Human T-cell lymphotropic virus type-1 infection associated with sarcopenia: community-based cross-sectional study in Goto, Japan

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ABSTRACT

Sarcopenia is characterized by a progressive skeletal muscle disorder that involves the loss of muscle mass and low muscle strength, which contributes to increased adverse outcomes. Few studies have investigated the association between chronic infection and sarcopenia. This study aimed to examine the association between human T-cell lymphotropic virus type-1 (HTLV-1) and sarcopenia. We conducted a cross-sectional study and enrolled 2,811 participants aged ≥ 40 years from a prospective cohort study in Japanese community dwellers during 2017–2019. Sarcopenia was defined as low appendicular skeletal muscle mass and low handgrip strength. The association between HTLV-1 seropositivity and sarcopenia was assessed using multivariable logistic regression. Odds ratio (OR) and 95% confidence interval (CI) of sarcopenia were analysed using HTLV-1 seropositivity. We adjusted for age, sex, body mass index, physical activity, systolic blood pressure, glycated haemoglobin, low-density lipoprotein cholesterol, and smoking and drinking status. Of 2,811 participants, 484 (17.2%) HTLV-1 infected participants were detected. HTLV-1 infection was significantly associated with
sarcopenia (adjusted OR 1.46, 95% CI 1.03–2.07, P = 0.034). HTLV-1 was associated with sarcopenia among community-dwelling adults. Active surveillance and early detection of asymptomatic HTLV-1 infection might be beneficial to reinforce countermeasures to inhibit the progress of HTLV infection-associated sarcopenia.

INTRODUCTION

Sarcopenia is characterized by a progressive and generalized skeletal muscle disorder that involves the accelerated loss of muscle mass and low muscle strength [1]. Sarcopenia, a major problem associated with aging, is listed in the International Classification of Diseases-10 code [2], and is associated with increased adverse outcomes including falls, disability, hospital admission, long term care placement, poor quality of life, and mortality [3–5]. Estimates of disease frequency have varied, but became more precise with the evolution of its definition. One of the lowest pooled prevalence estimates (12.9% [95% confidence interval; CI 9.9–15.5]) was calculated using a 2010 definition of the European Working Group on Sarcopenia in Older People [1, 6]. Sarcopenia has a medical and economic burden; the total estimated cost of hospitalizations of individuals with sarcopenia in the USA was USD $40.4 billion with a mean per person cost of USD $260 [7].

Factors that cause and worsen sarcopenia are categorised as primary and secondary. Known risk factors include changes in sex steroid hormones and cytokines associated with aging, genetic susceptibility (as primary sarcopenia), physical inactivity, smoking, low 1,25-(OH) vitamin D, low nutritional intake, low protein intake, and atherosclerosis (as secondary sarcopenia) [6, 8–17].

A recent study reported that sarcopenia was more prevalent in a community cohort of human immunodeficiency virus (HIV) infection [18]. In the cross-sectional analysis of 315 HIV-infected cases and matched controls, sarcopenia was more prevalent in HIV-infected cases compared with matched controls [19]. Except for HIV infection, however, no study has investigated the association between chronic infection and sarcopenia.

Human T-cell lymphotropic virus type-1 (HTLV-1) was the first retrovirus shown to cause diseases including adult T-cell leukaemia, HTLV-1 associated myelopathy/tropic spastic paraparesis, polynymositis and dermatomyositis [20–22]. HTLV-1-infected CD4+ T-lymphocytes were found to infiltrate the muscle of patients with inflammatory myopathies, and cytotoxic T-lymphocyte immune reactions to the TAX gene induced tumour necrosis factor-alpha and cytotoxic effects on muscles [22]. However, little is known about the effect of HTLV-1 infection on muscles in asymptomatic carriers.

We hypothesized that chronic inflammation caused by HTLV-1 infection has a negative impact on skeletal muscle and strength. However, the relationship between HTLV-1 infection and sarcopenia has not been investigated to date. The aim of this study was to investigate whether there is an association between HTLV-1 infection and sarcopenia and to examine whether chronic inflammation is associated with sarcopenia.

RESULTS

General characteristics of the study population

Among 2,811 participants with a mean age of 70 years (standard deviation [SD] ± 10.0), 502 (18%) HTLV-1-infected participants were detected using a chemiluminescent enzyme immunoassay (CLEIA). Samples from 488 of these 502 participants were available for real-time PCR (RT-PCR) testing. Of these 474 were positive for HTLV-1 and 14 were negative by RT-PCR. For the negative cases, western blotting showed that three cases were positive, one was negative, one was indeterminate, and Innogenetics line immunoassay showed that seven cases were positive, one was indeterminate, and one was negative. The 484 (17%) participants who were positive for HTLV-1 by RT-PCR, western blotting or Innogenetics line immunoassay were included in the analysis.

Table 1 shows the characteristics of participants with HTLV-1 infection. Compared with HTLV-1-uninfected participants, HTLV-1-infected participants included a lower proportion of men (29.1% vs 39.8%, P < 0.001), and those with older age (mean age 74.0 vs 69.4, P < 0.001), lower weight (55.6 kg vs 57.8 kg, P < 0.001), lower handgrip strength (24.7 kg vs 28.4 kg, P < 0.001), lower appendicular skeletal muscle mass (ASM) (15.4 kg vs 16.5 kg, P < 0.001), and higher proportion of antihypertensive drug use (50.6% vs 40.7%, P < 0.001). The body mass index (BMI), proportion of hypoglycaemic drug use, lipid-lowering drug use, physical activity, systolic blood pressure (SBP), glycated haemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL), triglycerides (TG), high sensitive C-reactive protein (hs-CRP), and white blood cells (WBC) were not different between HTLV-1-infected participants and HTLV-1-uninfected participants.
Table 1. Demographic and clinical characteristics of HTLV-1 infected and uninfected participants.

|                      | HTLV-1 uninfected Mean ± SD or N (%) | HTLV-1 infected Mean ± SD or N (%) | P-value |
|----------------------|-------------------------------------|-----------------------------------|---------|
| N                    | 2327 (82.8)                         | 484 (17.2)                        | <0.001  |
| Age (year)           | 69.4 ± 10.1                         | 74.0 ± 8.2                        | <0.001  |
| Sex (male)           | 925 (39.8)                          | 141 (29.1)                        | <0.001  |
| Height (cm)          | 156.7 ± 8.8                         | 153.3 ± 8.2                       | <0.001  |
| Weight (kg)          | 57.8 ± 10.4                         | 55.6 ± 9.8                        | <0.001  |
| Body mass index      | 23.4 ± 3.1                          | 23.6 ± 3.3                        | 0.604   |
| Handgrip strength (kg)| 28.4 ± 9.6                         | 24.7 ± 8.8                        | <0.001  |
| Appendicular skeletal muscle mass (kg) | 16.5 ± 4.1 | 15.4 ± 3.7 | <0.001  |
| Sarcopenia           | 143 (6.2)                           | 59 (12.2)                         | <0.001  |
| Smoking status       |                                     |                                   |         |
| Current              | 230 (9.9)                           | 26 (5.4)                          |         |
| Past                 | 568 (24.4)                          | 92 (19.0)                         |         |
| Never                | 1529 (65.7)                         | 366 (75.6)                        |         |
| Drinking status      |                                     |                                   | 0.019   |
| Current              | 850 (36.5)                          | 145 (30.0)                        |         |
| Past                 | 96 (4.1)                            | 19 (3.9)                          |         |
| Never                | 1381 (59.4)                         | 320 (66.1)                        |         |
| Antihypertensive drug use | 946 (40.7) | 245 (50.6) | <0.001  |
| Hypoglycemic drug use | 157 (6.8)                           | 37 (7.6)                          | 0.478   |
| Lipid-lowering drug use | 483 (20.8) | 108 (22.3) | 0.444   |
| Physical activity    | 1.23 ± 0.76                         | 1.23 ± 0.77                       | 0.889   |
| Systolic blood pressure (mmHg) | 134.8 ± 18.1 | 135.7 ± 18.1 | 0.214   |
| Diastolic blood pressure (mmHg) | 75.7 ± 11.0 | 74.3 ± 10.5 | 0.018   |
| Glycated haemoglobin (%) | 5.76 ± 0.55 | 5.77 ± 0.51 | 0.147   |
| Low-density lipoprotein cholesterol (mg/dl) | 122.2 ± 30.4 | 117.9 ± 29.9 | 0.014   |
| High-density lipoprotein cholesterol (mg/dl) | 61.8 ± 15.2 | 60.4 ± 15.0 | 0.055   |
| Triglycerides (mg/dl) | 105.2 ± 60.8                        | 106.5 ± 65.1                      | 0.595   |
| High sensitive C-reactive protein (μg/dl) a | (191, 389, 827) | (190, 423, 923) | 0.187   |
| White blood cells (/μl)b | (4500, 5300, 6300) | (4500, 5300, 6400) | 0.503   |

Data on high sensitive C-reactive protein and white blood cells were expressed as the median and interquartile range.

a N=2712, b N=2804
c P values from Wilcoxon rank sum test.
d P values from McNemar chi-square test.

Sarcopenia and HTLV-1 infection

In univariable linear regression analysis, HTLV-1 infection had a positive association with sarcopenia (β = 0.09, P < 0.001) (Table 2). The standardized β coefficient was positively significant for age, antihypertensive agent use, hypoglycaemic agent use, SBP and WBC. This coefficient was inversely significant for male sex, height, weight, BMI, smoking and drinking status, diastolic blood pressure and HDL.

In logistic regression analysis, HTLV-1 infection was significantly associated with low handgrip strength (odds ratio [OR] 2.06, 95% CI 1.62–2.62, P < 0.001). This association remained significant after further adjustment for age, sex, BMI, physical activity, SBP, HbA1c, low-density lipoprotein cholesterol (LDL), and smoking and drinking status (adjusted OR [aOR] 1.35, 95% CI 1.04–1.76, P = 0.024) (Table 3). HTLV-1 infection was associated with low skeletal muscle mass index (SMI) (OR 1.24, CI 1.01–1.53, P = 0.040), but this association was not significant after further adjustment (aOR 1.11, 95% CI 0.87–1.40, P = 0.402).

HTLV-1 infection was significantly associated with sarcopenia (OR 2.12, 95% CI 1.54–2.92, P < 0.001), and remained significant after further adjustment (aOR 1.46, 95% CI 1.03–2.07, P = 0.034).

We also tested the association between HTLV-1 infection and sarcopenia among participants who were
Table 2. Univariable linear regression analysis for the effect of each exposure on handgrip strength, appendicular skeletal muscle mass and sarcopenia (N=2811).

| Variable                        | Handgrip strength | Appendicular skeletal muscle mass | Sarcopenia |
|--------------------------------|-------------------|----------------------------------|------------|
|                                | β   | P-value | β   | P-value | β   | P-value |
| HTLV-1 infection               | -0.14 | <0.001 | -0.11 | <0.001 | 0.09 | <0.001 |
| Age (year)                     | -0.38 | <0.001 | -0.24 | <0.001 | 0.24 | <0.001 |
| Sex (male)                     | 0.71  | <0.001 | 0.63  | <0.001 | -0.04 | 0.041 |
| Height (cm)                    | 0.73  | <0.001 | 0.74  | <0.001 | -0.22 | <0.001 |
| Weight (kg)                    | 0.57  | <0.001 | 0.68  | <0.001 | -0.22 | <0.001 |
| Body mass index                | 0.13  | <0.001 | 0.27  | <0.001 | -0.14 | <0.001 |
| Smoking status                 | 0.51  | <0.001 | 0.45  | <0.001 | -0.05 | 0.013 |
| Drinking status                | 0.42  | <0.001 | 0.37  | <0.001 | -0.06 | 0.001 |
| Antihypertensive agent use     | -0.12 | <0.001 | -0.04 | 0.044  | 0.10 | <0.001 |
| Hypoglycemic agent use         | -0.01 | 0.568  | 0.05  | 0.008  | 0.04 | 0.042 |
| Lipid-lowering drugs use       | -0.07 | <0.001 | -0.06 | 0.003  | 0.04 | 0.059 |
| Physical activity              | 0.03  | 0.166  | 0.01  | 0.673  | -0.03 | 0.067 |
| Systolic blood pressure (mmHg) | -0.08 | <0.001 | -0.08 | <0.001 | 0.06 | 0.001 |
| Diastolic blood pressure (mmHg)| 0.14  | <0.001 | 0.09  | <0.001 | -0.04 | 0.045 |
| Glycated haemoglobin (%)       | -0.01 | 0.640  | 0.03  | 0.107  | 0.01 | 0.682 |
| Low-density lipoprotein cholesterol (mg/dl) | -0.05 | 0.010  | -0.07 | <0.001 | -0.03 | 0.102 |
| High-density lipoprotein cholesterol (mg/dl) | -0.14 | <0.001 | -0.18 | <0.001 | -0.05 | 0.010 |
| Triglycerides (mg/dl)          | 0.08  | <0.001 | 0.07  | 0.001  | -0.02 | 0.348 |
| High sensitive C-reactive protein (µg/dl)  | 0.00  | 0.935  | 0.04  | 0.019  | 0.03 | 0.172 |
| White blood cells (/µl)         | 0.10  | <0.001 | 0.07  | <0.001 | 0.05 | 0.009 |

<sup>a</sup>N=2712, <sup>b</sup>N=2804

Table 3. Adjusted odds ratio and 95% confidence interval for HTLV-1 infection in relation to sarcopenia (N=2811).

| Variable                        | Low handgrip strength | Low appendicular skeletal muscle mass | Sarcopenia |
|--------------------------------|-----------------------|--------------------------------------|------------|
|                                | aOR  | 95% CI | P-value | aOR  | 95% CI | P-value | aOR  | 95% CI | P-value |
| Model 1                         | 1.38 | (1.06, 1.79) | 0.016 | 1.09 | (0.86, 1.37) | 0.473 | 1.48 | (1.05, 2.09) | 0.027 |
| Model 2                         | 1.35 | (1.04, 1.76) | 0.024 | 1.11 | (0.87, 1.40) | 0.402 | 1.46 | (1.03, 2.07) | 0.034 |

Model 1. Adjusted for age, sex and body mass index.
Model 2. Model 1 + physical activity, systolic blood pressure, glycated haemoglobin, low-density lipoprotein cholesterol, smoking and drinking status.

<sup>a</sup>OR: adjusted odds ratio, CI: confidence interval.

excluded as premenopausal women to avoid pre/postmenopausal changes to muscle mass and strength. The aOR did not differ after excluding premenopausal women (aOR 1.46, 95% CI 1.03–2.06, P = 0.035).

Sarcopenia and inflammatory markers

Logistic regression analysis was performed to examine the association between sarcopenia and inflammatory markers (logarithm of hs-CRP and WBC). Hs-CRP was significantly associated with low SMI after adjustment for age, sex, BMI, physical activity, SBP, HbA1c, LDL, and smoking and drinking status (aOR 1.19, 95% CI 1.10–1.29, P < 0.001) (Table 4). WBC was significantly associated with low SMI and sarcopenia after adjustment (aOR 2.31, 95% CI 1.62–3.31, P < 0.001; aOR 3.26, 95% CI 1.77–5.99, P < 0.001, respectively).

**DISCUSSION**

This community-based cross-sectional study demonstrated that asymptomatic HTLV-1 infection is a risk factor for sarcopenia. To the best of our knowledge, this is the first report to show chronic HTLV-1 infection is a risk factor for sarcopenia. In addition, inflammatory markers were identified as risk factors for low SMI and sarcopenia.
Sarcopenia has recently been recognized as an emerging issue in HIV infection [18]. Multicenter AIDS cohort studies of over 7000 HIV patients in the USA reported that handgrip strength and walking speed declined more rapidly in HIV infected people compared with uninfected controls [23, 24]. In these studies, the authors suggested the possible mechanism of functional decline might have resulted from inflammation induced by co-infection with hepatitis C virus, diabetes mellitus, chronic kidney disease, or peripheral neuropathy. In a cross-sectional study in Malaysia, HIV-infected individuals had a higher proportion of sarcopenia defined by the Asian Working Group for Sarcopenia than HIV-uninfected individuals [17% (n = 8) vs 4% (n = 2), P = 0.049] [19]. In that study, the authors suggested that higher sarcopenia susceptibility in HIV-infected individuals was associated with chronic immune activation and inflammation. Contrary to symptomatic HIV infection under antiretroviral therapy, participants of our study were asymptomatic carriers of HTLV-1 infection and were not treated with any viral therapy. Therefore, there was no bias related to drug-induced modification of the association between HTLV-1 infection and sarcopenia in our study. Furthermore, our results suggested that HTLV-1 infection might have a cumulative risk for sarcopenia, even in the asymptomatic phase.

A putative mechanism of HTLV-1 associated sarcopenia is warranted. Potential explanations include anabolic resistance induced by inflammation and triggered catabolism. Because HTLV-1 promotes the production of cytokines such as interferon-gamma, tumour necrosis factor-alpha, and interleukin-6 [25], through the activation of nuclear factor-kB and cyclic AMP response element-binding protein [26], inflammatory factors might be induced even during asymptomatic infection. CRP and WBC are well-known surrogate markers of infection, and are activated by interleukin-6 or tumour necrosis factor-alpha produced by monocytes or macrophages. Inflammation contributes to the impaired mammalian/mechanistic target of rapamycin signalling (anabolic resistance), which leads to insufficient muscle protein synthesis [27]. Furthermore, inflammatory cytokines also promote protein catabolism [28].

Another putative pathway of HTLV-1 associated sarcopenia is an overabundance of reactive oxygen species (ROS). HTLV-1 encodes viral structural genes of the pX region encoding TAX, which increases the production of ROS [29, 30]. ROS, chemically unstable reactive free radicals that cause endothelial dysfunction, were reported as risk factors for sarcopenia [31]. ROS contribute to age-related deficits in muscle through increased oxidative damage to cell constituents and/or through the induction of defective redox signalling. ROS induced oxidative stress also damages other cellular components such as DNA, proteins, and lipids resulting in further damage to the cells and tissues. Consequently, the intra and intercellular membranes of the muscle fibres, in particular those of the sarcoplasmic reticulum, may be modified and the Ca2+ transport mechanism altered [32].

In a retrospective study, thirteen French HTLV-1 infected-patients with polymyositis or dermatomyositis showed moderate muscle inflammation compared with HTLV-1 infected-controls without myopathy. However, the level of the proviral load did not differ between these groups [22]. Although a high proviral load is a major risk factor for adult T-cell leukaemia and HTLV-1 associated myelopathy/tropic spastic paraparesis [33], level of proviral load was not a determinant of HTLV-1 infection inducing muscle inflammation [22]. Therefore, even though HTLV-1 infected study participants were asymptomatic carriers, HTLV-1 infection may lead to subclinical muscle inflammatory reaction and sarcopenia.

### Table 4. Adjusted odds ratio and 95% confidence interval for sarcopenia in relation to inflammatory markers.

| Variable                      | Model | Low handgrip strength | Low appendicular skeletal muscle mass index | Sarcopenia |
|-------------------------------|-------|-----------------------|--------------------------------------------|------------|
|                               |       | aOR  95% CI            | P-value                                    | aOR  95% CI | P-value | aOR  95% CI | P-value |
| High sensitive CRP (logarithm) | Model 1 | 1.04 (0.94, 1.15)   | 0.450                                      | 1.19 (1.10, 1.29) | <0.001 | 1.12 (0.98, 1.27) | 0.089 |
|                               | Model 2 | 1.04 (0.94, 1.14)   | 0.490                                      | 1.19 (1.10, 1.29) | <0.001 | 1.10 (0.96, 1.25) | 0.156 |
| White blood cells (logarithm)  | Model 1 | 1.44 (0.93, 2.23)   | 0.104                                      | 2.32 (1.64, 3.29) | <0.001 | 3.37 (1.86, 6.11) | <0.001 |
|                               | Model 2 | 1.46 (0.93, 2.29)   | 0.097                                      | 2.31 (1.62, 3.31) | <0.001 | 3.26 (1.77, 5.99) | <0.001 |

Model 1. Adjusted for age, sex and body mass index.
Model 2. Model 1 + physical activity, systolic blood pressure, glycated haemoglobin, low-density lipoprotein cholesterol, smoking and drinking status.

aOR: adjusted odds ratio, CI: confidence interval.
The associations between HTLV-1 infection and low handgrip strength, and HTLV-1 infection and sarcopenia were significant, but not between HTLV-1 infection and low SMI. These inconsistent results may be partially explained by the loss of muscle strength, which is typically clinically apparent before the loss of muscle mass. Data from a longitudinal study in Baltimore showed that a decline in muscle strength was much greater than that predicted by the decline in muscle mass [32].

Some limitations of the present study should be mentioned. First, as this was a cross-sectional study, we were not able to establish cause–effect relationships. Second, we had no data on the infectious period of each participant. Because effects of HTLV-1 infection on sarcopenia progression are thought to be cumulative, differences in the duration of infection may bias the results. Third, although the study participants were recruited from healthy community dwellers, we cannot deny the mixture of HTLV-1 infected-patients with polymyositis or dermatomyositis. However, although the association between HTLV-1 infection and sarcopenia was not significant, the same tendency was observed after excluding participants with joint pain (n = 639), which is a common symptom of inflammatory myopathy (aOR 1.47, 95% CI 0.98–2.21, P = 0.062) [34].

In conclusion, HTLV-1 was associated with sarcopenia in Japanese community dwellers. Similar to HIV infection, active surveillance and early detection of asymptomatic HTLV-1 infection might help reinforce countermeasures to prevent and inhibit the progress of HTLV-1 infection associated sarcopenia.

MATERIALS AND METHODS

Study settings and participants

We conducted this cross-sectional study using data from the Nagasaki Islands Study, which was a prospective cohort study performed in Goto City in the western islands of Japan [35]. Details of the selection process and procedures of the examination in this study were published previously [35, 36].

The participants were recruited at medical check-ups, and members of the general population aged ≥ 40 years living in Goto City were targeted for enrolment. The Ethical Committee of Nagasaki University approved this study (project registration number: 14051404, 20141002-5; Nagasaki, Japan), which was conducted according to the ethical standards defined in the 1964 Declaration of Helsinki as well as its subsequent amendments. Written informed consent was obtained from all participants. Of 3,365 participants enrolled from 2017 to 2019, 2,811 participants were included after exclusion for the following: age <40 years (n = 73), history of stroke (n = 155), BMI < 18.5 to avoid the effects of undernutrition on sarcopenia (n = 233), missing data for HTLV-1 serostatus (n = 14), handgrip strength (n = 7), ASM (n = 70), LDL (n = 1), and history of hypoglycaemic agent use (n = 1). Finally, 2,811 participants (1,066 men and 1,745 women) with a mean age of 70.2 years (SD, 10.0 years; range, 40–97 years) were evaluated.

Data collection and laboratory measurements

Body weight and height were measured with participants wearing light-weight clothes and without shoes, and the BMI was then calculated. Body composition was analysed by multi-frequency bioelectrical impedance analysis using InBody 430 (InBody Japan, Tokyo, Japan). The muscle mass of the four limbs as ASM was summed. SMI (kg/m^2) was calculated as the ASM (kg) divided by the square of the height (m) defined by Baumgartner’s formula [37]. Handgrip strength was recorded with the participant in a standing posture with his/her arm extended in a natural position. The handgrip dynamometer was adjusted for the participants so that their second proximal phalanxes were positioned around the handle. Handgrip strength was measured twice in both hands and the maximum scores of all recorded values for both sides were considered for analysis (Matsumiya Ika Seiki Seisakujo Smedley Dynamometer 0-1019-01).

SBP and diastolic blood pressure (DBP) at rest were recorded with a blood pressure measuring device (HEM-907: Omron, Kyoto, Japan). The measurements were repeated when the SBP was ≥ 140 mmHg or DBP was ≥ 90 mmHg, and the mean values were used for analyses. We used a questionnaire to obtain information regarding each participant’s medical history of stroke, use of antihypertensive agents, hypoglycaemic agents, and lipid-lowering drugs. Smoking status and drinking status were categorized as “never”, “ex”, or “current”. Physical activity was evaluated using two questions: “Do you have a daily walking habit?” and “Do you regularly exercise more than 30 minutes in a day? (Yes, No)”. Physical activity was scored as the total sum of “Yes” answers to the two questions.

Fasting blood samples were collected at the time of clinical examination. Blood samples were collected in an EDTA-2K tube, a siliconized tube, and a sodium fluoride tube. Samples from the EDTA-2K tube were used to measure the levels of WBC using an automated procedure at SRL, Inc. (Tokyo, Japan). Serum concentrations of LDL, HDL, TG, creatinine, HbA1c,
and hs-CRP were measured by standard laboratory procedures.

**Measurements of HTLV-1**

CLEIA kit (Fujiirebio Inc., Tokyo, Japan) was used for HTLV-1 detection. As a confirmatory test, we used RT-PCR using the Hydrolysis probe method with the LightCycler 480 (Roshe, Basel, Schweiz) as previously reported [38]. Sample DNA was purified from whole blood using GENE PREP STAR NA-480 (KURABO, Osaka, Japan). In addition, we used western blotting (Problot HTLV-1, Fujiirebio Inc., Tokyo, Japan) or Innogenetics line immunossay (INNO-LIA HTLV, Fujiirebio Inc., Tokyo, Japan) for the RT-PCR-negative cases.

**Definition of sarcopenia**

Patients with a handgrip strength <26 kg for men and <18 kg for women, and SMI <7.0 kg/m² for men and <5.7 kg/m² for women were diagnosed as sarcopenia using Asian cutoff values [6, 39]. Low handgrip strength or low SMI were also defined using these cutoff values.

**Statistical analyses**

Differences in mean values or proportions of variables by HTLV-1 positivity were analysed using the Wilcoxon rank sum test for continuous variables (age, height, weight, BMI, handgrip strength, ASM, physical activity, SBP, DBP, HbA1c, LDL, HDL, TG, hs-CRP and WBC), or the McNemar chi-square test for categorical variables (sex, sarcopenia, smoking status, drinking status, antihypertensive drug use, hypoglycemic drug use and lipid-lowering drug use). We performed simple linear regression analysis of handgrip strength and ASM as continuous variables. Then, we performed logistic regression analysis using clinical cutoff points of low handgrip strength, low SMI and sarcopenia. In the multivariable logistic regression analysis, adjustments were made a priori for age, BMI, SBP, HbA1c, LDL, physical activity (continuous variables), sex (dichotomous variable), and smoking and drinking status (categorical variable; never, ex, current: 1, 2, 3, respectively) [17, 35]. Age, sex, and BMI were included in adjustment Model 1. Age, sex, BMI, physical activity, SBP, HbA1c, LDL, and smoking and drinking status were included in Model 2. Because hs-CRP and WBC had a skewed distribution, they were expressed as the median and interquartile range, followed by logarithmic transformation.

Because markers of chronic inflammation may play an important role in sarcopenia progression [14], we also evaluated the association between sarcopenia and inflammation markers (hs-CRP and WBC). For sensitivity analyses, we performed analysis among participants who were excluded as premenopausal women (n = 84) because menopause is associated with a decline in oestrogen that decreases muscle mass and strength [40]. All P values for statistical tests were two-tailed and P < 0.05 was considered significant. All statistical analyses were performed using STATA v14 (StataCorp, College Station, TX, USA).

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**CONFLICTS OF INTEREST**

Hirotomo Yamanashi, Kenichi Nobusue, Fumiaki Nonaka, Yukiko Honda, Yuji Shimizu, Shin-ya Kawashiri, Mai Izumida, Yoshinao Kubo, Mami Tamai, Yasuhiro Nagata, Katsunori Yanagihara, Bharati Kulkarni, Sanjay Kinra, Atsushi Kawakami, and Takahiro Maeda declare that they have no conflicts of interest.

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