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Frailty prevalence using Frailty Index, associated factors and level of agreement among frailty tools in a cohort of Japanese older adults

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ABSTRACT

Frailty prevalence defined by the deficit accumulation model (Frailty Index) has limited exploration in a Japanese population. The objective of this paper is to investigate the prevalence of frailty by Frailty Index among a cohort of healthy Japanese older adults, define risk factors associated with pre-frailty and frailty status and evaluate Frailty Index's agreement with Frailty Phenotype and Kihon checklist.

Methods: Data from 673 participants of the 2014 wave of the Nagoya Longitudinal Study - Healthy Elderly were used. Annual assessments include investigation of mood, memory, health status, nutrition, physical performance and oral health. The Frailty Index was compared to Frailty Phenotype and Kihon Checklist, and factors associated to Frailty Index were investigated through univariate and multivariate logistic regression.

Results: Frailty prevalence was 13.5% (n = 91) by Frailty Index, 1.5% (n = 10) by Frailty Phenotype and 4% (n = 27) by Kihon Checklist. Although the correlations between the three scales were moderate to high, the agreement between the scales was poor. In terms of risk factors, age, polypharmacy and physical activity level were associated with being pre-frail and frail. Having a higher waist circumference was associated with being pre-frail, and lower handgrip strength and lower walking speed were associated with being frail.

Conclusions: The Frailty Index showed similar metrics and agreement comparable to findings of previous studies, and was able to identify a higher number of individuals who were pre-frail and frail. Age, polypharmacy, physical activity, waking speed and waist circumference were associated with pre-frailty and frailty by frailty index.

1. Introduction

Japan remains the country with the highest proportion of older adults in the world, with the 2018 estimate being 28.2% of the population aged over 65 years old (Japan Statistics Bureau, 2018). This phenomenon will continue and is expected to reach its peak of 37% in 2042, when the second baby boomer cohort enters this older age group (National Institute of Population and Social Security Research, 2017). This large proportion of older adults will require a dramatic shift from previous concepts of “disease-oriented”, hospital-based care to integrated models of care focused on community based and preventive care (Arai et al., 2015; Tinetti & Fried, 2004).

To address these demographic changes, Japan has invested in promoting preventive care and identifying individuals at higher risk of frailty (Fukutomi et al., 2013). Frailty is a geriatric syndrome determined by a reduced capacity to recover from health stressors due

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reduced "strength, endurance and physiologic function" (Topinkova, 2008). This state of vulnerability leads to an increased risk of adverse outcomes, such as functional decline, multiple hospitalizations and death (Topinkova, 2008). Although increasing in prevalence with age, frailty is not a synonym of ageing, and lies in the other end of the spectrum of the "healthy ageing" definition (Beard et al., 2016).

Although several health tools have been developed in the past three decades to identify frail subjects, no consensus exists to the optimal detection of frailty either for clinical practice or research studies (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Topinkova, 2008). The two most often used frailty assessments are the Frailty Phenotype (FP) (Fried et al., 2001) and Frailty Index (FI) (Mitnitski, Mogilner, & Rockwood, 2001), but multiple screening tools have been developed. FI followed the concept that the accumulation of multiple health deficits through life were predictors of hospitalization, disability and death (Mitnitski et al., 2001). The operationalization of this methodology allows the selection of multiple health deficits as long as established criteria are fulfilled thus making it possible for the index to be constructed from existing research and administrative databases retrospectively (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). The criteria to be met include: (1) variables had to be related to health status, (2) health issues had to increase with age, (3) variables did not saturate too early within the aging process, (4) covered a range of health systems and (5) when used serially over time in the same population, the same items are used. At least 30 variables must be selected, and the higher the number, the more precise the estimate becomes. Although FI was developed as a continuous variable, studies have used various number of items to classify people as frail or pre-frail (Hoover, Rotermann, Sanmartin, & Bernier, 2013). A study investigating the ideal cut-off points for frailty in a representative national sample of the Canadian community dwelling older population has shown that the likelihood of hospitalization start to increase with an FI of 0.10 and are significantly higher when reaches levels above 0.21, establishing the pre-frail (between 0.10 and 0.21) and frail (above 0.21) strata, which have been used in several cohort studies (Hoover et al., 2013; Orkaby, Hshieh, Gaziano, Djousse, & Driver, 2017; Rockwood, Song, & Mitnitski, 2011).

In Japan, the Kihon checklist (KCL) was developed in 2000 by the Japanese Ministry of Health, Labour and Welfare to identify older adults at risk of requiring care or support in the near future (Arai & Satake, 2015). This questionnaire evaluated physical strength, nutrition, eating and oral function, socialization, memory, mood and lifestyle to detect patients at-risk of becoming dependent (Sewo Sampaio, Sampaio, Yamada, & Arai, 2016). It was initially validated against the FP for use as a screening tool for frailty (Satake et al., 2016).

Although one study conducted in a Japanese population has created a FI using the established methodology to identify older adults at risk of hospitalization and mortality (Kojima, Taniguchi, Kitamura, & Shinkai, 2018), it was not able to describe its relationship with the FP, the most frequently used tool to detect frailty (Dent, Kowal, & Hoogendijk, 2016). Additionally it did not investigate which socio-demographical and clinical variables were associated with frailty, as defined by the frailty index, assessing its usefulness in this population. In this study, a high correlation between the FI and KCL (Spearman rho = 0.88, $p < 0.001$) was seen and both were able to predict long-term care insurance certification and/or mortality (HR 1.04, 95% CI 1.02–1.06, $p < 0.001$ and HR 1.03 (1.01–1.04), $p < 0.001$, respectively for FI and KCL).

Whilst also describing the construction of a FI for the Nagoya Longitudinal Study-Healthy Elderly (NLS-HE), the aim of this study is to investigate the prevalence of frailty, the risk factors associated with pre-frailty and frailty as well as to describe the agreement between FI, KCL and FP in a cohort of Japanese older adults from Nagoya, Japan.

2. Methodology

2.1. Study design and participants

This study was a cross-sectional analysis of the Nagoya Longitudinal Study – Healthy Elderly (NLS-HE), and initial baseline characteristics of participants have been published elsewhere (Matsushita et al., 2017). The NLS-HE is an observational cohort of healthy older adults recruited from students of a 2-year course at a community college for older adults in Nagoya, Japan. The students attend several weekly lectures and take part in club activities.

The initial cohort commenced in 2014, with 712 participants, with an inclusion criteria of age between 60–89 years old, being resident of Nagoya city and able to walk independently. Participants were excluded if they had incomplete data on frailty and had comorbidities that predisposed them to frailty such as Parkinson's disease, stroke or dementia. All participants provided informed consent. The study received institutional review board approval from the Nagoya University Graduate School of Medicine (approval number 2013-0055-2), and followed the principles of the Helsinki declaration.

2.2. Frailty Index

The FI in this study was constructed based on the criteria described by Rockwood et al. (2005) and Searle et al. (2008) (as described in Section 1). Whilst individual questions from geriatric assessment scales were considered, overrepresentation or repetition of themes were minimised and duplicated items or items with more than 5% of missing values were discarded (Rockwood et al., 2005). The final FI included 54 items (Appendix A Table A1). The domains covered by FI include physical strength, fatigue, physical activity (PA), nutrition and oral health, activities of daily living (ADL), falls, social network and isolation, memory, mood, and comorbidities. The index is constructed by assigning one point for the presence of each deficit, with the total value divided by the total number of variables present to create a score. If participants had more than 20% of missing items, they were excluded from the analysis (Theou, Brothers, Mitnitski, & Rockwood, 2013). Some ordinal and continuous variables were recoded to include an intermediate value of 0.5. Particular care was taken to consider the cut-off value for pre-frailty (> 0.10 and ≤ 0.21) and frailty (> 0.21), as discussed above (Section 1), given that these values have been shown to be correlated with a higher risk of adverse outcomes (Hoover et al., 2013; Rockwood et al., 2011).

2.3. Kihon Checklist (KCL)

The Kihon Checklist (KCL) consists of 25 items, in the following domains: ADL, physical strength, nutrition, oral function, isolation, memory and mood. Each answer has dichotomous answer as "yes" or "no", and a point given if depicted the presence of a deficit in this domain. (Appendix A Table A1). A score between zero and three was considered robust, between four and seven was considered pre-frail and eight and above as frail, as previously used in the validation studies (Satake et al., 2016).

2.4. Frailty Phenotype (FP)

The FP criteria used were determined by the Cardiovascular Health Study (Fried et al., 2001) with adaptation established in the Obu Study of Health Promotion for the Elderly (Makizako, Shimada, Doi, Tsutsumimoto, & Suzuki, 2015). FP includes five components: loss of weight, low walking speed, low handgrip strength, exhaustion and low PA levels. Modifications to original study (Fried et al., 2001) were limited to the question for weight loss, defined by the question: "Have you lost more than 2–3 kg in the past 6 months?" and low PA level, defined by the questions: "Do you engage in moderate levels of PA

aimed at health? And "Do you engage in low levels of PA aimed at health?" Each item scored one point and participants were determined as robust if they scored zero out of five items, pre-frail if 1 or two positive items and frail if three or more items. Additionally, the cut-off for low walking speed and low hand grip strength defined as appropriate in the Japanese older population by the Obu Study of Health Promotion for the Elderly were used (respectively < 1.0 m/s and < 26 kg for men and < 18 kg for women) (Makizako et al., 2015).

2.5. Covariates

The covariates investigated for its relationship with frailty index included age, gender, education (less or more than 10 years of education), marital status (currently married or other [never married, divorced, separated or widowed]), living arrangements (living alone or with family or friends), smoking status (never smoked and ever smoker, combining previous and current smokers), multimorbidity (presence of 2 or more comorbid conditions), polypharmacy (using 5 or more medications daily), PA (assessed by Baecke Physical Activity Questionnaire) (Baecke, Burema, & Frijters, 1982), walking speed (m/s), waist circumference (cm), appendicular muscle mass index (kg/m^2), (analysed as appendicular muscle mass over height squared), subcutaneous fat thickness (in cm),dementia screening (by the 5-Cog assessment, where scores below 14 were suggestive of dementia) (Sugiyama et al., 2015) and hand grip strength (in Kg). A bioelectrical impedance analysis system (InBody 430, Biospace, Tokyo, Japan) was used to measure appendicular skeletal muscle. Appendicular muscle mass index was calculated as appendicular skeletal muscle (in kilograms, divided by height in meters. Subcutaneous fat thickness was measured in centimetres on the left triceps using a skinfold calliper twice and an average of the two measurements was considered. Geriatric depression scale-15 (GDS), multimorbidity and the Mini-Nutritional Assessment (MNA) were analysed as descriptive data, but since the majority of its items are part of FI, they are not included in the logistic regression.

2.6. Statistical analysis

Continuous variables are presented as mean and standard deviation, while categorical variables are presented as frequencies and ratios (%). Differences in descriptive data between frailty groups was assessed using 2-tailed, independent samples one-way ANOVA for continuous variables, and Chi-square test for categorical variables. Post-hoc Tukey analysis was conducted to investigate specific differences between the three groups, assuming homogeneity of variances. Statistical significance was determined by an alpha value of 0.05. The distribution of FI was assessed using histogram (Fig. 1). Agreement between the three scales for the at-risk of frailty was measured using kappa statistic and correlations between the three scales was assessed using Spearman rho's correlation.

The associations between risk factors and frailty status was determined using binary logistic regression. Univariate logistic regression was carried out as a first step and variables with $p < 0.10$ were included in the multivariable logistic regression. A backwards eliminations process of non-significant variables from the initial model was carried out to establish the final multivariate model, with exit $p < 0.05$.All analysis were performed in SPSS 25 (IBM Corp, Armonk, NY, USA). Potential multicolinearity were analysed by Pearson correlation and analysing variance inflation factor between covariates over five. BMI and abdominal circumference had a potential cofounding effect (Pearson correlation 0.810, p value < 0.001) and VIF of 3.185. To avoid potential cofound factors, only abdominal circumference was kept in the logistic regression model.

3. Results

The FI was calculated for 673 out of 771 (87.3%) participants. Of the 673 included participants, 635 (92.4%) had no missing values on 54 items, 27(4.0%) participants had one missing item, six (0.9%) participants had between 2–5 missing items, and only five participants had 6–8 missing items (0.7%). Participants that were excluded due to more than 20% of missing items (98 participants) did not differ from the participants included in the study in regards to marital status, or educational status. However, they were significantly older (mean ± SD, 70.8 ± 5.1 years vs 69.4 ± 4.4 years, $p = 0.037$), with slower walking speed (1.30 ± 0.22 m/sec vs 1.39 ± 0.22 m/sec, $p = 0.019$), larger abdominal circumference (86.6 ± 9.3 cm vs 83.6 ± 8.2 cm, $p = 0.030$), and higher BMI (23.5 ± 3.6 kg/m^2 vs 22.5 ± 2.7 kg/m^2, $p = 0.031$) than participants where FI was possible to be calculated (data not shown).

Participants mean age was 69.4 ± 4.5 years old, 56.8% were female, 72.8% married and 19.5% living alone. Using FI criteria, 13.5% and 37.3% were classified as frail and pre-frail respectively (Table 1). Significant differences were found between participants by frailty status using the FI definition (Table 1). Participants with a higher frailty status were significantly older, used more medications, had a higher number of chronic diseases and were more at risk of malnutrition. Participants classified as pre-frail and frail had lower PA levels (7.4 ± 1.2 and 7.0 ± 1.2 vs 7.9 ± 1.2, respectively, $p < 0.001$, and post-Hoc Tukey analysis: $p < 0.001$, between robust and pre-frail and robust and frail groups). Pre-frail participants had significant higher abdominal circumference ($p < 0.001$) and higher BMI ($p < 0.001$) than robust participants. Frail participants also showed a weaker handgrip strength than robust participants ($p = 0.006$) (Table 1).

The mean FI was 0.12 ± 0.08 (SD), with a histogram distribution skewed to the right (gamma distribution) (Fig. 1). Scores ranged from 0 to 0.50, similar to that reported by other frailty indices (Rockwood, Andrew, & Mitnitski, 2007). KCL ranged from 0 to 15 (2.95 ± 2.38) and FP scores ranges from 0 to 4 deficits (0.50 ± 0.71) with no individuals scoring five points (maximum score). None of the measures showed any ceiling effect, with the 99th percentile score for FI 0.378, 11.26 for KCL and 3.0 for FP. Only FP demonstrated a floor effect with 61.2% demonstrating a score of zero. The correlations between the three scales was moderate to high (Spearman rho = 0.361 between FI and FP, $p < 0.001$; rho = 0.689 between FI and KCL, $p < 0.001$; rho = 0.435 between KCL and FP, $p < 0.001$). The agreement between three scales in classifying individuals within frailty status was poor (KCL and FI: kappa = 0.386 (SE = 0.03, $p < 0.001$), FP and FI: kappa = 0.218, SE = 0.031, $P < 0.001$ and FP and KCL (kappa = 0.291, SE = 0.035, $p < 0.001$).

Comparing the prevalence of frailty among three instruments to identify frailty, 13.5% were classified as frail (n = 91) using FI criteria, 1.5% (n = 10) using the FP criteria, and 4.0% (n = 27) of the sample using KCL. (Table 2).Considering pre-frailty prevalence, 37.7% (257), 37.3% (251) and 29.3% (197) were classified as pre-frail by FI, FP and KCL respectively. Of participants categorized as frail by KCL, all participants were also frail by FI, while 6 out 10 participants (60%) classified frail by FP were also classified as frail by FI. However, considering the participants classified as robust by KCL (n = 449) and FP (n = 412), one third of participants, 38.8% and 33.6% respectively, where classified as pre-frail or frail by the FI criteria (Table 2).

Several individual factors were individually associated with pre-frailty and frailty in the univariate multinomial logistic regression (Table 3). Pre-frailty (vs robust) was positively associated with age (Odds ratio (OR): 1.04, 95% confidence interval (95%CI): 1.00–1.08, $p = 0.038$), polypharmacy (OR: 2.48, 95%CI:1.44-4.26, $p < 0.001$), body mass index (BMI) (OR: 1.14, 95%CI: 1.07–1.21, $p < 0.001$), and waist circumference (OR:1.05, 95% CI: 1.03–1.07, $p < 0.001$). In addition, was negatively associated to PA level (OR: 0.71, 95%CI: 0.62-0.82, $p < 0.001$) and walking speed (OR: 0.28, 95%CI: 0.14-0.65, $p = 0.002$). Frailty (vs robust) was positively associated with age (OR: 1.08, 95%CI: 1.03–1.14, $p < 0.001$), living alone (OR: 1.82, 95%CI: 1.05–3.15, $p = 0.033$),

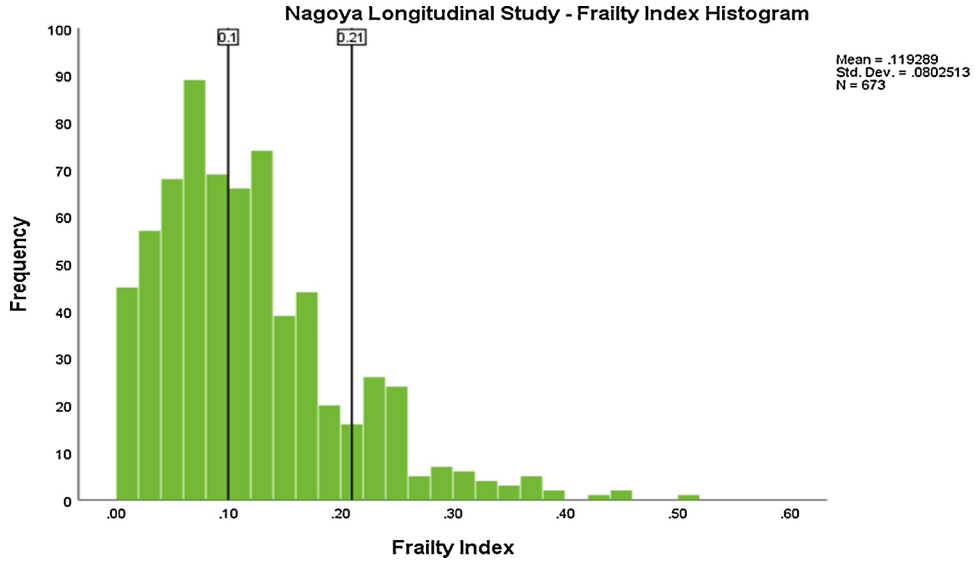

Fig. 1. Distribution of Frailty Index in the Nagoya Longitudinal Study of Healthy Elderly.

Table 1
Baseline characteristics of participants.

n (%)/ mean(SD)	Robust^	Pre-frail^	Frail^	Total	P value
Total	328(48.7)	254(37.7)	91(13.5)	673(100)	
Gender (Female)	187(57.0)	140(55.1)	55(60.4)	382(56.8)	0.673
Age (years)	68.9(4.3)*	69.7(4.2)	70.6(5.3)	69.4(4.5)	**0.003**
Education(10 years or more) †	313(95.4)	235(92.5)	86(94.5)	634(94.2)	0.325
Marital Status (Widowed/divorced/single)	80(24.4)	76(29.9)	27(29.7)	183(27.2)	0.277
Living Arrangement (Live Alone)	54(16.5)	53(20.9)	24(26.4)	131(19.5)	0.083
Smoking Status (Previous/current smoker)	129(39.3)	114(45.1)	38(41.8)	281(41.8)	0.381
Multimorbidity (2 or more chronic diseases)	92(28.0)*	145(57.1)**	69(75.8)***	306(45.5)	< **0.001**
Polypharmacy (5 or more medications)¶	23(7.0)*	40(15.7)**	24(26.4)***	87(12.9)	< **0.001**
Physical Activity (range 5-15 points)¶¶	7.9(1.2)*	7.4(1.2)**	7.0(1.2)	7.6(1.3)	< **0.001**
5- Cog Assessment (Positive screening)‡	116(37.5)	80(34.5)	24(28.9)	220(35.3)	0.332
MNA (At-risk of Malnutrition) ‡‡	33(10.1)*	37(14.6)	32(35.2)***	102(15.2)	< **0.001**
Waist circumference (cm)	82.2(8.0)	85.2(8.3)**	84.3(8.1)	83.6(8.2)	< **0.001**
BMI (kg/m^2) ‡‡‡	22.1(2.6)	23.1(2.7)**	22.4(2.5)	22.5(2.7)	< **0.001**
Low muscle mass ††	82(25.2)	60(23.6)	28(30.8)	170(25.3)	0.403
Subcutaneous fat thickness (cm)	14.3(5.6)	14.7(6.0)	15.5(5.9)	14.6(5.8)	0.236
Walking Speed (m/s)	1.4(0.2)	1.4(0.2)	1.3(0.2)	1.4(0.2)	0.135
Hand Grip Strength (kg)	29.5(8.3)*	28.8(8.2)	26.5(6.9)	26.5(6.9)	**0.009**

^ Frailty Index categories: robust 0 to ≤0.10, pre-frail between 0.10 to 0.21, frail > 0.21; one-way ANOVA for continuous variables, and Chi-square for categorical variables, p value < 0.05 is bolded.

* Post-hoc Tukey test – p value < 0.05 - differences between robust and frail groups.

** Post-hoc Tukey test – p value < 0.05 -difference between robust and pre-frail group.

*** Post-hoc Tukey test – p value < 0.05 – difference between pre-frail and frail group.

† 0 -9 years of education is equivalent to secondary education in Japan.

¶ Polypharmacy: use of 5 or more prescribed medications regularly.

¶¶ Baecke Physical Activity Questionnaire – continuous scale ranging from 5 to15 points, more points denoting higher physical activity level.

‡ 5-Cog Assessment: range from 5 to 15 points, with positive screening (5–14) for cognitive decline.

‡‡ Mini-nutritional Assessment – complete assessment; at-risk of malnutrition: less than 24 points, normal nutritional status: 24–30 points.

‡‡‡ BMI: Body Mass Index: weight in kilos/ height in metres squared.

†† Appendicular muscle mass index: Appendicular muscle mass/height^2 (Low muscle mass for men: < 7 kg/m^2 low muscle mass for women: < 5.7kg/m^2).

polypharmacy (OR: 4.75, 95%CI 2.53–8.92, p < 0.001), waist circumference (OR: 1.03, 95%CI: 1.00–1.07, p = 0.029), and negatively associated with PA scale (OR: 0.56, 95%CI: 0.45-0.69, p < 0.001), hand grip strength (OR: 0.95, 95%CI: 0.92-0.98, p < 0.001), and walking speed (OR: 0.10, 95%CI: 0.03-0.30, p < 0.001).

In a multivariate model (Table 4), being older, using five or more medications, and less PA were associated with being pre-frail and frail (vs robust). Having a higher waist circumference (OR: 1.04, 95%CI: 1.02–1.07, p < 0.001) was associated only with pre-frailty; while having lower handgrip strength (OR: 0.96, 95%CI: 0.92-0.99, p = 0.024) and lower walking speed (OR 0.25, 95%CI 0.07-0.91, p = 0.036) were associated only with frailty (vs robust). In the pre-frailty and frailty comparison, being frail was associated with lower BMI (OR: 0.86, 95%CI: 0.76-0.95, p = 0.004), doing less PA (OR: 0.76, 95% CI: 0.62-0.94, p < 0.001), and using five or more medications (OR: 2.47, 95%CI: 1.34–4.58, p < 0.001).

4. Discussion

Little is known of the prevalence of frailty by the FI and its associated factors in the Japanese population. We observed that in a population of older adults from Nagoya, the prevalence of frailty was

Table 2
Proportion of participants by each frailty category by Frailty Index, Frailty Phenotype and Kihon Checklist.

Frailty Phenotype	Frailty Index - n (%) [range]				Frailty Phenotype - n (%)			
	Robust^	Pre-frail^	Frail^	Total	Robust	Pre-frail	Frail	Total
Robust	252(76.8)	130(51.2)	30(33.0)	412(61.2)				
Pre-frail	75(22.9)	121(47.6)	55(60.4)	251(37.3)				
Frail	1(0.3)	3(1.2)	6(6.6)	10(1.5)				
Kihon Checklist								
Robust	298(90.9)	137(53.9)	14(15.4)	449(66.7)	327(79.4)	122(48.6)	0(0.0)	449(66.7)
Pre-frail	30(9.1)	117(46.1)	50(54.9)	197(29.3)	83(20.1)	110(43.8)	4(40.0)	197(29.3)
Frail	0 (0.0)	0 (0.0)	27(29.7)	27(4.0)	2(0.5)	19(7.6)	6(60.0)	27(4.0)
Total	328(48.7)	254(37.7)	91(13.5)	673 (100)	412(61.2)	251(37.3)	10(1.5)	673 (100)

^ Frailty Index categories: robust 0 to ≤0.10, pre-frail between 0.10 to 0.21, frail > 0.21.

13.5% by the FI, and frailty was significantly associated with being older, using five or more medications, doing less PA, and having lower walking speed and hand grip strength.

In our study, frailty prevalence (FI: 13.5%, FP: 1.5%, KCL: 4%) was considerably lower than previous meta-analysis (Kojima et al., 2017) of Japanese cohort of community-dwelling older adults (range 4.6%–9.5%) using FP criteria, and also lower considering a systematic review with mostly Caucasian population (FP: 14% and FI: 24%) (Shamliyan, Talley, Ramakrishnan, & Kane, 2013). This lower prevalence is best explained by the recruitment strategy in this study, where a convenience sample of older college students were recruited and therefore, participants might be younger (mean age 69.5 ± 4.5 years) and healthier when compared to previous meta-analysis of Japanese cohort studies (mean age 73.3–74.3 years old) (Kojima et al., 2017), where a mix of different studies were included, including locally representative cohorts and convenience samples. When looking more closely at the 65–70 years age bracket in various cohorts from around the world (Shamliyan et al., 2013), frailty prevalence ranged between 3–6% for the FP, and between 8–17% for the FI which is similar to the findings from our study.

Our FI (0.12 ± 0.08) has shown similar metrics of previous studies, showing closer mean scores (Kusatsu Longitudinal Study, FI mean 0.14) (Kojima et al., 2018), and similar skewed distribution to the right (Fig. 1) as previous studies in Japanese population. The low Kappa agreement score between FI and FP are consistent with previous cohorts (Theou et al., 2013; Thompson et al., 2018), and corroborate the perspective that whilst these instruments detect individuals at increased risk of adverse outcomes, different instruments result in different prevalence rates, and identify slightly different but overlapping groups of at-risk individuals (Theou et al., 2013). These differences in the ability to detect frailty have been described in multiple cohorts in different countries (Orkaby et al., 2017; Rockwood et al., 2007; Thompson et al., 2018). Furthermore, especially considering healthier and younger cohorts such as the NLS-HE study, FI has shown a stronger association with the risk of adverse outcomes than FP, and better discriminative ability in the lower to middle of the frailty spectrum (Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015).

The moderate agreement (kappa = 0.386, p < 0.001) and correlation (Spearman rho = 0.689, p < 0.001) found between FI and KCL, is also consistent with previous literature (previously described in Section 1 (Kojima et al., 2018)), and can be partially explained by the fact that both scales evaluate multiple overlapping health domains (see Appendix A Table A1) and FI included 13 out 25 questions of the original KCL. KCL shares the same concepts of multidimensionality of frailty as FI, and has similar predictive ability of adverse outcomes (Kojima et al., 2018). Some might argue that the longer the scale the

Table 3
Univariate multinomial logistic regression – Dependent Variable: Frailty Index.

	Pre-frail vs. Robust^		Frail vs Pre-frail^		Frail vs Robust^	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Gender (Female)	0.93 (0.67-1.29)	0.648	1.24 (0.76-2.03)	0.380	1.15 (0.72-1.85)	0.558
Age (years)	1.04 (1.00-1.08)	0.034	1.05(0.92-1.10)	0.096	1.08(1.03-1.14)	0.002
Education (10 years or more)†	0.59(0.30-1.19)	0.142	1.39(0.50-3.84)	0.525	0.82(0.29-2.33)	0.715
Marital Status (Unmarried)	1.32(0.92-1.91)	0.140	0.99(0.59-1.67)	0.964	1.31(0.78-2.19)	0.308
Living Arrangement (Live Alone)	1.34(0.88-2.04)	0.175	1.36(0.78-2.37)	0.280	1.82(1.05-3.15)	0.033
Smoking Status (Previous/current smoker)	1.27(0.91-1.76)	0.165	0.87(0.54-1.42)	0.587	1.11(0.69-1.77)	0.675
Polypharmacy (5 or more medications)*	2.48(1.44-4.26)	0.001	1.92(1.08-3.41)	0.027	4.75(2.53-8.92)	< 0.001
Physical Activity Scale (range 5-15 points)**	0.71(0.62-0.82)	< 0.001	0.80(0.65-0.97)	0.027	0.56(0.45-0.69)	< 0.001
5 –Cog Assessment (At risk of cognitive decline)‡	0.88(0.61-1.25)	0.464	0.77(0.45-1.34)	0.355	0.68(0.40-1.15)	0.147
BMI (kg/m^2)‡‡‡	1.13(1.07-1.21)	< 0.001	0.91(0.82-0.99)	0.035	1.03(0.94-1.13)	0.495
Waist circumference (cm)	1.05(1.03-1.07)	< 0.001	0.99(0.96-1.02)	0.344	1.03(1.00-1.07)	0.029
Skeletal Muscle index (kg/m^2) ‡	1.12(0.95-1.32)	0.167	0.77(0.59-1.00)	0.050	0.90(0.71-1.13)	0.363
Subcutaneous Fat Thickness (cm)	1.01(0.98-1.04)	0.408	1.02(0.98-1.06)	0.305	1.04(1.00-1.08)	0.090
Hand Grip Strength (kg)	0.99(0.97-1.01)	0.338	0.96(0.93-0.99)	0.019	0.95(0.92-0.98)	0.002
Walking Speed (m/s)	0.28(0.13-0.63)	0.002	0.38(0.11-1.02)	0.054	0.10(0.03-0.30)	< 0.001

Binary Logistic regression, between robust vs pre-frail, pre-frail vs frail and robust vs frail, p value below 0.10 (in bold) included in multivariate logistic regression.
‡Skeletal Muscle Index: defined as Appendicular Muscle Mass (kg)/ height (metres) squared.
^ Frailty Index categories: robust 0 to ≤0.10, pre-frail between 0.10 to 0.21, frail > 0.21.
† 0 -9 years of education is equivalent to reaching secondary education in Japan.
* Polypharmacy: use of 5 or more prescribed medications regularly.
** Baecke Physical Activity Questionnaire – continuous scale ranging from 5 to15 points, more points denoting higher physical activity level.
‡ 5-Cog Assessment: range from 5 to 15 points, with positive screening (5–14) for cognitive decline.
‡‡‡ BMI: Body Mass Index: weight in kilos/ height in metres squared.

Table 4
Multivariable Multinomial Logistic Regression - Dependent Variable: Frailty Index.

Multivariate logistic regression						
	Pre-frail vs. Robust[^]		Frail vs Pre-frail[^]		Frail vs Robust[^]	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Age (years)	1.06(1.02-1.10)	0.007			1.08(1.02-1.15)	0.015
Polypharmacy (5 or more medications)[*]	2.21(1.25-3.93)	0.007	2.47(1.34-4.58)	0.004	4.99(2.38-10.5)	< 0.001
Physical Activity Scale[**] (range 5-15 points)	0.66(0.57-0.77)	< 0.001	0.76(0.62-0.94)	0.011	0.55(0.43-0.70)	< 0.001
BMI (kg/m^2) [‡]			0.86(0.76-0.95)	0.004		
Waist circumference (cm)	1.04(1.02-1.07)	< 0.001				
Hand Grip Strength (kg)					0.96(0.92-0.99)	0.024
Walking Speed (m/s)					0.25(0.07-0.91)	0.036

Multivariate binomial logistic regression.
[^] Frailty Index categories: robust 0 to ≤0.10, pre-frail between 0.10 to 0.21, frail > 0.21.
[‡] BMI: weight in kilos over height in metres squared.
[*] Polypharmacy: use of 5 or more prescribed medications regularly.
[**] Baecke Physical Activity Questionnaire – continuous scale ranging from 5 to15 points, more points denoting higher physical activity level.

more accurate its predictive ability. In a previous study (Kojima et al., 2018), KCL alone (with 25 items) had an inferior ability to predict institutionalization than a 68-item FI that combined all KCL items, but was superior to a 32-item FI that excluded all KCL variables, suggesting that not only the number of items but also the domains covered are important in terms of detection of risk of adverse outcomes.

Two potentially modifiable factors have been associated with pre-frailty and frailty by FI: polypharmacy and PA. Polypharmacy has been consistently associated with frailty in cross sectional and longitudinal studies, independently of number of comorbidities (Gutierrez-Valencia et al., 2018; Mitnitski et al., 2001; Rockwood et al., 2011; Searle et al., 2008; Thompson et al., 2018) and de-prescribing and reducing inappropriate medications are strong recommendations from the Asia-Pacific Clinical Practice Guidelines for the Management of Frailty (Dent et al., 2017). Increasing PA levels, including lower levels of sedentary behaviour and higher levels of moderate to vigorous PA, have been associated with a reduction of frailty scores using FI (Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015). Additionally, PA levels, walking speed, and handgrip strength were independently associated with being frail by FI in the multivariate analysis, which illustrate the ability of FI to detect older adults at risk of reduced muscle power and strength. Current proposed PA interventions strategies targeting frailty have found improvement in lower limb muscle strength, number of daily steps and light-intensity PA, decrease in sedentary behaviour and reduction of frailty levels both in Japanese and European studies (Cesari et al., 2015; Nagai et al., 2018).

Finally, having a higher waist circumference was associated with pre-frailty in our study, in line with previous investigations of cardiovascular risk factors being associated with frailty (Ramsay et al., 2015), even in participants with normal BMI (Liao, Zheng, Xiu, & Chan, 2018). Elevated C-reactive protein and increased insulin resistance have been linked as mediating factors between abdominal adiposity and frailty in a longitudinal study (Garcia-Esquinas et al., 2015). In our logistic regression, BMI was also inversely associated with frailty (vs pre-frailty), with pre-frail participants showing a higher BMI than frail participants. BMI and frailty have a U-shaped relationship, with lowest FI appearing in BMI around 25 kg/m^2 (Hubbard, Lang, Llewellyn, & Rockwood, 2010), and higher FI levels associated with lower and higher BMI values. The partial association found in our results can be explained by the fact that within our sample a minority of participants had a BMI over 28 kg/m^2 (2.7%), and possibly only the descending part of the U-shaped curve between BMI and frailty can be observed, with only lower BMI being associated with higher frailty.

Our study has several strengths. Although most comparative studies require the use of substitutions of original questions, especially considering the feasibility of FP, our study was able to use minimum modifications to FP, by objectively assessing walking speed and handgrip strength in all participants and all original questions from KCL. Furthermore, this cohort provided a comprehensive assessment of health domains, to allow for enough variety of questions included in the final FI. Finally, our study adds to the literature as the first study to assess risk factors associated to FI in a Japanese population. A limitation of our study was the use of a convenience sample of older adults where participants might have higher health literacy and the results may not be generalizable to the Japanese population at large. Additionally, the cross sectional design does not allow for an assumption of cause and effect.

5. Conclusion

In this study, despite the recruitment of a healthier population, FI showed similar distribution, association with age, and agreement with other frailty scales. Age, polypharmacy, PA, waist circumference, BMI, handgrip strength and walking speed were associated with pre-frailty and frailty, and many of these factors may be amenable to intervention. This profile corroborates the use of FI as a useful tool that can be introduced into existing cohorts of older adults, and successfully differentiate individuals pre-frail and frail in healthier cohorts of older adults.

Author contributions

BAM – study concept, data analysis, interpretation, preparation of manuscript.
RV – study concept, data interpretation, preparation of manuscript.
HB – study concept, data interpretation, preparation of manuscript.
CHH - data analysis, interpretation, preparation of manuscript.
EM – acquisition of subjects and data, study design, preparation of manuscript.
KO - acquisition of subjects and data, study design, preparation of manuscript.
SS – study concept and design, preparation of manuscript.
CU – acquisition of data, preparation of manuscript.
MK – study concept and design, interpretation of data and preparation of manuscript.

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Appendix A

Table A1
Frailty Phenotype, Kihon Checklist and Frailty Index variables.

	Frailty Phenotype	Kihon Checklist Variables	Frailty Index Variables
Physical Strength	Handgrip score < 26 kg in men and < 18 kg in women; Walking speed < 1.0 m/s	Climbing stairs Stand up from a chair without help	Climbing stairs Stand up from a chair without help
Fatigue	Felt tired in the past 2 weeks	Difficulty in doing things usually did Felt tired in the past 2 weeks	Dropped usual activities
Physical Activity	Engage in low levels of physical exercise	Walk continuously for 15 minutes	
Nutrition and Oral Health	Loss of weight (2 kg in past 6 months)	Eating tough/hard foods Food decline in the past 6 months‡ Loss of weight (2 kg in past 6 months) Choke on tea or soup Dry mouth	Eating tough/hard foods Food decline in the past 6 months‡ Loss of weight (2 kg in past 6 months) Choke on tea or soup Pressure sores or skin ulcers Number of teeth Self-rated nutritional Status‡
Activities of Daily Living		Use public transportation Shopping independently Managing banking	Shopping Independently Managing banking
Falls		Falls in the past year Fear of Falling	Falls in the past year Fear of Falling
Social Network and Isolation		Go out less frequently Visit friends Turn to family and friends for advice Go out at least once a week	Go out less frequently Lives independently Preferred staying at home
Memory		Family points out memory loss Look up phone numbers Not knowing today's date	Family points out memory loss Look up phone numbers Not knowing today's date More memory problems than most
Mood		Lack of fulfilment in daily life Lack of joy doing things you used to enjoy Felt helpless	Feel that people are better off than you Life satisfaction Felt helpless Empty life Felt Bored Felt in Good spirits Feel worthless Feel full of energy Feel hopeless Felt happy Afraid something will happen to you Wonderful to be alive
Comorbidities			Hypertension Ischemic Heart Disease Heart Failure Peripheral Vascular Disease Atrial Fibrillation COPD Diabetes mellitus Dyslipidaemia Chronic Kidney Disease Cerebral Infarction Malignant tumour Metastatic cancer Rheumatoid Arthritis Osteoarthritis Fracture Recent psychological distress or acute disease
Symptoms and self-health evaluation			Self-rated health‡ Self-rated pain‡ Vision problems Hearing problems Incontinence Constipation

Frailty Index: All variables answers were coded to 0 (absence of deficit), or 1 (presence of deficit), except when marked with ‡, which admitted the 0.5 to represent partial presence of the deficit, Kihon Checklist: All variables if positive receive 1 point; COPD: Chronic Obstructive Pulmonary Disease.

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