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# Accuracy of glomerular filtration rate equations for chronic kidney disease patients at the G3a stage: a single-center cross-sectional study

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## Abstract

**Background:** Kidney disease improving global outcomes provided a new classification for chronic kidney disease (CKD) by subdividing the G3 stage into G3a and G3b stages based on glomerular filtration rate (GFR) in 2012. Currently, a few methods are used to evaluate GFR, including measured GFR (mGFR) and estimated GFR (eGFR). One of the mGFR was <sup>99m</sup>Tc-DTPA scintigraphy method and eGFR using GFR equations were used clinically. Equations were modification of diet in renal disease (MDRD), chronic kidney disease epidemiology collaboration (CKD-EPI), and Chinese adapted MDRD (C-MDRD). This study assessed the accuracy of three different equations for estimated glomerular filtration rate (eGFR) with mGFR using DTPA scintigraphy method as the standard in a population of Chinese chronic kidney disease patients at the G3a stage.

**Results:** One hundred and twenty-two patients (age  $52.0 \pm 15.6$  years, 69 were male) were determined as CKD stage 3 based on mGFR. Patients were divided into G3a (47 patients) and G3b (75 patients) subgroups. Bias between eGFR for CKD-EPI and reference mGFR was 0.92 mL/min and 95% limits of agreement was  $-38.82$  to  $40.67$  mL/min. Bias between eGFR for C-MDRD and mGFR was 3.76 and 95% limits of agreement was  $-39.32$  to  $46.85$  mL/min. Bias between eGFR for MDRD and mGFR was 3.53 and 95% limits of agreement was  $-43.35$  to  $50.4$  mL/min. The CKD-EPI equation showed better diagnostic value with a greater area under the receiver operating characteristic curve (AUC: 0.763). AUC for MDRD and C-MDRD were 0.75 and 0.757, respectively.

**Conclusions:** There were no obvious advantages in accuracy, sensitivity, and specificity for the diagnosis of patients at the G3a stage using the CKD-EPI equation.

**Keywords:** G3a stage, Glomerular filtration rate equations, Accuracy, Chronic kidney disease

## Background

In 2012, kidney disease improving global outcomes provided a new classification for chronic kidney disease (CKD) by subdividing the G3 stage into G3a and G3b stages based on glomerular filtration rate (GFR). GFR for G3a is between 45 and 59 mL/min and GFR for G3b is

between 30 and 44 mL/min. The risk for end-stage renal disease and death increased for patients at G3b more so than for patients at G3a. Go et al. reported the adjusted hazard ratio for death was 1.2 for patients at G3a (95% confidence interval (CI) 1.1–1.2) and 1.8 at G3b (95% CI 1.7–1.9) [1]. Over a median follow-up of 2.98 years, rates per 100 patient-years for end-stage renal disease were lower for G3a than G3b, at 0.6 (95% CI 0.1–1.0) vs. 1.4 (95% CI 0.8–2.1). Death prior to end-stage renal disease for G3a was 2.2 (95% CI 1.2–3.1;  $p < 0.001$ ), which is lower than G3b, at 4.4 (95% CI 3.3–5.6;  $p < 0.001$ ) [2].

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Following from these classifications, it is important that patients are accurately assessed for G3 staging.

Currently, a few methods are used to evaluate GFR, including measured GFR (mGFR) and estimated GFR (eGFR). mGFR is determined by analysis of the clearance of some exogenous markers, such as inulin, or of alternative exogenous markers, such as iothalamate, EDTA, diethylene triamine pentaacetic acid (DTPA), and iothexol. These methods are, however, invasive, inconvenient, and expensive, and are unsuitable for use in routine clinical practice [3]. The most commonly used creatinine-based formulas include modification of diet in renal disease (MDRD) [4], chronic kidney disease epidemiology collaboration (CKD-EPI) [5], and the Chinese adapted MDRD equation (C-MDRD), the latter of which was validated as being more accurate than other MDRD equations for people of Chinese origin [6].

In this study, we compared the accuracy of eGFR using three equations and mGFR as the standard in Chinese CKD patients at the G3a stage.

## Methods

### Study design

This study was conducted at The First Affiliated Hospital of Zhengzhou University between June 2013 and July 2014. It was a cross-sectional study performed at a single center. mGFR based on  $^{99m}\text{Tc}$ -DTPA scintigraphy and eGFR using the GFR equations detailed below were assessed. Bias, sensitivity, and specificity of eGFR were analyzed with mGFR in participants at the G3a stage. The study was approved by the Review Board of The First Affiliated Hospital of Zhengzhou University and all participants provided informed consent in written format.

### Population

Chinese adult inpatients with CKD between the ages of 18 and 80 years were included. Patients who were not at the G3 stage based on mGFR were excluded. CKD and its stages were defined according to K/DOQI guidelines: (1) renal damage >3 months, established by structural or functional damage, with or without decrease in GFR, shown by histological anomalies and renal damage markers, including those found in blood, urine, or images; or (2) GFR <60 mL/min/1.73 m<sup>2</sup> >3 months, with or without renal damage [7]. CKD was divided into five stages, including G3a and G3b stages.

### Studies

Fasting serum creatinine,  $^{99m}\text{Tc}$ -DTPA scintigraphy, and renal sonogram studies were performed. Blood samples and gammagraphic studies were performed at The First Affiliated Hospital of Zhengzhou University by the same professionals.

Dynamic gammagraphy with  $^{99m}\text{Tc}$ -DTPA is regarded as the gold standard [8].  $^{99m}\text{Tc}$ -DTPA dynamic images were acquired using a detector of gamma camera with the patient in the supine position. Patients were injected with 200  $\mu\text{Ci/kg}$  (at least 2 mCi) of  $^{99m}\text{Tc}$ -DTPA and dynamic images were recorded in a 128  $\times$  128 matrix format every second for 1 min and every 30 s for 20 min. Relative renal function was measured in a composite image (1–3 min after injection).

GFR was estimated by serum creatinine using the CKD-EPI equation [5], the MDRD [4] equation, and the C-MDRD equation [6]. Creatinine was determined using the dry chemistry sarcosine oxidase method with traceable calibration using a Roche Cobas 8000. The normal serum creatinine level is 20–115  $\mu\text{mol/L}$ .

### Equations

$$\begin{aligned} \text{CKD-MDRD: eGFR} & \left[ \text{mL min}^{-1} (1.73 \text{ m}^2)^{-1} \right] \\ &= 186 \times [\text{Scr (mg/dL)}]^{-1.154} \\ & \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \end{aligned} \quad (1)$$

$$\begin{aligned} \text{CKD-C-MDRD: eGFR} & \left[ \text{mL min}^{-1} (1.73 \text{ m}^2)^{-1} \right] \\ &= 175 \times [\text{Scr (mg/dL)}]^{-1.234} \times \text{age}^{-0.179} \\ & \times 0.79 \text{ (if female)} \end{aligned} \quad (2)$$

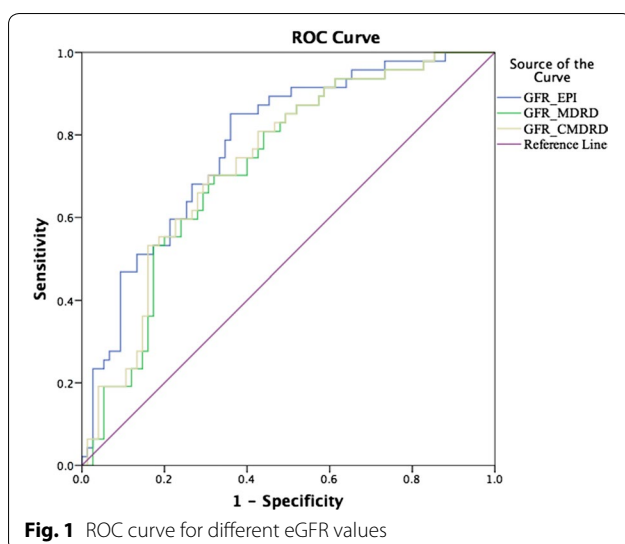
$$\begin{aligned} \text{CKD-EPI: eGFR} & \left[ \text{mL min}^{-1} (1.73 \text{ m}^2)^{-1} \right] \\ &= 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \\ & \times 0.993^{\text{age}} \times 1.018 \text{ (if female)} \_ 1.159 \text{ (if black)} \end{aligned} \quad (3)$$

(Female:  $\kappa = 0.7$ ,  $\alpha = -0.329$ ; male:  $\kappa = 0.9$ ,  $\alpha = -0.411$ ; min indicates the minimum Scr/ $\kappa$  or 1, and max indicates the maximum Scr/ $\kappa$  or 1). Scr: serum creatinine.

### Statistical analysis

Continuous data are expressed as mean  $\pm$  standard deviation or medians (25, 75%). The independent *t* test and nonparametric tests were used to compare general information between the G3a and G3b groups. Bland–Altman plots were used to compare different estimates of GFR (bias and 95% limits of agreement). Results were considered significant if  $p \leq 0.05$ . Accuracy was calculated as the proportion of eGFR within 15, 30, and 50% of measured GFR (mGFR) (P15, P30, and P50, respectively). The McNemar test was used to compare P15, P30 and P50 values of eGFR against P15, P30 and P50 values of mGFR. A receiver operating characteristic (ROC) curve was plotted and the area under the ROC curve (AUC) was calculated.

[illegible]



the C-MDRD equation, creatinine levels were measured at a single laboratory using a Hitachi 7600 analyzer and Jaffe's kinetic method. The researchers randomly selected 57 fresh-frozen plasma samples from their specimens and analyzed them at both their own laboratory and the Cleveland Clinic Research Laboratory (Cleveland, OH, USA) [6]. The creatinine value at their laboratory was calibrated to the creatinine value measured by the Cleveland Clinic Research Laboratory where the MDRD Study samples were measured. For the CKD-EPI equation, for all studies, serum creatinine was recalibrated to the standardized creatinine measurement using the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay, Hoffman-La Roche, Ltd., Basel, Switzerland) at the Cleveland Clinic Research Laboratory. For the current study, we used the Roche enzymatic method at our laboratory. Based on this, the discrepancy of eGFR caused by the creatinine value is less. However, the creatinine generation is associated with the muscle mass [11], and the influence of muscle mass on creatinine estimation cannot be completely ignored.

The biases between mGFR and eGFR using the C-MDRD and MDRD equations are greater than that using the CKD-EPI equation. One possible reason may be mGFR data obtained using different methods, which may influence the bias of the different eGFR equations. The method used to obtain mGFR should be taken into consideration when evaluating GFR estimating equations. The MDRD study used renal clearance of  $^{125}\text{I}$ -iothalamate, the Chinese study used plasma clearance of  $^{99\text{m}}\text{Tc}$ -DTPA, and the CKD-EPI group used iothalamate in the development of datasets. Chen et al. and Shanshan Dai et al. confirmed that GFR measured by  $^{99\text{m}}\text{Tc}$ -DTPA plasma clearance and  $^{99\text{m}}\text{Tc}$ -DTPA dynamic imaging

significantly overestimates GFR when compared with inulin clearance, especially in groups with low GFR, low body mass index, and a younger age [12, 13]. Soveri et al. suggested that renal clearance of DTPA, renal clearance of iothexol, and plasma clearance of inulin had sufficient accuracy (limited evidence) [14]. The muscle mass may also contributed to the accuracy of CKD-EPI equation [5]. Because the average muscle mass among healthy persons in the cohort of CKD-EPI equation was higher than other equations, and the CKD-EPI equation includes the indicators of age, race and sex and these variables are associated with muscle mass.

There are some limitations of this study. First, this is a single center study, and a multi-center study is necessary to validate the results. Second, though the CKD-EPI equation showed less bias in the G3a stage, but this equation could not avoid the disadvantage of serum creatinine, that the value of serum creatinine would be affected by the muscle mass. And Segarra et al. suggest that the use of equations based on cystatin C (CysC) is more appropriate in hospitalized patients to estimate GFR, since these equations are much less dependent on patient's nutritional status or muscle mass than the CKD-EPI equation [15]. We will explore the accuracy of eGFR equations based on CysC in the G3a stage.

## Conclusions

The bias between mGFR and eGFR using the CKD-EPI equation at the G3a stage was less than that for the other two equations. However, there was no obvious advantage in accuracy, sensitivity, and specificity for diagnosis at the G3a stage using the CKD-EPI equation.

## Additional file

**Additional file 1.** The initial data of the GFR evaluation in G3a stage. The data is all the initial information of GFR evaluation in G3a stage of Chinese patients. It includes the general information of the patients, and the measuring variables of the patients.

## Abbreviations

CKD: chronic kidney disease; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease; CKD-EPI: chronic kidney disease epidemiology collaboration; C-MDRD: Chinese adapted MDRD equation; DTPA: diethylene triamine pentaacetic acid; mGFR: measured GFR; eGFR: estimated GFR; ROC: receiver operating characteristic; AUC: area under ROC curve.

## Authors' contributions

Conceived and designed the experiments: ZZ, YD. Performed the experiments: XS, DL, LZ. Analyzed the data: YD, XS. Contributed reagents/materials/analysis tools: JX, GC, DY. Wrote the paper: YD. All authors read and approved the final manuscript.

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# Competing interests

The authors declare that they have no competing interests.

# Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information file name: GFR\_DTPA submit.xlsx, title of data: the initial data of the GFR evaluation in G3A stage. Description of data: The data is all the initial information of GFR evaluation in G3A stage of Chinese patients]. It includes the general information of the patients, and the measuring variables of the patients.

# Ethics approval and consent to participate

This study was approved by the Review Board of The First Affiliated Hospital of Zhengzhou University and the consents were acquired from the patients in written format.

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