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Comparison of Three Cardiovascular Risk Scores among HIV-Infected Patients in Korea: The Korea HIV/AIDS Cohort Study

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ABSTRACT

Background: We investigated cardiovascular disease (CVD), risk factors for CVD, and applicability of the three known CVD risk equations in the Korean human immunodeficiency virus/ Acquired Immune Deficiency Syndrome (HIV/AIDS) cohort.

Materials and Methods: The study participants were HIV-infected patients in a Korean HIV/AIDS cohort enrolled from 19 hospitals between 2006 and 2017. Data collected at entry to the cohort were analyzed. The 5-year CVD risk in each participant was calculated using three CVD risk equations: reduced CVD prediction model of HIV-specific data collection on adverse effects of anti-HIV drugs (R-DAD), Framingham general CVD risk score (FRS), and Korean Coronary Heart Disease Risk Score (KRS).


Results: CVD events were observed in 11 of 586 HIV-infected patients during a 5-year (median) follow-up period. The incidence of CVD was 4.11 per 1,000 person-years. Older age (64 vs. 41 years, $P = 0.005$) and diabetes mellitus (45.5% vs. 6.4%, $P < 0.001$) were more frequent in patients with CVD. Using R-DAD, FRS, and KRS, 1.9%, 2.4%, and 0.7% of patients, respectively, were considered to have a very high risk ($\geq 10\%$) of 5-year CVD. The discriminatory capacities of the three prediction models were good, with c-statistic values of 0.829 ($P < 0.001$) for R-DAD, 0.824 ($P < 0.001$) for FRS, and 0.850 ($P = 0.001$) for KRS.

Conclusion: The FRS, R-DAD, and KRS performed well in the Korean HIV/AIDS cohort. A larger cohort and a longer period of follow-up may be necessary to demonstrate the risk factors and develop an independent CVD risk prediction model specific to Korean patients with HIV.


Keywords: HIV; Korea; Cardiovascular diseases; Coronary disease

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Conflict of Interest

HJC is editorial board of *Infect Chemother*; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions

Conceptualization: HJC, JYB, SMK, BYC. Data curation: SMK, YSC, BYP, BYC. Formal analysis: SMK, YSC, BYP, BYC, JYB, HJC. Methodology: SMK, YSC, BYP, BYC, HJC. Investigation: SMK, YSC, BYP. Validation: BYC, HJC, JYC, SIK, SWK. Software: SMK, YSC, BYP, BYC. Writing - original draft: JYB, SMK. Writing - review & editing: JYB, SMK, HJC, JYC, SWK, SIK.

INTRODUCTION

Advances in antiretroviral therapy have improved the life expectancies for persons infected with human immunodeficiency virus (HIV) to reach those of HIV-negative people [1]. Accordingly, aging-related chronic health complications such as hypertension, diabetes mellitus (DM), dyslipidemia, and renal impairment, have become more prevalent in HIV-positive populations [2, 3]. Cardiovascular disease (CVD) is an important health issue in HIV populations, attributed to both HIV-related and traditional risk factors [4, 5]. Current care for HIV-positive persons comprises the prevention and management of comorbidities, including thorough monitoring and interventions for risk factors of CVD.

Several CVD risk prediction models have been introduced to assist in CVD risk assessment in the HIV population [6]. The Framingham general CVD risk score (FRS) is a risk model developed from the general population [7]. The data-collection on adverse effects of anti-HIV drugs CVD risk equation (DAD) and reduced DAD equation (R-DAD) were developed from an exclusively HIV-positive population [8]. However, both FRS and R-DAD were derived from a Caucasian cohort, causing concern regarding the applicability of these equations to the Korean population. The Korean coronary heart disease (CHD) risk score (KRS) is a CHD risk prediction model developed from the general Korean population [9]. Such prediction models derived from the general population omit HIV-specific risk factors and therefore the applicability to the Korean HIV population need to be evaluated.

This study aimed to investigate CVD, its risk factors, and applicability of the three known CVD risk equations in the Korean HIV/AIDS cohort.

MATERIALS AND METHODS

1. Study population and design

Participants in this prospective cohort study were HIV-infected patients who visited 19 hospitals affiliated with the Korean HIV/AIDS Cohort from December 2006 to December 2017. Male participants older than 18 years who were free of CVD at entry into the cohort were eligible for the present study. Participants with missing information on the CVD risk factor profiles were excluded. Data collected at entry into the cohort were used for analyses [10, 11].

2. Ethics statement

The study was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital (IRB no. 2007-10-001-019), and informed consent was obtained from all patients participating in the study.

3. Data collection

The demographic and clinical characteristics of all participants were obtained. Biological data such as age, sex, body weight, body mass index (BMI), and blood pressure were collected. Regarding comorbidities, data on DM, dyslipidemia, CVD, smoking history, and family history were collected. In terms of history related to HIV infection, data on sexual habits, history of exposure route, time of entry to cohort, time of diagnosis, baseline CD4+ T-cell count, nadir CD4+ T-cell count, baseline HIV viral load, antiviral treatment status, and antiretroviral regimen were collected. Laboratory data related to metabolic complications, such as total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol, and triglycerides (TG), were evaluated.

4. Cardiovascular risk assessment

The 5-year CVD risk in each participant was calculated using three CVD risk equations: R-DAD, FRS, and KRS. The FRS estimates CVD risk through a combination of age, sex, systolic blood pressure, antihypertensive therapy, serum TC, HDL-cholesterol values, current smoking status, and diabetes [12]. The R-DAD estimates CVD risk by combining information on age, sex, systolic blood pressure, serum TC and HDL-cholesterol level, CD4+ count, DM, smoking status, and family history of CVD [13]. The KRS estimates CVD risk by combining information on age, hypertension, TC, HDL cholesterol, smoking history, and DM [9]. The outcome events of R-DAD and FRS include CHD, cerebrovascular events, and peripheral artery disease. The outcome events of the KRS are limited to CHD. Participants were ranked based on their estimated 5-year CVD risk as low (<1%), moderate (1–5%), high (5–10%), and very high risk (≥10%) [8].

5. Statistical analysis

We presented descriptive statistics by classifying the group characteristics of HIV-infected patients in Korea by CVD status after enrollment. Receiver operating characteristic (ROC) curves were constructed to compare the predictive values of the R-DAD, FRS, and KRS models. The 5-year survival rate required to calculate the CVD risk score was calculated using Cox proportional hazard regression using data from a Korean HIV/AIDS cohort study. The statistical program SAS Enterprise Guide 7.1 ver. (SAS Institute, Cary, NC, USA) and MedCalc 9 (ScyMed, Houston, TX, USA), were used in this study.

RESULTS

1. Study population

A total of 1,486 HIV-infected patients were enrolled between December 2006 and December 2017. Owing to missing data, 897 patients were excluded from the analyses. We analyzed data from 589 patients eligible for inclusion in this study (Fig. 1).

CVD events were observed in 11 patients (1.9%) during the follow-up period (Fig. 1). The median follow-up period was 5 years in both the CVD and non-CVD group. The incidence of CVD and CHD was 4.11 and 1.48 per 1,000 person-years (PY) respectively. The median patient age was higher in the CVD group than in the non-CVD group (64 *vs.* 41 years, $P = 0.005$). Diabetes was more frequent in the CVD group than in the other group (45.5% *vs.* 6.4%, $P < 0.001$). BMI was higher in the non-CVD group than in the CVD group (22.4 *vs.* 20.2, $P = 0.006$). Traditional risk factors of CVD, such as blood pressure, TC, HDL cholesterol, TG, family history of CVD, and smoking history, were not significantly different between the groups. The median cumulative combination antiretroviral treatment (cART) exposure at enrollment was 0.52 years in the CVD group and 0.51 years in the non-CVD group ($P = 0.915$). The median duration of protease inhibitor (PI) exposure at enrollment was 0.25 years in the CVD group and 0.00 years in the non-CVD group ($P = 0.197$). The CD4+ count and the proportion of patients with viral suppression were not significantly different between the groups.

The proportions of cART-experienced patients were 81.8% and 74.2% at the time of enrollment in the CVD and non-CVD groups, respectively. The proportions of patients who were being treated with 2 nucleoside reverse transcriptase inhibitor (NRTI) + PI, 2 NRTI + non-NRTI (NNRTI), and 2 NRTI + integrase strand transfer inhibitor (INSTI) at the time of enrolment were 45.5%, 18.2%, and 9.1% in the CVD group and 39.6%, 18.3%, and 13.8% in the non-CVD group (Table 1).

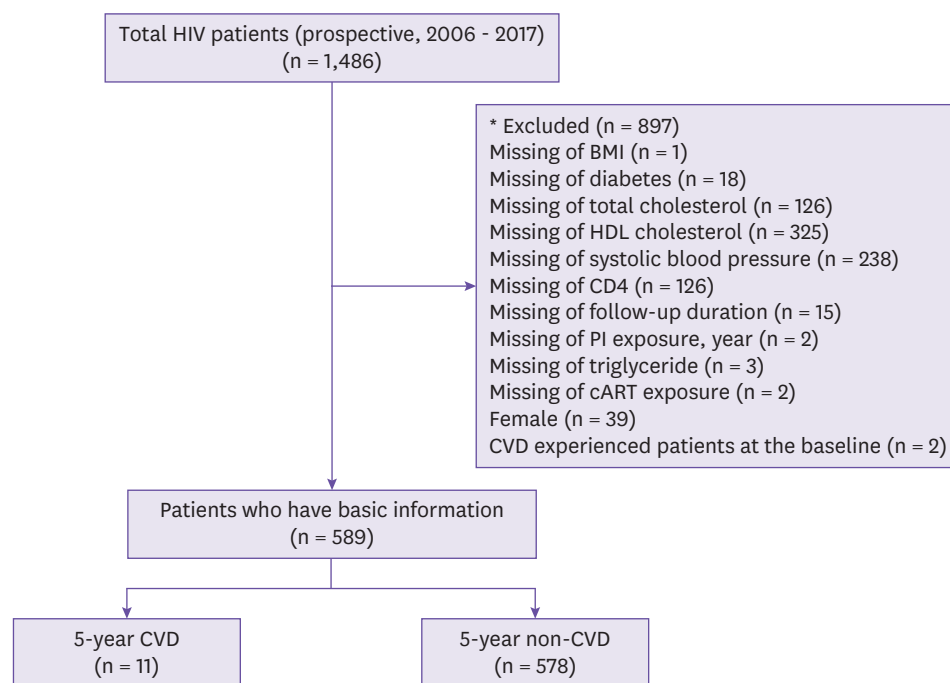


Figure 1. Flowchart of participating patients along with exclusion criteria.

HIV, human immunodeficiency virus; BMI, body mass index; HDL, high-density lipoprotein; PI, protease inhibitor; cART, combination antiretroviral treatment; CVD, cardiovascular diseases.

2. CVD risk stratification at enrollment

The predicted risk of experiencing a CVD event within 5 years of enrollment was assessed using the R-DAD, FRS, and KRS. The patients were stratified into low (<1%), moderate (<5%), high (<10%), and very high ($\geq 10\%$) risk groups according to the calculated risk score (Table 2). The proportions of patients in the low, moderate, high, and very high risk groups were comparable between the R-DAD (36.3%, 53.1%, 8.7%, and 1.9%, respectively) and FRS (Men) (38.4%, 50.4%, 8.8%, and 2.4%, respectively). Using the KRS, the proportion of patients in the low risk group was increased, and the proportions of patients in the high and very high risk groups were lower than those in the other two risk scoring systems (50.4%, 43.5%, 5.4%, and 0.7% in the low- to very high-risk groups). The proportion of patients in the very high-risk group was highest using FRS and lowest using KRS. R-DAD and FRS showed very good agreement, with a kappa statistic of 0.82 (95% confidence interval [CI]: 0.78 – 0.86, $P < 0.001$). KRS revealed good agreement with both FRS (kappa = 0.64, 95% CI: 0.59 - 0.69, $P < 0.001$) and R-DAD (kappa = 0.62, 95% CI: 0.56 – 0.67, $P < 0.001$).

3. Comparison of predictive value using R-DAD, FRS, and KRS models

A comparison of the ROC curves for the three cardiovascular risk prediction models is shown in Figure 2. The area under the ROC curve (AUC) was 0.829 ($P < 0.001$) for R-DAD, 0.824 ($P < 0.001$) for FRS, and 0.850 ($P = 0.001$) for KRS. There were no significant differences in the discrimination ability among the three prediction models ($P = 0.534$). The optimal cutoff value estimated by the Youden Index was 2.9% for R-DAD, 5.9% for FRS, and 3.9% for KRS. Using these cut off values, the sensitivity and specificity were 0.818 and 0.734 for R-DAD, 0.636 and 0.929 for FRS, and 0.750 and 0.906 for KRS. Negative predictive values were comparable among the three prediction models. The positive predictive values for R-DAD, FRS, and KRS were 0.055, 0.146, and 0.052, respectively. CVD risk stratification based on the highly discriminated point in each prediction model and the actual incidence of CVD events are shown in Table 3.

Table 1. Baseline characteristics of the study participants, 2006 - 2017, the Korean HIV cohort study at enrollment

Characteristics	CVD event status after the baseline		P-value ^{a, b}
	Yes (n = 11)	No (n = 578)	
Median (IQR)			
Follow-up, years	5 (1.0 - 6.0)	5 (2.0 - 7.0)	0.870
Age, years	64 (50 - 67)	41 (32 - 49)	0.005
cART exposure, years	0.52 (0.00 - 4.59)	0.51 (0.00 - 1.94)	0.915
PI exposure, years	0.25 (0.00 - 2.78)	0.00 (0.00 - 1.05)	0.197
CD4 count, cells/mm ³	337 (195 - 627)	387 (237 - 562)	0.365
Nadir CD4 count, cells/mm ³	165 (77 - 278)	210 (82 - 320)	0.363
Systolic blood pressure, mmHg	120 (110 - 130)	122 (115 - 133)	0.763
Diastolic blood pressure, mmHg	73 (69 - 80)	79 (70 - 85)	0.363
Total cholesterol, mmol/l	3.70 (3.39 - 5.02)	4.34 (3.72 - 5.02)	0.127
HDL cholesterol, mmol/l	1.06 (0.67 - 1.27)	1.09 (0.88 - 1.32)	0.762
Ratio total cholesterol / HDL cholesterol	4.28 (3.29 - 5.76)	4.02 (3.24 - 5.00)	-
Triglyceride, mmol/L	1.99 (1.29 - 2.74)	1.65 (1.15 - 2.52)	0.757
BMI, kg/m ²	20.2 (19.6 - 21.3)	22.4 (20.7 - 25.0)	0.006
N (%)			
HIV-RNA <50 copies/ml	6 (54.6)	305 (52.8)	0.907
Family history of CVD	0 (0.0)	66 (11.4)	0.234
Diabetes	5 (45.5)	37 (6.4)	<0.001
Current cigarette smoker	5 (45.5)	289 (50.0)	0.949
Ex-smoker	2 (18.2)	103 (17.8)	
Mode of HIV acquisition			
Heterosexual	4 (36.4)	200 (34.6)	0.939
Homosexual	6 (54.6)	357 (61.8)	
Intravenous drug use	0 (0.0)	0 (0.0)	
Others	1 (9.1)	21 (3.6)	
Antiretroviral treatment at entry to cohort			
Not on treatment	2 (18.2)	149 (25.8)	0.596
2 NRTI + PI	5 (45.5)	229 (39.6)	
2 NRTI + NNRTI	2 (18.2)	106 (18.3)	
2 NRTI + INSTI	1 (9.1)	80 (13.8)	
Other	1 (9.1)	10 (1.7)	

^aMedian two-sample test.

^bChi square test.

CVD, cardiovascular disease; IQR, interquartile range; cART, combination antiretroviral treatment; PI, protease inhibitor; HDL, high-density lipoprotein; BMI, body mass index; RNA, ribonucleic acid; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor.

Table 2. Five-year CVD risk stratification at enrollment

Stratification	Reduced DAD score ^a	FRS (Men) ^a	KRS ^b
Low (<1%)	214 (1) ^c , 36.3%	226 (1), 38.4%	297 (0), 50.4%
Moderate (1 - 5%)	313 (4), 53.1%	297 (3), 50.4%	256 (2), 43.5%
High (5 - 10%)	51 (4), 8.7%	52 (4), 8.8%	32 (2), 5.4%
Very high (≥10%)	11 (2), 1.9%	14 (3), 2.4%	4 (0), 0.7%

^aReduced DAD score and FRS estimated risk of CVD comprising coronary heart disease and cerebrovascular disease.

^bKRS estimated risk of coronary heart disease.

^c() indicates the number of patients with CVD development.

CVD, cardiovascular disease; DAD, The Data-collection on Adverse Effects of Anti-HIV Drugs; FRS, Framingham general cardiovascular disease risk score; KRS, Korean Coronary Heart Disease Risk Score.

DISCUSSION

In the Korean HIV-positive cohort, CVD events were observed in 11 (1.9%) of 586 HIV-infected patients during the 5-year (median) follow-up period. Using R-DAD, FRS, and KRS, 1.9%, 2.4%, and 0.7% of patients, respectively, were considered to have a very high risk of 5-year CVD. The discriminatory capacities of the three prediction models were good.

Table 3. CVD risk stratification by highly discriminated point of each prediction model and actual incidence of CVD events

R-DAD (2.9%) ^a	5-year CVD ^b event		FRS (5.9%) ^a	5-year CVD ^b event		KRS (3.9%) ^a	5-year CHD ^c event	
	No (%)	Yes (%)		No (%)	Yes (%)		No (%)	Yes (%)
<1%	213 (99.5)	1 (0.5)	<1%	225 (99.6)	1 (0.4)	<1%	297 (100.0)	0 (0.0)
<3%	218 (99.1)	2 (0.9)	<6%	312 (98.7)	4 (1.3)	<4%	234 (99.2)	2 (0.9)
≥3%	147 (94.8)	8 (5.2)	≥6%	41 (87.2)	6 (12.8)	≥4%	54 (96.4)	2 (3.6)
Total	578	11	Total	578	11	Total	585	4

^aRepresents the optimal cutoff value of each prediction model estimated by the Youden Index.

^bCVD included CHD and cerebrovascular disease.

^cOnly CHD was counted as outcome event in KRS.

CVD, cardiovascular disease; R-DAD, reduced DAD score; FRS, Framingham general cardiovascular disease risk score; KRS, Korean Coronary Heart Disease Risk Score; CHD, coronary heart disease.

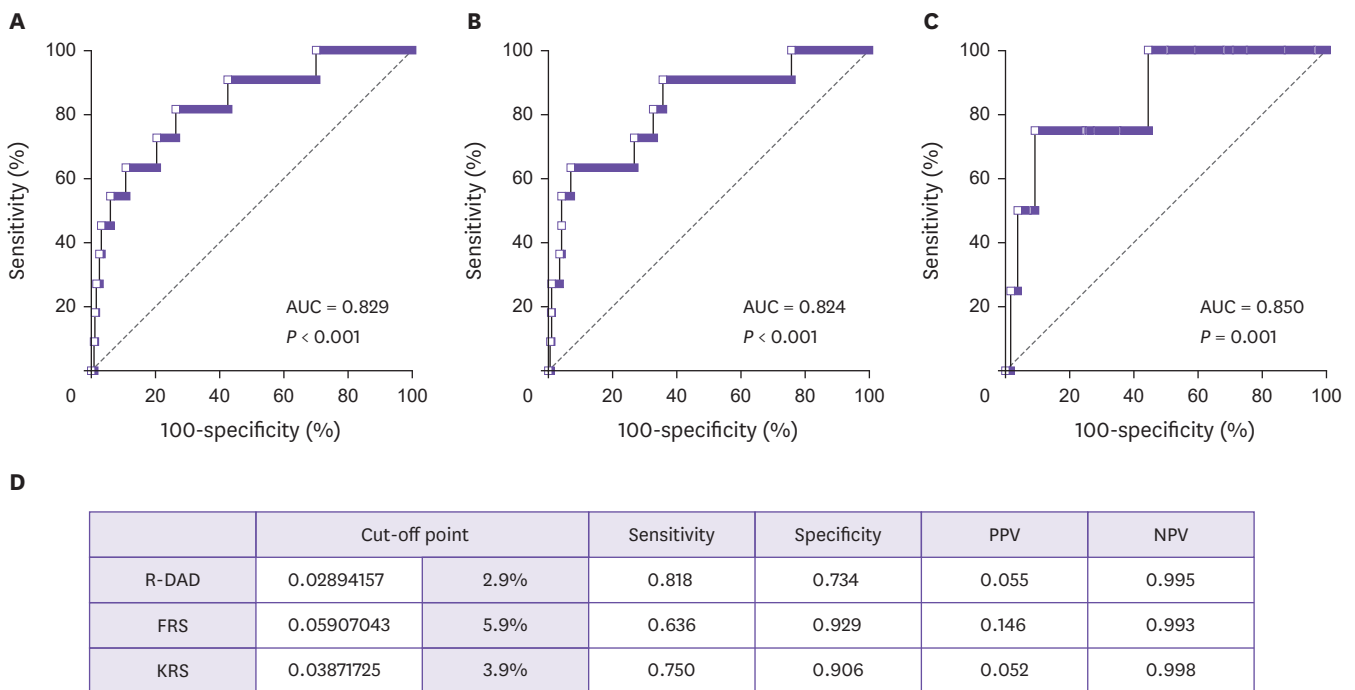


Figure 2. ROC curves for R-DAD (A), FRS (B), KRS (C) and the sensitivity, specificity, PPV, NPV of each prediction model (D). R-DAD and FRS estimates risk of CVD comprising coronary heart disease and cerebrovascular disease. KRS estimates risk of coronary heart disease.

ROC, receiver operating characteristic; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; R-DAD, reduced DAD score; FRS, Framingham general cardiovascular disease risk score; KRS, Korean Coronary Heart Disease Risk Score.

The incidence of CHD in our study was 1.48 per 1,000 PY, which is greater than the incidence found in the general Korean population (1.21 per 1,000 PY for men and 0.52 per 1,000 PY for women) [9]. This supports previous knowledge that HIV-positive patients have an increased risk of CVD. The incidence of CVD in our study was 4.11 per 1,000 PY, which was lower than that in the DAD study (5.42 per 1,000 PY) [13]. This result is in line with previous reports of a lower CVD risk in East Asians than in Europeans [14-16].

As expected, older age and a higher prevalence of DM were observed in the CVD group. Other known CVD risk factors, such as smoking, cholesterol, HDL cholesterol, blood pressure, family history of CVD, CD4 count, and PI use, were not significantly different at baseline between the CVD and non-CVD groups. However, it was difficult to determine the effect of PI and cART on CVD because the duration of exposure to PI and cART was shorter than that in other cohorts. Cox regression analysis with a larger cohort may be necessary to evaluate the

effect of individual risk factors; however, we did not perform Cox regression analysis due to the small number of CVD outcome events.

Compared with the DAD study, lower total cholesterol, lower BMI, and higher prevalence of DM were observed in our study. This is consistent with previous reports that East Asians tend to have low total cholesterol, BMI, and high serum glucose levels compared with other ethnicities [13, 15].

HIV-specific inflammation and immune activation are known to mediate CVD risk, even in patients with viral suppression [17-22]. In addition, several individual HIV medications, including PI-containing regimens, are considered to increase the CVD risk [23, 24]. Thus, the DAD score included PI exposure, abacavir use, NRTI exposure, and CD4 count as covariates. However, we did not find a significant difference in the CD4 count or PI exposure at baseline between the CVD and non-CVD groups.

It is important to develop CVD prediction models suitable for a specific population since the model performance may differ between populations. Risk prediction models that were developed based on a Caucasian study population may result in over-estimation when applied to the Korean population [25, 26]. The DAD study included only 10.5% of non-white patients, and its applicability to the Korean population is uncertain. In addition, risk prediction models developed from the general population may not function accurately in the HIV population [27].

In the present study, FRS, R-DAD, and KRS revealed good discriminative functions, as the c-statistics were above 0.8 for all three prediction models. For the FRS, the Youden index-derived cut-off value was higher than that obtained using the R-DAD and KRS, which led to a lower sensitivity and higher specificity of the FRS compared to the other two prediction models. The FRS classified more patients into high- and very high-risk groups compared to the other two prediction models, which is in line with the previous knowledge that the FRS overestimates CVD risk in Asian people as well as in the Korean population [9, 25].

To date, one study has investigated the FRS in Korean HIV-positive persons [28]. In this study, the proportion of very low-, low-, moderate-, and high-risk patients was similar between HIV-infected and uninfected patients, and there was no significant difference in FRS between the groups. This was a cross-sectional case-control study, and the number of HIV-positive patients recruited was small.

The R-DAD is a simplified prediction model for HIV-positive patients. The full DAD considers the CD4+ count, use of abacavir, and time of exposure to PI and NRTI, in addition to classic cardiovascular risk factors. Therefore, a history of ART exposure is essential for estimation; unfortunately, it is frequently missed in medical records. R-DAD does not include the class and time of exposure to ART, which makes it easy to use in the clinic [8, 13].

The agreement between DAD and FRS varied among studies performed with diverse ethnicity [29-34]. For R-DAD, fewer studies have evaluated the agreement with the FRS [32]. Studies from different ethnic groups have reported different results on the discriminative function and agreement of the prediction models; hence, it is important to evaluate whether these prediction models function well in a specific ethnic group of concern. We found that the R-DAD and FRS revealed very similar discriminative power and risk stratification in the Korean HIV/AIDS cohort.

Our study has some limitations. Owing to missing data, the number of patients enrolled in the analysis was reduced compared to the entire cohort population. The number of observed CVD events in this cohort was not sufficient to investigate the effect of traditional and HIV-related risk factors on CVD and to develop an independent risk prediction model applicable to the Korean HIV population. Third, baseline cART and PI exposure were relatively short compared with those in other cohort studies, making it difficult to examine the effects of these ART treatments on the development of CVD. Fourth, female patients were excluded from this study. The 5-year event-free rate of the group is necessary to calculate FRS. However, the 5-year event-free rate for females in this cohort could not be determined because none of the female participants experienced a CVD event during the follow-up period. Because FRS was not calculable for women, only male patients were included in the analysis. Fifth, the HIV cohort group may not reflect the characteristics of all Korean HIV-infected patients because the HIV cohort group is likely to be more interested in their own health than the non-cohort group. Therefore, real CVD events in Korean HIV-infected patients may occur more frequently during the course of the disease. A larger cohort and a longer period of follow-up may be necessary to demonstrate the risk factors and develop an independent CVD risk prediction model specific to Korean patients with HIV.

In conclusion, the incidence of CVD was 4.11 per 1,000 PY, and the three risk prediction models (FRS, R-DAD, and KRS) revealed good performance in the cohort of Korean patients with HIV. To the best of our knowledge, this is the first study to evaluate the applicability of R-DAD, FRS, and KRS in the population of Korean patients with HIV. This study may help clinicians understand the CVD risk in Koreans with HIV and help modulate patient management.

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