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ORIGINAL ARTICLE

Prevalence of and associated factors with chronic kidney disease in human immunodeficiency virus-infected patients in Taiwan

Min-Han Hsieh [a], Po-Liang Lu [a,b,c], Mei-Chuan Kuo [d], Wei-Ru Lin [a], Chun-Yu Lin [a,b,e], Chung-Chih Lai [a], Jih-Jin Tsai [a,b,f], Tun-Chieh Chen [a,b,g,*], Shang-Jyh Hwang [d], Yen-Hsu Chen [a,b,e]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[b] *School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Department of Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[d] *Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[e] *Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[f] *Tropic Medicine Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[g] *Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*

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KEYWORDS
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Background: Chronic kidney disease (CKD) is an important issue for individuals who live with human immunodeficiency virus (HIV) following the use of highly active antiretroviral therapy; however, the prevalence rate of CKD varies between countries.
Methods: The present study screened HIV-infected patients in a medical center and a regional teaching hospital in southern Taiwan from January 2008 to December 2012. CKD was defined as

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Number 100, Tzyou 1st Road, Kaohsiung 807, Taiwan.
E-mail address: idchen.tunchieh@gmail.com (T.-C. Chen).

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Human immunodeficiency virus;
Prevalence

a urine microalbumin-to-creatinine ratio ≥30 mg/g, and/or a protein ≥1 + on urine dipstick examination, and/or an estimated glomerular filtration rate <60 mL/min/1.73 m^2 for 3 months. The prevalence rate and the analyzed associated factors of CKD were determined.
Results: Among 1639 HIV-infected patients, only 512 had adequate data to be enrolled in the study. Thirty-six (7.03%) of these patients had CKD, and 476 did not. In a univariate analysis, CKD was associated with an older age, a higher peak HIV RNA load, diabetes mellitus (DM), hypertension, exposure to antiretroviral therapy, and cholesterol levels ≥240 mg/dL. Multivariate analysis revealed that DM, hypertension, and cholesterol ≥240 mg/dL were statistically significant factors.
Conclusion: In Taiwan, the prevalence of CKD in HIV-infected patients was low (7.03%). The classical risk factors for CKD, such as DM, hypertension, and hypercholesterolemia, were demonstrated to be associated with CKD in Taiwanese HIV-infected patients.

Introduction

Following the introduction of the wide use of highly active antiretroviral therapies (ARTs), the median survival of human immunodeficiency virus (HIV)-infected patients has increased remarkably, and the outcome of renal complications, such as the risk of end-stage renal disease and 1-year survival in patients with dialysis, also improved.[1–3] Despite this improvement, chronic kidney disease (CKD) is an important issue in managing HIV-infected patients due to the associated higher mortality rate.[4] The literature states that CKD in HIV-infected patients results from various factors, including HIV-associated nephropathy, severe HIV infection, black ethnicity, diabetes mellitus (DM), hypertension, and aging.[3,5] Although highly active ART can reduce HIV-associated nephropathy, nearly all antiretroviral drugs have been reported to cause renal dysfunction.[3] The most notable antiretroviral drugs to be associated with renal disease have been indinavir and tenofovir.[3] Regular urinalyses are recommended in the USA and Europe.[5,6] The prevalence of CKD in HIV-infected patients ranges from 3% to 38% in different races and countries.[7–11] Among the different races, African Americans have been determined to be more prone to develop CKD and end-stage renal disease.[12,13] The prevalence of CKD in the general Taiwanese population was found to be 11.93%, with CKD cases having a higher mortality rate and cardiovascular disease risk.[14] However, the data for CKD in Taiwanese HIV-infected patients are lacking. We conducted a study to evaluate the prevalence and associated factors of CKD in HIV-infected patients in Taiwan.

Materials and methods

Study population

This was a retrospective cross-sectional study. The data were collected from HIV-infected patients who were followed in a medical center and a regional teaching hospital in southern Taiwan. In the medical center, the study period was from January 2008 to December 2012; in the regional teaching hospital, the study period was from January 2010 to December 2012. The present study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital; registration number, KMUHIRB-20120020.

Definitions

The CKD diagnostic criteria were defined as a urine microalbumin-to-creatinine ratio (ACR) ≥30 mg/g, and/or a protein ≥1 + on urine dipstick examination, and/or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 persisting for at least 3 months.[15] The estimated glomerular filtration rate was calculated using the simplified modification of diet in renal disease formula.[16] The CKD cases were classified into five stages according to the eGFR level. The eGFRs for Stage 1 to Stage 5 were defined as follows: ≥90 mL/min/1.73 m^2; 60–89 mL/min/1.73 m^2; 30–59 mL/min/1.73 m^2; 15–29 mL/min/1.73 m^2; and <15 mL/min/1.73 m^2 or dialysis.[15] The patients who did not meet any given diagnostic criterion were defined as non-CKD. The method to determine urine microalbumin was tested by conjugation of specific antigen and urine microalbumin, and detected by the Synchron System (Beckman Coulter, Pasadena, CA, USA).

Each patient's characteristics were also recorded, including the following metrics: age; sex; body weight; serum creatinine; DM status; hypertension; hepatitis B and C infection status; cholesterol level; triglycerides; high- and low-density lipoprotein levels; HbA1c level; the duration of HIV infection; the peak HIV RNA load and the CD4 cell count nadir following the diagnosis of HIV infection; and the exposure to ARTs. DM was defined as a diagnosis of DM previously, or use of oral antidiabetic agents or insulin. Hypertension was defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg, or use of antihypertensive agents. Hepatitis B infection was defined as being positive for the surface antigen, and hepatitis C (HCV) infection was defined as being anti-HCV antibody-positive. The lipid profiles were recorded as cholesterol ≥240 mg/dL, high-density lipoprotein <40 mg/dL,[17] triglycerides >150 mg/dL, and low-density lipoprotein >130 mg/dL.

Exposure to ART was defined as exposure to ART for at least 3 months. The exposure to each antiretroviral drug

was required to be at least 3 months for it to be considered in the present analysis. The patients who did not have a medical record of receiving ART from the beginning of such treatment were not included in the analysis of the effects of exposure to the given antiretroviral drug. The patients without a medical record for the initial CD4 cell count or HIV RNA load were not included for the analysis of these variables.

Statistical analysis

SPSS version 19 software (SPSS, Chicago, IL, USA) was used for the statistical analysis. The characteristics of patients with and without CKD were compared. The data are presented as the mean ± standard deviation. For the univariate analysis, the independent samples *t* tests were used for the continuous variables, and the Chi-square test or Fisher's test were used for the categorical variables. Fisher's test was used if the magnitude of the categorical variable was <5. Logistic regression analysis was applied for the multi-variable analyses. The variables with $p < 0.05$ in the univariate analyses were included in the logistic regression. The CD4 cell count nadir was also included in the logistic regression given that this metric is an important factor in HIV-infected patients.

Results

The present study screened 1639 patients who were followed during the study period. Of these, 487 patients had never received a urine dipstick examination or an ACR measurement. The CKD status of 624 patients could not be determined due to inadequate data (Fig. 1). The patients without adequate data for the determination of CKD had only urine dipstick or ACR data or proteinuria for <3 months. Of the remaining 512 patients, 36 had CKD and 476 did not. Among the patients with CKD, 11.11% (4/36) matched the diagnostic criterion of eGFR <60 mL/min/1.73 m^2, 41.67% (15/36) matched the diagnostic criterion of ACR >30 mg/g, and 52.78% (19/36) matched the diagnostic criterion of traceable proteinuria by urine dipstick examination. The prevalence rate of CKD diagnosed by K/DOQI diagnostic criteria was 7.03%. The prevalence rates of CKD diagnosed by diagnostic criteria of eGFR <60 mL/min/1.73 m^2, eGFR <60 mL/min/1.73 m^2 combined with ACR >30 mg/g, and eGFR <60 mL/min/1.73 m^2 combined with traceable proteinuria detected by dipstick were 0.78%, 3.52%, and 4.49%, respectively. The mean age of the included 512 patients was 36.87 ± 10.24 years, and 471 were male. The prevalence rates of DM and hypertension were 5.4% (26/482) and 7.56% (31/410), respectively. The mean creatinine level was 0.86 ± 0.47 mg/dL, and the mean eGFR was 113.36 ± 24.51 mL/min/1.73 m^2. The mean peak plasma HIV RNA load was 4.93 ± 0.88 $\log_{10}$/mL (n = 240), and the mean CD4 cell count nadir was 206.15 ± 152.92 cells/μL (n = 241). Among the examined population, 55.69% (279/501) received ART. The mean duration of ART was 57.56 ± 48.10 months (n = 234).

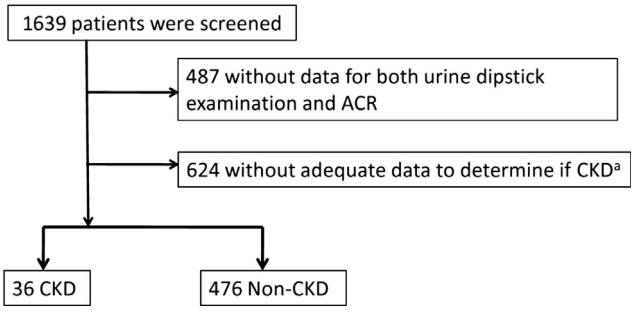
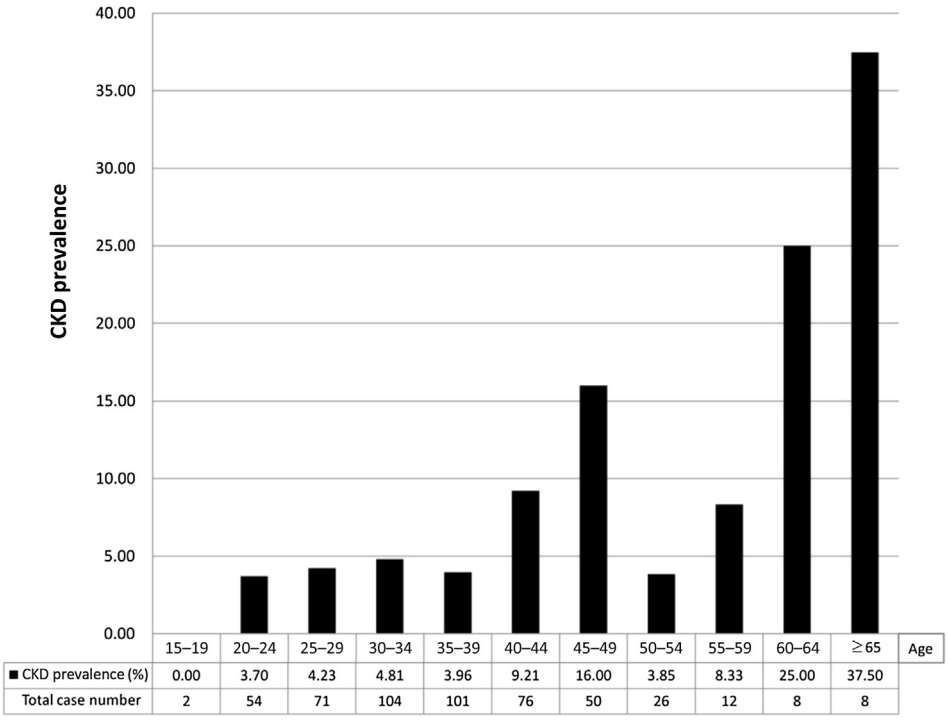


Figure 1. Flow chart of study design. [a] Patients without adequate data included patients with only normal urine dipstick examination or normal ACR which cannot be determined if non-CKD, and patients with proteinuria without fulfilled with criteria of lasting for 3 months. ACR = urine microalbumin-to-creatinine ration; CKD = chronic kidney disease.

The prevalence rates of CKD in the different age groups were as Fig. 2: 0% (0/2) in those who were aged 15–19 years, 3.7% (2/54) in those who were aged 20–24 years, 4.23% (3/71) in those who were aged 25–29 years, 4.81% (5/104) in those who were aged 30–34 years, 3.96% (4/101) in those who were aged 35–39 years, 9.21% (7/76) in those who were aged 40—44 years, 16% (8/50) in those who were aged 45–49 years, 3.85% (1/26) in those who were aged 50–54 years, 8.33% (1/12) in those who were aged 55–59 years, 25% (2/8) in those who were aged 60–64 years, and 37.5% (3/8) in those who were aged ≥65 years. The majority of our cases were younger than 50 years. In the patients who were younger than 50 years, the prevalence of CKD increased remarkably in the group that was age 40–49 years. The estimated crude incidence of CKD is 9.77/1000 person–years in those patients who were newly diagnosed with HIV infection and received follow-up during the study period.

The characteristics of the HIV-infected patients with and without CKD are compared in Table 1. The analyses indicated that CKD was associated with an older age, DM, hypertension, cholesterol ≥240 mg/dL, higher peak plasma HIV RNA load, ART exposure, and non-HCV coinfection. No specific category of ART was associated with CKD. In the multivariate analysis, age, peak plasma HIV RNA load, and CD4 cell nadir were analyzed as continuous variables and the others were as categorical variables. As a result, CKD was only related to DM [odds ratio (OR), 9.822; 95% confidence interval (CI), 1.862–51.803; p = 0.007], hypertension (OR 23.060; 95% CI, 4.670–113.874, p <0.001), and cholesterol ≥240 mg/dL (OR, 5.523; 95% CI, 1.236–24.686; p = 0.025; Table 2). Based on the multivariate analysis, there were no statistically significant results with respect to ART exposure, even when using 6-month, 12-month, or 24-month treatment duration as the definition of ART exposure.

In 36 patients with CKD, 17 (47%) were CKD Stage 1, 13 (36%) were Stage 2, three (8%) were Stage 3, one (3%) was Stage 4, and two (6%) were Stage 5. In 21 CKD patients with data of ACR, six with ACR >300 mg/g, 12 with ACR 30–300 mg/g, and the remaining three had ACR <3 mg/g. Fourteen cases had CKD at the time of HIV diagnosis. For the 12 patients who did not have CKD at the time of HIV diagnosis, 11 received ART when CKD was confirmed. The mean time of CKD development following ART in these patients was 80.0 ± 55.2 months.



	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	≥65	Age
■ CKD prevalence (%)	0.00	3.70	4.23	4.81	3.96	9.21	16.00	3.85	8.33	25.00	37.50	
Total case number	2	54	71	104	101	76	50	26	12	8	8	

Figure 2. Prevalence of chronic kidney disease (CKD) in each age group.

Discussion

In the present study, we evaluated the prevalence of CKD in HIV-infected patients in two teaching hospitals in southern Taiwan. The prevalence of CKD in this population was 7.03%, a rate similar to the general Taiwanese population of the same age,[18] but much lower than other Asian HIV-infected populations (15.4% in Japan and 16.8% in Hong Kong).[9,10] Yanagisawa et al[9] analyzed 732 HIV-infected Japanese with a mean age of 46.7 ± 12 years, and the prevalences of DM, hypertension, and CKD were 7.9%, 30.3% and 15.4%, respectively. Of the patients in this previous cohort, 90.7% received ART; specifically, 50.5% had received tenofovir, and 7.9% had received indinavir. In another study conducted in Hong Kong by Cheung et al,[10] the data from 322 HIV-infected Chinese patients (mean age: 45.2 ± 11.7 years) were analyzed. The prevalences of DM, hypertension, and CKD were 7.4%, 10.6%, and 16.8%, respectively. Of this group, 93.5% had received ART; specifically, 5.3% of the patients had received tenofovir, and 33.2% had received indinavir. Compared to the previous studies, the percentage of ART exposure was lower in the present study population and had lower rates of tenofovir or indinavir exposure. Moreover, the mean age of the present study population was 36.87 ± 10.24 years, which was approximately 10 years younger than the populations from Hong Kong and Japan. The prevalence of CKD in the general population has been reported to increase with age.[14,18] The younger age of the participants in the present study may in part explain the low prevalence of CKD observed. The majority of the present study population was younger than 50 years. In the patients who were younger than 50 years, the CKD prevalence increased remarkably after age 40 years. This finding was consistent with the CKD prevalence in the general Taiwanese population.[14]

According to current recommendations, urinalysis was suggested when HIV-infected patients enter into care and during their regular annual monitoring.[19] However, approximately 29.7% of patients never received a urinalysis in our hospitals. Early stage CKD screening is of poor quality, and the majority of the patients with CKD in the present study were Stage 1 or Stage 2. Efforts to encourage physicians to screen for proteinuria in HIV-infected patients are required. This testing can identify patients with early stage CKD and rapidly avoid the use of nephrotoxic agents.

In previous studies, the risk factors that have been associated with CKD in HIV-infected patients included lower CD4 cell count nadir, the duration of ART, exposure to indinavir or tenofovir, the duration of tenofovir use, older age, hypertension, and DM.[3,7,8,10,20] In the present study, the peak HIV RNA load and ART exposure were associated with CKD in the univariate but not in the multivariate analysis.

Previous studies have reported that tenofovir, indinavir, or tenofovir in combination with protease inhibitors were related to CKD.[20–22] Drugs have been shown to be highly associated with tubulointerstitial nephropathy in HIV-infected patients in a study by Zaidan et al,[23] which including renal biopsy result, and antiretroviral drugs were strongly associated with tubulopathy, especially tenofovir. However, in the present study, the individual drugs were not statistically significantly associated with CKD, not even tenofovir or indinavir. This result is likely to be primarily due to the low rate of tenofovir and indinavir exposure in the examined population.

Nevertheless, DM, hypertension, and cholesterol ≥240 mg/dL were significantly associated with CKD in both

Table 1 The characteristics of HIV-infected patients with and without chronic kidney disease

	CKD, $n = 36$ (%)	Non-CKD, $n = 476$ (%)	p
Age (y)	43.22 ± 12.78	36.38 ± 9.87	<0.001
Male	34	437	0.758
Creatinine (mg/dL)	1.40 ± 1.61	0.82 ± 0.14	0.037
eGFR (mL/min/1.73 m^2)	91.62 ± 42.45	115.01 ± 21.80	0.002
ACR (mg/g)	656.43 ± 1475.80 ($n = 21$)	6.96 ± 9.42	0.057
Weight (kg)	69.59 ± 22.71	66.32 ± 11.36 ($n = 356$)	0.399
Duration of HIV diagnosed (mo)	59.69 ± 41.66 ($n = 26$)	46.48 ± 43.42 ($n = 216$)	0.142
Peak plasma HIV RNA load (log_{10}/mL)	5.3 ± 0.75 ($n = 26$)	4.89 ± 0.89 ($n = 214$)	0.024
CD4 cell count nadir (cells/μL)	176.29 ± 147.65 ($n = 26$)	209.76 ± 153.49 ($n = 215$)	0.293
Underlying disease, n (%)			
DM	12/36 (33.33)	14/446 (3.14)	<0.001
Hypertension	13/35 (37.14)	18/375 (4.8)	<0.001
HBV	6/34 (17.65)	76/444 (17.12)	0.973
HCV	3/36 (8.33)	168/452 (37.17)	<0.001
ART exposure	31/36 (86.11)	248/465 (53.33)	<0.001
IDV	2/30 (6.67)	7/204 (3.43)	0.324
TDF	2/30 (6.67)	7/204 (3.43)	0.324
NNRTI	25/30 (83.33)	145/204 (71.08)	0.160
PI	18/30 (60)	100/204 (49.02)	0.261
rPI	9/30 (30)	78/204 (38.24)	0.384
II	3/30 (10)	6/204 (2.94)	0.094
Duration of ART use (mo)	78.4 ± 62.62 ($n = 30$)	54.5 ± 44.96 ($n = 204$)	0.052
Cholesterol ≥240 mg/dL, n (%)	6/32 (18.75)	18/373 (4.83)	0.001
TG >150 mg/dL	15/31 (48.39)	135/374 (36.10)	0.173
HDL <40 mg/dL	12/30 (40)	166/310 (53.55)	0.156
LDL >130 mg/dL	8/30 (26.67)	47/309 (15.21)	0.104
HbA1c (%)[a]	7.88 ± 1.92 ($n = 11$)	7.09 ± 1.72 ($n = 12$)	0.310

[a] Only patients with diabetes were included in this analysis.
ACR = urine microalbumin-to-creatinine ratio; ART = antiretroviral therapy; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HBV = hepatitis B; HCV = hepatitis C; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; IDV = indinavir; II = integrase inhibitor; LDL = low-density lipoprotein; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; rPI = boosted protease inhibitor; TDF = tenofovir; TG = triglycerides.

the univariate and multivariate analyses, a result that is consistent with the general population.[15,17] This result may suggest that in Asian HIV-infected patients without indinavir or tenofovir exposure, DM, hypertension, and hypercholesterolemia are much more important associated factors of CKD. The odds ratios of CKD in patients with DM and hypertension were 9.82 and 23.06, respectively. However, the odds ratio of CKD in the general Taiwanese population with DM and hypertension were 4.707 and 3.892, respectively.[18] The relative association of DM and hypertension was therefore much higher in the present study group than for the general population. However, a larger scale study is required to clarify whether DM or hypertension increases the risk of CKD in HIV-infected patients to a greater extent than is observed in the general population.

Table 2 Multivariate analysis for risks of chronic kidney disease in HIV-infected patients

Variable	OR	95% CI	p
Age	0.975	0.916–1.038	0.433
DM	9.822	1.862–51.803	0.007
Hypertension	23.060	4.670–113.874	<0.001
Cholesterol ≥240 mg/dL	5.523	1.236–24.686	0.025
Peak plasma HIV RNA load (log_{10}/mL)	2.159	0.929–5.015	0.074
CD4 cell count nadir (cells/μL)	1.001	0.997–1.005	0.722
ART exposure	6.44	0.529–78.346	0.144
HCV	0.148	0.007–3.052	0.216

ART = antiretroviral therapy; CI = confidence interval; DM = diabetes mellitus; HCV = hepatitis C; HIV = human immunodeficiency virus; OR = odds ratio.

In Taiwanese HIV-infected patients, the mortality rate decreased after the introduction of highly active antiretroviral therapy.[24] With the prolonged survival, HIV-infected patients received long-term antiretroviral therapy. Wu et al[25] demonstrated that hyperlipidemia was associated with prolonged antiretroviral therapy, especially protease inhibitor, in Taiwanese HIV-infected patients. Furthermore, the association between hypercholesterolemia followed by antiretroviral therapy and decreased eGFR were also observed in Abraham et al's[26] study. In Lo et al's[27] study, DM was associated with protease inhibitor exposure in Taiwanese HIV-infected patients. DM is a traditional risk factor of CKD. Despite DM having predominant association

with CKD in our study, protease inhibitors were not. This may be because protease inhibitors used in Lo et al's[27] study were mostly indinavir, which has been identified as a risk factor for DM.[28,29] However, the percentage of indinavir exposure in the present study was low, which may suggest that the protease inhibitor was not an associated factor of CKD in our study population.

A meta-analysis of studies of HIV-infected patients reported that HCV coinfection is associated with an increased risk of CKD and proteinuria.[30] In patients with HIV and HCV coinfection, the presence of HCV viremia was associated with an increased risk of developing CKD.[31] However, in the present study, we found that HIV and HCV coinfection was not associated with CKD.

In HIV-infected patients, HCV coinfection was more commonly associated with intravenous drug abuse in southern Taiwan.[32] A HIV CRF07_BC outbreak has been noted in intravenous drug abusers since 2004.[33] In the outbreak in southern Taiwan, of all of the patients with HIV and HCV coinfection, 93.7% were intravenous drug abusers. Moreover, the HIV RNA load was lower and the mean $CD4^+$ cell counts were higher in intravenous drug abusers.[32] Therefore, patients with HCV and HIV coinfection in the present study were assumed to have had a shorter duration of HCV and HIV infection. Moreover, the majority of the HIV and HCV coinfected patients in the present study were intravenous abusers and did not receive regular follow-up visits. This fact may explain why HCV infection was not associated with CKD in the present study.

There were limitations of the present study. First, this is a retrospective study. Many of patients were excluded from the analysis, which may have influenced the reported prevalence rates. Moreover, in comparing HIV-infected patients with and without CKD, the number of patients with CKD was limited, and many data cannot be completely obtained, including peak HIV RNA load, CD4 cell count nadir, complete medical history of ART, and biochemical data. This limitation may have influenced the results of the associated factors. Second, the present study did not analyze the possible nephrotoxic agents that are often used in HIV-infected patients, such as trimethoprim/sulfamethoxazole, acyclovir, amphotericin B, and nonsteroidal anti-inflammatory drugs. This fact may have influenced the analysis of the CKD associated factors. Third, this is a cross-sectional study, and causality could not be determined. Antiretroviral drugs, especially nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors, are known to cause hypercholesterolemia, which is believed to be related to CKD.[17,34] In the present study, there were 12 patients with diabetes in the CKD group, and eight patients had DM at the time of HIV infection diagnosis. There were 13 patients with hypertension in the CKD group, and five had hypertension at the time of HIV infection diagnosis. Despite these facts, the present study cannot distinguish whether DM or hypertension is an HIV-related illness. Forth, we compared the risk, sex, and age of our patients studied with those of patients reported to Taiwan Centers for Disease Control. The sex and risk of our patients studied were similar to all HIV-infected patients in Taiwan. However, the percentage of patients older than 40 years was higher in our study population compared to that from Taiwan CDC (35.16% and 22.78%, respectively). Therefore, our study population may not represent the general HIV-infected patients in Taiwan. Because our study population was older, the prevalence rate may be overestimated for all HIV-infected patients in Taiwan.

In conclusion, the prevalence of CKD in HIV-infected patients in Taiwan was lower than in other Asian populations. To avoid severe renal disease, regular urinalysis to detect early stage CKD should be encouraged among physicians who care for HIV-infected patients. The associated factors between CKD and HIV-infected patients in Taiwan were as the classic risk factors for CKD for general population, including DM, hypertension, and hypercholesterolemia. However, further large-scale prospective studies are required to clarify the impact of HIV status and ART exposure on CKD in Taiwanese patients with HIV infection.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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