The incidence and dynamic risk factors of chronic kidney disease among people with HIV

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Objectives: We investigate the incidence of chronic kidney disease (CKD) among people with HIV (PWH) and the dynamic risk factors associated with CKD incidence.

Design: A population-based cohort study of PWH in South Carolina.

Methods: Adults (age $\geq$18 years) PWH diagnosed between 2006 and 2019 who were CKD-free at baseline were included. The associations of HIV-related risk factors and conventional risk factors with the incidence of CKD were investigated during the overall study period and by different follow-up periods (i.e. 5, 10, and 15 years) by multivariate logistic regression.

Results: Among 9514 PWH, the incidence of CKD was 12.39 per 1000 person-years. The overall model indicated that conventional risk factors, such as hypertension, dyslipidemia, cardiovascular disease, and diabetes, were significantly associated with a higher risk of developing CKD. HIV-related characteristics, such as high percentage of days with viral suppression, recent $CD4^+$ cell count, and percentage of retention in care, were associated with a lower risk of CKD compared with their counterparts. In the subgroup analysis, the results were similar for the 5-year and 6–10 years follow-up groups. Among patients who did not develop CKD by the 10th year, the risk factors for developing CKD within 11–15 years were dyslipidemia, diabetes, low recent $CD4^+$ cell count, and short duration of retention in care while other predictors vanished.

Conclusion: Diabetes, $CD4^+$ cell count, and retention in care were persistently associated with CKD despite of follow-up duration. Closely monitoring diabetes and improving $CD4^+$ cell count and retention in care are important to lower the risk of CKD in PWH.

AIDS 2023, **37**:1783–1790

Keywords: chronic kidney disease, cohort study, conventional risk factor, HIV, HIV-related risk factor, people with HIV

Introduction

With the advances in antiretroviral therapy (ART), the life expectancy of people with HIV (PWH) has been significantly improved, with expectations that PWH will live into their seventies and beyond [1–3]. However, increasing life expectancy has led to a growing population of aging PWH and is accompanied by an increased

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Received: 31 December 2022; revised: 9 July 2023; accepted: 12 July 2023.

DOI:10.1097/QAD.0000000000003662

ISSN 0269-9370

burden of chronic diseases in PWH. One of these chronic diseases is chronic kidney disease (CKD) that is a significant concern with the reported prevalence ranging from 4.1 to 24% in the USA [4–8]. Existing literature suggested that PWH had a 1.8 to seven-fold increased risk of CKD compared with HIV-negative populations [9,10].

As CKD is a major risk factor for end-stage renal disease and all-cause mortality, further understanding of the incidence and risk factors of CKD among PWH is of great importance. Existing studies have investigated the incidence and risk factors of CKD among PWH in different countries. In the USA, the incidence of CKD among PWH ranges from 5 to 11.2 cases per 1000 person-year due to different study population, study design, and definition of CKD [11–15]. Multiple factors are associated with the incidence of CKD among PWH, including the traditional age-related risk factors (e.g. hypertension and hypercholesterolemia), behavioral factors (e.g. tobacco and other substance use), comorbidities (e.g. diabetes mellitus and hepatitis C), side effects of antiretroviral drug use (e.g. mitochondrial injury, renal tubular damage), HIV-related factors (e.g. $CD4^+$ cell counts, HIV viral suppression), and their synergistic effects [16–20].

Despite the existing efforts in investigating CKD incidence and associated factors in PWH, certain knowledge gaps remain. First, the study population for CKD incidences mostly came from the Western or Northeastern USA or using the Veteran's Affairs cohort [9,11,13]. Little is known of CKD incidence in Southern states of the USA. Second, the majority of studies are restricted to examining the risk factors at a single timepoint [21], while risk factors such as different ART eras and aging process have evolved over time. Third, a number of studies used single or only baseline measurements of HIV-related factors [9] due to the short follow-up time or restriction of data collection, which lacks sufficient longitudinal measurement. For example, Sutton *et al.* [9] examined the risk factors for CKD in HIV patients by using data from the Veterans Affairs healthcare system. Whereas only the HIV viral load at baseline was used and analyzed during a short follow-up period [9]. Fourth, some studies investigated the risk factors for multiple chronic conditions as a composite outcome among PWH, instead of investigating particularly for CKD [22], or investigated the temporal changes rather than the dynamic of risk factor for chronic conditions [23,24].

In the present study, we proposed to address these gaps by using the electronic health records (EHR) data from a population-based statewide cohort in South Carolina (SC), which include the longitudinal medical records for each HIV patient. We aimed to describe the incidence of CKD among PWH and investigate the dynamic changes of conventional and HIV-related risk factors associated with CKD incidence.

Materials and methods

Study design and participants

This is a population-based cohort study, with data being retrieved from integrated EHR database in South Carolina, USA. Specifically, the electronic records of HIV diagnosis, risk factors, and laboratory tests ($CD4^+$ cell count and viral load) were extracted from the SC Department of Health and Environmental Control (DHEC). The SC DHEC's enhanced HIV/AIDS reporting system (e-HARS) is a statewide confidential name-based reporting of HIV/AIDS, to which $CD4^+$ cell count and viral load tests for all patients are reported since 1 January 2004, as mandated [25–27]. All payer claim databases in South Carolina were extracted from the SC Office of Revenue and Fiscal Affairs (RFA), which is a state agency that captures individual-level longitudinal health utilization data from various state agencies. The SC RFA serves as an honest broker to link data from e-HARS and all payer claim database. The study protocol received approval from the institutional review board at the University of South Carolina and relevant SC state agencies (USC IRB number: #Pro00068124) [28].

The study population were adult PWH (age $\geq$ 18 years) with a confirmed HIV diagnosis from 1 January 2006, to 31 December 2019, and were CKD-free at HIV diagnosis. PWH who have at least one laboratory test for $CD4^+$ cell count and viral load and with a South Carolina residence at diagnosis were included in the study. The study population was first fully considered (overall group) and then divided into three groups by different follow-up time periods. Follow-up time for each participant starts from the date of HIV diagnosis until the event time, death, or end of the study (31 December 2020), whichever occurred first. In the first group (group 1), we included the participants in the cohort who have at least one $CD4^+$ cell count and viral load test during the first 5 years follow-up period ($n = 9364$). The follow-up records within the first 5 years of these individuals were used for analysis. In the second group (group 2), we further restricted the population to those who did not develop CKD diagnosis in the first 5 years and used their 6–10 years of follow-up records for analysis. In this group, we only included those who have at least one $CD4^+$ cell count and viral load between 6–10 years follow-up time window ($n = 4581$). Using similar inclusion and exclusion criteria, we defined the third group among individuals with 11–15 years of follow-up records (group 3, $n = 1742$).

Outcomes

The primary outcome of this study was CKD occurrence, which was defined as the first diagnosis of CKD during the study period and identified by the presence of corresponding International Classification of Diseases 9^{th} (ICD-9) and 10^{th} (ICD-10) revision codes in the EHR.

(Supplement Table 1, http://links.lww.com/QAD/C936). The CKD incidence rates (per 1000 person-year) for the entire study period were calculated by the number of new cases divided by the total person year at risk. And the total person year at risk was the sum of the individual follow-up year.

Predictors

Social-demographic characteristics

Information on social demographics included age at HIV diagnosis (e.g. 40–49, 50–59 years), sex (e.g. female, male), race (i.e. white, black, Hispanic, and Other), mode of HIV transmission (e.g. men who have sex with men, injecting drug use), and residence type (i.e. rural and urban). All variables were measured at baseline.

Conventional risk factors

Eight conventional risk factors were tobacco use, alcohol use, illicit substance use (e.g. opioids, cannabis, cocaine, psychoactive substances), hypertension, dyslipidemia, obesity, cardiovascular disease (CVD), and diabetes mellitus, which were ascertained by the presence of corresponding ICD-9/10 codes in the record between HIV diagnosis and end of follow-up. We update these variables in three subgroups.

HIV-related characteristics

The dynamic $CD4^+$ cell count and viral load measurements were used in the current analysis. For the overall model, the initial $CD4^+$ cell count was defined as the first $CD4^+$ cell count at HIV diagnosis; the most recent $CD4^+$ cell count, which is defined as the most recent value before the first CKD occurrence or, where applicable, before censoring at death, or end of the study, were also included. Both variables were classified as less than 200, 200–350, and more than 350 cells/μl. In addition, we considered the duration of viral suppression [percentage of days with viral suppression (viral load <200 copies/ml)], and the duration of immunodeficiency (percentage of days with low $CD4^+$ cell counts (<500 cells/μl)] as predictors. Specifically, the percentage of days with viral suppression was defined as the days with viral suppression over the total follow-up days. It was calculated as the sum of the mid-point in days between the date of viral load less than 200 copies/ml to the previous adjacent detectable date and the mid-point in viral suppression date to the next adjacent date. A similar calculation method was applied to measure the percentage of days with low $CD4^+$ cell counts. The percentage of days with viral suppression was categorized as 0–20, 21–50, and 51–100%. And the percentage of days with low $CD4^+$ cell counts was categorized as 0–25, 26–70, and 71–100%. In addition, the HIV diagnosis year and the clinical AIDS diagnosis at the time of HIV diagnosis were also extracted as predictors. For the three sub-groups, the same variables of interest as the overall model were measured during the specific follow-up period. Different from the overall model, the $CD4^+$ cell count at the starting timepoint of the follow-up year at each period (i.e., 6^{th}-years, 11^{th}-year) was also used as the predictor.

HIV treatment cascade predictors

HIV treatment cascade predictors were measured using the timely linkage to care and the percentage of retention in care in years. Timely linkage to care was measured at baseline and defined as the first $CD4^+$ test or viral load test '30 days' after HIV diagnosis. For the percentage of retention in care, we first defined 'in HIV care.' 'In HIV care' refers to having either two or more $CD4^+$ cell count or viral load measurements, separated by at least three months within a follow-up year. Patients were considered either as being retained in care (1 = in HIV care) or not (0 = not in HIV care) each year. Then, the proportion of retention in care was calculated as the sum of years in care divided by the total follow-up years. We update this value in three subgroups. The three classifications for the proportion of retention in care were 0–30, 31–75, and 76–100%.

Statistical analysis

All categorical predictors were presented as frequency counts and percentages (%), and continuous predictors were presented as mean values and standard deviation (SD). The differences in categorical predictors were tested with the chi-square test. The difference in continuous predictors was investigated by t-test. The association of HIV-related risk factors and conventional risk factors with the incidence of CKD during the overall study period, and different follow-up periods (groups 1–3) were investigated using multivariable logistic regression models. Cystic kidney disease was considered a specific nonmodifiable cause of CKD that is unrelated to HIV. Therefore, we conducted a sensitivity analysis by excluding cystic kidney disease in our CKD diagnosis. We reported odds ratio (OR) and 95% confidence interval (95% CI) for each model in the results table and forest plots. P value less than 0.05 was considered significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of participants

A total of 9514 PWH met the inclusion criteria and were included in this study. The mean age was 35 years (SD = 12.7), and the plurality of participants was the age group of 18–29 years (4061, 42.7%). There were 7292 (76.6%) men, 6571 (68.7%) were black, and 7926 (83.3%) were living in urban areas. The prevalence of CKD is 8.72% during the entire study period (Table 1).

Table 1. Demographic, conventional, and HIV-related characteristics of the study population.

Characteristic	Overall $N = 9514$	CKD (No) $n = 8684$ (91.28%)	CKD (Yes) $n = 830$ (8.72%)	*P*
Age group (%)				<0.0001
18–29	4061 (42.68)	3901 (44.92)	160 (19.28)	
30–39	2033 (21.37)	1883 (21.68)	150 (18.07)	
40–49	1882 (19.78)	1648 (18.98)	234 (28.19)	
50–59	1138 (11.96)	939 (10.81)	199 (23.98)	
≥60	400 (4.2)	313 (3.6)	87 (10.48)	
Sex (%)				<0.0001
Female	2222 (23.36)	1970 (22.69)	252 (30.36)	
Male	7292 (76.64)	6714 (77.31)	578 (69.64)	
Race (%)				<0.0001
White	2121 (22.29)	1998 (23.01)	123 (14.82)	
Black	6571 (69.07)	5901 (67.95)	670 (80.72)	
Hispanic and other	822 (8.64)	785 (9.04)	37 (4.46)	
Risk (%)				<0.0001
Heterosexual	1733 (18.22)	1507 (17.35)	226 (27.23)	
MSM	5010 (52.66)	4724 (54.4)	286 (34.46)	
IDU	493 (5.18)	439 (5.06)	54 (6.51)	
Other	2278 (23.94)	2014 (23.19)	264 (31.81)	
Residence (%)				0.0889
Rural	1588 (16.69)	1432 (16.49)	156 (18.8)	
Urban	7926 (83.31)	7252 (83.51)	674 (81.2)	
Tobacco (%)				<0.0001
No	5270 (55.39)	4918 (56.63)	352 (42.41)	
Yes	4244 (44.61)	3766 (43.37)	478 (57.59)	
Alcohol (%)				<0.0001
No	8,532 (89.68)	7,855 (90.45)	677 (81.57)	
Yes	982 (10.32)	829 (9.55)	153 (18.43)	
Hypertension (%)				<0.0001
No	6849 (71.99)	6463 (74.42)	386 (46.51)	
Yes	2665 (28.01)	2221 (25.58)	444 (53.49)	
Dyslipidemia (%)				<0.0001
No	8684 (91.28)	8038 (92.56)	646 (77.83)	
Yes	830 (8.72)	646 (7.44)	184 (22.17)	
Obesity (%)				<0.0001
No	8634 (90.75)	7944 (91.48)	690 (83.13)	
Yes	880 (9.25)	740 (8.52)	140 (16.87)	
CVD (%)				<0.0001
No	8213 (86.33)	7678 (88.42)	535 (64.46)	
Yes	1301 (13.67)	1006 (11.58)	295 (35.54)	
DM (%)				<0.0001
No	8610 (90.5)	8008 (92.22)	602 (72.53)	
Yes	904 (9.5)	676 (7.78)	228 (27.47)	
Illicit substance use (%)				<0.0001
No	8086 (84.99)	7439 (85.66)	647 (77.95)	
Yes	1428 (15.01)	1245 (14.34)	183 (22.05)	
HIV diagnosis year (SD)	2012.4 (4.05)	2012.58 (4.06)	2010.87 (3.63)	<0.0001
Percentage of viral suppression (%)				<0.0001
0–20%	2986 (31.39)	2552 (29.39)	434 (52.29)	
21–50%	2298 (24.15)	2144 (24.69)	154 (18.55)	
51–100%	4230 (44.46)	3988 (45.92)	242 (29.16)	
Initial $CD4^+$ cell count (%)				<0.0001
<200	2778 (29.2)	2415 (27.81)	363 (43.73)	
200–350	1996 (20.98)	1820 (20.96)	176 (21.2)	
>350	4740 (49.82)	4449 (51.23)	291 (35.06)	
Recent $CD4^+$ cell count (%)				<0.0001
<200	1279 (13.44)	969 (11.16)	310 (37.35)	
200–350	1183 (12.43)	1046 (12.05)	137 (16.51)	
>350	7052 (74.12)	6669 (76.8)	383 (46.14)	
Percentage of low $CD4^+$ cell count (%)				<0.0001
0–25%	3918 (41.18)	3745 (43.13)	173 (20.84)	
26–70%	3094 (32.52)	2789 (32.12)	305 (36.75)	
71–100%	2502 (26.3)	2150 (24.76)	352 (42.41)	
Percentage of retention in care (%)				<0.0001
0–30%	2019 (21.22)	1778 (20.47)	241 (29.04)	
31–75%	2778 (29.2)	2621 (30.18)	157 (18.92)	
76–100%	4717 (49.58)	4285 (49.34)	432 (52.05)	
Timely linkage to care (%)				0.1335
No	3588 (37.71)	3295 (37.94)	293 (35.3)	
Yes	5926 (62.29)	5389 (62.06)	537 (64.7)	
AIDS at HIV diagnosis (%)				<0.0001
No	7477 (78.59)	6916 (79.64)	561 (67.59)	
Yes	2037 (21.41)	1768 (20.36)	269 (32.41)	

CVD, cardiovascular disease; DM, diabetes mellitus; IDU, injecting drug use; MSM, men who have sex with men.

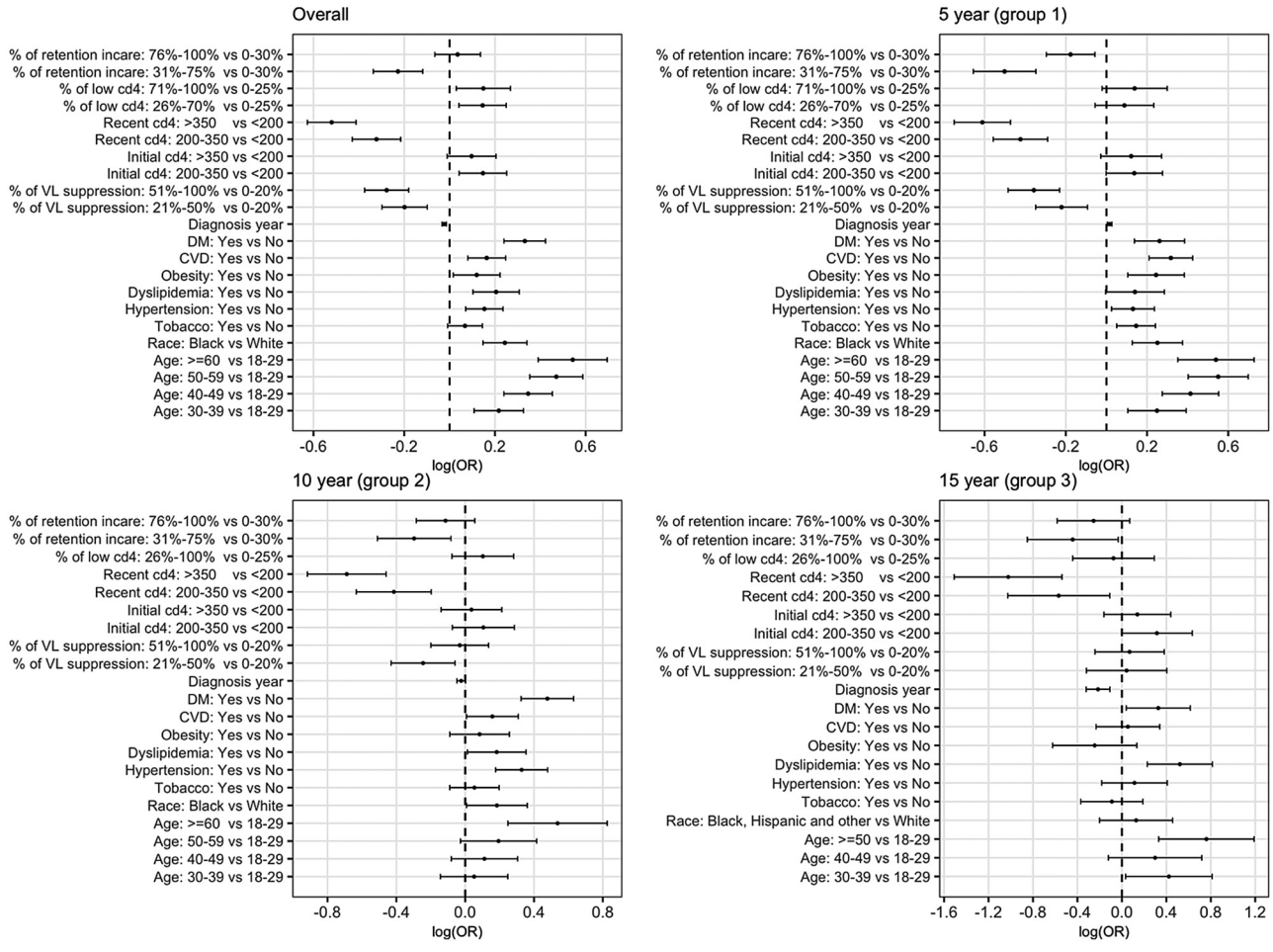

Fig. 1. Forest plot for the dynamic significant predictors among overall and three sub-group analyses. CVD, cardiovascular disease; DM, diabetes mellitus; log(OR), log of odds ratio; VL, viral load.

Incidence rates and evolving risk factors of chronic kidney disease

Among a total of 9514 individuals who were CKD-free at baseline, the median duration of follow-up is 6.74 years. There were 830 incident cases of CKD over 66 963.5 person-years of follow-up, resulting in an overall incidence rate of 12.39 per 1000 person-years.

Among the overall population, compared with a younger age (i.e. 18–29 years), all the other age groups were more likely to experience CKD and the odds increased as the age increased (OR range: 1.65–3.49). Black race was positively associated with subsequent CKD diagnosis (OR = 1.75, 95% CI: 1.40–2.19) than white. Of the three subgroups, group 1 ($\leq$ 5 years) has 9364 patients and demonstrated the same demographic distribution as the overall population. The effects of age were attenuated in group 2 (6–10 years) with only people aged over 60 years showing significantly high risk (OR = 3.44, 95% CI: 1.77–6.69). Individuals of black race remained at a higher risk for CKD than white. In group 3 (11–15 years), age was the only remaining significant risk factor with a similar pattern as group 2 (Fig. 1 and Supplement Table 2, http://links.lww.com/QAD/C936).

For conventional risk factors, hypertension (OR: 1.42, 95% CI: 1.18–1.72), dyslipidemia (OR: 1.60, 95% CI: 1.27–2.03), obesity (OR: 1.32, 95% CI: 1.04–1.67), CVD (OR = 1.46, 95% CI: 1.20–1.77), and diabetes mellitus (OR = 2.15, 95% CI: 1.74–2.65) were significant risk factors for CKD. In terms of subgroups, dyslipidemia was not a significant factor in group 1, while tobacco use (OR = 1.40, 95% CI: 1.12–1.74) became a risk factor for CKD. In group 2, similar significant variables were observed as the overall group except that the significance of obesity disappeared. In group 3, only dyslipidemia (OR = 3.33, 95% CI: 1.69–6.52) and diabetes mellitus (OR = 2.13, 95% CI: 1.10–4.13) remained associated with CKD (Fig. 1 and Supplement Table 2, http://links.lww.com/QAD/C936).

The higher percentage of days with viral suppression (21–50 vs. 0–20%: OR = 0.63; 51–100 vs. 0–20%: OR = 0.53), higher recent $CD4^+$ value (200–350 vs.

<200 cells/μl: OR = 0.48; >350 vs. <200 cells/μl: OR = 0.30), and a greater percentage of time retained in care (31–75 vs. 0–30%: OR = 0.59) were associated with a lower risk of CKD. The HIV diagnosis year was a significant predictor of CKD occurrence. Individuals who were diagnosed in the recent calendar year had a lower risk of developing CKD (OR = 0.95, 95% CI: 0.93–0.97). Patients with a higher percentage of days with low CD4$^+$ cell count (26–70 vs. 0–25%: OR = 1.40; 71–100 vs. 0–25%: OR = 1.41) were more likely to develop CKD. Notably, compared with patients with an initial CD4$^+$ cell count less than 200 cells/μl, the initial CD4$^+$ cell count between 200 and 350 cells/μl had a higher risk of CKD (OR = 1.40). In the three separate subgroup analyses, most of the variables in group 1 have same effect as the overall group except the effect of percentage of low CD4$^+$ cell counts, which became insignificant. In group 2, the effect of HIV diagnosis year vanished, while the effects for other variables remained. The effect of recent CD4$^+$ cell count, percentage of time retained in care, and HIV diagnosis year remained significant in group 3 (Fig. 1 and Supplement Table 2, http://links.lww.com/QAD/C936). After excluding cystic kidney disease, the sensitivity analysis showed similar results as the main analyses (Supplement Table 3 and 4, http://links.lww.com/QAD/C936).

Discussion

The current study examined the CKD incidence and the dynamic risk factors of CKD among PWH in South Carolina who were diagnosed with HIV between 1 January 2006, and 31 December 2019. Our findings highlighted the alarming incidence of CKD among PWH in South Carolina. The conventional risk factors, such as hypertension, diabetes mellitus, and dyslipidemia, were important factors associated with an increased risk of developing CKD. In addition, HIV-related factors, such as viral suppression, high CD4$^+$ cell count, and retention in care, were associated with a decreased risk of CKD. These findings highlight the potential role of HIV-related factors in reducing the risk of CKD among PWH and informed us about the importance of maintaining an optimal immune function in improving clinical outcomes. Noteworthy, our findings on changes in risk factors emphasize the necessity of tailored intervention strategies for individuals in different follow-up periods.

To the best of our knowledge, this is one of the first population-based cohort studies that discuss the dynamic risk factors of CKD among PWH over a 15-year follow-up period. The large sample size at the statewide PWH cohort leads to more robust and comprehensive results. In addition, we used separate analyses with different follow-up periods to mirror the long-term effects of risk factors. Our study design ensures we continuously measure the effect of predictors and better illustrate the variation of CKD risk factors.

We found an incidence rate of CKD of 12.39 per 1000 person-years in the current study. This alarming incidence warns us of the importance of preventing CKD among PWH, especially older PWH. The difference in the CKD incidence rate exists between our results and previous studies [11,12,14,15]. Heterogeneity in the study populations, datasets, and the duration of follow-up is partially responsible for the differences in incidence rates. In addition, we used ICD-9 and ICD-10 codes to identify CKD, while other criteria, such as estimated glomerular filtration rate (eGFR), were used to define the CKD in previous studies, which may result in a different CKD incidence.

The conventional risk factors we identified in the overall model were consistent with previous studies. Patients with hypertension, dyslipidemia, obesity, CVD, and diabetes mellitus have an increased risk of CKD and have been reported in a number of published studies [13,20,23], including those among the general population [29,30]. In addition, over 20% of days with viral suppression (<200 copies/ml), high recent CD4$^+$ cell counts (>200 cells/μl), and over 30% of retention in care showed a significant protective effect on CKD occurrence. Although different measurements of viral suppression, CD4$^+$ cell count categories, and retention in care were used, similar conclusions were drawn in other studies. For example, a retrospective cohort study conducted in France illustrated that HIV patients with a durable CD4$^+$ cell count more than 200 cells/μl had a lower risk of CKD [31]. A randomized trial conducted by the SMART study group indicated the renal events rate declined significantly when the patients were treated following the standard guidelines and achieved sustained viral suppression [32]. And recent research shows patients with HIV viral load more than 1000 copies/ml had over three times the risk of CKD compared with undetectable viral load [21]. There is a counterintuitive finding that participants with an initial CD4$^+$ cell count between 200 and 350 cells/μl were more likely to develop CKD compared with their counterparts who had an initial CD4$^+$ cell count less than 200 cells/μl. Existing studies indicated that people who have higher CD4$^+$ cell counts gained longer life expectancy [3]. Therefore, our finding might be explained by the longer life expectancy of those with baseline higher CD4$^+$ cell counts.

The three sub-groups analyses exhibited the dynamic risk factors of CKD over time. Fewer changes in conventional and HIV-related risk factors between the 5-year and 10-year groups were observed. Although the effects of tobacco use, obesity, and HIV diagnosis year disappeared, dyslipidemia presented an increased risk of CKD in the 10-year follow-up group. Dyslipidemia was reported as a progression factor for CKD, which could lead to

worsening kidney damage and subsequent impaired kidney function [33] as suggested in other studies [23]. The reported risk factor of hypertension was in accordance with other published studies [20,23]. A vicious circle proposed in recent research may explain why hypertension is an important and persistent factor for CKD, namely that hypertension may lead to cardiovascular events, and the events can degenerate renal function, which in turn leads to exacerbating hypertension [34]. Although many conventional and HIV-related risk factors were significantly associated with the development of CKD in the first two groups, the effects of most predictors vanished over time, with only dyslipidemia, diabetes mellitus, HIV diagnosis year, high recent $CD4^+$ cell count, and high percentage of HIV retention in care remaining as significant predictors in group 3. The negative association between HIV diagnosis year and the outcome might be explained by the improvement in ART, people who were diagnosed in more recent years could receive more advanced ART and further leading to a lower risk of CKD development. Furthermore, the patients who were diagnosed in recent years have not yet had enough time to develop CKD. When comparing three subgroups, diabetes mellitus, recent $CD4^+$ cell count, and retention in care were three consistently significant factors associated with CKD development. It is no surprise that diabetes mellitus was found to be a major risk factor for CKD, which is in accordance with other published studies [13,16–20]. A national cohort study investigating the rate of progression to CKD indicated the highest rate of CKD progression among patients with both HIV and diabetes mellitus than patients with only HIV or diabetes mellitus [35]. Retention in care may provide protection for CKD through the incremental $CD4^+$ cell count and prolonged viral suppression supported by other U.S. studies [36,37].

Despite the strengths of the current study, the findings should be interpreted carefully given several limitations. First, solely relying on ICD codes to define CKD might underestimate its diagnosis. However, we were not able to measure CKD diagnosis more accurately due to the absence of laboratory (such as eGFR) information in our dataset. Second, certain ARTs (e.g. tenofovir) have been suggested to be associated with renal dysfunction [19]. However, the HIV treatment information was not available in our dataset; thus, we were unable to examine the association between ART and CKD development. Third, due to the inherent limitation of EHR data that different individuals have different duration of follow-up, the results may be biased by the potential association between variables and different duration of follow-up. Moreover, some health behaviors such as drinking cannot be accurately measured due to the limitation of EHR data; hence, the results should be discreetly understood. Finally, although the South Carolina statewide cohort is representative of PWH in the Southern states of the USA, our findings may not be generalizable to other U.S. states or other resource-limited settings with substantial regional differences.

In conclusion, in this population-based cohort study of CKD incidence, the dynamic of CKD risk factors elucidated the importance of both conventional and HIV-related factors (e.g. diabetes mellitus, hypertension, viral suppression, $CD4^+$ cell count, and so on) for PWH, especially those who have a shorter duration of HIV diagnosis. Close monitoring of HIV disease progression (e.g. $CD4^+$ and VL) to enhance immune recovery and keep a healthy lifestyle to reduce the risk of comorbidities are the top priorities at the stage of early diagnosis. However, as PWH lives longer, some conventional and HIV-related factors might not be as important as before. But still diabetes mellitus, $CD4^+$ cell count, and retention in care are always critical for improving health outcomes of PWH and reducing the incidence and economic burden of CKD. Effective intervention approaches related to controlling diabetes mellitus, maintaining a high $CD4^+$ cell count, and stimulating patient retention in care should be proposed for reducing the risk of CKD development, especially for aging HIV patients who have been living with HIV for many years. Moreover, a more precise measurement of CKD (e.g. eGFR) should be applied in future studies. Although the risk factors were recognized, the pathogenesis is still not clear. Further study could focus on the pathology between the risk factors and CKD among PWH during different follow-up times.

Acknowledgements

H.G. conceptualized and wrote the first draft and critical revision of the manuscript. J.Z. and X.Y. conceptualized the study design. J.Z. set up the statistical test design. H. G. and S.C. conducted the data analysis, which was reviewed and verified by J.Z. H.G. prepared tables and figures. S.W. and R.M. provided clinical input. J.Z., X. Y., R.M., S.W., B.O., and X.L. reviewed and edited the manuscript. Authorship was determined using ICMJE recommendations.

The authors thank the South Carolina Department of Health and Environmental Control (DHEC), the office of Revenue and Fiscal Affairs (RFA), and other South Carolina agencies for contributing the data in South Carolina.

The research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number R01AI127203 and R01AI164947. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Both NIAID and NIH had no role in the design of the study, collection, analysis, and interpretation of the data.

Conflicts of interest

There are no conflicts of interest.

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