

# Comparisons of Five Equations Used for Estimating the Glomerular Filtrations Rate in Chinese Adults

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## Research article

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# Abstract

## Background

We aimed to assess the performance of revised MDRD, CKD-EPI, BIS, FAS and XiangYa equation in Chinese adults

## Methods

We collected blood biochemical data of 623 Chinese adult hospitalised patients within 48 hours before they underwent <sup>99m</sup>Tc-DTPA GFR measurement. We computed the bias (mGFR-eGFR), the precision (IQR), the accuracy (P30) and root mean square error (RMSE) relative to mGFR of each equation to evaluate performance. The ROC curves, Kappa value of McNemar test, Bland-Altman plot and the Intraclass correlation coefficient (ICC) were used to evaluate diagnostic accuracy and concordance.

## Results

Totally, the FAS combined Scr and cysC equation performed supreme accuracy (P30=57.5%, RMSE=19.26), the cysC-based equation performed superior to Scr-based equation. Detailed P30 of the CKD-EPI cysC, FAS cysC, MDRD, CKD-EPI Scr-cysC, CKD-EPI Scr, FAS Scr, XiangYa was 56.7%, 56.0%, 53.5%, 52.2%, 48.8%, 51.4%, 43.0%. The CKD-EPI cysC equation showed the lowest bias and the highest accuracy (bias=-2.23, P30=57.4%) in GFR<60ml/min/1.73m<sup>2</sup>, followed by the FAS Scr-cysC equation (bias=-6.89, P30=55.4%). The XiangYa equation performed best in GFR≥60ml/min/1.73m<sup>2</sup> while worst in GFR<60 ml/min/1.73m<sup>2</sup> with bias(-5.79 vs -19.05), IQR(18.21 vs 10.85), P30(86.2% vs 21.1%), RMSE(16.68 vs 21.34). The CKD-EPI cysC equation had the lowest bias and the best accuracy (bias=-2.23, P30=59.4%) in age ≥70 years adults, followed by the FAS Scr-cysC equation equivalent to BIS-2 Scr-cysC equation (bias -5.33 vs -4.90, P30=57.3%), while the XiangYa equation performed worstly (bias=-20.39, P30=26.6%). Best ROC AUC was given by the FAS Scr-cysC equation(0.951), so was it had the highest Kappa value(0.364). The lowest Bias showed in Bland-Altman plot was the CKD-EPI cysC equation(bias=7.46). The highest ICC value was given by the FAS Scr-cysC equation(0.921). Secondly, it was the XiangYa equation with the ICC of 0.912.

## Conclusions

The FAS Scr-cysC equation is verified most suitable and simpler applied to Chinese population. The CKD-EPI cysC equation is appropriate used in moderately and severely injured GFR(CKD3-5stage) and Seniors over 70 years old. The XiangYa equation performed perfectly in slightly injured GFR (CKD1-2stage), while further verification of XiangYa equation in multiple region need to be carried out especially in moderately and severely injured GFR and older adults.

## Introduction

Chronic kidney disease (CKD) is a global medical problem with a high incidence that affects a large proportion of the world's population[1]. The current prevalence of CKD is approximately 13.4% according to a global systematic review[2]. However, the prevalence of CKD varies widely both within and between countries. On the one hand, there are indeed regional differences in the prevalence of CKD. On the other hand, the diagnosis of CKD using eGFR, the different GFR thresholds for CKD in the elderly, and the use of one-time testing for eGFR or urine protein results to evaluate CKD all lead to different prevalence rates in large-scale epidemiological studies[3]. Population-based studies indicate that CKD epidemiology differs by sex, affecting more women than men, especially with regard to

stage G3 CKD. The difference in CKD epidemiology by sex may be due to the natural decline in glomerular filtration rate (GFR) with age, as well as the potential overdiagnosis of CKD through the inappropriate use of GFR equations[4]. Thus, quick and accurate assessment of GFR is important for classifying the stage of chronic kidney disease because it can help assess the patient's current renal function, determine the dose of clinical drugs, and improve judgements regarding the reasonable timing of kidney dialysis or transplantation.

Presently, technetium-99m-diethylenetriaminepentaacetic acid ( $^{99m}\text{Tc}$ -DTPA) renal dynamic imaging is recommended for the measurement of GFR by the Nephrology Committee of the Society of Nuclear Medicine[5] and has been widely accepted as the standard value of GFR in clinical practice[6]. The calculation of the glomerular filtration rate in clinical practice mainly relies on the renal biomarkers serum creatinine (Scr) and serum cystatin C (ScysC). Several studies have shown that ScysC is a better marker than Scr[7–9] and is less affected by muscle mass and nutritional status. Current research confirms that within-subject variability in estimated GFR was lower than measured GFR, which indicates that estimates of GFR are at least as reliable as measured GFR for monitoring patients over time[10]. According to the epidemiology of mGFR in China, China has a large population base, with obvious differences in sex, region and race compared to these parameters in white people[11]. Therefore, it is necessary to evaluate the appropriate GFR equation for the Chinese population.

Since the traditional Cockcroft-Gault (CG) equation was widely applied in clinical practice in 1969, the exploration and correction of formulas are progressing consistently. With the standardization of the creatinine and cystatin C determination methods[12, 13], the traditional calculation formula is obviously not applicable in the current clinical setting, so the Revised Modification of Diet in Renal Disease (MDRD) equation has emerged, incorporating standard creatinine measured by Roche enzyme assay dating back to isotope dilution mass spectrometry (IDMS) calibration[14]. The 2012 KDIGO guidelines recommend Scr-based and ScysC-based equations and the combined creatinine-cystatin C Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation used to calculate eGFR for adults[15]. Subsequently, correction can be performed according to Asian race[16].

Since the establishment of the guideline recommendations, there has been progress in the exploration of formulas in recent years, including the Berlin Initiative Study (BIS) equation for people over 70[17], the full age spectrum (FAS) equation[18, 19] (calibrated in Korea[20]), and the latest XiangYa equation based on the Chinese population[21]. At present, the applicability of various equations in Chinese adults still needs to be verified by a large multicentre population study. The purpose of this study is to compare the applicability of current authoritative and popular equations in the population in central China.

## Methods

### Study population

We performed a retrospective study by reviewing the electronic medical records of inpatients from June 2017 to July 2019 at Zhongnan Hospital of Wuhan University (Wuhan, China). The inclusion criteria were as follow: patients who underwent GFR measurement using  $^{99m}\text{Tc}$ -DTPA; age  $\geq 18$  years; and Scr and ScysC concentrations measured within 48 hours before the time measuring  $^{99m}\text{Tc}$ -DTPA mGFR. We exclude the participants with acute renal failure, severe heart disease, pleural or abdominal effusion, renal stenosis, urinary obstruction, kidney tumour, severe malnutrition, physical disabilities, during pregnancy or lactation and patients who were taking trimethoprim, cimetidine, cefoxitin or underwent hemodialysis previously. Among the initial 681 selected inpatients, 19 had incomplete data for mGFR(unilateral renal insufficiency or without surface area

calibration), 17 lacked ScysC concentration, 14 lacked Scr concentration measured by Jaffe's alkaline picrate method, 8 subjects with Scr concentration too high (Scr levels > 700umol/l). Finally, a total of 623 subjects were included in the study. The detailed characteristics of the study subjects are presented in Table 2.

Table 2  
The Characteristics of the study population

Characteristic	All subjects	Age < 70 years	Age ≥ 70 years
Sample size	623	480	143
Age,years	56.89(16.07)	50.93(13.07)	76.92(5.54)
Gender(male/female)	383/240	297/183	86/57
Height(m)	166.13(7.37)	167.06(7.36)	162.97(6.55)**
Weight(kg)	66.09(11.54)	66.90(11.71)	63.35(10.55)**
Scr(mg/dl)	1.75(1.46)	1.71(1.45)	1.87(1.48)*
cysC(mg/l)	1.74(1.06)	1.65(1.05)	2.01(1.04)**
Primary disease	188(30.2%)	120(25.0%)	68(47.6%)
Hypertensive nephropathy	95(15.2%)	72(15.0%)	23(16.1%)
Diabetic nephropathy	209(33.5%)	178(37.1%)	31(21.7%)
Chronic glomerulonephritis	1(2%)	1(2%)	0(0%)
Polycystic kidney	130(20.9%)	109(22.7%)	21(14.7%)
Others	49.31(26.13)	53.01(26.60)	36.86(20.03)
mGFR, ml/min/1.73 m <sup>2</sup>	61.53(37.86)	65.12(39.37)	49.48(29.38)**
eGFR, ml/min/1.73 m <sup>2</sup>	62.35(35.30)	66.74(36.49)	47.62(26.14)**
MDRD	65.59(37.13)	70.21(38.38)	50.10(27.50)**
CKD-EPI <sub>Scr</sub>	56.77(36.11)	62.06(37.65)	38.99(22.78)**
Asian CKD-EPI <sub>Scr</sub>	60.79(38.79)	66.10(40.57)	42.96(24.93)**
CKD-EPI <sub>cysC</sub>	---	---	44.50(20.75)**
CKD-EPI <sub>Scr-cysC</sub>	---	---	41.15(19.20)**
BIS-1 <sub>Scr</sub>	62.91(36.29)	68.60(37.55)	43.81(23.12)**
BIS-2 <sub>Scr - cysC</sub>	63.64(37.19)	69.54(38.54)	43.82(23.12)**
FAS <sub>Scr</sub>	59.14(35.83)	64.52(37.74)	41.06(19.81)**
Korean FAS <sub>Scr</sub>	59.59(33.54)	65.03(34.89)	41.36(19.67)**
FAS <sub>cysC</sub>	63.73(21.87)	66.48(22.51)	54.48(16.52)**
FAS <sub>Scr-cysC</sub>			
XiangYa			

Values for continuous variables were presented as means(SD); Values for categorical variables were presented as frequency(percentage); \*P < 0.05, \*\*P < 0.01, compared with age < 70 years group

## Laboratory assay

We measured serum creatinine with use of Roche enzymatic method and IDMS calibration ( Beckman AU5800 Coulter chemistry analyzers, Ltd, Tokyo, Japan), traceable to National Institute of Standards and technology(NIST) creatinine standard reference material(SRM 967)[13], with a reported coefficient of variation of 2.3%(reference range:64-104umol/L). we measured serum cystatin C with use of particle-enhanced nephelometric immunoassay(Beckman AU5800 Automatic biochemical analyzers, Ltd, Tokyo, Japan),traceable to international standards[22], with a reported coefficient of variation of 10%(reference range:0-1.2 mg/L). mGFR was measured by using the radioactive isotope <sup>99m</sup>Tc-DTPA, Patients were required to have an fasting state on the day of examination, empty the bladder, drink 500 ml water within 30 minutes before examination, get a bolus injection of 5mCi<sup>99m</sup>Tc-DTPA via the cubital vein projectile, We perform renal dynamic imaging by a single photon emission computed tomography (CT) scanner, and obtain standardized mGFR by Gates method[23] according to the patient's weight and height.

# Calculation of eGFR

The eGFR was calculated by using 2007MDRD, 2012CKD-EPI, 2012BIS, 2017FAS, 2018XiangYa equations, the detailed expressions are presented in Table 1.

Table 1  
The expression of the eGFR cacularion equations

Year	Name	Equation
2007	MDRD	$175 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times (0.742, \text{ if female}) \times 1.210, \text{ if black}$
2009	CKD-EPI <sub>Scr</sub>	$a \times (\text{Scr}/b)^c \times 0.993^{\text{age}}$ $\times 1.157, \text{ if black}$
2011	Asian CKD-EPI <sub>Scr</sub>	$a \times (\text{Scr}/b)^c \times 0.993^{\text{age}}$ $\times 1.160, \text{ if black}$ $\times 1.052, \text{ if Asian}$
2012	CKD-EPI <sub>cysC</sub>	$133 \times (\text{cysC}/0.8)^a \times 0.996^{\text{age}}$ $\times 0.932, \text{ if female}$
2016	CKD-EPI <sub>Scr-cysC</sub>	$a \times (\text{Scr}/b)^c \times \text{cysC} / 0.8^d \times 0.995^{\text{age}}$ $\times 1.08, \text{ if black}$
2017	BIS-1 <sub>Scr</sub>	$3736 \times \text{Scr}^{-0.87} \times \text{age}^{-0.95} \times (0.82, \text{ if female})$
2018	BIS-2 <sub>Scr-cysC</sub>	$767 \times \text{cysC}^{-0.61} \times \text{Scr}^{-0.40} \times \text{age}^{-0.57} \times (0.87, \text{ if female})$
	FAS <sub>Scr</sub>	$107.3 / (\text{Scr} / Q_{\text{Scr}}) \times 0.988^{(\text{age}-40)}, \text{ if age} > 40$
	FAS <sub>cysC</sub>	$107.3 / (\text{cysC} / Q_{\text{cysC}}) \times 0.988^{(\text{age}-40)}, \text{ if age} > 40$
	FAS <sub>Scr-cysC</sub>	$107.3 / (\alpha \times \text{Scr} / Q_{\text{Scr}} + (1-\alpha) \times \text{cysC} / Q_{\text{cysC}}) \times 0.988^{(\text{age}-40)}, \text{ if age} > 40$
	XiangYa	$2374.78 \times \text{Scr}^{-0.54753} \times \text{age}^{-0.25011} \times (0.8526126, \text{ if female})$

eGFR was shown as ml/min/1.73 m<sup>2</sup>; Scr was shown as mg/dl (except in XiangYa equation shown as umol/l), to convert Scr from umol/l to mg/dl, divide by 88.4; cysC was shown as mg/l. For CKD-EPI<sub>Scr</sub> and Asian CKD-EPI<sub>Scr</sub> equation, a = 141, if male; a = 144, if female; b = 0.9 if male; b = 0.7, if female; c = -0.411, if male, Scr ≤ 0.9 mg/dl; c = -1.209, if male, Scr > 0.9 mg/dl; c = -0.329, if female, Scr ≤ 0.7 mg/dl; c = -1.209, if female, Scr > 0.7 mg/dl. For CKD-EPI<sub>cysC</sub> equation, a = -0.499, if cysC ≤ 0.8 mg/l; a = -1.328, if cysC > 0.8 mg/l. For CKD-EPI<sub>Scr-cysC</sub> equation, a = 135, if male; a = 130, if female; b = 0.9, if male; b = 0.7, if female; c = -0.207, if male, Scr ≤ 0.9 mg/dl; c = -0.061, if male, Scr > 0.9 mg/dl; c = -0.248, if female, Scr ≤ 0.7 mg/dl; c = -0.061, if female, Scr > 0.7 mg/dl. d = -0.375, if cysC ≤ 0.8 mg/l; d = -0.711, if cysC > 0.8 mg/l. For FAS<sub>Scr</sub> equation, Q<sub>Scr</sub> was the mean or median Scr value for age-/specific healthy populations, matched with age or with median height obtained from Belgian national growth curves; Q<sub>Scr</sub> = 0.9 mg/dl, if male; Q<sub>Scr</sub> = 0.7 mg/dl, if female; But for Korean revised, Q<sub>Scr</sub> = 0.96 mg/dl, if male; Q<sub>Scr</sub> = 0.7 mg/dl, if female. For FAS<sub>cysC</sub> equation, Q<sub>cysC</sub> = 0.82 mg/l, if age < 70; Q<sub>cysC</sub> = 0.95 mg/l, if age ≥ 70. For FAS<sub>Scr-cysC</sub> equation, α and 1-α are weighted by Scr / Q<sub>Scr</sub> and cysC / Q<sub>cysC</sub>, α = 0.5 in the study.

## Statistical analysis

Continuous variables were performed as mean ± standard (SD), categorical variables were performed as percentage (%). Normally distributed groups of variables were computed with t-test, Skewed distributed variables were tested using nonparametric tests Wilcoxon and Mann-Whitney U, Categorical variables were computed with chi-square test, P < 0.05 were considered statistically significant. <sup>99m</sup>Tc-DTPA mGFR was taken as reference value of actual GFR, Bias was assessed as the median difference between mGFR and eGFR (mGFR-eGFR). Precision was assessed as the inter-quartile range (IQR) for the differences. Accuracy was assessed as root mean square error (RMSE) relative to mGFR and the percentage of eGFR deviating within 30% of mGFR (P30), which was proposed in K/DOQI clinical practice guideline [24]. Receiver-operating characteristic (ROC) curves were computed for CKD diagnosis according to mGFR and eGFR (CKD are diagnosed based on 2012 clinical practice guideline [15]). Concordance between mGFR and eGFR were compared using the Intraclass correlation coefficient (ICC). The Bland-Altman plot analysis was used to calculate mean difference and precision between mGFR and eGFR. McNemar test

and kappa value was used to assess the CKD stages agreement between mGFR and eGFR categories. Subgroups were based on mGFR < 60 or  $\geq 60$  ml/min/1.73 m<sup>2</sup> and age < 70 or  $\geq 70$  years old. All statistical analysis were computed using SPSS software (version 22.0; SPSS Chicago, IL, USA) and GraphPad Prism for Windows (version 7.04; GraphPad software, San Diego, California, IL, USA).

## Results

### Basic characteristics

Of the 623 patients, 383 were male and 240 were female. The mean age was 56.89 years. There were 480 adults under 70 years old and 143 elderly people over 70 years old. The mean height and weight were 166.13 meters and 66.09 kg. The average values of Scr and cysC were 1.75 mg/dl and 1.74 mg/l, respectively. The primary cause of CKD was chronic glomerulonephritis (33.5%), followed by hypertensive nephropathy (30.2%) and diabetic nephropathy (15.2%), which was consistent with the world epidemiological survey of chronic kidney disease [25]. In the elderly group over 70 years old, the most common primary disease was hypertensive nephropathy (47.6%), followed by chronic nephritis (21.7%) and diabetic nephropathy (16.1%). The mean <sup>99m</sup>Tc-DTPA mGFR was 49.31 ml/min/1.73 m<sup>2</sup>, and it was 53.01 ml/min/1.73 m<sup>2</sup> in adults under 70 years old and 36.86 ml/min/1.73 m<sup>2</sup> in the elderly population over 70.

### Performance results of different equations in all subjects

The bias, precision and accuracy of each eGFR equation computed for all subjects are shown in Table 3. All equations were compared with the CKD-EPI<sub>Scr</sub> equation. Regarding the equation based on only the Scr concentration, the MDRD equation performed superior to the others, with the lowest bias (-8.53), relatively lower precision (IQR of 21.99), and the highest accuracy (P30 of 53.5%) but was not significantly different from the results of CKD-EPI<sub>Scr</sub>. The XiangYa equation performed the worst, with the highest bias (-15.31), highest precision (IQR of 14.92), and lowest accuracy (P30 of 43.0%). The equation based on only cysC performed integrally superior to those based on Scr alone. The CKD-EPI<sub>cysC</sub> and FAS<sub>cysC</sub> equations showed relatively lower bias (-4.65 and -7.49, respectively), moderate precision (IQR of 21.97 and 18.41, respectively), and higher accuracy (P30 of 56.7% and 56.0%, RMSE was 21.1 and 23.16, respectively), and both equations were significantly different from CKD-EPI<sub>Scr</sub>. The FAS<sub>Scr-cysC</sub>, combining both Scr and cysC, exhibited moderate bias (-8.10) and precision (IQR of 17.66), supreme accuracy (P30 reached 57.5%, RMSE was 19.26), and significantly higher performance than the CKD-EPI<sub>Scr-cysC</sub> equation (P30 of 52.2%). Generally, the FAS equation based on the combination of Scr and cysC performed better than the other equations, and the cysC-based equation showed higher accuracy than the Scr-based equation.

Table 3  
The performance of the eGFR equations in all subjects

	Bias	Precision	Accuracy	
	Median difference	IQR of the difference	P30	RMSE
All subjects	-8.53**	21.99	53.5%	25.09
MDRD	-10.67	24.83	48.8%	22.40
CKD-EPI <sub>Scr</sub>	-13.88**	27.71	42.9%*	25.43
Asian CKD-EPI <sub>Scr</sub>	-4.65**	21.97	56.7%**	21.11
CKD-EPI <sub>cysC</sub>	-7.39**	25.09	52.2%	23.10
CKD-EPI <sub>Scr-cysC</sub>	-10.16	20.51	51.4%	23.82
FAS <sub>Scr</sub>	-10.37*	21.38	50.4%	24.88
Korean FAS <sub>Scr</sub>	-7.49**	18.41	56.0%*	23.16
FAS <sub>cysC</sub>	-8.10**	17.66	57.5%**	19.26
FAS <sub>Scr-cysC</sub>	-15.31*	14.92	43.0%*	19.89
XiangYa				

Bias was median difference between mGFR and eGFR; IQR was the inter-quartile range of the difference; P30 was the proportion of eGFR within 30% of mGFR, RMSE was root mean square error relative to mGFR; \*P < 0.05, \*\*P < 0.01, compared with CKD-EPI<sub>Scr</sub>

## Performance results of different equations in subgroups

The performance of each eGFR equation in the CKD subgroups and age subgroups is shown in Tables 4 and 5. mGFR  $\geq$  60 ml/min/1.73 m<sup>2</sup> was defined as slightly reduced GFR, and mGFR < 60 ml/min/1.73 m<sup>2</sup> was defined as moderately-to-severely reduced GFR. The results of the subgroup analyses differed from the results of all subjects. In subgroups with mGFR  $\geq$  60 ml/min/1.73 m<sup>2</sup>, the XiangYa equation showed the lowest bias (-5.79), highest precision (IQR of 18.21) and the highest accuracy (P30 of 86.2%, RMSE was 16.68), which met the criterion of P30  $\geq$  75% established in the 2002 K/DOQI clinical practice guidelines[24]. The equation with the second best performance was the FAS<sub>cysC</sub> equation (bias of -10.49, P30 of 61.9%), followed by the FAS<sub>Scr-cysC</sub> equation, which performed equivalent to the MDRD equation (bias of -16.16 and -16.62, P30 of 61.4%). However, in the subgroups with mGFR < 60 ml/min/1.73 m<sup>2</sup>, the XiangYa equation had the worst performance, with the highest bias (-19.05), highest precision (IQR of 10.85) and lowest accuracy (P30 of 21.1%). The CKD-EPI<sub>cysC</sub> equation showed the lowest bias (-2.23), moderate precision (IQR of 15.16) and the highest accuracy (P30 of 57.4%), followed by the FAS<sub>Scr-cysC</sub> equation (P30 of 55.4%). All of the equations were significantly associated with the CKD-EPI<sub>Scr</sub> equation.

Table 4  
The performance of the eGFR equations in mGFR subgroups

	Bias	Precision	Accuracy	
	Median difference	IQR of the difference	P30	RMSE
<b>mGFR ≥ 60 ml/min/1.73 m<sup>2</sup></b>				
MDRD	-16.62**	25.76	61.4%	33.31
CKD-EPI <sub>Scr</sub>	-19.55	23.78	55.2%	26.57
Asian CKD-EPI <sub>Scr</sub>	-24.68**	23.63	44.8%*	30.79
CKD-EPI <sub>cysC</sub>	-15.84*	36.17	55.2%	29.71
CKD-EPI <sub>Scr-cysC</sub>	-22.77**	32.29	48.1%	33.68
FAS <sub>Scr</sub>	-18.63	25.17	57.6%	32.24
Korean FAS <sub>Scr</sub>	-19.82	25.51	54.8%	34.01
FAS <sub>cysC</sub>	-10.49**	33.95	61.9%	34.43
FAS <sub>Scr-cysC</sub>	-16.16**	27.21	61.4%	27.27
XiangYa	-5.79**	18.21	86.2%**	16.68
<b>mGFR &lt; 60 ml/min/1.73 m<sup>2</sup></b>				
MDRD	-5.31**	18.59	49.4%	19.63
CKD-EPI <sub>Scr</sub>	-7.14	21.20	45.5%	19.94
Asian CKD-EPI <sub>Scr</sub>	-9.21**	23.16	41.9%	22.21
CKD-EPI <sub>cysC</sub>	-2.23**	15.16	57.4%*	14.94
CKD-EPI <sub>Scr-cysC</sub>	-3.38**	16.27	54.2%	15.10
FAS <sub>Scr</sub>	-7.14*	16.05	48.2%	18.09
Korean FAS <sub>Scr</sub>	-7.14*	16.02	48.2%	18.59
FAS <sub>cysC</sub>	-6.69*	14.49	53.0%*	14.36
FAS <sub>Scr-cysC</sub>	-6.89*	13.36	55.4%**	13.46
XiangYa	-19.05**	10.85	21.1%**	21.34
Bias was median difference between mGFR and eGFR; IQR was the inter-quartile range of the difference; P30 was the proportion of eGFR within 30% of mGFR, RMSE was root mean square error relative to mGFR; *P < 0.05, **P < 0.01, compared with CKD-EPI <sub>Scr</sub>				

Table 5  
The performance of the eGFR equations in age subgroups

	Bias	Precision	Accuracy	
	Median difference	IQR of the difference	P30	RMSE
<b>Age &lt; 70 years</b>				
MDRD	-7.99**	23.15	57.9%*	25.13
CKD-EPI <sub>Scr</sub>	-11.36	25.79	51.0%	22.81
Asian CKD-EPI <sub>Scr</sub>	-15.25**	29.61	43.8%*	26.09
CKD-EPI <sub>cysC</sub>	-5.69**	24.76	55.8%	22.44
CKD-EPI <sub>Scr-cysC</sub>	-8.86*	29.19	51.9%	24.59
CKD-EPI <sub>Scr-cysC</sub>	-12.00**	21.54	51.5%	25.22
FAS <sub>Scr</sub>	-12.87**	22.78	50.2%	26.51
Korean FAS <sub>Scr</sub>	-8.12**	20.24	56.7%	25.05
FAS <sub>cysC</sub>	-9.43*	20.27	57.5%*	20.55
FAS <sub>cysC</sub>	-14.71	14.84	47.9%	18.96
FAS <sub>Scr-cysC</sub>				
XiangYa				
<b>Age ≥ 70 years</b>				
MDRD	-10.23**	19.96	38.5%	24.96
CKD-EPI <sub>Scr</sub>	-9.13	20.47	41.3%	20.97
Asian CKD-EPI <sub>Scr</sub>	-11.30**	22.60	39.9%	23.07
CKD-EPI <sub>cysC</sub>	-2.23**	13.21	59.4%**	15.83
CKD-EPI <sub>cysC</sub>	-4.86**	14.49	53.1%*	17.17
CKD-EPI <sub>Scr-cysC</sub>	-8.05**	13.38	48.3%	17.27
BIS-1 <sub>Scr</sub>	-4.90**	12.98	57.3%**	14.05
BIS-2 <sub>Scr-cysC</sub>	-6.12**	14.06	51.0%	18.34
BIS-2 <sub>Scr-cysC</sub>	-6.12**	14.06	51.0%	18.34
FAS <sub>Scr</sub>	-5.78**	14.27	53.8%*	15.14
Korean FAS <sub>Scr</sub>	-5.33**	13.25	57.3%**	14.08
FAS <sub>cysC</sub>	-20.39**	14.75	26.6%**	22.75
FAS <sub>cysC</sub>				
FAS <sub>Scr-cysC</sub>				
XiangYa				
Bias was median difference between mGFR and eGFR; IQR was the inter-quartile range of the difference; P30 was the proportion of eGFR within 30% of mGFR, RMSE was root mean square error relative to mGFR; *P < 0.05, **P < 0.01, compared with CKD-EPI <sub>Scr</sub>				

In the subgroups of adults aged < 70 years, the MDRD equation performed almost equivalent to the FAS<sub>Scr-cysC</sub> equation (P30 of 57.9% and 57.5%, respectively); however, the MDRD equation had lower bias (-7.99 and - 9.43, respectively) and lower precision (IQR of 23.15 and 20.27, respectively). Both equations were significantly associated with the CKD-EPI<sub>Scr</sub> equation. In older adults aged ≥ 70 years, the CKD-EPI<sub>cysC</sub> had the lowest bias (-2.23), relatively higher precision (IQR of 13.21) and the best accuracy (P30 of 59.4%). The FAS<sub>Scr-cysC</sub> equation had a similar performance to the BIS-2<sub>Scr-cysC</sub> equation (bias of -5.33 and - 4.90, IQR of 13.25 and 12.98, respectively; P30 of 57.3). The XiangYa equation had the worst performance, with the highest bias (-20.39), moderate precision (IQR of 14.75) and the lowest accuracy (P30 of 26.6%). These four equations mentioned above were significantly associated with the CKD-EPI<sub>Scr</sub> equation.

## Comparison between mGFR and eGFR

The CKD stage diagnostic accuracy of eGFR equations and the ICC values between mGFR and eGFR are shown in Table 6. CKD was defined by  $mGFR < 60 \text{ ml/min/1.73 m}^2$ , and CKD stage was divided according to the 2012 clinical practice guidelines. The ROC curves of the main equations, including the  $FAS_{Scr-cysC}$ ,  $CKD-EPI_{cysC}$ , XiangYa, and  $CKD-EPI_{Scr}$  equations, are graphed in Fig. 1. In total, the best  $ROC^{AUC}$  was from the  $FAS_{Scr-cysC}$  Eq. (0.951), with a sensitivity of 88.57% and specificity of 87.65%. Next, was  $CKD-EPI_{Scr-cysC}$  (0.950), with a sensitivity of 85.71% and a specificity of 88.62%. Nevertheless, the MDRD equation had the lowest  $ROC^{AUC}$  (0.925). For the division concordance of CKD stages, the  $FAS_{Scr-cysC}$  equation had the highest kappa value (0.364), followed by the  $CKD-EPI_{Scr-cysC}$  Eq. (0.345). The concordance between the mGFR and each eGFR was graphed as a Bland-Altman plot, as shown in Fig. 2. The  $CKD-EPI_{cysC}$ ,  $FAS_{cysC}$  and  $FAS_{Scr-cysC}$  equations showed relatively higher concordance with mGFR, as the mean bias between them was 7.46, 9.84, and 10.29  $\text{ml/min/1.73 m}^2$ , respectively. In addition, the  $BIS-2_{Scr-cysC}$  equation showed higher concordance than the  $BIS-1_{Scr}$  equation with a lower bias of 4.30  $\text{ml/min/1.73 m}^2$ . The highest ICC value was obtained by the  $FAS_{Scr-cysC}$  Eq. (0.921). Second, the XiangYa equation had an ICC of 0.912. These two eGFR equations showed very good correlation with mGFR, with an ICC > 0.91.

Table 6  
The concordance and diagnostic accuracy between mGFR and eGFR

Equation	CKD stages						ROC <sup>AUC</sup>	Sensitivity	Specificity	kappa	ICC
	1	2	3a	3b	4	5					
All subject											
mGFR	53	157	114	124	123	52	0.925**	84.19	82.26	0.333**	0.872
MDRD	128	177	80	86	92	60	0.935**	82.86	89.35	0.264**	0.906
CKD-EPI <sub>Scr</sub>	171	149	75	78	90	60	0.935**	82.86	89.35	0.243**	0.898
Asian	195	135	75	76	85	57	0.938**	88.10	83.78	0.331**	0.891
CKD-EPI <sub>Scr</sub>	134	127	68	104	133	57	0.950**	85.71	88.62	0.345**	0.899
CKD-EPI <sub>cysC</sub>	153	137	71	92	108	62	0.936**	89.52	82.57	0.301**	0.894
CKD-EPI <sub>cysC</sub>	148	157	86	92	100	40	0.935**	90.00	82.32	0.291**	0.889
EPI <sub>Scr-cysC</sub>	154	151	87	94	97	40	0.937**	92.38	80.87	0.315**	0.874
CKD-EPI <sub>Scr-cysC</sub>	107	150	94	136	123	13	0.951**	88.57	87.65	0.364**	0.921
FAS <sub>Scr</sub>	127	142	99	111	113	31	0.930**	87.14	84.02	0.126**	0.912
FAS <sub>cysC</sub>	68	279	137	101	38	0					
FAS <sub>Scr-cysC</sub>											
XiangYa											
Age ≥ 70 years											
mGFR	3	13	27	39	44	17	0.828**	87.50	75.59	0.248**	0.830
BIS-1 <sub>Scr</sub>	2	35	33	34	28	11	0.870**	87.50	74.80	0.322**	0.867
BIS-2 <sub>Scr-cysC</sub>	1	25	33	34	38	12					
*P < 0.05, **P < 0.01, equations were compared with mGFR in all subjects except for BIS equations used in older people age ≥ 70 year old; Kappa was K interpretation; 0.81-1 almost perfect(very good); 0.61–0.80 substantial(good); 0.41–0.60 moderate; 0.21–0.40 fair; 0.00-0.20 slight; <0.00 poor;											
ICC was intraclass correlation coefficient; ICC > 0.91 showed very good correlation; 0.71 < ICC < 0.91 showed good correlation; 0.51 < ICC < 0.71 showed moderate correlation; 0.31 < ICC < 0.51 showed bad correlation and ICC < 0.31 showed very bad correlation											

## Discussion

We have been committed to evaluating the most accurate and clinically practical equation for the Chinese population out of the internationally popular GFR estimation equations in recent years. The results of our study showed that the FAS<sub>Scr-cysC</sub> equation was most suitable for estimating GFR in Chinese adults because of its superior accuracy (P30 of 57.5%), excellent concordance with mGFR (ICC of 0.921) and good diagnostic accuracy (ROC<sup>AUC</sup> of 0.951, Kappa value was 0.364) for all subjects. Moreover, its advantage that it can be used for the full age spectrum increases its clinical practicality. However, we still found that the CKD-EPI<sub>cysC</sub> equation had advantages when applied to individuals with moderately and severely reduced GFR (GFR < 60 ml/min/1.73 m<sup>2</sup>) and adults over 70 years, as its low bias (-2.23), high accuracy (57.4% and 59.4%), and lowest mean bias (7.46) were shown in Bland-Altman plots. Otherwise, the XiangYa equation was confirmed to be appropriate for individuals with

slightly reduced GFR ( $\text{GFR} \geq 60 \text{ ml/min/1.73 m}^2$ ) due to its low bias (-5.79), high precision (18.21), high accuracy (86.2%), and very good concordance with mGFR (ICC of 0.912).

The FAS equation was developed on the basis of the average GFR of the human body before the age of 40 being approximately  $107.3 \text{ ml/min/1.73 m}^2$ . After 40 years of age, the GFR decreases at the level of  $1 \text{ ml/min/1.73 m}^2$  per year, and the rate of decline is approximately 0.988[26]. Chai L et al performed the first study to suggest the applicability of the FAS equation in Chinese CKD patients and showed that the  $\text{FAS}_{\text{Scr}}$  equation had lower bias (1.28) and higher accuracy (P30 of 63.64, RMSE was 19.49 in adults under 70 years and 14.06 in elderly individuals over 70 years) than the CKD-EPI equation or the MDRD equation in a single-centre study of 396 subjects in eastern China [27]. Another single-centre study of 162 subjects conducted by Xie P et al in northern China found that the  $\text{FAS}_{\text{Scr}}$  equation had excellent concordance with the result measured by the  $^{99\text{m}}\text{Tc-DTPA}$  dual plasma sample clearance method ( $\text{mGFR} = -0.374 + 1.029\text{eGFR}$  ( $p < 0001$ )), even performing better than the results measured by the  $^{99\text{m}}\text{Tc-DTPA}$  renal dynamic imaging method (bias-1.22 vs 8.92, precision 15.69 vs 18.36, P30 75.31% vs 59.26%) [28]. A Korean study by Jeong TD et al compared the  $\text{FAS}_{\text{Scr}}$  equation with the  $\text{CKD-EPI}_{\text{Scr}}$  equation in a retrospective study of 1312 patients and found that the performance of the Korean  $\text{FAS}_{\text{Scr}}$  equation was equivalent to that of the  $\text{CKD-EPI}_{\text{Scr}}$  equation with low bias (-0.2) and high accuracy (P30 of 75.8%, RMSE was 15.8) [20]. However, we did not find that the Korean calibrated  $\text{FAS}_{\text{Scr}}$  equation performed better than the primitive  $\text{FAS}_{\text{Scr}}$  equation in our study of a Chinese population (bias - 10.37 vs -10.16, IQR 21.38 vs 20.51, P30 50.4% vs 51.4%, RMSE 24.88 vs 23.82). Yong Z et al first conducted a multicentre validation study comparing the FAS and CKD-EPI equations in Chinese adults and verified that the  $\text{FAS}_{\text{Scr-cysC}}$  equation performed favourably with the lowest bias (-2.87), highest precision (IQR of 19.01), highest accuracy (P30 of 74.16%, RMSE was 17.84) and an  $\text{ROC}^{\text{AUC}}$  of 0.953. Furthermore, the  $\text{FAS}_{\text{Scr-cysC}}$  equation exhibited an absolute advantage in the elderly population over 60 years with the highest accuracy (P30 of 70.37%, RMSE was 15.21)[29]. In our study, we found that the  $\text{FAS}_{\text{Scr-cysC}}$  equation performed second only to the  $\text{CKD-EPI}_{\text{cysC}}$  equation in individuals with  $\text{mGFR} < 60 \text{ ml/min/1.73 m}^2$  or adults over 70 years. However, we also obtained similar results in that the  $\text{FAS}_{\text{Scr-cysC}}$  equation performed best in all subjects and had good diagnostic accuracy. Several factors may explain the conclusion. First, the FAS equation was developed for a Caucasian population. The Q value in the FAS equation is mainly based on the characteristics of the white Belgian growth curve. The nutritional status and dietary structure of Chinese people are differentiated from those of European or American white or black individuals[30]. The ideal Q value that is applicable should match the different characteristics of the Chinese population[11]. Second, the FAS combined equation assigns  $\text{Scr}/\text{Q}_{\text{Scr}}$  and  $\text{cysC}/\text{Q}_{\text{cysC}}$  according to weight. The weights of the two factors in this study each account for 50%. In fact, the optimal proportion of creatinine and cystatin C for the calculation results is not yet conclusive. However, regardless of the development of the CKD-EPI equation or FAS equation, the combination of creatinine and cystatin C could reduce the imprecision of either biomarker alone[19, 31]. Third, we found that the  $\text{CKD-EPI}_{\text{cysC}}$  equation obviates the race/ethnicity coefficient. However, the calibration coefficients of the various equations in the Chinese race are all greater than 1[32], and there is a paradox between them. Therefore, it is necessary to carry out multicentre and multiethnic equation verification for Chinese people.

Creatinine is produced by muscle catabolism and secretion by kidney tubular cells. Its concentration is greatly affected by the body's nutritional status and muscle mass. Poor nutritional status, infection along with an inflammatory state, or disability will affect the production of creatinine, leading to an inability to accurately assess renal function, especially between sexes. Cystatin C is less affected by muscle protein content and is totally reabsorbed in the proximal tubules. The changes in the concentration of cystatin C are relatively stable. A

retrospective cohort study conducted by Wang Y et al with 308 patients with diabetic nephropathy in southwestern China reclassified 39% of patients with poor prognosis in CKD stages 1–2 to CKD stages 3–5 by the CKD-EPI<sub>cysC</sub> equation compared with the results of the CKD-EPI<sub>Scr</sub> equation (the median survival of the reclassified and not reclassified groups was 52 and 94 months, respectively)[33], which indicated that the CKD-EPI<sub>cysC</sub> equation could sensitively detect kidney injury, especially in individuals with moderately and severely reduced GFR; the same conclusion was reached in our study. Yang M et al performed a retrospective study of 632 CKD patients from two general hospitals in southeastern China and verified that the cystatin C-based equation had an advantage over the creatinine-based equation, especially in patients with CKD stages 3–5; the CKD-EPI<sub>cysC</sub> equation had the lowest bias (-4,10), best precision (IQR of 17.35), and best accuracy (P30 of 50.5%, RMSE was 0.93) when GFR was < 60 ml/min/1.73 m<sup>2</sup>[34]. These results were similar to those in our study, proving the advantage of the CKD-EPI<sub>cysC</sub> equation in Chinese individuals with moderately and severely reduced GFR. Moreover, a cohort study of 70 patients who underwent kidney transplantation conducted in Korea revealed that the ROC<sup>AUC</sup> for cystatin C at the cut-off value of 45 ml/min/1.73 m<sup>2</sup> was 0.800 (that for creatinine was 0.763), and the best predictive value for cystatin C was 1.27 mg/L, with a sensitivity of 77.8% and specificity of 78.8%[35]. The study also showed the diagnostic advantage for the cystatin C-based equation in predicting renal function, as GFR < 45 ml/min/1.73 m<sup>2</sup> may indicate significant kidney injury among transplant recipients.

In this study, we also found that the CKD-EPI<sub>cysC</sub> equation performed well in elderly individuals over 70 years of age. According to the law of GFR decline with age, whether GFR < 60 ml/min/1.73 m<sup>2</sup> is used as the diagnostic criterion for CKD in the elderly population is controversial, which was proposed in the BIS equation study[17]. Epidemiological studies have shown that elderly patients over 65 years old account for 53.07% of the CKD population in China[36]. A single-centre study conducted by Ye X et al among Chinese elderly CKD patients aged ≥ 60 years showed that the CKD-EPI<sub>cysC</sub> equation did not perform well (bias of -9.05, IQR of 19.61, P30 of 71.74%, RMSE was 18.50). However, the BIS-1<sub>Scr</sub> and BIS-2<sub>Scr-cysC</sub> equation performed better, with lower bias (-5.20 and -8.65), better precision (IQR of 21.58 and 16.31), and higher accuracy (P30 of 79.1%, RMSE was 17.20 and 16.94) [37]. Another cross-sectional study of 218 elderly patients over 75 years of age conducted by Changjie G et al in southern China found that the BIS-2<sub>Scr-cysC</sub> equation performed best (bias of 0.63, IQR of 4.36, P30 of 94.50%, RMSE was 7.21) rather than the CKD-EPI<sub>cysC</sub> equation (bias of 3.86, IQR of 17.07, P30 of 67.89%, RMSE was 17.22) [38]. These results both showed the opposite conclusion compared to the conclusion of our study. We found that the FAS<sub>Scr-cysC</sub> equation performed equivalently to the BIS-2<sub>Scr-cysC</sub> equation but had slightly more bias in our study. However, considering the constitution of the equation, it was convenient to use the FAS equation in clinical practice. As a special population, the elderly population often combines various complications other than nephropathy with decreases in nutritional status and immune function. For cardiovascular disease, cerebrovascular diseases, and people who take vasoactive drugs, the applicability of eGFR equations remains to be further verified.

The MDRD equation performed best among the equations based on creatinine alone in all subjects, but the accuracy was significantly lower when GFR was < 60 ml/min/1.73 m<sup>2</sup>, which is consistent with the conclusion that the accuracy of the MDRD equation decreased when renal function was moderately reduced, as previously reported by Murata K et al. Even though the CKD-EPI<sub>Scr</sub> equation enhanced the specificity of the detection of GFR < 60 ml/min/1.73 m<sup>2</sup> compared with that of the MDRD Eq. (98% vs 94%), at the cost of reducing the sensitivity (50% vs 70%), the creatinine-based equation was still maligned in CKD patients [39]. The XiangYa equation is a new creatinine-based equation developed in recent years based on the central Chinese population. This equation has been externally verified in a Han population in central China and the Uighur population in western China. To our

knowledge, we performed the first study to validate the XiangYa equation with four other main equations together in one centre. Surprisingly, we found that the XiangYa equation performed excellently in individuals with a  $GFR \geq 60$  ml/min/1.73 m<sup>2</sup> and had a good ICC value with mGFR. However, we also made a similar conclusion that it performed terribly in individuals with  $GFR < 60$  ml/min/1.73 m<sup>2</sup> and the elderly population. This issue may be related to the original development subjects of the XiangYa equation causing significant bias, as the mean age was 52.34 with an SD of 13.23, and the mean mGFR was 71.320 ml/min/1.73 m<sup>2</sup> with an SD of 23.96[21].

In this study, the accuracy P30 of each equation was found to be less than 70%. This is because the plasma biochemical indexes included in this study were from 48 hours before kidney nuclear radiograph, and it was not necessarily the same result as in the morning. This was in line with the current procedures of most hospitals in China. Due to the large population in China, the imbalance between doctors and patients, and limited medical resources, biochemical blood tests and imaging examinations are often unable to be synchronized. Using biochemical test results from within 48 hours to assess renal function is not unacceptable for CKD. In recent reports, the rate of change in biomarkers was shown to be smaller than that in kidney nuclear radiography. The eGFR computed by equations is at least as reliable as the mGFR measured by nuclear medicine for monitoring patients over time[10]. The comparative verification data adopted in this study are more applicable to China's national conditions, and its statistical results have more practical clinical significance.

We verified the effect of the current popular equation on the evaluation of renal function in adult patients in central China. We must take into account the limitations of this study. First, we only enrolled Chinese Han individuals in this single-centre experiment. China is a multi-ethnic and multi-regional country. Different living customs lead to diverse human physiques, and different medical conditions contribute to inconsistent diagnoses of CKD in various regions. We will consider involve more ethnic groups in our multi-center verification research. Second, the method of assaying serum creatinine and cystatin C in this study may be different from those used in the derivation studies for the above equations, so was the <sup>99m</sup>Tc-DTPA used for mGFR measurement. Although the difference may exist in assaying equipment and materials, the current assaying level can be traced back to international certification standards, as a consequence its results are acceptable. Systematic assessment can be performed to evaluate the influence of different assaying methods on the performance of eGFR equation forward. Third, this was a retrospective validation study, and the concentration of blood biochemical indexes came from one-time testing. We were not able to evaluate the accuracy of eGFR assessed by each equation in terms of a dynamic change in renal function. Considering that the renal function of CKD patients does not change significantly in the short term, it is advisable to evaluate the calculation results of patients in hospitalization and discharging together for a comprehensive analysis in the future study.

## Conclusion

The FAS equation based on the combination of Scr and cysC is considered more suitable and simpler for the Chinese population. The CKD-EPI<sub>cysC</sub> equation is most accurate in individuals with moderately and severely reduced GFR and seniors over 70 years old. The Chinese-developed XiangYa equation is appropriate for normal or mildly injured GFR; however, its prediction accuracy still needs to be verified in individuals with moderately or severely reduced GFR and older adults.

## Abbreviations

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; <sup>99m</sup>Tc-DTPA: Technetium-99m-diethylenetriaminepentaacetic acid; MDRD: Modification of Diet in Renal Disease; CKD-EPI :Chronic Kidney Disease Epidemiology Collaboration; BIS: Berlin Initiative Study; FAS: Full age spectrum; IDMS: Isotope dilution mass spectrometry; Scr: serum creatinine; cysC: Cystatin C; KDIGO: Kidney disease improving global outcomes ; IQR: Inter-quartile range; RMSE: Root mean square error; ICC: Intraclass correlation coefficient; ROC: Receiver-operating characteristic; AUC: Area Under the Curve.

## Declarations

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### Availability of data and materials

The datasets analyzed during the current study are not publicly available due to the privacy of patients as well as joint ownership of research data in our institution. The data are available from the corresponding author on reasonable request, and the contact way can get through by email to [xiliusa2000@126.com](mailto:xiliusa2000@126.com)

### Authors' contributions

SF, YGH, and XNL conceived the study and participated in the design of the study; MY, SX and SW collected the data; SF analyzed the data and drafted the manuscript; XX and YGH carried out the experiments. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

This study was conducted with the permission of the Ethics Committee of the Zhongnan Hospital of Wuhan University. Written informed consent was obtained from each subject prior to participation.

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### Consent for publication

Not applicable.

### Competing interests

All the authors declare that there is no conflict of interest

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## Figures

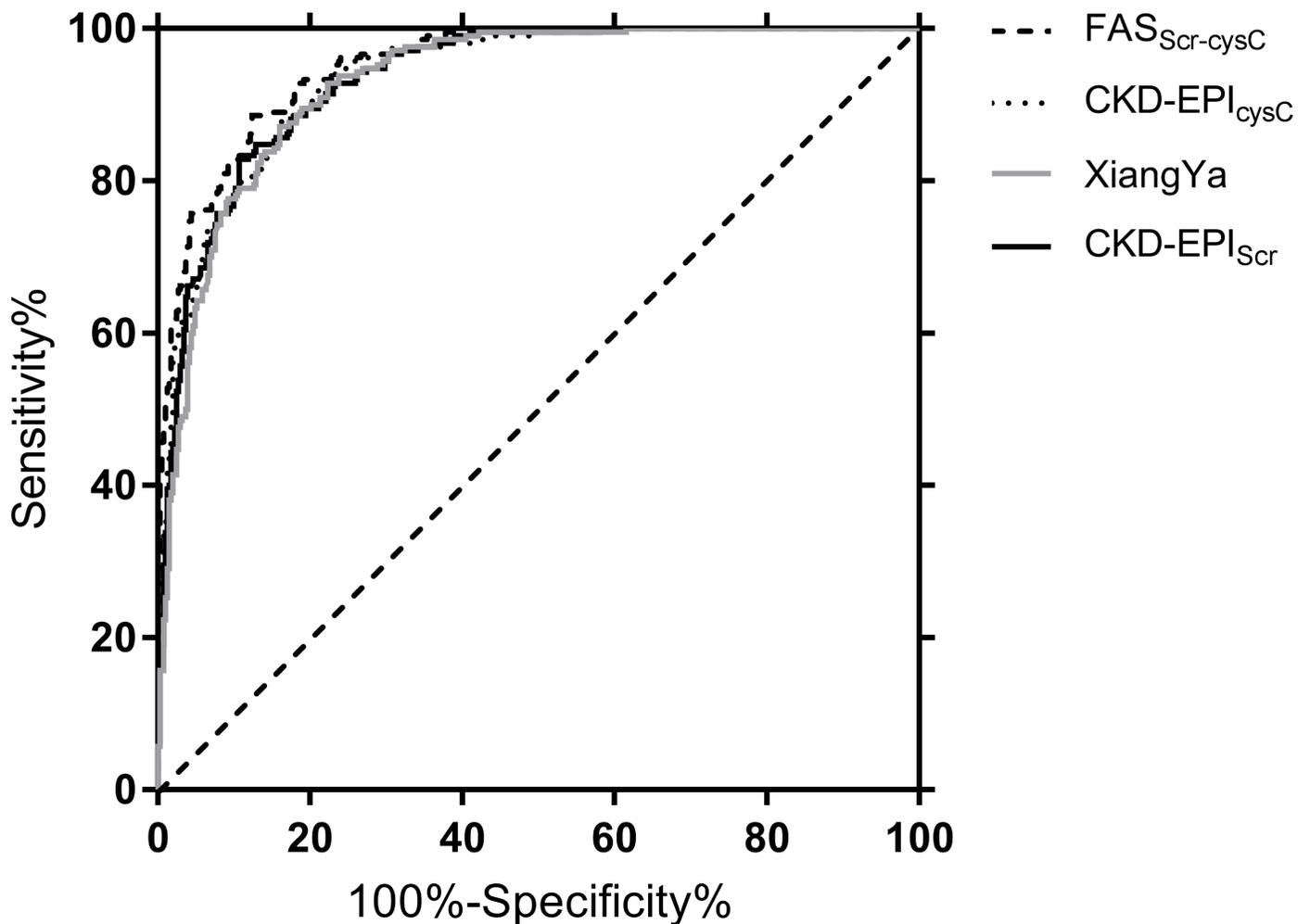


Figure 1

The ROC curve of equations for diagnose CKD in all subjects

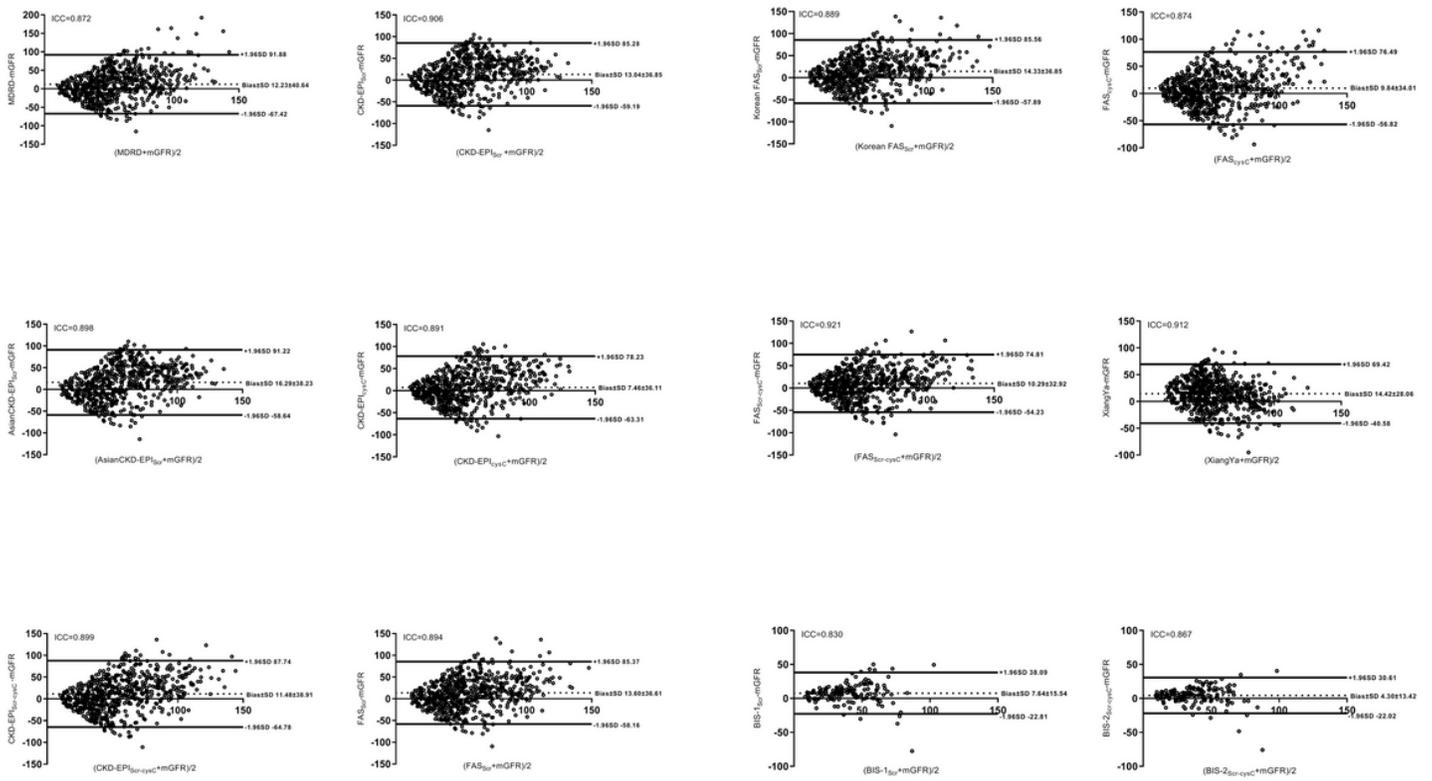


Figure 2

The Bland-Altman plot of comparison between eGFR and mGFR