

## Accuracy of plasma sample methods for determination of glomerular filtration rate with $^{99m}\text{Tc}$ -DTPA

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The plasma sample method following a single injection of radioactive markers has been proved to be simple and accurate for the determination of glomerular filtration rate (GFR) in clinical practice. The aim of this study was to assess clinical accuracy of single-, two- and multi-sample methods. **Methods:** The study was performed on 50 patients with various degrees of renal dysfunction (29 males and 21 females; aged 27 to 90 years). As a reference the true GFR (GFR<sub>t</sub>) was determined by means of the two-compartment model curve fitting 10 plasma samples following a single-injection of  $^{99m}\text{Tc}$ -DTPA. The GFR<sub>t</sub> was compared to the GFR estimated by the Christensen and Groth's single-sample (GFR<sub>cg</sub>), two-sample (GFR<sub>2s</sub>) and multi-sample (GFR<sub>m</sub>) between 75 and 300 min after the injection. The GFRs by two- and multi-sample methods were determined with the slope and intercept algorithm and its overestimation was corrected by Brochner-Mortensen's formula. **Results:** In 49 patients with GFR between 12 and 169 ml/min/1.73 m<sup>2</sup>, the standard deviation of difference (95% limits of agreement) between GFR<sub>t</sub> and GFR<sub>cg</sub> at 180 min was 6.513 ml/min/1.73 m<sup>2</sup> (–16.5 ~ 9.5 ml/min/1.73 m<sup>2</sup>), which was somewhat closer than 7.311 ml/min/1.73 m<sup>2</sup> (–12.5 ~ 16.5 ml/min/1.73 m<sup>2</sup>) in GFR<sub>2s</sub> in slow clearance phase at 120 min and 240 min. However, the single-sample method tended to show some scattering in GFR below 30 and above 140 ml/min/1.73 m<sup>2</sup>. On the contrary, the 2-sample method tended to be scattered in GFR above 120 ml/min/1.73 m<sup>2</sup>. **Conclusion:** In view of its accuracy and technical simplicity, the single-sample method is first choice in a routine practice. The two-sample method is essential of choice for a patient in whom the GFR is expected to be below 30 ml/min/1.73 m<sup>2</sup>. These two methods may be chosen selectively in dependence on the preserved renal function which is expected at time of the test.

**Key words:** glomerular filtration rate, plasma sample method,  $^{99m}\text{Tc}$ -DTPA

### INTRODUCTION

THE GLOMERULAR FILTRATION RATE (GFR) is generally considered the best functional measure among several important functions of the kidney.<sup>1</sup> Simple and accurate methods are still needed to determine GFR in routine clinical practice. A plasma sample method following a single-injection of radioactive<sup>2</sup> or non-radioactive markers<sup>3,4</sup> has been proved effective as an alternative to the con-

tinuous infusion method with inulin for the determination of GFR in a clinical practice and for clinical research.<sup>5–7</sup> Among plasma sample methods, a single-sample method is recommended as the first choice in a clinical practice.<sup>2</sup> However, this method has been reported inaccurate in severe renal failure with a GFR below 20–30 ml/min/1.73 m<sup>2</sup>.<sup>8,10</sup> The two- or multi-sample method is considered to be more accurate in the determination of GFR in such cases.<sup>11–13</sup> However, it is still unclear whether the single-sample method or the two-sample method should be chosen in clinical practice and whether either of the two simplified sample methods should be chosen selectively in a case with preserved renal function.

In the present paper, the GFR determined with 10 plasma samples was compared with its determination by single-, two- and multi-sample algorithms.

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## MATERIALS AND METHODS

### Subjects

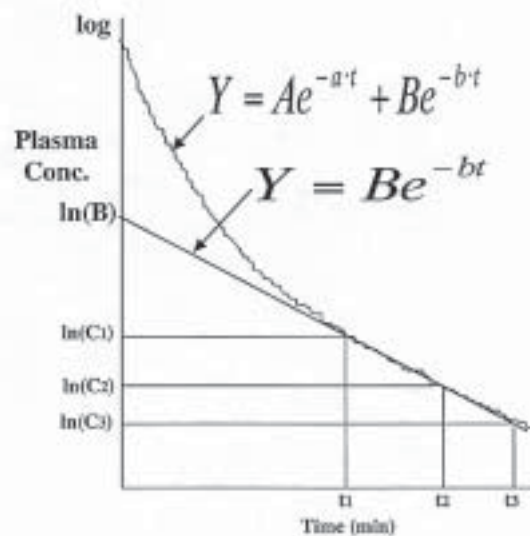
The study was performed on 50 patients, 29 males and 21 females, with diabetes mellitus (all type II) and various degrees of renal dysfunction. Their age ranged from 25 to 90 years old (mean  $\pm$  SD: 69.2  $\pm$  14.6 years), height from 142.7 to 175.6 cm (159.4  $\pm$  8.3 cm), body weight from 41 to 154.1 kg (63.5  $\pm$  17.8 kg) and body surface area (BS) from 1.3 to 2.59 m<sup>2</sup> (1.65  $\pm$  0.021 m<sup>2</sup>) which was estimated by Du Bois' formula, BS (m<sup>2</sup>) = BW<sup>0.425</sup> · H<sup>0.725</sup> · 0.007184 (BW = body weight (kg), H = height (cm)).<sup>14</sup> Serum creatinine and BUN ranged from 0.34 to 6.49 mg/dl (0.98  $\pm$  1.09 mg/dl) and from 5.7 to 48.5 mg/dl (16.8  $\pm$  8.0 mg/dl), respectively. All patients were admitted for education on their disease and control therapy for hyperglycemia. The study was performed after informed consent was given.

### Radionuclide Study

Each patient was hydrated with 300 ml of water 20 min prior to the examination. <sup>99m</sup>Tc-DTPA was labeled in our hospital with a commercially available freeze-dried kit (Daiichi Radioisotope Co., Tokyo, Japan), which had a labeling yield of over 95%. The radiotracer was prepared to contain 300 MBq per 2 ml in an injection syringe to which a 3-way cock and butterfly needle were attached. The injection of <sup>99m</sup>Tc-DTPA was administered through an indwelling butterfly needle during infusion of 20 ml normal saline solution. Standard renal scintigraphy was carried out in a supine position. Ten venous blood samples were drawn at 5, 15, 30, 45, 75, 120, 150, 180, 240 and 300 min after the injection through an indwelling needle placed in the opposite arm. After scintigraphy, the injection site of the arm was scanned with a gamma camera. The residual radioactivity at the injection site was less than 0.1% in all patients. The patients were confined to bed throughout scintigraphy but their movement and oral intake of water and food were not restricted during the sampling of blood. Total blood was separated and plasma was counted together with a diluted standard solution of the injected radiotracer with a Na(Tl) well scintillation counter (Autowell Gamma System ARC-380, Aloka Co., Ltd., Japan). The average radioactivity of the duplicated samples of plasma and diluted standard solution was used for the calculation. the function of protein-bound <sup>99m</sup>Tc-DTPA was not measured.

### Calculation of Plasma Clearance as Gold Standard

The two-compartment model<sup>15,16</sup> determines plasma clearance (Cl) of <sup>99m</sup>Tc-DTPA with multiple sample data. In this model, plasma disappearance of <sup>99m</sup>Tc-DTPA fits the exponential curve,  $Y = Ae^{-at} + Be^{-bt}$  (t: time after injection). The plasma clearance of <sup>99m</sup>Tc-DTPA is determined by the equation, ID/(A/a + B/b) (ID: total injected dose). In real curve fitting, the plasma concentration was



**Fig. 1** Calculation of slope and intercepts of the linear regression equation in mono-compartment model. In final slow clearance phase, linear regression equation between plasma concentration and time (t) is expressed as the following:  $Y = \ln(B) - bt$  (b: slope, B: intercept). Plasma clearance (uncorrected; Cl<sub>uc</sub>) was calculated from the equation of  $Cl_{uc} = Q_0/B/b$  ( $Q_0$ : totally injected dose). In two samples, slope and intercept are calculated from the following equations:  $b = \text{abs}(\ln(C_1) - \ln(C_2))/(t_2 - t_1)$ ,  $B = \exp(\ln(B)) = \ln(C_1) + bt_1$  or  $\ln(C_2) + bt_2$ . In samples > two, linear regression equation between plasma concentration and time is calculated by least squares method using a computer.

**Table 1** Results of least squares linear regression and linear correlation analyses between true GFR and estimated GFR

Methods	GFR Range 12.7–168.9 ml/min/1.73 m <sup>2</sup> (92 $\pm$ 39.0* ml/min/1.73 m <sup>2</sup> , n = 49)			
	a	b	r	RMSE
Single-Sample Method				
Christensen & Groth (180 min)	7.6109	0.9555	0.9861	6.3442
Two-Sample Method				
120–180 min	-18.5681	0.7843	0.9280	12.4072
120–240 min	1.2954	0.9657	0.9822	7.2642
120–300 min	-1.0418	0.9815	0.9643	7.4346
180–240 min	-12.8270	1.0901	0.9820	20.4888
180–300 min	-6.6426	1.0533	0.9780	8.8550
Multi-Sample Method				
75–300 min (6 points)	2.2473	0.9359	0.9862	6.2001
120–300 min (5 points)	-1.5492	0.9979	0.9880	6.1383

\*: mean  $\pm$  SD, n = the number of samples. a: intercept; b: slope; r: correlation coefficient; RMSE: root mean square error

converted to a percentage of the injected dose per liter of plasma (%ID/l). Each constant of the exponential curve was automatically determined by means of the mathematical algorithm on non-linear least squared by using commercially available software (JMP v.3.1, SAS Institute, USA). The equation for calculation of plasma clear-

ance is expressed as  $CI = 100 \times 1000 (ab)/(Ab + aB)$  (ml/min). The measured clearance was standardized for a BS of 1.73 m<sup>2</sup> and was referred to as true GFR (GFR<sub>t</sub>).

Disappearance of the plasma concentration (% ID/l) fitted the exponential curve in most cases, except for only one patient with mild ascited which was disclosed on the CT scan taken after the radionuclide examination. This patient was excluded from the analysis. The GFR<sub>t</sub> in 49 patients ranged from 12.7 to 168.9 ml/min/1.73 m<sup>2</sup>.

#### Single-Sample Method

The GFR was estimated by the previously proposed single-sample method of Christensen and Groth (GFR<sub>cg</sub>)<sup>17</sup> rewritten by Watson.<sup>18</sup> The estimated GFR was standardized for a BS of 1.73 m<sup>2</sup>.

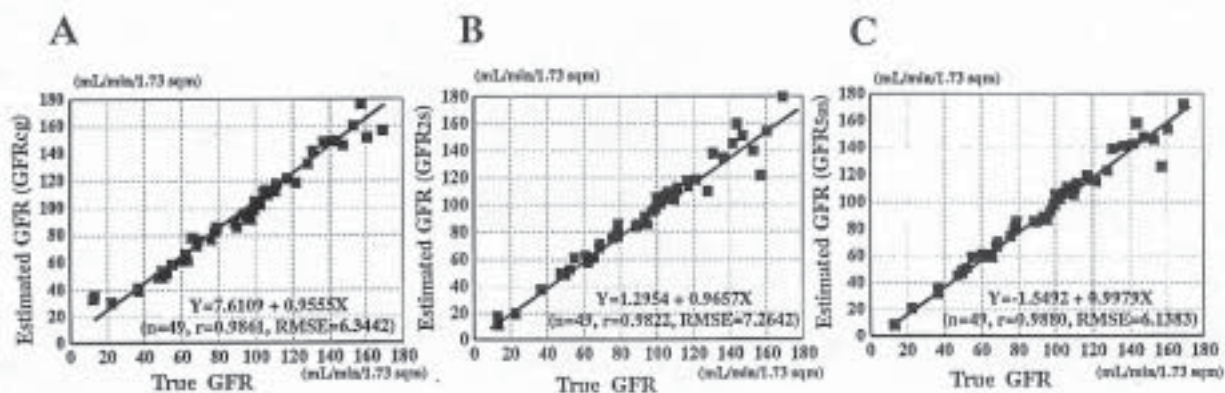
#### Two- and Multi-Sample Methods

The plasma clearance (Cl') of <sup>99m</sup>Tc-DTPA was calculated from slope and intercept of the regression equation in the final slow clearance<sup>2,19</sup> (Fig. 1). In 2 samples (GFR<sub>2s</sub>) between 120 and 300 min, slope and intercept of

the regression equation were calculated from data of the points according to simple mathematical equations in Figure 1. In 6 samples (GFR<sub>6s</sub>) from 75 to 300 min and 5 samples (GFR<sub>5s</sub>) from 120 to 300 min, the slope and intercept of the regression equation were determined by least squared method between time and plasma concentration using a commercially available software (JMP v.3.1, SAS Institute, USA). The GFR calculated by this algorithm was overestimated. Then, the calculated plasma clearance was corrected by Brochner-Mortensen's formula,<sup>19</sup>  $GFR = 0.990778Cl' - 0.001218Cl'^2$ . The corrected clearance (GFR<sub>2s</sub>, GFR<sub>5m</sub>, GFR<sub>6m</sub>) was also standardized for a BS of 1.73 m<sup>2</sup>.

#### Statistical Analysis

Least squares linear regression and linear correlation analyses between true GFR (GFR<sub>t</sub>) and single-plasma method (GFR<sub>cg</sub>) or mono-compartment model (GFR<sub>2s</sub>, GFR<sub>5m</sub> and GFR<sub>6m</sub>) were performed with commercially available software (JMP v.3.1, SAS Institute, USA). In this analysis, the correlation coefficient (r), root mean

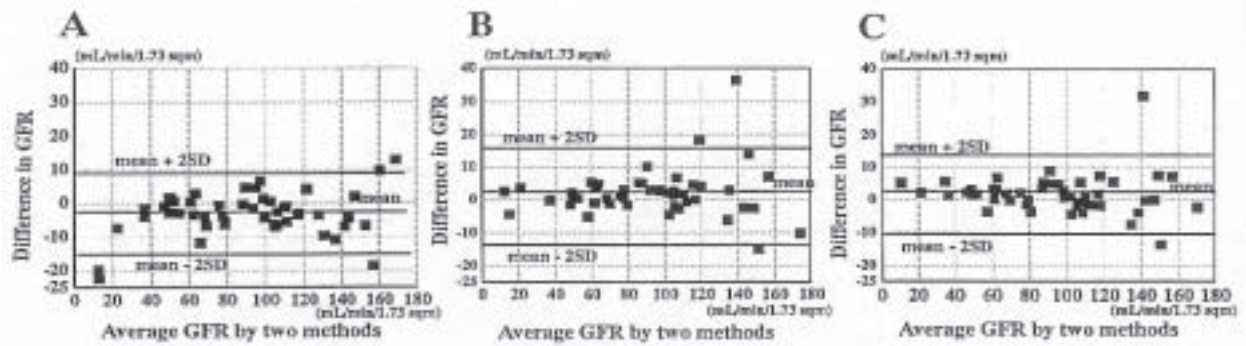


**Fig. 2** Scatter plots of estimated GFR against true GFR. A: Christensen & Groth's method, B: two-sample method between 120 min and 240 min, C: 5-sample method from 120 to 300 min.

**Table 2** Results of difference in GFR between true GFR and estimated GFR

Methods	GFR Range 12.7–168.9 ml/min/1.73 m <sup>2</sup> (92 ± 39.0* ml/min/1.73 m <sup>2</sup> , n = 49)				
	mean	SD	95% Agree	SEM	95% Conf. Interv.
<b>Single-Sample Method</b>					
Christensen & Groth (180 min)	-3.498	6.513	-16.5 ~ 9.5	0.930	-5.4 ~ -1.6
<b>Two-Sample Method</b>					
120–180 min	38.483	14.879	8.7 ~ 68.2	2.126	34.2 ~ 42.8
120–240 min	1.869	7.311	-12.5 ~ 16.5	1.044	-0.3 ~ 4.0
120–300 min	2.749	7.395	-12.0 ~ 17.5	1.056	0.6 ~ 4.9
180–240 min	4.610	20.576	-16.6 ~ 45.7	2.939	-1.4 ~ 10.4
180–300 min	1.723	9.005	-26.6 ~ 45.7	1.286	-0.9 ~ 4.3
<b>Multi-Sample Method</b>					
75–300 min (6 points)	3.672	6.625	-9.6 ~ 16.9	0.946	1.8 ~ 5.6
120–300 min (5 points)	1.742	6.075	-10.4 ~ 13.9	0.868	0.0 ~ 3.5

\*: mean ± SD, n = the number of samples. 95% Agree: 95% limits of agreements (true GFR – estimated GFR), SEM: standard error of mean, 95% Conf. Interv.: 95% confidence interval for mean



**Fig. 3** Scatter plots of difference in GFR ( $GFR_t - GFR_c$ ) against average GFR by two methods. A: Christensen & Groth's method, B: two-sample method between 120 min and 240 min, C: 5-sample method from 120 to 300 min. The identity lines are indicated.

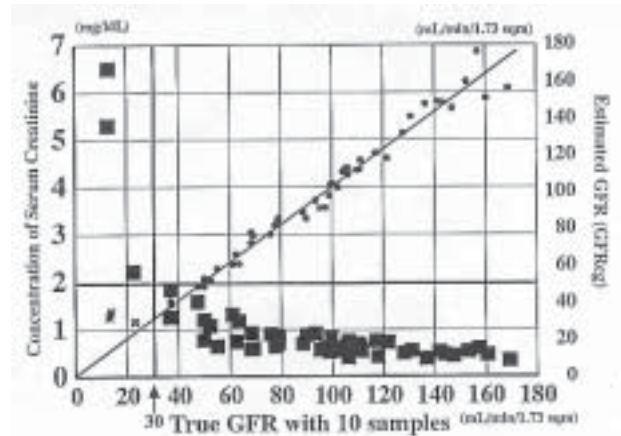
square error (RMSE), intercept and slope of the regression equation were determined. The correlation of the regression equation was considered to be significant, if the p-value was less than 0.05. In addition, agreement between true GFR and GFR determined by each sample method was assessed.<sup>20</sup>

## RESULTS

Correlation coefficients for all method were higher than 0.90 (Table 1, Fig. 2). The best regression equation among two-sample methods was obtained in sample time at 120 min and 240 min ( $r = 0.982$ ,  $RMSE = 7.2642$ ). The Christensen-Groth's single-sample method was closer in RMSE than any of the two-sample method. The multi-sample method with 5 samples from 120 min to 300 min was closest in RMSE. However, each correlation coefficient of  $GFR_{cg}$ ,  $GFR_{2s}$  (120 min and 240 min) and  $GFR_{5m}$  was not significantly different.

Agreement analyses in GFR ( $GFR_t - \text{estimated GFR}$ ) in 49 patients with a GFR from 12.7 to 168.9  $\text{ml}/\text{min}/1.73 \text{ m}^2$  showed that the standard deviation of difference (SD) in the Christensen and Groth's method was 6.513  $\text{ml}/\text{min}/1.73 \text{ m}^2$ , which was closer than that for two-sample methods (Table 2). The SD of GFR difference in the 5-sample method from 120 to 300 min was 6.075  $\text{ml}/\text{min}/1.73 \text{ m}^2$ , which was closest among all compared methods. However,  $GFR_{cg}$  was scattered below the average GFR of 30  $\text{ml}/\text{min}/1.73 \text{ m}^2$  and above the average GFR of 140  $\text{ml}/\text{min}/1.73 \text{ m}^2$  (Fig. 3A). On the contrary,  $GFR_{2s}$  at 120 min and 240 min was widely scattered above the average GFR of 120  $\text{ml}/\text{min}/1.73 \text{ m}^2$  (Fig. 3B). The  $GFR_{5m}$  from 120 to 300 min also showed slight scattering over the average GFR of 150  $\text{ml}/\text{min}/1.73 \text{ m}^2$  (Fig. 3B).

Figure 4 shows the scatter plots of serum creatinine and  $GFR_{cg}$  against  $GFR_t$ . The relationship between  $GFR_t$  and serum creatinine was non-linear and hyperbolic. The regression equation between the  $GFR_t$  and the  $GFR_{cg}$  in the figure was obtained in 46 patients with the  $GFR_t$  above



**Fig. 4** Superimposed scatter plots of true GFR ( $GFR_t$ ) against serum creatinine (■, the left x-axis) and estimated GFR ( $GFR_{cg}$ ) by Christensen and Groth's method (×:  $GFR > 30 \text{ ml}/\text{min}/1.73 \text{ m}^2$  and □:  $GFR \leq 30 \text{ ml}/\text{min}/1.73 \text{ m}^2$ , the right x-axis). The straight line between  $GFR_t$  and  $GFR_{cg}$  shows the regression line ( $y = 2.5269 + 1.0011x$ ,  $r = 0.9878$ ,  $RMSE = 5.5386 \text{ ml}/\text{min}/1.73 \text{ m}^2$ ) in 46 patients with GFR above 30  $\text{ml}/\text{min}/1.73 \text{ m}^2$  (□). A thick line on the x-axis indicates 30  $\text{ml}/\text{min}/1.73 \text{ m}^2$  of GFR. A thick line on the y-axis indicates serum creatinine 2.0  $\text{mg}/\text{dL}$ , which seems to cross the point of 30  $\text{ml}/\text{min}/1.73 \text{ m}^2$   $GFR_t$  on the x-axis.

30  $\text{ml}/\text{min}/1.73 \text{ m}^2$ . The regression equation is closer than that in 49 patients including 3 patients with the  $GFR_t$  below 30  $\text{ml}/\text{min}/1.73 \text{ m}^2$ . The  $GFR_{cg}$  is obvious in over-estimation of the  $GFR_t$  below a  $GFR_t$  of 30  $\text{ml}/\text{min}/1.73 \text{ m}^2$  of the regression line. The level of 30  $\text{ml}/\text{min}/1.73 \text{ m}^2$  of the GFR on the x-axis appeared to correspond to 2.0  $\text{mg}/\text{dL}$  of serum creatinine on the y-axis.

## DISCUSSION

Mathematical algorithms on the determination of GFR based on plasma clearance following a single injection of renal markers has been established 20 and 30 years ago.<sup>15,17,19,21,22</sup> The exponential curve fit of multiple plasma

samples following a single injection of radioactive markers is proved alternative to steady infusion of inulin.<sup>23,24</sup> The accuracy of the estimate based on this mathematical model is affected by the following radiopharmaceutical and pharmacokinetic properties: (1) dependency on elimination of the radiotracer by glomeruli in the kidney, (2) free filtration through glomeruli and no reabsorption in the renal tubules, (3) radiochemical purity, (4) binding to serum protein and red blood cells and (5) volume of distribution in a patient. In comparison with inulin as a gold standard GFR marker, the average renal clearance ratio of <sup>99m</sup>Tc-DTPA to inulin was 0.97.<sup>23</sup> Nonetheless, the plasma clearance of <sup>99m</sup>Tc-DTPA correlated well with the renal clearance of inulin, but overestimated it by 3.5 ml/min on average.<sup>23</sup> The overestimation of <sup>99m</sup>Tc-DTPA clearance was more pronounced in normal subjects.<sup>24</sup> On the contrary, protein binding of <sup>99m</sup>Tc-DTPA tended to cause underestimation of GFR in the presence of good renal function.<sup>25</sup> Accuracy may depend on the supplier of the radiopharmaceutical.<sup>25,26</sup> The GFR determined by the exponential curve fit following a single injection of <sup>99m</sup>Tc-DTPA may not be identical to GFR determined by continuous infusion of inulin. But the plasma clearance technique is considered to be accurate enough to measure GFR in subjects with renal dysfunction. The method, however, is not practical in a routine study. As a matter of fact, the fewer sample is, the simpler the procedure. In this context, the single- and/or two-sample methods have been recommended as the methods of choice for the determination of GFR following a single injection of glomerular filtration markers in routine practice.<sup>2,5-7</sup>

The single-sample method maintains consensus as the recommended as the first choice method of GFR.<sup>2</sup> However, this method proved inaccurate in patients with severe renal failure of GFR below 20–30 ml/min/1.73 m<sup>2</sup>.<sup>8-10</sup> For such patients, the appropriate sample time is indicated as 24 hours rather than the standard sample time of 3 to 4 hours.<sup>9,10</sup> In the present study, the single-sample method tended to give an apparently higher GFR value than true GFR, for a ranged below 30 ml/min/1.73 m<sup>2</sup>. These results agree with previous reports.<sup>8-13</sup>

The two-sample method in a mono-compartment model was proved more accurate in GFR determination than the single-sample method.<sup>11-13</sup> The appropriate sample times are reported to be at 120 and 240 min following the injection.<sup>11-13,27</sup> In the present study, the 95% limit of agreement between true GFR and estimated GFR from two samples at 120 and 240 min respectively was also the closest. The difference between GFR<sub>t</sub> and GFR<sub>2s</sub> was greater than that between GFR<sub>t</sub> and GFR<sub>cg</sub>. This result was due to some scattering in GFR above 120 ml/min/1.73 m<sup>2</sup>. In the two-sample method based on the mono-compartment model, the difference between uncorrected GFR and true GFR appears to be greater in range of high GFR than low GFR.<sup>19</sup> Although it has not been indicated that the two-sample method is unreliable in a hyperfiltrative

state of the kidney, our results suggest that the two-sample method may limit in accuracy in a range of GFR over 120 ml/min/1.73 m<sup>2</sup>. On the contrary, the two-sample method was more accurate than the single-sample method, even for a GFR below 30 ml/min/1.73 m<sup>2</sup>. These results indicate that the two-sample method is preferable for a patient with severe renal dysfunction in whom GFR is expected to be below 30 ml/min/1.73 m<sup>2</sup>. In such cases, the single sample method needs a delayed blood sample at 24 hour-injection for proper estimation of GFR.<sup>2,10</sup> The two-sample method is useful in shortening the sampling time and eliminating a revisit to the outpatient clinic on the day following the test for patients with severe renal failure.

The present study suggests that the accuracy of each sample method for the measurement of GFR may depend on the preserved renal function of the patients at the time of the test. The differences between true GFR and GFR estimated by simplified methods were insignificant, but either the single- or the two-sample method should be chosen for determining GFR in routine practice as accurately and simply as possible. Serum creatinine is the most employed parameter in the assessment of renal function in daily clinical practice but is not sensitive in detecting mild to moderate renal dysfunction.<sup>28-30</sup> Our results (Fig. 4) may suggest that the serum creatinine concentration is a good indicator for choosing either the single- or the two-sample method in a routine renal function study with <sup>99m</sup>Tc-DTPA. It means that the two-sample method should be chosen, when the serum plasma level is lower than 2.0 mg/dl. Although the single-sample method is considered the first choice in a routine practice, it must be effective in the determination of GFR above 30 ml/min/1.73 m<sup>2</sup>, presumably serum creatinine lower than 2.0 mg/dl. However, whether the serum creatinine level of 2.0 mg/dl is appropriate or not for choice of either the single- or the two-sample method may need further clinical study, because a serum creatinine is affected by several factors such as muscle mass, age, gender and race.<sup>31,32</sup>

## CONCLUSION

The simplified sample methods for the determination of GFR following a single-injection with <sup>99m</sup>Tc-DTPA exhibited high accuracy. As a matter of fact, the Christensen and Groth's single sample method is the first choice for the measurement of GFR in clinical practice. The two-sample method at 120 min and 240 min is chosen selectively for a patient with severe renal failure. The serum creatinine concentration at the time of the test may help for the choice of either the single- or the two-sample method.

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