MAJOR ARTICLE

Prevalence of Chronic Kidney Disease and Poor Diagnostic Accuracy of Dipstick Proteinuria in Human Immunodeficiency Virus-Infected Individuals: A Multicenter Study in Japan

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Background. Chronic kidney disease (CKD) has become one of the common comorbid conditions affecting the human immunodeficiency virus (HIV) population. Human immunodeficiency virus-infected individuals are at increased risk of developing CKD, and they are likely to experience faster progression of renal dysfunction compared with HIV-uninfected individuals. Albuminuria represents not only kidney damage but also manifests metabolic syndrome and vascular dysfunction.

Methods. We conducted a multicenter, cross-sectional study involving 2135 HIV-infected individuals in Japan to test the prevalence of CKD and proteinuria/albuminuria. Urine sample was analyzed by both dipstick test and albumin-to-creatinine ratio (ACR) assay. Chronic kidney disease was classified according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. The diagnostic performance of dipstick test to detect albuminuria (ACR ≥30 mg/g) was evaluated.

Results. The prevalence of CKD, evaluated by K/DOQI and KDIGO guidelines, was 15.8% and 20.4%, respectively. Age, total cholesterol level, prevalence of hypertension, diabetes mellitus, and hepatitis C infection tended to increase, whereas levels of hemoglobin, serum albumin, and CD4 cell count tended to decrease as CKD risk grades progressed. Proteinuria and albuminuria were present in 8.9% and 14.5% of individuals, respectively. Dipstick test ≥1+ to detect albuminuria had an overall sensitivity of 44.9% and specificity of 97.2%.

Conclusions. The KDIGO guideline may enable physicians to capture HIV-infected patients at increased risk more effectively. The sensitivity of dipstick proteinuria to detect albuminuria is so poor that it may not serve as an alternative in HIV-infected individuals.

Keywords. albuminuria; chronic kidney disease; dipstick proteinuria; HIV.

Introduction of antiretroviral therapy (ART) has dramatically improved the longevity among persons with human immunodeficiency virus (HIV) infection [1, 2]. However, this reduction in HIV-related mortality has been accompanied by an increase in age-related noncommunicable disease including chronic kidney disease (CKD) [3]. Chronic kidney disease has now become one of the common comorbid conditions affecting HIV-infected individuals [4, 5]. Patients with HIV infection not only are at increased risk of developing CKD, but they are also more likely to experience faster progression of renal dysfunction comparted with HIV-uninfected individuals [6–8]. Because of the impact of ART, HIV is now considered to be a chronic manageable disease, especially in resource-rich settings, and maintaining kidney function is one of the cornerstones of HIV patient management.

The early and accurate assessment of kidney damage, most commonly done by detecting albuminuria or proteinuria, is critical in management of kidney disease among HIV-infected individuals. Previous studies have demonstrated that albuminuria is an independent risk factor for poor prognosis in HIV-infected individuals [9–12]. Furthermore, albuminuria, even in

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the middle to high levels within the normal range, is reported to be a significant risk factor for near-term development of overt kidney disease [13]. In addition to its role as a marker for kidney damage, albuminuria may also be a manifestation of metabolic syndrome and vascular dysfunction [14]. Kopp [15] has reported that HIV-infected individuals on ART with long-term viral suppression have a proinflammatory state and that the kidney, especially the glomerular endothelium, is a common and perhaps a sensitive target of systemic inflammatory process. This adds further importance of assessing albuminuria among HIV-infected individuals not just from a renal perspective.

The current HIV-CKD guideline [4] recommends quantitative measure of albuminuria/proteinuria, which was in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [16]. This succeeded the initial guideline [17] recommendation to use urine dipstick measurement as a screening tool, following the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) [18]. This change in the recommendation was because, among many other reasons, urine dipstick testing for proteinuria was shown to be less sensitive than quantitative proteinuria [19]. Similarly, a subsequent study revealed that dipstick analysis has limited diagnostic value to detect albuminuria [20]. However, both studies had relatively small sample sizes and high prevalence of proteinuria that could lead to a selection bias, which might diminish the proportion of patients with low level albuminuria or proteinuria. Therefore, these results may not reflect levels of the HIV population who undergo screening. In addition, the prevalence of CKD and proteinuria/albuminuria has been reported among several Asian countries to date, but many of the reports have been from a single-center in which selection bias could not be avoided due to the nature of the study design [21–24].

The aims of our study were to (1) evaluate the prevalence and factors of CKD among HIV-infected individuals classified according to the K/DOQI and KDIGO guidelines and (2) assess the diagnostic accuracy of dipstick proteinuria to identify albumin-to-creatinine ratio (ACR) in HIV-infected individuals.

MATERIALS AND METHODS

Study Design and Population
We performed a multicenter, cross-sectional study of HIV-infected individuals at 5 tertiary hospitals in Japan. The following hospitals participated: Tokyo Metropolitan Komagome Hospital (TMKH), Tokyo Medical University Hospital (TMUH), Juntendo University Hospital (JUH), Tokyo Women's Medical University Hospital (TWMU), and IMSUT Hospital of The Institute of Medical Science, The University of Tokyo (IMSUT). Human immunodeficiency virus-infected individuals were recruited at the time of a routine outpatient HIV care appointment and were enrolled consecutively from April 2012 to March 2013. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board at each participating hospital (approval certificate nos. 1014 [TMKH], 1684 [TMUH], 12-16 [JUH], 2719 [TWMU], and 24-10 [IMSUT]). Informed consent was obtained from all participants.

Classification of Chronic Kidney Disease According to K/DOQI and KDIGO Guidelines
Chronic kidney disease was classified into 5 stages using according to the K/DOQI guideline [17, 18]. Chronic kidney disease stages 1 and 2 were defined based on the presence of dipstick proteinuria as a marker for kidney damage ($CKD_{K/DOQI}$). In addition, CKD was classified according to the KDIGO guideline, which combined glomerular filtration rate (GFR) level and albuminuria level to create a colored table [4, 16]. The colors in the table reflect degree of risk for clinical outcomes including end-stage renal disease (ESRD), cardiovascular events and related mortality, and all-cause mortality. Green represents low risk, yellow is moderately increased risk, orange is high risk, and red is very high risk. We defined CKD as estimated GFR (eGFR) <60 mL/min per 1.73 m^2 and ACR ≥30 mg/g (CKD_{KDIGO}). Albuminuria in the normal range was divided into 3 groups (0–9, 10–19, and 20–29 mg/g), and prevalence of these subgroups were evaluated.

Diagnostic Value of Dipstick Proteinuria Compared to Albuminuria
The KDIGO guideline recommends albuminuria as the preferred marker for staging CKD [4]. We evaluated the ranges of quantitative albuminuria corresponding to each dipstick result. Albuminuria expressed as ACR was divided into 3 strata: <30 mg/g, 30–300 mg/g, and >300 mg/g. The sensitivity and specificity of dipstick result of ≥1+ to detect both ACR of 30–300 mg/g and ≥300 mg/g was calculated. The cutoff value of 1+ was chosen based on the previous HIV-CKD guideline [17].

Measurements
Nonfasting blood and random urine samples were collected for analysis as part of routine clinical visits. Potential risk factors associated with CKD, such as levels of serum albumin, hemoglobin, total cholesterol, triglyceride, and HIV parameters, were tested [4, 23, 25, 26]. CD4 cell counts were determined using a specific monoclonal antibody and flow cytometry analysis. The HIV-ribonucleic acid level was measured using the Cobas TaqMan HIV-1 real-time polymerase chain reaction (Roche Diagnostics, Branchburg, NJ). Serum creatinine (Cr) was measured by an enzymatic method. Estimated GFR was calculated using the 3-variable Japanese equation constructed by the Japanese Society of Nephrology using serum Cr: eGFR (mL/min per 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 study equation has been shown to be less accurate in Asian patients including Japanese [27]. Urine dipstick measurement and urine ACR was measured on the same urine sample. Urinary albumin was measured by a turbidimetric immunoassay, and urine Cr was assayed using an enzymatic

method. Proteinuria and albuminuria were defined as ≥1+ on urine dipstick examination and ACR ≥30 mg/g, respectively.

The medical records of all the subjects were reviewed to determine the presence of comorbidities such as hypertension, diabetes mellitus (DM), and hepatic viral infections. Hypertension was defined as (1) a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or (2) the use of antihypertensive agents at baseline. Diabetes mellitus was defined as (1) a diagnosis of DM before baseline or (2) the use of oral antidiabetic agents or insulin at baseline. Hepatitis C virus (HCV) infection was defined as a positive reactive HCV antibody test, whereas hepatitis B virus (HBV) infection was defined as a positive HBV surface antigen test. Information on the use of ART and the concurrent use of tenofovir disoproxil fumarate (TDF), abacavir (ABC), and ritonavir-boosted protease inhibitor (PI/r) were collected from the medical records.

Statistical Analysis

All data are expressed as the mean ± standard deviation unless otherwise stated. Demographic characteristics and laboratory values of individuals with and without $CKD_{K/DOQI}$ were compared. Group comparisons were performed using Student's t test and χ^2 tests where appropriate. 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 in categorical and continuous variables, respectively. P values <.05 were considered statistically significant; all tests were 2-sided. All statistical analyses were performed using SPSS version 21 for Windows (IBM Corp., Armonk, NY).

RESULTS

Table 1 summarizes the baseline demographic and clinical characteristics of individuals enrolled in the study. Among the 2135 individuals enrolled in the study, proteinuria determined by dipstick analysis was observed in 190 subjects (8.9%). The prevalence of proteinuria was as follows: 1+, 67.4%; 2+, 21.1%; and ≥3+, 11.5%. The prevalence of $CKD_{K/DOQI}$ stage 1–5 and ≥3 was 15.8% (338 of 2135) and 9.6% (204 of 2135), respectively.

Table 1.   Baseline Demographic and Clinical Characteristics of the Study Cohort

Baseline Characteristics	Total n = 2135	CKD (+) n = 338	CKD (−) n = 1797	P Value
Age, years	44.5 ± 11.5	51.5 ± 13.1	43.1 ± 10.6	<.0001
Men, no. (%)	2008 (94.1)	315 (93.2)	1693 (94.2)	.4682
Japanese race, n (%)	2029 (95.0)	331 (97.9)	1698 (94.5)	.0059
Body weight, kg	66.5 ± 12.3	66.7 ± 14.5	66.4 ± 11.9	.7501
Body mass index, kg/m²	23.2 ± 3.7	23.6 ± 4.3	23.1 ± 3.6	.0535
Hypertension (+), no. (%)	501 (23.5)	153 (45.3)	348 (19.4)	<.0001
Diabetes mellitus (+), no (%)	154 (7.2)	64 (18.9)	90 (5.0)	<.0001
Current smoking (+), no. (%)	721 (33.8)	90 (26.6)	631 (35.1)	.0025
Hepatitis B virus (+), no. (%)	114 (5.3)	23 (6.8)	91 (5.1)	.1916
Hepatitis C virus (+), no. (%)	109 (5.1)	22 (6.5)	87 (4.8)	.2013
CD4 cell count, cells/µL	484 ± 220	436 ± 197	494 ± 223	<.0001
HIV-RNA <400 copies/mL, no. (%)	1911 (89.5)	309 (91.4)	1602 (89.1)	.2112
HIV-RNA <50 copies/mL, no. (%)	1794 (84.0)	291 (86.1)	1503 (83.6)	.2583
Patients receiving ART, no. (%)	1938 (90.8)	314 (92.9)	1624 (90.4)	.1409
Current TDF usage, no. (%)	1249 (58.5)	127 (37.6)	1122 (62.4)	<.0001
Current ABC usage, no. (%)	573 (26.8)	164 (48.5)	409 (22.8)	<.0001
Current PI/r usage, no. (%)	1060 (49.6)	172 (50.9)	888 (49.4)	.6195
Serum creatinine, mg/dL	0.87 ± 0.53	1.23 ± 1.24	0.80 ± 0.13	<.0001
eGFR, mL/min per 1.73 m²	82.1 ± 18.9	62.8 ± 22.3	85.7 ± 15.7	<.0001
eGFR, <60 mL/min per 1.73 m²	204 (9.6)	-	-	-
Proteinuria, no. (%)*	190 (8.9)	-	-	-
Albuminuria, no. (%)*#	287 (14.5)	-	-	-
Hemoglobin, g/dL	14.6 ± 1.44	14.1 ± 1.75	14.6 ± 1.35	<.0001
Serum albumin, g/dL[a]	4.55 ± 0.31	4.45 ± 0.42	4.56 ± 0.29	<.0001
Total cholesterol, mg/dL[b]	184 ± 36	191 ± 40	183 ± 36	.0004
Triglycerides, mg/dL[c]	183 ± 127	213 ± 156	177 ± 120	<.0001

Abbreviations: ABC, abacavir; ACR, albumin-to-creatinine ratio; ART, antiretroviral therapy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; K/DOQI, Kidney Disease Outcomes Quality Initiative; PI/r, ritonavir-boosted protease inhibitor; RNA, ribonucleic acid; TDF, tenofovir disoproxil fumarate.

NOTE: Data are expressed as mean ± standard deviation. The CKD classification was based on the K/DOQI guideline. Proteinuria and albuminuria were defined as ≥1+ on urine dipstick examination and ACR ≥30 mg/g, respectively.

*Eight subjects on hemodialysis were included.

#Albuminuria was measured on 1976 subjects.

Missing data for [a]29, [b]30, and [c]8 individuals.

Individuals with CKD, compared with those without CKD, were significantly older and less likely to be a current smoker, had higher prevalence of hypertension and DM, had higher levels of total cholesterol and triglycerides, and had lower levels of CD4 cell count, hemoglobin, and serum albumin. The current use of TDF was higher in the non-CKD group, whereas the current use of ABC was higher in the CKD group.

Urine albumin was measured in 1976 individuals (92.3%). In this subgroup, the prevalence of $CKD_{K/DOQI}$ and dipstick proteinuria was the same as the total cohort (stage 1–5, 15.8% [313 of 1976]; stage ≥3, 9.6% [190 of 1976]; proteinuria, 8.9% [176 of 1976]) (data not shown). Albuminuria was observed in 287 subjects (14.5%), and the prevalence was as follows: category A1 (<29 mg/g), 85.5%; category A2 (30–299 mg/g), 11.7%; and category A3 (≥300 mg/g), 2.8%. Figure 1 demonstrates the distribution of 1976 individuals classified by the KDIGO guideline. The prevalence of individuals in the green, yellow, orange, and red risk zones was 79.6%, 15.1%, 3.0%, and 2.3%, respectively. Accordingly, the prevalence of CKD_{KDIGO} was 20.4%. Among the category A1 individuals, the prevalence of ACR 0–9, 10–19, and 20–29 mg/g were 67.3% (1330 of 1976), 14.3% (282 of 1976), and 3.9% (77 of 1976), respectively.

Table 2 shows the prevalence of risk factors in each colored risk zones determined by the KDIGO guideline. Age, total cholesterol level, prevalence of hypertension, DM, HCV infection, and the current use of ABC tended to increase as CKD_{KDIGO} risk grades progressed (P < .0001 for trend). On the other hand, hemoglobin, serum albumin, CD4 cell count, and the current use of TDF tended to decrease (P < .0001 for trend).

Tables 3 and 4 demonstrate the paired dipstick proteinuria and albuminuria results. Among individuals with ACR <30 mg/g, 2.8% (47 of 1689) had positive urine dipstick results (false positive rate [FPR]; ≥1+). Similarly, among individuals with ACR 30–300 mg/g, 67.4% (157 of 233) had negative dipstick result (false negative rate [FNR]; <1+). The overall sensitivity of a ≥1+ dipstick result to detect ACR >30 mg/g was 44.9% (129 of 287), but it was reduced to 32.6% (76 of 233) when restricted to detect ACR 30–300 mg/g. The positive predictive value of positive urine dipstick for ACR >30 mg/g was 73.3% (129 of 176), and the negative predictive value was 91.2% (1642 of 1800).

DISCUSSION

This is the first multicenter study that addresses the prevalence of CKD and proteinuria/albuminuria among HIV-infected individuals in Japan. The prevalence of CKD, evaluated by K/DOQI and KDIGO guidelines, was 15.8% and 20.4%, respectively. Age, total cholesterol level, prevalence of hypertension, DM, and HCV infection tended to increase, whereas levels of hemoglobin, serum albumin, and CD4 cell count tended to decrease as CKD_{KDIGO} risk grades progressed. We found that proteinuria and albuminuria were

GFR categories (mL/min per 1.73 m^2), description and range	Albuminuria categories, description and range			Total
	A1 (<30mg/g) Normal to mildly increased	A2 (30–300 mg/g) Moderately increased	A3 (>300mg/g) Severely increased	
G1 (≥ 90) Normal or high	529 (26.8%)	51 (2.6%)	7 (0.4%)	587 (29.7%)
G2 (60–89) Mildly decreased	1044 (52.8%)	141 (7.1%)	14 (0.7%)	1199 (60.7%)
G3a (45–59) Mildly to moderately decreased	107 (5.4%)	29 (1.5%)	12 (0.8%)	148 (7.5%)
G3b (30–44) Moderately to severely decreased	8 (0.4%)	9 (0.5%)	6 (0.3%)	23 (1.2%)
G4 (15–29) Severely decreased	1 (0.1%)	3 (0.2%)	7 (0.4%)	11 (0.6%)
G5 (<15) Kidney failure	0 (0.0%)	0 (0.0%)	8 (0.4%)*	8 (0.4%)
Total	1689 (85.5%)	233 (11.8%)	54 (2.7%)	1976 (100%)

Figure 1. Distribution of HIV-infected individuals determined by the KDIGO guideline. The percentage of human immunodeficiency virus-infected individuals in each category is expressed in each color box. Green represents low risk (79.6%), yellow is moderately increased risk (15.1%), orange is high risk (3.0%), and red is very high risk (2.3%). *All subjects were on hemodialysis. GFR, glomerular filtration rate.

Table 2. Prevalence of Risk Factors in Each Colored Risk Zones Determined by the KDIGO Guideline[a]

	Colored Risk Zones				
Risk factors	Green (n = 1573, 79.6%)	Yellow (n = 299, 15.1%)	Orange (n = 58, 3.0%)	Red (n = 46, 2.3%)	P for Trend
Age, years	42.5 ± 10.4	51.2 ± 12.1	54.1 ± 13.8	57.0 ± 10.7	<.0001
Hypertension (+), no. (%)	295 (18.8)	122 (40.8)	28 (48.3)	39 (84.8)	<.0001
Diabetes mellitus (+), no (%)	60 (3.8)	46 (15.4)	14 (24.1)	22 (47.8)	<.0001
Hepatitis B virus (+), no. (%)	79 (5.0)	21 (7.0)	4 (6.9)	2 (4.4)	.3221
Hepatitis C virus (+), no. (%)	64 (4.1)	15 (5.0)	6 (10.3)	7 (15.2)	.0002
CD4 cell count, cells/µL	497 ± 218	454 ± 194	430 ± 205	383 ± 161	<.0001
HIV-RNA <50 copies/mL, no. (%)	1309 (83.2)	270 (90.3)	45 (77.6)	42 (91.3)	.0518
Hemoglobin, g/dL	14.6 ± 1.3	14.5 ± 1.6	13.9 ± 1.7	12.8 ± 2.1	<.0001
Serum albumin, g/dL	4.57 ± 0.28	4.54 ± 0.37	4.39 ± 0.34	4.25 ± 0.58	<.0002
Total cholesterol, mg/dL	182 ± 36	192 ± 37	193 ± 37	204 ± 44	<.0001
Current use of TDF	964 (61.3)	158 (52.8)	16 (27.6)	2 (4.3)	<.0001
Current use of ABC	363 (23.1)	116 (38.8)	28 (48.3)	34 (73.9)	<.0001

Abbreviations: ABC, abacavir; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; TDF, tenofovir disoproxil fumarate.

[a]Data are expressed as mean ± standard deviation.

present in 8.9% and 14.5% of individuals, respectively. Furthermore, dipstick proteinuria had low sensitivity to detect albuminuria.

The prevalence of CKD ($CKD_{K/DOQI}$: 15.8%) was slightly higher to previous studies conducted in Japan, which ranged between 13.0% and 15.5% [23, 24, 28]. The prevalence among other countries varies widely, ranging from 7% to 24% [21, 22, 29, 30]. The difference in the clinical profile of the studied cohort could probably explain the variety of the results. Nevertheless, prevalence of CKD is likely to increase even more due to increasing life expectancy and frequency of comorbidities such as hypertension and DM among HIV-infected individuals [2, 31]. In addition, our results elucidated that the KDIGO classification demonstrate a higher prevalence in CKD compared with the K/DOQI classification by 4.6%. Because the presence of proteinuria/albuminuria and the decrease in eGFR are both independently associated with poor prognosis in HIV-infected populations [9–11, 32], the KDIGO classification may facilitate targeting of individuals who have a substantially high risk for a poor prognosis. Furthermore, our results demonstrate that the frequency of well known risk factors for CKD

Table 3. Comparison Between Dipstick Proteinuria and Albuminuria

	Levels of Albuminuria			
Threshold	<30 mg/g	30–300 mg/g	>300 mg/g	Total
Negative	1362	**71**	**0**	1433
Trace	280	**86**	**1**	367
1+	*44*	63	12	119
2+	*2*	12	22	36
3+	*1*	1	19	21
Total	1689	233	54	1976

The numbers in italics correspond to false positive dipstick results. The numbers in bold correspond to false negative results.

such as age, presence of hypertension, DM, and HCV infection increased as CKD_{KDIGO} risk grades progressed. Thus, our results strongly support the use of the KDIGO classification as recommended by the current HIV-CKD guideline [4]. Although previous studies report the prevalence of CKD mainly using the K/DOQI classification, the KDIGO classification should be used to determine CKD prevalence instead because it may serve better stratification of risk in clinical practice.

Our study revealed the prevalence of dipstick proteinuria as 8.9%, which was slightly lower than previous studies conducted in Japan (9.5% [23], 9.8% [28]). However, this result is still prominent when compared with the general population in Japan. The prevalence of proteinuria among 232 025 patients in a large Japanese nationwide database was 3.8% [33]. This was much lower even though their cohort involved a much older population (mean age, 61.8 years), but with similar prevalence of CKD (14.1%) and levels of eGFR (76.9 ± 16.0 mL/min per 1.73 m²). Considering that our cohort comprised a much younger population (mean age, 44.5 years), our results provide strong evidence for a higher prevalence of kidney damage among HIV-infected individuals. This hold true even when the general population data was restricted to men (proteinuria 5.4%, CKD 17.0%, eGFR 76.8 ± 16.3 mL/min per 1.73 m²) [33], which is important to make a fair comparison because the majority of our HIV cohort was male (94.1%). The high prevalence of proteinuria probably arises from the presence of traditional risk factors in addition to the unique clinical characteristics of HIV-associated renal diseases. Human immunodeficiency virus infection itself is a risk factor for the development of albuminuria [34], which may be one explanation for the high prevalence of proteinuria. The prevalence of hypertension and DM, both well known risk factors for kidney damage, was similar in HIV-infected individuals and subjects in the general population who were 10 years

Table 4. Diagnostic Accuracy of Dipstick Quantitative Thresholds

	Sensitivity		Specificity
Threshold	≥30 mg/g	30–300 mg/g	<30 mg/g
≥Negative, %	100	100	0
≥Trace, %	75.3	69.5	80.6
≥1+, %	44.9	32.6	97.2
≥2+, %	18.8	5.6	99.8
≥3+, %	7.0	0.4	99.9

older [31]. It is noteworthy that renal biopsy and autopsy among Japanese HIV-infected individuals revealed mainly diabetic nephropathy and immunoglobulin A nephropathy, both common causes for ESRD in Japan, and no HIV-associated nephropathy, which is probably due to genetic predispositions [14, 24, 35].

Among studies that reported prevalence of albuminuria which data was obtained from a single urine specimen range from 11–20% [20, 23, 34, 36, 37]. Our result (14.5%) was within the range of these previous studies. Compared with dipstick proteinuria, testing for albuminuria identified 5.6% more patients with kidney damage. Routine monitoring of albuminuria may lead to earlier diagnosis of kidney damage, which could ultimately ameliorate the progression of renal dysfunction and decrease the risk of cardiovascular events. Furthermore, albuminuria, even in the middle to high levels within the normal range, is reported to be a significant risk factor for near-term development of overt kidney disease [13]. Among individuals with ACR <30 mg/g, 21.3% (359 of 1689) were classified as middle-to-high range (ACR 10–29 mg/g) in our cohort. This may serve as a warning sign for physicians to be aware of the potential risk, and a dipstick test would be incapable of doing so. Although the cost-benefit studies for ACR among HIV-infected individuals have not been published, we feel that there are many strengths from a clinical perspective.

Dipstick proteinuria demonstrated poor diagnostic validity in detecting individuals with moderately increased albuminuria (ACR 30–300 mg/g). Our result revealed an FNR of 67.4%, meaning 2 of 3 individuals were misclassified into a lower risk category. Previous studies reported an FNR of 21.0% [19] and 47.6% [20]. The overall sensitivity of a ≥1+ dipstick result to detect ACR ≥30 mg/g was much lower compared with the previous study as well (44.9% versus 60%) [20]. Thus, our result supports these previous findings with more magnitude and robustness. The differences in the demographic and laboratory characteristics of the studied cohort could explain the variability. The prevalence of proteinuria in our cohort was 8.9%, whereas the prevalence was 79.0% (291 of 365) [19] and 41.3% (97 of 235) [20] for the other cohorts. The high prevalence of proteinuria may have induced a bias toward higher sensitivity of dipstick analysis when assessing all levels of albuminuria. On the other hand, the FPR was much smaller compared with

previous studies (2.8% versus 12.5% [19], 36.2% [20]), which was reassuring because a positive dipstick analysis would effectively screen patients at high risk. Nevertheless, considering that early and accurate assessment of kidney damage is a critical aspect in HIV patient care, our results strongly supports the current recommendation to use albuminuria as a screening tool.

Although albuminuria is useful for assessing kidney damage, proteinuria caused by tubular dysfunction needs to be considered as well when managing HIV-infected individuals with CKD. Tenofovir disoproxil fumarate, which is one of the most frequently used antiretroviral agents, is well known for its renal toxicity and its damage to the proximal tubules. In individuals with TDF-associated kidney injury, the glomerular basement is usually intact so the urine contains mostly tubular protein. As a result, some researchers recommend measuring urine protein-to-creatinine ratio in this population as well [38, 39]. Urine albumin/total protein ratio at a cutoff value of 0.4 has been suggested as a useful tool to distinguish HIV-infected individuals whether they possess predominantly glomerular injury or tubular injury [39]. Physicians need to be well aware of tubular dysfunction due to antiretroviral toxicity, and that checking the urine for albumin alone as recommended by KDIGO may cause them to miss a cohort of individuals with tubular injury.

The current study has several strengths. To the best our knowledge, this study included the largest HIV-infected population (n = 2135) from multiple tertiary hospitals in Japan, thus mitigating the possibility of a selection bias. We were able to test the prevalence of CKD using both guidelines on the same dataset enabling direct comparison. Urine albumin and dipstick testing was performed on the same fresh urine sample without long-term freezing and repeated thawing to ensure accuracy. However, we need to address several limitations in this study. First, albuminuria was not measured in 159 individuals (7.4%) among the total study cohort. Nevertheless, the prevalence of CKD$_{K/DOQI}$ stage 1–5, stage ≥3, and dipstick proteinuria of the subgroup (n = 1976) was identical to that of the study cohort. Therefore, we could postulate that the prevalence of albuminuria would be similar if we were able to measure it for every individual. Second, we determined ACR based on a single urine specimen, which could have overestimated the prevalence of albuminuria [40]. However, no cost-benefit studies for multiple urine ACR testing in the HIV population have not been reported to date. Furthermore, a single ACR value within the normal range can largely exclude microalbuminuria [40], reassuring clinicians that they would not miss patients who are at risk. Third, the study population comprised mainly well controlled HIV-infected Japanese men, with the proportion of women being relatively low at 5.9%. Therefore, the results may not be generalizable to women or other ethnic groups.

CONCLUSIONS

In conclusion, the prevalence of CKD was higher when classified by the KDIGO guidelines, which may enable physicians

to more effectively capture HIV-infected patients who are at high risk. The sensitivity of dipstick proteinuria to detect albuminuria is so poor that this methodology for screening HIV-infected individuals for kidney disease is limited.

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