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# Choosing an appropriate glomerular filtration rate estimating equation: role of body mass index

Jiayong Li[1†], Xiang Xu[1†], Jialing Luo[1], Wenjing Chen[1], Man Yang[2], Ling Wang[2], Nan Zhu[2], Weijie Yuan[2] and Lijie Gu[2*]

## Abstract

**Background:** We aimed to investigate the accuracy of different equations in evaluating estimated glomerular filtration rate (eGFR) in a Chinese population with different BMI levels.

**Methods:** A total of 837 Chinese patients were enrolled, and the eGFRs were calculated by three Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, three full-age spectrum (FAS) equations and two Modification of Diet in Renal Disease (MDRD) equations. Results of measured GFR (mGFR) by the 99Tcm-diathylenetriamine pentaacetic acid (99Tcm-DTPA) renal dynamic imaging method were the reference standards. According to BMI distribution, the patients were divided into three intervals: below 25th($BMI_{P25}$), 25th to 75th($BMI_{P25-75}$) and over 75th percentiles ($BMI_{P75}$).

**Results:** The medium BMI of the three BMI intervals were 20.9, 24.8 and 28.9 $kg/m^2$, respectively. All deviations from mGFR (eGFR) were correlated with BMI ($p < 0.05$). The percentage of cases in which eGFR was within mGFR ±30% (P30) was used to represent the accuracy of each equation. Overall, $eGFR_{FAS\_Cr\_CysC}$ and eGFREPI_Cr_2009 performed similarly, showing the best agreement with mGFR among the eight equations in Bland-Altman analysis (biases: 4.1 and − 4.2 mL/min/1.73$m^2$, respectively). In $BMI_{P25}$ interval, $eGFR_{FAS\_Cr}$ got − 0.7 of the biases with 74.2% of P30, the kappa value was 0.422 in classification of CKD stages and the $AUC_{60}$ was 0.928 in predicting renal insufficiency, and eGFREPI_Cr_2009 got 2.3 of the biases with 71.8% of P30, the kappa value was 0.418 in classification of CKD stages and the $AUC_{60}$ was 0.920 in predicting renal insufficiency. In $BMI_{P25-75}$ interval, the bias of $eGFR_{FAS\_Cr\_CysC}$ was 4.0 with 85.0% of P30, the kappa value was 0.501 and the $AUC_{60}$ was 0.941, and $eGFR_{FAS\_Cr\_CysC}$ showed balanced recognition ability of each stage of CKD (62.3, 63.7, 68.0, 71.4 and 83.3% respectively). In $BMI_{P75}$ interval, the bias of $eGFR_{EPI\_Cr\_CysC\_2012}$ was 3.8 with 78.9% of P30, the kappa value was 0.484 the $AUC_{60}$ was 0.919, and $eGFR_{EPI\_Cr\_CysC\_2012}$ equation showed balanced and accurate recognition ability of each stage (60.5, 60.0, 71.4, 57.1 and 100% respectively). In $BMI_{P75}$ interval, the bias of $eGFR_{FAS\_Cr\_CysC}$ was − 1.8 with 78.5% of P30, the kappa value was 0.485, the $AUC_{60}$ was 0.922. However, the recognition ability of each stage of $eGFR_{FAS\_Cr\_CysC}$ eq. (71.1, 61.2, 70.0, 42.9 and 50.0% respectively) was not as good as $GFR_{EPI\_Cr\_CysC\_2012}$ equation.

* Correspondence: lijiegu82@126.com
†Jiayong Li and Xiang Xu contributed equally to this work.
[2]Department of Nephrology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, China
Full list of author information is available at the end of the article

**Conclusion:** For a Chinese population, we tend to recommend choosing $eGFR_{FAS\_Cr}$ and $eGFR_{EPI\_Cr\_2009}$ when BMI was around 20.9, $eGFR_{FAS\_Cr\_CysC}$ when BMI was near 24.8, and $eGFR_{EPI\_Cr\_CysC\_2012}$ when BMI was about 28.9.

**Keywords:** Body mass index, Estimated glomerular filtration rate, Chronic kidney disease

## Introduction

Chronic kidney disease (CKD) is defined as a reduced glomerular filtration rate (GFR), increased urinary albumin excretion, or both, and has been recognized as an increasing public health issue worldwide [1]. Rising prevalence, poor outcomes, and high costs of CKD have led to considerable social and economic burdens in both developed and developing countries. Prevalence of CKD is estimated to be 8–16% worldwide [2]. In 2017, there were 132.3 million [95% confidence interval (95% CI) 121.8 to 143.7] people were diagnosed as CKD in China [3]. Therefore, the early prevention and accurate detection of CKD are particularly important.

Ideally, GFR should be measured. Measured (m) GFR gives an accurate assessment of kidney function and avoids confounding by interactions with variables, such as age or weight. Tc-99 m DTPA renal dynamic scintigraphy is a useful tool for clinicians in assessing renal function [4]. Because of the complicated process and nuclear pollution of above method, estimated GFR (eGFR) was considered as a convenient and no-invasive means which had been widely used in clinical diagnosis and treatment.

Many eGFR equations are based on the creatinine or/and cystatin C concentrations in serum. However, multiple factors such as muscle mass, weight, race, sex, gender and other individual differences affect the levels of serum creatinine [5]. Performance of Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations remains suboptimal for estimating GFR in obese populations [6, 7]. Serum cystatin C also has the disadvantage in obesity population. Enlarged adipose tissues lead to elevation of serum cystatin C [8]. In fact, overweight and obesity account for a large proportion in CKD, while the muscle percentage is not synchronized with body weight. Therefore, the accuracy of eGFR assessments is affected by irregular fluctuation in creatinine and cystatin C.

How to choose an appropriate eGFR equation which can estimate renal function accurately? We used the body mass index (BMI) as the breakthrough point. There are many researches on the comparison of different eGFR equations, but still lack of researches on which special equation should be recommended in certain BMI range. In the present study, we assessed the accuracy of eight eGFR equations [CKD-EPI cr_2009 ($eGFR_{EPI\_Cr\_2009}$) [9], CKD-EPI cys_2012 ($eGFR_{EPI\_CysC\_2012}$) [1], CKD-EPI cr_cys_2012 ($eGFR_{EPI\_Cr\_CysC\_2012}$) [1, 10]], three full age spectrum (FAS) equations ($eGFR_{FAS\_Cr}$, $eGFR_{FAS\_CysC}$, and $eGFR_{FAS\_Cr\_CysC}$) [11], abbreviated_MDRD ($eGFR_{a\_MDRD}$) [12], and Chinese_MDRD ($eGFR_{c\_MDRD}$) [13] compared with GFR measurement using 99Tcm-DTPA scintigraphy. Our research aimed to identify which equation performed better at estimating GFR and ideally predicting the CKD stage in the corresponding BMI interval, and finally, provide credible eGFR in certain BMI intervals to the clinicians.

## Methods

### Participants

A total of 904 patients who underwent GFR measurement using 99Tcm-diathylenetriamine pentaacetic acid (99Tcm-DTPA) scintigraphy from January 2016 to September 2017 in Shanghai General Hospital, were observed. Exclusion criteria included amputation, pregnant women, obstructive nephropathy, solitary kidney or a single kidney, urinary tract infection, acute kidney injury, any history of malignancy or kidney surgery, hyperthyroidism, use of antibacterial agents within 2 weeks, and malignant hypertension. Finally, a total of 837 patients were enrolled in this study. General characteristics were included such as sex, age, body mass index (BMI), serum creatinine, serum cystatin C, measured GFR (mGFR) and the situation of basic diseases. BMI was calculated following the equation: BMI ($Kg/m^2$) = weight (kg) /$height^2$ (m). Three intervals were divided based on BMI percentiles, percentile 25% ($BMI_{P25}$), percentile 25% ~ 75% ($BMI_{P25-75}$) and percentile 75% ($BMI_{P75}$). Research has been conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai General Hospital. Written informed consent was obtained from all participants. All methods were carried out in accordance with the relevant guidelines and regulations.

### Measurement of reference GFR (mGFR)

The mGFR was measured by gate's method of radionuclide renal dynamic imaging. The instrument used Siemens Excel Evo SPECT which equipped with low energy and high resolution parallel hole collimator, energy peak 140 keV, window width ± 20%. 99TcmDTPA

(radiochemical purity, > 95%; percentage of 99TcmDTPA bound to plasma protein, < 5%) was provided by Shanghai Atom Kexing Pharmaceutical Co., Ltd., China. Determined the mGFR by gate's method.

### Definition of renal insufficiency and CKD classification

The definition of renal insufficiency and CKD classification were referred to the 2012 KDIGO clinical practice guideline [1]. Renal insufficiency was defined as mGFR < 60 mL/min/1.73 $m^2$. CKD was classified into five stages based on the mGFR values as follows: stage 1, mGFR ≥90 mL/min/1.73 $m^2$; stage 2, 60 mL/min/1.73 $m^2$ ≤ mGFR < 90 mL/min/1.73 $m^2$; stage 3, 30 mL/min/1.73 $m^2$ ≤ mGFR < 60 mL/min/1.73 $m^2$; stage 4, 15 mL/min/1.73 $m^2$ ≤ mGFR < 30 mL/min/1.73 $m^2$; stage 5, mGFR < 15 mL/min/1.73 $m^2$.

### Measurement of serum creatinine (Scr) and cystatin C (CysC) levels and GFR-estimating equations

Blood samples were obtained after the patients had fasted for 12 h. Both Scr and CysC were measured by an automatic biochemical autoanalyzer (Cobas 8000; Roche Products Ltd. Basel, Switzerland), used original matching assay kit (Roche Diagnostics, Mannheim, Germany). Based on the Scr, eGFR was calculated by CKD-EPI Cr_2009 ($eGFR_{EPI\_Cr\_2009}$) [9], FAS Cr ($eGFR_{FAS\_Cr}$) [11], abbreviated _MDRD ($eGFR_{a\_MDRD}$) [12], and Chinese _MDRD ($eGFR_{c\_MDRD}$) [13]. Based on the CysC, eGFRs was calculated by CKD-EPI CysC_2012 ($eGFR_{EPI\_CysC\_2012}$) [1] and FAS CysC ($eGFR_{FAS\_CysC}$) [11]. Based on both SCr and CysC, eGFR was calculated by CKD-EPI Cr_CysC_2012 ($eGFR_{EPI\_Cr\_CysC\_2012}$) [10] and FAS Cr_CysC ($eGFR_{FAS\_Cr\_CysC}$) [11].

The equations used in the study population (with no correction for race and ethnicity) were the following (SCr indicates serum creatinine):

(1) CKD-EPI Cr_2009 equation:

$$\begin{aligned}
&\text{Female, SCr} \le 61.88\mu\text{mol/L}: \text{eGFR} \\
&\quad = 144 \times (\text{SCr}/61.88)^{-0.329} \times 0.993^{\text{age}} \\
&\qquad \times (1.159 \text{if black}) \\
&\text{Female, SCr} > 61.88\mu\text{mol/L}: \text{eGFR} \\
&\quad = 144 \times (\text{SCr}/61.88)^{-1.209} \times 0.993^{\text{age}} \\
&\qquad \times (1.159 \text{if black}) \\
&\text{Male, SCr} \le 79.56\mu\text{mol/L}: \text{eGFR} \\
&\quad = 141 \times (\text{SCr}/79.56)^{-0.411} \times 0.993^{\text{age}} \\
&\qquad \times (1.159 \text{if black}) \\
&\text{Male, SCr} > 79.56\mu\text{mol/L}: \text{eGFR} \\
&\quad = 141 \times (\text{SCr}/79.56]^{-1.209} \times 0.993^{\text{age}} \\
&\qquad \times (1.159 \text{if black})
\end{aligned}$$

(2) CKD-EPI CysC_2012 equation:

$$\begin{aligned}
&\text{Female, SCr} \le 61.88\mu\text{mol/L and SCys} \le 0.8\text{mg/dL}: \text{eGFR} = 130 \\
&\quad \times (\text{Scr}/61.88)^{-0.248} \times (\text{Scyst}/0.8)^{-0.375} \times 0.995^{\text{age}} \times (1.08 \text{ if black}) \\
&\text{Female, SCr} \le 61.88\mu\text{mol/L and SCys} > 0.8\text{ mg/dL}: \text{eGFR} = 130 \\
&\quad \times (\text{Scr}/61.88)^{-0.248} \times (\text{Scyst}/0.8)^{-0.711} \times 0.995^{\text{age}} \times (1.08 \text{ if black}) \\
&\text{Female, SCr} > 61.88\mu\text{mol/L and SCys} \le 0.8\text{ mg/dL}: \text{eGFR} = 130 \\
&\quad \times (\text{Scr}/61.88)^{-0.601} \times (\text{Scyst}/0.8)^{-0.375} \times 0.995^{\text{age}} \times (1.08 \text{ if black}) \\
&\text{Female, SCr} > 61.88\mu\text{mol/L and SCys} \ge 0.8\text{mg/dL}: \text{eGFR} = 130 \\
&\quad \times (\text{Scr}/61.88)^{-0.601} \times (\text{Scyst}/0.8)^{-0.711} \times 0.995^{\text{age}} \times (1.08 \text{ if black}) \\
&\text{Male, SCr} \le 79.56\mu\text{mol/L and SCys} \le 0.8\text{ mg/dL}: \text{eGFR} = 135 \\
&\quad \times (\text{Scr}/79.56)^{-0.207} \times (\text{Scyst}/0.8)^{-0.375} \times 0.995^{\text{age}} \times (1.08 \text{ if black}) \\
&\text{Male, SCr} \le 79.56\mu\text{mol/L and SCys} > 0.8\text{mg/dL}: \text{eGFR} = 135 \\
&\quad \times (\text{Scr}/79.56)^{-0.207} \times (\text{Scyst}/0.8)^{-0.711} \times 0.995^{\text{age}} \times (1.08 \text{ if black}) \\
&\text{Male, SCr} > 79.56\mu\text{mol/L and SCys} \le 0.8\text{ mg/dL}: \text{eGFR} = 135 \\
&\quad \times (\text{Scr}/79.56)^{-0.601} \times (\text{Scyst}/0.8)^{-0.375} \times 0.995^{\text{age}} \times (1.08 \text{ if black}) \\
&\text{Male, SCr} > 79.56\mu\text{mol/L and SCys} > 0.8\text{ mg/dL}: \text{eGFR} = 135 \\
&\quad \times (\text{Scr}/79.56)^{-0.601} \times (\text{Scyst}/0.8)^{-0.711} \times 0.995^{\text{age}} \times (1.08 \text{ if black})
\end{aligned}$$

(3) CKD-EPI CysC_2012 equation:

$$\begin{aligned}
&\text{SCys} \le 0.8\text{mg/L}: \text{eGFR} = 133 \times (\text{Scyst}/0.8)^{-0.499} \\
&\quad \times 0.996^{\text{age}} (\times 0.932 \text{ if female}) \text{SCys} > 0.8\text{mg/L}: \\
&\quad \text{eGFR} = 133 \times (\text{Scys}/0.8)^{-1.328} \times 0.996^{\text{age}} (\times 0.932 \text{ if female})
\end{aligned}$$

(4) FAS Cr equation:

$$\begin{aligned}
&\text{eGFR} = 107.3/(\text{SCr}/\text{QCys}) \times \left[0.988^{(\text{age}-40)}, \text{when age} > 40 \text{ years}\right] \\
&\quad (\text{female}: \text{QScr} = 0.70 \text{ mg/dl}; \text{male}: \text{QScr} = 0.90 \text{ mg/dl});
\end{aligned}$$

(5) FAS CysC equation:

$$\begin{aligned}
&\text{eGFR} = 107.3/(\text{SCys}/\text{QCys}] \times \left[0.988^{(\text{age}-40)} \text{ when age} > 40 \text{ years}\right] \\
&\quad (\text{age} < 70 \text{ years old}: \text{QCys} = 0.82 \text{ mg/l}; \text{age} \ge 70 \text{ years old}: \\
&\quad \text{QCys} = 0.95 \text{ mg/l})
\end{aligned}$$

(6) FAS Cr-CysC equation:

$$\begin{aligned}
&\text{eGFR} = 107.3/[\alpha \times (\text{SCr}/\text{QScr}) + (1-\alpha) \times (\text{SCys}/\text{QCys})] \\
&\quad \times \left[0.988^{(\text{age}-40)} \text{ when age} > 40 \text{ years}\right] \\
&\quad (\text{female}: \text{QScr} = 0.70 \text{ mg/dl}; \text{male}: \\
&\quad \text{QScr} = 0.90 \text{ mg/dl}; \text{age} < 70 \text{ years old}: \\
&\quad \text{QCys} = 0.82 \text{ mg/l}; \text{age} \ge 70 \text{ years old}: \\
&\quad \text{QCys} = 0.95 \text{ mg/l}; \alpha = 0.5)
\end{aligned}$$

(7) abbreviated_MDRD equation:

$$\begin{aligned}
&\text{eGFR} = 175 \times \text{SCr } (\mu\text{mol/L} \times 0.0011312)^{-1.154} \times \text{age (years)}^{-0.203} \\
&\quad \times (0.742, \text{if female}) \times (1.212, \text{if black})
\end{aligned}$$

(8) Chinese _MDRD equation:

$$\begin{aligned}
&\text{eGFR} = 175 \times \text{SCr } (\mu\text{mol/L} \times 0.0011312)^{-1.234} \times \text{age (years)}^{-0.179} \\
&\quad \times (0.79, \text{if female})
\end{aligned}$$

### Statistical analysis

Statistical analyses were performed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, USA) and Medcalc 11.4 for windows. Kolmogorov-Smirnov test (K-S) was used to test the normality of variables [14]. Continuous variables were presented as the means ± standard deviation and were analyzed using unpaired Student's t-tests. Nonnormally distributed variables were presented as medians with corresponding 25th and 75th percentiles (interquartile ranges) and compared using the Mann–Whitney U test [15]. Wilcoxon test was used to compare the differences of the deviation from mGFR (△eGFR, which is mGFR minus eGFR) by these eight eGFRs when in different BMI interval. Plotting scatter diagrams were used to observe the trend of each △eGFR when in different BMI state. Partial correlation analysis was used to evaluate correlations between △eGFR and BMI. Bland-Altman analysis [16] was used to determine the agreement between the mGFR and eGFR values, similar to the study by Chi et al [17], which were calculated by different equations. The percentage of cases in which eGFR was within mGFR ±30% (P30) was used to represent the accuracy of each equation. Kappa statistics were used to evaluate the agreement between stage classification from the mGFR values and from the eGFR values calculated by different equations, with the following interpretations: slight agreement (0–0.20), fair agreement (0.21–0.40), moderate agreement (0.41–0.60), substantial agreement (0.61–0.80), and almost perfect or perfect agreement (0.81–1.0) [18]. The receiver operating characteristic (ROC) curve was used to determine the diagnostic power at predicting the renal insufficiency ($ROC_{60}$) by the eight different equations, with the results reported as the areas under the ROC curve ($AUC_{60}$), sensitivity, and specificity [19]. Differences with $P < 0.05$ were considered statistically significant.

## Results

### Overview of the entire study population

The demographic and clinical features of the participants included in the analysis are listed in Table 1. The medium BMI was 24.8 Kg/m$^2$ which 25.1 Kg/m$^2$ for male, and 24.2 for female. According to the percentile of BMI, it was divided into three intervals, < 25% ($BMI_{P25}$), 25% ~ 75% ($BMI_{P25–75}$) and > 75% ($BMI_{P75}$), respectively. The average BMI was 20.9 Kg/m$^2$ in $BMI_{P25,}$ 24.8 Kg/m$^2$ in $BMI_{P25–75,}$ and 28.9 Kg/m$^2$ in $BMI_{P75}$ respectively. Among all the patients, 66.8% had diabetes and 64.5% had hypertension, and 71.6% had atherosclerosis which was the most common diagnosis. The average mGFR was 71.4 ± 28.1 mL/min/1.73 m$^2$, while the average eGFR varied according to different calculation formulas, ranging from 60.2(44.9, 74.9)mL/min/1.73 m$^2$ to 88.5 ± 49.1 mL/min/1.73 m$^2$.

### Relation between BMI and △eGFR based on different formulas

The correlation between △eGFR based on different formulas and BMI was shown by plotting scatter diagrams of △eGFR based on different formulas with the increase of BMI (Fig. 1). With the increase of BMI, trends of △eGFR differed with diverse formulas. Partial correlation coefficient was shown in Table 2, which was statistically significant ($p = 0.012$ for $\triangle eGFR_{c\_MDRD}$ while the rest $p < 0.001$).

The comparison of △eGFR among different BMI groups was shown in Table 3. Delta $eGFR_{EPI\_Cr\_2009}$, $\triangle eGFR_{EPI\_CysC\_2012}$, $\triangle eGFR_{EPI\_Cr\_CysC\_2012}$, $\triangle eGFR_{FAS\_Cr}$, $\triangle eGFR_{FAS\_CysC}$ and $\triangle eGFR_{FAS\_Cr\_CysC}$ showed significant differences in different BMI intervals ($p = 0.030$, 0.010, 0.000, 0.0029, 0.000 and 0.001 respectively). While $\triangle eGFR_{a\_MDRD}$ and $\triangle eGFR_{c\_MDRD}$ had no significant difference in different BMI intervals ($p = 0.234$ and 0.522, respectively).

### Consistency of eGFRs compared with mGFR

The consistency between the eGFR based on different formulas and the mGFR was analyzed by Bland-Altman plots (Fig. 2, Table 4). The accuracy of each equation was represented by the percentage of cases in which eGFR was within the range of mGFR ±30% (P30). Compared with mGFR, biases of $eGFR_{FAS\_Cr\_CysC}$ and $eGFR_{EPI\_Cr\_2009}$ (4.1 and – 4.2, respectively) were much less than those of $eGFR_{FAS\_Cr}$ $eGFR_{EPI\_CysC\_2012}$, $eGFR_{EPI\_Cr\_CysC\_2012}$, $eGFR_{FAS\_CysC}$, $eGFR_{a\_MDRD}$ and $eGFR_{c\_MDRD}$ (– 6.9, 8.4, 9.6, 10.8, – 8.4 and – 20.8, respectively). The accuracy of each eGFR was as follows: 81.5% for $eGFR_{FAS\_Cr\_CysC}$, 74.1% for $eGFR_{EPI\_Cr\_CysC\_2012}$, 74.1% for $eGFR_{EPI\_CysC\_2012}$, 73.4% for $eGFR_{FAS\_CysC}$, 70.1% for $eGFR_{EPI\_Cr\_2009}$, 69.3% for $eGFR_{FAS\_Cr}$, 63.0%for $eGFR_{a\_MDRD}$ and 47.0% for $eGFR_{c\_MDRD}$.

However, the accuracy of different formulas varied in different BMI intervals. In the $BMI_{P25}$ interval, the bias of $eGFR_{FAS\_Cr}$ was improved to – 0.7 mL/min/1.73 m$^2$($P = 0.679$) with 74.2% of P30. And the bias of $eGFR_{EPI\_Cr\_2009}$ was 2.3 mL/min/1.73 m$^2$ ($P = 0.061$) with 71.8% of P30. In the range of $BMI_{P25–75}$, the bias of $eGFR_{FAS\_Cr\_CysC}$ was 4.0 mL/min/1.73 m$^2$ with 85.0% of P30, and the bias of $eGFR_{EPI\_Cr\_2009}$ was 4.0 mL/min/1.73 m$^2$ with 74.7% of P30, which were most consistent with mGFR. In the $BMI_{P75}$ interval, the bias of $eGFR_{EPI\_Cr\_CysC\_2012}$ was 3.8 mL/min/1.73 m$^2$ ($P < 0.01$) with 78.9% of P30 and the bias of $eGFR_{EPI\_CysC\_2012}$ was 3.3 mL/min/1.73 m$^2$ *($P < 0.05$)* with 76.6% of P30. The bias of $eGFR_{FAS\_Cr\_CysC}$ was – 1.8 mL/min/1.73 m$^2$, but there was no statistical significance ($P = 0.095$). It was suggested that the consistency of eGFR compared with the mGFR was the best when eGFR calculated by $eGFR_{EPI\_CysC\_2012}$ and $eGFR_{FAS\_Cr\_CysC}$ formulas.

**Table 1** Baseline characteristics

| Variable | Total | Male($n$ = 505) | Female($n$ = 332) |
|---|---|---|---|
| Age, years | 60 (52, 69) | 59 (51, 67) | 62 (55, 71) * |
| Height, cm | 167 (160.0, 172.3) | 170 (167, 175) | 160 (155, 163) * |
| Weight, kg | 69 (60, 77) | 74 (66, 81) | 61 (54, 69) * |
| Body surface area (BSA), $m^2$ | 1.81 (1.67, 1.95) | 1.90 (1.80, 2.01) | 1.66 (1.56, 1.77) * |
| Body mass index (BMI), $Kg/m^2$ | 24.8 (22.7, 27.3) | 25.1(23.1, 27.4) | 24.2(21.6, 26.8) * |
| $BMI_{P25}$, $Kg/m^2$ ($n$ = 209) | 20.9 (19.6, 21.9) | | |
| $BMI_{P25-75}$, $Kg/m^2$ ($n$ = 419) | 24.8 (23.7, 25.9) | | |
| $BMI_{P75}$, $Kg/m^2$ (n = 209) | 28.9 (28.0, 30.6) | | |
| Serum creatinine (sCr), μmol/L | 79 (61, 113.3) | 86 (68, 120) | 66 (51, 100) * |
| Serum uric acids (sUA), μmol/L | 360 (289, 435) | 380 (311, 449) | 323 (268, 421) * |
| Serum urea (sUrea), mmol/L | 6.3 (5.0, 8.6) | 6.5 (5.2, 8.6) | 6.1 (4.8, 8.8) △ |
| Serum cystatin C (sCysc), mg/L | 1.17 (0.97, 1.53) | 1.18 (0.99, 1.53) | 1.16 (0.94, 1.58) △ |
| Urinary albumin creatinine ratio (ACR), μg/mg | 64.4 (18.3, 458.5) | 73.8 (15.7, 522.8) | 60.2 (23.9, 406.1) △ |
| ACR ≥ 30 μg/mg rate, % | 64.03 | 62.80 | 66.10△ |
| Diabetes | 559 (66.8%) | 373 (73.9%) | 186 (56.0%)* |
| Hypertension | 540 (64.5%) | 325 (64.4%) | 215 (42.6%)△ |
| coronary heart disease | 165 (19.7%) | 102 (20.2%) | 63 (12.5%)△ |
| atherosclerosis | 599 (71.6%) | 358 (70.9%) | 241 (47.7%)△ |
| mGFR, ml·min −1·1.73 m 2 | 71.4 ± 28.1 | 69.8 ± 27.3 | 73.8 ± 29.2▲ |
| distribution in each CKD stage | | | |
| CKD1 | 221 (26.4%) | 123 (24.4%) | 98 (29.5%)△ |
| CKD2 | 338 (40.4%) | 214 (42.4%) | 124 (37.4%)△ |
| CKD3 | 212 (25.3%) | 130 (25.7%) | 82 (24.7%)△ |
| CKD4 | 54 (6.5%) | 28 (5.5%) | 26 (7.8%)△ |
| CKD5 | 12 (1.4%) | 10 (2.0%) | 2 (0.6%)△ |
| eGFR | | | |
| $eGFR_{a\_MDRD}$ | 75.3(47.2, 105.1) | 78.6(55.8, 104.7)★ | 78.2(48.0, 110.0)★△ |
| $eGFR_{c\_MDRD}$ | 88.5 ± 49.1 | 87.9 ± 44.7★ | 98.4 ± 54.4★▲ |
| $eGFR_{EPI\_Cr\_2009}$ | 81.9 (52.2, 93.3) | 82.5 (55.5, 101.2) ★ | 80.4 (48.5, 97.8) ★△ |
| $eGFR_{EPI\_Cr\_CysC\_2012}$ | 63.3 (42.0, 81.2) | 63.5 (43.6,79.8) ★ | 62.2 (39.6, 82.2) ★△ |
| $eGFR_{EPI\_CysC\_2012}$ | 62.8 (43.4, 82.3) | 62.5 (44.1, 80.3) ★ | 62.8 (41.2, 84.5) ★△ |
| $eGFR_{FAS\_Cr}$ | 77.7(51.6, 104.0)★ | 78.8 ± 36.7★ | 74.1(48.1, 104.6)□△ |
| $eGFR_{FAS\_CysC}$ | 60.2(44.9, 74.9)★ | 60.8(45.9, 73.9)★ | 61.4 ± 24.8★△ |
| $eGFR_{FASCr\_CysC}$ | 66.8(47.8, 85.6)★ | 67.9 ± 28.3 ★ | 66.0(46.3, 87.3) ★△ |

△$P > 0.05$, ▲$P < 0.05$, *$P < 0.01$, compared with male; ★$P < 0.01$, □$P > 0.05$, compared with mGFR

### Accuracy of eGFR in CKD staging in different BMI intervals

The kappa values of $eGFR_{EPI\_Cr\_2009}$, $eGFR_{FAS\_Cr}$ and $eGFR_{a\_MDRD}$ were similar(0.418, 0.422 and 0.412 respectively), which were higher than that of other formulas when in $BMI_{P25}$ interval (Supplemental Table 1). They showed high accuracy (84.4, 76.6 and 88.3%, respectively) in the identification of stage 1 CKD and moderate accuracy in the identification of stage 2 and 3 CKD. In $BMI_{P25-75}$ interval, $eGFR_{FAS\_Cr\_CysC}$ had highest kappa value (0.504), which was higher than $eGFR_{EPI\_CysC\_2012}$ (0.431), $eGFR_{FAS\_Cr}$(0.415) and $eGFR_{EPI\_Cr\_CysC\_2012}$ (0.415). The $eGFR_{FAS\_Cr\_CysC}$ showed a better accuracy in the identification of stage 2 and 3 CKD (63.7 and 68.0% respectively) (Supplemental Table 2). In the $BMI_{P75}$ interval, eGFREPI_Cr_CysC_2012 was found to be the best, with a kappa value of 0.484, showing balanced and accurate recognition ability of each stage (60.5, 60.0, 71.4, 57.1 and 100% respectively) (Supplemental Table 3). However, the recognition ability of each

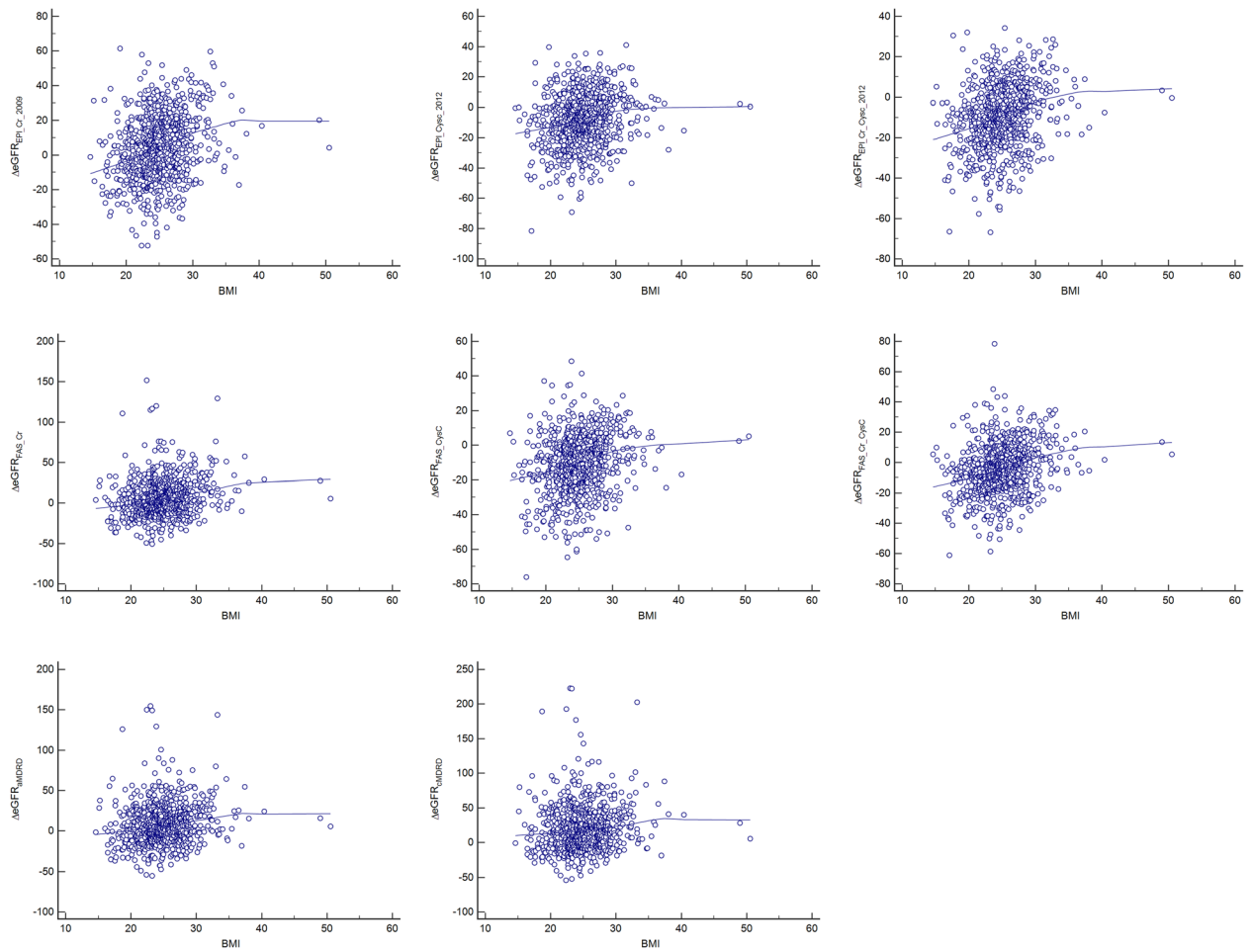


**Fig. 1** Plot scatter diagrams of ▵eGFR based on different formulas with the increase of BMI

CKD stage of FAS_Cr_CysC eq. (71.1, 61.2, 70.0, 42.9 and 50.0% respectively) was not as good as EPI_Cr_CysC_2012 equation.

### Diagnostic performance of each eGFR equation for predicting renal insufficiency in different BMI intervals

The diagnostic performance for predicting renal insufficiency based on each eGFR equation in three BMI intervals was summarized and showed in Supplemental Table 4, 5 and 6 and Fig.3. In the $BMI_{P25}$ interval, with a sensitivity of 89.7% and a specificity of 84.1%, at a cut-off point of 67.1 mL/min/1.73 $m^2$, eGFREPI_Cr_2009 got an $AUC_{60}$ of 0.920 which had no significant difference compared with other equations ($p > 0.05$), suggesting appropriate diagnostic ability for predicting renal insufficiency. In $BMI_{P25}$ interval, $eGFR_{FAS\_Cr}$ had similar performance with a sensitivity of 79.3%, specificity of 88.1%, and an $AUC_{60}$ of 0.928 at a cut-off point of 56.6 mL/min/1.73 $m^2$.

In $BMI_{P25-75}$ interval, the cut-off point of $eGFR_{FAS\_Cr\_CysC}$ was 62.9 mL/min/1.73 $m^2$, with an $AUC_{60}$ of 0.941 which had no significant difference compared with other equations (except $eGFR_{FAS\_CysC}$, $p = 0.021$). When the cut-off values of eGFREPI_CysC_2012 and eGFREPI_Cr_CysC_2012 were revised to 60.1 and 60.2 mL/min/1.73 $m^2$ respectively, the sensitivity was increased to 90.3 and 91.8% respectively, but the specificity was decreased to 78.9 and 77.2% respectively. Looking back at $eGFR_{FAS\_Cr\_CysC}$, when cut-off point of $eGFR_{FAS\_Cr\_CysC}$ was 62.9 mL/min/1.73 $m^2$, the sensitivity was 92.5% and the specificity was 78.6%, while after revising cut-off value to 60.0 mL/min/1.73 $m^2$, the sensitivity was 87.3% and the specificity was 82.0%, indicating that the diagnostic performance for predicting renal insufficiency was relatively stable. In $BMI_{P75}$ interval, the optimal cut-off point of $eGFR_{EPI\_Cr\_CysC\_2012}$ for predicting renal insufficiency was 60.5 mL/min/1.73 $m^2$, with an ideal sensitivity of 90.7%, a specificity of 80.5%, and an $AUC_{60}$ of 0.919 ($P < 0.05$ vs. $eGFR_{EPI\_CysC\_2012}$), highlighted itself. The optimal cut-off point of $eGFR_{FAS\_Cr\_CysC}$ for predicting renal insufficiency was 61.5 mL/min/1.73 $m^2$, with a sensitivity of 87.2%, a specificity of 84.6%, and an $AUC_{60}$ of

**Table 2** Partial correlation analysis between △eGFR based on different formulas and BMI

| | $^{\triangle}eGFR_{EPI\_Cr\_2009}$ | $^{\triangle}eGFR_{EPI\_CysC\_2012}$ | $^{\triangle}eGFR_{EPI\_Cr\_CysC\_2012}$ | $^{\triangle}eGFR_{FAS\_Cr}$ | $^{\triangle}eGFR_{FAS\_CysC}$ | $^{\triangle}eGFR_{FAS\_Cr\_CysC}$ | $^{\triangle}eGFR_{a\_MDRD}$ | $^{\triangle}eGFR_{c\_MDRD}$ |
|---|---|---|---|---|---|---|---|---|
| r | 0.264 | 0.197 | 0.260 | 0.210 | 0.222 | 0.267 | 0.140 | 0.087 |
| *p* value | < 0.0001 | < 0.0001 | < 0.0001 | < 0.0001 | < 0.0001 | < 0.0001 | 0.000 | 0.012 |

**Table 3** Comparison of △eGFR among different BMI groups

| | $^{\triangle}eGFR_{EPI\_Cr\_2009}$ | $^{\triangle}eGFR_{EPI\_CysC\_2012}$ | $^{\triangle}eGFR_{EPI\_Cr\_CysC\_2012}$ | $^{\triangle}eGFR_{FAS\_Cr}$ | $^{\triangle}eGFR_{FAS\_CysC}$ | $^{\triangle}eGFR_{FAS\_Cr\_CysC}$ | $^{\triangle}eGFR_{a\_MDRD}$ | $^{\triangle}eGFR_{c\_MDRD}$ |
|---|---|---|---|---|---|---|---|---|
| BMI < 25% | 10.8(5.6, 21.0) | 15.3(8.0, 26.9) | 15.1(8.4, 25.5) | 12.9(6.2, 21.8) | 16.7(8.4, 28.6) | 12.3(6.5, 22.1) | 15.8(6.8, 25.0) | 20.4(9.4, 37.5) |
| BMI 25–75% | 12.1(6.0, 20.0) | 12.2(6.2, 19.4) | 11.7(6.1, 19.0) | 11.9(6.0, 23.6) | 12.1(5.2, 21.5) | 9.1 (4.6, 16.6) | 13.7(6.1, 25.7) | 19.4(8.8, 38.5) |
| BMI > 75% | 15.5(7.0, 24.8) | 10.2(5.0, 18.9) | 9.3(4.6, 18.6) | 15.5(7.3, 25.2) | 9.6 (4.4, 17.5) | 10.3(4.7, 19.0) | 16.3(7.4, 27.6) | 21.9(10.2, 39.0) |
| p value | 0.030 | 0.010 | 0.000 | 0.029 | 0.000 | 0.001 | 0.234 | 0.522 |

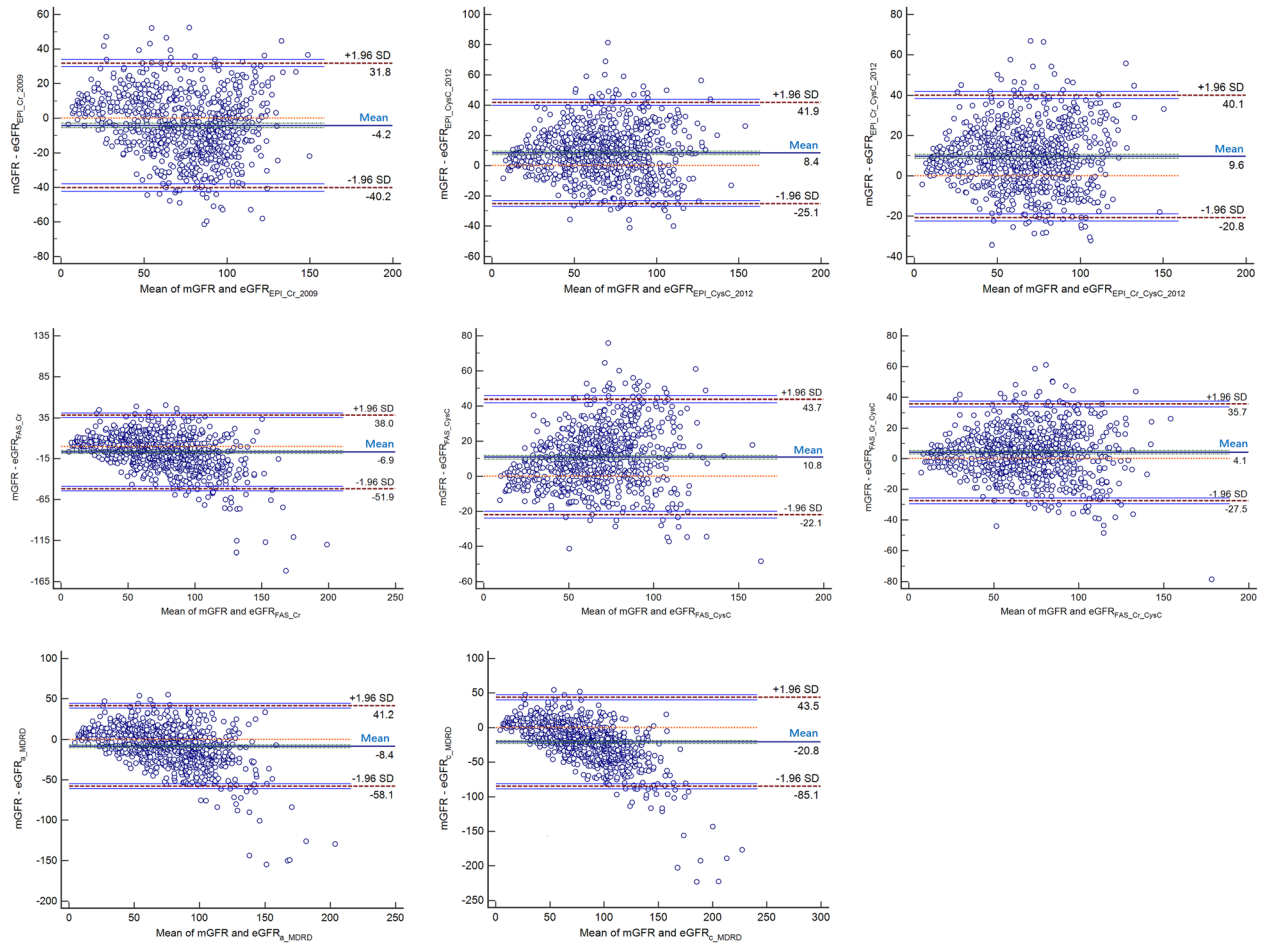


**Fig. 2** Bland-Altman plots of the mGFR and eGFR (mL/min/1.73 $m^2$)

**Table 4** Comparison of bias and accuracy between eGFRs and mGFR in different BMI groups

| BMI | Total | | < 25% | | 25–75% | | > 75% | |
|---|---|---|---|---|---|---|---|---|
| Equation | Bias (mL/min/1.73 $m^2$) (△eGFR, 95% CI) | 30% accuracy | Bias (mL/min/1.73 $m^2$) (△eGFR, 95% CI) | 30% accuracy | Bias (mL/min/1.73 $m^2$) (△eGFR, 95% CI) | 30% accuracy | Bias (mL/min/1.73 $m^2$) (△eGFR, 95% CI) | 30% accuracy |
| $eGFR_{EPI\_Cr\_2009}$ | −4.2(− 5.5 - -3.0)△ | 70.1% | 2.3(−0.1–4.8)□ | 71.8% | −4.0(−5.8 - -2.5)△ | 74.7% | −11.1(−13.5 - -8.4)△ | 59.3% |
| $eGFR_{EPI\_CysC\_2012}$ | 8.4(7.3–9.6)△ | 74.0% | 13.1(10.7–15.7)△ | 67.5% | 8.6(7.0–10.1)△ | 75.9% | 3.3(1.2–5.5)▲ | 76.6% |
| $eGFR_{EPI\_Cr\_CysC\_2012}$ | 9.6(8.6–10.7)△ | 74.1% | 15.2(13.1–17.3)△ | 64.1% | 9.8(8.4–11.2)△ | 75.4% | 3.8(1.7–5.8)△ | 78.9% |
| $eGFR_{FAS\_Cr}$ | −6.9(−8.5 - -5.4)△ | 69.3% | −0.7(−3.8–2.5)○ | 74.2% | −7.1(−9.2 - -4.9)△ | 70.6% | −12.9(− 16.0 −− 9.9)△ | 61.7% |
| $eGFR_{FAS\_CysC}$ | 10.8(9.7–11.9)△ | 73.4% | 15.9(13.5–18.3)△ | 64.1% | 11.0(9.5–12.6)△ | 76.1% | 5.3(3.2–7.4)△ | 77.0% |
| $eGFR_{FAS\_Cr\_CysC}$ | 4.1(3.0–5.1)△ | 81.5% | 9.9(7.8–12.1)△ | 77.5% | 4.0(2.5–5.5)△ | 85.0% | −1.8(− 3.9–0.3)● | 78.5% |
| $eGFR_{a\_MDRD}$ | −8.4(− 10.2 - -6.7)△ | 63.0% | −3.7(− 7.3 - -0.1)▲ | 64.6% | − 8.5(− 10.9 - -6.0)△ | 65.0% | −13.1(− 16.3 - -9.9)△ | 59.8% |
| $eGFR_{c\_MDRD}$ | −20.8(−23.0 - -18.6)△ | 47.0% | −8.8(− 12.6 - -4.9)△ | 45.5% | −20.5(−23.9 - -17.5)△ | 51.1% | −24.8(−28.6 - -20.5)△ | 40.2% |

△Compared with mGFR, $P < 0.01$;
▲Compared with mGFR, $P < 0.05$;
□Compared with mGFR, P = 0.061;
■Compared with mGFR, $P = 0.401$
○Compared with mGFR, P = 0.679;
●Compared with mGFR, P = 0.095;

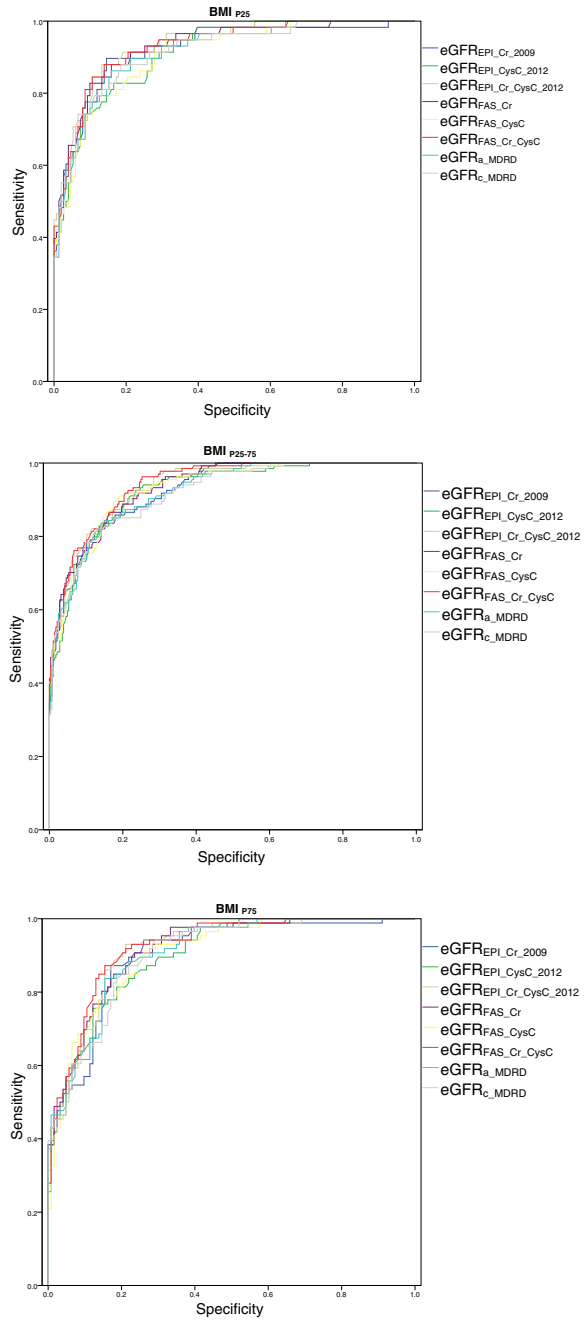


**Fig. 3** Receiver operating characteristic curve of eGFRs in different BMI intervals

0.922 ($P < 0.05$ vs. $eGFR_{FAS\_CysC}$). It suggested that $eGFR_{EPI\_Cr\_CysC\_2012}$ and $eGFR_{FAS\_Cr\_CysC}$ had the strongest ability to predict renal insufficiency in $BMI_{P75}$ interval.

## Discussion

There is high disease burden of CKD in China [2]. The global increase in this disease is mainly driven by the increase in the prevalence of diabetes mellitus, hypertension, obesity, and aging. To make matters worse, the risk of death gradually increases with the deterioration of CKD [20]. Therefore, screening, diagnosis, and staging CKD early as well as accurately are more and more important. Estimating GFR accurately is crucial for clinical practice, research, and public health. Although Tc-99 m DTPA renal dynamic scintigraphy is a useful tool for clinicians in assessing renal function, this method cannot be regularly used in clinical practice. On the contrary, GFR estimated from equations is a convenient approach to assess patients' renal function. Due to the convenience of testing, it can be used as a method for large-scale cases screening.

Each eGFR equation is established by statistically processing of certain population data, so it always performs less well outside the cohort in which they were developed [21]. All methods for the estimation of GFR have limitations, so no equation can perform best in all populations. Obesity is associated with a risk of CKD and is highly prevalent among patients with CKD [22, 23]. In our study, the average BMI of the cases was 24.8, of which 25.1 for males and 24.2 for females. A large number of patients were overweight or obese. Therefore, it inspired us to consider the influence of BMI, which can partly reflect the difference of body. If we properly handled this influence, can we make the best use of each eGFR equation? There are few studies on the applicability of different eGFR equations in different BMI intervals. In this study, we evaluated the value of different eGFR formulas in different BMI intervals.

After being analyzed by Bland-Altman plots, biases of $eGFR_{FAS\_Cr\_CysC}$ and $eGFR_{EPI\_Cr\_2009}$ were much less than that of others on the whole, showing the best agreement with mGFR. In $BMI_{P25}$ interval, $eGFR_{FAS\_Cr}$ and $eGFR_{EPI\_Cr\_2009}$ formulas had optimal accuracy, excellent ability to classify CKD stages, and best diagnostic performance for predicting renal insufficiency. In $BMI_{P25-75}$ interval, $eGFR_{FAS\_Cr\_CysC}$ was the best one, with optimal accuracy and excellent ability in staging CKD2 and CKD3. In $BMI_{75}$ interval, $eGFR_{EPI\_Cr\_CysC\_2012}$ equation showed excellent accuracy, stable identification power for CKD stages and the strongest ability to predict renal insufficiency. In $BMI_{75}$ interval, the accuracy and ability to predict renal insufficiency of $eGFR_{FAS\_Cr\_CysC}$ was similar to that of $eGFR_{EPI\_Cr\_CysC\_2012}$. However, $eGFR_{FAS\_Cr\_CysC}$ was not as good as $eGFRE_{PI\_Cr\_CysC\_2012}$ equation in identifying CKD stages. We found Scr-cysC-based eGFR equations had superiority in evaluating eGFR compared to the Scr-based formulas in overweight or obese people.

It's well known that SCr has limitations including its insensitivity to underlying changes in kidney function and the numerous non-kidney factors that are

incompletely accounted for in equations to eGFR [24]. Although as an endogenous biomarker, concentration of cysC also can be affected by other non-renal determinants, such as obesity, thyroid disorders, diabetes, and inflammation, however, compared to SCr, cysC appears to be less affected by age, race, sex, muscle mass, or dietary intake [25, 26]. It is increasingly accepted to use the use equations based on cystatin C or combined creatinine and cystatin C [27]. In fact, kidney function assessment in obese patients is challenging. Nephron number does not change with weight gain, and the increase of GFR observed in obese patients reflects compensatory hyperfiltration of nephrons. This hyperfiltration in obese patients can become maladaptive and is largely unaccounted for in existing eGFR equations [28]. According to our research, it may be acceptable to choose an eGFR formula based on combined creatinine and cystatin C before a better formula appears. It is worth mentioning that, our reseach proves that, the novel FAS equations [11] are suitable for Chinese population, and even have superiority compared to other formulas in many cases, especially the $eGFR_{FAS\_Cr\_CysC}$ equation. In a multicenter study of 1184 patients in China, the performance of the $eGFR_{FAS\_Cr\_CysC}$ equation was better than that of the $eGFR_{EPI\_Cr\_CysC\_2012}$ equation, particularly in the elderly [29]. It may be necessary to further modify the FAS equation from a larger-scale study to make it more suitable for the Chinese population.

Exactly, each eGFR formula shows different clinical value in different BMI intervals. Therefore, the BMI of patients with CKD is an aspect worthy considering when choosing the appropriate eGFR equation. Which is the best choice? In our study, in normal or low-weight population, the formula based on serum creatinine is preferred, and in overweight or obese population, the formula based on serum creatinine and cystatin C may be more suitable. The reason may be that the combination of both biomarkers can cancel out the non-GFR-related factors influencing creatinine and cystatin C in different directions compared with mGFR. Steubl et al. suggest that combining metabolites or proteins in equations to minimize the influence of nonkidney-related parameters appears to be a promising approach which is consistent with our view [30].

Our research had some strengths such as on ethnic factors that all were from Chinese population, concentrative age range, common high-risk diseases for CKD. These favoured us to identify the appropriate eGFR equation for Chinese population while considering the impact of BMI. However, it needs to be verified and confirmed by different types of studies based on a larger population. More comparative studies on different types of samples are needed to further illuminate which biomarkers are better tools for diagnosis and prognosis of CKD.

Nevertheless, our study has some limitations. Firstly, we did not obtain specific data such as appendicular lean mass index (ALMI) and total body fat percentage (TBF%) measured by dual-energy x-ray absorptiometry (DXA) of body composition [31, 32], so we cannot refine the population in the BMI intervals. Secondly, we didn't have enough data of proteinuria to define renal dysfunction because we only got one urine protein test result for each patient's first morning urine. Thirdly, as it was a cross-sectional analysis, and a retrospective, single-center study, the results of this study should be carefully applied in practical clinical practice. Finally, although we assessed eight eGFR equations that were commonly used, there are also some other equations which were well praised were not included in our study.

In conclusion, after comprehensive analysis of factors that included consistency, accuracy, classification ability and diagnostic performance, we tend to suggest that choosing $eGFR_{EPI\_Cr\_2009}$ or $eGFR_{FAS\_Cr}$ equation to estimate GFR of patients when BMI is around 20.9 $kg/m^2$, $eGFR_{FAS\_Cr\_CysC}$ for overweight patients (BMI around 24.8 $kg/m^2$), and $eGFR_{EPI\_Cr\_CysC\_2012}$ for obese patients (BMI is about 28.9 $kg/m^2$).

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-021-02395-x.

**Additional file 1: Supplemental Table 1.** CKD stage classification based on eGFRs in $BMI_{P25}$ interval. **Supplemental Table 2.** CKD stage classification based on eGFRs in $BMI_{P25-75}$ interval. **Supplemental Table 3.** CKD stage classification based on eGFRs in $BMI_{P75}$ interval. **Supplemental Table 4.** Diagnostic performance in $BMI_{P25}$ interval of eGFRs for predicting renal insufficiency (mL/min/1.73 m2). **Supplemental Table 5.** Diagnostic performance in $BMI_{P25-75}$ interval of eGFRs for predicting renal insufficiency (mL/min/1.73 m2). **Supplemental Table 6.** Diagnostic performance in $BMI_{P75}$ interval of eGFRs for predicting renal insufficiency (mL/min/1.73 m2).

**Additional file 2.**

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### Authors' contributions

Jiayong Li and Xiang Xu designed the study. Jialing Luo, Wenjing Chen and Man Yang collected data. Ling Wang and Nan Zhu analyzed and explained the data. Weijie Yuan critically reviewed the content of the article. Lijie Gu statistically analyzed and wrote the article. All authors reviewed and approved the manuscript.

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### Availability of data and materials

All data analysed during this study are included in Supplementary Information Files and also available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Research has been conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai General Hospital. Written informed consent was obtained from all participants. All methods were carried out in accordance with the relevant guidelines and regulations.

### Consent for publication

Written informed consent for publication was obtained from all participants.

### Competing interests

The authors declare that they have no competing interests.

### Author details

[1]Clinical Laboratory Medicine Center, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, China. [2]Department of Nephrology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, China.

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