A novel nomogram to predict the reliability of estimated glomerular filtration rate formula in oncology patients

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Research article

Keywords: estimated glomerular filtration rate, measured glomerular filtration rate, Cockcroft–Gault formula, nomogram

Posted Date: September 19th, 2019

DOI: https://doi.org/10.21203/rs.2.14670/v1

Version of Record: A version of this preprint was published at BMC Cancer on May 24th, 2020. See the published version at https://doi.org/10.1186/s12885-020-06997-w.

Abstract

Background Formulae of estimated glomerular filtration rate (eGFR) based on serum creatinine (Scr) are routinely used in oncology patients, however, they are inaccurate in some populations. Our aim was to identify population characteristics where eGFR formulae performed poorly and thereby build a nomogram to predict the reliability of estimates. Methods Measured GFR (mGFR) using isotope from 444 oncology patients were compared with eGFR from four formulae (Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration and Wright). Multivariate logistic regression was applied to identify characteristics associated with inaccurate eGFR and construct a predictive nomogram. Results The Cockcroft–Gault formula exhibited estimates with lowest bias and highest precision. Nonetheless, it was still unreliable in a relevant proportion of patients. The percentage of patients within 30%, 20%, and 10% of the accurate percentage error (APE) was seen in only 62.8%, 47.7% and 24.8% of patients respectively. Inaccuracy was found in overweight patients or in patients with BUN/Scr ratio greater than 20 or with eGFR greater than 120 ml/min. A novel nomogram was constructed to help oncologists to predict the risk of inaccuracy of eGFR. The calibration curve showed good agreement. Conclusions Our results suggest that all eGFR formulae tend to overestimate the eGFR in oncology patients. Our nomogram may assist oncologists in decision-making when mGFR is needed.

Background

Accurate assessment of the glomerular filtration rate (GFR) is important in drug dosing, decision making and assessing the prognosis of oncology patients. Radioisotopic methods have been used as accurate GFR measurements in clinical practice [1, 2]. However, these methods are relatively costly, time consuming and require blood sampling. As a substitute, several formulae have been developed to calculate the estimated glomerular filtration rate (eGFR) based on serum creatinine (Scr) concentration, as well as on age, sex and weight of the patient [3-6].

There have been some reports about the accuracy of these creatinine-based eGFR formulae in oncology patients. However, most of them showed that the performance of the eGFR formulae were unacceptable and thus the precision of chemotherapy dosing was low in some oncology patients [7-9]. Such inaccuracy may result in severe side effects, including death. Therefore, it is necessary to recognize the population where eGFR formulae are unreliable and alternative GFR measurements should be employed. Some studies indicated that creatinine-based eGFR formulae were less accurate in elderly and obese populations [10-12]. However, a limited number of studies were based on an oncology population [12].Furthermore, to our best knowledge, none of these studies took into account other potential confounding factors, such as sex, nutritional status and comorbidities.

To bridge the gap in current knowledge, we determined to evaluate the performance of the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration and Wright formulae in estimating GFR compared with the measurement of the GFR using technetium-99m diethyl triamine penta-acetic acid (^{99m}Tc-DTPA). More importantly, we aimed to identify

the characteristics influencing the accuracy of eGFR formulae. A clinically applicable nomogram was constructed to recognize the populations at high risk of inaccurate eGFR and thereby measurements of GFR should be used.

Methods

Patients

We enrolled oncology patients with histologically confirmed and measured GFR (mGFR) by ^{99m}Tc-DTPA in the Tongji Hospital of Huazhong University of Science and Technology (Wuhan, China) from January 2013 to December 2016.

Patients younger than 18 years old or with missing information were excluded. Patients with acute kidney injury or on any kind of renal replacement therapy were also excluded. Finally, the population consisted of 444 patients.

Laboratory method and GFR calculations

GFR was measured by radioisotopic method using ^{99m}Tc-DTPA. All procedures were performed at the Nuclear Medicine Department of Tongji Hospital of Huazhong University of Science and Technology. The GFR was measured after a single intravenous injection of approximately 185 MBq (in < 1 ml) ^{99m}Tc-DTPA. The mGFR was reported as ml/min.

Serum creatinine was measured by Roche enzymatic assay (Shanghai Roche Diagnostic Products Co, Ltd, China) within a week before measurement of GFR. The last one was chosen for patients with multiple records. The eGFR was calculated by 4 formulae, including Cockcroft–Gault, MDRD, CKD-EPI, and Wright. The details of formulae used in this study are presented in Table 1.

Statistical Analyses

Continuous variables are described as mean and standard error (SD), with univariate comparisons performed using the Student's t-tests. Categorical variables were assessed by $\chi 2$ or Fisher's exact test, as appropriate.

The performance of all formulae was assessed using bias, precision, and accuracy. The degree of bias for each formula was quantified by percentage error (PE) between the eGFR and mGFR. Precision was assessed by absolute percentage error (APE). Accuracy was assessed as the percentage of patients within 30%, 20%, and 10% of the APE (P30, P20, P10).

An estimate of the APE greater than 30 is defined as an inaccurate eGFR. To be able to construct a prediction model that is clinically relevant while also being simple to use, categorization were performed for continuous variables. The significant factors on univariate logistic regression analysis along with clinical relevant factors were entered into a multivariate logistic regression analysis. Backward selection

based on the Akaike information criterion (AIC) was used to filter out factors that were entered into a predictive model [13]. The final model equation was then organized as a nomogram. Discrimination of the nomogram was assessed using the area under the receiver operating characteristic curve (ROC). Calibration was assessed using a calibration curve. Given that the predictive model tends to be overfitted to the original sample, a bootstrapping resampling (200 repetitions) was used for internal validation to obtain relatively unbiased estimates.

Statistical analyses were performed with R version 3.4.0. All tests were two-sided and $P < 0.050$ was considered statistically significant.

Results

Patient characteristics

General demographic and clinical characteristics for the 444 identified patients are given in Table 2. Mean age was 57 ± 12 years old and 66.7% patients were women. The mean mGFR was 68 ± 21 ml/min.

Performance of eGFR formulae

The distribution of eGFR for the four formulae was shifted to the right, compared with the mGFR (Figure 1). For all formulae, the eGFR tended to overestimate the mGFR. The absolute difference between eGFR and mGFR was greater than 30% in more than one third of the oncology patients (Table 3). Given that Cockcroft-Gault formula exhibited best performance among four formulae, we explored factors that would affect the accuracy of eGFR based on the Cockcroft-Gault formula.

Factors associated with inaccurate eGFR

Using multivariate logistic regression analysis, we noted that the poor accuracy of the Cockcroft–Gault formula was independently associated with BMI, eGFR level and BUN/Scr ratio (Table 4). The percentage error of the Cockcroft-Gault formula was notably increased with increasing BMI, BUN/Scr ratio and eGFR (Figure 2).

Prediction model for inaccurate eGFR calculated by the Cockcroft–Gault formula

A nomogram was generated based on four variables, including sex, BMI, eGFR level and BUN/Scr ratio (Figure 3). A higher total point scores as calculated by the sum of the assigned number of points for each predictors in the nomogram was associated with a higher likelihood of inaccurate eGFR as calculated by the Cockcroft–Gault formula in oncology patients. For example, a man (1.5 points) with BMI over 28kg/m^2 (5.9 points), eGFR between 80 and 120 ml/min (0.5 points) and BUN/Scr ratio over 20 (1.9 points) would have a total of 9.8 points score, and therefore have a 65 percent predicted risk of inaccurate eGFR as calculated by the Cockcroft–Gault formula.

The predictive model had an area under curve (AUC) of 0.771 (95% CI, 0.698–0.845) after the 200 repetitions of bootstrap sample corrections. The goodness-of-fit of the nomogram was assessed by producing a calibration plot, which revealed good agreement between the predicted and observed probabilities (Figure 4).

Discussion

An accurate assessment of the Glomerular Filtration Rate (GFR) is essential in oncology patients to ensure safe prescribing of chemotherapy drugs, detecting kidney injury and assessing prognosis. Inulin clearance is considered as gold standard of the GFR measurement. Nonetheless, it cannot be applied in routine clinical practice. Radioisotopic methods have a high correlation with inulin clearance and thus remains the most widespread method for accurate calculation of the GFR. The most common radioisotopes used include chromium 51 EDTA□51Cr-EDTA□and technetium-99m diethyl triamine penta-acetic acid (^{99m}Tc-DTPA) [1, 2]. However, these methods are relatively expensive, invasive and time consuming. Consequently, oncologists often rely on formulae to estimate the GFR on the basis of serum creatinine and other parameters.

Oncologists should pay attention to the limitation of eGFR formulae. Oncology patients may have low muscle mass and reduced dietary protein intake, which would influence the concentration of serum creatinine and thus the performance of eGFR formulae [14]. In our study, the fraction of patients with eGFR absolute percentage error >30% is more than one-third in all formulae, which is consistent with previous studies [7, 15]. This means that a great number of oncology patients received wrong diagnosis and drug dosage. Therefore, it is inappropriate to apply eGFR formulae to all oncology patients. Oncologists should identify populations where eGFR formulae based on serum creatinine is not likely to provide an accurate estimate and thus alternative measurements of the GFR should be considered. Some studies have demonstrated that the performance of eGFR formulae may be affected by age, weight and GFR [10-12, 16]. However, a limitation among prior studies was that only univariate analysis was performed and thus confounding factors were not controlled. To address this limitation, we used multivariate logistic regression analysis to identify the independent factors associated with the poor accuracy of eGFR formulae.

Oncologists need to be vigilant when using formulae to assess the kidney function in overweight or obese populations. It has been reported that the Cockcroft–Gault formula showed a tendency to overestimate GFR in oncology and other populations where overweight or obesity were considered [10, 17]. We confirmed this finding in our study. It seems that lean oncology patients suffer more from cachexia and malnutrition in clinical practice and would exhibit worse estimates of the GFR. However, in fact, more attention is needed in overweight patients instead of lean ones when estimating the GFR. Of great interest is that Cockcroft and Gault clearly stated it was probably not applicable to use their formula in obese populations [3]. This is understandable because the Cockcroft–Gault formula is only one that incorporates body size as an important index. Besides, some studies suggested that application of the

alternate weight descriptors can improve the accuracy of Cockcroft–Gault formula, such as ideal body weight [18] and adjusted body weight [19], but these strategies is not yet validated in large population.

BUN/Scr ratio may be an indicator of the accuracy of eGFR formulae. BUN/SCr ratio greater than 20 is known as a marker of pre-renal renal dysfunction [20]. Poggio et al. found that the Cockcroft–Gault and MDRD formulae were not reliable in sick hospitalized patients, especially those with high BUN/SCr ratio [21]. However, little is known about the association of elevated BUN/SCr ratio and accuracy of eGFR formulae in oncology patients. We found that the Cockcroft–Gault formula was likely to be inaccurate in oncology patients with high BUN/SCr ratio. Possible explanation for our observations is that BUN/SCr ratio may rise in oncology patients with low rate of creatinine generation, and creatinine-based eGFR formulae would perform poorly accordingly.

Normal estimates of the GFR might not be actually that normal. In subgroup patients of higher eGFR, Cockcroft-Gault formula showed low accuracy and great degree of overestimation, which is consistent with reports from studies consisting of population with normal renal function, such as kidney donors [22, 23]. This means that kidney injury will be wrongly labeled as normal kidney function and the degree of renal damage will be underestimated, which encourages oncologists to make wrong decisions regarding the administration of iodinated contrast medium, employment of nephrotoxic drugs and the time to initiate renal replacement therapy. Besides, narrow therapeutic index is a pharmacokinetic characteristic of most chemotherapy agents. A well-known example of such agents is carboplatin, whose dose is adjusted by Calvert formula incorporating the GFR as an important variable [24]. As a consequence, overestimated GFR may result in overdosage of chemotherapy agents, particularly those agents which are entirely eliminated by the kidneys in unchanged active form. Ultimately, inaccurate assessment of the GFR means severe side effects, as well as increasing incidence of renal insufficiency, or even death.

An important facet of this study is that a nomogram was developed to predict the reliability of eGFR as calculated by the Cockcroft-Gault formula in oncology patients. The nomogram is a simple graphical prediction tool. By assigning points to the four variables, oncologists can assess the predictive risk of individuals. This provides clinically useful information and guide personalized clinical decision-making regarding whether to use accurate GFR measurements for oncology patients. Furthermore, our nomogram is constructed on the basis of readily available clinical data making it easy for clinicians to use. Internal validation indicated good performance with area under ROC of 0.743 and accurate calibration.

We acknowledge several limitations in this study. Firstly, due to the retrospective nature of our study, there might have been selection bias and unknown confounders in the analysis. Secondly, even though we collected many characteristics in our patient's population, there still exists some factors that were not analyzed in our study, including cancer type, dietary intake, prior treatments and other medications. Finally, although the nomogram was validated internally by bootstrap resampling, external validation using an independent data set was required before routine use.

Conclusions

On the basis of our findings, neither the Cockcroft–Gault formula nor other formulae can be a perfect substitute of the GFR as measured using radioisotopes. Oncologists must be aware of the limitations of eGFR formulae when treating overweight patients with eGFR greater than 120 ml/min, as well as patients with BUN/Scr ratio greater than 20. We constructed a nomogram that could help clinicians to predict the reliability of eGFR as calculated by the Cockcroft–Gault formula.

Abbreviations

GFR: Glomerular filtration rate; eGFR: Estimated glomerular filtration rate; Scr: Serum creatinine; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology; ^{99m}Tc-DTPA: Technetium-99m diethyl triamine penta-acetic acid; mGFR: Measured GFR; BSA: Body surface area; BMI: Body mass index; SD: Standard error; PE: Percentage error; APE: Absolute percentage error; AIC: Akaike information criterion; ROC: Receiver operating characteristic curve; BUN: Blood urea nitrogen; OR: Odds ratio; AUC: Area under curve; 51Cr-EDTA: Chromium 51 EDTA

Declarations

Ethics approval and consent to participate

The study protocol was approved by the medical ethics committee of Tongji Hospital. Because of the retrospective nature, plus no individually identifiable or sensitive information was involved, informed consents from all patients had been waived.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors have declared no conflicts of interest.

Funding

This work was financially supported by Major Research plan of the National Natural Science Foundation of China (Grant No. 91742204); International (regional) cooperation and exchange projects, (NSFC-DFG, Grant No. 81761138041), National Natural Science Foundation of China (Grants 81470948, 81670633, 81570667), National key research and development program Grants 2016YFC0906103and The

National Key Technology R&D Program (Grant 2013BAI09B06□2015BAI12B07). The funding body was not involved in the design of the study, collection, analysis, and interpretation of data, nor the writing the manuscript. The content is solely the responsibility of the authors.

Authors' contributions

SG and XG conceived and designed the study. CY and HY collected the data and performed statistical analysis. CY and VC wrote the paper. HL and GS reviewed and edited the manuscript. All authors read and approved the manuscript.

Acknowledgements

The authors are grateful to the Department of Nuclear Medicine, Tongji Hospital, Tongji medical College, Huazhong University of Science and Technology for their kind help.

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Tables

Table 1. Calculations used

	Equations
BSA (m^2)[DuBois]	$0.007184 \times Weight^{0.425} \times Height^{0.725}$
BMI (kg/m^2)	$Weight(kg)/Height(m)^2$
Calvert (mg)	AUC × (GFR + 25)
Cockcroft-Gault (ml/min)	(×0.85, if female)
MDRD (ml/min)	$175 \times SCr^{-1.154} \times Age^{-0.203} \times \times$(0.742,if female) (×1.212, if black)
CKD-EPI (ml/min)	$141 \times \min(,1)^{\alpha} \times \max(,1)^{-1.209} \times 0.993^{Age} \times$ (×1.018,if female)(×1.159,if black) Note: κ is 0.7 for females and 0.9 for males, α is−0.329 for females and −0.411 for males.
Wright（ml/min）	

BSA , body surface area (m^2); BMI, body mass index; GFR, glomerular filtration rate; Age, age in years; Weight, weight in kilograms; SCr, serum creatinine (mg/dl).

Table 2. Patients Characteristics

Characteristic	Mean ± SD	Range
Sex, male, n(%)	296 (66.7)	
Age	57 ± 12	23-88
Weight (kg)	64 ± 11	35-93
Height (cm)	165 ± 8	142-185
BSA (m^2)	1.71 ± 0.16	1.27-2.17
BMI(kg/m^2)	23.4 ± 3.2	14.2-32.0
Albumin (g/L)	38.5 ± 4.6	23.9-69.3
BUN (mmol/L)	5.9 ± 2.0	1.6-14.0
Scr (μmol/L)	88 ± 37	39-386
BUN/Scr ratio	17.6 ± 6.0	4.5-53.0
Hemoglobin (g/L)	126 ± 22	43-188
mGFR(ml/min)	68 ± 21	12-137
Diabetes, n (%)	44 (9.9)	
Hypertension, n (%)	140 (31.5)	
Metastasis, n (%)	49 (11.0)	
Obstructive nephropathy, n (%)	104 (23.4)	

Data are presented as the mean ± SD and *N* (%).BSA, body surface area; BMI, body mass index; BUN, blood urea nitrogen; Scr, serum creatinine; mGFR, measured glomerular filtration rate

Table 3. Performance of Equations

Equations	MPE	MAPE	P30	P20	P10
CG	17.8 [cd]	27.8[cd]	62.8[d]	47.7[d]	24.8
	(14.7, 20.8)	(25.5, 30.1)	(58.3, 67.3)	(43.2, 52.4)	(20.8, 28.8)
MDRD	19.2[cd]	27.8[cd]	63.0[d]	46.2[d]	24.3
	(16.2, 22.0)	(25.5,29.9)	(58.6, 67.6)	(41.5, 50.8)	(20.3, 28.3)
CKD-EPI	22.9[abd]	29.2[abd]	60.6[d]	43.7[d]	21.6
	(20.0, 25.7)	(26.9, 31.4)	(56.0, 65.1)	(39.1, 48.3)	(17.8, 25.5)
Wright	30.7[abc]	34.5[abc]	51.9[ab]	37.4[ab]	20.2
	(27.6, 33.6)	(27.6, 33.6)	(47.4, 56.7)	(32.9, 41.9)	(16.5, 24.0)

Data are presented with 95% CIs. MPE, mean percentage error; MAPE, mean absolute percentage error; P30, P20, P10, percentage of patients within 30%, 20%, 10% that estimated from the measured glomerular filtration rate.

[a]p < 0.01 compared with CG equation

[b]p < 0.01 compared with MDRD equation

[c]p < 0.01 compared with CKD-EPI equation

[d]p < 0.01 compared with Wright equation

Table 4. Logistic regression analysis for factors associated with inaccurate eGFR using Cockcroft-Gault.

	Univariate analysis		Multivariate analysis	
	OR(95%CI)	P value	OR(95%CI)	P value
Age (years)				
<50	1.00 (reference)		1.00 (reference)	
50-64	0.49 (0.31, 0.79)	0.003	0.68 (0.39, 1.20)	0.391
≥65	0.48 (0.28, 0.80)	0.006	0.83 (0.41, 1.67)	0.412
Sex, male	1.27 (0.84, 1.92)	0.264	1.5 (0.92, 2.46)	0.108
BMI (kg/m^2)				
<20	1.00 (reference)		1.00 (reference)	
20-24.9	1.76 (0.93, 3.46)	0.089	1.49 (0.75, 3.05)	0.263
25-27.9	2.90 (1.55, 5.72)	0.001	1.86 (0.92,3.93)	0.093
≥28	7.16 (2.98, 18.20)	<0.001	4.33 (1.65,11.87)	0.003
Albumin (g/L)				
<40	1.00 (reference)		1.00 (reference)	
≥40	1.45 (0.98, 2.16)	0.063	1.16 (0.73,1.84)	0.519
eGFR (ml/min)				
<80	1.00 (reference)		1.00 (reference)	
80-89	1.92 (1.25, 2.96)	0.003	1.55 (0.92,2.62)	0.103
≥120	14.24 (6.39, 36.37)	<0.001	10.3 (4.1,28.96)	<0.001
BUN/Scr ratio				
<20	1.00 (reference)		1.00 (reference)	
≥20	1.74 (1.14, 2.66)	0.011	1.63 (1,2.65)	0.048
Anemia	0.61 (0.39, 0.97)	0.035	1.09 (0.63, 1.88)	0.505
Obstructive nephropathy	0.59 (0.36, 0.95)	0.032	0.84 (0.48,1.45)	0.539

All variables listed in the table were included in the logistic regression model. OR, odds ratio; 95% CIs, 95% confidence intervals; BMI, body mass index; eGFR, estimated glomerular filtration rate; BUN, blood urea

nitrogen; Scr, serum creatinine; BUN/Scr ratio, blood urea nitrogen to creatinine ratio

Figures

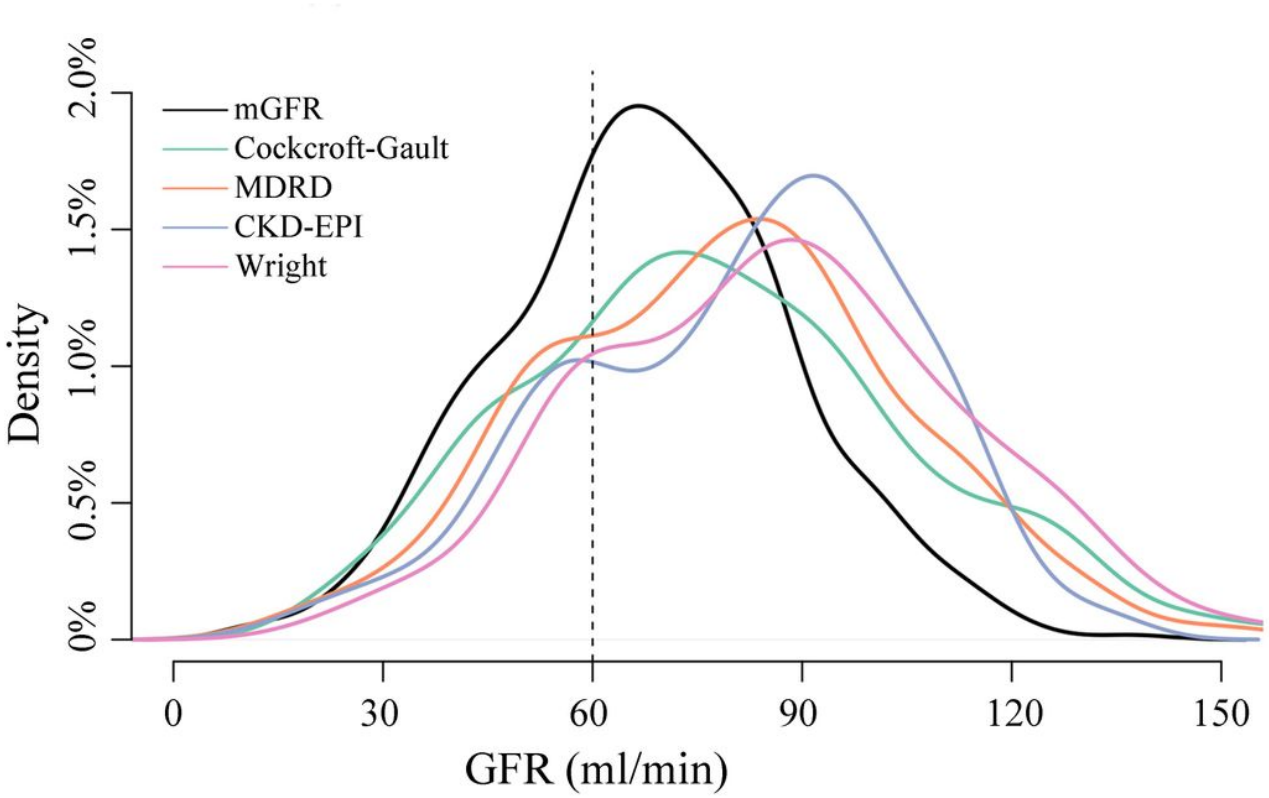

Figure 1

Distribution and CKD prevalence of eGFR and mGFR. Distributions are demonstrated using kernel density plots.

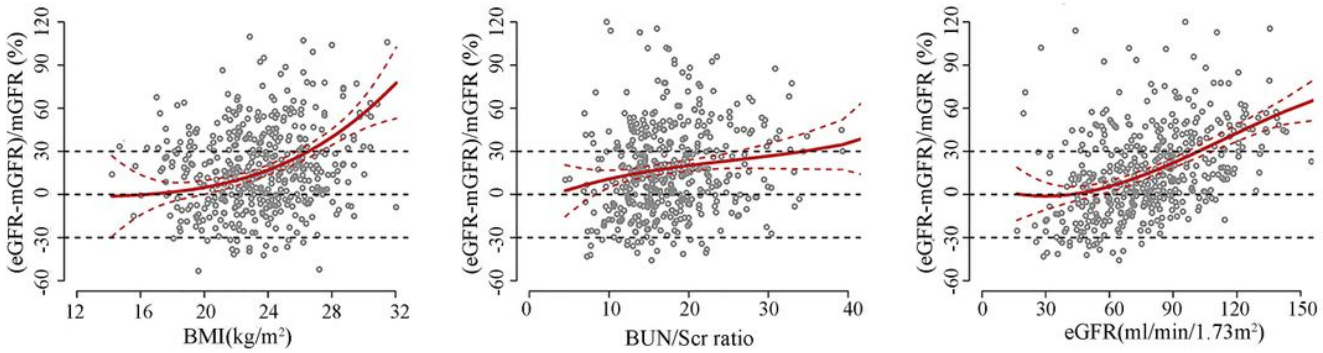

Figure 2

Percentage error of the Cockcroft-Gault formula by BMI, BUN/Scr ratio and estimated GFR. Solid line represents the regression line and dashed lines represent 95% confidence intervals for the regression line. eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; BMI, body mass index; BUN, blood urea nitrogen; Scr, serum creatinine; BUN/Scr ratio, blood urea nitrogen to creatinine ratio.

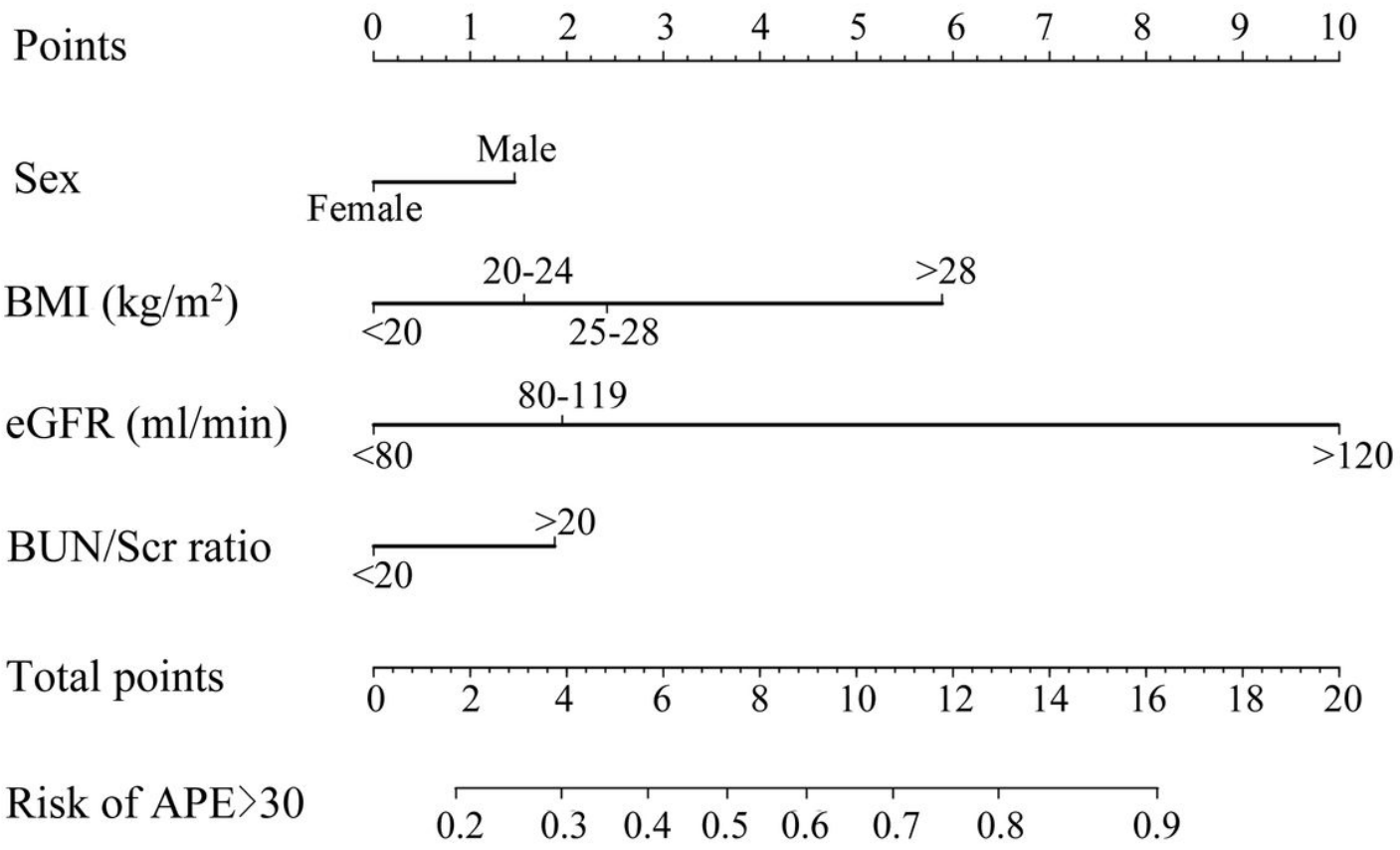

Figure 3

Nomogram predicting the risk of inaccurate eGFR calculated as by the Cockcroft-Gault formula. BMI, body mass index; BUN/Scr ratio, blood urea nitrogen to creatinine ratio; APE, absolute percentage error.

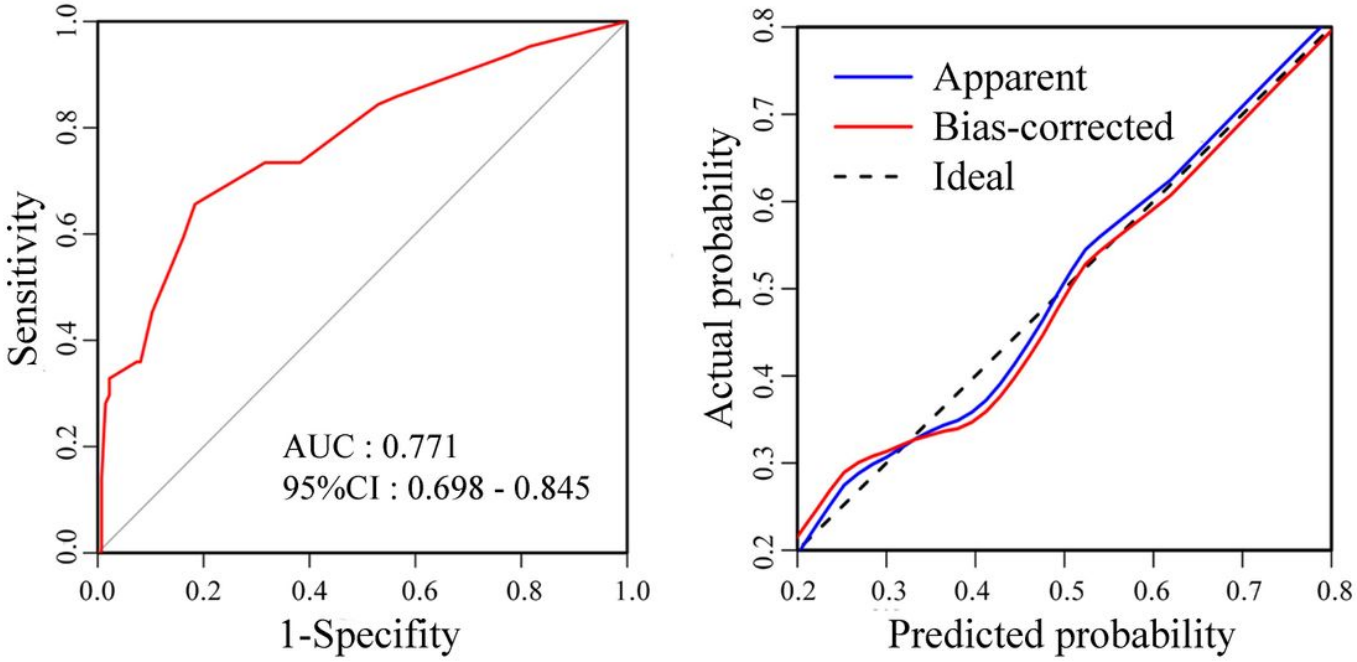

Figure 4

Internal validation of nomogram. (a) Receiver operating characteristic (ROC) curve. (b) Calibration curve.