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BRIEF REPORT
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Coronary artery stenosis in Japanese hemophiliacs living with HIV-1 progressed dramatically over two years

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Abstract: Patients with hemophilia living with HIV-1 are at increased risk for coronary artery disease (CAD) due to overlapping factors, including chronic vascular inflammation, antiretroviral therapy–associated dyslipidemia, and reduced physical activity from hemophilic arthropathy. However, longitudinal data on cardiovascular outcomes in this population have been scarce. In this two-year longitudinal follow-up study, 58 patients were evaluated. The cohort was stratified into three groups based on baseline CCTA findings and treatment history: 47 with normal-to-mild stenosis, 3 with prior PCI or CABG, and 8 with moderate-to-severe stenosis. Among the moderate stenosis group, 7 underwent repeat CCTA, and 4 showed progression of coronary lesions. Of these, 3 developed severe stenosis requiring percutaneous coronary intervention (PCI), despite improvement in LDL-C through pharmacologic and lifestyle interventions. Overall, LDL-C significantly decreased ($p < 0.05$); however, pulse wave velocity (PWV), an indicator of arterial stiffness, worsened in about half of patients. In the revascularization group, PWV deterioration was significant ($p = 0.017$). Our earlier cross-sectional analysis of this population demonstrated that a considerable proportion had moderate-to-severe stenosis requiring intervention, underscoring the need for longitudinal assessment. These findings suggest that even under guideline-based cardiovascular management, there remains a considerable risk for CAD progression in HIV-infected hemophilia patients with moderate or greater stenosis. Therefore, repeat CCTA at two-year follow-up could be considered to facilitate early detection and guide timely intervention. Continuous monitoring, including imaging, and early intervention targeting modifiable risk factors may be important to reduce long-term cardiac risk in this vulnerable population.

***Keywords*:** hemophilia, HIV-1, coronary artery disease, coronary computed tomography angiography, vascular inflammation, pulse wave velocity

1. Introduction

Hemophilia and HIV-1 infection are two distinct chronic conditions affecting Japanese hemophiliacs living with HIV-1 (JHLH). Traditionally, hemophilia has been considered protective against coronary artery disease (CAD) due to the inherent hypocoagulable state (*1*). However, recent advances in treatment have significantly extended life expectancy in these individuals, and recent epidemiological studies suggest that the incidence of CAD in hemophiliacs is now comparable to that of the general male population (*2,3*). Hemophiliacs often develop joint deformities from recurrent hemarthroses, limiting activity and masking CAD until advanced stages.

In addition to the risk imposed by hemophilia, HIV infection further elevates the risk of CAD. This is attributed to chronic vascular inflammation and dyslipidemia, both of which are exacerbated by antiretroviral therapy (*4*). Thus, JHLH may represent a population at high risk of silent or rapidly progressive atherosclerosis.

In our previous Hem-IHD study conducted from December 2018 to December 2019, coronary computed tomography angiography (CCTA) identified moderate or severe coronary stenosis in 24.6% (14 of 57) of JHLH (*5*). Among the 12 patients who underwent coronary angiography (CAG), 7 required therapeutic intervention, including percutaneous coronary intervention (PCI) in 5 patients and coronary artery bypass grafting (CABG) in 1 patient. These findings raised concerns about CAD progression in this high-risk population, especially

among patients managed only with medication. Over two years have passed since initial screening, necessitating follow-up.

Despite the absence of significant stenosis in certain patients, the overall cardiovascular risk remains elevated, and ongoing risk assessment and management are crucial. While pharmacological interventions were initiated in the prior study, their long-term efficacy has not yet been systematically evaluated. Therefore, this study aims to assess the progression of CAD and the effectiveness of medical management in JHLH through longitudinal follow-up, with the goal of informing appropriate screening and intervention strategies in this vulnerable population.

2. Patients and Methods

2.1. Patients

Patients were classified into three groups: the first group included those with normal to mild stenosis; the second group included patients who had undergone PCI or CABG; and the third group comprised patients with moderate-to-severe stenosis on CCTA.

In the first group, which showed normal to mild stenosis, cardiovascular risk was assessed, and efforts were made to control modifiable risk factors. When necessary, medical therapy and lifestyle guidance were provided, and their effects evaluated. Patients with prior PCI or CABG were managed with risk factor control, and effectiveness assessed.

The third group consists of patients who were previously identified with moderate-to-severe coronary artery stenosis on CCTA and had been managed with medical therapy alone. These patients underwent follow-up CCTA and cardiovascular risk assessment. If progression was identified, appropriate treatment was given. As HIV infection promotes vascular inflammation, inflammatory biomarkers were assessed in all participants.

This exploratory study, without a predefined endpoint, aimed to observe CAD progression in JHLH under routine care over two years.

2.2. Statistical analysis

Two-year changes in LDL-C, PWV, and HbA1c were assessed using paired *t*-tests in the overall cohort (n = 58). For CACS, available in a small subset of patients (n = 7), the Wilcoxon signed-rank test was used due to the small sample size and non-normal distribution. For Table 1, baseline characteristics were compared. Continuous variables were analyzed using the Mann–Whitney *U* test. Categorical variables were compared using the chi-square test. If expected cell frequencies were < 5 in > 20% of cells, Fisher's exact test was used. Analyses were conducted using SPSS version 26 (SPSS Inc., Chicago, IL, USA). A two-sided p value of < 0.05 was considered statistically significant.

2.3. Ethical considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. The study protocol was reviewed and approved by the Ethics Committee of Japan Institute for Health Security (JIHS), and was registered under the

Table 1. Baseline characteristics of patients with normal-to-mild *vs.* moderate-to-severe stenosis or prior PCI/CABG

Demographics and variables	Normal-to-mild stenosis (n = 47)	Moderate-to-severe stenosis (n = 11)	*p-value*
Age, median year (range)	47 (42–69)	62 (53–66)	0.07
BMI kg/m^2, median (IQR)	22.9 (20.2–24.2)	24.7 (22.4–26.4)	0.19
CAD risk factors			
Smoking history, *n* (%)	22 (46.8)	5 (45.5)	1.00
Hypertension, *n* (%)	24 (51.0)	5 (45.5)	1.00
Diabetes mellitus, *n* (%)	5 (10.6)	3 (27.3)	0.17
Dyslipidaemia, *n* (%)	20 (42.6)	7 (63.6)	0.32
Family history of CAS, *n* (%)	9 (19.1)	5 (45.5)	0.11
LVEF %, median (IQR)	64.6 (61.6–67.4)	65.4 (63.7–66.2)	0.64
PWV cm/sec, median (IQR)	1,425 (1,311–1,548)	1,653 (1,329–1,921)	0.13
HIV-related indicators			
Nadir CD4/μL, median (IQR)	130 (92–162)	112 (90–188)	0.64
Current CD4/μL, median (IQR)	461 (367–582)	399 (297–542)	0.18
Duration of undetectable VL, median year (IQR)	14.5 (11.5–17.8)	15.3 (7.2–17.5)	0.64
Duration of treatment for HIV, median year (IQR)	28 (25–30)	22 (20–28)	0.63
Duration of PI use, median year (IQR)	10 (3–17)	13.5 (1.6–18)	0.47
Duration of d-drug use, median year (IQR)	5.8 (0.2–9.1)	37 (0–90.5)	0.65
Hepatitis B, *n* (%)	3 (6.4)	1 (9.1)	1.00
Hepatitis C, *n* (%)	45 (95.7)	11 (100)	1.00

Abbreviations: BMI, body mass index; CAS, coronary artery stenosis; *n*, number; IQR, interquartile range; LVEF, left ventricular ejection fraction; PWV, pulse wave velocity; VL, viral load; PI, protease inhibitor; -drug, didanosine, zalcitabine, and stavudine.

approval number [NCGM-G-004171-00].

3. Results and Discussion

3.1. Overall evaluation over two years

A total of 58 patients participated in this study. The study population consisted of 47 patients with normal-to-mild stenosis on CCTA, 3 patients who had undergone therapeutic intervention in a previous study, and 8 patients with moderate-to-severe stenosis on CCTA, of whom 7 consented to repeat CCTA (Figure 1).

Characteristics were compared between normal-to-mild (n = 47) and moderate-to-severe or PCI/CABG patients (n = 11) (Table 1). Because of the small sample sizes in the moderate-to-severe stenosis group (n = 8) and the revascularization group (n = 3), these two groups were combined for statistical analysis. Continuous variables were expressed as median (IQR), except inflammatory markers as mean ± SD. Categorical variables were presented as counts and percentages. No statistically significant differences were observed between the two groups for any of the variables. A trend toward higher age was seen in the moderate-to-severe or PCI/CABG group (p = 0.07). Cardiovascular risk in JHLH was managed over a two-year follow-up period. Patients who required medical intervention received appropriate medical treatment, while those with parameters within normal limits were managed with lifestyle interventions including exercise and dietary therapy.

No significant changes were observed in PWV or HbA1c (p = 0.35 and 0.23). For HbA1c, no consistent differences were noted across subgroups, and PWV findings varied by subgroup. A significant reduction in low-density lipoprotein cholesterol (LDL-C) was observed ($p < 0.05$) (Figure 2).

3.2. Forty-seven patients with normal to mild stenosis determined by CCTA

Among the five patients with diabetes mellitus, three demonstrated an improvement in HbA1c levels during the observation period.

LDL-C levels improved in more than half of the 47 patients (26 out of 47) following the initiation or up-titration of statins and other lipid-lowering agents (9 patients), in combination with dietary and exercise counseling. LDL-C significantly decreased from 119.8 ± 28.8 to 107.9 ± 21.5 mg/dL (p = 0.007).

In patients with hypertension, initiation or intensification of antihypertensive medications (8 patients), combined with lifestyle interventions, led to an improvement in blood pressure and a trend toward PWV reduction, from 1,499 ± 215 cm/s to 1,478 ± 268 cm/s.

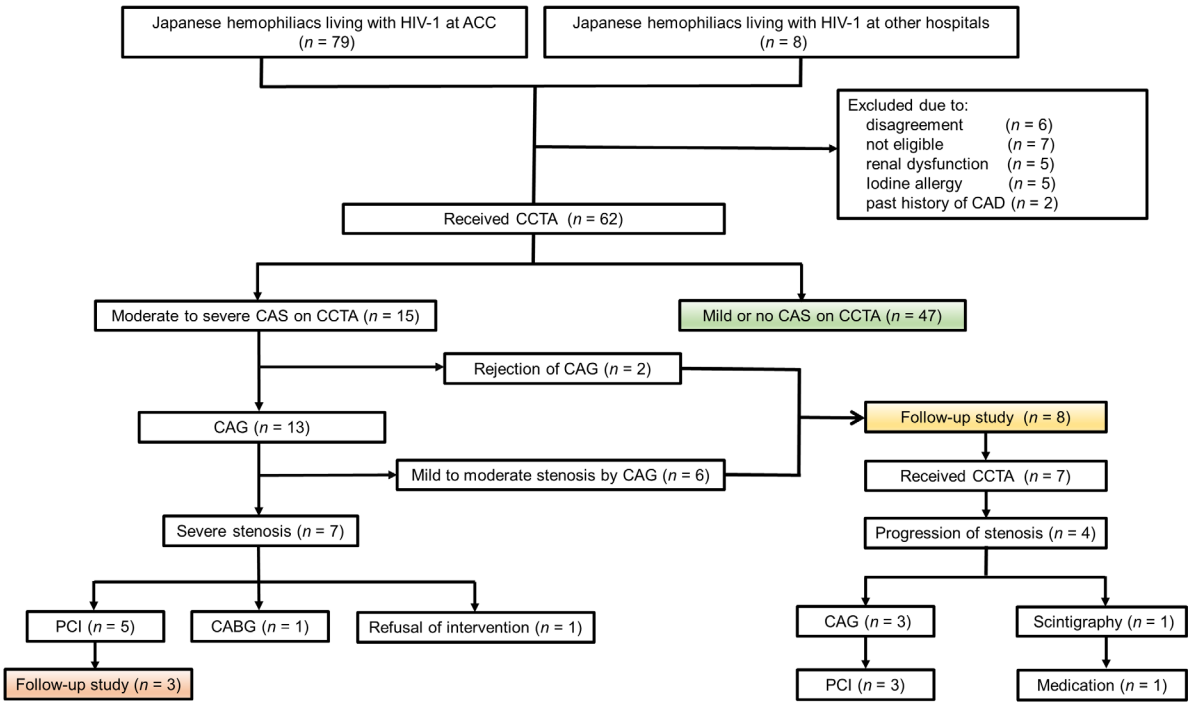

Figure 1. Study flow and patient selection. A total of 62 patients received screening tests. Of the 62 patients, 15 had moderate-to-severe stenosis at CCTA and 47 had no significant stenosis. Of the 15 patients with moderate-to-severe stenosis, 7 were determined to require treatment by CAG. Of the five patients who underwent PCI, three who gave consent participated in this study. Two patients who refused previous CAG and six patients who were not indicated for treatment also participated in this study. A total of 58 patients participated in the current 2-year follow-up. *Abbreviations*: CCTA, coronary computed tomography angiography; CAG, coronary angiography; PCI, percutaneous coronary intervention.

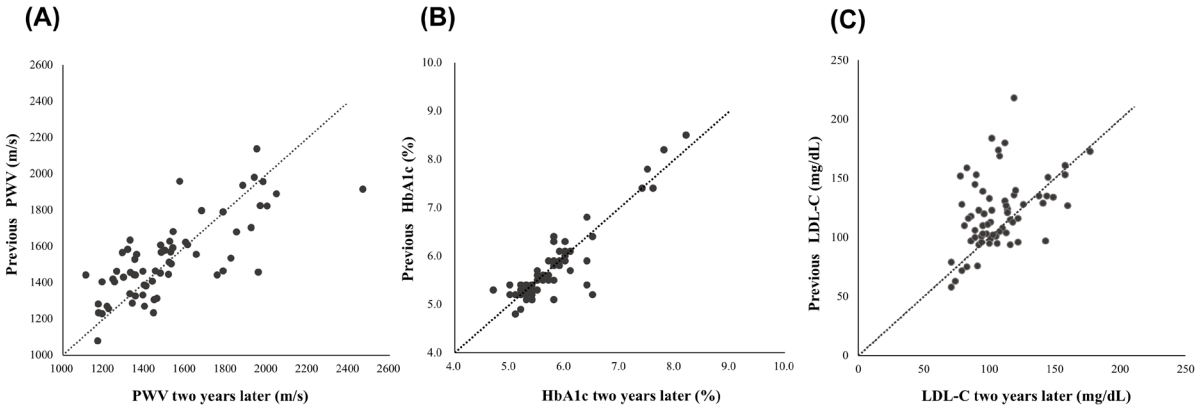

Figure 2. Scatter plot of PWV, HbA1c and LDL-C in 58 patients. (A) Scatter plot of PWV and **(B)** scatter plot of HbA1c, both showing no significant differences between the previous and current measurements; **(C)** Scatter plot of LDL-C, demonstrating a significant difference between the previous and current measurements. Scatter plots of PWV, HbA1c and LDL-C were created with previous values on the Y-axis and current values on the X-axis. Data points plotted to the left of the line of identity (Y = X) indicate improvement (decrease compared with baseline), while those to the right indicate worsening (increase compared with baseline). *Abbreviation*: PWV, pulse wave velocity.

3.3. Three patients who had undergone revascularization

In two patients who had undergone PCI in a previous study, follow-up coronary angiography at six months confirmed successful revascularization. The duration of dual antiplatelet therapy (DAPT) following drug-eluting stent (DES) implantation was approximately one month, with no reported bleeding complications associated with antiplatelet use. In patients who underwent CABG, graft patency was confirmed by CCTA at six months.

LDL-C levels improved in two patients following the initiation of statin therapy. In this small group of patients with a history of PCI or CABG, PWV significantly worsened during the observation period ($p = 0.017$).

3.4. Eight patients with suspected moderate or severe coronary artery stenosis on CCTA

Of the eight patients included in the study, two had a history of diabetes mellitus and were already receiving pharmacological treatment at baseline. Over the two-year observation period, one of these patients was instructed to initiate lifestyle modifications, including regular exercise and dietary changes, while continuing the same antidiabetic medication. As a result, the patient's HbA1c improved from 8.2% to 7.8%. The other patient had an increased dose of a sodium-glucose co-transporter 2 (SGLT2) inhibitor; however, no change in HbA1c was observed, remaining at 7.4%.

Following the initiation or up-titration of statins and ezetimibe, in combination with lifestyle counseling, all patients showed a significant improvement in LDL-C levels ($p = 0.020$).

Following dietary and exercise therapy instruction, PWV improved in 4 of the 8 patients. In contrast, 3 patients showed worsening, including one who initiated treatment with amlodipine during the study period. In the remaining patient, PWV remained unchanged. Overall, the findings demonstrated heterogeneity, with no consistent group-level trend in PWV despite risk factor management. CCTA was performed in seven of the eight patients who provided informed consent. Despite improvements in LDL-C levels, progression of coronary stenotic lesions was suspected in four patients over the two-year period. Four patients showed progression of coronary artery stenosis, with stenosis rates increasing from 48.9% to 74.7% (Case 1), 45.9% to 75.7% (Case 2), 59.4% to 87.3%, and 32.5% to 90.1% (Case 3), respectively (Figure 3, A–C). In one patient, quantification of the degree of stenosis was difficult due to severe coronary artery calcification (Figure 3D).

Three patients (Cases 1, 2, and 3) subsequently underwent CAG, all of whom were deemed appropriate candidates for revascularization and received PCI. The other one patient underwent myocardial scintigraphy, which revealed no evidence of myocardial ischemia (Case 4).

High-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and intercellular adhesion molecule-1 (ICAM-1) were measured in all participants. However, in this study, we present only the cross-sectional data from the eight patients included in the follow-up CCTA cohort. Most values were within the respective reference ranges, and no consistent abnormalities or trends were identified; therefore, these results are reported descriptively. In the subset of patients with available CACS data ($n = 7$), a significant increase was observed over two years (median change: +32; $p = 0.043$, Wilcoxon signed-rank test). Given the small sample size, this result should be interpreted with caution.

3.5. Longitudinal progression of coronary artery stenosis in JHLH: Impact of risk factor management and the need for regular CCTA follow-up

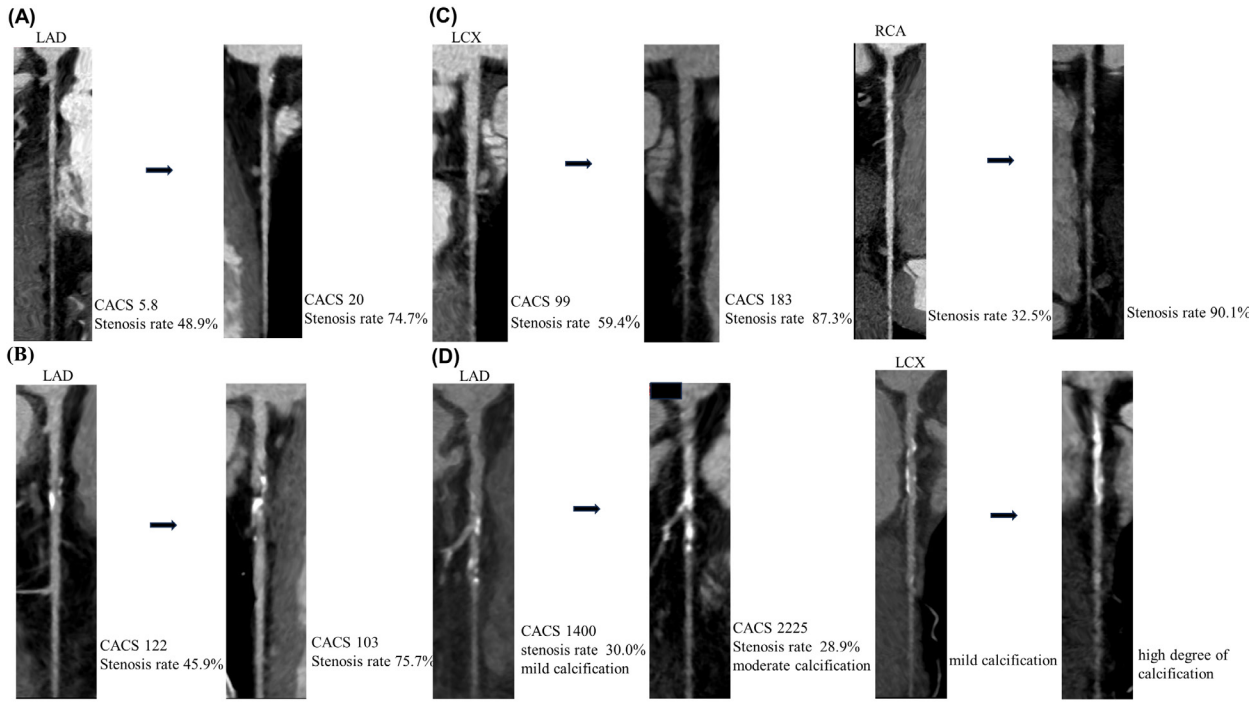

Figure 3. Comparison of CCTA findings in four patients with progression of stenosis. Panels A–D correspond to Cases 1–4. Images from each case are shown side by side, comparing baseline and two-year follow-up scans. Case 1 **(Panel A)**: The stenosis rate of the left anterior descending artery (LAD) increased from 48.9% to 74.7%, with the coronary artery calcium score (CACS) rising from 5.8 to 20. Case 2 **(Panel B)**: The LAD stenosis rate increased from 45.9% to 75.7%, while the CACS decreased from 122 to 103. Case 3 **(Panel C)**: The left circumflex artery (LCX) stenosis rate increased from 59.4% to 87.3%, and the right coronary artery (RCA) stenosis rate from 32.5% to 90.1%, with the CACS rising from 99 to 193. Case 4 **(Panel D)**: Coronary calcification reduced the accuracy of stenosis measurement, resulting in slightly lower values than two years earlier (LAD: 30.0% to 28.9%). No stenosis was detected in the LCX, but calcification was clearly aggravated.

We believe this study is the first to conduct a longitudinal follow-up of cardiovascular disease in JHLH, with a specific focus on coronary artery stenosis progression under guideline-based management. To support this claim, we performed a literature search in PubMed through August 2025 and found limited reports with serial CCTA or equivalent imaging in HIV-infected individuals, and none focused specifically on hemophilia. In particular, patients with moderate or severe coronary artery stenosis showed disease progression despite appropriate risk management, which differs from trends, reported in the general population (*6-9*).

According to Tarr *et al*., in a CCTA follow-up conducted over a mean period of two years, no significant progression in coronary artery stenosis was observed between HIV-positive and HIV-negative individuals when viral load was well controlled (*10*). In contrast, significant progression has been reported in individuals with inadequate HIV viral suppression (*11*).

Other studies have shown that, in the absence of cardiovascular risk management, HIV-positive individuals had approximately twice the odds of progression of calcified plaque compared to HIV-negative individuals (odds ratio [OR] = 1.99, $p = 0.01$), and a trend toward increased progression of non-calcified plaque was also observed (OR = 1.64, $p = 0.07$) (*12*).

In HIV-positive patients, statin intervention has been associated with plaque regression on follow-up CCTA, underscoring the importance of early initiation of statin therapy (*13,14*). Both studies evaluated plaque volume; however, the degree of stenosis was not described.

Early treatment of dyslipidemia is expected to improve LDL-C and PWV (*15*), whereas delayed intervention may result in PWV worsening despite LDL-C reduction. This suggests the importance of early risk factor control in this population.

In contrast to LDL-C, findings for arterial stiffness as measured by PWV were inconsistent. While overall changes were not significant, subgroup analyses showed divergent trends: improvement in some patients with normal-to-mild stenosis, significant worsening in the revascularization group, and heterogeneous responses in the moderate-to-severe stenosis group. These inconsistent results highlight the complexity of vascular remodeling in this population. However, due to the limited sample size, multivariate analyses could not be performed to identify contributing factors, and these findings should therefore be interpreted with caution.

In addition, blood pressure control (*16,17*), diabetes management (*18*), comprehensive cardiovascular risk management (*19*), and improvement in lifestyle habits (*20*) remain essential for preventing CAD.

The prior Hem-IHD study provided an opportunity to address coronary risk factors not only in patients with

significant stenosis but also in those without stenosis (*5*). In the present study, 4 of the 7 patients who underwent repeat CCTA showed progression of coronary artery lesions, and 3 developed severe stenosis requiring PCI despite improved risk factor management. Although a statistically significant increase in CACS was observed in this subset, the very small sample size limits the generalizability and statistical reliability of this finding; therefore, it should be interpreted as exploratory in nature.

These findings suggest that in JHLH, once moderate or greater stenosis is present, rapid progression is highly probable even under appropriate management. Therefore, repeat CCTA at approximately two years after Hem-IHD is recommended to enable early detection and timely intervention.

Potential contributing factors include persistent vascular inflammation due to HIV infection, co-infections such as HCV, and the administration of blood coagulation products (*21*).

Previous studies comparing HIV patients without hemophilia to JHLH have shown a significantly higher prevalence of CAD and elevated inflammatory markers in the latter (*22*), suggesting that hemophilia itself may contribute to vascular inflammation. In addition, FVIII administration has been reported to induce IL-6- and CXCL8-mediated inflammatory responses in patients with inhibitor formation (*23*), and regular intravenous administration of blood products may also play a role. Moreover, persistent HIV reservoirs have been linked to coronary artery plaque, indicating that HIV DNA quantification may serve as a marker for predicting cardiovascular events and guiding interventions (*24*).

All three patients who underwent revascularization experienced worsening PWV despite risk control, suggesting a potential for further lesion progression. Therefore, these findings highlight the potential importance of regular CCTA follow-up in JHLH patients with moderate-to-severe stenosis for the early detection of disease progression and timely intervention.

3.6. The limitations of this study

This study has several limitations. First, the sample sizes of the PCI/CABG group (n = 3) and the moderate-to-severe stenosis group (n = 8) were small, limiting the statistical power and reliability of subgroup analyses. Therefore, these results should be interpreted as descriptive. In addition, the overall number of eligible patients was inherently limited. The total number of Japanese patients with HIV infection due to contaminated blood products was 1,433, and approximately half have already passed away, leaving only 689 survivors nationwide. Despite this restriction, our cohort of 58 patients treated at the National Center for Global Health and Medicine represents one of the relatively larger series currently available, and conducting a similar study at other institutions may involve certain difficulties.

Second, the study was exploratory in nature and did not include a predefined primary endpoint. Third, no adjustments were made for multiple comparisons, increasing the risk of type I error. Fourth, sample size calculations and power analyses were not performed, which may affect the interpretability of non-significant findings. Larger prospective studies with adequate sample sizes and clearly defined endpoints, such as major adverse cardiovascular events (MACE), are needed to validate these observations and clarify cardiovascular risks in this vulnerable population.

In conclusion, our study suggests that even under guideline-based cardiovascular management, there remains a considerable risk of CAD progression in HIV-infected hemophilia patients with moderate or greater stenosis. Therefore, repeat CCTA at two-year follow-up could be considered to facilitate early detection and guide timely intervention. Continuous monitoring, including imaging, and early intervention targeting modifiable risk factors may be important to reduce long-term cardiac risk in this vulnerable population.

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

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