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Coronary artery stenosis in Japanese people living with HIV-1 with or without haemophilia

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Abstract: An extremely high prevalence (12.2%) of moderate-to-severe coronary artery stenosis (CAS) was documented in asymptomatic Japanese haemophiliacs living with HIV-1 (JHLH) in our previous study. The cause of this phenomenon remains unknown. We conducted the CAS screening in people living with HIV-1 without haemophilia (PLWH without haemophilia) to compare the prevalence of CAS in JHLH and PLWH without haemophilia and to identify the risk factors including inflammation markers. Ninety-seven age-matched male PLWH without haemophilia who consulted our outpatient clinic between June and July 2021 were randomly selected, and 69 patients who provided informed consent were screened for CAS using coronary computed tomography angiography (CCTA). The number of JHLH cases was 62 in this study. The prevalence of moderate (> 50%) to severe (> 75%) CAS was significantly higher in JHLH [14/57 (24.6%) *vs.* 6/69 (8.7%), $p = 0.015$], and the ratio of CAS requiring urgent interventions was significantly higher [7 (12.3%) *vs.* 1 (1.4%), $p = 0.013$] in JHLH than in PLWH without haemophilia. Among the inflammatory markers, serum titres of intercellular adhesion molecule-1 ($p < 0.05$) and interleukin-6 ($p < 0.05$) in JHLH were significantly higher than those in PLWH without haemophilia. Although some patient demographics were different in the age-matched study, it might be possible to speculate that intravascular inflammation might promote CAS in JHLH.

Keywords: HIV, haemophilia, coronary artery stenosis, coronary computed tomography, Japanese

Introduction

Generally, HIV-infected patients have higher mortality rates due to ischaemic heart disease compared with the general population (*1*). In our previous study, coronary artery stenosis (CAS) screening was performed using coronary computed tomography angiography (CCTA) in 57 almost asymptomatic Japanese haemophiliacs living with HIV-1 (JHLH), with an average age of 47 years (*2*). The study documented that seven patients (12.2%) had severe CAS that required urgent interventions. Five patients underwent percutaneous coronary intervention (PCI), while one patient underwent coronary artery bypass graft surgery (CABG). One patient refused any coronary intervention. The prevalence of CAS was unexpectedly high, suggesting an unknown aetiology that caused CAS in JHLH.

This prevalence was higher than that generally reported for HIV-1-infected patients. The possibility that the presence of haemophilia may have contributed to this higher prevalence was hypothesized. Studies on haemophiliacs without HIV-1 infection and people living with HIV-1 (PLWH without haemophilia) without haemophilia will clarify this issue. In this study, we examined PLWH without haemophilia because we did not encounter haemophiliacs without HIV-1 infection in our clinic. We performed the same screening tests on the asymptomatic randomly selected age-matched male PLWH without haemophilia because all the JHLH in the previous study were male and the results were compared with those of the previous study. Inflammatory markers, such as interleukin-6 (IL-6), highly sensitive C-reactive protein (hs-CRP), and D-dimer, have been reported to be associated with increased CAS risk in HIV-infected patients (*3*). We hypothesized that JHLH shows more severe coronary ischemic lesions with high levels of inflammatory markers.

Patients and Methods

Patients

Ninety-seven, age-matched male PLWH without haemophilia were selected at our outpatient clinic

between June and July 2021 and asked to participate in the study. They had no symptoms suggestive of ischemic heart disease, such as chest pain on exertion or at rest. Sixty-nine patients provided informed consent and underwent CAS screening using CCTA. The median age of patients who participated during the period was 47 years (range, 35–68). JHLH was the 57 participants in the previous study their median age of the participants was 47 years (range, 36–69 years) (Table 1).

Data collection

The CAS screening study included medical interviews, blood tests for inflammatory markers, physiological function tests, and CCTA. The medical interview included information on age, height, weight, history of hypertension, diabetes, dyslipidaemia, medications, smoking history, alcohol consumption history, history of cerebral and cardiovascular disease (CVD), allergies, and family history. Blood laboratory tests included biochemistry, blood counts, nadir and current CD4 lymphocyte counts, coagulation markers including fibrinogen and D-dimer, and inflammatory markers including hs-CRP, tumour necrosis factor-a (TNF-α), intercellular adhesion molecule-1 (ICAM-1), and IL-6. Coagulation and inflammatory markers were measured using frozen stored serum obtained from the 57 JHLH who participated in the previous study. Physiological function tests, such as electrocardiography, echocardiography, and pulse wave velocity (PWV) testing (Omron Healthcare, Kyoto, Japan) were performed in the physiological function testing laboratory. The laboratory has obtained ISO 15189 certification.

Diagnosis of CAS by CCTA and coronary angiography

Patients considered to have no severe renal dysfunction or allergy to the contrast agent underwent CCTA with 320-row multidetector computed tomography angiography (Aquilion ONE, Canon Medical System, Otawara, Japan). In CCTA, CAS is judged by visual appearance. If the coronary artery was 50–69% stenosed in appearance, it was considered as moderate, and if it was 70% or more stenosed, it was considered as severe (*4*). The result was evaluated by a cardiologist and radiologists with expertise in image reading.

Patients with moderate or greater stenosis on CCTA underwent coronary angiography (CAG). Generally, a stenosis of more than 75% at CAG is considered significant stenosis. If CAG showed stenosis of 75% or greater, evaluation of intravascular pressure measurements was performed if necessary to determine the appropriate indication for treatment (*5*). Then appropriate treatment such as PCI or CABG was performed. If those patients refused to undergo CAG, we performed myocardial perfusion scintigraphy to evaluate cardiovascular blood flow.

Classification of coronary artery calcium score

The coronary artery calcium score (CACS) was weighted by CT value as the cross-sectional area according to Agatston *et al.* (*6*). Based on previous study, CACS was classified into five categories: no calcification (score =

Table 1. Comparison of patient demographics between JHLH and PLWH without haemophilia

Demographics and variables	JHLH (*n* = 57)	PLWH without haemophilia (*n* = 69)	*p*
Age, median year (range)	47 (36–69)	47 (35–68)	0.62
BMI kg/m^2, median (IQR)	23.0 (22.0–25.0)	25.1 (22.3–27.7)	< 0.05
CAS risk factors			
SUITA score, median (IQR)	38 (31–45)	38 (31–45.5)	0.91
Smoking history, *n* (%)	30 (52.6)	43 (62.3)	0.24
Hypertension, *n* (%)	24 (42.1)	8 (11.6)	< 0.05
Diabetes mellitus, *n* (%)	8 (14.0)	2 (9.3)	< 0.05
Dyslipidaemia, *n* (%)	22 (38.6)	41 (59.4)	< 0.05
Family history of CAS, *n* (%)	13 (22.8)	12 (17.4)	0.45
LVEF, % (IQR)	65.0 (62.0–68.0)	64.3 (61.5–66.1)	0.23
PWV cm/sec, median (IQR)	1,512 (1,396–1,631)	1355 (1230–1474)	< 0.05
HIV-related indicators			
Nadir CD4/μL, median (IQR)	129 (74–175)	194 (109–277)	< 0.05
Current CD4/μL, median (IQR)	457 (370–627)	587 (482–723)	< 0.05
Duration of undetectable VL, median year (IQR)	16.1 (11.8–17.7)	9.3 (5.5–13.0)	< 0.05
Duration of treatment for HIV, median year	25 (22–28)	11 (7–15.5)	< 0.05
Duration of PI use, median year (IQR)	10 (3–17)	2 (0–7)	< 0.05
Duration of d-drug use, median year (IQR)	6 (1–9)	0 (0–0)	< 0.05
Hepatitis B, *n* (%)	6 (10.5)	36 (52.2)	< 0.05
Hepatitis C, *n* (%)	55 (96.5)	4 (5.8)	< 0.05
Treponema pallidum, *n* (%)	0 (0)	34 (49.3)	< 0.05

JHLH, Japanese haemophiliacs living with HIV-1; PLWH without haemophilia, Japanese people living with HIV-1; BMI, body mass index; CAS, coronary artery stenosis; *n*, number of patients; IQR, interquartile range; LVEF, left ventricular ejection fraction; PWV, pulse wave velocity; VL, plasma viral load; PI, protease inhibitor; d-drug, any of didanosine (ddI), zalcitabine (ddC), and stavudine (d4T).

0), minimal risk (score: 1–10), low risk (score: 11–100), moderate risk (score: 101–400), and high risk (score > 400) (*7,8*). It is reported that as CACS increases, cardiovascular events also increase (*9,10*). In particular, a cardiovascular event rate of 1.5% per year was reported for CACS of 100 or higher (*11*).

Statistical analysis

Categorical and continuous variables were evaluated using the Mann–Whitney *U* test, and categorical variables were evaluated using Fisher's exact test. *P*-values were two-sided, and a significance level of $p < 0.05$ was used. Odds ratios (OR) are presented with 95% confidence intervals (95% CI). The inflammatory markers in both groups were compared using a two-sample *t*-test. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS version 26, SPSS Inc., Chicago, IL).

Ethics statement

The study protocol was reviewed and approved by the Human Ethics Committee of the National Centre for Global Health and Medicine (NCGM) (#NCGM-G-003468-01) on 9 April 2021. Written informed consent was obtained from all participants at study entry in accordance with the Declaration of Helsinki. This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (registry number #UMIN000044328).

Data availability statement

This study was registered with the UMIN ---(#UMIN 000044328), and the previous study with the registry (#UMIN 000035307).

Results

CAS study in JHLH and PLWH without haemophilia

Among the 69 PLWH without haemophilia who underwent CCTA, six patients (8.7%) had moderate-to-severe CAS (Figure 1A). Among the six patients, four patients further underwent CAG, and severe stenosis was found in one patient (1.4%) who underwent PCI after CAG. Two patients underwent cardiac perfusion scintigraphy instead because they refused to undergo CAG. The scintigraphy showed that there were no perfusion defects. Fourteen of 57 JHLH (24.6%) who underwent CCTA was found moderate-to-severe CAS. Twelve of the 15 patients underwent CAG, and seven had significant stenosis requiring treatment. Five patients underwent PCI, and one underwent CABG (one refused both PCI and CABG) (Figure 1B) (*2*).

In patients who underwent PCI, intravascular characteristics were confirmed by intravascular ultrasound (IVUS) or optical frequency domain imaging (OFDI). In JHLH, three patients had fibrocalcific plaque lesions and the other two patients had lipid plaques. The one patient who underwent PCI for PLWH without haemophilia had a fibrocalcific plaque lesion.

JHLH has decreased or defective blood coagulation ability, and bleeding complications caused by antiplatelet drugs are a major problem. In this study, blood products were adjusted, and attention was paid to bleeding complications during dual antiplatelet therapy. No cases of major bleeding complications in the perioperative period were observed.

Comparison of patient demographics between JHLH and PLWH without haemophilia

Table 1 shows the patient demographics of the two age-matched groups. Regarding CAS risk factors, no significant differences existed in smoking or family history. Hypertension and diabetes mellitus were significantly higher in the JHLH group, whereas dyslipidaemia was significantly higher in the PLWH without haemophilia group. Additionally, the PWV in JHLH was significantly higher than that in PLWH without haemophilia, indicating that arteriosclerosis was more advanced in JHLH (Figure 2). However, there was no significant difference in the Suita score in predicting CVD in healthy Japanese subjects (*12*). As for HIV-1-related indicators, nadir CD4 and current CD4 were significantly lower in JHLH than in PLWH without haemophilia. The duration of HIV-1 treatment and undetectable viral load (VL) of JHLH were longer than those of PLWH without haemophilia, indicating a longer history of HIV infection. Regarding HIV treatment-related issues, the duration of protease inhibitor (PI) and d-drug use was longer in JHLH than in PLWH without haemophilia. The higher rates of hepatitis B and C infections in JHLH might have been caused by frequent transfusions of blood products before 1986 (*13*). Generally, in the two age-matched groups, HIV-related indicators were favourable to PLWH without haemophilia, whereas CAS risk factors varied and did not have a favourable tendency in either group.

Comparison of CAS studies between JHLH and PLWH without haemophilia

Table 2 presents a comparison of CAS studies between the two groups. The ratio of moderate-to-severe CAS on CCTA in the JHLH group (24.6%) was significantly higher ($p = 0.015$, OR [95% CI]: 3.42 [1.22, 9.60]) than that in the PLWH without haemophilia group (8.7%). The ratio of severe stenosis requiring urgent interventions in the JHLH group (12.3%) was also significantly higher ($p = 0.013$, OR [95% CI]: 9.52 [1.14, 79.86]) than that in the PLWH without haemophilia group (1.4%). At

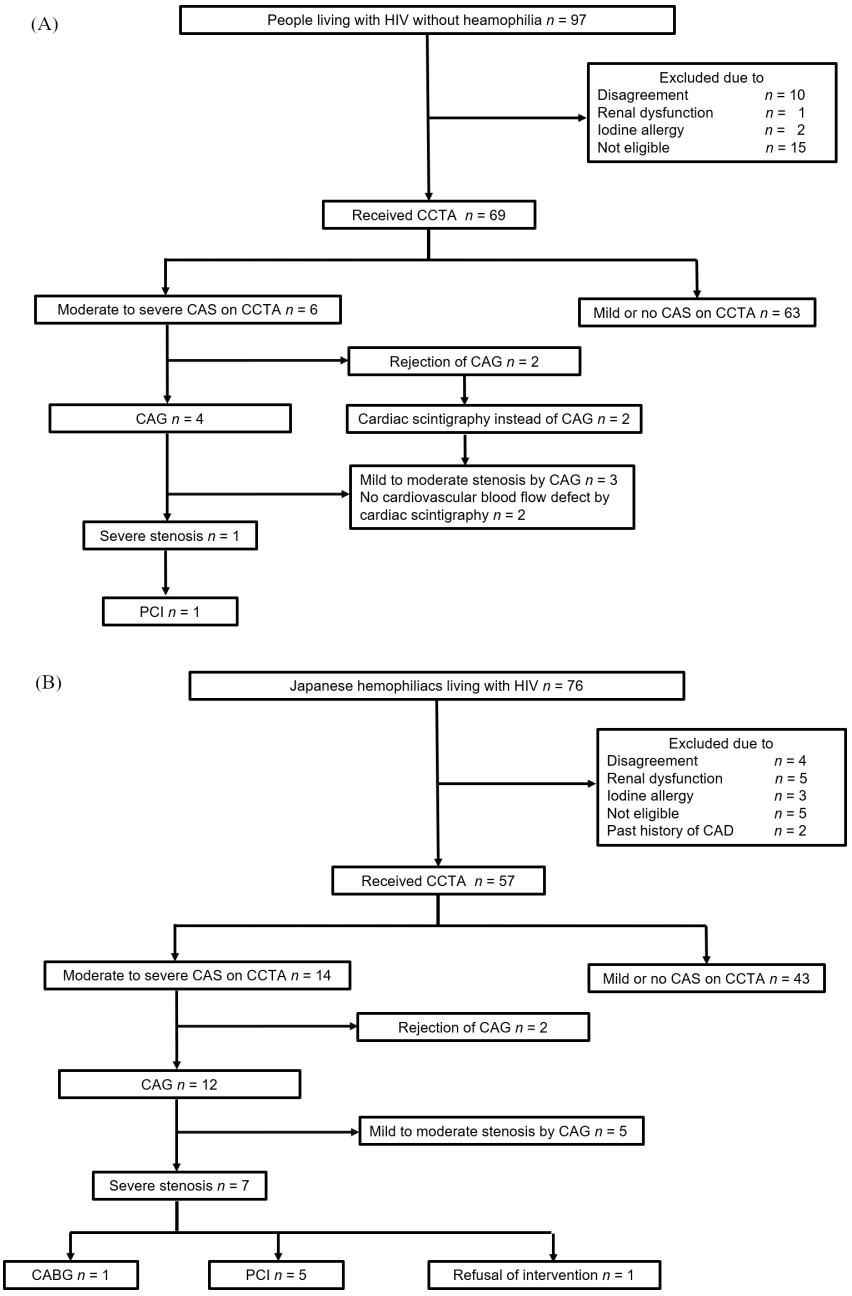

Figure 1. Study flow and patient selection. (A) Ninety-seven age- and gender-matched Japanese non-haemophiliacs living with HIV-1 in the previous study were randomly selected at AIDS Clinical Centre (ACC), National Centre for Global Health and Medicine, Tokyo, Japan. Among them, 69 patients gave written informed consent and received CCTA. If moderate-to-severe CAS were suspected on CCTA, CAG or cardiac perfusion scintigraphy was performed. Patients with severe stenosis who required urgent treatment underwent PCI. **(B)** After completion of the previous study, 11 new Japanese haemophiliacs living with HIV-1 (JHLH) consulted ACC. Subsequently, there were 87 JHLH in ACC during the study. Among them, five additional cases participated in the study and received CCTA. Thus, 62 cases received CCTA in JHLH. CCTA, coronary computed tomography angiography; CAS, coronary artery stenosis; CAG, coronary angiography; PCI, percutaneous coronary intervention.

this step, the prevalence of CAS in the JHLH group was higher than that in the PLWH without haemophilia group.

CACS were classified as follows: No classification (0) 33 (57.9%) *vs.* 53 (76.8%), Minimal risk (1–10) 6 (17.5%) *vs.* 1 (1.4%), Low risk (11–100) 10 (17.5%) *vs.* 6 (8 .7%), Moderate risk (101–400) and High risk (> 400) were 4 (7.0%) *vs.* 1 (1.4%). The rate of CACS of 101 or greater, which meant a moderate to high risk of CVD, did not differ between the two groups.

Comparison of coagulation factors and intravascular inflammation markers between the JHLH and PLWH without haemophilia

We measured coagulation factors and inflammatory markers in both groups. The levels of fibrinogen and D-dimer did not show any significant difference between the two groups (Table 3). The levels of the inflammatory markers IL-6 ($p < 0.05$) and ICAM-1 ($p < 0.05$) were significantly higher in JHLH than in PLWH

without haemophilia indicating higher intravascular inflammation in JHLH.

Discussion

This study demonstrated that the prevalence of CAS in JHLH was significantly higher than that in PLWH without haemophilia, indicating that JHLH had a higher risk of CVD compared with PLWH without haemophilia, namely HIV-1 infected individuals. Generally, only HIV-1 infection is associated with a high prevalence of CVD (*14*). The incidence of acute myocardial infarction in Japanese men has been reported to be 0.3–0.6/1,000 person-years (PY) in one study (*15*) while another reported a rate of 0.12–2.56/1,000 PY in middle-aged men (*16*). Triant *et al.* (*17*) reported that the incidence of acute myocardial infarction in HIV-1 patients was significantly higher at 11.13/1,000 PY than at 6.98/1,000 PY in non-HIV-1 patients. This is possibly because of high intravascular inflammation in this population (*18,19*). The SMART

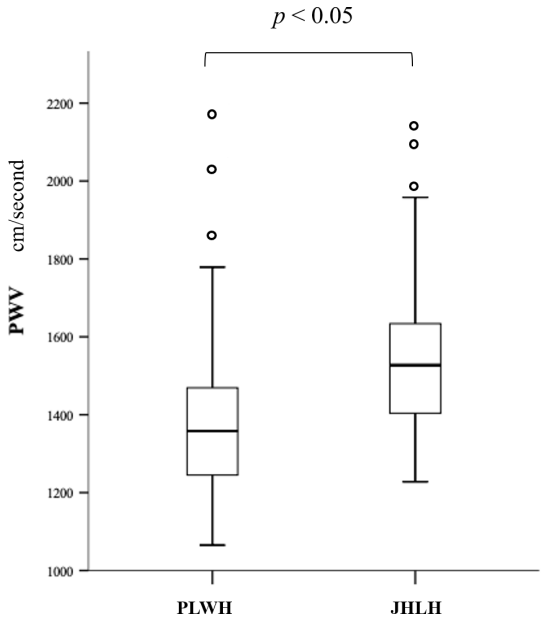

Figure 2. Box plot of PWV. PWV was measured in PLWH without haemophilia in this study, and the results were compared with those of JHLH in the previous study. PWV, pulse wave velocity; JHLH, Japanese haemophiliacs living with HIV-1; PLWH without haemophilia, Japanese non-haemophiliacs living with HIV-1.

Table 3. Comparison of coagulation factors and inflammatory markers between JHLH and PLWH without haemophilia

Characteristics	JHLH	PLWH without haemophilia	*p*
Coagulation factor			
Fibrinogen, mean (SD) mg/mL	249.1 (66.3)	255.2 (58.7)	0.62
D-dimer, positive rate %	7 (12.3%)	4 (5.8%)	0.20
Inflammatory marker			
hs-CRP, mean (SD) mg/mL	1.43 (2.4)	1.33 (1.3)	0.98
IL-6*, mean (SD) pg/mL	4.61 (13.2)	2.10 (6.52)	< 0.05
TNF-a, mean (SD) pg/mL	0.80 (0.47)	0.68 (0.26)	0.35
ICAM-1, mean (SD) pg/mL	239.7 (86.1)	201.2 (62.9)	< 0.05

JHLH, Japanese haemophiliacs living with HIV; PLWH without haemophilia, Japanese people living with HIV-1; SD, standard deviation; hs-CRP, highly sensitive C-reactive protein, IL-6; interleukin-6, TNF-, tumour necrosis factor-; ICAM-1, intercellular adhesion molecule-1; *$\log_{10}$ transformed, was used for this analysis.

Table 2. Comparison of CAS study between JHLH and PLWH without haemophilia

Characteristics	JHLH	PLWH without haemophilia	*p*, OR (95% CI)
Receive CCTA, *n*	57	69	
Moderate to severe stenosis by CCTA	14	6	*p* = 0.015 OR 3.42 (1.22, 9.60)
Further examinations, *n*			
CAG	12	4	
Cardiac perfusion scintigraphy	0	2	
Refused further examinations	2	1	
CAS with urgent interventions required, *n* (%)	7 (12.3%)	1 (1.4%)	*p* = 0.013 OR 9.52 (1.14, 79.86)
Interventions, *n*	6	1	
PCI	5	1	
CABG	1	0	
Refused coronary intervention	1	0	
CACS greater than 100, *n* (%)	8 (14.0%)	9 (13.0%)	*p* = 0.87
Risk classification by CACS on CCTA, *n* (%)			OR 1.09 (0.39, 3.03)
High risk (> 400)	4 (7.0%)	1 (1.4%)	
Moderate risk (101–400)	4 (7.0%)	8 (11.6%)	
Low risk (11–100)	10 (17.5%)	6 (8.7%)	
Minimal risk (1–10)	6 (17.5%)	1 (1.4%)	
No classification (0)	33 (57.9%)	53 (76.8%)	

CAS, coronary artery stenosis; JHLH, Japanese haemophiliacs living with HIV-1; PLWH without haemophilia, Japanese people living with HIV-1; CCTA, coronary computed tomography angiography; *n*, number of patients; CAG, coronary angiography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; OR, odds ratio; 95%CI, 95% confidence interval; CACS, coronary artery calcification score.

study documented that intravascular inflammation caused by circulating HIV-1 in plasma plays a major role in CVD (*20*). Duprez *et al.* reported in a sub-study that inflammatory markers of hs-CRP and IL-6 in HIV-1-infected patients with CVD were higher than those without CVD [hs-CRP 3.34 mg/mL (1.47–7.51 mg/mL) and IL-6 3.07 pg/mL (1.87–4.83 pg/mL) in CVD (+), while hs-CRP 1.67 mg/mL (0.70–4.02mg/mL) and IL-6 1.72 pg/mL (1.07–2.29 pg/mL) in CVD(-)], concluding that intravascular inflammation was associated with an increased risk of CVD independent of other CVD risk factors (*3*). Notably, CVD risks in JHLH were higher than those in PLWH without haemophilia in this study. In support of this result, serum titres of IL-6 and ICAM-1 were significantly higher in JHLH than in PLWH without haemophilia. It might be possible to speculate that the regular injection of blood products induced intravascular inflammation.

Patients with haemophilia have reduced vascular endothelial function compared to the general population (*21,22*). Thus, the haemophilia-associated risks added to HIV-1 infection might increase the prevalence of CAS. The detailed mechanism is not known so far. Future study of patients with haemophilia without HIV infection will help us to understand the mechanism.

We had believed that patients with haemophilia had a low incidence of ischaemic heart disease, attributed to their bleeding tendency. Van Der Valk *et al.* reported reduced cardiovascular events in patients with haemophilia (*23*). Nagao *et al.* also reported ischemic events are rare among Japanese adults with haemophilia (*24*).

However, advances in blood coagulation products have improved life expectancy of haemophilia patients, resulting in an increased risk of CAS (*25-27*). Thus, different results have been reported on the prevalence of ischemic heart disease in haemophilia patients. The results of this study might indicate that the combination of both HIV-1 infection and haemophilia synergistically increases the prevalence of ischemic heart disease. The same study of CAS screening for non-HIV-1 infected haemophiliacs will address this speculation in the future. The use of PI has been reported to increase dyslipidaemia, which in turn increases the incidence of myocardial infarction (*28*). However, in this study, the prevalence of dyslipidaemia was significantly lower in JHLH with a longer history of PI use. The use of d-drugs, such as stavudine, has been reported to increase the risk of cardiovascular events and was used significantly longer in JHLH (*29*). Therefore, the effects of d-drugs could not be ruled out.

In this study the rate of CACS of 101 or greater, which meant a moderate to high risk of CVD, did not differ between the two groups. Therefore, it is difficult to predict CVD based on CACS alone. Some cases required treatment even with a calcification score of 0, therefore, attention should be paid not only to calcified lesions but also to plaque lesions.

We speculated that both haemophilia and HIV-1 infection (JHLH) might be responsible for the high prevalence of CAS. JHLH has significantly higher coronary risks, such as hypertension and diabetes mellitus, which may cause atherosclerosis and increase the prevalence of CAS. Additionally, hepatitis C infection rates were significantly higher in the JHLH group [13]. Hepatitis C infection has been reported to be a risk factor for CAS (*30,31*). However, there were conflicting reports (*32*), and its involvement in CAS was unknown (*33*). Therefore, in this study, the effect of hepatitis C infection could not be ruled out.

This study had some limitations. This was a single-centre study and the number of participants was limited. Although all JHLH who provided informed consent in the previous study and PLWH without haemophilia randomly selected age- and sex-matched individuals in the current study were included, participants in the two groups were significantly different in some coronary risk factors, duration of HIV-1 infection, and other viral infections. When we matched age in the two groups, differences in factors, such as the duration of HIV-1 infection and co-infection with hepatitis C could not be avoided because of the unique history of the JHLH group. If we could match CAS risk factors, such as hypertension and diabetes mellitus, to age and sex, there would be a faint possibility that we would have a different result. The lack of studies on patients with haemophilia without HIV infection is a limitation.

Conclusion

The JHLH group had a significantly higher prevalence of CAS compared with the PLWH without haemophilia group. Despite differences in some patient demographics in the age-and sex-matched studies, it has been suggested that the coexistence of haemophilia and HIV infection may have a synergistic effect, contributing to an increased prevalence of CVD. The significantly higher intravascular inflammation in JHLH might also be involved.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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