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Correlation and concordance of glomerular filtration rate from renal scintigraphy and modified modification of diet in renal disease equation

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► ***Original article***

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ABSTRACT

***Background*:** The aim of this study is to find the correlation of the glomerular filtration rate (GFR) measured using Gate's method and modified Modification of Diet in Renal Disease (mMDRD) equation. ***Materials and Methods*:** Patients who received Tc-99 DTPA renal scintigraphy were enrolled in the study. The GFR obtained from Gate's method via renal scintigraphy and mMDRD equation from plasma creatinine were recorded. A comparison and correlation between the GFRs based on different time intervals was analyzed. ***Results*:** Sixty patients were enrolled in this study. They were divided into four groups based on different time intervals between radionuclide renal scintigraphy and plasma creatinine test. Group 1, 2, 3, and 4 consisted of patients whose plasma creatinine tests checked within ± 3 days, ± 4–7 days, ± 8–14 days, and ± 15–31 days from renal scintigraphy, respectively. Correlation coefficient of group 1, 2, 3, and 4 showed 0.87 ($p < 0.001$), 0.79 ($p = 0.007$), 0.67 ($p = 0.009$), and 0.58 ($p = 0.012$), respectively. ***Conclusion*:** Significant correlations were noticed in the GFR calculated from Gate's method and by mMDRD equation. It was found that the shorter the time interval between plasma creatinine test and radionuclide renal scintigraphy, the higher the correlation was.

INTRODUCTION

Chronic kidney disease (CKD) is a global issue and a systematic review study investigating CKD prevalence in general populations found a consistent estimated worldwide CKD prevalence of 11–13% [1]. In Taiwan, the diagnoses that account for the major portion of medical costs were related to acute renal failure and CKD. Early diagnosis of CKD can reduce medical expenditures and improve the quality of life. Glomerular filtration rate (GFR), which describes the flow rate of filtered fluid that takes place in the glomeruli, is the main strategy used to diagnose and monitor renal disease. Notably, using inulin clearance measured GFR nowadays is still considered the gold standard [2]; however, it is not routinely used clinically, because of its high cost and unavailability.

Plasma creatinine test is an easy method to monitor renal function. However, the creatinine level is affected by age, gender, race, body composition, food, and drugs [3], contra-indicating the use of plasma creatinine value as the only way to evaluate the level of renal function. Therefore, the guidelines established by the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation suggest the Modification of Diet in Renal Disease (MDRD) equation [4] to estimate GFR in clinical settings, as the equations modify some of the factors relevant to addressing the problem. However, the MDRD equation is not suitable for the Asian population [5]. Ma *et al.* modified the MDRD equation (referred to as mMDRD) [6], finding using the equation to evaluate GFR better than using radionuclide renal scintigraphy [7].

Radionuclide renal scintigraphy with Technetium-99m (Tc-99m) diethylenetriaminepentaacetic acid (DTPA) using Gate's method is a common and convenient method to calculate the GFR [8]. This examination provides valuable information such as the renal blood flow, difference between obstructive or non-obstructive hydronephrosis, evaluation of unilateral renal function, and diagnosing ectopic kidney, congenital abnormality, mass, etc. However, past studies have questioned the accuracy of Gate's method for measuring the GFR. Compared to inulin as a reference standard, using radionuclide renal scintigraphy to calculate the GFR may result in overestimation for low GFR levels and underestimation for high levels [9]. Researchers have confirmed this finding [10]. A recent study suggests

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that renal scintigraphy combined with biochemical tests is a useful method for early detection of chronic renal failure in patients [11].

Moreover, patients who suffer from renal problems (e.g., hydronephrosis, urolithiasis, malignant neoplasm of urinary system, etc.) receive radionuclide renal scintigraphy and are advised to check plasma creatinine level regularly. Compared to the radionuclide renal scintigraphy, which takes about half an hour during examination and for which the waiting period is long, checking the plasma creatinine level is relatively easy and fast. However, there are interval differences between checking the creatinine level and radionuclide renal scintigraphy. The present study attempts to find a correlation between the GFR measured by radionuclide renal scintigraphy and calculated by mMDRD equation based on the different time intervals.

MATERIAL AND METHODS

Patients

The present study was retrospective; it analyzed the medical records of 60 patients from nuclear medicine databases during September 2018 to August 2019 in Kaohsiung Medical University Hospital. The inclusion criteria were patients who (i) were more than 20 years, (ii) had received a radionuclide renal scintigraphy; and (iii) had laboratory tests for plasma creatinine clearance done within 31 days, apart from the renal scintigraphy. The exclusion criteria included history of previous renal transplantation and patients who had one unilateral kidney. The study review process was approved by the Institutional Review Board of Kaohsiung Medical University Hospital [KMUHIRB-E (I)-20200250].

Radionuclide renal scintigraphy

All participating patients were encouraged to drink about 300 ml of water 20 minutes before the scintigraphic scan. The scans were performed on a gamma camera (E. Cam, Siemens, Erlangen, Germany), equipped with low-energy, high-resolution collimators. Before injecting radiopharmaceutical, the pre-syringe radioactivity counts were acquired with a one-minute static image by placing a syringe containing 185-222 MBq (5-6 mCi) Tc-99m DTPA (Global Medical Solutions, Kaohsiung, Taiwan) on the surface of the collimator.

Each patient was in a supine position. After the bolus intravenous injection of Tc-99m DTPA was administered, the dynamic image was acquired immediately in a 128 × 128 frame matrix for approximately 22 minutes divided into three periods. The first period was of 32 seconds at an acquisition rate of 2 seconds per frame, the second was of 320 seconds at an acquisition rate of 20 seconds per frame, and the last period was of 960 seconds, with a frame rate of 30 seconds. The post-syringe counts were acquired through the one-minute static image, which was the same as the pre-syringe counting.

The regions of interest (ROI) were manually drawn for each kidney by an experienced nuclear medicine technician. The semilunar ROI for background evaluation was automatically set in the outer-lower aspect of each kidney (figure 1). GFR was calculated by Gate's formula (1).

$$GFR = \left[\frac{(RC - R_bC)}{e^{-udR}} + \frac{(LC - L_bC)}{e^{-udL}}\right] \times 100 \times 9.8127 - 6.82519 \quad (1)$$

Where RC: right kidney scintigraphic counts, R_bC: right background scintigraphic counts, LC: left kidney scintigraphic counts, L_bC: left background scintigraphic counts, dR: right kidney depth, dL: left kidney depth, $Count_{pre}$: pre-syringe scintigraphic counts, $Count_{post}$: post-syringe scintigraphic counts, u: attenuation coefficient of Tc-99m in soft tissue (i.e. 0.153 cm^{-1}), and e: Euler's number.

Estimated GFR (eGFR)

The patients' eGFRs were obtained from plasma creatinine level using mMDRD equation (2) [6]:

$$mMDRD\left(\frac{ml}{\min 1.73m^2}\right) = 175 \times P_{Cr}^{-1.234} \times Y_r^{-0.179} \times (0.79\ if\ female) \quad (2)$$

Where P_{Cr}: plasma creatinine level (in mg/dL); Yr: patient's age;

P_{Cr} was measured on a Beckman coulter analyzer in the laboratory in the Department of Laboratory Medicine, Kaohsiung Medical University Hospital, with the normal reference range of 0.64–1.27 mg/dL for males and 0.44-1.03 mg/dL for females.

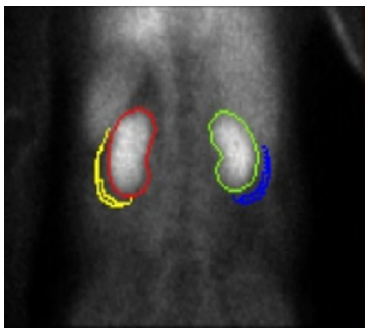


Figure 1. Demonstration of the selected ROI while calculating the GFR after the radionuclide renal scintigraphy. The ROI was drawn manually for each kidney via the posterior acquisition for the 62-year-old man. The semilunar ROI in the outer-lower aspect of each kidney was automatically set for the background subtraction. The calculated GFR of the patient by Gate's method was 45.6 mL/min.

Subgrouping

All the data was divided into four groups based on the different intervals between plasma creatinine level test and radionuclide renal scintigraphy performed on the same patient, as follows: Group 1: patients' plasma creatinine tests were performed within ± 3 days from renal scintigraphy (N=18).

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Group 2: patients' plasma creatinine tests were performed within ± 4–7 days from renal scintigraphy (N=10). Group 3: patients' plasma creatinine tests were performed within ± 8–14 days from renal scintigraphy (N=14) and Group 4: patients' plasma creatinine tests were performed within ± 15–31 days from renal scintigraphy (N=18).

Statistical analysis

The Kolmogorov-Smirnov test was used to test the normality of the different variables. Continuous variables were presented as mean ± standard deviation. Regression analysis was used to compare the relationship between the GFR calculated by Gate's method and by mMDRD equation (eGFR). The scatter diagram and regression line were achieved. Statistical analysis was performed using the MedCalc Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). All statistical tests were two-sided and a two-tailed $p < 0.05$ was considered significant.

RESULTS

The clinical characteristics are summarized in table 1. There were 35 men (58%) and 25 women (42%), with a mean age of 61.1 years (ranging from 21 to 88). The mean value of plasma creatinine was 1.56 ± 1.23 mg/dL. The average of GFR by Gate's method was 47.4 ± 19.5 ml/min and eGFRs estimated by mMDRD equation was 61.7 ± 29.2 ml/min/1.73m^2.

The results of all the four groups are shown in table 2. There were 18 patients in group 1, 10 in group 2, 14 in group 3, and 18 in group 4. The GFRs were calculated by Gate's method in groups 1, 2, 3, and 4 as 42.9 ± 19.8, 53.4 ± 21.8, 40.2 ± 14.8, and 54.2 ± 19.3, respectively. The eGFRs were 56.7 ± 29.9, 81.2 ± 38.9, 51.0 ± 20.9, and 64.5 ± 23.8, respectively.

The scatter plot and regression lines are shown in figure 2. The correlation coefficients of Group 1 and Group 2 were 0.87 (p<0.001) and 0.79 (p=0.007) respectively, while those of Group 3 and 4 were 0.67 (p=0.009) and 0.58 (p=0.012), respectively.

Table 1. Characteristics of all 60 patients underwent Tc-99m DTPA renal scintigraphy.

Variable	n (%)	Mean ± SD
Age		61.1 ± 14.1
Sex		
Male	35(58)	
Female	25(42)	
Body height (cm)		162.2 ± 8.6
Body weight (kg)		67.0 ± 13.1
Plasma creatinine (mg/dl)		1.56 ± 1.2
eGFR (ml/min/1.73m^2)		61.7 ± 29.2
Gate's GFR (ml/min)		47.4 ± 19.5

GFR, glomerular filtration rate; eGFR, estimated GFR by modified Modification of Diet in Renal Disease study equation; Gate's GFR, calculated GFR by radionuclide renal scintigraphy using Gate's method; SD, standard deviation.

Table 2. Differences between GFR measured by Gate's method and eGFR by mMDRD in patients of different groups.

Group	Patient number	GFR (ml/min)	eGFR (ml/min/1.73m^2)	Correlation coefficient	*p* value
1	18	42.9 ± 19.8	56.7 ± 29.9	0.87	< 0.001*
2	10	53.4 ± 21.8	81.2 ± 38.9	0.79	0.007*
3	14	40.2 ± 14.8	51.0 ± 20.9	0.67	0.009*
4	18	54.2 ± 19.3	64.5 ± 23.8	0.58	0.012*

GFR, glomerular filtration rate; eGFR, estimated GFR by modified Modification of Diet in Renal Disease study equation; mMDRD, modified Modification of Diet in Renal Disease study equation. * statistically significant

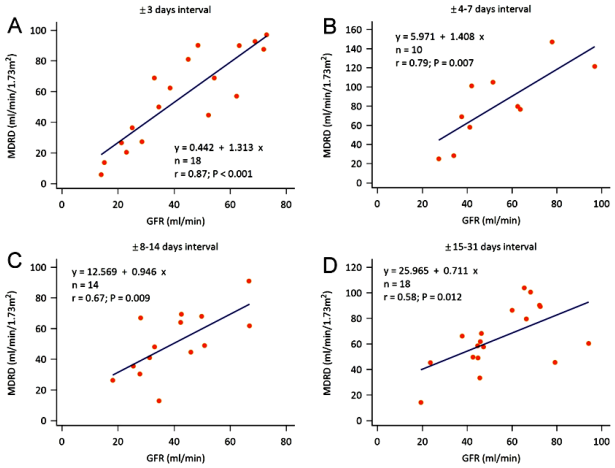


Figure 2. The linear regression of the GFR measured by Gate's method and eGFR by mMDRD equation in patients belonging to different groups. **A,** eighteen patients enrolled in Group 1. Correlation coefficient was 0.87 (p < 0.001). **B,** ten patients enrolled in Group 2. Correlation coefficient was 0.79 (p = 0.007). **C,** fourteen patients enrolled in Group 3. Correlation coefficient was 0.67 (p = 0.009). **D,** eighteen patients enrolled in Group 4. Correlation coefficient was 0.58 (p = 0.012). The regression lines for each ground are shown respectively.

DISCUSSION

The results showed that GFRs measured by radionuclide renal scintigraphy were well correlated with the GFRs calculated with the mMDRD equation through plasma creatinine checking. In our patient groups, the value of the correlation coefficient of Group 1 was higher than that of the other three groups. The coefficient value declined as the time interval between plasma creatinine check and renal scintigraphy increased. This result has greater implications for the time interval of the two examinations and indicates that more factors that can change this relationship should be considered. It is probable that the disease may progress or some treatment plan may change the creatinine level [3]. Although mMDRD equation corrected some relevant factors for increased accuracy, it still changed with the creatinine level. We consider that the creatinine level changes multiple times in a short interval; thus, using renal scintigraphy to evaluate the GFR might offer more stable and accurate information in a

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clinical setting.

Besides, compared to the GFRs estimated by the mMDRD formula as the reference standard, the GFRs calculated by Gate's method in our patient's group were underestimated at high GFRs and overestimated at low levels. In past studies, researchers have confirmed the results and found that GFRs evaluated by the formula are close to the real GFRs [9]. The Cockcroft-Gault (CG) equation [12] and the MDRD equation are both commonly used in clinical settings. However, these two equations, developed for Caucasian populations, might not suit Asian populations. Zuo *et al.* indicated that both the equations were underestimated in high GFRs and overestimated in low GFRs in CKD patients [5]. Later, Ma *et al.* modified the MDRD equation (i.e., mMDRD) [6], suggesting that the GFRs estimated by the mMDRD equation are better than those evaluated by the Gate's method, with radionuclide renal scintigraphy [7]. Hence, we chose the mMDRD equation as the reference method for the present study. Additionally, some researchers implied that the CG equation was unsuitable for evaluating GFRs in the patient population in Taiwan, especially for young patients and those with obesity and metabolic syndrome [13]. Further, since both the equations were developed on CKD patients, we must consider this while dealing with non-CKD patients in clinical settings.

The advantages of the radionuclide renal scintigraphy method include good reproducibility, absence of the need to collect a blood sample multiple times and making the examination easily and widely usable in clinical settings. Further, the GFRs for each kidney can also be available due to separate ROI collection. However, the accuracy of GFRs may vary [9, 10]. It needs to be reiterated that there are some technical problems which may lead to errors in radionuclide renal scintigraphy, such as accurate counting rate in kidney and background, renal depth, scintigraphic counts pre- and post-injection and linear attenuation coefficient. These factors may influence the accuracy of the calculated GFR [8].

Precise ROI and renal depth can improve the accuracy of the GFR calculation; but motion and some renal diseases (e.g., masses or hydronephrosis) may cause difficulty in depicting the margin of the kidneys. And the renal depth calculated by the formula is not suitable for ectopic kidneys or post-renal transplantation. Using single-photon emission computed tomography combined computed tomography (SPECT/CT) can help us to solve this issue, but additional patient's radiation dose should be taken into consideration. Automatic ROI setting can reduce the inter-observer errors while drawing the kidney and background on the images [14]. Direct measurement of the renal depth by ultrasound and lateral view during image acquisition can resolve this problem and increase the accuracy of GFR measurement [15].

The limitations of the current study were its being of retrospective design, and its relatively small sample size. Further confirmatory experiments may be conducted with a prospective study design and larger study population.

CONCLUSION

It was noted that the shorter the time interval between plasma creatinine tests and radionuclide renal scintigraphy, the higher was the correlation in GFRs calculated using Gate's method and mMDRD equation.

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Author contribution: Conceptualization, (W-L.H) and (C-C.C); Data curation, (S-M.C); Formal analysis, (W-L.H); Investigation, (C-C.C); Methodology, (W-L.H) and (C-C.C); Resources, (S-M.C); Supervision, (C-C.C); Writing – original draft, (W-L.H); Writing – review & editing, (C-C.C).

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