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Estimation of renal function by three CKD-EPI equations in Chinese HIV/AIDS patients
A STROBE-compliant article

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Abstract

Assessing renal function accurately is important for human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) patients. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recommended three equations to calculate estimated glomerular filtration rate (eGFR). There is evidence that eGFR based on the combination of serum creatinine and cystatin C is the most accurate of the three equations. But there is limited data on the comparison of three CKD-EPI equations in Chinese HIV/AIDS patients. The aim of our study was to compare the three CKD-EPI equations in Chinese HIV/AIDS population and assess renal function.

Cross-sectional, single center, prospective study.

One hundred seventy two Chinese adult HIV/AIDS patients were enrolled, including 145 (84.3%) males and 27 (15.7%) females. Mean age was 40($\pm$12) years old. Overall mean eGFR based on serum creatinine, cystatin C and the combination of the 2 markers was 112.6($\pm$19.0) mL/min/1.73m^2, 92.0($\pm$24.2)mL/min/1.73m^2, and 101.7($\pm$21.8)mL/min/1.73m^2, respectively (P=.000). The eGFR calculated by serum creatinine alone is higher than eGFR calculated by combination of serum creatinine and cystatin C, and eGFR calculated by cystatin C individual is lower than eGFR calculated by combination of the 2 markers.

Of the 3 CKD-EPI equations, the CKD-EPI$_{scr-cys}$ equation may have the most accuracy in evaluating renal function in Chinese HIV/AIDS patients while the CKD-EPI$_{scr}$ equation may overestimate renal function and the CKD-EPI$_{cys}$ equation may underestimate renal function.

Abbreviations: AIDS = acquired immune deficiency syndrome, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated GFR, GFR = glomerular filtration rate, HIV = human immunodeficiency virus, .

Keywords: cystatin C, glomerular filtration rate, human immunodeficiency virus/acquired immune deficiency syndrome, serum creatinine

1. Introduction

Renal dysfunction is common in human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) patients and a risk factor for poor prognosis of these patients.[1–4] Assessing renal function accurately in the HIV/AIDS patients is essential, because we need to adjust the drug dosage according to kidney function. Gold standard of measuring glomerular filtration rate (GFR) is testing the clearance of inulin, iohexol, or ^{99}Tc^{m}-diathylenetriamine pentaacetic acid, but it's so cumbersome that we rarely use it in clinical settings.[5] Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recommended 3 equations to calculate estimated glomerular filtration rate (eGFR) for clinical applications in 2012[6]: eGFR$_{scr}$, eGFR$_{cys}$, and eGFR$_{scr-cys}$ based on serum creatinine, cystatin C and the combination of the 2 markers respectively.

Prior studies indicated that, the sensitivity of eGFR equations based on serum creatinine is poor in HIV/AIDS patients, because serum creatinine values in these patients are significantly lower than general population.[7,8] In addition, a clinical study in USA demonstrated HIV-RNA > 400 copies/mL or lower CD4+ T cell count can lead to larger bias of eGFR based on cystatin C.[9] A meta-analysis revealed that serum cystatin C is a better biomarker for the diagnosis of CKD in the West than in Asia.[10] Inker LA found eGFR based on the combination of serum creatinine and cystatin C was more accurate than eGFR based on

serum creatinine or cystatin C individually in HIV-positive population.[11]

Until now, there is limited data on the comparison of 3 CKD-EPI equations in Chinese HIV/AIDS patients. The aim of our study was to contrast the 3 CKD-EPI equations in Chinese HIV/AIDS population in a single center and evaluating renal function in these patients.

2. Methods

2.1. Study population

This was a cross-sectional prospective study on HIV/AIDS patients. A total of 190 Chinese HIV/AIDS patients admitted to Beijing Ditan Hospital from February to May 2019 were observed. Exclusion criteria were

1. younger than 18 years old;
2. the patients who had missing data.

Clinical information was collected from electronic medical records. The Ethics Committee of Beijing Ditan Hospital, Capital Medical University approved the study protocol. The approval numbers is Jdlkz 2019-056-02. We obtained written informed consent from each subject.

2.2. Laboratory measurements and eGFR equations

Serum creatinine was measured at Department of Clinical Laboratory in Beijing Ditan Hospital affiliated to Capital Medical University using enzymatic assay. Collected 3.5 ml fasting venous blood of eligible subjects, took serum after centrifugation for 15 min under 3000 r /min, conserved the serum in −80°C. Finally, remelted the frozen serum together for testing cystatin C. The cystatin C test reagent kit was produced by Zhangjiagang DIALAB Biotechnology Co. Ltd, China. Serum cystatin C was measured with automatic biochemical analyzer HITACHI 7600 using a latex enhanced immunoturbidimetric assay. The eGFR was calculated by 3 CKD-EPI equations[6] (Table 1).

2.3. Statistical analysis

Data were analyzed using SPSS20.0 (SPSS Institute, Chicago IL, USA). Homogeneity of quantitative data were tested by Kolmogorov-Smirnov one-sample test. Data with normal distribution was presented as mean±SD. If data was in abnormal distribution, it was presented as median (interquartile range). Categorical variables were prescribed as frequency and percentage. Comparisons between eGFR values calculated by 3 CKD-EPI equations ($eGFR_{scr}$, $eGFR_{cys}$, and $eGFR_{scr-cys}$) were carried out by using the Wilcoxon signed rank test. P values <.05 were considered statistically significant in this study.

3. Results

One of the 190 Chinese HIV/AIDS patients admitted to Beijing Ditan Hospital from February to May 2019 was ineligible because he was younger than 18 years old, and 17 of them were excluded because of missing values for serum cystatin C. Finally, 172 Chinese adult HIV/AIDS patients were enrolled, including 145 (84.3%) males and 27 (15.7%) females.

3.1. Patient characteristics

Mean age was 40(±12) years old, the youngest patient was 19 years old, and the oldest 1 was 76 years old. Mean body mass index was 22 (±4) kg/m^2. 17 (9.9%), 13 (7.6%), 65 (37.8%), and 14 (8.1%) patients had hypertension, diabetes, dyslipidemia, and tumor, respectively. HBV, HCV and Syphilis existed in 11 (6.4%), 8 (4.7%), 43 (25.0%) patients, respectively. Median duration of HIV infection was 12 months (IQR 0–72). 44 (25.6%) of them were newly discovered cases. The longest duration of HIV-infection was 276 months. One hundred fourteen patients (66.3%) were receiving antiretroviral therapy. Sixty nine patients (40.1%) had HIV-RNA <20 copies/ml or undetectable. Median CD4+T cell count was 120 (IQR 42–458) cells/μL. More details are described in Table 2.

Table 1

Three CKD-EPI equations for eGFR.

Subjects	Gender	Scr (mg/dL)	Scys (mg/L)	Equation (mL/min/1.73 m^2)
$eGFR_{scr}$	female	≤0.7		$141 \times (Scr/0.7)^{-0.329} \times 0.993^{age} \times 1.018$
		>0.7		$141 \times (Scr/0.7)^{-1.209} \times 0.993^{age} \times 1.018$
	male	≤0.9		$141 \times (Scr/0.9)^{-0.411} \times 0.993^{age}$
		>0.9		$141 \times (Scr/0.9)^{-1.209} \times 0.993^{age}$
$eGFR_{cys}$	female		≤0.8	$133 \times (Scys/0.8)^{-0.499} \times 0.996^{age} \times 0.932$
			>0.8	$133 \times (Scys/0.8)^{-1.328} \times 0.996^{age} \times 0.932$
	male		≤0.8	$133 \times (Scys/0.8)^{-0.499} \times 0.996^{age}$
			>0.8	$133 \times (Scys/0.8)^{-1.328} \times 0.996^{age}$
$eGFR_{scr-cys}$	female	≤0.7	≤0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$
			>0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$
		>0.7	≤0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$
			>0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$
	male	≤0.9	≤0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$
			>0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$
		>0.9	≤0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$
			>0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$

Scr = serum creatinine, Scys = serum cystatin C, $eGFR_{scr}$ = GFR estimated by the CKD-EPI-creatinine formula, $eGFR_{cys}$ == GFR estimated by the CKD-EPI-cystatin C formula, $eGFR_{scr-cys}$ = GFR estimated by the CKD-EPI-combinatin of creatinine and cystatin C formula.

Table 2

Main demographic characteristics of 172 HIV/AIDS patients included in the study.

Variables	Estimates
Mean age, yr (±SD)	40 (±12)
Gender, n (%)	
Male	145 (84.3%)
Female	27 (15.7%)
Mean body mass index, kg/m^2 (±SD)	22 (±4)
Hypertension, n (%)	17 (9.9%)
Diabetes mellitus, n (%)	13 (7.6%)
Dyslipidemia, n (%)	65 (37.8%)
Tumor, n (%)	14 (8.1%)
Hepatitis B coinfection, n (%)	11 (6.4%)
Hepatitis C coinfection, n (%)	8 (4.7%)
Syphilis, n (%)	43 (25.0%)
Median duration of HIV infection, months (IQR)	12 (0–72)
Current ART regimen, n (%)	
No treatment	58 (33.7%)
TDF + 3TC + EFV	66 (38.4%)
TDF + 3TC + LPV/r	18 (10.5%)
TDF + 3TC + DTG	5 (2.9%)
EVG/C/TAF/FTC	5 (2.9%)
Others*	20 (11.6%)
Current HIV infection status, n (%)	
Suppression under treatment (viral load <20 copies/ml)	69 (40.1%)
No suppression (including no treatment)	103 (59.9%)
Median CD4+ T cell count, cells/μL (IQR)	120 (42–458)

* Others indicate regimen which included 1-3 drugs of Abacavir, Lamivudine, Zidovudine, Stavudine, Tenofovir disoproxil fumarate, Emtricitabine, Nevirapine, Efavirenz, Dolutegravir, Raltegravir, and ritonavir-boosted lopinavir, meanwhile patients on each regimen ≤3.
ART = antiretroviral therapy, 3TC = Lamivudine, DTG = dolutegravir, EFV = efavirenz, EVG/C/TAF/FTC = Elvitegravir, Cobicistat, Emtricitabine and Tenofovir Alafenamide Fumarate Tablet, HIV = human immunodeficiency virus, LPV/r = ritonavir-boosted lopinavir, TDF = tenofovir disoproxil fumarate.

3.2. eGFR calculated by 3 CKD-EPI equations

The overall mean eGFR based on serum creatinine, cystatin C and the combination of the 2 markers was 112.6(±19.0) mL/min/1.73 m^2, 92.0(±24.2) mL/min/1.73 m^2, and 101.7(±21.8) mL/min/1.73 m^2, respectively (P = .000). The differences of mean eGFR by the 3 equations were provided in Table 3.

The frequencies of patients in each eGFR category are described in Table 4. If we use different equations to calculate eGFR, we can see that the frequencies and percentages of patients in each eGFR category is different. Generally, we can see that, eGFR calculated by serum creatinine is higher than eGFR calculated by combination of the 2 markers, and eGFR calculated by serum cystatin C is lower than eGFR calculated by combination of the 2 markers.

Table 5 provided more details about the comparison of eGFR classifications between CKD-EPI$_{scr-cys}$ equation and the other 2 equations. Of the 154 patients with eGFR$_{scr}$≥90 mL/min/1.73 m^2,

Table 3

Differences of mean eGFR calculated by 3 CKD-EPI equations.

Comparation of variables	Difference of mean (mL/min/1.73 m^2)	*P* value*
eGFR$_{scr}$ - eGFR$_{cys}$	20.6	.000
eGFR$_{scr}$ - eGFR$_{scr-cys}$	10.9	.000
eGFR$_{cys}$ - eGFR$_{scr-cys}$	−9.7	.000

See Table 1.
* Comparisons by Wilcoxon signed rank test.

Table 4

Frequencies and percentages of patients in each eGFR category.

eGFR category (mL/min/1.73 m^2)	Number (%) of patients with each eGFR category by 3 equations		
	CKD-EPI$_{scr}$	CKD-EPI$_{cys}$	CKD-EPI$_{scr-cys}$
≥90	154 (89.5%)	102 (59.3%)	131 (76.2%)
60–89	14 (8.1%)	53 (30.8%)	32 (18.6%)
30–59	4 (2.3%)	14 (8.1%)	8 (4.7%)
15–29	0 (0%)	3 (1.7%)	1 (0.6%)
<15	0 (0%)	0 (0%)	0 (0%)

eGFR = estimated glomerular filtration rate, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, Cys = cystatin C, Scr = serum creatinine.

Table 5

Comparison of eGFR classifications between CKD-EPI$_{scr-cys}$ equation and the other 2 equations.

N	eGFR$_{scr-cys}$ (mL/min/1.73 m^2)					
	≥90	60–89	30–59	15–29	<15	Total
eGFR$_{scr}$ ≥90	131	22	1	0	0	154
60–89	0	10	4	0	0	14
30–59	0	0	3	1	0	4
15–29	0	0	0	0	0	0
<15	0	0	0	0	0	0
eGFR$_{cys}$ ≥90	101	1	0	0	0	102
60–89	30	23	0	0	0	53
30–59	0	8	6	0	0	14
15–29	0	0	2	1	0	3
<15	0	0	0	0	0	0
Total	131	32	8	1	0	172

See Table 1.

23 patients presented eGFR$_{scr-cys}$ < 90 mL/min/1.73 m^2, and 1 among them even showed eGFR$_{scr-cys}$ < 60 mL/min/1.73 m^2. In the 14 patients who had eGFR$_{scr}$ located in 60-89 mL/min/1.73 m^2, 4 of them presented eGFR$_{scr-cys}$ located in 30-59 mL/min/1.73 m^2. Of the 131 patients with eGFR$_{scr-cys}$≥90 mL/min/1.73 m^2, 30 patients had eGFR$_{cys}$ < 90 mL/min/1.73 m^2. Of the 53 patients with eGFR$_{cys}$ located in 60-89 mL/min/1.73 m^2, 30 patients had eGFR$_{scr-cys}$≥90 mL/min/1.73 m^2.

4. Discussion

We used enzymatic method for the determination of serum creatinine, because previous studys indicated the enzymatic method is more accurate than Jaffe method.[12,13] In our study, the eGFR calculated by serum creatinine alone was 112.6(±19.0) mL/min/1.73 m^2, which was the highest in the 3 CKD-EPI equations. And our data are consistent with prior studies.[8,14] Clara et al revealed serum creatinine may overestimate renal function in HIV-infected subjects.[8] In a cohort of HIV-infected women, Driver et al[14] found that the prevalence of CKD was higher with eGFR$_{cys}$ compared to eGFR$_{scr}$. The overestimation of renal function and thus underestimating kidney impairment by serum creatinine in HIV/AIDS patients is due to decreasing serum creatinine concentrations in this population. Low muscle mass is common in HIV/AIDS patients.[15] Both HIV itself and HIV antiretroviral medications could lead to muscle disease and decrease the concentration of creatinine.[8,16–18]

It should be noted that, although dolutegravir or rilpivirine may inhibit renal creatinine secretion, leading to an increase in

serum creatinine in HIV/AIDS patients treated with these drugs,[19,20] this phenomenon was not been observed in our study. Maybe it's because there are few patients taking these drugs in our study (8 patients used dolutegravir and none took rilpivirine).

Cystatin C is produced by all nucleated cells at a constant rate in the body and is less affected by muscle mass than creatinine.[21] An analysis on 922 HIV-infected subjects conducted by Choi A and colleagues revealed that eGFR based on cystatin C was significantly associated with 5-year all-cause mortality, whereas eGFR based on serum creatinine did not appear to be associated with mortality substantially.[22] Nevertheless, Bhasin et al found[9] eGFR based on cystatin C was significantly more biased than eGFR based on combination of serum creatinine and cystatin C in the HIV-positive group, and eGFR based on cystatin C was lower than measured GFR using plasma iohexol clearance. In our present study, we found the eGFR calculated by serum cystatin C is lower than eGFR calculated by combination of serum creatinine and cystatin C [92.0($\pm$24.2) mL/min/1.73 m^2 vs 101.7($\pm$21.8) mL/min/1.73 m^2]. So our result is in accordance with Bhasin et al despite we did not measure GFR with gold standard method. That is to say, eGFR based on combination of serum creatinine and cystatin C has greater GFR fidelity while eGFR based on cystatin C is a better predictor of clinical outcomes. This is not a contradiction. eGFR based on cystatin C had strong correlations with HIV-RNA viral load, CD4+ T cell count, hs-CRP, IL-6, and D-dimer in HIV-infected persons.[21] Emerging data from HIV-infected populations exhibited the strong associations between clinical events including all-cause mortality and inflammatory markers, notably IL-6 and D-dimer.[23–25] Consequently, inflammation may mediate the association between eGFR based on cystatin C and clinical events.

Similar outcomes were discovered in general populations.[26–29] Inker LA[26] found that the eGFR equation based on combination of serum creatinine and cystatin C was significantly more accurate than the eGFR equation based on cystatin C alone. A research performed by Chi[27] et al showed that the CKD-EPI$_{scr-cys}$ equation was more suitable for estimating renal function than the other equations in a Chinese general population. Zhu Y[29] also corroborated that CKD-EPI $_{scr-cys}$ formula had better diagnostic value, especially in young participants.

Our study has following advantages. Firstly, this is the first clinical study to compare 3 CKD-EPI equations conducted in Chinese HIV/AIDS population. Secondly, we used standardized serum creatinine and cystatin C measurements.

Our study also has limitations. Firstly, we did not directly measure GFR using gold standard method. Secondly, the number of patients was relatively small. Thirdly, there was no HIV/AIDS patients with eGFR < 15 mL/min/1.73 m^2. A prospective larger scale study comparing the performance of different eGFR formulas with gold standard of measuring GFR in Chinese HIV/AIDS patients should be conducted in the future.

5. Conclusion

In conclusion, of the 3 CKD-EPI equations, the CKD-EPI$_{scr-cys}$ equation may have the most accuracy in evaluating renal function in Chinese adult HIV/AIDS patients as the CKD-EPI$_{scr}$ equation may overestimate renal function and the CKD-EPIcys equation may underestimate renal function.

Author contributions

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