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Risk factors for frailty in elderly Japanese people who received Ningen Dock: a cross-sectional study

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Abstract

Background: Frailty is a clinical condition characterized by increased vulnerability to adverse health outcomes. Elderly people are screened for frailty as part of preventative care. However, the risk factors for frailty among older adults who undergo Ningen Dock, a comprehensive medical checkup, remain unclear. Thus, this cross-sectional study aims to identify the risk factors for frailty in older adults who received Ningen Dock. The study included 372 participants over 65 years of age who underwent Ningen Dock at the Health Care Center of Gunma Chuo Hospital between April 2019 and March 2020. Frailty was defined using the Kihon Checklist, a basic checklist. Clinical variables were obtained from Ningen Dock records, a vascular function test, and a questionnaire on medication, among others. Multivariate ordinal logistic regression models were used to assess risk factors.

Results: Prevalence for frailty and pre-frailty was 12.6% and 26.6%, respectively. The mean age of participants was 72.0 ± 5.1 years old, and 43.5% were female. Compared with systolic blood pressure (SBP) ≥ 130 mmHg, the odds ratios for the 100–129 mmHg and < 100 mmHg groups were 2.43 ($P = 0.020$) and 8.95 ($P < 0.001$). The odds ratio for the ≥ 7 medications group medications was 3.64 ($P = 0.003$) compared to 0–2 medications. Compared with serum iron ≥ 126 μg/dL, the odds ratio for ≤ 85 μg/dL was 2.91 ($P = 0.002$). The odds ratio for total bilirubin ≤ 0.6 mg/dL was 2.49 ($P = 0.011$) compared with > 0.6 mg/dL. Compared with an exercise habit of ≥ 4 metabolic equivalents (METs), the odds ratio for < 2 METs/week was 2.45 ($P < 0.001$). The odds ratio for the cardio-ankle vascular index (CAVI) ≥ 9 group was 1.84 ($P = 0.020$) compared to < 9.

Conclusions: In older adults who received Ningen Dock, SBP < 100 mmHg, medications ≥ 7, serum iron ≤ 85 μg/dL, total bilirubin ≤ 0.6 mg/dL, exercise habits < 2 METs, and CAVI ≥ 9 were associated with frailty.

Keywords: Risk factors for frailty, Ningen Dock, Serum iron, Systolic blood pressure (SBP), Number of medications

Background

According to demographic statistics compiled by the Ministry of Internal Affairs and Communications in 2020, 28.9% of Japan's population is over the age of 65, and the country is facing a super-aging trend. As an increase in the number of people requiring nursing care is a problem in an aging society, frailty is attracting attention as a factor that can be addressed to prevent many older adults from requiring nursing care. Frailty is a clinical condition among older adults that combines psychophysiological aspects, such as cognitive dysfunction and depression, physical vulnerability associated with muscle weakness, and social aspects, such as living alone and economic deprivation [1]. The Kihon Checklist (KCL) is a basic and helpful questionnaire for frailty screening [2]. In Japan, the KCL has been used since 2006 for older

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adults aged 65 years or older when it is difficult to determine whether they are eligible to receive preventative care and life support services under the Comprehensive Care Prevention and Daily Life Support Project [2]. In April 2020, a frailty health checkup using a 15-item questionnaire called the "the Questionnaire for Latter-stage Elderly People," which partially overlaps with the KCL questionnaire, was launched as a medical care system for people aged 75 years and older [3].

Several studies have reported risk factors for frailty in community-dwelling older adults. For example, Borda et al. examined the effects of health behaviors such as vaccination, visiting a physician, physical activity, and smoking cessation and reported that physically active older adults had a lower risk of frailty [4]. Arakawa et al. reported an association between age, more than five combined medications, physical activity, grip strength, and walking speed in a comparison of robustness and frailty [5]. Watanabe et al. found that low and high BMIs were risk factors for frailty after adjusting for factors other than BMI [6]. Pérez-Ros et al. reported that frailty was associated with women aged 75 years and older, anemia, a history of falls within the last 12 months, fear of falling, and physical activity of at least 3 hours per week, while five or more medications and comorbidities were not significant factors [7]. Associations between cognitive impairment and vascular lesions have also been reported as risk factors for frailty [8–11]. As mentioned above, even though all studies involved community-dwelling elderly individuals, there were differences in the variables examined and the independent risk factors.

There are two primary types of health checkups in Japan: Ningen Dock, a comprehensive medical checkup, and periodic medical examinations. The Ningen Dock includes a physician consultation, more laboratory tests than a regular exam, and a health education program [12] but involves a higher cost to the recipient than periodic medical examinations. Many of the costs of periodic medical examinations are subsidized by employers and local governments, but employer subsidies for those receiving the Ningen Dock are limited. Compared with periodic medical examination recipients, Ningen Dock recipients have been reported to have lower rates of abnormal blood pressure, anemia, lipids, and blood glucose, after adjusting for age and sex [13]. Therefore, it is likely that the risk factors for frailty are different in Ningen Dock recipients compared with those in the population of periodic medical examination recipients and community-dwelling older adults due to their high health consciousness.

Although the population of older adults undergoing Ningen Dock appears to be healthy [13], active screening for frailty in this population may be necessary to prevent frailty. However, the risk factors for frailty in older adults who receive Ningen Dock are unknown. In this study, we searched for risk factors for frailty in elderly patients who underwent 2-day Ningen Dock, mainly based on clinical laboratory values, medication use, smoking habits, drinking habits, exercise habits, and vascular function tests.

Methods

Study design and participants

This was a single-center cross-sectional study. The inclusion criteria were as follows: elderly patients aged 65 years or older who underwent 2-day Ningen Dock at the Japan Community Healthcare Organization (JCHO) Gunma Chuo Hospital Health Care Center and those who obtained informed consent for the research use of laboratory data, additional testing of vascular function, and measurement of salt intake. Participants without test or input omissions were analyzed. Of the 1517 people who underwent the 2-day Ningen Dock, 609 were over the age of 65 years. Of the 376 people who provided informed consent, 372 without data omissions were analyzed (Fig. 1).

The Kihon Checklist (KCL)

Frailty was identified using the KCL as the primary endpoint [2]. The KCL is a simple self-reporting "yes" or "no" survey comprising 25 questions regarding instrumental (three questions) and social (four questions) activities of daily living, physical functions (five questions), nutritional status (two questions), oral function (three questions), cognitive function (three questions), and depressive mood (five questions). This comprehensive questionnaire assessed the physical, psychological, functional, and social status of nondisabled older adults in multiple domains. Satake et al. verified the usefulness of the KCL as an index of frailty [2]. A KCL score of 0–3, 4–7, and ≥ 8 indicated robust, pre-frail, and frail, respectively.

Clinical variables

Laboratory values and background information of the participants were extracted from the Ningen Dock records: age, sex, comorbidities, body mass index (BMI), abdominal circumference, skeletal muscle percentage, body fat percentage, SBP, diastolic blood pressure, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-guanosine triphosphate (γ-GTP), alkaline phosphatase (ALP), total protein (TP), total bilirubin (T-Bil), albumin (ALB), hemoglobin (Hb), serum iron, uric acid (UA), estimated glomerular filtration rate (eGFR), fasting blood glucose, HbA1c, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, C-reactive protein

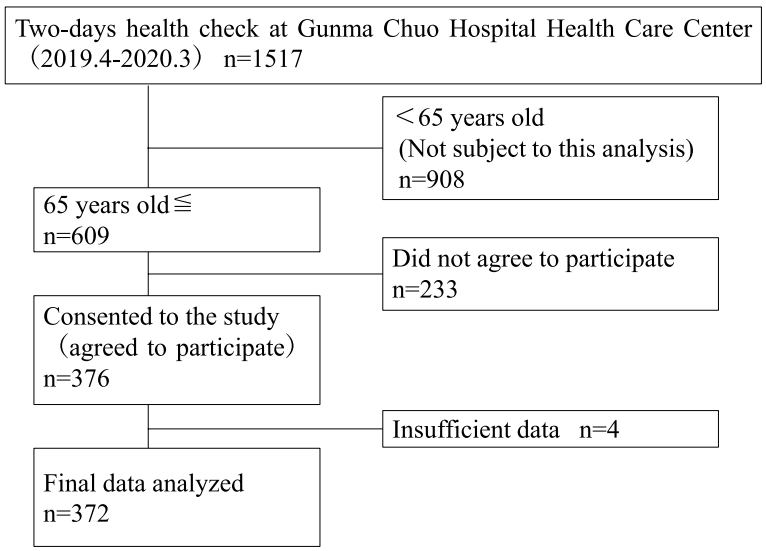

Fig. 1 Flow chart of the study population

(CRP), and medical history. The eGFR was calculated using the Modification of Diet in Renal Disease study equation modified for the Japanese population: 194 × serum creatinine^ (−1.094) × age^ (−0.287) × 0.739 (if women) [14].

The following methods were used to obtain the data, except for the tests performed during Ningen Dock; as a vascular function test, the cardio-ankle vascular index (CAVI) was measured using VaSera 1500 (Fukuda Denshi Co., Ltd.). The CAVI is an index that reflects the stiffness of the arteries from the heart to the ankles, including the aorta, and increases as atherosclerosis progresses. The CAVI is calculated based on the stiffness parameter β method measured by carotid artery echocardiography or other methods and represents blood pressure-independent vascular stiffness [15]. A CAVI > 9 was defined as abnormal. Dietary salt intake was calculated from the urinary sodium concentration (mEq/L) and creatinine concentration (mg/dL) using the Tanaka method [16]. Body composition was measured using an In Body 430 instrument (In Body Japan Inc.). Skeletal muscle percentage was expressed as the percentage of skeletal muscle mass (kg)/body weight (kg), and body fat percentage was expressed as the percentage of body fat mass (kg)/body weight (kg). In addition, a questionnaire survey was conducted on medication use, voluntary exercise, alcohol consumption, and smoking habits. The names and dosages of the medications regularly used by the participants were obtained from the questionnaire and personal medication records at the time of the Ningen Dock. The presence or absence of voluntary health-promoting exercise habits, type of exercise, and duration of exercise per week, excluding work or daily activities, was examined. The intensity of exercise per week (METs/week) was calculated based on the 2011 Compendium of Physical Activities [17].

Statistical analysis

Normality was assessed using the Shapiro-Wilk test for continuous variables. The participants were divided into three groups: robust, pre-frail, and frail groups based on the KCL, and the proportions of variables and differences in means were compared. For continuous variables, a one-way analysis of variance or Kruskal-Wallis test was conducted according to normality. For categorical variables, the chi-square test was used.

To adopt variables for ordinal logistic multivariate analysis, we considered clinical importance, linearity of the mean values between groups, and a *P*-value of less than 0.1. For continuous variables, those that showed linear or L-shaped group means in the order of robust, pre-frail, and frail were adopted, whereas variables that were U-shaped were not adopted. The adopted continuous variables were transformed into categorical variables for two or three groups by referring to clinical reference values or distributions.

Ordinal logistic regression analysis was performed to assess the association between clinical variables and frailty. Robust, pre-frail, and frail were set as 0, 1, and 2, respectively. Multivariate model 1 was created, including SBP, number of drugs, serum iron, T-Bil, exercise strength, CAVI, and ALB as categorical variables. Based on model 1, model 2 was created by adjusting for age,

sex, and BMI. In addition to model 2, model 3 was created by adjusting for disease and medication.

All analyses were performed using the SPSS ver. 27 (IBM, New York, USA), and statistical significance was set at $P < 0.05$.

Results

Of the 372 recipients, 12.6% and 26.6% were frail and pre-frail as shown in Table 1, respectively. The proportions of women in the robust, pre-frail, and frail groups were 41.6%, 48.5%, and 42.6%, respectively. The mean ages of the robust, pre-frail, and frail groups were 71.8, 72.2, and 72.7 years, respectively, and the proportions of participants aged 75 years or older were 25.2%, 28.3%, and 34.0%, respectively. There were no significant differences in age or sex among the three groups, nor were there differences in BMI.

The mean SBP showed an L-shape among the three groups and was 3.0 mmHg higher in the robust group compared to the frail group. The mean number of medications taken was linear, with 0.3 more medications in the pre-frail group and 1.7 in the frail group compared to the robust group. The mean serum iron concentrations were linear and within the regular range but were 16.7% lower in the frail group compared to the robust group. Hb denoted the same tendency of serum iron but was only 3.7% lower in the frail group compared to the robust group. The mean T-Bil was also in the regular range, but 12.6% lower in the frail group compared to the robust group, with an L-shape. The mean of the total intensity per week of the habitual exercise was linear, showing a 25.4% lower value for the frail group compared to the robust group. The CAVI mean demonstrated an L-shape and was 4.1% higher in the frail group compared to the robust group and 6.7% higher in the frail group compared to the pre-frail group. The mean values of ALBs were linear and all in the regular range but were 1.9% lower in the frail group compared to the robust group. There were significant differences or trends in the mean values of the CAVI, SBP, ALB, T-Bil, Hb, serum iron, number of medications, and habitual exercise intensity among the three groups. ALT, γ-GTP, and FEV1/FVC also showed $P < 0.1$, but the mean values of the three groups showed a U-shaped trend. The following variables showed a trend toward higher rates in the frail group, but no significant differences were found: hypoglycemic medication, hypolipidemic medication, stroke, cardiac disease, and anemia.

The following variables were transformed into categorical variables, and chi-square tests were conducted: SBP, number of medications, serum iron, T-Bil, exercise habits, CAVI, and ALB (Table 2). All categorical variables showed significant differences or trends among the three groups.

Multivariate ordinal logistic analysis was performed using the adopted variables (Table 3). In model 1, the following variables were used: SBP, the number of medications, serum iron, T-Bil, exercise habits, CAVI, and ALB. Significant differences were observed in SBP, the number of medications, serum iron, T-Bil levels, exercise habits, and CAVI. Based on model 1, model 2 was adjusted for age, sex, and BMI, but the results were similar to those of model 1. In contrast, model 3, which was adjusted for disease, medication, and the variables in model 2, showed significant differences in SBP, the number of medications, serum iron and T-Bil levels, exercise habits, and CAVI as independent risk factors for frailty.

Compared with SBP $\geq$ 130 mmHg, odds ratios were 2.43 (95% confidence interval (CI) 1.15–5.11, $P = 0.020$) for SBP of 100–129 mmHg and 8.95 (95% *CI* 2.98–26.83, $P < 0.001$) for SBP < 100 mmHg. As a result, the odds ratio was 1.73 (95% *CI* 0.97–3.08, $P = 0.062$) for three-six medications and 3.64 (95% *CI* 1.54–8.62, $P = 0.003$) for seven or more medications compared with the zero-two medications group. The serum iron level of 85–125 μg/dL group tended to show a higher odds ratio of 1.88 (95% *CI* 1.00–3.55, $P = 0.050$) compared to the group with those of 126 μg/dL or higher; the group with those of 85 μg/dL or less showed a significantly higher odds ratio of 2.91 (95% *CI* 1.46–5.81, $P = 0.002$). The odds ratio for T-Bil less than 0.6 mg/dL was 2.49 (95% *CI* 1.23–5.05, $P = 0.011$) compared with those greater than 0.6 mg/dL. As 1 h of fast walking per week is approximately four METs/week, we compared three groups: $\leq$ 2 METs/week, > 2 but $\leq$ 4 METs/week, and > 4 METs/week. Compared to the group with an exercise habit of > 4 METs/week, the odds ratio was 1.18 (95% *CI* 0.65–2.15, $P = 0.585$) in the group with > 2 but $\leq$ 4 METs/week and 2.45 (95% *CI* 1.50–4.03, $P < 0.001$) in those with $\leq$ 2 METs/week. Since the cutoff value for arterial stiffness is a CAVI of 9 or higher, the odds ratio was 1.84 (95% *CI* 1.10–3.07, $P = 0.020$) for a CAVI of 9 or higher compared to those of less than 9. The odds ratio was 1.59 (95% *CI* 0.90–2.80, $P = 0.112$) for ALB less than 3.8 g/dL compared to ALB greater than 3.8 g/dL, and there was no significant difference.

Discussion

In this study, we examined the risk factors for frailty based on the KCL in elderly patients aged $\geq$ 65 years who underwent Ningen Dock. The following variables were associated with frailty: SBP, the number of medications, serum iron, T-Bil, exercise habits, and CAVI.

BMI, abdominal circumference, skeletal muscle percentage, and body fat percentage were risk factors in

Table 1 Characteristics of participants and bivariate analysis stratified by frailty status

Variables	Total	Robust	Pre-frail	Frail	*p*-values
Number	372 (100)	226 (60.8)	99 (26.6)	47 (12.6)	
Age, sex, and body size					
Age (years)	72 ± 5.1	71.8 ± 5.0	72.2 ± 5.4	72.7 ± 5.1	0.460[a]
Age ≥ 75 years	101 (27.2)	57 (25.2)	28 (28.3)	16 (34.0)	0.445[c]
Female	162 (43.5)	94 (41.6)	48 (48.5)	20 (42.6)	0.509[c]
BMI (kg/m^2)	23.3 ± 3.2	23.3 ± 3.1	23.1 ± 2.7	23.4 ± 4.1	0.982[a]
Waist circumference (cm)	82.4 ± 8.4	82.1 ± 8.6	82.2 ± 7.0	84.1 ± 10.0	0.320[b]
Skeletal muscle percentage (%)	40.1 ±4.2	40.3 ± 4.2	39.7 ± 4.2	39.9 ± 4.6	0.437[b]
Body fat percentage (%)	25.9 ± 7.0	25.7 ± 6.9	26.4 ± 6.9	26.0 ± 7.9	0.582[a]
Laboratory data and physical exam					
CAVI	8.57 ± 1.07	8.58 ± 0.86	8.37 ± 0.98	8.93 ± 1.82	0.091[a], †
SBP (mmHg)	117.2 ± 12.7	118.6 ± 12.7	114.7 ± 11.0	115.6 ± 14.7	0.062[a], †
DBP (mmHg)	67.7 ± 9.0	68.7 ± 9.3	65.8 ± 7.9	66.7 ± 9.3	0.022 [b], †, *
Fasting blood glucose (mg/dL)	103.1 ± 20.5	102.5 ± 19.3	103.6 ± 20.6	104.7 ± 25.7	0.955[a]
HbA1c (NGSP) (%)	6.0 ± 0.6	5.9 ± 0.6	6.0 ± 0.7	6.0 ± 0.7	0.418[a]
LDL-C (mg/dL)	119.0 ± 26.9	119.2 ± 25.5	121.1 ± 28.6	113.7 ± 29.6	0.291[b]
HDL-C (mg/dL)	65.3 ± 16.5	66.5 ± 17.0	62.8 ± 14.3	64.6 ± 18.3	0.299[a]
Triglyceride (mg/dL)	96.7 ± 53.1	96.9 ± 56.1	94.2 ± 44.1	101.0 ± 56.0	0.883[a]
Uric acid (mg/dL)	5.4 ± 1.3	5.4 ± 1.3	5.4 ± 1.3	5.1 ± 1.1	0.369[b]
eGFR (mL/min/1.73 m^2)	63.7 ± 12.3	63.4 ± 12.3	63.8 ± 11.7	64.9 ± 13.9	0.750[b]
AST (U/L)	22.2 ± 7.3	22.3 ± 6.9	22.5 ± 8.5	21.6 ± 7.0	0.704[a]
ALT (U/L)	19.0 ± 11.2	18.7 ± 9.8	20.2 ± 12.5	17.7 ± 14.2	0.069[a], †
γ-GTP (U/L)	27.0 ± 17.9	26.2 ± 16.8	30.4 ± 19.9	23.4 ± 17.7	0.016[a], †, *
ALP (U/L)	208.2 ± 59.9	204.8 ± 55.2	212.3 ± 62.5	215.7 ± 74.8	0.700[a]
TP (g/dL)	6.97 ± 0.40	6.97 ± 0.38	6.95 ± 0.39	7.03 ± 0.53	0.848[a]
ALB (g/dL)	4.09 ± 0.27	4.11 ± 0.26	4.05 ± 0.27	4.03 ± 0.34	0.117[a]
T-Bil (mg/dL)	0.93 ± 0.29	0.95 ± 0.29	0.94 ± 0.29	0.83 ± 0.23	0.069[a], †
Hb (g/dL)	13.5 ± 1.4	13.6 ± 1.3	13.6 ± 1.4	13.1 ± 1.4	0.046[a], †, *
Serum iron (μg/dL)	103.8 ± 30.4	106.6 ± 31.3	104.6 ± 29.6	88.8 ± 22.4	0.001[a], †, *
CRP (mg/dL)	0.113 ± 0.345	0.083 ± 0.123	0.099 ± 0.255	0.285 ± 0.844	0.142[a]
Vital capacity percentage (%)	95.6 ± 14.6	95.7 ± 14.8	97.0 ± 13.2	92.1 ± 16.5	0.160[b]
FEV1/FVC (%)	77.0 ± 7.0	77.0 ± 7.0	77.9 ± 6.8	75 ± 7.5	0.044[a], †, *
Medication, past history, and habits					
Number of medications	2.9 ± 2.9	2.6 ± 2.7	2.9 ± 3.0	4.3 ± 3.7	0.015[a], †, *
Antihypertensive medication	146 (39.2)	88 (38.9)	39 (39.4)	19 (40.4)	0.982[c]
Hypoglycemic medication	52 (14.0)	29 (12.8)	12 (12.1)	11 (23.4)	0.135[c]
Hypolipidemic medication	123 (33.1)	76 (33.6)	29 (29.3)	18 (38.3)	0.535[c]
Stroke	21 (5.6)	11 (4.9)	5 (5.1)	5 (10.6)	0.283[c]
Cardiac disease	39 (10.5)	21 (9.3)	9 (9.1)	9 (19.1)	0.116[c]
Anemia	47 (12.6)	25 (11.1)	14 (14.1)	8 (17.0)	0.465[c]
Exercise strength (METs/week)	11.1 ± 18.3	11.8 ± 19.0	10.5 ± 17.4	8.8 ± 16.2	0.024[a], †, *
Sodium intake (g/day)	9.47 ± 2.21	9.55 ± 2.32	9.19 ± 1.95	9.63 ± 2.21	0.291[a]
Drinking	150 (40.3)	96 (42.5)	34 (34.3)	20 (42.6)	0.367[c]
Smoking	17 (4.6)	9 (4.0)	5 (5.1)	3 (6.4)	0.746[c]

Numerical data are shown as mean ± SD. Categorical data are shown as number of data points (%)

BMI, body mass index, *CAVI* cardio-ankle vascular index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Hb* hemoglobin, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γ-GTP* gamma guanosine triphosphate, *ALP* alkaline phosphatase, *TP* total protein, *ALB* albumin, *T-Bil* total bilirubin, *CRP* C-reactive protein, *FEV1* forced expiratory volume in a second, *FVC* forced vital capacity

[a] Kruskal-Wallis, [b]ANOVA, [c]chi-square test, †$P < 0.1$, *$P < 0.05$

Table 2 Chi-square test for categorical variables created from continuous variables stratified by frailty status

Categorical variables	Robust	Pre-frail	Frail	*p*-values
CAVI ≥ 9	69 (30.5)	31 (31.3)	22 (46.8)	0.090[a], †
SBP				
< 100 mmHg	9 (4.0)	11 (11.1)	7 (14.9)	0.005[a], †, *
≥ 100, < 130 mmHg	177 (78.3)	81 (81.8)	34 (72.3)	
≥ 130 mmHg	40 (17.7)	7 (7.1)	6 (12.8)	
ALB ≤ 3.8 g/dL	32 (14.2)	21 (21.2)	14 (29.8)	0.025[a], †, *
T-Bil ≤ 0.6 mg/dL	16 (7.1)	11 (11.1)	12 (25.5)	0.001[a], †, *
Serum iron				
≤ 85 μg/dL	50 (22.1)	27 (27.3)	24 (51.1)	< 0.001[a], †, *
> 85, ≤ 125 μg/dL	125 (55.3)	52 (52.5)	22 (46.8)	
> 125 μg/dL	51 (22.6)	20 (20.2)	1 (2.1)	
Number of medications				
0–2 medications	132 (58.4)	55 (55.6)	16 (34.0)	0.001[a], †, *
3–6 medications	75 (33.2)	31 (31.3)	17 (36.2)	
≥ 7 medications	19 (8.4)	13 (13.1)	14 (29.8)	
Exercise strength				
≤ 2 METs/week	53 (23.5)	38 (38.4)	22 (46.8)	0.004[a], †, *
> 2, ≤ 4 METs/week	50 (22.1)	16 (16.2)	10 (21.3)	
> 4 METs/week	123 (54.4)	45 (45.5)	15 (31.9)	

Data are shown as number of data (%)

CAVI cardio-ankle vascular index, *SBP* systolic blood pressure, *ALB* albumin, *T-Bil* total bilirubin

[a] Chi-square test, †$P < 0.1$, *$P < 0.05$

previous studies of the general population [5, 18, 19], but no association was found in the present study. Older adults who underwent Ningen Dock have been found to have lower rates of abnormal findings in blood pressure, anemia, lipids, and blood glucose than those who underwent regular physical examinations [13]. It is reasonable that the abovementioned anthropometric indices were not found to be risk factors for frailty because older adults who undergo the Ningen Dock are considered more health conscious than other older adults.

The prevalence of frailty based on the KCL in this study was 12.6% for the frail group and 26.6% for the pre-frail group, respectively. The mean ages of the frail, pre-frail, and robust groups were 72.7, 72.2, and 71.8 years, respectively, and there was no difference in age among the three groups according to frailty status. Although age was a risk factor for frailty in previous studies [5, 7], it is also reasonable that age was not found to be a risk factor for frailty for the same reason as BMI. In a study of 5542 independent elderly community residents aged 65 years and older who were not certified for nursing care, the prevalence of frailty based on the KCL was reported to be 955 (17.2%) for frail and 1625 (29.3%) for pre-frail [20]. According to a systematic review by O'Caoimh et al., frailty prevalence based on physical frailty was 11%, and that based on the frailty index was 25% in Asia [21]. Although it is difficult to make direct comparisons because of the differences in the target population and criteria for determining frailty, we considered that there is not a large discrepancy in frailty prevalence between this study and previous reports.

The association between SBP and frailty remained significant even after adjusting for variables such as antihypertensive medications and comorbidities. A previous study reported an association between low blood pressure and frailty [22], which is similar to the present study. Although the odds ratio for frailty is lower at an SBP of 100 mmHg or higher, the burden on the vascular wall associated with increased SBP should be considered. Blood pressure fluctuates with various substances and stressors. Typically, physical activity tends to affect the sympathetic nervous system, resulting in increased pressure. On the other hand, dietary habits in Asian countries, including Japan, are characterized by high salt intake, and according to an announcement by the Ministry of Health, Labor and Welfare in 2020, salt intake in Japan in 2019 was 10.9 g/day for men and 9.3 g/day for women, which is much higher than the WHO recommendation of less than 5.0 g/day. The impact on the blood vessels and kidneys is undeniable. The mean salt intake of the study population was also high (9.47 g/day), but there was no difference in salt intake between the three frailty groups. Additionally, frailty is a risk factor for cardiovascular disease [23, 24], and heart failure is strongly associated with frailty [25]. Hypotension due to left ventricular failure, a finding of heart failure, may be a risk factor for frailty. The involvement of heart failure in the present study is unclear because we were unable to specifically investigate heart failure, although there were findings of cardiovascular disorders.

In addition to the CAVI, there are other methods for measuring arterial stiffness, such as carotid-femoral pulse wave velocity and brachial-ankle pulse wave velocity. Among them, the CAVI is a measurement method that is relatively unaffected by blood pressure [15]. In the present study, we clarified for the first time the relationship between frailty based on the KCL and CAVI. The arterial wall stiffens with age and is accelerated by the coexistence of cardiovascular risk factors [26]. Muscle blood flow decreases with age, which has been suggested to be partially related to the degree of arterial stiffness [27]. Atherosclerosis involves ongoing temporary or chronic inflammation due to the remodeling and calcification associated with plaque accumulation [26]. It has been suggested that inflammation may cause muscle weakness, weight loss, decreased activity, and anorexia, which may lead to loss of lean body mass and induce frailty [19, 28]. Although there are several measures of frailty and arterial

Table 3 Multivariate ordinal logistic regression analysis of risk factors for frailty

Categorical variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*-values	OR (95% CI)	*p*-values	OR (95% CI)	*p*-values
SBP						
≥ 130 mmHg	1		1		1	
≥ 100, < 130 mmHg	2.61 (1.27- 5.35)	0.009*	2.74 (1.32-5.68)	0.007*	2.43 (115-5.11)	0.020*
<100 mmHg	10.01 (3.56-28.12)	< 0.001*	11.10 (3.82-32.29)	< 0.001*	8.95(2.98-26.83)	< 0.001*
Number of medications						
0–2 medications	1		1		1	
3–6 medications	1.42 (0.88-2.30)	0.151	1.41 (0.86-2.31)	0.176	1.73 (0.97-3.08)	0.062
≥ 7 medications	2.88 (1.50-5.53)	0.002*	2.91 (1.45-5.85)	0.003*	3.64(1.54-8.62)	0.003*
Serum iron						
> 125 μg/dL	1		1		1	
> 85, ≤ 125 μg/dL	1.81 (0.97-3.36)	0.061	1.76 (0.94-3.28)	0.078	1.88 (1.00-3.55)	0.050
≤ 85 μg/dL	2.85 (1.45-5.62)	0.002*	2.82 (1.42-5.58)	0.003*	2.91 (1.46-5.81)	0.002*
T-Bil						
> 0.6 mg/dL	1		1		1	
≤ 0.6 mg/dL	2.22 (1.14-4.36)	0.020*	2.12(1.07-4.19)	0.030*	2.49 (1.23-5.05)	0.011*
Exercise strength						
> 4 METs/week	1		1		1	
> 2, ≤ 4 METs/week	1.25 (0.69-2.26)	0.456	1.25 (0.69-2.26)	0.467	1.18 (0.65-2.15)	0.585
≤ 2 METs/week	2.57 (1.57-4.19)	< 0.001*	2.52 (1.54-4.12)	< 0.001*	2.45 (1.50-4.03)	< 0.001*
CAVI						
< 9	1		1		1	
≥ 9	1.8 (1.11-2.90)	0.016*	1.89 (1.14-3.12)	0.013*	1.84 (1.10-3.07)	0.020*
ALB						
> 3.8 g/dL	1		1		1	
≤ 3.8 g/dL	1.55 (0.90-2.67)	0.116	1.63 (0.93-2.84)	0.089	1.59 (0.90-2.80)	0.112

Model 1: multivariate ordinal logistic regression model including SBP, number of medications, serum iron, T-Bil, exercise strength, CAVI, and ALB. Model 2: model 1+ adjusted with age, sex, and BMI. Model 3: model 2+ adjusted for antihypertensive medication, hypoglycemic medication, hypolipidemic medication, stroke, cardiac disease, and anemia

CI confidence interval, *CAVI* cardio-ankle vascular index, *SBP* systolic blood pressure, *ALB* albumin, *T-Bil* total bilirubin

*$P < 0.05$

stiffness, the Framingham Heart Study and Qi Xue et al.'s cross-sectional study of elderly community-dwelling participants used a measure of frailty that was not the KCL and reported that arterial stiffness was a risk factor for frailty [10, 29]. Meanwhile, a study that assessed frailty using Fried's frailty phenotype reported that the CAVI could be used to determine frailty risk [29]. Previous reports and our results suggest that arterial stiffness is an independent risk factor for frailty, regardless of the method of measuring frailty or arterial stiffness.

The mean number of medications taken by the study population did not reach the Japanese standard of six medications for polypharmacy, even in the frail group; however, there was a significant association between taking seven or more medications and frailty. Polypharmacy has been reported to be significantly associated with frailty in both cross-sectional and longitudinal studies [30–32], whereas no significant difference in polypharmacy has been found in some reports [7]. In a previous report, the cutoff value for the number of medications taken for frailty was 6.5 [33], suggesting that the use of more than the five or six medications that are commonly defined as polypharmacy is a risk factor for frailty. In addition, although specific chronic diseases and polypharmacy have been reported to be associated with frailty [9, 31], in this study, there was no association with stroke, cardiovascular disease, hyperlipidemia medication, or antihypertensive medication. Therefore, the association between the number of medications taken and the frailty observed in this study may result from the effects of these diseases and the accumulation of medications for other diseases.

According to the results of this study, an exercise habit of < 2 METs per week was associated with frailty. Lack of exercise habits, which do not include daily activities such as housework, was associated with frailty, similar

to previously reported results [4, 34, 35]. In the Physical Activity Standards for Health Promotion 2013 established by the Ministry of Health, Labor and Welfare, the standard for physical activity, including daily activities and exercise, for older adults aged 65 years or older is ten METs per week regardless of intensity. Previous reports have shown that moderate-intensity aerobic exercise, such as walking and other moderate-intensity aerobic exercises over 150 min/week, reduces the risk of morbidity, mortality, and function-dependent frailty, and in sedentary individuals, even small amounts of physical activity are reduced [36, 37]. There are also reports that participation in exercise is associated with the progression of frailty, regardless of an active lifestyle, physical activity, or exercise intensity [35]. On the other hand, although BMI, abdominal circumference, and skeletal muscle have been previously associated with frailty [6, 18, 19], there was no association in the present study population. This may be since few participants in the present study showed abnormalities in these factors, and the activity level of the present study population was not high enough to affect body size.

In the present study, the mean serum iron levels in the three groups were within the normal range; however, an association with frailty was suggested. Serum iron, which is mobilized from the storage iron pool, is bound to transferrin and flows through the bloodstream via reticulocytes in the bone marrow, where it is ingested by erythroblasts cells and is used for the synthesis of Hb. Iron levels are generally decreased due to bleeding, pregnancy, and inflammatory diseases. Since iron is supplemented by diet, it is also related to long-term nutritional status, and if a diet low in iron is continued, storage iron and serum iron levels decrease. Hb concentration and CRP, an inflammatory indicator, have been reported to be associated with frailty [1, 38], but the relationship between frailty and serum iron has not been reported. In the Ningen Dock, the test is performed while fasting, so it is not affected by the meal of the day but may reflect the meal of the previous day and mobilization from the iron storage pool. In other words, serum iron levels in Ningen Dock may be indicative of future anemia. In combination with the lack of an association between frailty and CRP in this population, it is likely that low serum iron levels, but not anemia, are associated with frailty, although the mechanism is not known. To the best of our knowledge, this is the first study to report an association between frailty and serum iron level.

Although T-Bil level was within the reference range, low levels were suggested to be associated with frailty. Bilirubin is a potent endogenous antioxidant [39, 40]. It has been suggested that low T-Bil levels reduce antioxidant activity and may lead to various oxidative stress-related diseases and impairment, such as diabetes and activity of daily living impairment owing to decreased antioxidant activity or increased oxidative stress [39]. Increased oxidative stress and pro-inflammatory biomarkers have also been reported in frail and pre-frail individuals [39, 41–44]. Skeletal muscle consumes large amounts of oxygen and produces large amounts of reactive oxygen species. Their accumulation is thought to cause a decline in muscle mass and quality via several mechanisms [39, 45]. Thus, although the mechanism is not beyond expectations, it has been suggested that a decrease in T-Bil levels may induce frailty.

Serum ALB accounts for approximately 60% of TP and is considered an indicator of nutritional status, primarily reflecting long-term nutritional status. It is also decreased by hepatic dysfunction and by increased protein loss and consumption. In this analysis, the association between ALB levels and frailty was not significant. Since previous studies have shown a close relationship between nutritional status and frailty [21, 26, 27, 46], it is possible that the present study population was well-nourished by protein intake and other factors.

In Japan, a frailty health checkup was launched in April 2020 for the general population aged $\geq$ 75 years. The purpose of the program was to comprehensively assess the health status of the elderly based on their characteristics, such as frailty. In 2020, the average life expectancy in Japan was 81.6 years for men and 87.7 years for women, making Japan the country with the longest life expectancy in the world. Awareness and prevention of frailty are one of the current highest priorities, given the growing concern about economic pressures due to the increasing number of people who will be receiving care when the baby boomers turn 75 or older in 2025 [47]. To our knowledge, this study is the first cross-sectional study to collect information on vascular function and frailty in addition to general items in older adults who underwent the Ningen Dock and is valuable for its comprehensive study of risk factors for frailty. The results of this study provide clues for designing optimal interventions for frailty prevention.

This study has several limitations. First, limitations and biases inherent in cross-sectional observational studies are expected. It was related to frailty at the time of the study, and we were not able to investigate the onset or prognosis of the disease. Longitudinal studies are needed to assess these issues. Second, we used only the KCL as a measure of frailty, which has been evaluated as a measure of frailty but does not provide an objective assessment of physical ability, like other assessment criteria. Third, the medications used by the recipients were those used at the time of Ningen Dock, and the duration and dosage of the medications were

not assessed. Fourth, the number of participants was limited because the study was conducted at a single institution and people typically undergo Ningen Dock only once a year.

Conclusions

In elderly Japanese people aged 65 years and older who underwent Ningen Dock, independent risk factors for frailty based on the KCL were SBP < 100 mmHg, medications ≥ 7, serum iron ≤ 85 μg/dL, T-Bil ≤ 0.6 mg/dL, exercise habits < 2 METs/week, and CAVI ≥ 9.

Abbreviations

ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CAVI: Cardio-ankle vascular index; CI: Confidence interval; CRP: C-reactive protein; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; FEV1: Forced expiratory volume in a second; FVC: Forced vital capacity; γ-GTP: Gamma guanosine triphosphate; Hb: Hemoglobin; HDL-C: High-density lipoprotein cholesterol; JCHO: Japan Community Health Care Organization; KCL: The Kihon Checklist; LDL-C: Low-density lipoprotein cholesterol; METs: Metabolic equivalents; SBP: Systolic blood pressure; T-Bil: Total bilirubin; TP: Total protein; UA: Uric acid; WHO: World Health Organization.

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Authors' contributions

MA and YT contributed equally to this work. MA designed the study, created the protocol, collected the data, interpreted the results, and wrote the manuscript.YT designed the study, prepared the protocol, interpreted the results, and wrote the manuscript. YO was involved in study design, protocol development, data evaluation, interpretation of results, and writing the manuscript. AN and ET were involved in study design and interpretation of results. KI was involved in data collection, data evaluation, and clinical diagnosis.TN and MK were involved in the evaluation of the data, clinical diagnosis, and interpretation of the results. KH was involved in the study design and interpretation of the results. KO was involved in all stages of the study and managed the study. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets are not publicly available due to concerns of participants' confidentiality but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committees of Takasaki University of Health and Welfare (study numbers 1950 and 3079) and Gunma Chuo Hospital (study numbers 2018-038 and 2018-038-001). This study was conducted in accordance with the guidelines of the Declaration of Helsinki and Medical and Health Research Involving Human Subjects in Japan. We obtained informed consent from the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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