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Estimating Glomerular Filtration Rate with Creatinine and Cystatin C-based Equations in Cirrhotic Patients

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ABSTRACT

Objectives: To assess the performance of estimated GFR (eGFR) equations based on serum creatinine (Cr) and cystatin C (Cys) with measured GFR (mGFR) in cirrhotic patients.

Materials and Methods: Cirrhotic patients were enrolled. The mGFR was calculated from plasma iohexol clearance using a two compartment method. The plasma iohexol concentration was measured at 10-time points between 5-300 minutes after injection of 5 mL of iohexol. Baseline Cr and Cys were transformed into different eGFR values using previously published equations. Pearson's correlation and Bland-Altman analysis were used to analyze the performance of each eGFR equation in comparison to mGFR.

Results: Twenty-one cirrhotic patients were enrolled. Mean (SD) of serum Cr and Cys were 0.88 (0.3) mg/dL and 1.04 (0.4) mg/L. GFR (mL/minute/1.73m^2) were mGFR 80.50 (24.9), MDRD 96.9 (40.8), Cockcroft-Gault 86.7 (31.9), CKD-EPI 76.1 (24.5), Cys Hoek 79.8 (21.9), and Cys Steven 81.7 (24.8). The eGFR from all equations were found to correlate with mGFR, but with low correlation coefficients. The accuracy at 30% ranged from 59.1 (for MDRD) to 72.7 % (for Cys equations).

Conclusions: The eGFR by using Cr or Cys-based equations correlated with mGFR, but may be inaccurate in some individuals. In cirrhotic patients, MDRD is not recommended for GFR estimation because of larger bias and lower accuracy. There is no clear advantage to use Cys-based equations over Cr-based CKD-EPI or Cockcroft-Gault equations.

Key words : Glomerular filtration rate, creatinine clearance, cystatin C, cirrhosis, Cockcroft-Gault equation, MDRD equation, CKD-EPI equation, Hoek equation

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INTRODUCTION

Renal dysfunction is one of the most powerful predictors of death in cirrhotic patients. Decrease in renal function implies poor survival outcome both in mortality rate[1] and success rate of liver transplantation. Glomerular filtration rate (GFR) is the best measurement to represent renal function[2]. Many exogenous markers are used to represent GFR. Plasma clearance of iohexol, a non-ionic low-osmolar contrast medium with molecular weight of 821 dalton, has been demonstrated in many studies to be an accurate method in measuring GFR[3-5].

GFR can be estimated from plasma creatinine using many published equations. However, these GFR estimating (eGFR) equations may provide an inaccurate GFR estimation, especially in cirrhotic patients who generally have less muscle mass causing a lower plasma creatinine concentration. Thus, estimation of GFR using creatinine by any equations may lead to overestimate the true GFR[6].

Cystatin C, a non-glycosylated 13 kD protein, is synthesized by nucleated cells. The concentration of plasma cystatin C is less affected by age, sex and muscle mass[7]. Thus, in patients with chronic liver disease, cystatin C-based GFR estimation may be a more sensitive indicator of GFR than plasma creatinine[8, 9].

The aim of this study is to compare the performance of estimated GFR equations based on plasma creatinine and cystatin C with measured GFR in cirrhotic patients.

MATERIAL AND METHODS

Subjects

Cirrhotic patients who had stable condition and were regularly followed up at the Division of Gastroenterology and Tropical Disease, Ramathibodi Hospital during October, 2009 to January, 2011 were included in this study. The study protocol was approved by Ramathibodi Ethics Committee. The study protocol was clearly explained to patients. Then, inform consent was obtained prior to the beginning of the study. Patients were excluded if they had a history of reaction to any contrast media or had recently been diagnosed with acute kidney injury, acute gastrointestinal bleeding or sepsis.

Study protocol

After needles with catheters were placed at both forearms of a patient, 5 mL of iohexol (Omnipaque 300 mg/ml) was injected intravenously into the first forearm over 1 minute followed by 10 mL of normal saline solution. Blood samplings were obtained from the other forearm for determination of plasma creatinine concentration by modified Jaffe's method and for cystatin C concentration at baseline (t=0). Then, blood drawing was done at 5, 10, 20, 30, 45, 60, 105, 120, 240 and 300 minutes and the collected samples were sent for iohexol measurement by high-performance liquid chromatography (HPLC) technique.

Measurement of GFR

The plasma iohexol concentration was plotted into plasma disappearance curve by the use of GraphPad Prism software, version 5.0 (GraphPad Software Inc.). The best fit curve from each cirrhotic patient was obtained with a bi-exponential equation, two-phase decay. The dosage of injected iohexol was calculated from the difference in syringe weight (pre- and post-injection) multiplied by the concentration of iohexol and divided by its density at room temperature (1.345). The area under the iohexol concentration-time curve was calculated from the coefficients and exponents of the best fit equation.

The measured GFR (mGFR), iohexol clearance, was calculated by the dosage of injected iohexol divided by area under the plasma iohexol concentration-time curve.

Estimation of GFR

Plasma creatinine concentration was determined by modified Jaffe's method. Creatinine clearance that represents estimated GFR (eGFR) was calculated by the equation of Cockcroft-Gault[10], simplified MDRD (sMDRD)[11] and CKD-EPI[12]. For clearance values of Cockcroft-Gault equation was normalized to a standard body surface area of 1.73 m^2.

Plasma cystatin C concentration was determined by using Siemen reagent. Plasma cystatin C-based eGFR was calculated by the equation of Hoek[13] and Steven[14] (Figure 1)

Statistical analysis

Basic characteristic populations were described in mean±SD. The correlation of mGFR and eGFR were analyzed by Pearson's correlation coefficient with statistically significant of $p< 0.05$, by using SPSS software version 16.0.

Bland and Altman plots, GraphPad Prism software, version 5.0 (GraphPad Software Inc.), were used

	Equation
Cockcroft-Gault[11]	(140 - age) x body weight x 0.85 (if female) / (72xCr)
simplified MDRD[12]	$186 \times Cr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)
	for male
CKD-EPI[13]	$Cr < 0.9 : 141 \times (Cr / 0.9)^{-0.411} \times 0.993^{age}$
	$Cr > 0.9 : 141 \times (Cr / 0.9)^{-1.209} \times 0.993^{age}$
	for female
	$Cr \leq 0.7 : 144 \times (Cr / 0.7)^{-0.329} \times 0.993^{age}$
	$Cr > 0.7 : 144 \times (Cr / 0.7)^{-1.209} \times 0.993^{age}$
Hoek[14]	-4.32 + (80.35 / Cys)
Steven[15]	$76.7 \times (Cys)^{-1.19}$

**age (years), body weight (Kgs), Cr (mg/dL), Cys (mg/L)*

Figure 1. Formula of estimated GFR equations.

to analyze the agreement between measured and estimated GFR. Bias was defined as the average of absolute difference between eGFR from each equation, and mGFR. Precision was defined as the standard deviation of the average of absolute difference between eGFR and mGFR. Comparisons of the bias between each equation were performed by *t*-tests. The accuracy was defined by calculate the percentage of eGFR values that fall within 10%, 30% and 50% deviated from mGFR.

RESULTS

Twenty-one cirrhotic patients were enrolled into this study with age ranging 30 to 77 (mean 58.05 ± 10.9 yrs.). Seven patients (33.33%) were classified as decompensated liver cirrhosis. Means of plasma creatinine and cystatin C concentration were 0.88 ± 0.3 mg/dL (range 0.4 - 1.5 mg/dL), 1.04 ± 0.4 mg/L (range 0.65 - 2.3 mg/L), respectively (Table 1).

The mean mGFR was 80.50 ± 24.5 ml/min/1.73 m2. The average eGFRs calculated by each equation are shown in Table 2. All eGFRs calculated from either creatinine- or cystatin C-based equations were found to correlate significantly with mGFR but all had a correlation coefficient (R) less than 0.7. The overall eGFR calculated from sMDRD produced a strong positive bias to mGFR and Cockcroft-Gault produced a lower level of positive bias. Of creatinine based equations, CKD-EPI produced the lowest bias. Both of the cystatin C-based equations produced low bias.

Nonetheless, there were considerable variations in accuracy when individual patients are considered. Precision was the lowest for sMDRD, whereas CKD-EPI and Cockcroft- Gault produced better precision, comparable to cystatin C-based equations. The accuracy was calculated from the percentage of eGFR values that fell within 10%, 30% and 50% of the mGFR value. The accuracy within 10% from all equations was between 22.7 and 27.3%. The accuracy within 30%

Table 1. Characteristics of all cirrhotic patients.

Characteristics	n = 21
Age, years (mean ± SD)	58.05 ± 10.9
Male : Female	12 : 9
Weight, kg	62.20 ± 9.0
Height, m	161 ± 0.1
Body mass index, kg/m^2	24.08 ± 3.6
Body surface area, m^2	1.66 ± 0.1
Serum creatinine, mg/dL	0.88 ± 0.3
Serum cystatin C, mg/L	1.04 ± 0.4
Albumin, g/L	34.20 ± 8.7
Measured GFR, mL/min/1.73 m^2	80.50 ± 24.9
Child-Pugh Class	
A	14
B	6
C	1
Risk factors of liver disease	
Alcohol	8
Viral hepatitis B	14
Viral hepatitis C	4
Autoimmune hepatitis	1

Table 2. Correlations of estimated GFR equations and measured GFR.

	Mean GFR ± SD (mL/min/1.73 m^2)	Correlation	*p*-value	Bias*	Precision**	Accuracy within 10%	30%	50%
mGFR	80.5 ± 24.5	-	-	-	-	-	-	-
Cockcroft-Gault	86.7 ± 31.9	0.68	0.001	6.2	23.7	22.7	63.6	81.8
sMDRD	96.9 ± 40.8	0.65	0.001	16.4	31.0	22.7	59.1	72.7
CKD-EPI	76.1 ± 24.5	0.60	0.004	-4.4	22.1	27.3	68.2	68.2
Hoek	79.8 ± 21.9	0.68	0.001	-0.7	19.1	22.7	72.7	86.4
Steven	81.7 ± 24.8	0.68	0.001	1.2	20.0	27.3	72.7	81.8

*mean absolute difference between mGFR and eGFR
**standard deviation value of the mean absolute difference
GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate

Table 3. Characteristics including measured and estimated GFR levels between compensated and decompensated cirrhosis.

Characteristics	Compensated cirrhosis (n=14)	Decompensated cirrhosis (n=7)	*p*-value
Age, years	61.07 ± 9.6	52.00 ± 11.5	0.070
Weight, Kg	62.96 ± 8.6	60.67 ± 10.3	0.597
Height, m	1.64 ± 0.1	1.55 ± 0.05	0.027
Serum creatinine, mg/dL	0.88 ± 0.3	0.89 ± 0.4	0.960
Serum cystatin C, mg/L	0.92 ± 0.2	1.27 ± 0.6	0.040
Albumin, g/L	38.66 ± 5.0	25.29 ± 7.7	0.000
Measured GFR, ml/min/1.73 m^2	81.95 ± 25.6	77.6 ± 25.2	0.716
Estimated GFR, ml/min/1.73 m^2			
Cockcroft-Gault	86.07 ± 31.8	87.88 ± 34.5	0.906
sMDRD	100.26 ± 39.8	90.25 ± 45.1	0.609
CKD-EPI	74.04 ± 24.8	80.10 ± 25.2	0.606
Hoek	85.62 ± 17.2	68.23 ± 26.9	0.086
Steven	88.05 ± 20.0	68.85 ± 29.83	0.796

was above 70% for cystatin C-based equations but less than 60% for sMDRD. The accuracy of CKD-EPI equation was the lowest percentage value (68.2%) at the 50% cut-off.

The data of compensated and decompensated cirrhotic patients were compared (Table 3). There were no significant differences in age, body weight, serum creatinine and mGFR between groups. Plasma cystatin C was higher and albumin was lower in patients with decompensated cirrhosis. There was no significant difference in eGFR of both creatinine- and cystatin C-based equations between groups.

DISCUSSION

GFR is used to define kidney function. The clearance of many exogenous markers, such as iohexol, has been found to be an accurate method to measure GFR. Endogenous markers such as plasma creatinine and cystatin C became alternative clinical tools to assess GFR. In cirrhotic patients, the estimation of GFR from plasma creatinine-based equations has been shown to be relatively inaccurate in various populations[14,15]. This study confirms the inaccuracy of creatinine-based GFR equations. Furthermore, cystatin C equations are not found to improve the accuracy of renal function assessment in Thai cirrhotic patients.

The measured GFR and eGFR from 5 validated equations are shown to be significantly correlated. Nonetheless, the correlation was fairly weak. This may be due to the small populations in the study or non-GFR related factors that could affect serum creatinine

or cystatin C measurement in cirrhotic patients. In cirrhotic patients, the estimation of GFR by using creatinine based sMDRD equation yields the largest degree of bias and the lowest precision and accuracy. There was no clear cut benefit in using cystatic C-based equations since all cystatin C-based equations (Hoek, Cockcroft-Gault, CKD-EPI and Steven) yielded similar degrees of bias and accuracy. It is shown from this study that caution needs to be exercised when using MDRD as eGFR in cirrhotic patients, especially since MDRD is used widely in Thailand. In cirrhotic patients, CKD-EPI or Cockcroft-Gault may provide more accurate estimation. The result of this study does not support the routine use of cystatin C-based equations over serum creatinine. Cystatin C-based equations should be considered as a supplementary test for renal function assessment in uncertain situations.

There were significantly higher cystatin C levels in decompensated cirrhotic patients while there were no significant differences in plasma creatinine or mGFR levels between compensated and decompensated groups. The reason for this discrepancy in the findings is unclear. It has been proposed that serum cystatin C level may increase in some malignancy. In this study, there were more patients with hepatocellular carcinoma in the decompensated cirrhosis group. Further study is required to evaluate the impact of hepatocellular carcinoma on plasma cystatin C levels.

In conclusion, all validated eGFR equations using Cr and Cys-based correlated with mGFR but none is accurate enough to determine true GFR in patients with cirrhosis. The sMDRD equation, which is used widely in Thailand, is the least accurate with the largest degree of bias. There is no clear advantage of cystatin C-based equations over creatinine-based Cockcroft-Gault or CKD-EPI equations. In spite of its inconvenience if used in all patients, measurement of GFR by plasma clearance of exogenous markers such as iohexol provides a more accurate assessment of kidney function and is useful in some circumstances that require precise evaluation.

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