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Evaluation of Serological Indicators and Glomerular Filtration Rate Equations in Chinese Cancer Patients

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The performance of estimated glomerular filtration rate (eGFR) have been proved to vary according to the races of the target population. The eGFR equations have not been validated in the Chinese cancer population received chemotherapy. Meanwhile, serum cystatin C (CysC), urea, β2 microglobulin (β2-MG), and creatinine (SCr) were also evaluated in a cohort of Chinese cancer patients.

Material/Methods: A total of 1000 cancer patients undergoing combination chemotherapy and 108 healthy volunteers were included in this study, and their renal function parameters were evaluated. The eGFR values were compared with reference GFR (rGFR) according to correlation, consistency, precision, and accuracy. Receiver operating characteristic (ROC) curves were used to evaluate the discriminating ability of the GFR equations and serological indicators of renal function.

Results: (1) The equations contained CysC had the same varying tendency as rGFR in relation to the chemotherapeutic cycle. (2) $eGFR_{scr+cysc}$ and $eGFR_{Chinese\ scr+cysc}$ worked better than the other equations, as indicated by a stronger correlation, less bias, improved precision, higher accuracy, and greater AUC. (3) CysC was more sensitive than the other serological indicators for identifying early renal injury. (4) Each parameter showed different characteristics in subgroups of Chinese cancer patients.

Conclusions: CysC was the most sensitive marker for early renal injury. Among the 8 most commonly used eGFR equations, the combination equation $eGFR_{scr+cysc}$ and $eGFR_{Chinese\ scr+cysc}$ exhibited the best performance in the assessment of the renal function of Chinese cancer patients.

MeSH Keywords: Cystatin C • Drug Therapy, Combination • Glomerular Filtration Rate • Renal Insufficiency, Chronic

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Background

As the average age of a population increases, a corresponding increase in the prevalence of malignant tumors can be seen. The use of chemotherapeutic agents in patients with malignant tumors has led to a major increase in the overall survival time of cancer patients. Despite this survival increase, patients with malignant tumors are at high risk for renal impairment (RI) caused by chemotherapy. Chronic kidney disease (CKD) has been reported in 15–50% of cancer patients [1,2]. Therefore, kidney function should be monitored to recognize RI as early as possible [3]. The evaluation of renal function should be performed as part of the follow-up during and after chemotherapy in cancer patients.

Glomerular filtration rate (GFR) is the most important parameter of kidney function, and inulin clearance remains the criterion standard GFR tracer; however, it is inconvenient and difficult to measure. The clearance of radionuclide (^{51}Cr-EDTA or ^{99m}Tc-DTPA) is considered to be closest to that of inulin, but it is radioactive and its use is time-consuming. Therefore, there is growing interest in finding accurate and simple methods to estimate the GFR to access glomerular filtration function. Serum creatinine (SCr) is most commonly used to estimate GFR, but the serum levels of creatinine are often influenced by many non-renal factors, such as sex, muscle mass, protein intake, and metabolism. The low-molecular-weight protein (12.8 kDa) cystatin C (CysC) is being considered as a replacement for SCr for the estimation of GFR. Unlike SCr, it is not affected by dietary protein intake and is independent of changes in GFR [4]. The Cockcroft-Gault (CG) formula, published in 1976, was developed to predict creatinine clearance [5]. The formula derived from the Modification of Diet in Renal Disease (MDRD) study included 6 variables (creatinine, urea, albumin, age, sex, and race) [6]; this equation was simplified in 2000 to include only 4 variables and was subsequently re-expressed for use with standardized SCr in 2007 [7]. Both the creatinine and CysC methods have been standardized, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for the estimation of GFR were established in 2012 [8,9]. To exclude the influence of race, the CKD-EPI developed a creatinine-based equation with an ethnicity adjustment in 2011 [10]. The Chinese eGFR Investigation Collaboration developed a modified equation for use in Chinese CKD patients [11,12]. The utility of eGFR equations in evaluating renal function in cancer patients has been reported in many studies [13–16]. However, the aim of the present study was to reappraise the performances of the new CKD-EPI 2012 equations, the Chinese equations, and the MDRD equations in a Chinese oncology cohort who had received chemotherapy. We also evaluated SCr, urea, β2-microglobulin (β2-MG), and CysC performance in the diagnosis of RI in the cohort of Chinese cancer patients.

Material and Methods

Patient selection

A total of 1000 cancer patients (596 males and 404 females) aged 25–83 years (average age 60.3±10.4 years) were recruited from the patients admitted to Tianjin Medical University Cancer Institute and Hospital during the period from October 2012 to December 2014. All patients received combination chemotherapy (with or without platinum), and when they finished chemotherapy, we screened out 545 cancer patients with CKD. The inclusion criteria for patients with CKD according to the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease included the following: (1) Presence of 1 or more of the following markers of kidney damage: a. albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g [≥3 mg/mmol]), b. urine sediment abnormalities, c. electrolyte and other abnormalities due to tubular disorders, d. abnormalities detected by histology, f. structural abnormalities detected by imaging, and g. history of kidney transplantation; and (2) GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5). Either of the above criteria needed to be present for >3 months for inclusion. The exclusion criteria were: (1) acute kidney function deterioration, (2) severe cardiac insufficiency, (3) pleural or abdominal effusion, (4) edema, (5) diabetes, (6) primary kidney disease, and (7) disabled limbs or amputation. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. The members of the control group were selected from a group of volunteers and healthy individuals (n=108).

Ethics statement

All patients signed a written informed consent form prior to inclusion in the study and our study was approved by our local Ethics Committee.

Specimen and data collection

Three days before specimen collection, patients were asked to avoid a high-protein diet, meat, and strenuous exercise. In addition, the specimens were collected after 8 h of fasting, and the optimal blood sampling time was 7: 00 AM to 9: 00 AM. For outpatients, sitting for 15 min was required before specimen collection. Then, we collected serum specimens before chemotherapy and after the first, second, third, fourth, fifth, and last chemotherapy cycles. Prior to chemotherapy and after all chemotherapy cycles, all collected serum specimens were allowed to stand for 2 h, followed by centrifugation at 3000 rpm for 5 min. The ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) dual-plasma clearance was applied to measure GFR on the same day. The procedures used to process the samples were the same for the control and experimental groups. For each enrolled individual, age, sex, race, body surface area (BSA),

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Table 1. GFR-predicting equations used in this study.

2009 CKD-EPI creatinine equation($eGFR_{scr}$) $=141\times\min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [×1.018 if female] [×1.159 if black], (κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males)
2012 CKD-EPI cystatin C equation($eGFR_{cysc}$) $=133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age}$ [×0.932 if female]
2012 CKD-EPI creatinine-cystatin C equation($eGFR_{scr+cysc}$) $=135 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-0.601} \times \min(SCysC/0.8, 1)^{-0.375} \times \max(SCysC/0.8, 1)^{-0.711} \times 0.995^{Age}$ [× 0.969 if female] [× 1.08 if black](κ is 0.7 for females and 0.9 for males, α is –0.248 for females and –0.207 for males)
CKD-EPI 4 level equation($eGFR_{CKD\text{-}EPI\ Asian}$) $= 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.210} \times 0.993^{Age} \times 0.993$ [if female] × 1.16 [if Black] × 1.05 [if Asian] × 1.01 [if Hispanic and Native American] (κ is 0.7 for females and 0.9 for males, α is –0.412 for females and –0.328 for males)
MDRD equation using 4 variable ($eGFR_{MDRD}$) $=186 \times SCr^{-1.154} \times Age^{-0.203}$[× 0.742 if female]
IDMS-MDRD equation($eGFR_{IDMS\text{-}MDRD}$) $=175 \times SCr^{-1.154} \times Age^{-0.203}$[× 0.742 if female]
Modified MDRD equation for Chinese CKD patients($eGFR_{Chinese\ MDRD}$) $=186 \times SCr^{-1.154} \times Age^{-0.203}$[× 0.742 if female] × 1.233(if Chinese)
Estimated GFR equation combining SCr and cysC by Chinese eGFR Investigation Collaboration($eGFR_{Chinese\ scr+cysc}$) $=169 \times SCr^{-0.608} \times SCysC^{-0.63} \times Age^{-0.157} \times 0.83$(if female)

SCr, CysC, urea, β2-MG, and reference GFR (rGFR) before chemotherapy and after each chemotherapy cycle were recorded.

Laboratory tests

The serum creatinine was measured by the enzymatic method (IDMS calibrated) (Shanghai Rongsheng Biotech Co., Ltd, Shanghai, China.). The GLDH Kinetic Assay (Beckman-Coulter Experiment System (SuZhou.) Co., Ltd, Suzhou, Jiangsu, China.) was used to measure urea levels. In addition, β2-MG and CysC were determined using the latex-enhanced immunoturbidimetric method (Beijing Strong Biotechnologies, Inc, Beijing, China.) and latex immunoturbidimetric method (Beijing Strong Biotechnologies, Inc, Beijing, China), respectively. The levels of all 4 parameters were determined using a BECKMAN-COULTER AU5800 device (Beckman-Coulter Instruments, Brea, CA, USA).

GFR measurement

The reference method for measuring GFR was the ^{99m}Tc-DTPA dual-plasma clearance, and the following equation was used to calculate rGFR (ml/min/1.73 m^2): [D ln(P1/P2)/(T2–T1)] exp{[(T1 ln P2)–(T2 ln P1)]/(T2–T1)}×0.93×1.73/BSA (D: dosage of drug injected, T1: 120 min, P1: amount of plasma activity at T1, counts per min×ml^{-1},T2: 240 min, P2: amount of plasma activity at T2, counts per min×ml^{-1}).

Estimated GFR equation

The expression of all equations is summarized in Table 1. GFR was calculated using 8 estimation formulas: MDRD equation [6], IDMS-MDRD equation [7], Chinese equations [11,12], CKD-EPI equations using creatinine alone [9], CysC alone or both [8], and the CKD-EPI 4-level equation [10]. rGFR categories were assigned according to the KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease as follows: G1 normal or high (>90 ml/min/1.73 m^2), G2 mildly decreased (60–89 ml/min/1.73 m^2), G3a mildly to moderately decreased (45-59 ml/min/1.73 m^2), G3b moderately to severely decreased (30–44 ml/min/1.73 m^2), G4 severely decreased (15–29 ml/min/1.73 m^2), and G5 kidney failure (<15 ml/min/1.73 m^2). In this study, early and moderate RI were defined as a GFR <90 ml/min/1.73 m^2 and GFR <60 ml/min/1.73 m^2, respectively.

Statistical analysis

All results are expressed as the mean values ± standard deviations. Results were considered to be significant at $p<0.05$. The independent samples *t* test was used to compare the experimental and control groups or 2 subgroups. One-way analysis of variance (ANOVA) was used for the comparison of the 3 subgroups. The paired *t* test was used to compare the indexes before and after chemotherapy. Correlations of parameters

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Table 2. Characteristics of the enrolled population.

	Cancer (pre chemotherapy)	Control	*p*
Number	1000	108	
Gender (M/F)	596/404	55/53	0.099
Age (years)	60.25±10.42	61.82±11.01	0.251
BSA (m^2)	1.73±0.12	1.73±0.15	0.834
Serum Cr (μmol/l)	72.38±21.12	52.02±7.44	<0.001*
Urea (mmol/l)	5.79±5.02	4.55±1.32	0.169
β2-MG (mmol/l)	2.60±1.26	1.71±0.44	0.065
CysC (mg/l)	1.03±0.34	0.83±0.18	0.003*
rGFR (ml/min/1.73 m^2)	90.07±23.96	106.04±19.69	0.057
Operated/unoperated	457/543		
Cancer type	n	Chemotherapy regimens	
Non-Hodgkin lymphoma	185	R-CHOP	
Hodgkin lymphoma	40	ABVD	
Lung cancer	443	TP/EC	
Esophagus cancer	168	FP/DC	
Gastric cancer	164	FOLFOX4	

Data were expressed mean ±SD. * Independent samples T test, $p<0.01$. R-CHOP – Rituximab + Cyclophosphamide + Adriamycin + Vincristine + Prednisone; ABVD – Adriamycin + Bleomycin + Vinblastine + Dacarbazine; TP – Taxol + Cis-platinum; EC – Epirubicin + Cyclophosphamide; FP – Fluorouracil + Cis-platinum; DC – Docetaxel + Camptosar; FOLFOX4 – Oxaliplatin + Calcium folinatc + Fluorouracil.

with rGFR were assessed using Pearson's (r) correlation coefficients. The accuracy refers to the percentage of GFR estimates within 10% and 30% of the rGFR. Accuracy between the formulas was compared using the chi-square test. A Bland-Altman plot, created using GraphPad Prism 6.00, was used to analyze the agreement between the rGFR and the values derived from the 8 eGFR equations. To determine the diagnostic consistency of the equations compared with the rGFR, receiver operating characteristic (ROC) curves were constructed and analyzed. A cutoff value was then proposed for each marker or equation with the best sensitivity and specificity. All statistical analyses were performed in SPSS 17.0 for Windows.

Results

Clinical characteristics of the enrolled population

The characteristics of the cancer population (n=1000) and the control population (n=108) are listed in Table 2. The serum Cr and CysC levels increased significantly in the cancer patients compared with the control group ($p<0.01$).

Evaluation of renal function parameters in different cycles of chemotherapy

The cancer patients were divided into 2 subgroups according to their chemotherapy regimen. rGFR and the 4 serological indicators of renal function in different cycles of chemotherapy are presented in Table 3. The number of chemotherapy cycles depends on what the physician at the beginning had decided to give to the patient, depending on cancer disease, performance state, and comorbidities. Patients may also stop chemotherapy for different reasons (such as renal failure). To eliminate the influence of these factors, methods are needed to compare the parameters after chemotherapy with those before chemotherapy. When cancer patients finished their chemotherapy, they were no longer involved in the study. rGFR began to decrease after 1 chemotherapeutic cycle in patients who received platinum-containing protocols, while β2-MG and CysC in the serum increased significantly (Table 3). However, for patients who received non-platinum-containing protocols, rGFR instead began to decrease after 4 chemotherapeutic cycles, and only CysC demonstrated an obvious rise at the same time (Table 3).

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Table 3. Comparison of parameters of patients in different cycles of chemotherapy.

	n	rGFR (ml/min/1.73 m²)	Serum Cr (μmol/l)	Urea(mmol/l)	β2-MG (mmol/l)	CysC (mg/l)
Platinum-containing protocols						
Before CT	440	91.48±24.26	74.40±25.11	6.44± 7.27	2.52± 1.10	1.01±0.37
After 1 cycle chemotherapy	440	84.45±24.35**	75.09±26.16	5.73 ±2.89	2.73 ±1.59*	1.19 ±0.49**
After 2 cycles chemotherapy	424	83.55±25.17**	74.76 ±33.18	5.81 ±3.73	2.83 ±1.69**	1.25 ±0.54**
After 3 cycles chemotherapy	398	83.65±26.28**	73.53±25.69	5.92±5.41	2.77 ±1.25**	1.25 ±0.49**
After 4 cycles chemotherapy	365	78.68±24.01**	74.92 ±25.07	5.83±1.99	2.82 ±1.27**	1.34±0.45**
After 5 cycles chemotherapy	323	70.74±21.52**	82.13±53.54	6.09 ±3.05	3.09±1.82**	1.57±0.59**
After 6 or more cycles chemotherapy	274	62.13±19.31**	81.38 ±32.02**	7.29 ±3.95	3.44±2.29**	2.09 ±1.68**
Non-platinum-containing protocols						
Before CT	560	88.97±23.73	70.80±17.26	5.28±1.73	2.67± 1.38	1.05±0.32
After 1 cycle chemotherapy	560	90.67±23.90	68.20±16.63	5.17 ±1.77	2.64 ±1.07	1.07±0.38
After 2 cycles chemotherapy	555	90.97±25.03	67.37±16.16	5.16±1.64	2.69 ±1.09	1.09 ±0.41
After 3 cycles chemotherapy	528	91.90±26.66	66.20±16.14	5.16±1.83	2.61 ±1.10	1.09 ±0.37
After 4 cycles chemotherapy	485	87.84±24.81*	66.29 ±18.27	5.50±4.31	2.51 ±1.31	1.19±0.39**
After 5 cycles chemotherapy	428	84.37±22.91*	67.06±23.02	5.37±2.06	2.60±1.06	1.25±0.41**
After 6 or more cycles chemotherapy	356	73.73±20.46**	71.06 ±31.82	5.96 ±3.60*	3.12±2.08	1.52±0.48**

Data were expressed mean ±SD. CT – chemotherapy. * Paired t-test, make comparison to before CT, $p<0.05$. ** Paired t-test, make comparison to before CT, $p<0.01$.

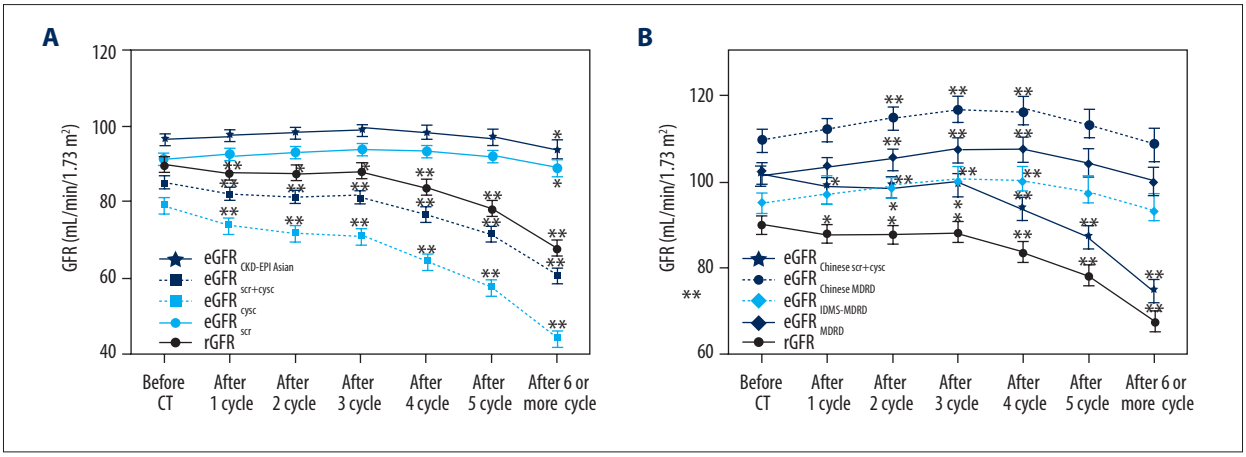

Figure 1. (**A, B**) cGFR (thick line) and the various eGFR presented according to chemotherapeutic cycle with 95% confidence intervals. * Paired *t* test, comparison before and after CT, $p<0.05$. ** Paired *t* test, make comparison before and after CT, $p<0.01$.

In Figure 1, the mean rGFR and eGFR values from all estimates for all 1000 cancer patients are presented in relation to the chemotherapeutic cycle. The results show that with the increasing number of chemotherapeutic cycles, rGFR gradually decreased and the rGFR began to decrease significantly after 1 cycle of chemotherapy ($p<0.05$). $eGFR_{cysc}$, $eGFR_{scr+cysc}$, and $eGFR_{Chinese\ scr+cysc}$ had the same varying tendency as rGFR. $eGFR_{scr}$ and $eGFR_{CKD\text{-}EPI\ Asian}$ began to decrease after 6 or more cycles of

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Table 4. Comparison of the eGFR regarding correlation, bias, precision and accuracy in control group and experimental group.

Performance	eGFRscr	eGFRcysc	eGFRscr+ cysc	eGFRCKD-EPI Asian	eGFRMDRD	eGFRIDMS-MDRD	eGFRChinese MDRD	eGFRChinese scr+cysc
Control (n=108) rGFR 106.04±19.69								
eGFR	105.84± 11.92	92.01± 18.60	99.81± 14.93	111.45± 12.50	118.76± 23.62	111.74± 22.22	131.26± 27.91	119.14± 22.28
Correlation (r)	0.785**	0.772**	0.866**	0.709**	0.698**	0.698**	0.696**	0.927**
ICC	0.629**	0.745**	0.833**	0.642**	0.685**	0.692**	0.656**	0.920**
Bias (95%CI)	–0.20 (–25.88~ 25.48)	–14.03 (–37.73~ 9.67)	–6.23 (–21.84~ 9.38)	5.41 (–20.05~ 30.87)	12.73 (–18.16~ 43.61)	5.70 (–23.73~ 35.13)	25.22 (–11.14~ 61.58)	13.10 (6.99~ 19.22)
Absolute values of bias	25.48	37.73	21.84	30.87	43.61	35.13	61.58	19.22
SD of bias	13.10	12.09	7.97	12.99	15.76	15.01	18.55	3.12
Accuracy P10%	60.19%	34.26%	75%	52.78%	36.11%	50.93%	21.30%	50.93%
Accuracy P30%	99.07%	92.59%	100%	96.30%	87.96%	93.52%	65.74%	100%
Patients with CKD (n=545) rGFR 62.36±21.90								
eGFR	79.36± 24.45	42.63± 17.63	56.38± 18.44	83.70± 25.82	88.18± 35.25	82.98± 33.14	94.90± 40.05	71.14± 25.65
Correlation (r)	0.785**	0.772**	0.898**	0.785**	0.784**	0.784**	0.721**	0.911**
ICC	0.780**	0.754**	0.885**	0.775**	0.738**	0.758**	0.691**	0.900**
Bias (95%CI)	17.00 (–8.81~ 42.82)	–19.72 (–43.66~ 4.22)	–5.97 (–18.30~ 6.36)	21.34 (–5.80~ 48.48)	25.82 (–11.07~ 62.72)	20.62 (–12.87~ 54.12)	32.54 (–12.80~ 77.89)	8.78 (–3.02~ 20.58)
Absolute values of bias	42.82	43.66	18.30	48.48	62.72	54.12	77.89	20.58
SD of bias	13.17	12.21	6.29	13.85	18.82	17.09	23.13	6.02
Accuracy P10%	15.78%	9.17%	62.94%	7.89%	10.09%	15.60%	4.22%	46.24%
Accuracy P30%	55.60%	40.92%	99.45%	40.55%	34.31%	51.19%	24.77%	97.98%

rGFR and eGFR were expressed as mean ±SD in mL/min/1.73 m^2; r – Pearson's correlation with the rGFR; ** $p<0.01$. ICC – Intraclass Correlation Coefficient; P10 – refers to percentage of GFR estimates within 10% of rGFR; P30 – refers to percentage of GFR estimates within 30% of rGFR.

chemotherapy. However, with more cycles of chemotherapy, $eGFR_{MDRD}$, $eGFR_{IDMS-MDRD}$, and $eGFR_{Chinese\ MDRD}$ gradually increased, before decreasing after 5 cycles of chemotherapy.

Evaluation of renal function parameters in cancer patients with CKD

Of the 1000 cancer patients, 545 patients with CKD were selected as a second experimental group when they finished chemotherapy. As shown in Table 4, CysC and $eGFR_{Chinese\ scr+cysc}$

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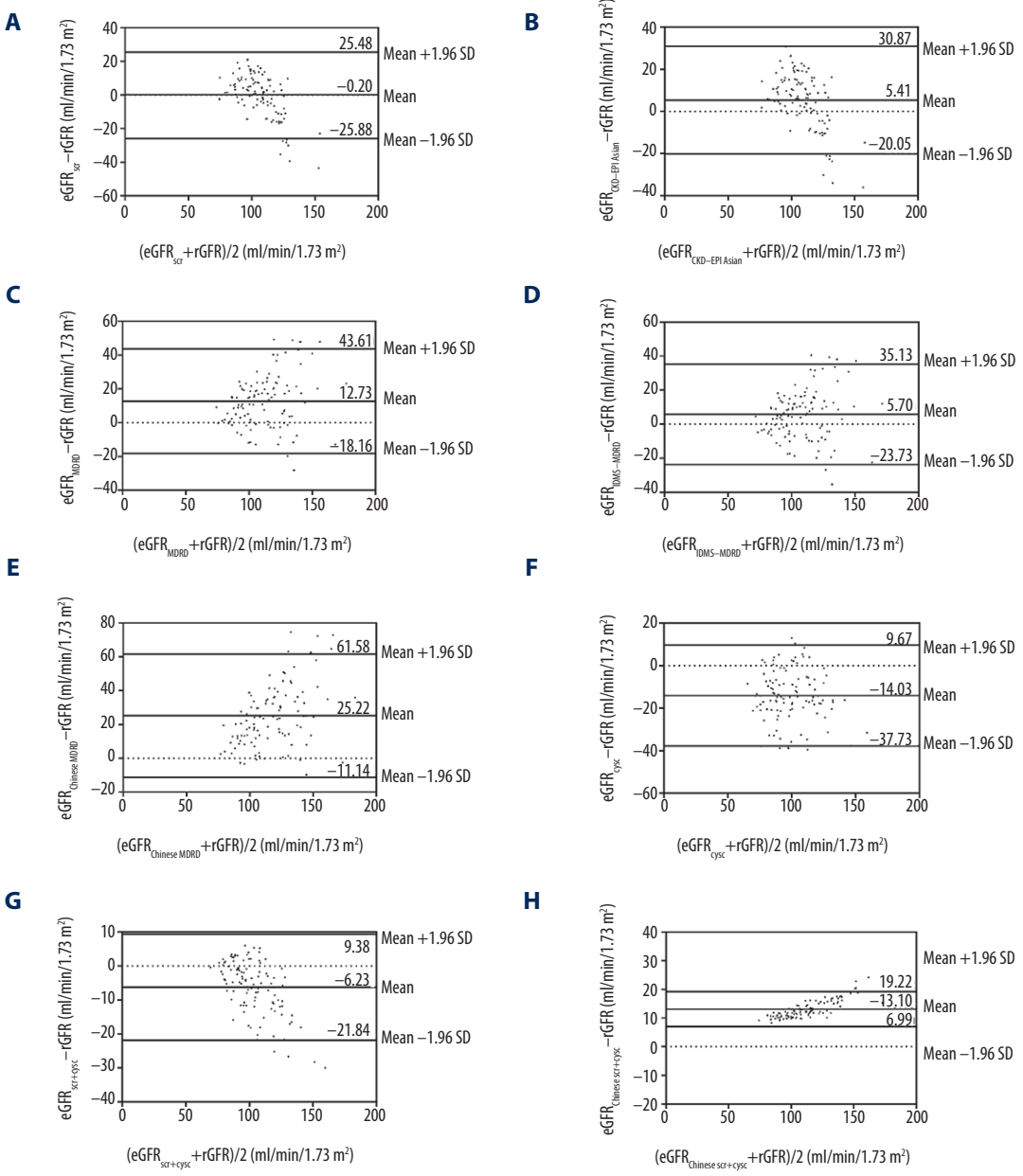
had strong correlations with rGFR in both the experimental and control groups. We also found that for the control group, the combined SCr and CysC(SCr-CysC) equations had good test-retest reliability, as the ICC calculations were greater than 0.75. However, in the experimental group, all equations had good test-retest reliability except the $eGFR_{MDRD}$ and $eGFR_{Chinese\ MDRD}$ equations. The $eGFR_{scr}$ and $eGFR_{scr+cysc}$ equations yielded the least amount of bias in the control and experimental groups, respectively. However, $eGFR_{Chinese\ scr+cysc}$ and $eGFR_{scr+cysc}$ equations had the least absolute values of bias in the control and experimental groups, respectively. The best precision and accuracy for the 2 groups were obtained with the $eGFR_{Chinese\ scr+cysc}$ and $eGFR_{scr+cysc}$ equations. We considered that the combination equation $eGFR_{scr+cysc}$ performed best for the control and experimental groups, while the $eGFR_{scr}$ and $eGFR_{Chinese\ scr+cysc}$ equations performed better for the control and experimental groups, respectively.

A Bland-Altman plot analysis was then applied to describe agreement between the rGFR and different estimated GFR



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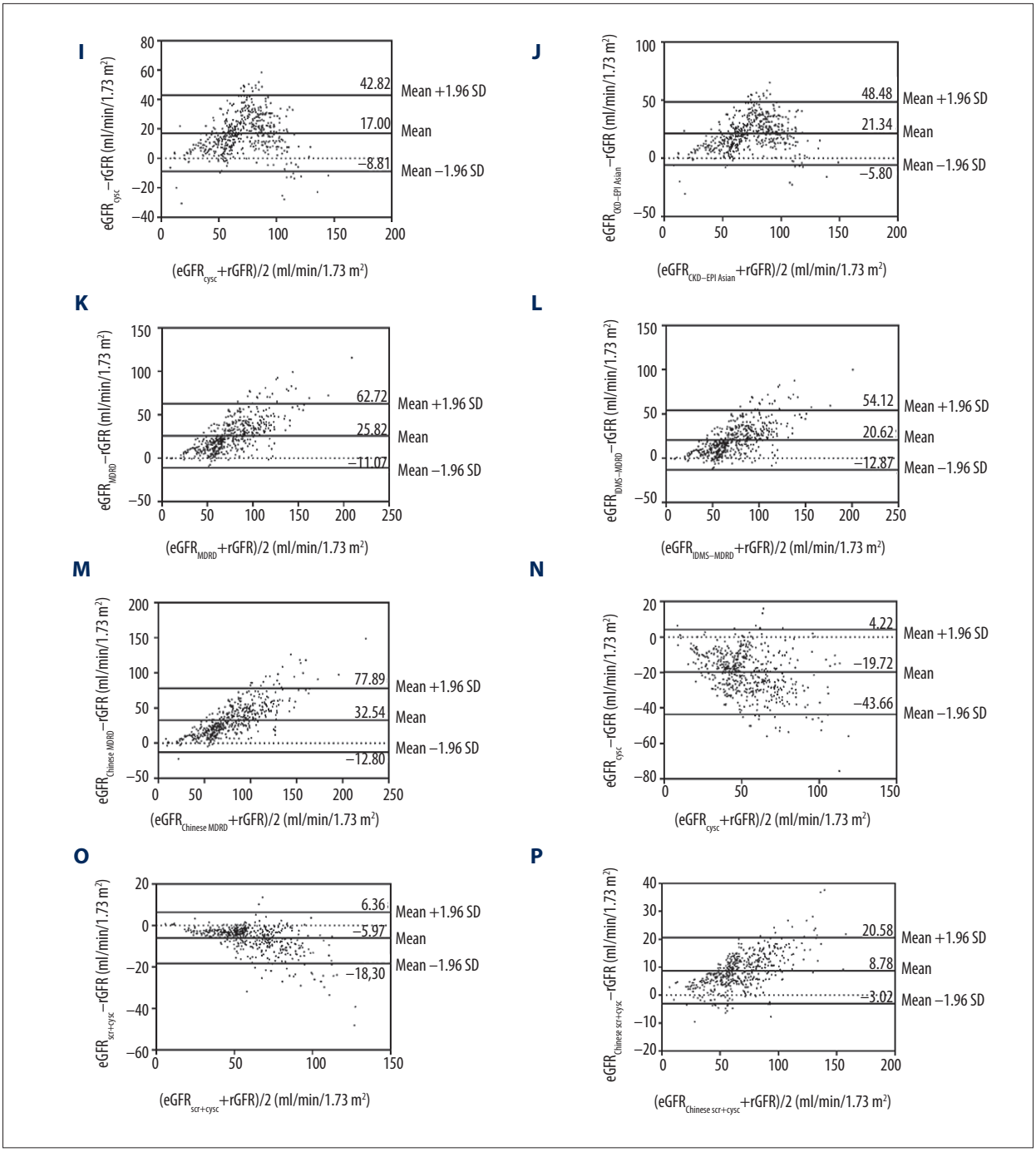

Figure 2. Bland-Altman plot for differences between estimated GFR and cGFR. Solid line represents the mean of difference and 95% limits of agreement of the mean of difference between GFR. The estimated GFR of control and experimental groups are respectively shown in the (**A–H**) and (**I–P**) plots, respectively.

values in the control and experimental groups (Figure 2). The results showed that compared with the other estimated GFR equations, the $eGFR_{scr}$ and $eGFR_{scr+cysc}$ equations yielded minimum bias for the control and experimental groups, respectively.

Comparison of the diagnostic accuracy of various GFR equations and serological indicators

The ROC curve was used to evaluate the discriminating ability of the GFR equations and serological indicators of renal function (Figure 3). In this study, GFR <90 ml/min/1.73 m² and GFR

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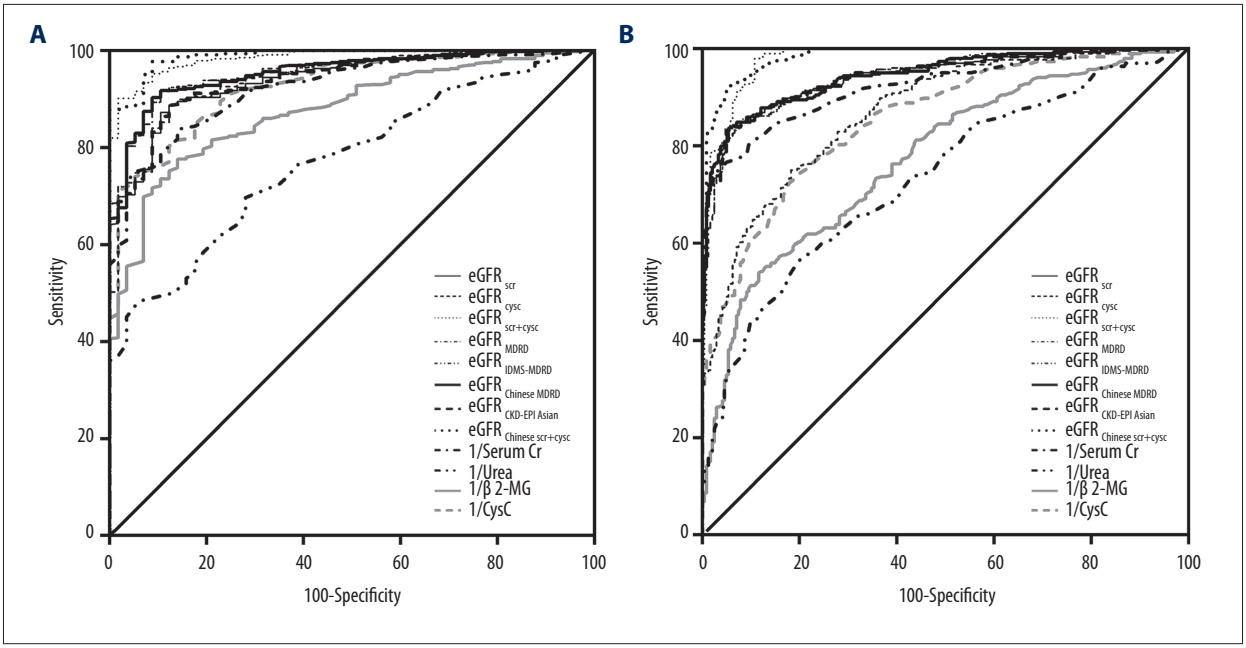

Figure 3. Receiver operator characteristic (ROC) curve analysis for measures and various formulas in Chinese cancer patients with CKD. a: ROC curves with cGFR <90 ml/min/1.73 m^2; b: ROC curves with cGFR <60 ml/min/1.73 m^2.

<60 ml/min/1.73 m^2 were set as critical values, which were regarded as markers of early and moderate RI, respectively. In addition, the KDIGO guidelines recommend a decrease in cisplatin dose when GFR is <60 ml/min/1.73 m^2, which was the other reason for setting 60 ml/min/1.73 m^2 as a critical value. The results indicated that for both early and moderate RI, eGFR$_{\text{Chinese scr+cysc}}$ and eGFR$_{\text{scr+cysc}}$ had the largest and second largest AUCs, respectively, indicating that the combination SCr-CysC equations had improved diagnostic accuracy over the other equations. Among the 4 serological indicators, CysC had the largest AUC (0.926, p<0.001) for early RI, and serum Cr had the largest AUC (0.924, p<0.001) for moderate RI. The coordinates of the ROC curves were used to define cutoff values with acceptable sensitivity and specificity for each formula, and serological indicators, cutoff values, sensitivities, specificities, and AUCs are presented in supplemental data, Table 2.

Results according to subgroup

We further conducted a subgroup analysis for the experimental group according to GFR category, sex, age, and surgical options (Table 5). The results of our investigation were as follows: 1) The rGFR values for the 545 cancer patients with CKD were divided into 6 categories. SCr, urea, β2-MG, and CysC increased with increasing CKD stage, but the increases followed different trends. One-way ANOVA showed that the serum CysC increased significantly in the experimental group compared with the control group in each category (p<0.05), while SCr began to increase significantly in G3a. Urea and β2-MG showed a marked increase in G2 (p<0.05). 2) Male patients had higher SCr and CysC levels compared with female patients. 3) rGFR was significantly decreased in cancer patients over the age of 55 years, and the other parameter values were not significantly different between any of the age groups. 4) None of the renal parameter values were significantly different between the operated and unoperated cancer patients.

Discussion

Because of the high prevalence of RI, it is necessary to monitor renal function in cancer patients receiving chemotherapy, especially platinum-containing chemotherapy. Notably, several studies have indicated that platinum-based chemotherapy causes acute kidney injury in 25% of patients [17–19]. GFR is the best indicator of renal function and is the main basis for the diagnosis and staging of CKD, as well as for evaluation of the severity of kidney disease and therapeutic outcomes [20]. Many studies, as well as the KDIGO guidelines, indicate the dose of cisplatin should be reduced when GFR is below 60 ml/min/1.73 m^2 [13,21,22]. Thus, precise measurement of GFR is needed for renal function monitoring after chemotherapy in these patients to adjust to appropriate medication doses as well as to detect early renal injury.

Inulin clearance remains the criterion standard GFR tracer; however, it is inconvenient and difficult to measure. The clearance of radionuclide (^{51}Cr-EDTA or ^{99m}Tc-DTPA) is considered to be closest to that of inulin, but it is radioactive and its use is time-consuming. Therefore, scholars have developed many

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Table 5. Results of renal function parameters in subgroups.

	n	rGFR (ml/min/1.73 m²)	Serum Cr (μmol/l)	Urea (mmol/l)	β2-MG (mmol/l)	CysC (mg/l)
Stratification by GFR category						
G1	57	≥90	52.07±9.96	4.63±1.26	1.95±0.50	1.09±0.20*
G2	184	60–89	66.10±10.88	5.64±1.68**	2.81±1.02**	1.43±0.27**
G3a	204	45–59	89.09±16.19**	6.50±2.28**	3.49±1.57**	1.76±0.42**
G3b	71	30–44	117.44±23.81**	8.57±2.69**	4.84±1.86**	2.30±0.50**
G4	22	15–29	188.50±41.66**	14.96±7.83**	7.49±3.85**	3.09±0.43**
G5	7	<15	438.14±225.06**	25.34±8.83**	15.14±8.05**	6.59±4.26**
Stratification by gender						
Male	325	63.08±23.18	94.66±62.20	7.09±3.73	3.60±2.22	1.84±0.98
Female	220	60.71±18.61	78.19±40.41**	6.37±4.42	3.55±2.94	1.60±0.69**
Stratification by age						
<55	112	70.88±23.40$^{\#,@}$	85.71±69.46	6.33±2.98	3.21±2.10	1.62±0.55
55~65	206	60.04±22.11$^{\&}$	95.65±67.56	7.10±3.98	3.84±3.10	1.88±1.13
≥65	227	60.26±19.92$^{\&}$	86.14±35.18	6.92±4.34	3.54±1.90	1.73±0.81
Stratification by surgical options						
Operated	259	62.25±22.85	90.97±59.65	6.80±3.60	3.38±1.83	1.76±0.82
Unoperated	286	62.45±21.05	88.45±54.42	6.93±4.27	3.78±2.91	1.77±0.98

Data were expressed as mean ±SD. * Independent samples T test, p<0.05; ** Independent samples T test, p<0.01; $^{\&, \#, @}$ One way ANOVA compared with patients aged <55, 55~65, ≥65, respectively.

equations to estimate GFR, which can be divided into 3 categories: creatinine-based, which remain the most prevalent, followed by cystatin C-based and creatinine/cystatin C-based. All the equations were developed in CKD patients without cancer. However, whether these equations can be used to replace the assessment of rGFR in cancer patients whose SCr and CysC production has been changed by the disease is unclear.

In our study, creatinine-based equations ($eGFR_{scr}$, $eGFR_{CKD\text{-}EPI\ Asian}$, $eGFR_{MDRD}$, $eGFR_{IDMS\text{-}MDRD}$, and $eGFR_{Chinese\ MDRD}$) were studied. Their changes with increased numbers of chemotherapeutic cycles were not obvious compared with those obtained from equations containing CysC. We also found that creatinine-based equations overestimated rGFR during chemotherapy (Figures 1, 2, Table 4). These findings are in accordance with the results of Salek et al. [13]. This is likely because creatinine is not only filtrated through glomeruli, but is also secreted from the proximal tubuli, leading to overestimation [23]. $eGFR_{scr}$ is the current equation recommended for use in clinical practice [24]. Nonetheless, in our study, the $eGFR_{scr}$ equation did not provide the best reflection of the GFR value for Chinese cancer patients with CKD, although it did perform better in the control group. The 4-level race equation $eGFR_{CKD\text{-}EPI\ Asian}$ was considered more accurate than the 2-level race equation $eGFR_{scr}$ in the Chinese dataset [10]. However, in our study, the $eGFR_{scr}$ equation was found to be superior to the $eGFR_{CKD\text{-}EPI\ Asian}$ equation in Chinese cancer patients with CKD, which is consistent with the results of previous studies [25,26]. In addition, Levey considered that when the calibration of SCr methods is traceable to the SCr reference system, the GFR should be estimated using the $eGFR_{IDMS\text{-}MDRD}$ equation [7]. Accordingly, our study showed similar results; specifically, $eGFR_{IDMS\text{-}MDRD}$ performed the best among the 3 MDRD equations. However, they all seemed to be unsuitable for assessing renal function in Chinese cancer patients with CKD. SCr did not increased until the GFR had already deteriorated to below 60 mL/min/1.73 m² (Table 5), and GFR at this level indicates the dose of cisplatin should be reduced. From this point of view, the creatinine-based equations to estimate GFR are not safe for patients with injured renal function. Therefore, we do not recommend this method in cancer patients, whose renal function gradually deteriorate with reinforced courses of chemotherapy.

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We evaluated whether a cystatin C-based equation provided by CKD-EPI ($eGFR_{cysc}$) is also applicable in Chinese cancer patients. It is disappointing that CysC alone did not improve the estimation. The comparison of $eGFR_{cysc}$ with rGFR indicates that $eGFR_{cysc}$ was underestimated rGFR during chemotherapy (Figures 1, 2, Table 4). It is easy to establish a deteriorative staging of CKD or erroneous diagnosis as CKD to influence the dose of chemotherapy in cancer patients. In addition, $eGFR_{cysc}$ had lower AUC in both early and moderate RI (supplemental data, Table 2). This finding may be due to an elevation in the CysC value due to cancer (Table 2). Our findings are consistent with those of previous studies [13,27–29], probably due to the role of CysC as a cysteine protease inhibitor. However, several studies have revealed no correlation between CysC concentration and tumor burden [30,31].

It is important to note that the combination of equations using both SCr and CysC performed better in the studied cohort of Chinese cancer patients. $eGFR_{scr+cysc}$ was the most appropriate because it had the least bias, the highest accuracy, and second largest AUCs for early and moderate RI (Table 4, Figures 2, 3, supplemental data, Table 2). In addition, the $eGFR_{Chinese\ scr+cysc}$ equation had the strongest correlation, best precision, and largest AUCs for early and moderate RI (Table 4, supplemental data, Table 2, Figure 3), indicating that the combination creatinine-cystatin C equations had higher diagnostic accuracy than the others. Our results are in accordance with previous studies [32–35]. The GFR of Chinese cancer patients with CKD can be estimated accurately by creatinine-cystatin C equations, which is of great help for the choice of therapeutic strategies and adjustment of drug dosage.

Our results regarding the evaluation of 4 serological indicators for renal function indicated that CysC, which can detect minor changes in renal function at an early stage with the largest AUC (supplemental data, Table 2, Figure 3) and increased significantly when rGFR ≥90 ml/min/1.73 m^2 (Table 5), is a superior indicator to other contemporary markers and traditional markers, which is consistent with the results of several previous studies [20,23,36,37]. CysC increased significantly after the early cycle of chemotherapy (Table 3). These results indicate that CysC is an early indicator of injured renal function in all cancer patients. In patients with moderate RI, SCr had the largest AUC, and the cutoff value was 83.33 μmoL/L for moderate RI, indicating that SCr had high diagnostic accuracy and that the dosage of cisplatin should be reduced when the concentration of SCr is >83.33 μmoL/L. Interestingly, CysC and SCr increased significantly in cancer patients, which was in agreement with the results of several studies [38–40]. It is necessary and helpful to refine the equations to estimate GFR for cancer patients, which will be a future focus of further research.

We found that β2-MG also demonstrated good sensitivity for detecting early RI for patients receiving platinum-containing protocols (Table 3). In addition, β2-MG was also a remarkable indicator for monitoring early renal injury in patients receiving chemotherapy with platinum-containing protocols. We found that the operation did not affect kidney function index in our study. As shown in our results, sex and age are important factor for the assessment of kidney function, due to the higher levels of SCr and CysC in male patients and lower rGFR in patients over the age of 55 years (Table 5). Therefore, physicians should use different standards in patients of different sexes or ages to evaluate renal function.

Conclusions

Cancer patients differ from the general population and are a very special group of patients. Our study showed that individual differences exist between rGFR and all eGFR, which has a great impact on the discovery rate of CKD and potential drug dosage adjustment. In summary, our study shows that CysC is the most sensitive marker for early renal injury, and the combination equations using both SCr and CysC performed better in the studied cohort of Chinese cancer patients. It is important to monitor the change in GFR when CysC is abnormal to detect early renal injury in time. One important limitation of this study is that only 7 patients with CKD stage 5 were enrolled. Therefore, a further study is necessary to broaden the research to include a larger patient population.

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Conflict of interest

None.

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