 (80%) |
| | Jacobsson240 | 5.34 | 6.35 | -7.10, 17.79 | 19 (18%) |
| $30 \leq GFR_{ref} < 60$ (n=22) | G&A | 12.09 | 19.46 | -26.06, 50.24 | 10 (45%) |
| | Ham | 9.66 | 15.54 | -20.79, 40.11 | 7 (32%) |
| | C&G120 | -22.99 | 25.63 | -73.23, 27.25 | 19 (86%) |
| | C&G240 | 3.73 | 9.67 | -15.22, 22.68 | 5 (23%) |
| | Jacobsson120 | 8.15 | 27.36 | -45.48, 61.78 | 20 (91%) |
| | Jacobsson240 | 5.43 | 5.86 | -6.06, 16.91 | 3 (14%) |
| $60 \leq GFR_{ref} < 90$ (n=84) | G&A | 11.20 | 3.43 | 4.47, 17.94 | 51 (62%) |
| | Ham | 2.92 | 3.24 | -3.42, 9.27 | 3 (4%) |
| | C&G120 | 0.24 | 6.18 | -11.87, 12.34 | 10 (12%) |
| | C&G240 | 12.98 | 9.01 | -4.69, 30.65 | 44 (54%) |
| | Jacobsson120 | 9.89 | 10.30 | -10.30, 30.08 | 63 (77%) |
| | Jacobsson240 | 5.32 | 6.51 | -7.44, 18.08 | 16 (20%) |
| $90 \leq GFR_{ref}$ (n=203) | G&A | 7.14 | 4.98 | -2.62, 16.90 | 58 (29%) |
| | Ham | 11.08 | 8.16 | -4.90, 27.07 | 94 (46%) |
| | C&G120 | 10.16 | 3.88 | 2.56, 17.76 | 99 (49%) |
| | C&G240 | 11.52 | 11.04 | -10.11, 33.15 | 114 (56%) |
| | Jacobsson120 | 9.16 | 4.90 | -0.45, 18.77 | 96 (47%) |
| | Jacobsson240 | 0.71 | 9.98 | -18.85, 20.28 | 61 (30%) |

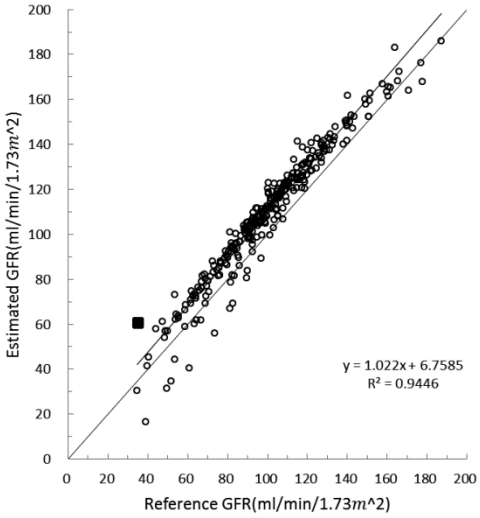
*SD* Standard deviation, *CI* Confidence interval.

[a] $N_{10\%}$: the number of cases with difference between $GFR_{est}$ and $GFR_{ref}$ was > 10% when referring to $GFR_{ref}$

**Figure 1.** Scatter plots of the GFR estimates calculated from SPSMs against the reference GFR; (a) Groth and Aasted's method, (b) Ham's method, (c) Christensen and Groth's method at 120 min, (d) Christensen and Groth's method at 240 min, (e) Jacobsson's method at 120 min, (f) Jacobsson's method at 240 min



e


Estimated GFR(ml/min/1.73m^2)
Reference GFR(ml/min/1.73m^2)
y = 1.022x + 6.7585
R² = 0.9446

f

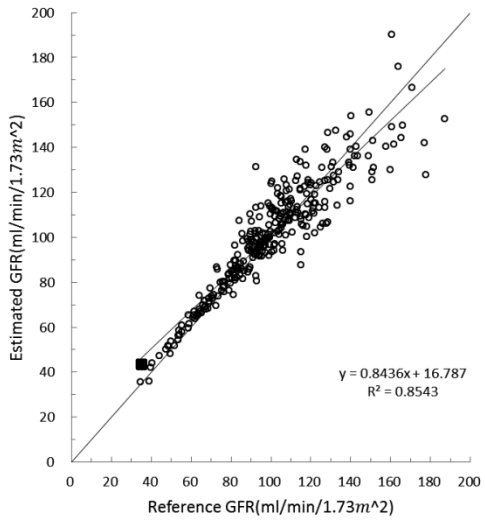
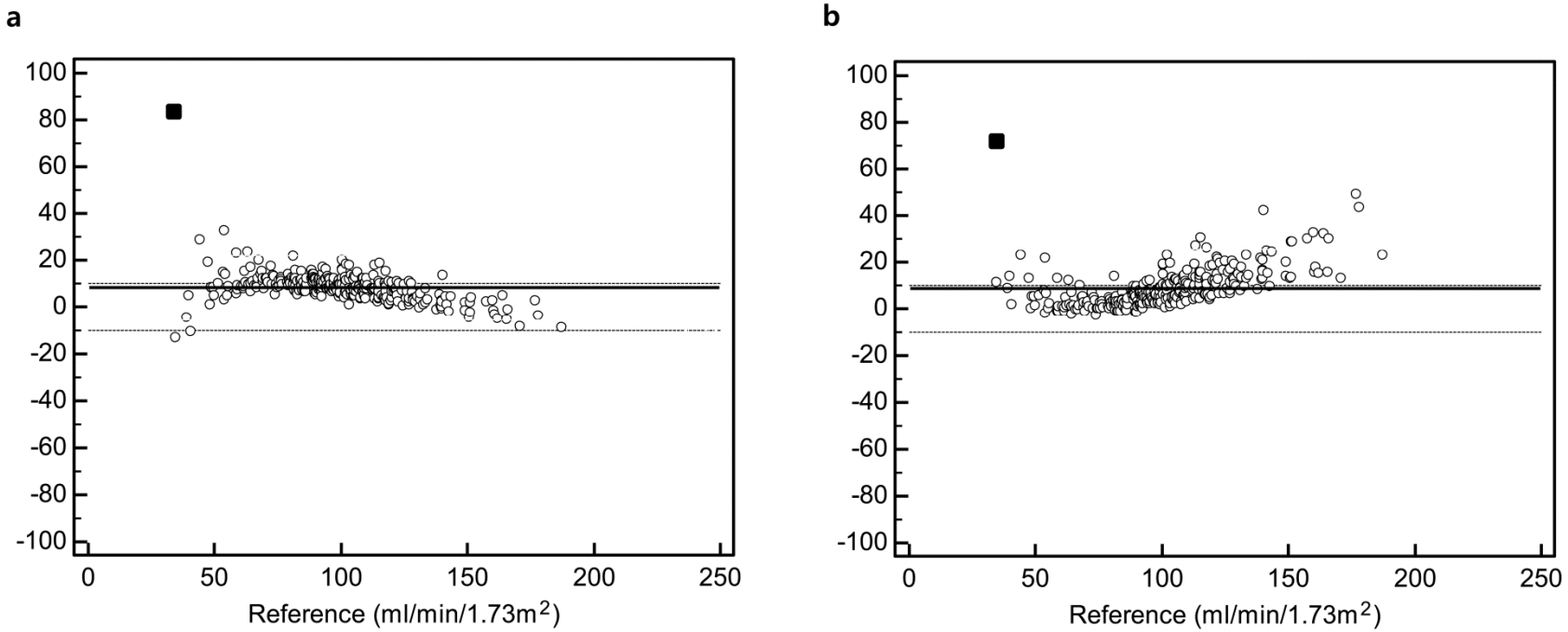
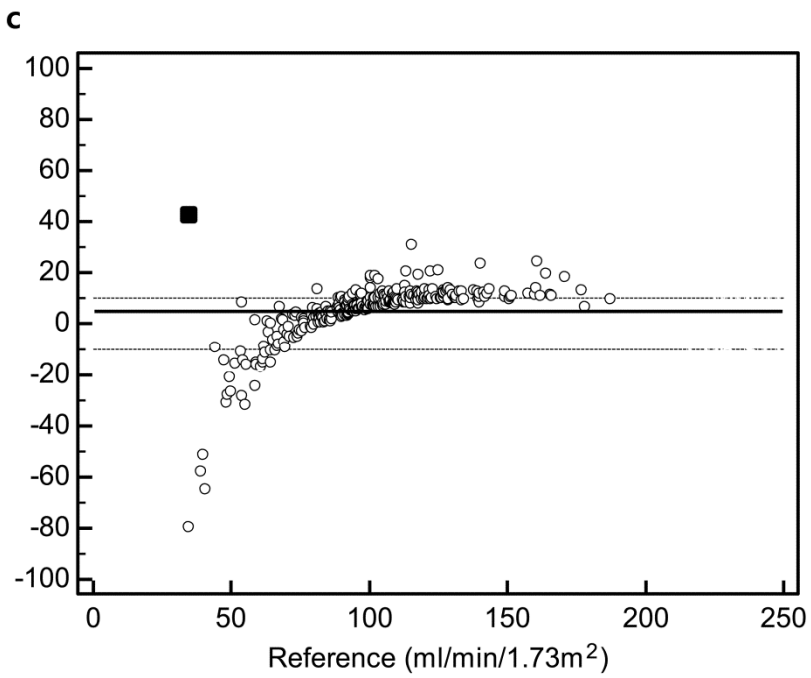
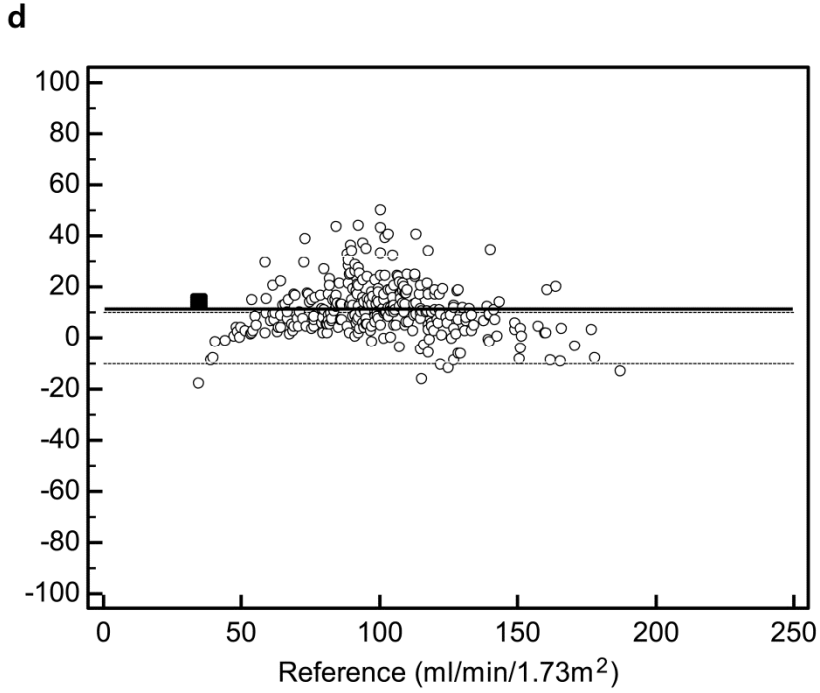

Estimated GFR(ml/min/1.73m^2)
Reference GFR(ml/min/1.73m^2)
y = 0.8436x + 16.787
R² = 0.8543

**Figure 2.** Bland-Altman plots drawn by plotting the percentage difference between the estimated and reference values of GFR against reference values of GFR; (a) Groth and Aasted's method, (b) Ham's method, (c) Christensen and Groth's method at sample time = 120 min, (d) Christensen and Groth's method at sample time = 240 min, (e) Jacobsson's method at sample time = 120 min, (f) Jacobsson's method at sample time = 240 min




c
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
50
100
150
200
250
Reference (ml/min/1.73m2)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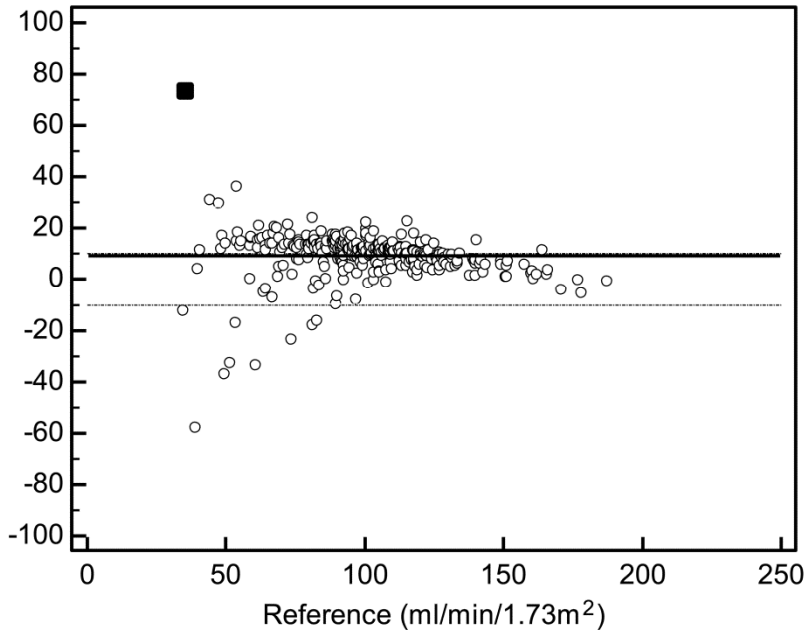
-20
-40
-60
-80
-100
0
50
100
150
200
250
Reference (ml/min/1.73m2)

e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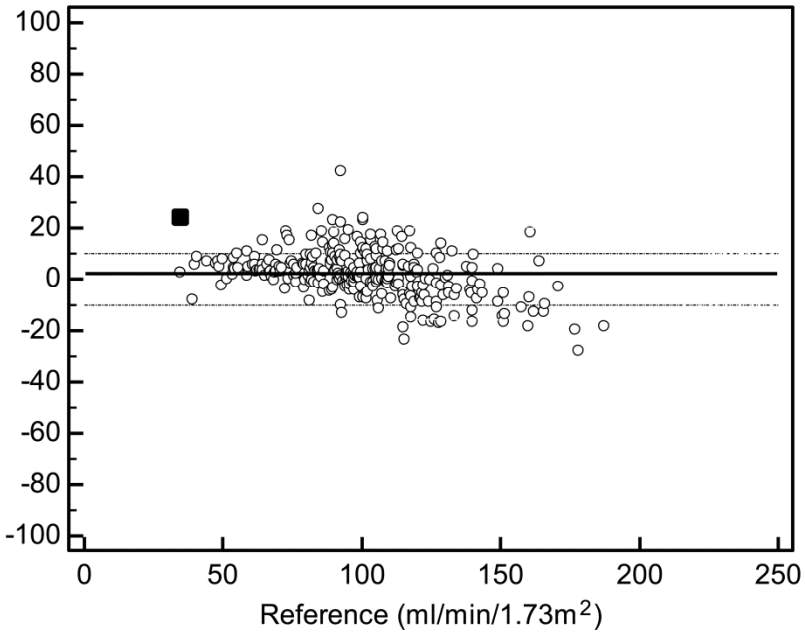
Reference (ml/min/1.73m2)

f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Reference (ml/min/1.73m2)

## 국문요약

**목적:** Cr-51 EDTA를 사용한 사구체여과율 (Glomerular filtration rate: GFR) 측정 방법들 중에서 2회 측정법 (two-plasma-sample method: TPSM)이 높은 정확도 때문에 흔히 사용된다. 반면, 소아에서는 1회 측정법 (single-plasma-sample method: SPSM)은 비교적 덜 정확하나 덜 침습적이고 더 간단하여 소아에서 사용이 필요하다. 이 연구는 소아에서 TPSM을 기준으로 여러가지 SPSM의 정확도를 평가하고자 시행하였다.

**방법:** 전체 122명의 소아에서 (65명의 남아와 57명의 여아, 평균 나이: 7.3 ± 4.6 세, 나이 범위: 6개월 ~ 15세) 측정된 307회의 GFR을 후향적으로 분석하였다. Cr-51 EDTA 정맥주사 후 120분과 240분에 2번 채혈된 자료를 사용하였고, GFR 기준값은 slope-intercept technique을 이용하는 TPSM을 Jodal and Brochner-Mortensen (JBM) 공식으로 보정하여 계산하였다. GFR 기준값이 30 ml/min/1.73 $m^2$ 미만인 환자는 분석에서 제외되었다. 다음의 6가지 SPSM 방법들로 GFR 추정값을 구하였다: 1) 120분 째 혈장을 이용한 Groth & Aasted의 방법 (G&A), 2) 120분 째 혈장을 이용한 Ham의 방법 (Ham), 3) 120분 째 혈장을 이용한 Christensen & Groth의 방법 (C&G120) 4) 240분 째 혈장을 이용한 Christensen & Groth의 방법 (C&G240), 5) 120분 째 혈장을 이용한 Jacobsson의 방법 (Jacobsson120), 6) 240분 째 혈장을 이용한 Jacobsson의 방법 (Jacobsson240). 피어슨 상관계수 (Pearson correlation: r), 선형회귀분석 (linear regression analysis)과 블랜드-앨트먼 분석 (Bland-Altman analyses)이 시행되었다. GFR 추정값들의 정확도는 추정표준오차 (standard error of the estimate, SEE)와 GFR 기준값과 GFR 추정값이 10% 이상 차이가 나는 환자들의 숫자 ($N_{10\%}$) 를 이용하여 평가하였다.

**결과:** SPSM을 이용하여 계산한 GFR추정값들은 GFR기준값과 전반적으로 좋은 상관관계를 보였다 (r = 0.92 ~ r = 0.99). SPSM의 정확도는 GFR 기준값에 따라 달라지는 경향을 보였다. 전체 구간에서, G&A가 가장 작은 SEE, Jacobsson240이 가장 작은 $N_{10\%}$ 값 및 평균 차이를 보였다. Ham 방법은 $60 \leq GFR_{ref} < 90$ ml/min/1.73 $m^2$ (경증 신기능 저하), Jacobsson240 방법은 $30 \leq GFR_{ref} < 60$ ml/min/1.73 $m^2$ (경증

신기능 저하), $30 \leq GFR_{ref} < 60$ ml/min/1.73 $m^2$ (전체 신기능 저하)에서는 Ham방법이 가장 정확하였다.

**결론:** 평가된 SPSM은 TPSM과 좋은 상관관계를 보였다. 평가된 방법 중에서는 Jacobsson240이 다양한 GFR 구간에서 좋은 정확도를 보여주었고, Ham은 신장 기능이 저하된 소아들에서 가장 정확하였다.

**핵심단어:** 사구체여과율; 소아; 1회 측정법; $^{51}$Cr-EDTA;