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Prevalence and associated factors of low vigor in patients living with HIV and hemophilia in Japan: A cross-sectional observational study

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Abstract: People living with human immunodeficiency virus (HIV) are at high risk of mental health problems. However, little is known about this risk in HIV-infected patients with hemophilia (HPH) who contracted the virus through blood products. This cross-sectional, observational study assessed patients' mood states and the factors associated with them among Japanese HPH to evaluate the need for psychosocial support. HPH completed self-administered questionnaires (Profile of Mood States [POMS] and General Health Questionnaire-28), neuropsychological tests, and brain magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography/computerized tomography scans. HIV-infected patients with no hemophilia (HPnH) completed POMS and neuropsychological tests. Socio-demographic characteristics and HIV- and hemophilia-related data were obtained from participants' medical records and interviews. A Mann–Whitney *U* test and chi-squared analyses were conducted. Fifty-six HPH and 388 HPnH completed the questionnaires and neuropsychological tests. HPH had a significantly lower prevalence of tension–anxiety (HPH, 7%; HPnH, 18%; $p = 0.049$) and a significantly higher prevalence of low vigor (HPH, 63%; HPnH, 32%; $p < 0.001$). Low vigor in HPH was significantly associated with impaired executive function (low vigor, 66%; high vigor, 33%; $p = 0.019$) and a social dysfunction score ≥ 3 (moderate; low vigor, 26%; high vigor, 5%; $p = 0.047$). Our results highlight the high prevalence of low vigor among HPH, leading to impairments in executive and social functions. Therefore, healthcare workers need to pay attention to the vigor, executive function, and social function of HPH.

***Keywords*:** mental health, blood products, mood states, executive function, psychosocial support, healthcare

Introduction

People living with human immunodeficiency virus (HIV) are at high risk of mental illness or mental health problems (*1*). Mental health and mental illness are not the same. Mental health includes emotional, psychological, and social well-being. It affects how we think, feel, and act. It also helps determine how we handle stress, relate to others, and make healthy choices. Mental illness collectively refers to all diagnosable mental disorders, such as depression, anxiety, bipolar disorder, or schizophrenia (*2*). Mental health is a concept that encompasses mental illness and includes mental and psychological conditions that are not diagnosed as illnesses. Poor mental health or mental illness can contribute to poorer healthcare behaviors across the HIV care continuum, leading to negative HIV health outcomes (*i.e.*, elevated viral load (VL), decreased CD4+ levels, and increased opportunistic illnesses) (*3,4*). Depression can increase the risk of mortality among people living

with HIV (*5,6*). The World Health Organization recommends that attention to the mental health of people living with HIV should be an integral part of HIV care and that an integrated approach to HIV, mental health, and psychosocial problems is needed (*7*).

However, most previous studies on the mental health and mental illness of people living with HIV target patients for whom the virus was sexually transmitted, with few studies targeting HIV-infected patients with hemophilia (HPH) who were infected through blood products (*8-12*). In the 1970s and 1980s, many patients with hemophilia worldwide became infected with HIV through contaminated products. For example, nearly 5,000 (*i.e.,* half of all patients), 1,300, and 1,200 patients with hemophilia were infected in the United States of America, the United Kingdom, and France, respectively (*13-15*). In addition, recent reports indicate that approximately 50–80% of those infected with HIV have already died (*15,16*). In Japan, 1,432 patients with hemophilia became infected with HIV through contaminated products in the mid-1980s (*17*). As of 2023, 697 HPH are still alive and entering their fifties (*17,18*). As HPH are a minority group of people living with HIV, their mental health and potential mental illnesses have not been adequately considered. Catalan *et al.* found that HIV-seropositive men with hemophilia had higher levels of psychological distress and sexual problems than HIV-seronegative men with hemophilia (*12*). However, Marsettin *et al.* reported that HIV-seropositive and -seronegative men with hemophilia presented the same degree of emotional involvement; there were no significant differences in the average scores between groups – either on the anxiety or depression scales (*8,11*). In addition, Drotar *et al.* (*9*) found that HIV-seropositive children and adolescents with hemophilia demonstrated psychological resilience and levels of psychological adjustment comparable to their seronegative counterparts. While many studies on mental health problems of HPH were in the pre-anti-retroviral therapy (ART) era, there is no unified view on this subject in the post-ART era.

A meta-analysis of mental health disorders in patients with hemophilia suggested that the prevalence of depression, anxiety, and attention-deficit/hyperactivity disorder across decades is significantly higher in patients with hemophilia compared to the general population (*19*). HPH are exposed to stigma and discrimination about HIV as well as comorbidities such as hemophilic arthropathy, muscle hemorrhage, and hepatitis C virus (HCV) infection (*20*). Therefore, even if they do not have a mental illness, their mental health may be poorer than that of non-HPH. Thus, it is important to investigate the mental health associated with HPH in the post-ART era.

We used the Profile of Mood States (POMS) (*21,22*) and General Health Questionnaire (GHQ)-28 (*23,24*) to investigate mental health problems among HPH. The POMS scale assesses temporal mood states that change according to condition and allows simultaneous assessment of six subscales: tension–anxiety, depression–dejection, anger–hostility, vigor, fatigue, and confusion. Assessing a variety of moods is important for this study because moods influence our overall sense of well-being and impact behavior patterns and perceived health (*25*). The GHQ-28 is a screening device for identifying minor psychiatric disorders (somatic symptoms, anxiety and sleeplessness, social dysfunction, and depression) (*23,24*). This study assessed mental health problems of Japanese HPH in the post-ART era using the POMS and GHQ-28 and examined the associated factors to evaluate the need for psychosocial support.

Participants and Methods

Participants and procedures

Participants were HPH who received outpatient treatment from May 2016 to February 2018 at the National Center for Global Health and Medicine (NCGM) in Tokyo, Japan. Exclusion criteria were determined based on the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders 5th ed. (DSM-5) (*12*). The exclusion criteria were as follows: *i*) individuals currently with an active AIDS-defining illness requiring treatment; *ii*) those with congenital mental retardation; *iii*) those diagnosed with major depressive disorder and/or schizophrenia; *iv*) individuals diagnosed with Alzheimer's disease, frontotemporal lobar degeneration, Lewy body dementia, prion diseases, Parkinson's disease, and/or Huntington's disease; *v*) those with cerebrovascular disease; *vi)* those with traumatic brain lesion; *vii*) individuals who were habitual illicit drug users and/or severe alcoholics; *viii*) those undergoing treatment for central nervous system opportunistic disease or with clear physical impediments; *ix*) those exhibiting other pathologies that clearly caused cognitive impairment; *x*) those with a fever ≥ 38.5°C or any active infectious symptoms during examination; *xi*) individuals for whom neuropsychological (NP) testing was judged to be performed inaccurately; and *xii*) those who had undergone NP testing within the past year. Patients with acute or subacute lesions detected on brain magnetic resonance imaging (MRI) that could potentially impact cognitive function, as well as patients with foreign materials that were deemed unsuitable for an MRI scan, were also excluded (*12*).

When applicable patients visited the hospital for an outpatient visit, the coordinator provided a written explanation of this study and obtained written consent. Thereafter, patient information was collected from medical records. Other necessary information was collected by interviews on the morning of the POMS, GHQ, and NP testing day. Psychiatric diagnosis was based on a brief screening using the Mini International Neuropsychiatric Interview (*26*). In addition, a single

psychiatrist, a board-certified doctor of psychiatry with more than 20 years of clinical psychiatric experience, examined all HPH.

Data for the control group comprising HIV-infected patients with no hemophilia (HPnH) were obtained from NCGM from the J-HAND study (for more details, see Kinai *et al.* (*27*)). Three time zones (9 a.m. to 10 a.m., 10 a.m. to 11 a.m., and 11 a.m. and later) were set at each of three outpatient examination rooms. Patients who met the selection criteria were recruited in the order of visit time, and verbal consent was obtained from up to three patients per day in each room. The control group included 388 randomly extracted Japanese HIV-infected patients who received outpatient treatment at the NCGM between July 2014 and July 2016 (route of infection: sexual transmission, n = 385; other and unknown, n = 3). Participant exclusion criteria were in accordance with DSM-5 (*12*).

Measures

Socio-demographic characteristics and HIV- and hemophilia-related factors

The following data were obtained from the medical records and interviews: age, sex, education level, current employment, presence of partner or housemate, history of smoking, current alcohol use and amount, documented HIV transmission route, history of AIDS-defining illness, and incomplete virologic suppression, defined as two or more times of HIV-RNA ≥ 200 copies/mL – after virologic suppression or after 24 weeks on ART, current treatment for hypertension, diabetes and hyperlipidemia, HCV coinfection, qualitative Treponema pallidum latex agglutination (TPHA), time since HIV diagnosis, nadir CD4 cell count, current CD4 cell count, highest VL, current VL, ART regimen, time on ART, Hemophilia A or B, history of cerebrovascular disorder, and presence of hemophilic arthropathy. Body temperature and systolic and diastolic blood pressures were measured on the same day. Using blood samples obtained within three months of NP tests, we measured hemoglobin, serum triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and hemoglobin A1c levels.

POMS

Mood was assessed using the Japanese edition of the POMS (*21,22*). The POMS is a 30-item self-report questionnaire used to assess psychological distress. It measures mood using six subscales: tension–anxiety, depression–dejection, anger–hostility, vigor, fatigue, and confusion. The POMS total mood disturbance score is calculated by summing the scores across all six factors, while weighing vigor negatively. Respondents were asked to rate the degree to which an adjective was applied to them during the preceding week on a five-point scale (0 = "not at all" and 4 = "extremely"). Scores for each subscale ranged from 0 to 20, with higher scores indicating more severe symptoms, except for the vigor scale, in which lower scores indicated more severe symptoms (*28*). The Cronbach's alpha was 0.760 in this study and showed acceptable internal consistency.

GHQ

Mental states were assessed using the 28-item Japanese version of the GHQ (*23,24*). The GHQ assesses general psychopathology and measures mental state using four scales: somatic symptoms, anxiety/insomnia, social dysfunction, and severe depression; these were summed to obtain a total score. Respondents were asked to rate each item according to the degree to which it was applicable during the preceding two or three weeks. Two scoring systems were used: a Likert scale and a two-point scale. On the Likert scale, the four possible answers, "better than usual", "same as usual", "worse than usual", and "much worse than usual", were assigned scores of 0, 0, 1, and 1, respectively. The minimum possible total score for each scale was 0, and the maximum possible score was 7. The Cronbach's alpha was 0.756 in this study and showed acceptable internal consistency.

NP tests

Participants' NP states were assessed using the 14 NP tests for eight cognitive domains: Verbal Fluency (category and letter) in verbal/language (*29*), Digit Span (forward and backward) in attention/working memory (*30*), Trail Making Test (TMT)-A (*31*) and Digit Symbol Subset (*30*) in speed of information processing, TMT-B (*31*) in executive function, Rey-Osterrieth Complex Figure test (ROCFT) (*32,33*) in visuospatial construction, ROCFT (immediate) and Story Memory Test (SMT) (*34*) in verbal and visual learning, ROCFT (delayed recall), SMT (delayed recall), and Grooved Pegboard (dominant and non-dominant) (*35*) in motor skills.

Assessment of imaging

Brain MRIs were performed on a clinical 3.0-Tesla MRI unit (MAGNETOM Verio; Siemens AG, Erlangen, Germany). These included three-dimensional T1-weighted images (magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo sampling) used for the computed analysis of Voxel-based Specific Regional Analysis System for Alzheimer's disease (*36*), T2-weighted images to evaluate microbleeding, MR angiography to evaluate cerebrovascular disorder, diffusion-weighted images to evaluate acute or subacute cerebrovascular attack, and T2-weighted images and fluid-attenuated inversion recovery images to evaluate general brain disorders. All MRIs were evaluated by an observer (TN) with 10 years of experience in neuroradiology.

For brain fluorodeoxyglucose positron emission tomography/computerized tomography (FDG-PET/

CT), ^{18}F-FDG was synthesized in the hospital using a cyclotron (F200, Sumitomo Heavy Industries, Ltd.) at the NCGM. Participants fasted for > 6 h. After resting for more than 15 min with an eye mask in a decubitus position in a dark, quiet room, the ^{18}F-FDG (5 MBq/kg; lower limit, 185 MBq; upper limit, 370 MBq) was injected intravenously. The conditions described were maintained until imaging was performed. Imaging was initiated with PET/CT equipment (Biograph mCT S20; Siemens Medical Solutions) 45 min after ^{18}F-FDG administration. Blood glucose levels at the time of scanning were confirmed to be ≤ 200 mg/dL in all participants. The PET data were analyzed using the data analysis software SIEMENS, MI Neurology, in which 18 regions were set: left/right frontal lobes, left/right temporal lobes, left/right parietal lobes, left/right cingulate and paracingulate gyri, left/right central regions, left/right occipital lobes, left/right basal ganglia, left/right mesial temporal lobes, and left/right cerebellum. The ^{18}F-FDG accumulation in each region (mean standardized uptake value; SUV) was measured, and the standard deviations (SD) of the mean SUV were compared. The mean value of the accumulation in the left and right regions, of which the SD was the smallest, was set as the value for the control region. The ratios of the values of the other 16 regions to the control value (SUVr) were calculated for the assessment.

Statistical analysis

A chi-squared analysis was used to compare the prevalence of mood problems between HPH and HPnH. Mood problems included *t*-scores of 60 and above on the five subscales of the POMS: tension–anxiety, depression–dejection, anger–hostility, and fatigue and confusion (*22*). The *t*-scores for mild to moderate problems ranged from 60 to 75, and those for severe problems ranged from 76 and above for *t*-score in five subscales. On the vigor scale, low vigor was a mood problem and included a *t*-score of 40 and below. Mild to moderate problems ranged from 26 to 40, and severe problems were 25 and below for the *t*-score in vigor. Data were expressed as the median (interquartile range [IQR]). To investigate the factors associated with low vigor in HPH, a Mann–Whitney *U* test and chi-squared analyses with two groups (high and low vigor in HPH) were conducted. Serious issues regarding health were indicated by a score of 5 or more points for the total GHQ score. Moreover, in the GHQ subscale, moderate symptoms were indicated by a score of 4 or higher in somatic symptoms, and 3 or higher in anxiety/insomnia, social dysfunction, and severe depression (*23,24*). In addition, regarding the assessment of imaging, the Mann–Whitney *U* test was performed to compare the two groups (high and low vigor in HPH). Tests were two-tailed, with $\alpha = 0.05$ as the criterion for significance. All data were analyzed using IBM SPSS Statistics 26.0. Values of $p < 0.05$ were considered statistically significant.

Ethical considerations

This cross-sectional observational study was approved by the ethics committee of the National Center for Global Health and Medicine (NCGM; Nos. NCGM-G-001973-0 and NCGM-G-003055-00). This study followed the principles of the Declaration of Helsinki. All study participants provided written informed consent prior to study enrollment.

Results

Eighty-two HPH received outpatient treatment at the NCGM. Of these, eight patients satisfied exclusion criteria, nine patients refused to participate in this study, one patient withdrew consent for participation, and one patient did not undergo the POMS, GHQ, or NP testing during the study period; thus, 63 patients underwent the testing and medical examination by a psychiatrist. Ten patients were diagnosed with psychiatric disorders: schizophrenia ($n = 1$), bipolar disorder ($n = 1$), dysthymia ($n = 2$), developmental disorder ($n = 2$), alcoholism ($n = 1$), and sleep disorder ($n = 3$). Of these, three patients with psychiatric disorders that could affect cognitive function (schizophrenia, bipolar disorder, and alcoholism) and four patients with unavailable recent brain imaging findings were excluded. Finally, 56 patients were included in the analysis.

Regarding the control group comprising HPnH, 716 HIV-infected patients were recruited; 205 patients were excluded based on the exclusion criteria, and the remaining 388 patients completed the same tests, except for GHQ-28, brain MRI, and FDG-PET/CT scans. The routes of HIV infection in HPnH included sexual transmission ($n = 385$) and other and unknown ($n = 3$). In Japan, the transmission route is relatively identifiable; thus, when a patient is diagnosed with HIV infection, the doctor is required to confirm the symptoms and transmission route with the patient and notify the health center. This information was used in this study.

Mood problems in HPH and HPnH

Figure 1 shows the differences in the prevalence of mood problems between HPH and HPnH. HPH had a significantly lower prevalence of tension–anxiety (HPH, 7%; HPnH, 18%; $p = 0.049$, power = 0.445) and a significantly higher prevalence of low vigor (HPH, 63%; HPnH, 32%; $p < 0.001$, power = 0.859).

Association factors with low vigor in HPH

Table 1 shows the sample characteristics and factors associated with low vigor among HPH. Regarding the factors associated with low vigor in HPH, socio-

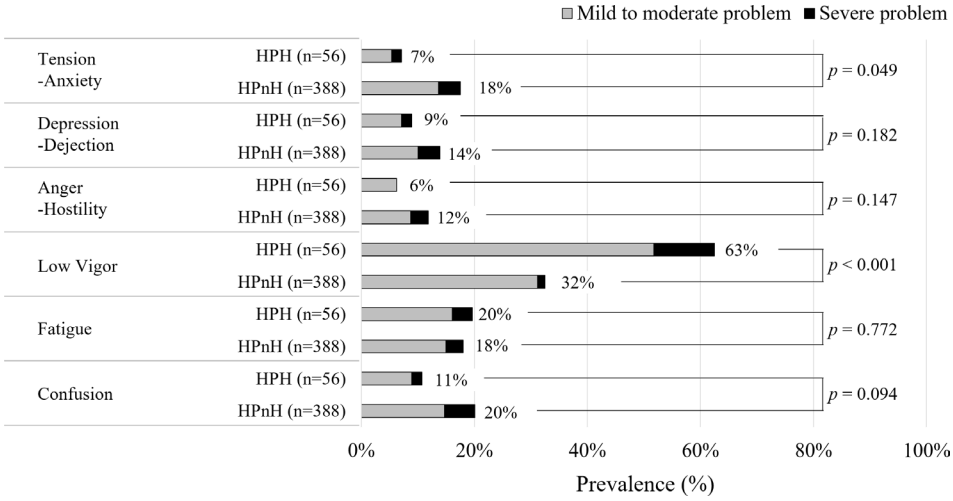

Figure 1. Prevalence of mood problems among HIV-infected patients with hemophilia (HPH) and HIV-infected patients with no hemophilia (HPnH).

demographic factors – neither HIV-related nor hemophilia-related factors – were significantly associated with vigor. However, compared with high vigor, low vigor was significantly associated with impaired executive function (low vigor, 66%; high vigor, 33%; $p = 0.019$, power = 0.4) and a social dysfunction score ≥ 3 (low vigor, 26%; high vigor, 5%; $p = 0.047$, power = 0.438). In addition, there was no difference in FDG accumulation between the high- and low-vigor groups (Table 2).

Discussion

This is one of the few studies to analyze the mental health problems of HPH in the post-ART era. Previous studies have reported low psychosocial distress and psychological quality of life in hemophilia patients in the post-ART era (*37,38*). Hirabayashi *et al.* (*37*) reported that psychological quality of life scores in patients with hemophilia were lower than those in patients with sexually transmitted infections in Japan. Further, Talaulikar *et al.* (*38*) reported that patients with chronic coagulation disorders had significantly lower vitality, general health, and physical role limitation in the measurement of health-related quality of life, compared with normative data obtained from the Australian Bureau of Statistics. Imai *et al.* (*12*) reported that HPH had a higher rate of neurocognitive dysfunction than HPnH, particularly impaired executive function.

One of the most important findings of this study is that the prevalence of low vigor among HPH was 63%, which is much higher than that among HPnH, even though they did not have a mental illness. This study suggests that low vigor among HPH is associated with a higher rate of impaired executive function and social dysfunction compared with high vigor.

Various factors can influence vigor. The reasons for low vigor among HPH were as follows: organic changes in the brain, poor exercise habits, and psychological distress owing to HIV-related stigma or multimorbidity. Long-term exposure of the central nervous system to HIV leads to organic changes in the brain. HPH were infected with HIV in the 1980s and, therefore, have likely been infected with HIV for longer than HPnH (*12*). However, the results indicate that the influence of organic factors in the brain on vigor could be less, as there was no difference in FDG accumulation between the high- and low-vigor groups.

Low vigor among HPH could be associated with exercise habits. Patients with hemophilia could have poorer exercise habits than those without hemophilia, as they have been restricted from an early age to prevent bleeding. Physical exercise enhances executive function and improves positive moods, such as vigor (*39-42*). Healthcare workers' assessment of their physical capabilities, along with the degree of hemophilic arthropathy and the risk of bleeding, can enhance their vigor. In addition, proposing an exercise program tailored to each HPH could lead to further improvement. However, to clarify these associations, multivariate analyses on HPH with vigor, executive function, and social function, using exercise habits as an indicator, as well as comparative studies involving HPH and HPnH, should be conducted. It could also be useful to conduct intervention studies to create moderate exercise programs tailored to the physical function of HPH and examine the effects of such programs on vigor, executive function, and social function.

The HPH group also experienced psychological distress owing to HIV-related stigma or multimorbidity for many years (*20,43*). Some studies have suggested an association between HIV-related stigma and psychological distress or mood (*44,45*). Long-term experiences of HIV-related stigma could have prevented HPH from connecting with people and society, affected various life events such as employment and marriage,

Table 1. Participant characteristics and association factors with low vigor in HIV-infected patients with hemophilia

Characteristics	Total *n* = 56	High Vigor (T-score > 40) *n* = 21	Low Vigor (T-score ≤ 40) *n* = 35	*p*-value
Socio-demographic characteristics				
Age (years), median (IQR)	47 (43–54)	45 (43–54)	48 (42–55)	0.728
Older than 50 years, *n* (%)	24 (43)	8 (38)	16 (46)	0.577
Gender (Male), *n* (%)	56 (100)	21 (100)	35 (100)	-
Educational level (university or higher), *n* (%)	21 (38)	8 (38)	13 (37)	0.943
Employed, *n* (%)	36 (64)	15 (71)	21 (60)	0.388
Living alone, *n* (%)	14 (25)	3 (14)	11 (31)	0.151
Current or recent smoking, *n* (%)	30 (54)	13 (62)	17 (49)	0.333
Alcohol use, *n* (%)	19 (34)	9 (43)	10 (29)	0.274
History of illicit drug use within 12 months, *n* (%)	0 (0)	21 (100)	35 (100)	-
Hypertension (SBP ≥ 140 or DBP ≥ 90 mmHg), *n* (%)	24 (43)	11 (52)	13 (37)	0.265
Diabetes (HbA1c ≥ 7.0 or on treatment), *n* (%)	9 (16)	3 (14)	6 (17)	0.778
Anemia (Male <12 g/dL, Female <10 g/dL), *n* (%)	9 (16)	2 (10)	7 (20)	0.301
HCV-Ab positive, *n* (%)	55 (98)	21 (100)	34 (97)	0.434
TPHA positive, *n* (%)	0 (0)	21 (100)	35 (100)	-
HIV-related factors				
Time since diagnosis (month), median (IQR)	314 (273–332)	408 (404–411)	408 (404–414)	0.799
History of AIDS-defining illness, *n* (%)	7 (13)	3 (14)	4 (11)	0.754
Current CD4 (cells/mm^3), median (IQR)	525 (342–662)	520 (336–631)	540 (342–765))	0.283
Nadir CD4 (cells/mm^3), median (IQR)	141 (91–184)	150 (70–167)	131 (87–199)	0.788
Current HIV-RNA < 20 (copies/mL), *n* (%)	49 (89)	18 (86)	31 (91)	0.528
History of incomplete virological suppression, *n* (%)	20 (36)	8 (38)	12 (34)	0.773
Current antiretroviral therapy use, *n* (%)	55 (98)	20 (95)	35 (100)	0.375
Current antiretroviral treatment				
NNRTI-based regimen, *n* (%)	15 (27)	4 (19)	11 (31)	0.311
PI-based regimen, *n* (%)	18 (32)	5 (24)	13 (37)	0.301
INSTI-based regimen, *n* (%)	41 (73)	16 (76)	25 (71)	0.697
Hemophilia-related factors				
Hemophilia A, *n* (%)	45 (80)	17 (81)	28 (80)	0.609
Hemophilia B, *n* (%)	11 (20)	4 (19)	7 (20)	
Presence of history of cerebrovascular disorder, *n* (%)	13 (23)	2 (10)	11 (31)	0.056
Presence of hemophilic arthropathy, *n* (%)	30 (54)	9 (43)	21 (60)	0.213
Neuropsychological factors				
Neuropsychological impairment, *n* (%)	27 (48)	9 (43)	18 (51)	0.534
Impaired cognitive domain				
Verbal/language, *n* (%)	2 (4)	1 (5)	1 (3)	0.614
Attention/working memory, *n* (%)	7 (13)	1 (5)	6 (17)	0.176
Speed of information processing, *n* (%)	13 (23)	3 (14)	10 (29)	0.186
Executive function, *n* (%)	30 (54)	7 (33)	23 (66)	0.019
Visuospatial construction, *n* (%)	14 (25)	5 (24)	9 (26)	0.873
Verbal and visual learning, *n* (%)	10 (18)	4 (19)	6 (17)	0.857
Verbal and visual memory, *n* (%)	8 (14)	3 (14)	5 (14)	0.644
Motor skills, *n* (%)	9 (16)	1 (5)	8 (23)	0.075
GHQ-28				
Somatic symptoms score ≥ 4 (moderate), *n* (%)	14 (25)	3 (14)	11 (31)	0.151
Anxiety/insomnia score ≥ 4 (moderate), *n* (%)	8 (14)	3 (14)	5 (14)	0.644
Social dysfunction score ≥ 3 (moderate), *n* (%)	10 (18)	1 (5)	9 (26)	0.047
Severe depression score ≥ 3 (moderate), *n* (%)	4 (7)	0 (0)	35 (11)	0.143

HCV-Ab, hepatitis C antibody; TPHA, Treponema pallidum latex agglutination; NRTI, Nucleoside reverse transcriptase inhibitor; NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; INSTI, integrase inhibitors; GHQ, General Health Questionnaire.

and reduced their vigor. Multimorbidity – the presence of two or more chronic physical conditions (*46*) – may also influence the vigor of HPH. Patients with multimorbidity tend to experience psychological distress (*47*). HPH have many chronic physical conditions, such as hemophilic arthropathy, muscle hemorrhage,

Table 2. Comparison of SUVr values between high and low vigor in HIV-infected patients with hemophilia (HPH)

	Total $n = 55$	High Vigor (T-score > 40) $n = 21$	Low Vigor (T-score ≤ 40) $n = 34$	*p*-value
Frontal lobe (L)	1.17 (1.10–1.23)	1.17 (1.11–1.26)	1.17 (1.10–1.22)	0.499
Frontal lobe (R)	1.18 (1.09–1.23)	1.18 (1.10–1.26)	1.18 (1.09–1.23)	0.579
Temporal lobe (L)	1.15 (1.08–1.21)	1.16 (1.09–1.19)	1.14 (1.08–1.21)	0.377
Temporal lobe (R)	1.19 (1.10–1.24)	1.19 (1.11–1.23)	1.18 (1.10–1.26)	0.795
Parietal lobe (L)	1.15 (1.09–1.23)	1.18 (1.12–1.24)	1.12 (1.09–1.24)	0.368
Parietal lobe (R)	1.17 (1.10–1.24)	1.18 (1.11–1.22)	1.17 (1.10–1.25)	0.903
Cingulate and paracingulate gyri (L)	1.17 (1.12–1.24)	1.17 (1.14–1.25)	1.17 (1.09–1.24)	0.556
Cingulate and paracingulate gyri (R)	1.21 (1.15–1.28)	1.21 (1.16–1.29)	1.22 (1.14–1.27)	0.621
Central region (L)	1.12 (1.05–1.17)	1.12 (1.05–1.16)	1.12 (1.06–1.17)	0.678
Central region (R)	1.14 (1.06–1.20)	1.14 (1.08–1.20)	1.14 (1.06–1.20)	0.568
Occipital lobe (L)	1.16 (1.12–1.23)	1.18 (1.12–1.23)	1.16 (1.11–1.23)	0.591
Occipital lobe (R)	1.21 (1.14–1.26)	1.22 (1.15–1.28)	1.21 (1.13–1.25)	0.640
Basal ganglia (L)	1.22 (1.15–1.27)	1.20 (1.16–1.27)	1.23 (1.14–1.27)	0.959
Basal ganglia (R)	1.18 (1.15–1.23)	1.17 (1.14–1.23)	1.18 (1.14–1.23)	0.652
Mesial temporal lobe (L)	0.91 (0.87–0.96)	0.91 (0.87–0.96)	0.91 (0.87–0.95)	0.903
Mesial temporal lobe (R)	0.92 (0.88–0.97)	0.92 (0.88–0.98)	0.92 (0.88–0.96)	0.795
Thalamus (L)	1.16 (1.11–1.25)	1.22 (1.11–1.26)	1.15 (1.11–1.24)	0.416
Thalamus (R)	1.17 (1.09–1.23)	1.20 (1.09–1.24)	1.14 (1.09–1.23)	0.579

Data are median (interquartile range; IQR). SUVr, Standard uptake value ratio; L, left; R, right.

HCV, hemophilia, and HIV infection; therefore, their vigor could have been low. Although the association between a history of cerebrovascular disorder and low vigor was not significant in this study, a significant trend was observed. It is quite difficult to remove HIV-related stigma from society or to cure multimorbidity completely. However, providing a space (*e.g.*, mental health counseling, psychotherapy, or self-help groups) where these patients can feel comfortable talking about the long-term emotional burden of these problems could help prevent a decline in vigor or mental health deterioration. In addition, previous studies suggest that supplementation with a multi-vitamin/mineral leads to improved vigor ratings and improved cognitive performance (*48-50*). Therefore, we suggest that healthcare workers pay attention to the vigor, executive function, and social function of HPH – even if they do not have a mental illness – and that they help HPH enhance their health through exercise tailored to the physical condition of each patient, by offering mental healthcare, or by promoting the use of multi-vitamin-mineral supplements.

Despite its valuable findings, our study had some limitations. First, although the facility from which participants were recruited is one of the largest hospitals in Japan providing HIV treatment and treating several HPH, our sample was not representative of the entire population of HPH in Japan. Second, the sample size of 56 HPH was insufficient to conduct statistical testing and compare the high- and low-vigor groups; therefore, a multicenter survey should be conducted to increase the sample size and improve the accuracy of the results in the future. Third, two or more psychiatrists should be asked to examine a patient's mental status to further improve the accuracy of psychiatric diagnosis. Fourth, although this study applied a self-administered anonymous questionnaire – the POMS and GHQ-28 – potentially biased self-reports cannot be ruled out.

In conclusion, the prevalence of low vigor among Japanese HPH without mental illness is high. Those with low vigor had impairments in executive and social functions. Therefore, healthcare providers should approach patients' low vigor by suggesting exercise programs that are appropriate for their physical and medical condition, providing a safe space to talk about the problems of living with multimorbidity in a society with HIV-related stigma, and promoting the use of multi-vitamin supplements. Thereafter, the effectiveness of such interventions should be scientifically tested.

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