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ORIGINAL ARTICLE

Classification of human immunodeficiency virus-infected patients with chronic kidney disease using a combination of proteinuria and estimated glomerular filtration rate

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Abstract
Background In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) updated the 2002 Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline for chronic kidney disease (CKD). The 2012 KDIGO guideline elaborated the identification and prognosis of CKD by combining albuminuria with estimated glomerular filtration rate (eGFR). Identification of CKD with a high risk for a poor prognosis was investigated in human immunodeficiency virus (HIV)-infected individuals by applying the new guideline.
Methods A total of 1,447 HIV-infected patients (1,351 male, 96 female; mean age 44.4 ± 11.5 years) were classified using a combination of eGFR and dipstick proteinuria, as a convenient alternative to albuminuria. Proteinuria was classified into 3 grades—(A1) − and +/− , (A2) 1+ and 2+ , and (A3) 3+ and 4+. eGFR was classified into 6 grades—(G1) ≤90, (G2) 60–89, (G3a) 45–59, (G3b) 30–44, (G4) 15–29, and (G5) <15 mL/min/1.73 m^2.
Results Mean CD4 cell count was 487 ± 214 /μL, with 80.7 % of patients having an undetectable HIV-RNA level. The prevalence of CKD stage ≤2 and stage ≥3 classified according to KDOQI staging was 93.4 and 6.6 %, respectively. Using the new KDIGO classification, the prevalence of CKD with either a low (green) or moderately increased (yellow) risk was 96.9 %, while the prevalence for a high (orange) and very high (red) risk was 3.1 %.
Conclusion The use of the new KDIGO classification may reduce the prevalence of HIV-infected CKD individuals who are at high risk for a poor prognosis by nearly a half.

Keywords Proteinuria · Chronic kidney disease · HIV

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Introduction

Highly active antiretroviral therapy (HAART) has markedly reduced acquired immune deficiency syndrome (AIDS)-related deaths and opportunistic infectious diseases. This has resulted in prolonged survival of individuals infected with the human immunodeficiency virus (HIV) [1, 2]. However, this improvement in survival has been accompanied by an increase in the incidence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [3–6]. CKD is now epidemic among HIV-infected populations in both Western and Eastern countries. According to the staging classification of CKD proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002 [11], the prevalence of CKD in HIV-infected patients was reported to range between 15.5 and 23.7 % in the USA [7, 8]. Other studies showed that the prevalence was 16.8 % in China and

15.4 % in Japan [9, 10]. In addition to longevity induced by HAART, the increasing frequency of comorbidities such as hypertension and diabetes mellitus (DM) has contributed to a higher prevalence of CKD in the contemporary HIV-infected population receiving HAART [12, 13]. It is possible that the common use of the nephrotoxic antiretroviral agent, tenofovir disoproxil fumarate (TDF), may also have contributed to this increased prevalence [14]. It is therefore highly likely that clinicians will encounter further problems related to kidney illness when caring for HIV-infected patients.

CKD is not only a risk factor for ESRD, but also for cardiovascular disease (CVD), anemia, bone disorders, and cancers [15–18]. All these diseases are associated closely with a poor prognosis in HIV-infected patients. Therefore, healthcare providers have to correctly identify patients with CKD who are at risk for such adverse outcomes and refer them to a nephrologist for special care. It has been proposed to use the KDOQI CKD staging system to identify these patients [11]. This system stratifies CKD into 5 stages largely on the basis of estimated glomerular filtration rate (eGFR). Although this classification has contributed considerably to the general treatment of CKD, it may have insufficient accuracy to predict adverse outcomes, due to a lack of focus on proteinuria and albuminuria. There is considerable evidence that the presence of proteinuria or albuminuria is associated with a poor prognosis, independent of the impact of a decrease in eGFR [19–21]. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) updated the 2002 KDOQI Clinical Practice Guideline for CKD to overcome this inadequacy. The new KDIGO guideline elaborates on the identification and prognosis of CKD by combining albuminuria with eGFR [22, 23].

Numerous reports have demonstrated that albuminuria is an independent risk factor for a poor prognosis in HIV-infected individuals [24, 25]. It is therefore reasonable to assume that the KDIGO classification would be more practical for identification of CKD and estimating prognosis in HIV-infected individuals than the KDOQI staging. To our knowledge, classification of CKD according to the new KDIGO guideline has not been carried out in an HIV-infected population. However, the measurement of albuminuria is expensive, with public health care insurance systems in most countries limiting the application of albuminuria to identification and follow-up for diabetic nephropathy.

The aims of our study were (1) to classify HIV-infected individuals according to the classification included in the 2012 KDIGO guideline, with the exception of using dipstick proteinuria as a convenient alternative of albuminuria, and (2) to compare the prevalence of CKD with a high likelihood of a poor prognosis with that assessed by KDOQI staging.

Materials and methods

Study design and population

The study was a cross-sectional, point prevalence design and was carried out at Tokyo Metropolitan Komagome Hospital and Tokyo Medical University Hospital. HIV-infected patients were recruited at the time of a routine outpatient HIV care appointment and were enrolled consecutively between February and June 2011. A total of 1,447 HIV-infected individuals (1351 male, 96 female; mean age 44.4 ± 11.5 years) who regularly visited either of the two hospitals were enrolled in the study. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of both hospitals [approval certificate no. 1014 (Tokyo Metropolitan Komagome Hospital), and 1684 (Tokyo Medical University Hospital)]. Informed consent was obtained from all participants.

Classification of HIV-infected individuals, combining dipstick proteinuria with eGFR levels

eGFR was calculated on the basis of serum creatinine and then classified into 6 grades—(G1) ≥90, (G2) 60–89, (G3a) 45–59, (G3b) 30–44, (G4) 15–29, and (G5) <15 mL/min/1.73 m^2. Proteinuria was measured using a dipstick test and its level classified into 3 grades—(A1) −and +/−, (A2) 1+ and 2+, and (A3) 3+ and 4+. The 6 eGFR and 3 proteinuria grades were classified into 4 colored risk zones for prognosis—low risk, green (G1A1, G2A1); moderately increased risk, yellow (G3aA1, G1A2, and G2A2); high risk, orange (G3bA1, G3aA2, G1A3, and G2A3); and very high risk, red (G4A1, G5A1, G3bA2, G4A2, G5A2, G3aA3, G3bA3, G4A3, and G5A3) [22, 23].

Measurements

Non-fasting blood and random urine samples were collected for analysis as part of routine clinical visits. Proteinuria was defined as ≥1+ on urine dipstick examination. The same urine test paper was used in both hospitals (Uropaper αIII EIKEN, Eiken Chemical Co., Japan). eGFR was calculated using the 3-variable Japanese equation constructed by the Japanese Society of Nephrology—eGFR (mL/min/1.73 m^2) = 194 × serum $Cr^{-1.094}$ × $age^{-0.287}$ × 0.739. This equation was used because the worldwide Modification of Diet in Renal Disease (MDRD) study equation has been shown to be less accurate in Asian patients including Japanese [26]. eGFR and proteinuria were measured in at least two consecutive analyses conducted 3 months apart. CKD stage was classified according to the guideline of the KDOQI [11]. CKD stages 1 and 2

were defined on the basis of the presence of dipstick proteinuria and eGFR values. CD4 cell counts in HIV-infected patients were determined using a specific monoclonal antibody and fluorescence-activated cell-sorter analysis. The HIV-RNA level was measured using the Cobas TaqMan HIV-1 real-time polymerase chain reaction version 1.0 assay (Roche Diagnostics, Branchburg, NJ, USA; lower detection limit, 40 copies/mL).

The electronic medical charts of all the subjects were reviewed to determine the presence of comorbidities such as hypertension, DM, and hepatic viral infections. Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive agents at baseline. DM was defined as a diagnosis of DM prior to baseline, or the use of oral antidiabetic agents or insulin at baseline. Hepatitis C virus (HCV) infection was defined as a positive reactive HCV antibody test, while hepatitis B virus (HBV) infection was defined as a positive HBV surface antigen test.

Statistical analysis

All data are expressed as the mean ± standard deviation unless otherwise stated. Difference between data on clinical characteristics of individuals within each colored risk zones were analyzed using the Cochrane−Armitage test and Jonckheere−Terpstra test for trend for continuous and categorical variables, as appropriate. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, accessed 13 June 2013, at http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6–3) that includes statistical functions that are frequently used in biostatistics. Values of $P < 0.05$ were considered statistically significant.

Results

Baseline demographic and clinical characteristics

Table 1 summarizes the baseline demographic and clinical characteristics of individuals enrolled in the study. Mean CD4 cell count was 487 ± 214 /μL, with 80.7 % of the study participants having an undetectable HIV-RNA level (<40 copies/mL). A total of 1,305 subjects (90.2 %) were receiving HAART, with 804 (61.6 %) administered TDF and 372 (28.5 %) administered abacavir. Efavirenz, a ritonavir-boosted protease inhibitor and raltegravir were used in 764 (58.5 %), 356 (27.3 %) and 199 (15.2 %) of the subjects, respectively. Comorbidities such as hypertension, DM, HBV and HCV infection were observed in 24.7, 4.8, 6.2 and 4.4 % of the subjects, respectively. The mean serum creatinine was 0.81 ± 0.18 mg/dL and eGFR 85.4 ± 18.5 mL/min/1.73 m^2. Proteinuria determined by dipstick analysis was observed in 142 subjects (9.8 %). The prevalence of proteinuria assessed by dipstick analysis was 1+, 74.6 %; 2+, 19.0 %; and ≥3+, 6.4 %.

Table 1 Baseline demographic and clinical characteristics of the study cohort

Patients, *n*	1,447
Age, years	44.4 ± 11.5
Men, *n* (%)	1,351 (93.4)
Hypertension (+), *n* (%)	358 (24.7)
DM (+), *n* (%)	70 (4.8)
Current smoking (+), *n* (%)	536 (37.0)
HBV (+), *n* (%)	89 (6.2)
HCV (+), *n* (%)	64 (4.4)
CD4 cell count, cells/μL	487 ± 214
HIV-RNA level <40 copies/mL, *n* (%)	1,168 (80.7)
Patients receiving HAART, *n* (%)	1,305 (90.2)
Serum creatinine, mg/dL	0.81 ± 0.18
eGFR, mL/min/1.73 m^2	85.4 ± 18.5
Proteinuria, *n* (%)	142 (9.8)
1+	106 (74.6)
2+	27 (19.0)
≥3+	9 (6.4)
Hemoglobin, g/dL	14.6 ± 1.41
Serum albumin, g/dL	4.53 ± 1.18
Total cholesterol, mg/dL	189 ± 40
Triglycerides, mg/dL	196 ± 156
C-reactive protein, mg/dl	0.30 ± 0.53

Data are expressed as mean ± standard deviation. Proteinuria was defined as ≥1+ on urine dipstick

HAART highly active antiretroviral therapy, *DM* diabetes mellitus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *eGFR* estimated glomerular filtration rate

Distribution of HIV-infected individuals according to KDOQI staging and the new KDIGO classification

The distribution of HIV-infected individuals classified by the KDOQI staging is shown in Table 2. The prevalence of CKD stage ≤2, CKD stage 3, CKD stage 4, and CKD stage 5 was 93.4, 6.2, 0.4 and 0.0 %, respectively. The results of the KDIGO classification are shown in Fig. 1. The prevalence of individuals in the green, yellow, orange, and red risk zones was 85.9, 11.0, 2.1, and 1.0 %, respectively. The prevalence of individuals at high (orange) and very high (red) risk for a poor prognosis in the KDIGO classification was nearly halved, compared to the risk for CKD stage ≥3

Table 2 Distribution of HIV-infected individuals in each stage determined by the 2002 KDOQI classification

Stage	eGFR (mL/min/1.73 $m^{2)}$	*n* (%)
0	–	1,243 (85.9)
1	≥90	25 (1.7)
2	60–89	83 (5.8)
3	30–59	90 (6.2)
4	15–29	6 (0.4)
5	<15	0 (0.0)
≤2	–	1,351 (93.4)
≥3	–	96 (6.6)

KDOQI Kidney Disease Outcomes Quality Initiative, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease

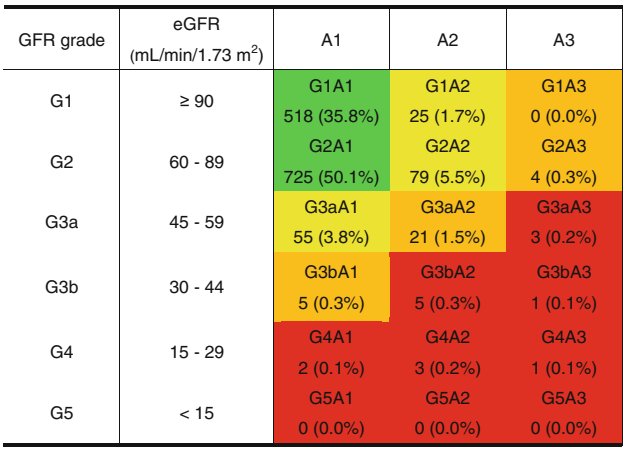

Fig. 1 Distribution of HIV-infected individuals determined by the 2012 KDIGO classification. The percentage of HIV-infected individuals in each category is expressed in each *color box*. The prevalence of individuals in the green, yellow, orange, and red zone was 85.9, 11.0, 2.1, and 1.0 %, respectively. *KDIGO* kidney disease: outcomes quality initiative, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate. (A1) no proteinuria (dipstick −or +/−), (A2) mild proteinuria (dipstick 1+ or 2+), (A3) heavy proteinuria (dipstick ≥3+) (color figure online)

in the KDOQI system (3.1 vs 6.6 %, respectively). Table 3 shows clinical characteristics of the HIV subjects included in each KDIGO category. Age, total cholesterol level and the prevalence of hypertension and DM are increased with increasing CKD categories ($P < 0.0001$ for trend); whereas current use of TDF are decreased ($P < 0.0001$ for trend).

Discussion

This study attempted to classify HIV-infected individuals according to the 2012 KDIGO guideline. The classification used, combining dipstick proteinuria with eGFR, may facilitate targeting of individuals in the HIV-infected population who have the likelihood of a poor prognosis, compared to those identified by KDOQI staging.

The use of the classification based on the new KDIGO guideline reduced the prevalence of HIV-infected CKD individuals who were high risk of a poor prognosis by nearly a half. Tonelli et al. [27] reported a comparison of the two CKD classifications in the general population, based on the 2002 KDOQI guideline and 2009 KDIGO conference proposal. In their report, fewer adults were classified with more advanced CKD using the classification system combining albuminuria and eGFR. Although our study included a much smaller sample size, we were able to confirm a similar result after reclassification in the HIV cohort. Furthermore, frequency of some known risk factors for CKD such as high age, high total cholesterol level, and presence of hypertension and DM increased with increasing CKD categories. This may indicate that the KDIGO classification serves as a risk category system in clinical practice for HIV individuals. However, both CKD classification systems were devised for the general population, where DM and hypertension are the leading causes of CKD. In contrast, chronic inflammation due to HIV and the use of TDF are relevant factors in the development of CKD in the HIV population. The KDIGO classification may facilitate targeting of patients who have a substantially high risk for a poor prognosis. Further prospective studies are therefore warranted to validate the clinical utility of this KDIGO classification in HIV-infected individuals.

The high prevalence rate of dipstick proteinuria (9.8 %) in the HIV cohort was noteworthy. Iseki et al. [28] reported the prevalence of proteinuria assessed by dipstick analysis was 5.4 % in a mass cohort of 332,174 Japanese participants. The mean age of their cohort was 63.6 ± 8.3 years, which provided strong evidence for a higher prevalence of kidney damage (CKD stage ≥3, 14.5 %, eGFR, 75.0 ± 16.2 mL/min/1.73 m^2) in elderly subjects compared with our much younger cohort (mean age 44.4 years). HIV infection itself is a risk factor for the development of albuminuria [29], which may be one reason for the high prevalence of proteinuria that we observed. Guaraldi et al. [12] also reported that the prevalence of hypertension and DM, both of which are closely interrelated to kidney damage, was similar in HIV-infected individuals and subjects in the general population who were 10 years older. Health-care professionals should therefore screen for proteinuria periodically, and not assess kidney damage using only serum creatinine level, especially in individuals with HIV.

The presence of proteinuria/albuminuria as well as a decrease in eGFR is a harbinger of CVD and mortality in HIV-infected populations. Wyatt et al. [24] showed that albuminuria was associated significantly with all-cause and AIDS mortality in a cohort of 1,547 HIV-infected women.

Table 3 Prevalence of risk factors in each colored risk zones determined by the 2012 KDIGO classification

Risk factors	Colored risk zones				*P* for trend
	Green ($n = 1{,}243$)	Yellow ($n = 159$)	Orange ($n = 30$)	Red ($n = 15$)	
Age, years	43.0 ± 10.9	51.0 ± 11.5	56.5 ± 11.4	58.1 ± 9.6	<0.0001
Hypertension (+), *n* (%)	260 (20.9)	70 (44.0)	18 (60.0)	10 (66.7)	<0.0001
DM (+), *n* (%)	46 (3.7)	13 (8.2)	6 (20.0)	5 (33.3)	<0.0001
HCV (+), *n* (%)	51 (4.1)	10 (6.3)	2 (6.7)	1 (6.7)	0.1758
Total cholesterol, mg/dL	187 ± 39	203 ± 44	208 ± 34	217 ± 73	<0.0001
CD4 cell count, cells/μL	491 ± 213	474 ± 227	438 ± 186	394 ± 200	0.0632
HIV-RNA level <40 copies/mL, *n* (%)	998 (80.3)	130 (81.8)	26 (86.7)	14 (93.3)	0.1485
Current use of TDF	723 (58.2)	69 (43.4)	10 (33.3)	2 (13.3)	<0.0001

Data are expressed as mean ± standard deviation. Risk factors such as age, hypertension, DM, and total cholesterol tended to increase ($P < 0.0001$), whereas current use of TDF decrease ($P < 0.0001$) as CKD stage progressed

DM diabetes mellitus, *HCV* hepatitis C virus, *TDF* tenofovir disoproxil fumarate

In addition, Choi et al. [30] demonstrated that patients with albuminuria and an increased serum cystatin C level had a high risk of mortality. They also demonstrated that levels of eGFR and albuminuria were associated strongly with the risk of CVD and heart failure in a mass cohort study [25]. While the prevalence of albuminuria differs across studies and ranges from 8.7−17.8 % [10, 29, 31], microalbuminuria predicts the development of proteinuria [32], which likely represents poorer outcomes [33, 34]. As the measurement of proteinuria/albuminuria is a standard of care for HIV-infected patients, the KDIGO guideline for CKD would meet the demands of clinicians who are treating HIV-infected patients.

There were several limitations in this study. First, due to the cross-sectional design of the study, we were unable to validate whether the KDIGO classification was more appropriate for predicting future adverse outcomes in an HIV-infected population than KDOQI staging. A validation study is now under way at our institute using an external data set. Second, this study population comprised mainly well-controlled HIV-infected Japanese men, with the proportion of women being relatively low at 6.6 %. Therefore, the results may not be generalizable to women or other ethnic groups. Third, our study was undertaken on the basis that dipstick proteinuria was used as a convenient alternative to albuminuria, and therefore our method differed from the original KDIGO classification. Although albuminuria would be expected to be more accurate for evaluating kidney glomerular damage and prognosis than dipstick proteinuria, it is more expensive and not readily applicable for use in general clinical settings. This is the reason that we insist on using proteinuria instead of albuminuria. The difference in distribution of CKD and impact on prognosis between data based on albuminuria and dipstick proteinuria is now under investigation using data collected from multiple tertiary HIV centers in Japan.

In conclusion, the use of the CKD classification according to the new KDIGO guideline may reduce the prevalence of HIV-infected CKD individuals who have a high likelihood of a poor prognosis by nearly a half. We therefore recommend the use of this classification in HIV-infected individuals, as the presence of proteinuria is of special interest to experts on HIV care.

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Conflict of interest None declared.

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