

Unexpected high prevalence of severe coronary artery stenosis in Japanese hemophiliacs living with HIV-1

Ran Nagai¹, Shuji Kubota¹, Mikiko Ogata², Masaya Yamamoto¹, Junko Tanuma², Hiroyuki Gatanaga², Hisao Hara¹, Shinichi Oka^{2,*}, Yukio Hiroi^{1,*}

¹ Department of Cardiology, National Center for Global Health and Medicine, Tokyo, Japan;

² AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: To determine the prevalence of coronary artery stenosis (CAS) in Japanese hemophiliacs living with HIV-1 (JHLH), a prospective study at AIDS Clinical Center, Tokyo, which provides care and treatment to nearly 10% of the JHLH was conducted. The study subjects were 76 JHLH who visited our clinic and received coronary computed tomography angiography (CCTA) between January through December 2019. CCTA with radiographic contrast media was used for CAS screening. Coronary artery calcium score (CACS) by CCTA, pulse wave velocity (PWV), electrocardiography, echocardiography, and chest radiography were also included to the screening process. Stenosis of 50% or more by CCTA was defined as moderate to severe CAS. All patients diagnosed with moderate to severe CAS were recommended to undergo coronary angiography (CAG). Among the 76 JHLH, 19 were excluded. Among the enrolled 57 patients, only 5 had complained of chest symptoms. Their median age was 47 years (interquartile range: 44-55 years), prevalence of hypertension 42.1%, diabetes mellitus 14.0%, dyslipidemia 38.6%, and smoking history 52.6%. Moderate to severe CAS was diagnosed in 14 patients by CCTA (24.6% of CCTA tested). Twelve patients agreed to undergo CAG. Seven patients were diagnosed as severe CAS by CAG (12.3% of CCTA received), although only 2 (28.6%) had chest symptoms. PWV and CACS were useful and significant non-invasive markers of moderate to severe CAS ($p = 0.016$, $p < 0.001$, respectively). In conclusions, our study identified high prevalence of severe CAS among JHLH. We recommend screening of all HIV-1-infected hemophiliacs with PWV and CACS, regardless of chest symptoms.

Keywords: coronary artery disease, coronary computed tomography angiography, coronary angiography, coronary artery calcium score, pulse wave velocity

Introduction

Nearly 30% of Japanese with hemophilia and other inherited bleeding disorders were infected with HIV-1 through contaminated non-heated blood products in the early 1980s. As of May 2019, 716 Japanese hemophiliacs infected with HIV-1 were alive (1). Thanks to advances of HIV-1 treatment, the prognosis of Japanese hemophiliacs living with HIV-1 (JHLH) has improved dramatically in the past two decades (2). The cause of death in JHLH has changed from AIDS before 2000 to other co-morbidities, such as non-AIDS defining malignancies (2,3).

Advances in the field of therapeutics, including blood clotting factor concentrates, and in the management of bleeding tendencies have dramatically improved the prognosis of hemophiliacs (4,5), resulting in enhancements in life expectancy. Consequently, the proportion of hemophiliacs with coronary risk factors,

such as hypertension, diabetes, and dyslipidemia for lifestyle-related diseases increases with age (6). In this regard, it is well known that prolonged exposure to HIV infection increases the risk of ischemic heart disease and the use of anti-HIV drugs, particularly protease inhibitors, causes dyslipidemia that increases the risk of coronary artery disease (CAD) (7,8). Therefore, JHLH survivors are at high risk of CAD associated with aging, long-term exposure to HIV-1 itself, use of protease inhibitors for HIV-1, and improvement in bleeding tendency.

Coagulation abnormalities are considered less common as the cause of CAD in hemophiliacs (9,10). Therefore, physicians have focused on prevention of bleeding, rather than infarction, in these patients. However, in 2018, we encountered a 61-year-old JHLH with subacute myocardial infarction. The diagnosis was difficult and required longer time than usual due to ill-defined and scarce clinical features. The patient had

severe joint deformities related to frequent bleeding, which restricted exercise and limited daily activities, and masked the chest symptoms, and ultimately caused delays in the diagnosis. The case prompted us to screen CAD in the JHLH population.

The purpose of this study was to determine the prevalence of coronary artery stenosis and establish non-invasive screening methods for early detection of CAD in JHLH.

Methods

Patients

This prospective study included all JHLH individuals who visited AIDS Clinical Center (ACC), National Center for Global Health and Medicine (NCGM), Tokyo, and had coronary computed-tomography angiography (CCTA) between January through December 2019.

Data collection

Patients' demographics and CAD risk factors, including age, height, weight, body mass index (BMI), history of hypertension, diabetes mellitus, dyslipidemia, used medications, smoking, alcohol drinking, cardiovascular diseases, and allergy, in addition to family history, were collected. Blood tests included hemoglobin A1c, LDL-cholesterol, HDL-cholesterol, creatinine, hemoglobin, CD4 counts, plasma HIV-RNA, D-dimer, and brain natriuretic peptide (BNP). Furthermore, information on nadir CD4 counts, use of blood products and severity of hemophilia, and period of use of protease inhibitors were collected by the medical records. Electrocardiography, echocardiography, and pulse wave velocity (PWV) (Omron Healthcare, Kyoto, Japan) were also performed in each patient and age-average data of PWV was referred to a Japanese survey (11). The presence of pleural effusion and calculated cardio thoracic ratio were checked on the chest X-ray. Coronary artery calcium score (CACS) was weighted by CT value as was the cross-sectional area according to Agatston *et al.* (12). In this study, CACS was classified into no calcification (score = 0), minimal risk (score: 1-10), low risk (score: 11-100), moderate risk (score: 101-400), and high risk (score: > 400) (13,14). 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). Based on CCTA image analysis, coronary artery stenosis was classified as mild stenosis (< 50% stenosis in the vessel area, non-CAD group), moderate stenosis (50 to 75% stenosis), and severe stenosis (> 75% stenosis). In this study, the CAD group included patients with moderate to severe CAS. Coronary angiography (CAG) was recommended to all

patients with moderate to severe stenosis, as defined by CCTA.

Statistics analysis

The above investigations were used to define the presence or absence of coronary artery stenosis and risks of CAD in the cohort. Differences in categorical variables between the groups were checked using the Pearson's chi-square test, while those in continuous variables were examined by the Mann-Whitney *U* test. Differences in the incidence of moderate to severe stenosis evaluated by coronary CT and absolute values of PWV and CACS were examined by the Mann-Whitney *U* test. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, SPSS Inc., Chicago, IL).

Ethics statement

The study protocol was reviewed and approved by the human ethics committee of NCGM (#NCGM-G-003086-00) on November 26, 2018. A 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 #UMIN000035307).

Results

A total of 76 (10.6%) patients visited ACC out of the 716 registered JHLH. All patients were males, including a single patient with von-Willebrand disease. The patient selection process is outlined in Figure 1. Nineteen patients were excluded from the study for a variety of reasons, including unwillingness to participation ($n = 4$), ineligibility for participation (*e.g.*, coexisting psychiatric diseases, $n = 5$), renal dysfunction ($n = 5$), allergy to iodine ($n = 3$), and past history of CAD ($n = 2$, one with myocardial infarction, aged 61 years, and another with angina pectoris, aged 44 years). Thus, 57 patients were enrolled in this study and each underwent CCTA during the study period. Among the 57 patients, only 5 had complained of chest symptoms. Table 1 summarizes the patients' characteristics. The median age was 47 years (interquartile range (IQR): 44-55 years). HIV-1 viral load (VL) was suppressed undetectable level in all patients except one whose VL was 51 copies/mL. The median duration of undetectable VL was 16 years (IQR: 12-18 years). Although their nadir CD4 counts were low, the current median CD4 count was 457/ μ L (IQR: 370-627/ μ L). Above all, HIV-1 infection was very well controlled in all patients. Most patients (86.0%) had been treated with protease inhibitors for the median period of 10 years (IQR: 4-16 years) and 77.2 % treated with d-drug (any

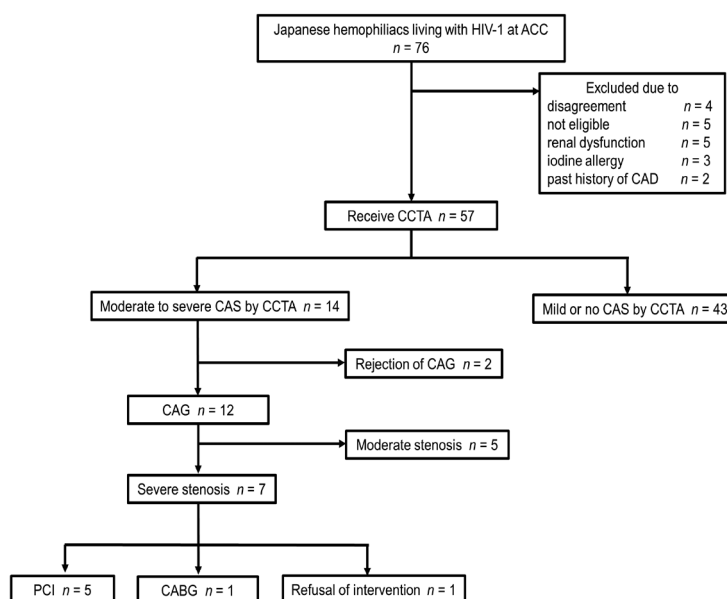


Figure 1. Study protocol and patient selection. Patients with moderate to severe CAS based on CCTA were classified into the CAD group and mild or no CAS as the non-CAD group. ACC, AIDS Clinical Center; CAS, coronary artery stenosis; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CAG, coronary angiography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 1. Patient demographics and comparison of variables with and without CAD by CCTA

Demographics and variables	All (n = 57)	CAD (n = 14)	Non-CAD (n = 43)	p
Age, median year (IQR)	47 (44-55)	55 (47-59)	47 (44-52)	0.089
BMI kg/m ² , median (IQR)	23 (22-25)	22 (20-27)	23 (22-25)	0.204
Hemophilia A, n (%)	46 (80.7)	9 (20)	37 (80)	0.073
Hemophilia B, n (%)	10 (17.5)	5 (50)	5 (50)	0.044
von Willebrand Disease, n (%)	1 (1.8)	-	1	
Nadir CD4/μL, median (IQR)	129 (59-169)	108 (12-177)	130 (69-168)	0.207
Current CD4/μL, median (IQR)	457 (370-627)	452 (370-610)	567 (375-690)	0.305
Duration of undetectable VL, median year (IQR)	16 (12-18)	16 (12-18)	16 (12-18)	0.566
PI use, median year (IQR)	10 (3-17)	14 (3-18)	10 (4-16)	0.362
d-drug use, median year (IQR)	6 (1-9)	5 (1-8)	7 (12-18)	0.074
Smoking history, n (%)	30 (52.6)	7 (50.0)	23 (53.5)	0.878
Current smoker, n (%)	11 (19.3)	3 (21.4)	8 (18.6)	0.875
Hypertension, n (%)	24 (42.1)	7 (50.0)	17 (39.5)	0.491
Diabetes mellitus, n (%)	8 (14.0)	4 (28.6)	4 (9.3)	0.071
Dyslipidemia, n (%)	22 (38.6)	6 (42.9)	16 (37.2)	0.826
SUITA score, median (IQR)	41 (33-46)	38 (33-44)	44 (40-58)	0.019
PWV cm/sec, median (IQR)	1,527 (1,404-1,657)	1,615 (1,417-1,798)	1,464 (1,336-1,599)	0.016
CACS, median (IQR)	0 (0-27)	111 (29-593)	0 (0-7)	< 0.001

CAD, coronary artery disease; CCTA, coronary computed-tomography angiography; n, number of patients; IQR, interquartile range; BMI, body mass index; VL, plasma viral load; PI, protease inhibitor; d-drug, any of ddI, ddC and d4T; PWV, pulse wave velocity; CACS, coronary artery calcium score.

of ddI, ddC and d4T) for the median duration of 6 years (IQR: 1-9 years). The prevalence of hypertension was 42.1%, diabetes mellitus 14.0%, dyslipidemia 38.6%, smoking history 52.6%, and current smoker 19.3%. The median SUITA score that is a predictive score of a 10-year risk of coronary heart disease (CHD) in Japanese (15) was 41 (IQR: 33-46).

CCTA showed moderate to severe coronary artery stenosis (CAS) in 14 out of 57 patients (24.6%). The classical risk factors of CAD, including age,

smoking history, hypertension, diabetes mellitus, and dyslipidemia, were not significantly different between the CAD and non-CAD groups (Table 1). Although the prevalence of CAD was higher in patients aged more than 40 years (33.3%) than in those less than 40 (18.2%), both age groups included a substantial number of patients with moderate to severe CAS (Figure 2). Electrocardiography, echocardiography, and chest radiography had no diagnostic values in all patients.

The PWV was above that of the age-matched

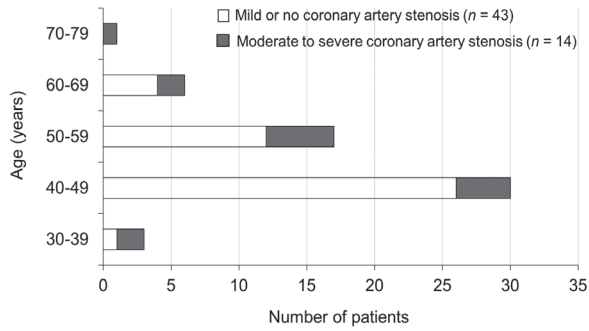


Figure 2. Prevalence of coronary artery stenosis by age. Coronary artery stenosis was diagnosed by coronary computed tomography angiography.

average +1SD and +2SD in 42 (73.7%) and 25 patients (43.9%), respectively (Figure 3). Furthermore, analysis of the CCTA of patients with +2SD PWV ($n = 25$), showed 10 (40.0%) of these patients had moderate to severe CAS. The finding that the PWV of JHLH was higher than that of the general population in almost all cases was surprising. Furthermore, the absolute values PWV highlighted the presence of significant difference between the CAD and non-CAD groups ($p = 0.016$). In addition to PWV, the absolute values of CACS were significantly higher in the CAD group than in the non-CAD group ($p < 0.001$) (Table 1, Figure 4). CACS values were more than 100 in 8 patients and all these patients except one had moderate to severe CAS. In

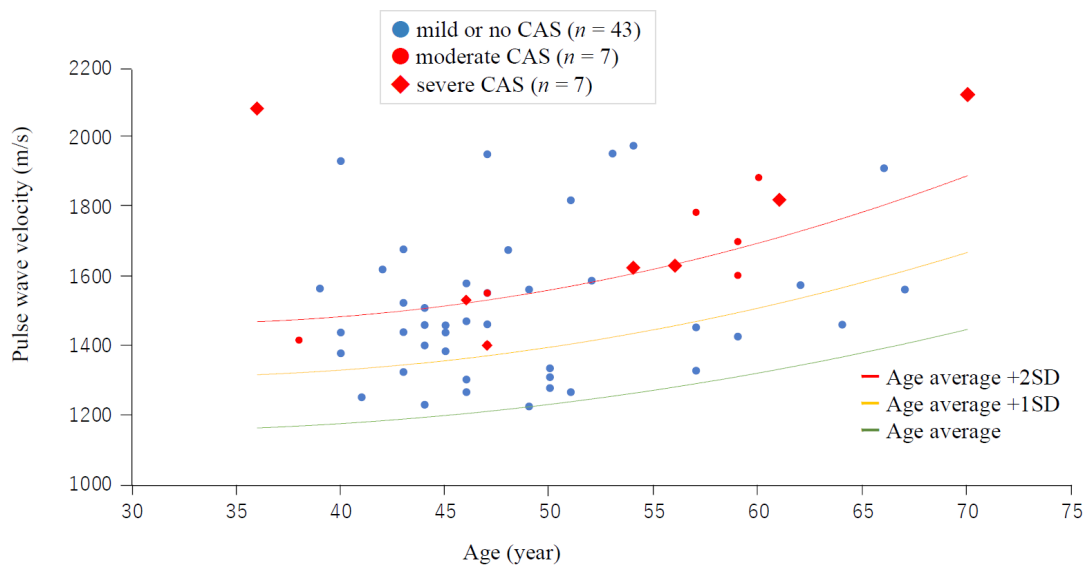


Figure 3. Pulse wave velocity, age, and coronary artery stenosis diagnosed by CCTA. Mild or no stenosis was diagnosed by CCTA. Moderate or severe stenosis was diagnosed by coronary angiography. CAS, coronary artery stenosis; CCTA, coronary computed tomography angiography; CACS, coronary artery calcium score.

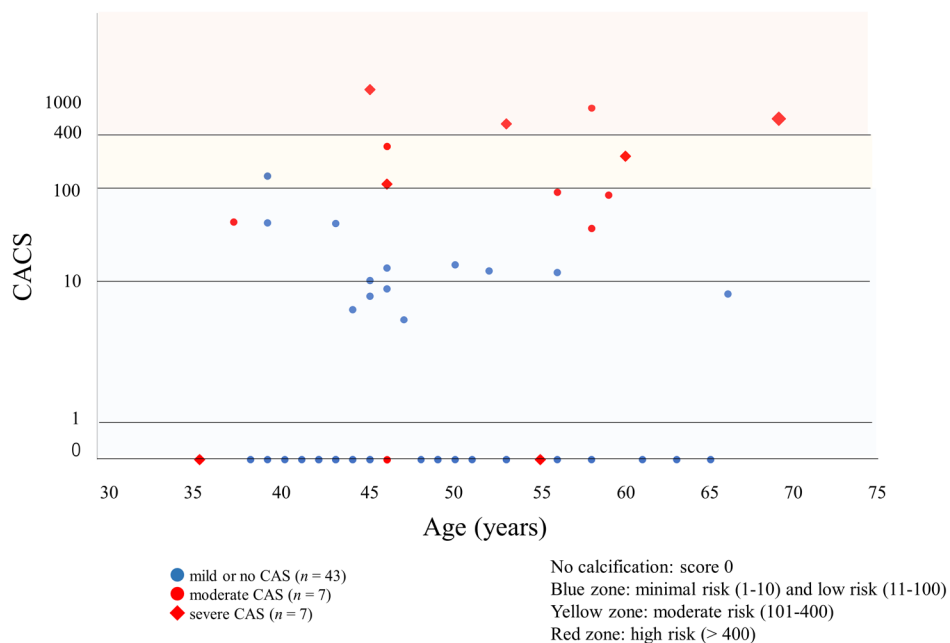


Figure 4. Coronary artery stenosis and risk of ischemic heart disease categorized by CCTA. Mild or no stenosis was diagnosed by CCTA. Moderate or severe stenosis was diagnosed by coronary angiography. (See Figure 3 for abbreviations)

these 7 patients with severe coronary artery stenosis, CACS was less than 100 in 3 patients (values: 92, 0, 0). However, the PWV values of these 3 patients were above +2SD. These results indicate that the combination of PWV and CACS can better predict CAD than either parameter alone.

Among the 14 patients diagnosed with moderate to severe CAS based on CCTA, 12 agreed to undergo CAG (Figure 1). CAG confirmed the presence of severe stenosis in 7 patients, requiring multivessel revascularization. Among the 7 patients, only 2 had complained of chest symptoms related to CAD. Of the 7-CAG confirmed patients, 5 subsequently underwent percutaneous coronary intervention (PCI) and one received coronary artery bypass grafting (CABG). The other one patient refused to undergo PCI due to fear of bleeding while under dual antiplatelet therapy and was accordingly treated by medications only.

Discussion

We conducted a prospective screening study for CAD in JHLH and found CAS in almost 25% of the cohort. Moreover, the prevalence of severe CAS confirmed by CAG was 12.3% in those JHLH patients with a median age of 47 years. It is noteworthy that only two patients had experienced chest symptoms, probably due to low physical activity. The prevalence of CAS was unexpectedly higher than in the general population, although the exact CAS prevalence in the general population is difficult to estimate. With regard to the prevalence of myocardial infarction in Japanese men, the available data in the 1990s showed a rate of 100.7 per 100,000 person/year (16). In our study, the identified 7 patients required early revascularization due to the severity of CAS.

The current guidelines for the clinical management of hemophiliacs do not mention the prevention of CAD (17). Recent years have seen emphasis on the control of cardiovascular risks in these patients (18) and establishment of screening methods for CAD is also important. The currently identified classical risk factors of CAD, such as age, smoking history, hypertension, diabetes mellitus, dyslipidemia, and the SUITA score are definitely useful for the prediction of CAD in the general population. However, their importance could not be established in the present study. According to the SUITA score, a 10-year probability of CAD would be only 2% and the score was too low to compare in this patient population. It is possible that other risk factors may override the classical risk factors in this unique population of HIV-1 infection and hemophilia.

In this study, HIV-1 infection of all patients has been very well controlled in terms of CD4 counts and VL for more than the past decade. However, Japanese hemophiliacs were infected with HIV-1 around 1983 (2). Before the highly active antiretroviral therapy became

available in Japan in 1997, JHLH survivors were exposed for 14 years to high plasma viral loads. The impact of HIV-1 on cardiovascular diseases (CVD) has been documented in a randomized study in which anti-HIV-1 therapy was either interrupted or tailored according to CD4 count (19). In this study, patients of the interrupted group had significantly higher CVD events due to high peripheral blood levels of proinflammatory cytokines and endovascular thrombosis (20), and the control of plasma viral load reduced markers of endothelial and coagulation activation (21). These results indicate the reversibility of hypercoagulability and endovascular reactivity. However, while this is true for short-term endothelial and coagulation dysfunctions, there were no evidence for the same during long-term exposure to high viral load like in the Japanese hemophiliacs. In addition to HIV-1 itself, the 10-year use of protease inhibitors in JHLH patients carried the risk of development of dyslipidemia. In this regard, Friis-Moller *et al.* (22) demonstrated that long term use of protease inhibitors increased the risk of myocardial infarction.

We have witnessed lessening of bleeding in hemophiliac patients in this decade thanks to new and improvement in anti-coagulation therapy. The current treatment regimens include regular injections of factor VIII or IX two-to-three times per week. The prophylactic use of coagulation factors has kept the incidence of CVD in hemophiliacs at levels similar to that in the normal population, with lower mortality, according to a report from Sweden (9). Wang *et al.* (23) studied the prevalence and risk factors of atherothrombotic events in 1,054 hemophiliacs and reported that such events occurred in younger hemophiliacs (mean age 49 years) compared with the general population (55.8 years). The prevalence in hemophiliacs was also comparable to that of the general population in this study. In contrast, Sharathkumar *et al.* (24) reported double the CVD rate found in the general population in their hemophiliacs from a single hemophilia center in the United States. Since the pathophysiology of CVD is closely related to hypercoagulability, the effects of long-term use of coagulant factors on atherosclerosis in hemophiliacs need to be analyzed in future studies.

The main finding of this study was the high rate of CAS, which is probably related to atherosclerosis. Evidence indicates that high PWV value is a marker of advanced atherosclerosis. In this study, the majority of JHLH patients had high PWV values. A high PWV value is usually caused by high blood pressure and peripheral artery disease, though neither was detected at the time of PWV measurement in this study. Importantly, atherosclerosis develops earlier in JHLH patients, compared with that in age-matched general population. The importance of high PWV is based on the fact that it correlates with coronary artery calcification (25,26) and CVD (27-29) in the general population.

Our results showed that the absolute values of PWV

were significantly different between patients of the moderate to severe CAS group and those of the mild to normal coronary artery group. Furthermore, the PWVs of all 14 patients with moderate to severe CAS were higher than those of the age average +1SD (Figure 3). Exercise stress test with ECG monitoring is usually used for assessment of CAD, however, this test is not suitable for at least some hemophiliacs due to the associated joint deformities. For such cases, PWV can be a useful screening test for CAD in JHLH especially as it is a non-invasive test. We also used another index to assess CAD in our patients, the absolute values of CACS were significantly higher in the CAD groups than the non-CAD group (Figure 4). For screening patients for CAD using CACS, it can be calculated on the CT scan without contrast agent. Thus, the use of CACS for CAD in JHLH can be also useful as a screening tool, although score zero does not mean no risk of CAD. In summary, we recommend the combination of PWV and CACS for early detection of CAD in hemophiliacs living with HIV-1 based on their high diagnostic value. Further large-scale studies are needed to establish the diagnostic values of these indexes in JHLH.

In spite of the above strengths, our study has certain limitations. First, the number of participants was not sufficient enough to demonstrate the statistical significance of the classical risk factors of CAD. However, around 10% of the current JHLH were included in this study. A larger study of JHLH should be performed to assess the significance of the classical risk factors. Second, our study demonstrated extremely high prevalence of CAS, high PWV and CACS values in JHLH, but the study did not include a control group. Therefore, the reasons for the high values and the factors that contributed to such high prevalence of CAD remain unclear. Further studies involving hemophiliacs free of HIV-1 infection and non-hemophiliacs who have been on long-term treatment for HIV-1 could provide answers to these questions.

In conclusion, we have demonstrated in the present study a high prevalence of severe CAD in a sample of JHLH community. We strongly recommend screening of hemophiliacs living with HIV-1 for CAD, with the combination of PWV and CACS, regardless of presence or absence of chest symptoms.

Acknowledgements

The authors thank all staff members of ACC and Department of Cardiology, NCGM. This study was supported in part by funds from NCGM (#30-A-2002).

References

1. Project entrusted by Ministry of Health, Labour And Welfare. Nationwide Survey on Coagulation Disorders 2019. https://api-net.jfap.or.jp/image/data/blood/r01_research/r01_research.pdf (accessed May 28, 2020). (in Japanese)

2. Oka S, Ikeda K, Takano M, Ogane M, Tanuma J, Tsukada K, Gatanaga H. Pathogenesis, clinical course, and recent issues in HIV-1-infected Japanese hemophiliacs: A three-decade follow-up. *Global Health & Medicine*. 2020; 2:9-17.
3. Oka S, Ogata M, Takano M, Minamimoto R, Hotta M, Tajima T, Nagata N, Tsukada K, Teruya K, Kikuchi Y, Gatanaga H, the Cancer Screening in Hemophiliac/HIV Patient Study Group. Non-AIDS-defining malignancies in Japanese hemophiliacs with HIV-1 infection. *Global Health & Medicine*. 2019; 1:49-54.
4. Darby SC, Kan SW, Spooner RJ, Giangrande PL, Hill FG, Hay CR, Lee CA, Ludlam CA, Williams M. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood*. 2007; 110:815-825.
5. Tagliaferri A, Rivolta GF, Iorio A, *et al*. Mortality and causes of death in Italian persons with haemophilia, 1990-2007. *Haemophilia*. 2010; 16:437-446.
6. Dolan G. The challenge of an ageing haemophilic population. *Haemophilia*. 2010; 16:11-16.
7. Rao SG, Galaviz KI, Gay HC, Wei J, Armstrong WS, Del Rio C, Narayan KMV, Ali MK. Factors associated with excess myocardial infarction risk in hiv-infected adults: A systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2019; 81:224-230.
8. Maggi P, Di Biagio A, Rusconi S, Cicalini S, D'Abbraccio M, d'Ettore G, Martinelli C, Nunnari G, Sighinolfi L, Spagnuolo V, Squillace N. Cardiovascular risk and dyslipidemia among persons living with HIV: A review. *BMC Infect Dis*. 2017; 17:551.
9. Lövdahl S, Henriksson KM, Baghaei F, Holmstrom M, Berntorp E, Astermark J. Incidence, mortality rates and causes of deaths in haemophilia patients in Sweden. *Haemophilia*. 2013; 19:362-369.
10. Mejia-Carvajal C, Czapek EE, Valentino LA. Life expectancy in hemophilia outcome. *J Thromb Haemost*. 2006; 4:507509.
11. Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, Hori S, Yamamoto Y, Doba N, Hinohara S. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement-a survey of 12517 subjects. *Atherosclerosis*. 2003; 166: 303-309.
12. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15:827-832.
13. Rumberger JA. Using noncontrast cardiac CT and coronary artery calcification measurements for cardiovascular risk assessment and management in asymptomatic adults. *Vasc Health Risk Manag*. 2010; 6:579591.
14. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate risk individuals. *JAMA*. 2012; 308:788-795.
15. Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, Kokubo Y, Okayama A, Miyamoto Y. Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the Framingham risk score: The Suita

- Study. *J Artheroscler Thromb.* 2014; 21:784-798.
16. Rumana N, Kita Y, Turin TC, Murakami Y, Sugihara H, Morita Y, Tomioka N, Okayama A, Nakamura Y, Abbott RD, Ueshima H. Trend of increase in the incidence of acute myocardial infarction in a Japanese population: Takashima AMI registry, 1990-2001. *Am J Epidemiol.* 2008; 167:1358-1364.
 17. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A; Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia.* 2013; 19: e1-47.
 18. Sousos N, Gavriilaki E, Vakalopoulou S, Garipidou V. Understanding cardiovascular risk in hemophilia: A step towards prevention and management. *Thromb Res.* 2016; 140:14-21.
 19. El-Sadr WM, Lundgren JD, Neaton JD, *et al.* CD4+ count guided interruption of antiretroviral treatment. *N Engl J Med.* 2006; 355 :2283-2296.
 20. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, Ledergerber B, Lundgren J, Neuhaus J, Nixon D, Paton NI, Neaton JD; INSIGHT SMART Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV-1 infection. *PLoS Med.* 2008; 5:e203.
 21. Wolf K, Tsakiris DA, Weber R, Erb P Battegay M. Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with HIV-1. *J Infect Dis.* 2002; 185:456-462.
 22. DAD Study Group, Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte Ad, El-Sadr W, Thiébaud R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med.* 2007; 356:1723-1735.
 23. Wang JD, Chan WC, Fu YC, Tong KM, Chang ST, Hwang WL, Lin CH, Tsan YT. Prevalence and risk factors of atherothrombotic events among 1054 hemophilia patients: a population-based analysis. *Thromb Res.* 2015; 135:502-507.
 24. Sharathkumar AA, Soucie JM, Trawinski B, Greist A, Shapiro AD. Prevalence and risk factors of cardiovascular disease with haemophilia: experience of a single haemophilia treatment center in the United States. *Haemophilia.* 2011; 17:597-604.
 25. Torii S, Arima H, Ohkubo T, *et al.* Association between pulse wave velocity and coronary artery calcification in Japanese men the shiga epidemiological study of subclinical atherosclerosis (SESSA). *J Atheroscler Thromb.* 2015; 22:1266-1277.
 26. Cainzos-Achirica M, Rampal S, Chang Y, Ryu S, Zhang Y, Zhao D, Cho J, Choi Y, Pastor-Barriuso R, Lim SY, Bruguera J, Elosua R, Lima JA, Shin H, Guallar E. Brachial-ankle pulse wave velocity is associated with coronary calcium in young and middle-aged asymptomatic adults: The Kangbuk Samsung Health Study. *Atherosclerosis.* 2015; 241:350-356.
 27. Munakata M, Konno S, Miura Y, Yoshinaga K; J-TOPP Study Group. Prognostic significance of the brachial-ankle pulse wave velocity in patients with essential hypertension: Final results of the J-TOPP study. *Hypertens Res.* 2012; 35:839-842.
 28. Takashima N, Turin TC, Matsui K, *et al.* The relationship of brachial-ankle pulse wave velocity to future cardiovascular disease events in the general Japanese population: The Takashima study. *J Hum Hypertens.* 2014; 28:323-327.
 29. Gao S, Liu Q, Ding X, Chen H, Zhao X, Li H. Predictive value of the combination of age, creatinine, and ejection fraction score and diabetes in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention. *Coron Artery Dis.* 2020; 31:109-117.
-
- Received September 4, 2020; Revised September 14, 2020; Accepted September 16, 2020.
- Released online in J-STAGE as advance publication September 20, 2020.
- *Address correspondence to:*
 Yukio Hiroi, Department of Cardiology, National Center for Global Health and Medicine. 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
 E-mail: yhiroii@hosp.ncgm.go.jp
- Shinichi Oka, AIDS Clinical Center, National Center for Global Health and Medicine. 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
 E-mail: oka@acc.ncgm.go.jp