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Short Communication

Close Monitoring of eGFR Should Be Performed in HIV-Infected Patients Aged over 37 Years

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SUMMARY: Chronic kidney disease (CKD) has been shown to be a poor prognostic factor in HIV patients. This study aimed to identify risk factors in HIV-infected patients with early decline in renal function or an estimated glomerular filtration rate (eGFR) less than 90 mL/min/1.73 m^2. The study was retrospectively conducted at Panyananthaphikkhu Chonprathan Medical Center, Thailand. The inclusion criteria were HIV-infected adult patients who were treated at the hospital's HIV clinic and whose eGFR levels at the first visit had been evaluated. Eligible patients were categorized according to their eGFR level being lesser or greater than 90 mL/min/1.73 m^2. Multivariate logistic analysis was performed to evaluate the association of risk factors with an eGFR of less than 90 mL/min/1.73 m^2. There were 301 HIV-infected patients included in the study. Of those, 89 patients (29.57%) had an eGFR of less than 90 mL/min/1.73 m^2. Age was the only significant risk factor associated with an eGFR of less than 90 mL/min/1.73 m^2 with an adjusted odds ratio of 1.072 (95% confidence interval: 1.015–1.132). Age of over 37 years predicted an eGFR of less than 90 mL/min/1.73 m^2 as a risk factor in HIV-infected patients, with a sensitivity of 80.9% and specificity of 34.91%. Age was independently associated with eGFRs of less than 90 mL/min/1.73 m^2 in HIV-infected patients. Close monitoring of eGFR should be performed in HIV-infected patients aged over 37 years.

The human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome were discovered in the 1980s. Opportunistic infections associated with the disease caused a large number of deaths in the following 2 decades. Due to effective anti-retroviral therapy, the annual mortality rates from HIV have been decreasing at a rate of 4.17% annually since 2006 (1).

Chronic kidney disease (CKD) has been shown to be a poor prognostic factor in HIV patients. It is recommended that all patients are evaluated for existing kidney disease by screening for proteinuria and estimating renal function at the time of HIV diagnosis (2). The risk of death is 2.5 times higher with the presence of proteinuria and/or elevated serum creatinine (3). Several factors, such as age, HIV viral load, and Indinavir treatment, are associated with CKD in HIV patients (2–6). Most studies that have reported risk factors for CKD in HIV patients were conducted in HIV patients with CKD at stages 3–5 or estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2. This study aimed to identify risk factors in HIV-infected patients with early decline in renal function or eGFR less than 90 mL/min/1.73 m^2 (eGFR $<$ 90), leading to earlier initiation of workups, treatment, and awareness.

This was a retrospective study conducted at Panyananthaphikkhu Chonprathan Medical Center, Nonthaburi, Thailand. The inclusion criteria were HIV-infected adult patients who were treated at the hospital's HIV clinic and whose eGFR levels at the first visit had been evaluated. We excluded pregnant women due to uncertain eGFR calculations. The HIV-infected patients in this clinic include both newly-diagnosed patients and those who have previously been treated at other hospitals. The study period was from April to October 2013. This study was a part of the HIV-CKD project at Panyananthaphikkhu Chonprathan Medical Center.

We recorded baseline clinical features when the eGFR was evaluated. The eGFR level was calculated based on the CKD EPI formula (7). Patients' eGFR were reported as mL/min/1.73 m^2. Eligible patients were categorized according to their eGFR level being lesser or greater than 90 mL/min/1.73 m^2. Clinical factors between the groups were compared using descriptive statistics. Univariate and multivariate logistic analyses were performed to evaluate the association of each factor with the presence of an eGFR $<$ 90.

Significant numerical factors were analyzed to identify the cutoff point associated with eGFR $<$ 90. A receiver operating characteristics (ROC) curve was created to predict eGFR $<$ 90. The cutoff points of factors associated with eGFR $<$ 90 were reported as sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR−) from the ROC curve. The appropriate cutoff point was chosen with the aim of screening for eGFR $<$ 90 which required a high

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sensitivity of approximately 80%. All statistical analyses were performed using STATA software (College Station, TX, USA).

There were 301 HIV-infected patients who met the study criteria. Of those, 89 patients (29.57%) had an eGFR of less than 90 mL/min/1.73 m^2. The average (S.D.) eGFR in those patients with eGFR $<$ 90 and those with eGFR $\geq$ 90 were 76.76 (11.23) and 115.43 (21.46) mL/min/1.73 m^2, respectively. Clinical features and types of anti-retroviral therapy are presented in Table 1 and Table 2, respectively.

Patients with an eGFR $<$ 90 had a significantly higher average age (44.70 vs 39.74 years) and average body mass index (BMI) (22.67 vs 21.10 kg/m^2) than those with eGFR $\geq$ 90 (Table 1). The proportion of patients with cryptococcosis was also significantly higher in patients with eGFR $<$ 90 (8.99 vs 1.89%; p value 0.007) as shown in Table 1. No statistically significant associations in either group were found with regard to types of anti-retroviral therapy (Table 2).

The multivariate logistic regression model was controlled for sex, BMI, CD4 level, HIV viral load,

Table 1. Baseline features of HIV-infected patients categorized by estimated glomerular filtration rate (eGFR)

Factor	eGFR $\geq$ 90 mL/min n = 212	eGFR $<$ 90 mL/min n = 89	p value
Mean (S.D.) age, yr	39.74 (8.46)	44.70 (9.67)	$<$ 0.001
Male sex	132 (62.26)	51 (57.30)	0.421
Mean (S.D.) BMI, kg/m^2	21.10 (3.17)	22.67 (4.11)	$<$ 0.001
Diabetes Mellitus	5 (2.36)	3 (3.37)	0.698
Hypertension	12 (5.66)	9 (10.11)	0.166
Coronary artery disease	2 (0.94)	2 (2.25)	0.584
HBV infection	17 (9.44)	8 (10.53)	0.790
HCV infection	24 (13.64)	5 (6.85)	0.191
HIV infection time, mo	72.85 (52.94)	75.82 (48.96)	0.690
Median (1st-3rd quartile range) of ARV treatment duration, mo	37 (21–64)	37 (23–68)	0.427
Median (1st-3rd quartile range) of CD 4 count, cells/mm^3	118 (29–301)	91 (24–286)	0.515
Median (1st-3rd quartile range) of HIV viral load, copies/mL	42 (40–60)	40 (40–51)	0.495
Routes of HIV transmission			
IVDU	4 (2.40)	0	0.322
Sexual	143 (85.63)	64 (91.43)	0.221
Vertical	2 (1.20)	0	0.999
Opportunistic infection	91 (42.92)	39 (43.82)	0.886
Tuberculosis	58 (27.36)	17 (19.10)	0.131
PJP	19 (8.96)	12 (13.48)	0.239
CMV	1 (0.47)	1 (1.12)	0.525
Cryptococcosis	4 (1.89)	8 (8.99)	0.007
PPE	13 (6.13)	3 (3.37)	0.410

Data presented as number (percentage) unless indicated otherwise.
BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; ARV, antiretroviral; CD4, cluster of differentiation 4; IVDU, intravenous drug users; PJP, pneumocystis jiroveci pneumonia; CMV, cytomegalovirus; PPE, pruritic papular eruption.

Table 2. Anti-retroviral therapy of HIV-infected patients categorized by estimated glomerular filtration rate (eGFR)

Factor	eGFR $\geq$ 90 mL/min n = 212	eGFR $<$ 90 mL/min n = 89	p value
AZT	7 (3.30)	5 (5.62)	0.347
D4T	19 (8.96)	6 (6.74)	0.650
3TC	38 (17.92)	19 (21.35)	0.489
TDF	14 (6.60)	11 (12.36)	0.099
AZT, 3TC	15 (7.08)	2 (2.25)	0.109
D4T, 3TC	13 (6.13)	4 (4.49)	0.785
NVP	9 (4.25)	4 (4.49)	0.999
EFV	44 (20.75)	23 (25.84)	0.333
RTV	3 (1.42)	1 (1.12)	0.999
IDV	4 (1.89)	1 (1.12)	0.999
Atazanavir	2 (0.94)	0	0.999
Lopi	12 (5.66)	3 (3.37)	0.565
GPO-VIR S 30	38 (17.92)	21 (23.60)	0.258
GPO-Z 250	24 (11.32)	12 (13.48)	0.598

Data presented as number (percentage).
AZT, zidovudine; D4T, stavudine; 3TC, lamivudine; TDF, tenofovir; DDI, didanosine; AZT+3TC, zilavir; D4T+3TC, lastavir; NVP, nevirapine; EFV, efavirenz; RTV, ritonavir; IDV, indinavir; Atazanavir, reyataz; Lopinavir, kaletra; GPO-VIR S30, D4T+3TC+NVP; GPO-Z 250, AZT+3TC+NVP.

history of tuberculosis, history of cryptococcosis, HCV infection, tenofovir disoproxil fumarate treatment, and GPO-vir S30 treatment. Age was the only significant risk factor associated with eGFR $<$ 90 with an adjusted odds ratio (OR) of 1.072 (95% confidence interval [CI]: 1.015–1.132). Age of over 37 years predicted eGFR $<$ 90 in HIV-infected patients with a sensitivity of 80.9% and specificity of 34.91%, and with an LR+ and LR− of 1.24 and 0.55, respectively (Fig. 1).

The prevalence of eGFR $<$ 90 was 29.57%. Age was the only independent factor associated with an eGFR of less than 90 mL/min/1.73 m^2. We recommend frequent screening for CKD in HIV-infected patients over 37 years old.

A recent study in Asia involving 7,455 HIV-infected patients (8) found that age over 50 years was an independent risk factor for both low viral load after 12 months (adjusted OR of 2.27, 95% CI: 1.37–3.77) and mortality (Hazard ratio 3.87, 95% CI: 2.69–5.57). According to the current study, age is associated with low eGFR levels, which may affect treatment outcomes and/or mortality. Previous studies have reported that age may be a risk factor for HIV-associated nephropathy (9,10).

This study confirms that age is independently associated with low eGFRs, as evidenced by multivariate logistic regression analysis. which can control confounding factors listed in the results. Our result showed that 30% of patients with an eGFR $<$ 90 with the average eGFR of 76.76 mL/min/1.73 m^2 did not reach the CKD level (11). Our results may motivate physicians to closely monitor renal function and avoid precipitating factors for kidney disease progression, such as nephrotoxic agents.

The appropriate cutoff point to screen for eGFR $<$ 90 in HIV-infected patients is 37 years. This cutoff point has fair screening properties (LR+ and LR−); however, the sensitivity is high at 80.9%. At least 80.9% of HIV-infected patients may have low eGFRs if aged over 37 years. We recommend close monitoring of eGFR or CKD using methods such as urinalysis and analysis of urine albumin/creatinine ratios in HIV-infected patients if they are over 37 years old.

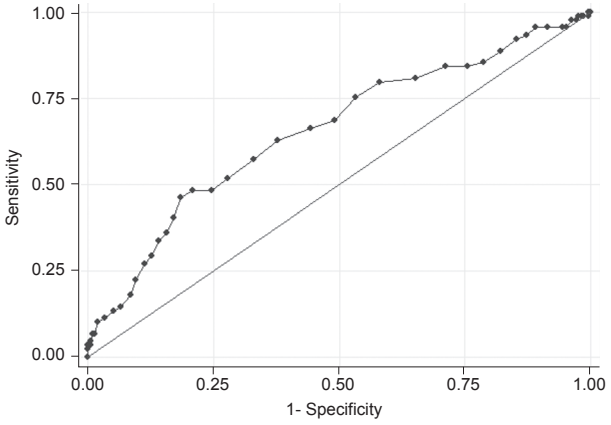

Fig. 1. A receiver operating characteristics (ROC) curve to predict an abnormal estimated glomerular filtration rate (eGFR) of less than 90 ml/min by age in HIV-infected patients. Note. Area under the ROC curve = 65.57% (95% confidence interval of 58.59, 72.55). Each point representing various age and giving particular sensitivity and specificity.

As has previously been reported, several factors were associated with low eGFR, including BMI, hypertension, HCV infection, tuberculosis, or cryptococcosis, as shown in Table 1 (2, 10–14). However, after adjustment using multivariate logistic regression, these factors were no longer significantly associated with eGFR $<$ 90. There is still no consensus on whether or not anti-retroviral therapy increases the risk of CKD in HIV-infected patients (11). One study found that tenofovir and ritonavir had a hazard ratio of 3.35 (95% CI: 1.40–8.02) for CKD or an eGFR of less than 60 mL/min/1.73 m^2 (15). Another cohort study did not find any association between anti-retroviral therapy and CKD (12), as was also the case in this study. However, it should be noted that the average eGFR in this study was higher than in those 2 reports.

Some limitations exist in this study. First, this study focused only on eGFR calculated by serum creatinine. Data on proteinuria were not collected or analyzed. Second, the group of HIV-infected patients in this study was diverse, including both newly-diagnosed patients and previously treated patients. Finally, all patients in this study were Thai. These results may not be applicable to Western countries.

In conclusion, age is independently associated with eGFR $<$ 90 in HIV-infected patients. Close monitoring of eGFR should be performed in HIV-infected patients aged over 37 years.

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Conflict of interest None to declare.

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