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NEPHROLOGY - ORIGINAL PAPER

How to estimate renal function in patients with liver disease: choosing the most suitable equation

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Abstract

Background Hepatitis B virus (HBV) infection is a public health challenge, especially in China. In clinical practice, HBV infection is associated with nephropathy. Impaired renal function is frequently observed in compensated Chronic Hepatitis B (CHB) and cirrhosis (LC). Thus, renal function must be monitored to avoid nephrotoxic effects before and during nucleoside analog treatment. Investigating the predictive markers of early renal dysfunction is essential. New GFR-predicting equations, based on Pcr and/or CystC, have been recently recommended in the general population, but their performance in liver disease patients has been rarely studied. In this study, we will discuss how to detect renal dysfunction in patients with HBV infection.

Methods A total of 16 LC patients and 23 CHB patients were enrolled in this study, and we collected and compared the clinical data of the two groups. The estimated glomerular filtration rates (eGFRs) were also calculated by several equations. All patients received 99mTc-DTPA dynamic radionuclide imaging examinations to obtain mGFRs as the reference standard. To evaluate the performance of any equation in the CHB and LC groups, paired *t* test, Pearson's correlation, Kappa analysis and Bland–Altman plots were utilized. Moreover, all 39 subjects were divided into two groups (according to GFR $>$ 90 mL/min/1.73 m^2). We compared the serum and urinary markers of kidney injury between the two groups and selected the indicators of renal injury by univariate analysis.

Results The mGFR was 72.26 $\pm$ 20.69 mL/min/1.73 m^2 in the LC group, and 87.49 $\pm$ 25.91 mL/min/1.73 m^2 in the CHB group. The paired *t* test results of eGFR and mGFR showed no difference between eGFR (estimated by the CHINAcr-cys equation) and mGFR ($p > 0.05$) in the compensated LC and CHB groups. The difference between mGFR and eGFR estimated by other methods was obvious ($p < 0.05$). Comparing the eGFRs (estimated by 5 different equations) with mGFR in the compensated LC and CHB groups, Pearson's correlation showed that only eGFR (estimated by the CHINAcr-cys equation) had a significant correlation coefficient in CHB ($r = 0.678$, $p = 0.000$) and had the highest R^2 ($R^2 = 0.459$) among all other measures. The kappa consistency test showed that eGFR from CHINAscr-cys had poor consistency with mGFR in the compensated LC group but moderate consistency in the CHB group. Bland–Altman consistency analysis showed that in the CHB group, the CHINAcr-cys and CKD-EPIcr equations presented narrower acceptable limits than did the aMDRD, c-aMDRD, and CKD-EPIcr-cys equations (62.8, 56.1 vs .85.7, 102.9, 93.6 mL/min per 1.73 m^2). In the compensated LC group, the CHINAcr-cys and CKD-EPIcr equations presented narrower acceptable limits than did the aMDRD, c-aMDRD, and CKD-EPIcr-cys equations (83.6, 81.3 vs. 98, 113.5, 106.3 mL/min per 1.73 m^2). Serum or urinary markers were compared with renal function (GFR $>$ 90 mL/min/1.73 m^2) and showed International normalized ratio (INR) ($p = 0.009$), creatinine ($p = 0.006$), urine *N*-acetyl-β-glucosaminidase (NAG) ($p = 0.001$) and serum cystatin C (CysC) ($p = 0.044$).

Conclusion The CHINAcr-cys equation may be more suitable for the estimation of GFR in Chinese patients with CHB or compensated cirrhosis. INR, creatinine, NAG, and CysC are proper biomarkers for screening renal dysfunction in Chinese patients with CHB or compensated LC.

Keywords Hepatitis B virus · Hepatic fibrosis · Renal injury · Glomerular filtration rate

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Introduction

Hepatitis B virus (HBV) infection is a worldwide threat to health, especially in China. HBV is generally not a cytopathic virus, and this liver disease is related to the host immunologic response to the virus. The inefficient immune response to HBV during chronic HBV infection results not only in liver destruction but also extrahepatic syndromes. The extrahepatic manifestations are observed in association with circulating immune complexes that activate serum complement. Many of the circulating immune complexes can present as renel injury such as glomerulonephritis. Renal function is frequently impaired in patients with compensated CHB and HBV-related liver cirrhosis (LC) [1–4]. A multicenter, retrospective and observational study recruited 90 patients with chronic HBV infection who had never received antiviral treatment was carried out in China. The serum creatinine levels were in a normal range. While, the incidence of renal impairment (eGFR < 90 mL/min/1.73 m^2) was 12.7% [5]. Edward J. assessed renal function of patients with CHB using eGFR and found that 35.84% of the 1367 CHB patients had eGFR at 60–89 mL/min [6].

Currently, there are two main treatment options for CHB patients: treatment with nucleos(t)ide analogs (NA) or Interferonα. The current first-line therapy recommendation is treatment with the second-generation NA, entecavir or tenofovir disoproxil fumarate (TDF). Both drugs show renal elimination and require dose adjustments in patients with renal dysfunction. Many Clinical Practice Guidelines recommend that patients at risk of renal disease treated with any NA and all patients regardless of renal risk treated with TDF should undergo periodical renal monitoring including at least the eGFR and serum phosphate levels [7, 8].

GFR is considered the best overall index of kidney function, but cannot be measured directly. Thus, some eGFR equations have been developed based on Scr and/or serum CysC, such as the Cockcroft-Gault equation, a series of MDRD equations, CKD-EPIcr, CKD-EPIcys, CKD-EPIcr-cys, CHINAcys, CHINAcr-cys and other approaches.

The abbreviated MDRD (aMDRD) equation, which includes only four variables-Pcr, gender, age, and ethnicity [9], has been the most widely used and was recommended by the Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines [10]. However, race is an important determinant of GFR estimation. For example, when the MDRD equations are applied to black individuals, a coefficient should be used [11], and this equation underestimated GFR in near-normal renal function and overestimated GFR in advanced renal failure in a group of Chinese patients with CKD [12]. Ma et al. improved the performance of the aMDRD equations by c-aMDRD equations, which was better than the original MDRD equations in Chinese patients [13]. Next, Levey [14] reported a new equation, CKD-EPIcr, showed that it is more accurate than the widely used MDRD equation. Additionally, many papers have shown that the CKD-EPIcr equation is more accurate and precise in the early stages of CKD [15–17]. Earley, BS [18] determined that neither the CKD-EPIcr nor the MDRD equation is optimal across all populations and GFR ranges. In 2012, Inker et al. reported two equations for estimated GFR [19], one based on standardized sCysC values (CKD-EPIcys equation) and the other based on standardized sCysC combined with Scr (CKD-EPIcr-cys equation). As reported, the CKD-EPIcr-cys equation was accurate compared to the equations based on either marker alone. Almost simultaneously, two GFR equations based on standardized sCysC (CHINAcys equation) and combined with Scr (CHINAcr-cys equation) were developed in 788 Chinese patients [20]. Guo [21] suggested that the addition of CysC to the equations for estimating GFR improved the equations' performance. It is noteworthy that most of these equations were specifically developed to estimate GFR in patients with chronic kidney disease. None of them were developed to estimate GFR in patients with liver disease.

Moreover, some serum or urinary markers are promising and may be particularly suitable for accurate assessment of renal function. These markers have abnormal levels during early kidney injury. Which serum or urinary markers can be used as the index of renal dysfunction in liver disease patients?

Renal dynamic imaging, also named Gate's method, is another method for measuring GFR and its result is not affected by the diet of the patient.

Inulin clearance is the standard GRF measurement, but its expense and lengthy measurement process limits its clinical use. And the American College of Nuclear Medicine recommends isotope dual plasma sampling as a clinical reference standard for GFR measurement. In this study, we compared the performance of different estimated equations and assessed those that are presently considered the best choice for estimating GFR with the performance of technetium-99m-dietheylenetriamine penta-acetic acid (99mTc-DTPA) renal dynamic imaging, as well which serum or urinary markers can be used as the index of renal dysfunction in liver disease.

Subjects and methods

Patients

Two groups of subjects with CHB or compensated LC were recruited, respectively, from the Affiliated Hospital of Logistical College of Chinese People's Armed Police Force from October 2016 to June 2017.

The diagnoses of CHB or compensated LC were according to the criteria provided by the Guideline of Prevention and Treatment for Chronic Hepatitis B (2nd Version). All patients received only direct-acting antiviral agents (entecavir). Patients were excluded if the patients were infected with hepatitis delta virus, hepatitis C virus or had HIV coinfection. Patients with hypertension, diabetes mellitus, hepatocellular carcinoma, autoimmune hepatitis, alcoholic LC, renal calculus, hyperuricemia, renal cyst or severe heart, renal and brain diseases were also excluded.

Written informed consent was provided by all the participants after education with regards to the potential benefits, risks, and study procedures. Studies were registered with the ClinicalTrials.gov identifiers NCT01938820. The flow chart of this study was shown in Fig. 1.

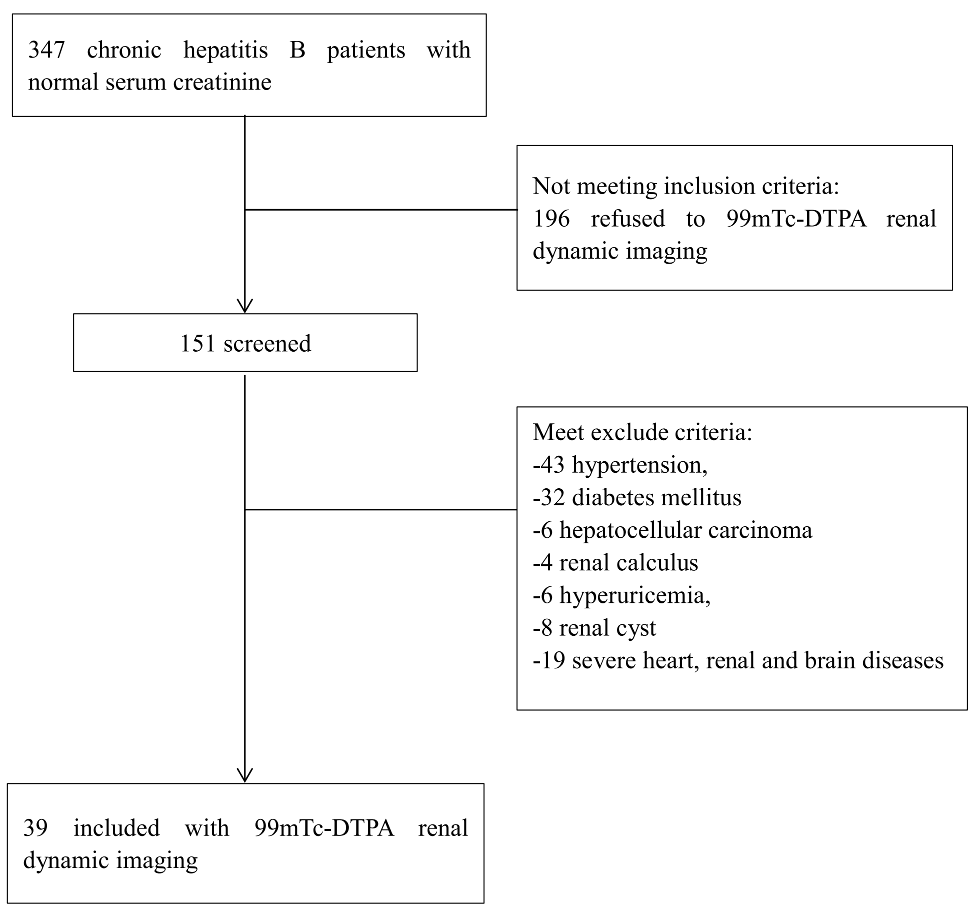
Screening protocol

All participants completed a questionnaire documenting their sociodemographic status (e.g., age, sex), personal and family health history and lifestyle habits (e.g., smoking, alcohol consumption). Histories of hepatitis and nephrotoxic medications (including nonsteroidal anti-inflammatory drugs and natural remedies, as well as herbal preparations containing aristolochic acid) were noted. The participant's height, weight, body mass index (BMI), waist circumference and hip circumference were recorded. Blood pressure was also measured.

Fasting venous blood and urine samples were drawn for laboratory test in our hospital. The liver function markers, including alanine aminotransferase (ALT), glutamic-oxal(o) acetic transaminase (AST), total bilirubin (Bil), alkaline phosphatase (AKP), γ-glutamyl transpeptidase (rGT), seralbumin, prothrombin time (PT), serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, uric acid, serum biochemistry and α-fetoprotein were measured.

Serum HBV markers, including HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc were detected using commercially available enzyme immunoassays. Serum HBV-DNA

Fig. 1 The flowchart of this study



was measured by PCR, with a linear range between 1×10^3 copies/mL and 5×10^8 copies/mL.

Renal function markers, including serum creatinine (sCr), serum ß2-microglobulin (sβ2-MG), urine ß2-microglobulin (uβ2-MG), urine *N*-acetyl-β-glucosaminidase (NAG), urine IgG, uTrf, serum cystatin C (sCysC), and serum retinol-binding protein (sRBP). The sCr determination was carried out automatically using a Roche Modular P model (Roche, Mannheim Germany) with a kinetic Jaffe test using rate-blanking and compensation.

The eGFR (measured as mL/min/1.73 m^2) was calculated using the aMDRD, the c-aMDRD, CKD-EPIcr, CKD-EPIcr-cys, and CHINAcr-cys equations, described in detail in Fig. 2A.

Detection of GFR by SPECT

All of the enrolled patients consumed 500 mL of water 20 min before the examination and voided their bladder immediately before the examination started. Patients were laid on the couch in a supine position with their back close to the scintillation detector of the SPECT/CT (NM/CT670, GE Healthcare, and Milwaukee, USA) to perform dynamic nuclear renography. The bilateral kidneys and the bladder were covered within the field of view of the scintillation detector. After a bolus of 10 mCi (370 MBq), 99mTc-DTPA was injected through the elbow vein, dynamic nuclear renography started with 60 frames of scintiscan at 1 frame per second and 40 frames of scintiscan at 2 frames per minute up to 21 min. In total, the examination acquired 100 frames of images of a 64×64 matrix with a 4.3 mm $\times$ 4.3 mm pixel size. The radioactivity of the syringes was determined before and after the examination. The dynamic renography was processed on a work station by a diagnostician with 17 years of experience. The regions of interest of the bladder and bilateral kidneys were drawn, respectively. The glomerular filtration rate was automatically calculated using the following equation after the patients' body weight and height were entered:

The general renal intake rate $(\%) = [(R - \mathrm{RB})/e^{-\mu\chi \mathrm{R}} + (L - \mathrm{LB})/e^{-\mu\chi \mathrm{L}}]/$ pre–post and the general GFR = general renal intake rate $(\%) \times 100 \times 9.81270–6.82519$. L and R are the radioactive counts of the left and right kidney. Pre- and post are the radioactive counts before and after the 99mTc-DTPA injection. χL and χR are the depth of the left and the right kidney, μ is the 99mTc attenuation coefficient in the soft tissue of 0.153/cm and e is a constant number of 2.71828.

The ultrasonography and FiroScan were examined for each participant.

Statistical methods

The data were statistically analyzed with multiple tests, including *t* test, paired *t* test, Wilcoxon two-sample test, Kappa consistency test (kappa value of less than 0.40 considered poor, 0.41–0.60 considered moderate, 0.61–0.80 considered good, and 0.81–1.00 considered excellent), and Bland–Altman consistency analysis, which were performed using SPSS software (SPSS Inc., Chicago, IL). $p < 0.05$ (2-tailed) was considered significant.

Fig. 2 eGFR equations used in the study (A). Scatter plots of the mGFR versus aMDRD, c-aMDRDc, CKD-EPIcr, CKD-EPIcr-cys and CHINAcr-cys in the compensated liver cirrhosis group(B) and the CHB group (C). Pearson's correlation of the variables with mGFR(D)

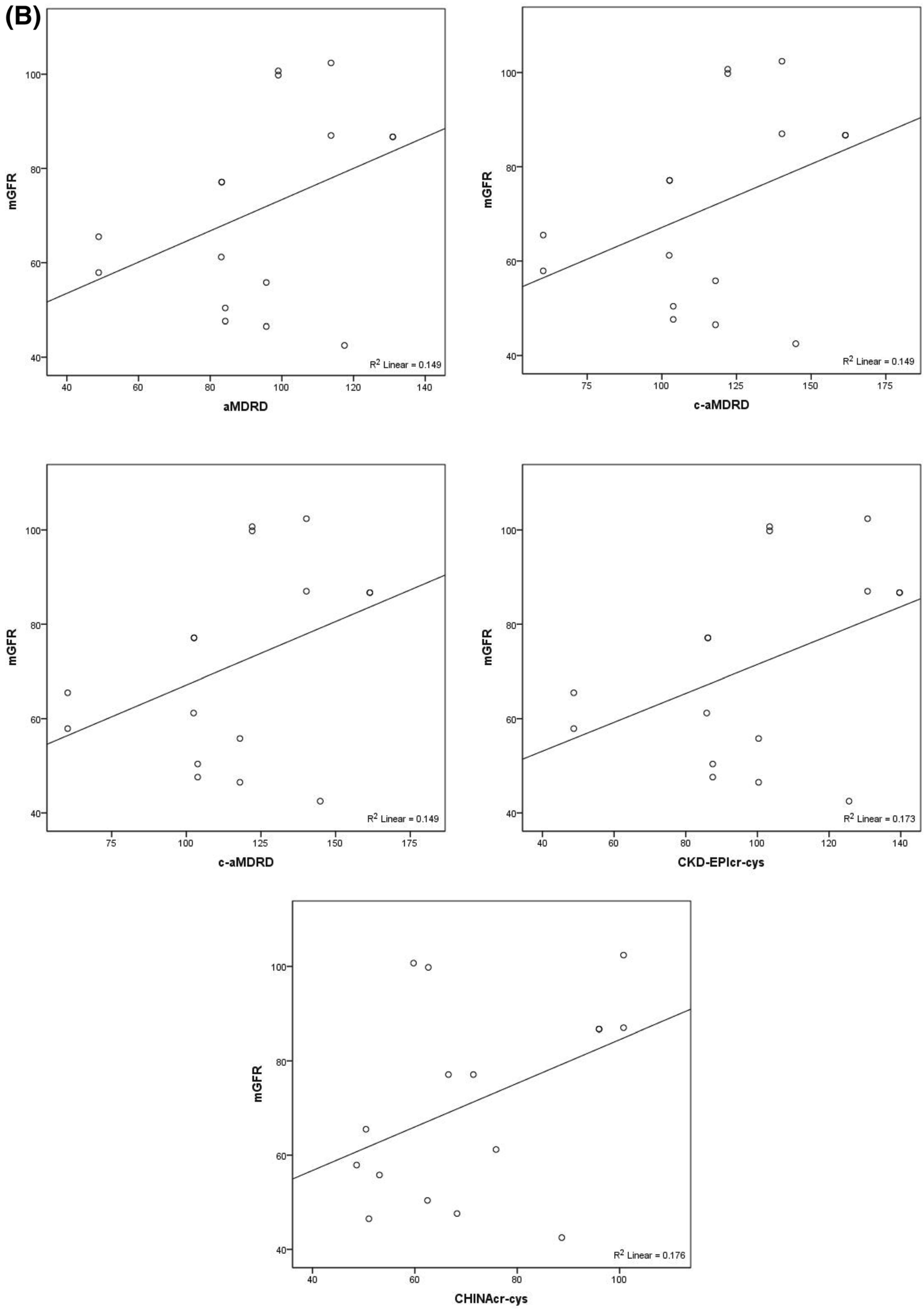
(A)

eGFR equations used in the study

Equation	Estimation method*		
aMDRD	$\text{eGFR} = 186.3 \times (\text{Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ female})$		
c-aMDRD	$\text{eGFR} = 186 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times (\text{female} \times 0.742) \times (\text{chinese} \times 1.233)$		
	Gender	Scr(μmol/L)	CKD-EPI
	Female	≤62	$\text{eGFR} = 144 \times (\text{Scr}/62)^{-0.329} \times (0.993)^{\text{Age}}$
	Female	> 62	$\text{eGFR} = 144 \times (\text{Scr}/62)^{-1.209} \times (0.993)^{\text{Age}}$
	Male	≤80	$\text{eGFR} = 141 \times (\text{Scr}/80)^{-0.411} \times (0.993)^{\text{Age}}$
CKD-EPI	Male	> 80	$\text{eGFR} = 141 \times (\text{Scr}/80)^{-1.209} \times (0.993)^{\text{Age}}$
CKD-EPIcr-cys	$\text{eGFR} = 169 \times \text{Scr}^{-0.608} \times \text{CysC}^{-0.63} \times \text{age}^{-0.157} \times 0.83$ (female)		
CHINAcr-cys	$\text{eGFR} = 173.9 \times \text{CysC}^{-0.729} \times \text{Scr}^{-0.184} \times \text{age}^{-0.193} \times 0.89$ (female)		

*:eGFR (mL/min /1.73 m^2), age (years), Scr (mg/dL) .

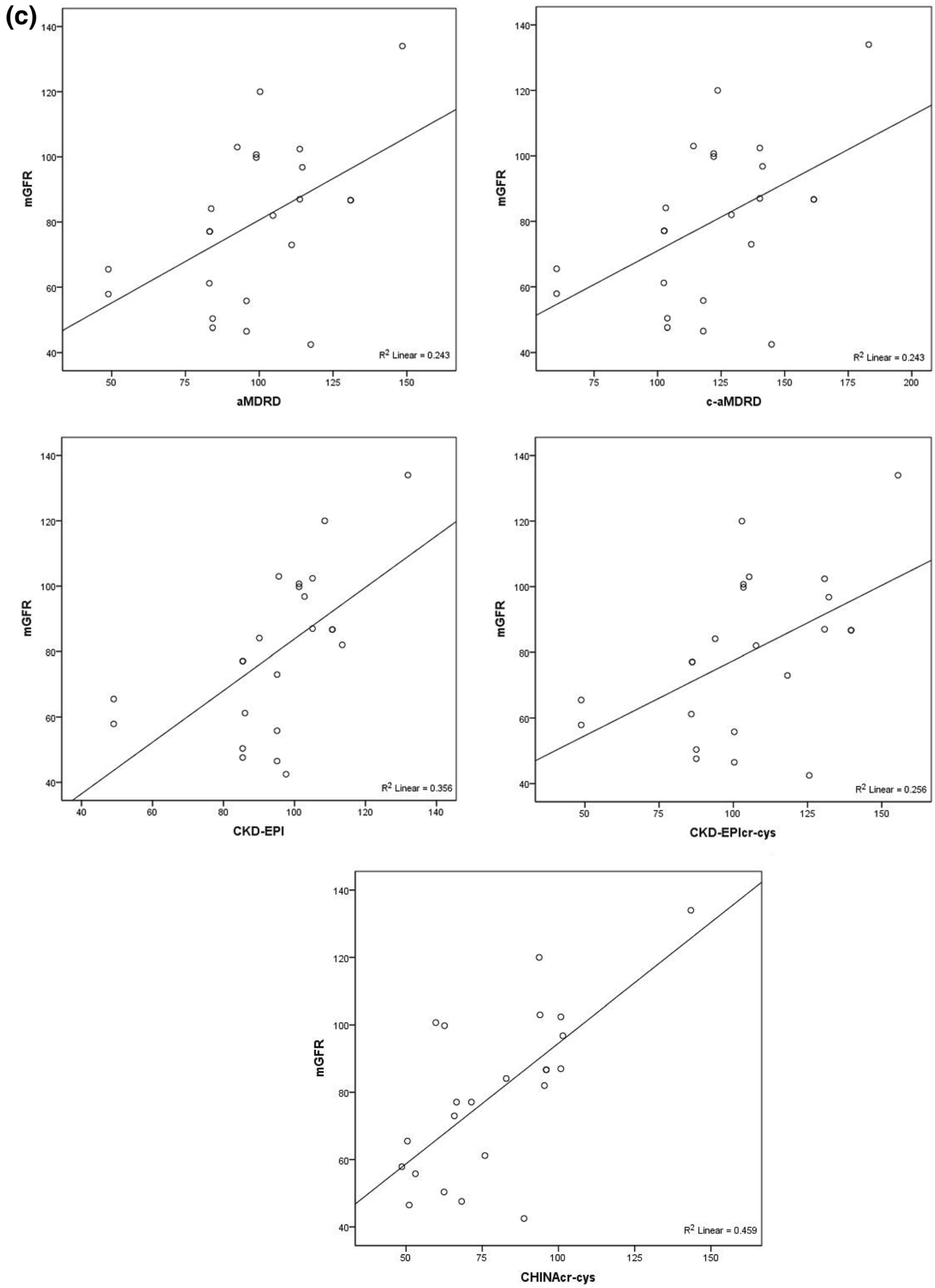
Fig. 2 (continued)



Results

A total of 16 subjects with compensated LC and 23 with CHB completed all examinations. These patients never received any antiviral treatment. Their general information and sociodemographic details are listed in Table 1. All

Fig. 2 (continued)



patients received screening of serum and urine markers of renal injury, which are listed in detail in Table 3.

In our study, we calculated five eGFR values and compared them to mGFR in CHB and compensated LC groups, respectively. Either mGFR or eGFRs in the CHB group were higher than that in the compensated LC group, but the differences were not significant, except for the CHINAcr-cys equation ($p = 0.020$), see Table 2.

Fig. 2 (continued)

(D)

Pearson's correlation of the variables with mGFR.

Characteristic	Compensated liver cirrhosis		CHB	
	r	*P*	*r*	*P*
aMDRD	0.386	0.139	0.493	0.017
c-aMDRD	0.386	0.139	0.493	0.017
CKD-EPI	0.444	0.085	0.597	0.003
CKD-EPIcr-cys	0.416	0.109	0.506	0.014
CHINAcr-cys	0.419	0.106	0.678	0.000

Table 1 Patients' general information and sociodemographic details

Characteristics	Compensated liver cirrhosis (*N* = 16)	CHB (*N* = 23)
Male [*n* (%)]	14	16
Age(year)	54.3 ± 4.3	46.5 ± 12.8
BMI (kg/m^2)	23.43 ± 2.43	24.73 ± 2.75
Systolic blood pressure (mmHg)	113.67 ± 9.18	110.37 ± 10.51
Diastolic blood pressure (mmHg)	85.71 ± 8.34	80.54 ± 9.31
ALT (U/L)	47.0 ± 28.4	73.1 ± 74.6
AST (U/L)	93.1 ± 136.9	53.3 ± 49.3
TBIL (μmol/L)	29.9 ± 13.7	15.4 ± 7.5
ALB (g/L)	37.1 ± 6.8	44.3 ± 4.0
HBV DNA	6081314.3 ± 18758493.1	1898913.0 ± 3025424.2
HBsAg quantification	2050.3 ± 1844.5	6784.0 ± 10971.7
INR	1.27 ± 0.24	1.01 ± 0.11
LSM (Kpa)	19.6 ± 5.8	9.5 ± 3.3
PLT (10^9/L)	84.5 ± 26.8	158.4 ± 53.7
Uric acid (μmol/L)	261.5 ± 71.7	233.5 ± 62.4
BUN (mmol/L)	6.0 ± 2.08	4.8 ± 1.0
Cr (μmol/L)	77.8 ± 15.5	68.1 ± 12.5
NAG (U/L)	14.1 ± 6.3	8.9 ± 4.2
Serum CysC (mg/L)	1.3 ± 0.4	0.9 ± 0.2
sRBP (mg/L)	28.9 ± 15.2	45.8 ± 15.4
Alb urine (mg/L)	13.2 ± 5.8	14.1 ± 12.1
uTrf (mg/L)	2.1 ± 0.1	2.23 ± 0.2
Urine lgG (mg/L)	4.6 ± 1.45	5.04 ± 3.0
uβ2-MG (mg/L)	0.2 ± 0.4	0.6 ± 1.0
sβ2-MG (mg/L)	2.8 ± 0.9	1.91 ± 0.7

The paired *t* test results of eGFR and mGFR showed no difference between eGFR and mGFR in the CHINA cr-cys equation ($p > 0.05$), both in the compensated LC group and CHB group. The difference between mGFR and eGFR estimated by other equations was obvious ($p < 0.05$). See Table 2 for details.

Table 2 Comparison of eGFR differences between the two groups and eGFR results compared with mGFR

Characteristics	Compensated liver cirrhosis (*N* = 16)	CHB (*N* = 23)	*t*1	*p* value	*t*2*	*p* value	*t*3*	*p* value
mGFR	72.26 ± 20.69	87.49 ± 25.91	1.995	0.058	–	–	–	–
aMDRD	91.79 ± 23.69	102.58 ± 32.37	1.136	0.263	3.669	0.002	3.462	0.002
c-aMDRD	113.18 ± 29.21	126.48 ± 39.91	1.136	0.263	6.212	0.000	7.556	0.000
CKD-EPI	88.71 ± 18.91	96.26 ± 26.88	0.968	0.340	3.649	0.002	3.354	0.003
CKD-EPIcr-cys	97.47 ± 28.01	110.33 ± 34.69	1.229	0.227	4.238	0.001	4.821	0.000
CHINA cr-cys	71.81 ± 18.11	91.57 ± 28.82	2.424	0.020	0.087	0.932	1.408	0.173

t1 comparison of eGFR differences between the compensated liver cirrhosis and CHB group, *t2** in the compensated LC group, a paired *t* test, statistical aMDRD ($\bar{d}$ = −22.93, SD = 24.99), c-aMDRD ($\bar{d}$ = −44.94, SD = 28.94), CKD-EPIcr ($\bar{d}$ = −18.92, SD = 20.74), CKD-EPIcr-cys ($\bar{d}$ = −28.73, SD = 27.12) and Chinacr-cys ($\bar{d}$ = −0.46, SD = 21.33) were all different from mGFR, and the *t* values were 3.669 (*p* = 0.002), 6.212 (*p* = 0.000), 3.649 (*p* = 0.002), 4.238 (*p* = 0.001), and 0.087 (*p* = 0.932), respectively, *t3** in the CHB group, a paired *t* test, statistical Amdrd ($\bar{d}$ = −15.77, SD = 21.85), c-aMDRD ($\bar{d}$ = −41.36, SD = 26.25), CKD-EPIcr ($\bar{d}$ = −9.68, SD = 13.85), CKD-EPIcr-cys ($\bar{d}$ = −23.99, SD = 23.7) and CHINAcr-cys ($\bar{d}$ = −4.70, SD = 16.03) were all different from mGFR, and the *t* values were 3.462 (*p* = 0.002), 7.556 (*p* = 0.000), 3.354 (*p* = 0.003), 4.821 (*p* = 0.000), and 1.408 (*p* = 0.173), respectively

We compared the correlations between different eGFRs and mGFR using Pearson's correlation (Fig. 2). The eGFRs (by five different equations) did not have a significant correlation coefficient in the compensated LC group. However, in the CHB group, eGFR (estimated by five different equations) had a correlation coefficient, eGFR estimated by the CHINAcr-cys equation had a significant correlation coefficient ($r = 0.678$, $p = 0.000$), and CHINAcr-cys had the highest R^2 ($R^2 = 0.459$) among all other measures.

We defined a result of GFR > 90 mL/min/1.73 m^2 as normal renal function and GFR < 90 mL/min/1.73 m^2 as renal injury, all 39 subjects were divided into two groups. Univariate analysis showed that the indicators of renal injury were INR ($p = 0.009$), CR ($p = 0.006$), NAG ($p = 0.001$) and CysC ($p = 0.044$). In addition, other indicators had no significant difference.

We defined a result of GFR > 90 mL/min/1.73 m^2 as normal renal function, 60 mL/min/1.73 m^2 < GFR < 90 mL/min/1.73 m^2 as mild injury to renal function, and GFR < 60 mL/min/1.73 m^2 as severe injury to renal function. The constituent ratios for each eGFR and mGFR are shown in Fig. 3.

By analysis with the Kappa consistency test, in the compensated LC group, compared with mGFR, aMDRD (Kappa = 0.299, $p = 0.147$), c-aMDRD (Kappa = 0.040, $p = 0.614$), CKD-EPIcr (Kappa = 0.209, $p = 0.147$), CKD-EPIcr-cys (Kappa = 0.209, $p = 0.147$) and CHINAcr-cys mGFR (Kappa = 0.127, $p = 0.477$) all had poor consistency.

In the CHB group, compared with mGFR, aMDRD (Kappa = 0.324, $p = 0.035$), c-aMDRD (Kappa = 0.161, $p = 0.156$), CKD-EPIcr (Kappa = 0.161, $p = 0.156$), and CKD-EPIcr-cys (Kappa = 0.161, $p = 0.156$) had poor consistency. However, CHINAcr-cys showed moderate consistency with mGFR (Kappa = 0.569, $p = 0.005$).

CHINAscr-cys had poor consistency with mGFR in terms of the Kappa statistic in the compensated LC group, but moderate consistency in the CHB group. However, we were concerned about the consistency with mGFR. Therefore, a Bland–Altman consistency analysis between mGFR and each eGFR was conducted, and the results are shown in Fig. 4a (compensated LC group) and Fig. 4b (CHB group).

Discussion

Measuring the glomerular filtration rate by gold standard methods [e.g., renal clearance of inulin, 125I-iothalamate or 99mTc-diethylene triamine pentaacetic acid (DTPA)] in clinical practice is laborious, time intensive and may involve radiation exposure. To facilitate the clinical use of GFR, some eGFR equations have been developed based on Scr and/or serum CysC. However, it is noteworthy that most of these equations were specifically developed to estimate GFR in patients with chronic kidney disease, and none of them were developed to estimate GFR in patients with liver disease incorporating their demographic.

In our study, all patients received only direct-acting antiviral agents (entecavir). None adefovir dipivoxil used among them, which can affect renal function. Systematic review and meta-analysis have reported that entecavir is safe for the kidneys of patients with Chronic Hepatitis B [22]. We calculated 5 eGFR values in CHB and compensated LC groups, respectively, and obtained mGFR in a 99mTc-DTPA dynamic radionuclide imaging examination. We compared the eGFRs in two groups (see Table 2). Either mGFR or eGFRs in the CHB group were higher than that in the compensated LC group, but the differences were not significant, except for the CHINAcr-cys equation ($p = 0.020$).

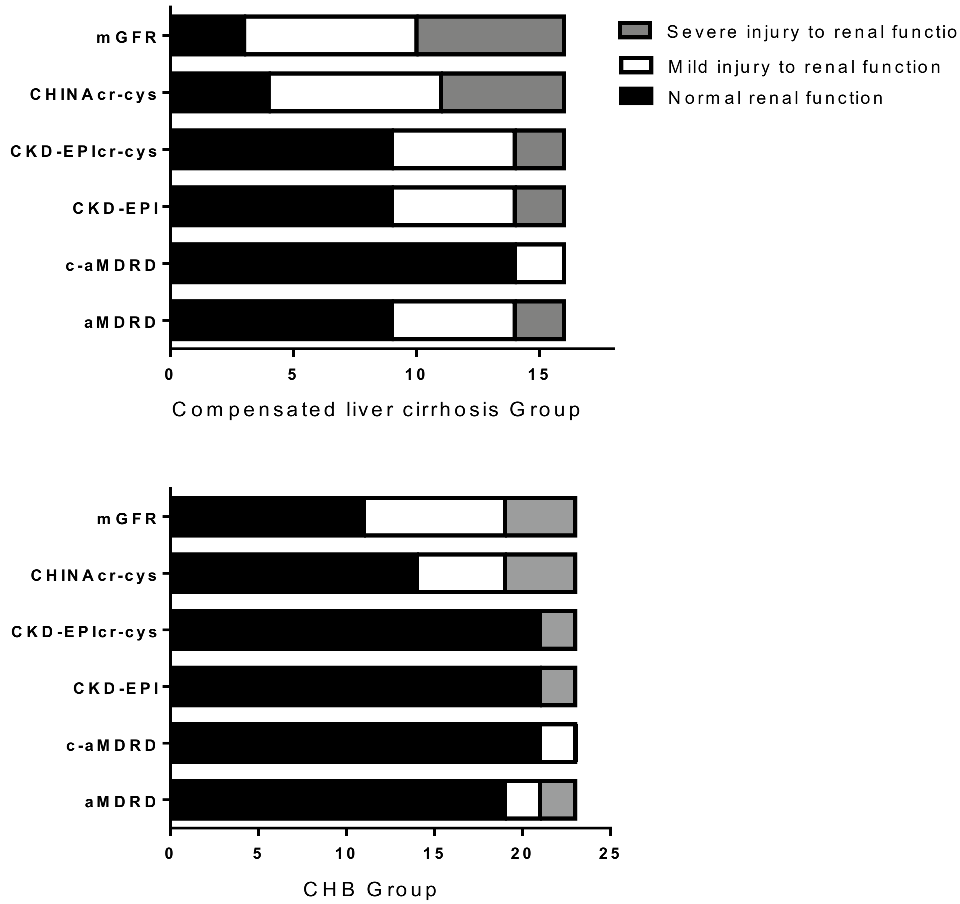


Fig. 3 The diagnostic performance of renal function by different equations

Bias between eGFR and mGFR was estimated by the median of the difference of them. The eGFR from the CHINAcr-cys equation had lower bias than any other equations. It was very clear that eGFR from the CHINAcr-cys equation was close to mGFR. The bias between eGFR and mGFR can be attributed to the development of these estimating equations specifically for GFR in patients with chronic kidney disease; they have not yet been tested in liver disease. Moreover, these estimating equations were derived from specific populations and may not be applicable to other populations. For example, the participants in the development study of CKD-EPIcys and CKD-EPIcr-cys were mostly of western origin; therefore, it is crucial to validate the performance of the equations in ethnically diverse groups, but CHINAcys and CHINAcr-cys were developed using a population of 788 Chinese CKD patients [21]. Therefore, our results showed that eGFR from the CHINAcr-cys equation was close to mGFR in the two groups.

Recently, some papers analyzed the performance of GFR estimating equations in subjects with liver cirrhosis. Mindikoglu [23] found that CKD-EPI cr-cysC equation (2012) was worse in subjects with cirrhosis, even it's the most accurate GFR estimating equation. The inaccuracy of the cr-based equations in liver disease and LC patients may be related to several factors. It has been shown that liver disease patients often have normal serum creatinine concentrations, while GFR is actually significantly decreased. In our study, all of the participants had normal Scr, but 25/39 had abnormal mGFR (13/16 for LC; 12/23 for CHB), and 6/16 had mGFR < 60 in the LC group.

An impaired liver results in decreased creatinine production and an overestimation of renal function [11]. Protein-calorie malnutrition and muscle wasting, which are common during cirrhosis [24], also contributed to decreased creatinine production. In this study, 3 of the equations (a-MDRD, c-aMDRD, and CKD-EPIcr) were based on Scr alone. It is not surprising that they are also inaccurate. Several studies have shown that MDRD tends to overestimate eGFR in cirrhotic patients [25]. Significant inter-laboratory variations have been observed in the dosage of Scr, mostly due to an interaction with Bil [26]. Routine Scr dosage is based on spectrophotometry. In patients with jaundice, Bil as a chromogen interferes with the Scr dosage, which results in deceptively low Scr values. We conclude that poor consistency between mGFR and eGFR in our study may be related to several factors. First, until now, no new equation has been developed that relies on data from patients with CHB and LC, and some specific factors influencing creatinine levels

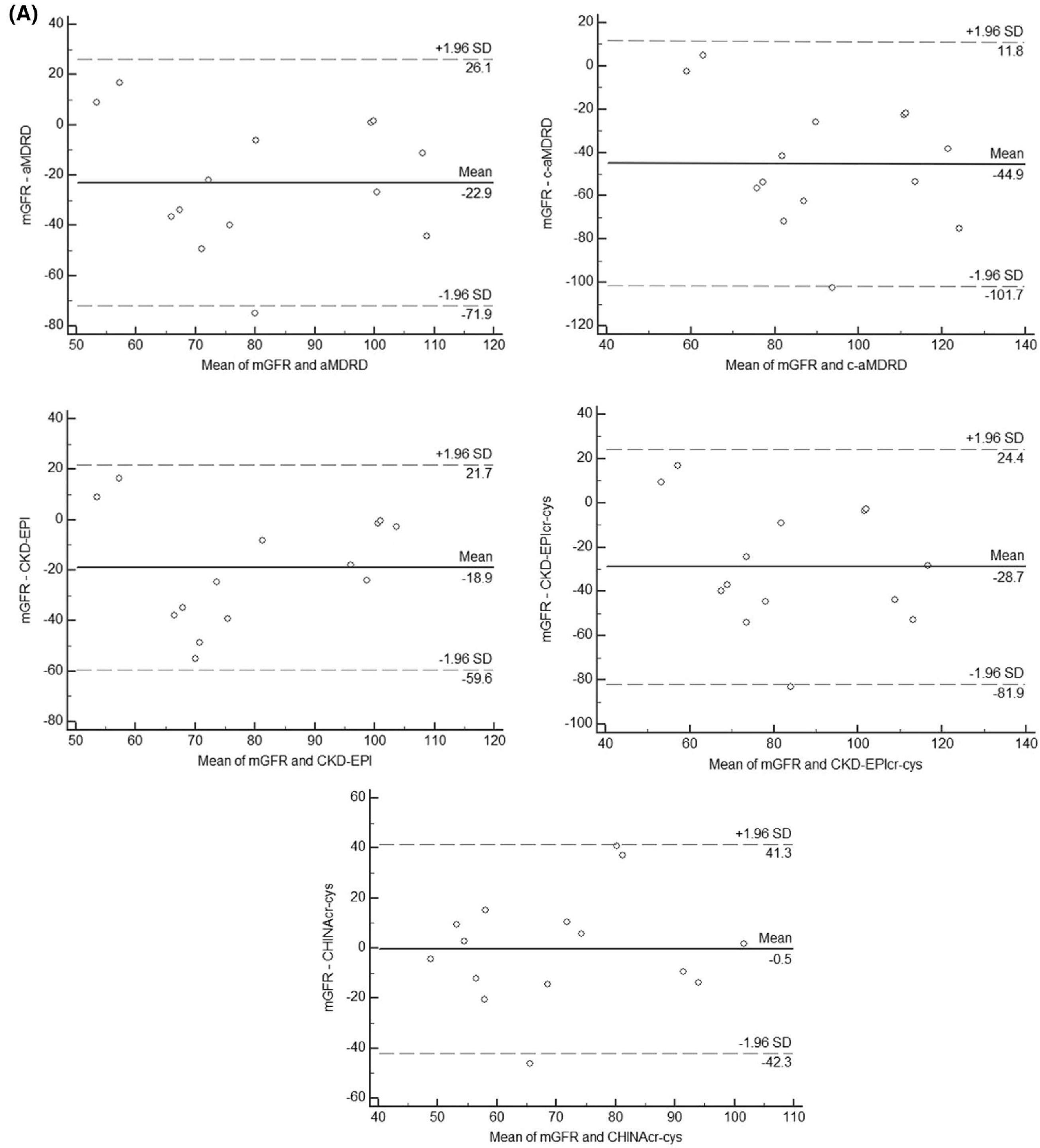


Fig. 4 Bland–Altman plot results in the compensated LC group (**a**) and in the CHB group (**b**). In the compensated LC group, Bland–Altman plots comparing the agreement between eGFR (by aMDRD, c-aMDRD, CKD-EPIcr, CKD-EPIcr-cys, and CHINAcr-cys) and mGFR. Full line, mean difference between two methods; dashed line, ± 1.96 SD difference against mean.In the CHB group, Bland–Altman plots showing the CHINAcr-cys and CKD-EPIcr equations presented narrower acceptable limits than did the aMDRD, c-aMDRD, and CKD-EPIcr-cys equations (62.8 and 56.1 vs. 85.7, 102.9, 93.6 mL/min per 1.73 m^2)

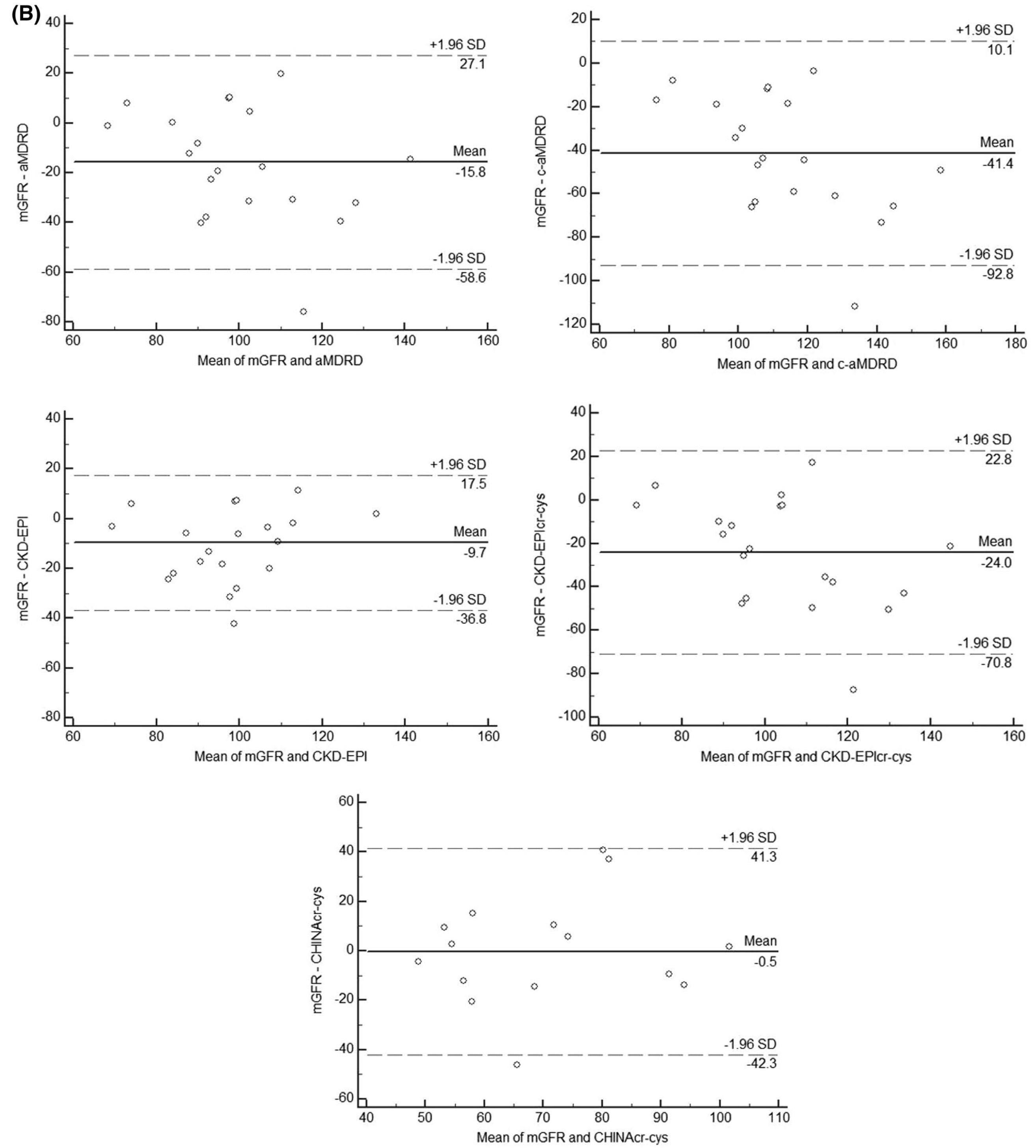


Fig. 4 (continued)

are not taken into account. Second, impaired liver function results in decreased creatinine production. Third, negative interference of Bil in Cr measurements is an additional unresolved problem in patients with liver disease. Finally, these equations are not adjusted for some variables, which are likely to have a determinantal impact on the estimation of GFR in liver disease patients. We cannot optimize the performance of any equation for all clinical populations across a wide range of GFRs. Indeed, these formulas may give falsely reassuring values since they tend to overestimate GFR.

Table 3 Univariate analysis of biomarkers versus mGFR in patients with liver disease

Characteristics	Kidney injury ($N=25$)	Normal renal function ($N=14$)	t/Z	p value
Age (year)	52.1 ± 8.9	45.4 ± 12.9	1.927	0.602
BMI (kg/m^2)	24.51 ± 2.37	24.12 ± 2.51	0.414	0.681
Systolic blood pressure (mmHg)	114.51 ± 8.34	109.12 ± 9.33	1.856	0.071
Diastolic blood pressure (mmHg)	83.45 ± 6.51	79.63 ± 8.40	1.582	0.122
ALT (U/L)	36 (27, 70)	70 (27.5, 93.5)	1.435	0.151
AST (U/L)	40 (32.5, 49)	38.5 (20.25, 191.5)	0.249	0.803
PLT (10^9/L)	122.41 ± 55.75	139.14 ± 61.34	0.889	0.391
LSM (Kpa)	14.42 ± 6.07	12.41 ± 7.88	0.889	0.380
INR	1.19 ± 0.24	1.01 ± 0.09	2.765	0.009
Uric acid (μmol/L)	253.2 ± 64.4	224.5 ± 57.6	1.385	0.174
Cr (μmol/L)	76.72 ± 14.53	63.86 ± 10.53	2.905	0.006
BUN (mmol/L)	5.53 ± 1.85	5.03 ± 1.23	0.889	0.379
Total Bilirubin (μmol/L)	19.4 (13.8,29.3)	13.5 (11.1, 32.9)	1.304	0.192
NAG (U/L)	13.29 ± 5.99	7.15 ± 1.94	3.709	0.001
Serum CysC (mg/L)	1.14 ± 0.39	0.88 ± 0.33	2.086	0.044
sRBP (mg/L)	39.12 ± 19.11	38.54 ± 14.29	0.100	0.921
Alb serum (mg/L)	40.60 ± 7.46	42.72 ± 3.67	0.994	0.327
Alb urine (mg/L)	14.12 ± 12.09	13.26 ± 4.70	0.254	0.801
uTrf (mg/L)	2.23 ± 0.24	2.2 ± 0.03	0.427	0.672
Urine lgG (mg/L)	4.82 ± 2.73	4.95 ± 2.13	0.157	0.876
uβ2-MG (mg/L)	0.12 (0.09, 0.26)	0.185 (0.15, 1.25)	0.807	0.420
sβ2-MG (mg/L)	2.43 ± 1.04	2.06 ± 0.65	1.190	0.242

We assessed the performance of different GFR-estimating equations in compensated LC and CHB groups, respectively, in terms of Pearson's correlation, Kappa consistency test and Bland–Altman Blots. Only the CHINAcr-cys equation was the most accurate in detecting renal impairment in patients with CHB ($r=0.678$, $p=0.000$) and had the highest R^2 ($R^2=0.459$) among all other measures.

In our study, Kappa statistics showed the eGFR from CHINAscr-cys had poor consistency with mGFR in the compensated LC group but moderate consistency in the CHB group. Using Pearson's correlation, CHINAscr-cys did not show dominance in the compensated LC group. We believe that the sample size was too small and influenced the results. We were concerned about the consistency with mGFR in the two groups. The Bland–Altman statistical method was used to assess the agreement between mGFR and eGFR. Bland–Altman plots showed CHINAcr-cys and CKD-EPIcr equations presented narrower acceptable limits than the aMDRD, c-aMDRD, and CKD-EPIcr-cys equations and were significantly superior according to mGFR. In conclusion, for the CHB group, the CHINAcr-cys equation was more accurate than other currently available equations in Chinese patients. In the compensated LC group, the paired t test and Bland–Altman plots showed that the CHINAcr-cys equation was more accurate than other equations, but using Pearson's correlation, Kappa analysis did not show dominance.

The uses of some serum or urinary markers are promising for accurate assessment of renal function in CKD. Donadio [27] found a high correlation between GFR (99mTc-DTPA) and SCr, Cys, ß2M and BTP in patients with < 90 mL/min/1.73 m^2. Uslu et al. [28] demonstrated that measuring serum Cys C levels and urinary NAG, ALP and LDH activities could be useful as screening markers to follow-up glomerular and tubular dysfunction in 56 patients and 20 health subjects. However, the performance of these markers for assessment of renal function in liver disease has been rarely studied. In our study, we compared the serum or urinary markers between two groups (Table 3). Univariate analysis demonstrated that INR ($p=0.009$), CR ($p=0.006$), NAG ($p=0.001$) and CysC ($p=0.044$) were identified as independently contributing factors for renal injury. CysC is independent of gender, age and muscle mass. Several studies have reported the superior diagnostic accuracy of serum CysC and CysC-based formulas over other markers and equations in patients with LC [29]. Omar [30] evaluated CysC as a marker of early renal impairment in patients with liver cirrhosis. They found that serum CysC was not only the best measure that reflected the actual renal performance but also the most accurate ones in detecting early stages of renal impairment in cirrhotic patients.

This study has several strengths. To our knowledge, this is the first study to evaluate the performance of currently available eGFR equations in CHB. All subjects obtained mGFR in a 99mTc-DTPA dynamic radionuclide imaging examination and used them as a reference standard. The study also has some limitations. All participants were from a single center, and the sample size was smaller than some other validation studies. Nevertheless, the conclusions we have drawn are valuable for further study in the future.

In conclusion, the GFR-estimating equations were specifically developed to estimate GFR in patients with CKD. Therefore, their superior performance in estimating GFR may not apply to populations with liver diseases. We compared the performance of different GFR-estimating equations in compensated LC and CHB Chinese patients. We found the CHINAcr-cys equation was superior to other currently available equations for estimating kidney function in Chinese patients. INR, CR, NAG, and cysC are proper biomarkers for screening of renal dysfunction in HBV-infected Chinese patients. Further studies should be conducted in a larger cohort of liver disease patients to correlate true GFR with potential markers.

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Compliance with ethical standards

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

References

1. Deterding K, Lampe N, Reijnders J, Manns MP, Janssen H, Zoulim F, Buti M, Santantonio T, Wedemeyer H (2011) 366 Prevalence and severity of kidney dysfunction in patients with chronic hepatitis B in Europe: data from the European Virgil Cohort. J Hepatol 54(Suppl 1):S147–S147
2. Ha NB, Ha NBGarcia RT (2009) Renal dysfunction in chronic hepatitis B patients treated with adefovir dipivoxil. Hepatology 50(3):727–734
3. Liu Y, Fan R, Chen J, Zheng Z, Liao B, Liang X, Yin J, Zhou Q, Sun J (2014) Assessment of renal function and risk factors for renal impairment in patients with hepatitis B virus-related liver cirrhosis. J South Med Univ 34(4):472–476
4. Mauss S, Berger F, Filmann N, Hueppe D, Henke J, Hegener P, Athmann C, Schmutz G, Herrmann E (2011) Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. J Hepatol 55(6):1235–1240
5. Hai LI, Han T, Yan LI, Chen LY, Wang YL, Xiang XH, Yang SG, Zhu LM (2015) The early renal injury and its related factors in patients with chronic HBV infection. Chin J Blood Purif 0(11):644–648
6. Gane EJ, Deray G, Liaw YF, Lim SG, Lai CL, Rasenack J, Wang Y, Papatheodoridis G, Di BA, Buti M (2014) Telbivudine improves renal function in patients with chronic hepatitis B. Gastroenterology 146(1):138–146
7. Hou J, Wang G, Wang F, Cheng J, Ren H, Zhuang H, Sun J, Li L, Li J, Meng Q (2017) Guideline of prevention and treatment for chronic hepatitis B (2015 update). J Clin Transl Hepatol 5(4):297–318
8. Ofliver EAF (2017) EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 67(2):370–398
9. Levey AS, Green T, Kuseket J, Beck G (2000) A simplified equitation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 11:A0828
10. Eknoyan G, Levin N (2001) NKF-K/DOQI clinical practice guidelines: update 2000. Foreword. Am J Kidney Dis 37(1):5–6
11. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 130(6):461–470
12. Zuo L, Ma YC, Zhou YH, Wang M, Xu GB, Wang HY (2005) Application of GFR-estimating equations in Chinese patients with chronic kidney disease. Am J Kidney Dis 45(3):463–472
13. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, Xu JS, Huang SM, Wang LN, Huang W (2006) Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol Jasn 17(10):2937–2944
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Rd CA, Feldman HI, Kusek JW, Eggers P, Van LF, Greene T (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604–612
15. Eriksen BO, Mathisen UD, Melsom T, Ingebretsen OC, Jenssen TG, Njølstad I, Solbu MD, Toft I (2010) Cystatin C is not a better estimator of GFR than plasma creatinine in the general population. Kidney Int 78(12):1305–1311
16. Stockman JA (2011) A new equation to estimate glomerular filtration rate. Yearb Pediatr 2011:193–194
17. Tent H, Rook M, Stevens LA, Son WJV, Pelt LJV, Hofker HS, Ploeg RJ, Heide JJHVD, Navis G (2010) Renal function equations before and after living kidney donation: a within-individual comparison of performance at different levels of renal function. Clin J Am Soc Nephrol 5(11):1960–1968
18. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K (2012) Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Ann Intern Med 156(11):785–795
19. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van LF, Zhang YL (2012) Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 367(1):20–29
20. Feng JF, Qiu L, Zhang L, Li XM, Yang YW, Zeng P, Guo XZ, Qin Y, Liu HC, Han XM (2013) Multicenter study of creatinine- and/or cystatin C-based equations for estimation of glomerular filtration rates in Chinese patients with chronic kidney disease. PLos ONE 8(3):e57240
21. Guo X, Qin Y, Zheng K, Gong M, Wu J, Shou W, Cheng X, Xia L, Xu E, Li X (2014) Improved glomerular filtration rate estimation using New equations combined with standardized cystatin C and creatinine in Chinese adult chronic kidney disease patients. Clin Biochem 47(13–14):1220–1226

22. Wu X, Cai S, Li Z, Zheng C, Peng J (2016) Potential effects of telbivudine and entecavir on renal function: a systematic review and meta-analysis. Virol J 13(1):64
23. Mindikoglu AL, Dowling TC, Weir MR, Seliger SL, Christenson RH, Magder LS (2014) Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. Hepatology 59(4):1532–1542
24. Pirlich M, Schütz T, Spachos T, Ertl S, Weiss ML, Lochs H, Plauth M (2000) Bioelectrical impedance analysis is a useful bedside technique to assess malnutrition in cirrhotic patients with and without ascites. Hepatology 32(6):1208–1215
25. Gonwa TA, Jennings L, Mai ML, Stark PC, Levey AS, Klintmalm GB (2004) Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. Liver Transplant 10(2):301–309
26. Badiou S, Dupuy AM, Descomps B, Cristolead JP (2003) Comparison between the enzymatic vitros assay for creatinine determination and three other methods adapted on the Olympus analyzer. J Clin Lab Anal 17(6):235–240
27. Donadio C (2010) Serum and urinary markers of early impairment of GFR in chronic kidney disease patients: diagnostic accuracy of urinary β-trace protein. Am J Physiol Ren Physiol 299(6):1407–1423
28. Uslu S, Efe B, Alataş O, Kebapçi N, Colak O, Demirüstü C, Yörük A (2005) Serum cystatin C and urinary enzymes as screening markers of renal dysfunction in diabetic patients. J Nephrol 18(5):559–567
29. Adachi M, Tanaka A, Aiso M, Takamori Y, Takikawa H (2016) The benefit of cystatin c in evaluation of renal function and prediction of survival in patients with cirrhosis. Hepatol Res 45(13):1299–1306
30. Omar M, Abdelrazek W, Aboraia G, Assem M, Elazab G (2015) Evaluation of serum cystatin C as a marker of early renal impairment in patients with liver cirrhosis. Int J Hepatol 2015:Article ID 309042

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