





Original Article



The Role of Age in Subclinical Atherosclerosis in Asian People Living with Human Immunodeficiency Virus

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ABSTRACT

Background: People living with human immunodeficiency virus (PLHIV) have an increased risk of atherosclerosis and cardiovascular disease, but specific guidance on when to suspect the onset of these diseases is limited.

Materials and Methods: We aimed to identify cardiovascular risk factors in PLHIV using carotid intima-media thickness (IMT) through a cross-sectional, retrospective cohort study that enrolled 217 PLHIV who underwent carotid IMT measurement at a teaching hospital in Korea. We compared clinical characteristics between PLHIV with subclinical atherosclerosis and PLHIV with IMT within the normal range, and used a receiver operating characteristic curve to determine the cut-off age for predicting subclinical atherosclerosis.

Results: Among the study population, 115 participants (53.0%) had subclinical atherosclerosis. In logistic regression, age and dyslipidemia were significantly associated with increased carotid IMT even after adjusting for other variables (odds ratio [OR]: 1.11, 95% confidence interval [CI]: 1.06 - 1.15, $P < 0.001$; OR: 3.92, 95% CI: 1.87 - 8.22, $P < 0.001$, respectively). The cut-off age for predicting subclinical atherosclerosis was 39.5 years (area under the curve 0.78, 95% CI: 0.72 - 0.84, $P < 0.001$).

Conclusion: Conventional risk factors including age and dyslipidemia were associated with subclinical atherosclerosis in Asian PLHIV. In particular, Asian PLHIV older than 40 years had an increased risk of subclinical atherosclerosis and may benefit from carotid IMT screening.

Keywords: HIV; Carotid intima-media thickness; Risk factors; Dyslipidemia; Cardiovascular disease

INTRODUCTION

Effective antiretroviral therapy (ART) provides longer life expectancy for people living with human immunodeficiency virus (PLHIV), and thus, the prevention and control of chronic comorbidities including cardiovascular disease (CVD) have become an important part of HIV management.

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Conflict of Interest

No conflict of interest.

Author Contributions

Conceptualization: SHP, EYL, THK. Data curation: SHP, EYL, SYP, EYL, THK. Formal analysis: SHP, EYL. Funding acquisition: EYL, THK. Investigation: SHP, EYL. Methodology: SHP, EYL. Project administration: SHP, EYL. Resources: SHP, EYL. Software: SHP, EYL. Supervision: EYL, SYP, EYL, THK. Validation: SHP, EYL. Visualization: SHP, EYL. Writing – original draft: SHP, EYL. Writing – review & editing: SHP, EYL, SYP, EYL, THK.

PLHIV are at an increased risk of developing atherosclerosis and CVD, and have a higher risk of mortality [1-3]. While traditional risk factors such as smoking and obesity may coexist, HIV itself is an independent risk factor for CVD among PLHIV [4, 5]. Acquired immunodeficiency syndrome (AIDS) was also reported to be associated with atherosclerosis and CVD [6, 7].

Carotid intima-media thickness (IMT) is frequently used in Korea as a surrogate marker of atherosclerosis and CVD due to its noninvasive, sensitive, and reproducible properties [8, 9]. Several studies have examined the association between carotid IMT and HIV infection, but the results have been largely inconclusive. While a couple of studies have reported increased carotid IMT in PLHIV [10, 11], other studies show an increase in carotid IMT only in certain subgroups, such as those taking protease inhibitors [12, 13].

Although Asia has a significant HIV burden with growing health issues concerning CVD, little is known about CVD in Asian PLHIV [14]. Since the prevalence of atherosclerosis varies according to ethnicity and region, building local epidemiologic data is a key step to updating guidelines [15]. Furthermore, as ART has become the generalized treatment for HIV/AIDS, cumulative data regarding atherosclerosis are needed on PLHIV who have received long-term ART. In this study, we aimed to compare the clinical characteristics of PLHIV in Korea according to their carotid IMT values and clarify the risk factors for subclinical atherosclerosis in PLHIV.

MATERIALS AND METHODS

1. Study population and design

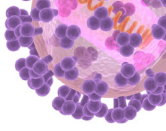
This cross-sectional, retrospective cohort study compared clinical information between two groups: PLHIV with subclinical atherosclerosis and PLHIV with IMT within the normal range. Due to the increased risk for CVD, carotid IMT measurement was performed as part of a routine clinical treatment plan for PLHIV at a 730-bed teaching hospital in Seoul, Korea. Among them, PLHIV who underwent carotid IMT measurement between January 2017 and January 2020 were included in the retrospective analysis. All of the individuals included in our study were over 18 years of age.

2. Ethics statement

The study protocol was approved by the institutional review board (IRB) of Soonchunhyang University Seoul Hospital (IRB No. 2019-11-033). The need for patient consent was waived due to the retrospective nature of the study, and the risk posed to the participants was considered negligible compared to the potential public health benefits it may provide.

3. Data collection

We collected data on demographic characteristics such as age, sex, smoking history, and body mass index (BMI), as well as each individual’s history of underlying diseases and opportunistic infections. The duration of HIV infection was calculated in months. We also collected laboratory findings including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, creatinine, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Dyslipidemia was defined as having levels of total cholesterol ≥ 240 mg/dL, LDL cholesterol ≥ 160 mg/dL, or HDL cholesterol < 40 mg/dL in blood samples; or those receiving lipid-lowering therapy. We recorded the nadir CD4⁺ T cell count of each individual, along with the CD4⁺ T cell count and HIV RNA level checked closest to the time of



IMT measurement (within 3 months). Individuals were considered to have AIDS if they had a CD4⁺ T cell count <200 cells/mm³ or any one of the AIDS-defining conditions [16] at any time before data collection. We recorded the current ART regimen at the time of IMT measurement, and specified the medications into groups based on 3 core agents: integrase inhibitors (INI), protease inhibitors (PI), and non-nucleoside reverse transcriptase inhibitors (NNRTI).

4. Intima-media thickness measurement

IMT measurement was performed as part of the recommended evaluation for all PLHIV attending the hospital's HIV/AIDS clinic. IMT was defined as the distance between the media-adventitia interface and the intima-lumen interface using the longitudinal view by ultrasound. Trained cardiologists measured IMT at a plaque-free area of the distal common carotid artery using automated software and a high-resolution B-mode ultrasound (EPIQ 5C or IE 33 ultrasound systems, Philips, Andover, MA, USA) equipped with an 11.0 MHz linear array transducer. The cardiologists measured both the right and left carotid IMTs, and selected the larger value. The normal range of IMT was defined as <0.8 mm, and values ≥0.8 mm were considered as increased IMT. Subclinical atherosclerosis was defined as either increased IMT or the presence of abnormal plaques in the carotid artery.

5. Statistical analysis

The Welch's *t*-test or Mann-Whitney test was used to compare continuous variables, while the Chi-square test or Fisher's exact test was used for categorical variables, as appropriate. A multivariable logistic regression model was designed using the variables that were different between the two groups (age, dyslipidemia, hypertension, total cholesterol, ESR, and HIV duration). In order to determine the cut-off value for predicting subclinical atherosclerosis, we calculated receiver operating characteristic (ROC) curves for age and HIV infection duration. Subsequently, we designed another binary logistic regression model as a subgroup analysis based on the age of 40 years. All tests were two-sided, and a *P*-value <0.05 was considered significant. All statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA).

RESULTS

A total of 298 PLHIV visited the clinic during the study period. Seventy-three patients who did not undergo carotid IMT measurement were excluded, as well as 8 who were previously diagnosed with CVD. Thus, we included a total of 217 individuals in the final analysis. Among them, 211 (97.2%) were male, and the mean age was 40.5 ± 10.8 years. The median HIV infection duration was 67.7 months (interquartile range [IQR]: 38.2 - 101.2 months), and 91 participants (41.9%) experienced AIDS. IMT screening detected 115 patients (53.0%) with subclinical atherosclerosis.

The clinical characteristics of the subclinical atherosclerosis group and the control group are compared in **Table 1**. The mean age was significantly higher in the subclinical atherosclerosis group (45.4 vs. 35.1 years, *P* < 0.001), and 32.2% had hypertension, compared to 19.6% in the control group (*P* = 0.04). The proportion of individuals with dyslipidemia was also significantly higher in the subclinical atherosclerosis group (55.7% vs. 16.7%, *P* < 0.001), as well as the proportion of patients who were on lipid-lowering agents at the time of IMT measurement (21.7% vs. 9.8%, *P* = 0.02). There were no significant differences in the proportion of PLHIV with diabetes mellitus, osteoporosis, or chronic hepatitis B or C between the two groups. The median duration of HIV infection was 74.3 months (IQR: 41.1 - 118.1 months) in the subclinical atherosclerosis group, as compared to the control group, which had a median duration of 57.1

Table 1. Clinical characteristics and laboratory findings of people living with HIV according to carotid IMT levels

	Total (n = 217)	Subclinical atherosclerosis (n = 115)	Normal IMT (n = 102)	P-value
Age (years)	40.5 ± 10.8	45.4 ± 10.9	35.1 ± 7.7	<0.001
Male	211 (97.2)	110 (95.7)	101 (99.0)	0.22
BMI (kg/m ²)	23.8 ± 3.2	24.1 ± 3.3	23.6 ± 3.2	0.30
Smoking history	125 (57.6)	66 (57.4)	59 (57.8)	0.95
Underlying diseases				
Hypertension	57 (26.3)	37 (32.2)	20 (19.6)	0.04
Diabetes mellitus	14 (6.5)	10 (8.7)	4 (3.9)	0.18
Dyslipidemia	81 (37.3)	64 (55.7)	17 (16.7)	<0.001
Lipid-lowering agent use	35 (16.1)	25 (21.7)	10 (9.8)	0.02
Osteopenia or osteoporosis	102 (47.0)	55 (47.8)	47 (46.1)	0.80
Chronic hepatitis B or C	10 (4.6)	8 (7.0)	2 (2.0)	0.11
HIV infection duration (months)	67.7 (38.2 - 101.2)	74.3 (41.1 - 118.1)	57.1 (33.9 - 88.6)	0.04
CD4 ⁺ T cell count (cells/mm ³)	654.0 (468.0 - 839.8)	680.0 (471.3 - 865.0)	622.5 (468.0 - 805.3)	0.21
Nadir CD4 ⁺ T cell count (cells/mm ³)	255.0 (145.0 - 361.0)	220.0 (129.0 - 361.5)	260.0 (177.5 - 358.0)	0.63
AIDS diagnosis	91 (41.9)	55 (47.8)	36 (35.3)	0.06
HIV RNA <200 copies/mL	199 (91.7)	104 (90.4)	95 (93.1)	0.47
Laboratory findings				
Total cholesterol (mg/dL)	185.4 ± 37.7	190.2 ± 37.1	180.0 ± 37.6	0.047
LDL (mg/dL)	118.3 ± 35.5	122.1 ± 37.0	114.0 ± 33.1	0.10
HDL (mg/dL)	50.7 ± 12.4	49.5 ± 13.7	52.1 ± 10.7	0.11
Glucose (mg/dL)	109.0 ± 39.7	111.2 ± 33.2	106.5 ± 45.7	0.39
Creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	0.64
C-reactive protein (mg/dL)	0.1 (0.0 - 0.2)	0.1 (0.0 - 0.2)	0.1 (0.0 - 0.1)	0.94
ESR (mm/h)	21.0 ± 19.8	24.4 ± 21.6	17.2 ± 16.8	0.007
Medication				
INI	193 (88.9)	102 (88.7)	91 (89.2)	0.90
PI	24 (11.1)	13 (11.3)	11 (10.8)	0.90
NNRTI	11 (5.1)	5 (4.3)	6 (5.9)	0.76

Data are expressed as mean ± standard deviation, median (interquartile range), or number (%).

HIV, human immunodeficiency virus; IMT, intima-media thickness; BMI, body mass index; AIDS, acquired immunodeficiency syndrome; RNA, ribonucleic acid; LDL, low density lipoprotein; HDL, high density lipoprotein; ESR, erythrocyte sedimentation rate; INI, integrase inhibitors; PI, protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors.

months (IQR: 33.9 - 88.6 months; $P = 0.04$). There were no significant differences in the nadir and most recent CD4⁺ T cell counts between the two groups.

Total cholesterol was found to be higher in the subclinical atherosclerosis group (190.2 ± 37.1 vs. 180.0 ± 37.6 mg/dL, $P = 0.047$). ESR was also significantly higher in the subclinical atherosclerosis group (24.4 ± 21.6 vs. 17.2 ± 16.8 mm/h, $P = 0.007$), although there was no significant difference in CRP levels between the two groups. The antiretroviral medications used in both groups were similar, regardless of whether the patients were administered INIs, PIs, or NNRTIs.

Age and dyslipidemia were found to be significant in the univariable logistic regression analysis (odds ratio [OR]: for age 1.13, 95% confidence interval [CI]: 1.09 - 1.17, $P < 0.001$; OR for dyslipidemia 6.28, 95% CI: 3.32 - 11.87, $P < 0.001$, respectively), and we thus designed a multivariable logistic regression model using the variables that were significantly different between the two groups. In the multivariable logistic regression model, age and dyslipidemia were still associated with subclinical atherosclerosis after adjustment for other conventional risk factors (OR for age 1.11, 95% CI: 1.06 - 1.15, $P < 0.001$; OR for dyslipidemia 3.92, 95% CI: 1.87 - 8.22, $P < 0.001$, respectively; **Table 2**). ROC curves for age and HIV infection duration were plotted in order to determine the cut-off value of age for predicting subclinical atherosclerosis (**Fig. 1**). The cut-off value for age was 39.5 years, with the area under the curve (AUC) calculated to be 0.78 (95% CI: 0.72 - 0.84, $P < 0.001$).

Table 2. Multivariable logistic regression model for identifying risk factors for subclinical atherosclerosis

	Odds ratio	95% confidence interval	P-value
Age	1.11	1.06 - 1.15	<0.001
Dyslipidemia	3.92	1.87 - 8.22	<0.001
Hypertension	0.99	0.45 - 2.18	0.98
HIV infection duration	1.00	0.99 - 1.01	0.78
ESR	1.01	0.99 - 1.03	0.26
Total cholesterol	1.00	0.99 - 1.01	0.83

HIV, human immunodeficiency virus; ESR, erythrocyte sedimentation rate.

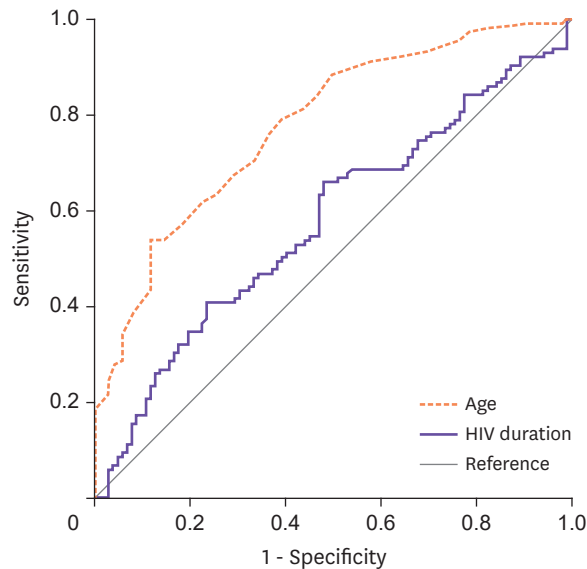


Figure 1. ROC curves of age and HIV infection duration for the prediction of subclinical atherosclerosis. The area under the ROC curve for age and HIV infection duration was 0.78 (95% CI: 0.72 - 0.84, $P < 0.001$) and 0.58 (95% CI: 0.50 - 0.65, $P = 0.052$), respectively. The cut-off value for age was 39.5 years.

ROC, receiver operating characteristic; HIV, human immunodeficiency virus; CI, confidence interval.

In the subgroup analysis of risk factors for subclinical atherosclerosis based on the age of 40 years, dyslipidemia was still significantly associated with subclinical atherosclerosis in both groups, but the association was stronger in the group aged <40 years than in the group aged ≥ 40 years (OR: 9.73, 95% CI: 3.03 - 31.27, $P < 0.001$; OR: 3.35, 95% CI: 1.22 - 9.22, $P = 0.02$, respectively; **Table 3**).

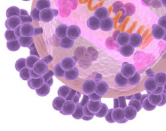
DISCUSSION

Age is an important risk factor in CVD, but the exact cut-off age remains unclear. In previous studies, study populations were either in their 40s or older, or 50s or older [10, 17]. In the 2019 update on the management of CVD in PLHIV, screening is recommended for those who are

Table 3. Subgroup analysis of risk factors for subclinical atherosclerosis based on age 40

	Age <40 years (n = 109)			Age ≥ 40 years (n = 108)		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Dyslipidemia	9.73	3.03 - 31.27	<0.001	3.35	1.22 - 9.22	0.02
Hypertension	2.69	0.88 - 8.29	0.08	0.48	0.16 - 1.41	0.18
HIV infection duration	1.01	1.00 - 1.02	0.24	1.00	0.99 - 1.01	0.92
ESR	1.01	1.00 - 1.03	0.32	1.02	0.99 - 1.05	0.13
Total cholesterol	1.01	0.99 - 1.02	0.26	1.00	0.99 - 1.01	0.85

HIV, human immunodeficiency virus; ESR, erythrocyte sedimentation rate.



over 40 and at risk for developing CVD [18]. However, our study showed that age ≥ 40 years was independently associated with atherosclerosis. Atherosclerosis is often diagnosed belatedly with the occurrence of an irreversible major cardiovascular event because of its asymptomatic nature during the early phase. Early diagnosis and statin therapy are associated with significant changes in the rate of disease progression, and thus may reduce the risk of acute cardiovascular events [19]. Therefore, even if there are no other risk factors, it is advisable to monitor the development of atherosclerosis in PLHIV over 40 years of age. Our subgroup analysis showed that the association between dyslipidemia and subclinical atherosclerosis was weakened in patients over the age of 40. In addition to the results of the ROC curve analysis, these findings indicate that age, which is an easily obtained indicator in the clinical setting, can be used to predict subclinical atherosclerosis and recommend screening in Asian PLHIV.

The results from our study showed the cut-off age for predicting subclinical atherosclerosis to be 39.5 years. This may be supporting evidence for routine carotid IMT screening of PLHIV over this age. This is approximately 5 years earlier than the guidelines on noninvasive screening of subclinical atherosclerosis in the general population (45 - 75 years in men, and 55 - 75 years in women) [9]. Initiating statin therapy based on high-risk subclinical atherosclerosis results in a relative risk reduction of 35.0%, and thus, an average of 0.58 years of life are saved compared to patients screened using only traditional risk factors such as the Framingham Risk Score [9].

The prevalence of subclinical atherosclerosis in PLHIV included in this study was higher than the prevalence of carotid atherosclerosis in the general population, which is approximately 25.4% in men and 26.4% in women [20]. Since a higher prevalence was found in Asians, in whom atherosclerosis is less noticeable than in other races [15], these results may be applicable in other races as well.

While there is scant knowledge on HIV-associated atherosclerosis in Korea, one previous study described the clinical factors associated with atherosclerosis among 145 PLHIV in Korea [21]. In their cohort, 23.4% of the participants had carotid plaques, while our study showed approximately 53.0% to have subclinical atherosclerosis. In addition to the difference in the definitions of abnormal IMT, the gap in the prevalence of abnormal IMT is likely due to the relatively longer HIV infection duration (67.7 *vs.* 53.0 months) or the higher total cholesterol levels of the patients in our study.

While the proportion of PLHIV with AIDS was not significantly different between the two groups, further analysis showed that PLHIV with AIDS were older (44.4 *vs.* 37.8 years, $P < 0.001$), and had a longer HIV duration (84.6 *vs.* 67.0 months, $P = 0.008$) than those without. This is likely associated with the fact that since 2013, PLHIV in Korea have been treated with ART regardless of their CD4⁺ T cell counts.

This study has limitations stemming from its retrospective nature. First, we could not compare the results based on sex, because most of our subjects were men. This result is consistent with the fact that approximately 90.9% of PLHIV in Korea are men [22]. However, monitoring for atherosclerosis in women is still necessary because more than 30% of female PLHIV in Korea are over 50 years old [23], and conventional risk factors alone are reported to be insufficient to detect atherosclerosis in women [24]. Second, this study could not reflect further changes in treatment over time. Certain ART medications, such as some PIs or abacavir, are reported to be associated with premature carotid lesions [25-27]. This study did not show any significant association regardless of the ART category. There could

be a bias since physicians tend to avoid medications with potential cardiovascular risks in patients with conventional risk factors. Also, the size of the study population may have been insufficient to show a meaningful comparison regarding this issue.

In conclusion, this study suggests that older age and dyslipidemia are significantly associated with subclinical atherosclerosis in PLHIV. PLHIV over 39.5 years of age have an increased risk of subclinical atherosclerosis and may benefit from carotid IMT screening regardless of conventional risk factors. Since dyslipidemia is strongly associated with subclinical atherosclerosis in PLHIV aged <40 years, carotid IMT screening might also be considered in younger PLHIV with dyslipidemia.

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