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# Vascular Function and Frailty in Community-Dwelling Older Individuals

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## Abstract

**Background:** Frailty is a condition characterized by a state of reduced physiological reserve and increased vulnerability to stressors. Frail individuals have a higher likelihood of developing cardiovascular disease (CVD). However, the mechanisms underlying the association between frailty and CVD remain unclear.

**Objectives:** This study investigated whether frailty is associated with vascular function in community-dwelling older individuals.

**Material and Methods:** We conducted a cross-sectional analysis of 92 community-dwelling individuals aged  $\geq 65$  years, including 30 non-frail, 43 pre-frail, 19 frail individuals. Vascular function was assessed by brachial-ankle pulse wave velocity (PWV, measuring arterial stiffness) and flow-mediated dilation of the brachial artery (FMD, measuring endothelial function).

**Results:** The PWV was significantly higher in both pre-frail and frail groups than in the non-frail group (non-frail:  $1615.7 \pm 209.9$  cm/s vs. pre-frail:  $1815.2 \pm 265.0$  cm/s vs. frail:  $1829.9 \pm 256.0$  cm/s, respectively,  $p = 0.003$ ). The FMD was significantly lower in both pre-frail and frail groups than in the non-frail group (non-frail:  $5.1 \pm 2.1\%$  vs. pre-frail:  $3.4 \pm 1.3\%$  vs. frail:  $3.1 \pm 1.2\%$  cm/s, respectively,  $p = 0.001$ ). Multiple logistic regression analyses indicated that pre-frail and frail group were associated with arterial stiffness (OR, 2.92; 95% CI, 1.01–8.42; OR, 3.56; 95% CI, 0.85–14.91) and endothelial dysfunction (OR, 2.17; 95% CI, 0.41–3.09; OR, 2.27; 95% CI, 0.31–6.97).

**Conclusions:** Thus, pre-frailty and frailty are associated with impaired vascular function in community-dwelling older adults, even when adjusting for confounding factors. These findings may help to prevent the potential consequences between CVD and frailty in community-dwelling older individuals.

**Keywords:** Frailty, Vascular function, Pulse wave velocity, Flow-mediated dilation

## 1 Introduction

Recently, frailty is increasing globally, but it is not well recognized in older adults [1]. In addition, a systemic review and meta-analysis reported that the prevalence of frailty is higher in the older age group and higher in the elderly women than in elderly men [2]. Frailty is a geriatric syndrome that reduced physiological reserve and

increased vulnerability to possible stressors. Frailty is characterized by reduced physical activities, sarcopenia, decreased energy, decreased walking speed, and chronic nutrient deficiency [1]. These factors are linked to a vicious cycle of frailty, aggravating frailty further. Therefore, preventing and managing frailty may become an important target to reduce the impact of aging.

Cardiovascular disease (CVD), one of the leading causes of death globally, is very common in older adults [2]. The mechanisms underlying CVD vary, depending on the disease, such as coronary artery disease, stroke, and atherosclerosis [3]. Due to the

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complex nature of aging, frailty has become an increasing issue in CVD medicine [4]. Frailty is an independent factor that is associated with CVD [1, 5]. Although frailty was a factor in the evaluation of older adults with CVD, there was a lack of information on the relationship between frailty and CVD in older adults. In previous studies on the association between CVD and frailty, Afilalo et al. [4] reported that the risk of CVD was two- or three-fold higher in frailty [4]. Sergi et al. [6] showed that, among symptoms of frailty, the onset of CVD was significantly related to low energy expenditure, exhaustion, and slow gait speed [6]. Frailty is associated with increased CVD by causing low-grade inflammation, cellular senescence, and endocrine dysregulation [7]. Taken together, these data suggest that CVD and frailty may be implicated in the bidirectional relationship [8].

Impaired vascular functions, such as arterial stiffness and endothelial dysfunction, play an important role in the progression and development of atherosclerosis [9]. Arterial stiffness is an independent risk factor for CVD. Carotid-femoral PWV cfPWV has been considered as a gold standard for the non-invasive measurement of arterial stiffness [10]. However, this measure is rarely used in Asian countries, due to methodological difficulties. brachial-ankle pulse wave velocity (baPWV) is widely used in Asian countries, including Korea and Japan [11, 12]. baPWV is strongly correlated with cfPWV [13] and easy, and its reproducibility is relevant [14]. Endothelial dysfunction, an early marker of CVD, can also be reliably assessed by brachial artery flow-mediated dilation (FMD) [15–17]. In the Framingham Heart Study, among community-dwelling older individuals aged 60 years and older, pre-frailty, and frailty were associated with increased arterial stiffness, assessed using cfPWV [18] and frailty is significantly associated endothelial dysfunction, evaluated by asymmetric dimethylarginine (ADMA) levels from Toledo Study for Healthy Aging [19]. Another study group demonstrated that frailty was positively related to endothelial dysfunction measured by FMD in older adults with chronic kidney disease [20]. However, to our knowledge, there is little information on the association between frailty and vascular function assessed by arterial stiffness and endothelial dysfunction in community-dwelling older individuals. This study was conducted to investigate whether frailty is associated with vascular function as measured by the baPWV and FMD among community-dwelling older adults.

## 2 Materials and Methods

### 2.1 Subjects

The study participants were visitors to recreational classes at Senior Complex in Korea. Data were collected from July 2018 to December 2019. Participants met the following inclusion criteria: (1) aged 65 years or older and (2) consent to participate in this study. Patients with severe cognitive impairment or dementia, secondary hypertension, cancer, overt CV disease, obstructive pulmonary disease, or other severe diseases, and those requiring a wheelchair, were excluded from the study [1]. Finally, we recruited 92 participants in this study. The study protocol was approved by the Institutional Review Board on Korea University (KUIRB-2019-0161-01), conducted by the Declaration of Helsinki. All participants signed informed consent to participate in the assessment. The recruitment of the participants is shown (Fig. 1).

### 2.2 Study Protocol

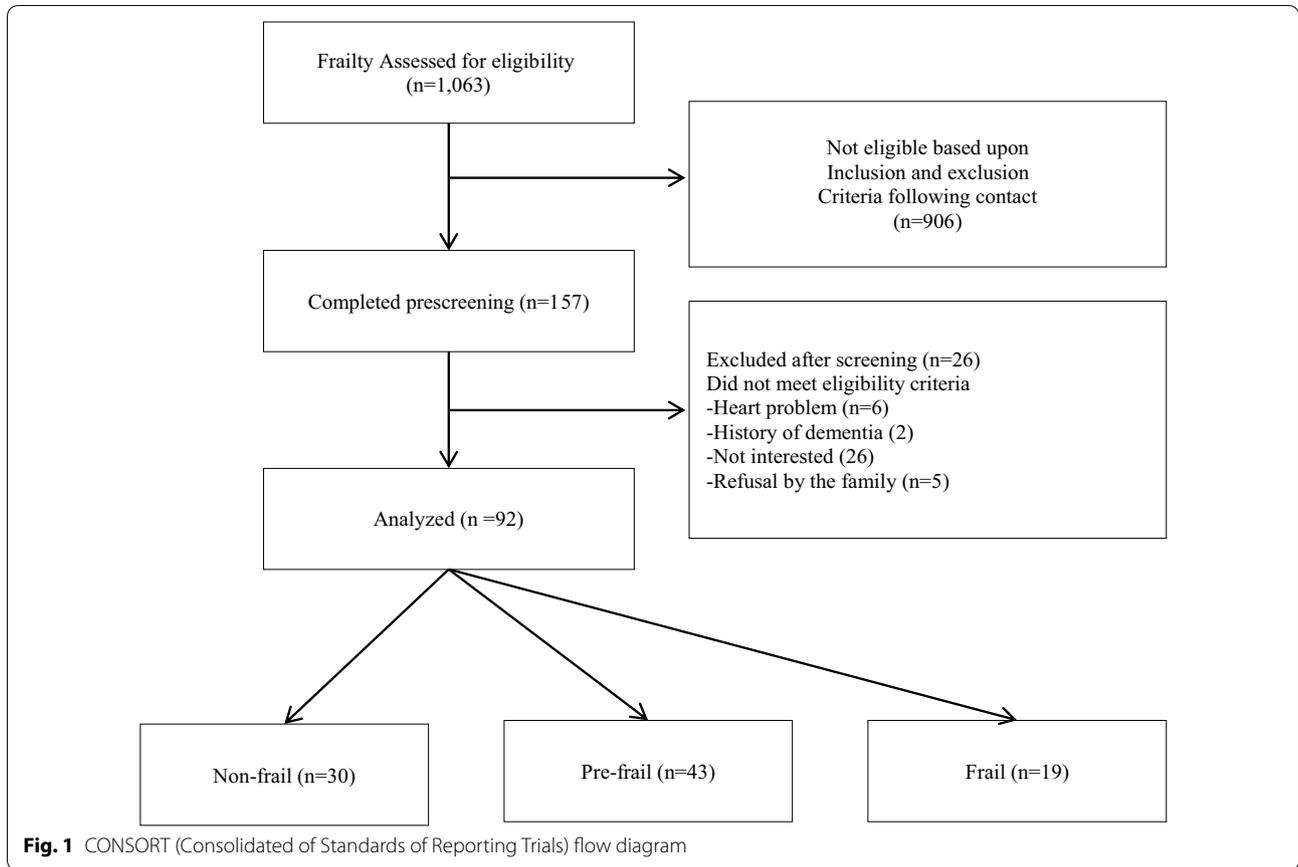
All experimental procedures were explained to the participants. In the screening visit (visit 1), we divided participants into three groups (e.g., non-frail, pre-frail, and frail). In the measurement visit (visit 2, subjects were instructed to visit the laboratory in the morning, after refraining from alcoholic beverages, caffeine, and food for at least 12 h and from strenuous exercise for 24 h before the experiments. All testing was conducted at the same time of day among the groups. Experiments were conducted under a quiet, comfortable, and ambient environment in a laboratory (ca. 24 °C and 40% relative humidity). The same investigator performed all measurements. Subjects were required to rest on a chair in a seated position for at least 20 min before the test.

### 2.3 Assessment of Frailty

The subjects were divided into three groups based on Fried's frailty phenotype, using the following criteria for frailty: (1) unintentional weight loss, (2) weakness (grip strength), (3) exhaustion, (4) slowness (gait speed), and (5) low physical activity [1]. The above criteria of frailty, weakness, and slowness were based on the best records, stratified by sex and body mass index (BMI) cutoffs, described by Fried et al. [1]. Subjects were considered to be "non-frail" if they met none of the frailty criteria, "pre-frail" if they met one or two of the criteria, and "frail" if they met three or more frailty criteria (Table 1).

### 2.4 Body Composition

Height and weight were measured using a physicians' balance scale (Seca, Hamburg, Germany) while the participants were lightly clothed and wearing no shoes. BMI was calculated using the equation body mass (kg)/height squared (m<sup>2</sup>). Lean mass and body fat percentage



**Table 1** Frailty phenotype (by Fried et al.'s criteria, 2001)

	Male	Female
Weight loss	Loss of $\geq 10$ lbs (4.5 kg) or $\geq 5\%$ of body weight in the last year	
Slowness (4.57 m)	Height $\leq 173$ cm: $\geq 7$ s Height $> 173$ cm: $\geq 6$ s	Height $\leq 159$ cm: $\geq 7$ s Height $> 159$ cm: $\geq 6$ s
Handgrip strength (kg)	BMI $\leq 24.0$ : $\leq 29$ BMI 24.1–26.0: $\leq 30$ BMI 26.1–28.0: $\leq 30$ BMI $> 28.0$ : $\leq 32$	BMI $\leq 23.0$ : $\leq 17$ BMI 23.1–26.0: $\leq 17.3$ BMI 26.1–29.0: $\leq 18$ BMI $> 29.0$ : $\leq 21$
Physical activity (MLTA)	$< 383$ kcal/week (about 2.5 h walk)	$< 273$ kcal/week (about 2 h walk)
Exhaustion	A score of 2 or 3 on either question on the CES-D How often did you feel this way in the last week? (a) I felt everything I did was an effort (b) I could not get going 0 = less than 1 day, 1 = 1–2 days, 2 = 3–4 days, 3 = more than 4 days	

BMI body mass index; CES-D center for epidemiologic studies depression scale; MLTA minnesota leisure time activity questionnaire

were determined using a bioelectrical impedance analysis device (Inbody 270, Biospace, South Korea). The waist-hip ratio (WHR) was calculated from the waist by hip measurements.

**2.5 Blood Pressure**

Blood pressure (BP) was measured with an automatic monitor (HEM-7200-AP3; Omron Healthcare, Kyoto, Japan) in duplicate on the right arm after 5 min of rest in the seated position, with the arm at heart level.

**2.6 Grip Strength**

The maximal isometric grip strength of both arms was assessed unilaterally using a standard grip strength dynamometer (T.K.K 5401, Takei Instruments, Japan).

**2.7 Endurance Test (6-Min Walk Test)**

Participants were instructed to walk as far as possible within 6 min on a flat surface following a circular circuit of 25 m with no feedback or encouragement during the test but were allowed to rest if needed [21].

## 2.8 Short Physical Performance Battery

The short physical performance battery was assessed by three lower body function tests as follows: (1) the standing balance test, including tandem, semi-tandem, and side-by-side standing, in which the participants were timed until they moved or after 10 s had elapsed; (2) walking speed test, in which the participants were asked to walk 4 m at their regular pace; and (3) repeated chair sit-to-stand test, in which the participants performed a pre-test of standing up from the sitting position with arms folded anteriorly, and if successful, performed five chair stands as quickly as possible, to which they were timed.

The performance on each subtest was scored from 0 to 4, thereby giving total scores ranging from 0 to 12, with higher scores reflecting better function. In addition, the walking speed was calculated using the faster of the two walking speed trials [22].

## 2.9 Arterial Stiffness

After a 15-min rest period on the supine position, arterial stiffness was measured as baPWV using an automatic oscillometric device (VP-1000plus, Omron Healthcare, Kyoto Japan). This was calculated from the traveling distance and foot-to-foot wave transit time between two arterial recording sites in the supine position [23].

## 2.10 Endothelial-Dependent Vasodilation (Flow-Mediated Dilatation)

Endothelial-dependent vasodilation (i.e., FMD) was measured using a UNEX EF-38G (UNEX Co. Ltd, Nagoya, Japan), an ultrasound instrument for FMD measurement equipped with an automated edge-detection system for measurement of the brachial artery diameter. The system has an electric linear-array transducer operating at 10 MHz. While subjects rested in the supine position, a BP cuff was placed on the forearm with the proximal edge of the cuff above the subject's antecubital fossa, while a second BP cuff was placed on the contralateral arm for standard BP measurements. Cross-sectional images of the artery were acquired utilizing an automated probe, which was self-adjusted to provide a clear longitudinal image of the artery and began baseline measurements. After the acquisition of the baseline measurement, the cuff was inflated to 50 mmHg above resting systolic blood pressure for 5 min, effectively occluding the arm below the antecubital fossa. Upon cuff deflation, ultrasound-derived measurements of the brachial artery diameters and blood flow velocity were taken for 2 min [24]. FMD was calculated as  $\{(\text{Diameter of the brachial artery at the baseline} - \text{diameter of the brachial artery at maximum dilatation}) \times 100\} / \text{Diameter of the brachial artery at baseline}$ .

## 2.11 Blood Biochemistry

Venous blood variables were analyzed by the Green Cross Medical Foundation (an organization certified by The Korea Society for Laboratory Medicine). Concentrations of the following blood variables were quantified: glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). A 5-mL sample of venous blood was collected into the serum-separating tube (SST) for serum. Clot formation was ensured in the SST by centrifuging the sample at 3,000 rpm for 20 min. Fasting blood samples were frozen at  $-80^{\circ}\text{C}$  and thawed before assay. An enzymatic colorimetric assay kit was used for Assessing TG (Roche, Basel, Switzerland), TC (Roche, Basel, Switzerland), HDL-C plus 3rd generation kit (Roche, Basel, Switzerland), and LDL-C plus 2nd generation kit (Roche, Basel, Switzerland). All blood assays were performed by using duplicate analysis.

## 2.12 Statistical Analysis

The results are presented as means and standard deviations. Data normality was verified with a Shapiro–Wilk test. Among the three groups, comparisons of continuous variables with normal distribution were carried out by one-way analysis of variance (ANOVA), and a Scheffe post-hoc test was used to investigate significant differences. Wallis H test was used for the comparison of continuous variables with a non-normal distribution. Categorical variables were performed using the chi-square test among three groups. Multiple logistic regression analyses were performed to indicate independent variables, which were confounding factors including BMI, lean mass, %bodyfat, WHR, SBP, HR, glucose, hypertension, diabetes mellitus, and dyslipidemia associated with arterial stiffness and endothelial dysfunction. All analyses were performed using Statistical Package for Social Science (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). A priori, the level of significance was set at 0.05.

## 3 Results

The demographic characteristics of the groups are summarized in Table 2. Ninety-two participants aged  $\geq 65$  years (mean age;  $74.9 \pm 3.2$  years, women; 80) were evaluated in this study. There were no significant differences in age ( $p=0.195$ ), but BMI, %bodyfat, and WHR were significantly different among the three groups ( $p=0.005$ ,  $p=0.001$ , and  $p=0.001$ , respectively).

### 3.1 BP and Biomarkers

Systolic BP was significantly higher in the pre-frail and frail groups than in the non-frail group ( $p=0.001$ ). However, diastolic BP was not significantly different among

groups ( $p=0.056$ ). Heart rate at rest was significantly lower in frail group than in both non-frail and pre-frail groups ( $p=0.016$ ) (Table 3). In terms of blood variables, glucose was significantly higher in both pre-frail and frail groups than in the non-frail group ( $p=0.001$ ). However, the other variables, including HbA1c, TC, TG, HDL-C, and LDL-C were not significantly different among the groups ( $p>0.05$ ) (Table 3).

### 3.2 Physical Capacity

As shown in Table 4, there were significant differences in maximal grip strength among groups (left:  $p=0.002$ , right: 0.002, respectively). Participants in both pre-frail and frail groups demonstrated significant reductions in distance covered during the 6-min walk test ( $p<0.001$ ). Also, SPPB scores in both pre-frail and frail groups were significantly lower than in the non-frail group ( $p<0.001$ ).

**Table 2** Demographic characteristics of subjects

Variables	Non-frail (n = 30)	Pre-frail (n = 43)	Frail (n = 19)	F/H/ $\chi^2$	p value
Age (years)	74.1 (2.5)	75.3 (3.7)	75.3 (2.6)	1.663	0.195
Women	23 (76.6%)	40 (93.0%)	17 (89.4%)	4.302	0.116
BMI (kg/m <sup>2</sup> )	22.6 (2.4)	24.7 (3.0) <sup>†</sup>	24.9 (3.7) <sup>†</sup>	5.549	0.005*
Lean mass (kg)	21.3 (3.9)	18.6 (2.2) <sup>†</sup>	18.8 (3.3) <sup>†</sup>	9.411	0.009*
Body fat (%)	29.7 (7.2)	36.3 (6.2) <sup>†</sup>	36.8 (6.5) <sup>†</sup>	17.630	0.001*
WHR	0.84 (0.05)	0.91 (0.06) <sup>†</sup>	0.91 (0.06) <sup>†</sup>	17.242	0.001*

Data are given as mean ( $\pm$ SD)

SD standard deviation, valid percentages (n %), BMI body mass index, WHR waist hip ratio

\* $P<0.05$ , <sup>†</sup> $P<0.05$  vs. Non-frail

**Table 3** Blood pressure and biomarkers among groups

Variables	Non-frail (n = 30)	Pre-frail (n = 43)	Frail (n = 19)	F/H/ $\chi^2$	p value
Blood pressure					
Systolic BP (mmHg)	120.4 (12.6)	140.3 (12.3) <sup>†</sup>	142.1 (14.1) <sup>†</sup>	26.171	0.001*
Diastolic BP (mmHg)	68.9 (8.1)	74.1 (8.6)	73.2 (11.6)	2.986	0.056
Heart rate (bpm)	76.8 (12.7)	70.5 (10.3)	68.7 (7.1) <sup>†</sup>	4.327	0.016*
Biomarkers					
Glucose (mg/dL)	85.7 (17.2)	121.0 (35.3) <sup>†</sup>	106.4 (21.4) <sup>†</sup>	14.192	0.001*
HbA1c (%)	5.9 (0.7)	6.4 (1.1)	6.2 (1.4)	2.541	0.084
Total cholesterol (mg/dL)	167.8 (36.6)	174.5 (29.1)	167.1 (33.5)	0.524	0.594
Triglycerides (mg/dL)	115.4 (45.9)	146.7 (68.5)	129.1 (53.8)	2.521	0.086
HDL cholesterol (mg/dL)	60.0 (15.3)	60.0 (16.2)	63.6 (18.2)	0.370	0.692
LDL cholesterol (mg/dL)	83.8 (35.2)	88.2 (28.3)	78.0 (30.9)	0.722	0.489

Data are given as mean ( $\pm$ SD)

SD standard deviation, valid percentages (n %), BP blood pressure, HDL high-density lipoprotein, LDL low-density lipoprotein

\* $P<0.05$ , <sup>†</sup> $P<0.05$  vs. Non-frail

**Table 4** Physical fitness level among groups

Variables	Non-frail (n = 30)	Pre-frail (n = 43)	Frail (n = 19)	F/H/ $\chi^2$	p value
Grip strength left (kg)	20.8 (6.6)	16.6 (4.1) <sup>†</sup>	15.3 (6.6) <sup>†</sup>	12.988	0.002*
Grip strength right (kg)	21.5 (6.9)	17.9 (4.5) <sup>†</sup>	15.4 (6.9) <sup>†</sup>	6.793	0.002*
Six-min walk test (m)	491.8 (57.0)	357.7 (97.6) <sup>†</sup>	349.9 (68.3) <sup>†</sup>	19.24	0.001*
SPPB (scores)	10.6 (0.9)	8.8 (1.3) <sup>†</sup>	8.1 (1.9) <sup>†</sup>	15.51	0.001*

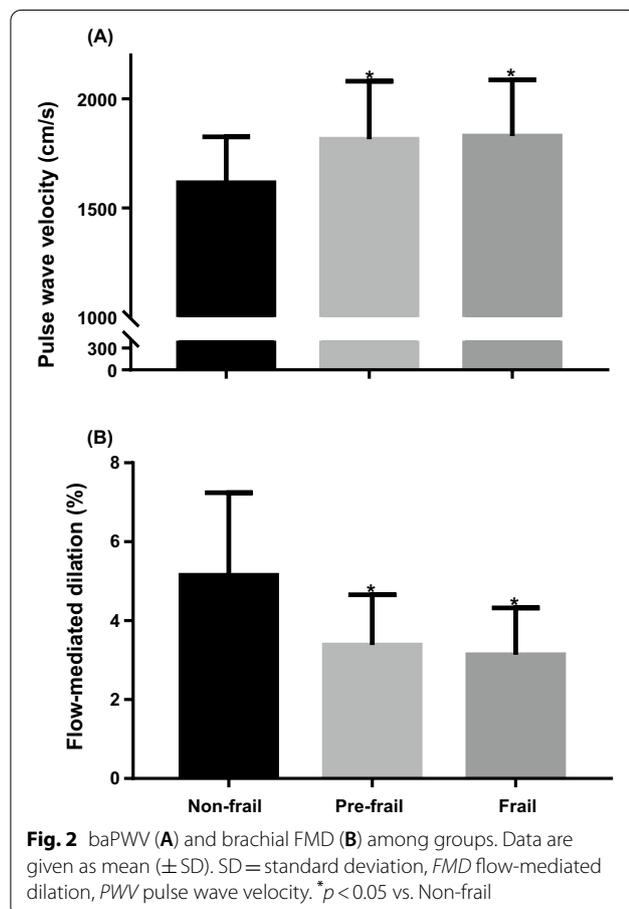
Data are given as mean ( $\pm$ SD)

SD standard deviation, SPPB short physical performance battery

\* $P<0.05$ , <sup>†</sup> $P<0.05$  vs. non-frail

### 3.3 Vascular Function

Figure 2 shows the results of arterial stiffness (Fig. 2A) and endothelial dysfunction (Fig. 2B). Subjects in both pre-frail and frail groups had a significantly higher PWV than those in the non-frail group ( $1815.2 \pm 265.0$  cm/s,  $1829.9 \pm 256.0$  cm/s, and  $1615.7 \pm 209.9$  cm/s in pre-frail, frail and non-frail groups, respectively,  $p = 0.003$ ). However, there was no significant difference between pre-frail and frail groups in this respect (Fig. 2A). As same as PWV, FMD was significantly lower in both pre-frail and frail groups than in their non-frail counterparts ( $p = 0.001$ ) whereas there was no significant difference between pre-frail and frail groups (Fig. 2B). The multivariate-unadjusted and adjusted odds ratios of arterial stiffness and endothelial dysfunction using non-frail participants as the reference. Multiple logistic regression analyses indicated that pre-frail and frail group were associated with arterial stiffness (OR, 2.92; 95% CI, 1.01–8.42; OR, 3.56; 95% CI, 0.85–14.91) and endothelial dysfunction (OR, 2.17; 95% CI, 0.41–3.09; OR, 2.27; 95% CI, 0.31–6.97).



### 4 Discussion

The present cross-sectional study was conducted to investigate the relationship between frailty and vascular function in community-dwelling older individuals. We demonstrated that pre-frail and frail groups showed worse vascular function than the non-frail group of community-dwelling older individuals. These results are consistent with the concept that more severe frailty may have an adverse effect on vascular function in older adults (Table 5).

Previous studies have shown that frailty is a biological syndrome resulting from dysfunction across multiple physiological systems [6, 25, 26]. Inflammation is related to many age-related chronic diseases including atherosclerosis, cancer, and dementia and chronic inflammation is associated with frailty [27]. In addition, atherosclerosis is risk factor concomitant mechanism for increasing frailty [28]. In the present study, arterial stiffness as assessed by baPWV was significantly higher in pre-frail and frail groups than in the non-frail group ( $1815.2 \pm 265.0$  cm/s,  $1829.9 \pm 256.0$  cm/s, and  $1615.7 \pm 209.9$  cm/s in pre-frail, frail and non-frail groups, respectively). This present finding was consistent with a previous study showing that pre-frailty and frailty were associated with higher arterial stiffness in a cohort of older adults [18]. A plausible mechanism underlying the association between frailty and arterial stiffness may involve greater arterial pulsatility or damage to the arterial circulation, which causes various phenomena associated with frailty [29]. Another mechanism that may underlie increased arterial stiffness in frailty may be related to aging and increased SBP, which are considered to be determinant factors for arterial stiffening. In frail older individuals, large arteries stiffen, and systolic BP and pulse pressure increase, due to wave reflections, more than in non-frail individuals [30]. However, our results showed that pre-frail and frail groups had

**Table 5** Association between frailty and vascular functions

Variable	Odds ratio (95% confidence interval)	
Arterial stiffness (cm/s)	Unadjusted	Model 1 <sup>a</sup>
Non-frail	1 (reference)	1 (reference)
Pre-frail	2.92 (1.01–8.42)	3.11 (1.04–9.29)
Frail	3.56 (0.85–14.91)	3.79 (0.85–16.82)
Endothelial dysfunction (%)	Unadjusted	Model 1 <sup>a</sup>
Non-frail	1 (reference)	1 (reference)
Pre-frail	2.17 (0.41–3.09)	2.13 (0.76–8.95)
Frail	2.27 (0.31–6.97)	2.27 (0.31–6.97)

<sup>a</sup> Model 1: adjusted for body mass index, lean mass, %bodyfat, waist-hip ratio, systolic blood pressure, heart rate, glucose, hypertension, diabetes mellitus, and dyslipidemia

significantly higher PWV. In addition, pre-frail and frail were associated with increased arterial stiffness by multiple logistic regression analyses. Taken together, both frailty and pre-frailty may be one of the risk factors for CVD in older adults.

Endothelial dysfunction causes the development and progression of atherosclerosis [9]. In this study, we found that FMD, a widely used measurement of endothelial function in humans, was significantly lower in the pre-frail and frail groups than in the non-frail group ( $3.4 \pm 1.3\%$ ,  $3.1 \pm 1.2\%$ , and  $5.2 \pm 2.1\%$  in pre-frail, frail, and non-frail groups, respectively) indicating that FMD was approximately two times lower in the frail group than in the non-frail group. This is in line with the results of Santillo et al. [31], who reported that FMD was approximately two times lower in the frail hospitalized older individuals than in non-frail older individuals of an equivalent age (5.45% and 10.42% in frail older individuals and non-frail older individuals, respectively;  $p < 0.021$ ) [31]. The mechanisms underlying the increased risk of endothelial dysfunction due to frailty are multifactorial. Aging may be a common mechanism for the progression of endothelial dysfunction and frailty. FMD decreases with advancing age [32]. However, our result of a lower FMD in pre-frail and frail older individuals may not be fully due to aging, because the three groups were not significantly different in age and the relationship between frailty and FMD was remained after adjusting for confounding factors in multiple logistic regression analyses. This result was supported by another study that reported that the relationship between FMD and frailty was not strongly age-related in hospitalized older individuals [33]. As another mechanism, a recent report suggested that decreases in nitric oxide bioavailability and/or increases in inflammation and oxidative stress, which induce endothelial dysfunction, also play a crucial role in frailty [32, 34].

There were several limitations in this study. First, this study cannot prove cause and effect as it had a cross-sectional study design. Second, this study may not fully represent the characteristics of frailty from this study, due to the relatively small number of participants. This study was not population-based and there may be unknown bias in the selection. Despite this small sample size, the group ratio for frailty in this study (approximately 33.3, 46.7, and 20.6% in non-frail, pre-frail, and frail older individuals, respectively) was similar to that of another previous studies study (approximately 40.9, 38.0, and 21.0% in non-frail, pre-frail and frail elderly, respectively) [28]. Third, the fact that most of the subgroup consists of older women, not older men, may not be strongly represented the relationship between frailty and vascular function in older adults. Fourth, due to the characteristics of the

frailty phenotype, participants' subjective judgment may have been involved (e.g., unintentional weight loss, exhaustion), and thus, the possibility of bias cannot be excluded. Fifth, baPWV might not be accurate due to the muscular arteries of lower limbs, compared with cfPWV. This limitation may be consistent in older adults. However, substantial of evidence have been published using the baPWV in the past years. Last, some covariates such as biomarkers, medication use, and smoking are not well addressed in this study which plays a significant impact on the relationship between frailty and vascular function. This study had strength in that it investigated the association of two major measurements of vascular function (baPWV and FMD) with the level of frailty in community-dwelling older individuals, whereas other previous studies measured either baPWV and FMD alone when analyzing a possible association between frailty and vascular function.

## 5 Conclusion

Despite these limitations, the present study demonstrated that older individuals who are pre-frail and frail have higher arterial stiffness and greater endothelial dysfunction than their non-frail counterparts. However, there was no significant difference in vascular function between pre-frail and frail older individuals. Accordingly, the development from a pre-frail state to frailty can be delayed or prevented, reducing the risk of CVD and clinical disorders. Further studies (on various interventions and nutritional factors) are needed to elucidate the relationship between frailty and vascular function to confirm our findings.

### Authors Contributions

Study conception and design, W.P. and J.P.; Investigation, W.P., J.L., H.Y.P., S.P., and J.P.; Interpretation of the findings, W.P. and J.P.; Manuscript preparation, W.P., J.L., H.Y.P., S.P., and J.P.; Critical revision of the manuscript, W.P., J.L., H.Y.P., S.P., and J.P. All authors have read and agreed to the published version of the manuscript.

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### Data Availability

The data in this study are available from the corresponding author, with a reasonable request.

### Declarations

#### Conflict of Interest

The authors declare no conflicts of interest.

### Ethical Approval

The study protocol was approved by the Institutional Review Board on Korea University (KUIRB-2019-0161-01), conducted by the Declaration of Helsinki and All participants signed informed consent to participate in the assessment.

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### References

- Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol Ser A*. 2001;56(3):M146–56. <https://doi.org/10.1093/gerona/56.3.m146>.
- Ofori-Asenso R, Chin KL, Mazidi M, Zomer E, Ilomaki J, Zullo AR, Gasevic D, Ademi Z, Korhonen MJ, LoGiudice D, Bell JS, Liew D. Global incidence of frailty and prefrailty among community-dwelling older adults: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(8): e198398. <https://doi.org/10.1001/jamanetworkopen.2019.8398>. PMID:31373653; PMID:PMC6681553.
- Thomas H, Diamond J, Vieco A, Chaudhuri S, Shinnar E, Cromer S, Perel P, Mensah GA, Narula J, Johnson CO, Roth GA, Moran AE. Global atlas of cardiovascular disease 2000–2016: the path to prevention and control. *Glob Heart*. 2018;13(3):143–63. <https://doi.org/10.1016/j.gheart.2018.09.511>.
- Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, Popma JJ, Ferrucci L, Forman DE. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol*. 2014;63(8):747–62. <https://doi.org/10.1016/j.jacc.2013.09.070>.
- Veronese N. Frailty as cardiovascular risk factor (and vice versa). *Adv Exp Med Biol*. 2020;1216:51–4. [https://doi.org/10.1007/978-3-030-33330-0\\_6](https://doi.org/10.1007/978-3-030-33330-0_6).
- Sergi G, Veronese N, Fontana L, De Rui M, Bolzetta F, Zambon S, Corti MC, Baggio G, Toffanello ED, Crepaldi G, Perissinotto E, Manzato E. Pre-frailty and risk of cardiovascular disease in elderly men and women: the ProVA study. *J Am Coll Cardiol*. 2015;65(10):976–83. <https://doi.org/10.1016/j.jacc.2014.12.040>.
- Soysal P, Arik F, Smith L, Jackson SE, Isik AT. Inflammation, frailty and cardiovascular disease. *Adv Exp Med Biol*. 2020;1216:55–64. [https://doi.org/10.1007/978-3-030-33330-0\\_7](https://doi.org/10.1007/978-3-030-33330-0_7).
- Orkaby AR, Kornej J, Lubitz SA, McManus DD, Trivison TG, Sherer JA, Trinquart L, Murabito JM, Benjamin EJ, Preis SR. Association between frailty and atrial fibrillation in older adults: the Framingham Heart Study offspring cohort. *J Am Heart Assoc*. 2021;10(1):e018557. <https://doi.org/10.1161/JAHA.120.018557>.
- Mudau M, Genis A, Lochner A, Strijdom H. Endothelial dysfunction: the early predictor of atherosclerosis. *Cardiovasc J Afr*. 2012;23(4):222–31. <https://doi.org/10.5830/CVJA-2011-068>. PMID:22614668; PMID:PMC3721957.
- O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens*. 2002;15(5):426–44. [https://doi.org/10.1016/s0895-7061\(01\)02319-6](https://doi.org/10.1016/s0895-7061(01)02319-6).
- Kim J, Song TJ, Song D, Lee KJ, Kim EH, Lee HS, Nam CM, Nam HS, Kim YD, Heo JH. Brachial-ankle pulse wave velocity is a strong predictor for mortality in patients with acute stroke. *Hypertension*. 2014;64(2):240–6. <https://doi.org/10.1161/HYPERTENSIONAHA.114.03304>.
- Benetos A, Waeber B, Izzo J, Mitchell G, Resnick L, Asmar R, Safar M. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. *Am J Hypertens*. 2002;15(12):1101–8. [https://doi.org/10.1016/s0895-7061\(02\)03029-7](https://doi.org/10.1016/s0895-7061(02)03029-7).
- Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *J Hypertens*. 2009;27(10):2022–7. <https://doi.org/10.1097/HJH.0b013e3283282e94e7>.
- Munakata M. Brachial-ankle pulse wave velocity: background, method, and clinical evidence. *Pulse (Basel)*. 2016;3(3–4):195–204. <https://doi.org/10.1159/000443740>.
- Maruhashi T, Kajikawa M, Kishimoto S, Hashimoto H, Takaeko Y, Yamaji T, Harada T, Hashimoto Y, Han Y, Aibara Y, Yusoff FM, Hidaka T, Chayama K, Nakashima A, Goto C, Kihara Y, Higashi Y. Vascular function is further impaired in subjects aged 80 years or older. *Hypertens Res*. 2020;43(9):914–21. <https://doi.org/10.1038/s41440-020-0435-z>.
- Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, Hori S, Yamamoto Y, Doba N, Hinohara S. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement—a survey of 12517 subjects. *Atherosclerosis*. 2003;166(2):303–9. [https://doi.org/10.1016/s0021-9150\(02\)00332-5](https://doi.org/10.1016/s0021-9150(02)00332-5). Erratum In: *Atherosclerosis*. 2003; 30(1):3.
- Tomiyama H, Kohro T, Higashi Y, Takase B, Suzuki T, Ishizu T, Ueda S, Yamazaki T, Furumoto T, Kario K, Inoue T, Koba S, Watanabe K, Takemoto Y, Hano T, Sata M, Ishibashi Y, Node K, Maemura K, Ohya Y, Furukawa T, Ito H, Ikeda H, Yamashina A. Reliability of measurement of endothelial function across multiple institutions and establishment of reference values in Japanese. *Atherosclerosis*. 2015;242(2):433–42. <https://doi.org/10.1016/j.atherosclerosis.2015.08.001>.
- Orkaby AR, Lunetta KL, Sun FJ, Driver JA, Benjamin EJ, Hamburg NM, Mitchell GF, Vasan RS, Murabito JM. Cross-sectional association of frailty and arterial stiffness in community-dwelling older adults: the Framingham Heart Study. *J Gerontol Ser A*. 2019;74(3):373–9. <https://doi.org/10.1093/gerona/gly134>. PMID:29917058; PMID:PMC6599281.
- Alonso-Bouzon C, Carcaillon L, García-García FJ, Amor-Andrés MS, El Assar M, Rodríguez-Mañas L. Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging. *Age (Dordr)*. 2014;36(1):495–505. <https://doi.org/10.1007/s11357-013-9576-1>. PMID:23959520; PMID:PMC3889911.
- Mansur HN, Lovisi JC, Colugnati FA, Raposo NR, Fernandes NM, Bastos MG. Association of frailty with endothelial dysfunction and its possible impact on negative outcomes in Brazilian predialysis patients with chronic kidney disease. *BMC Nephrol*. 2015;16:157. <https://doi.org/10.1186/s12882-015-0150-1>. PMID:26395776; PMID:PMC4579818.
- ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111–7. <https://doi.org/10.1164/ajrccm.166.1.at1102>.
- Pritchard JM, Kennedy CC, Karampatos S, Ioannidis G, Misiaszek B, Marr S, Patterson C, Woo T, Papaioannou A. Measuring frailty in clinical practice: a comparison of physical frailty assessment methods in a geriatric out-patient clinic. *BMC Geriatr*. 2017;17(1):264. <https://doi.org/10.1186/s12877-017-0623-0>. PMID:29132301; PMID:PMC5683585.
- Park W, Miyachi M, Tanaka H. Does aerobic exercise mitigate the effects of cigarette smoking on arterial stiffness? *J Clin Hypertens (Greenwich)*. 2014;16(9):640–4. <https://doi.org/10.1111/jch.12385>.
- Maruhashi T, Soga J, Fujimura N, Idei N, Mikami S, Iwamoto Y, Kajikawa M, Matsumoto T, Hidaka T, Kihara Y, Chayama K, Noma K, Nakashima A, Goto C, Tomiyama H, Takase B, Yamashina A, Higashi Y. Relationship between flow-mediated vasodilation and cardiovascular risk factors in a large community-based study. *Heart*. 2013;99(24):1837–42. <https://doi.org/10.1136/heartjnl-2013-304739>.
- Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752–62. [https://doi.org/10.1016/S0140-6736\(12\)62167-9](https://doi.org/10.1016/S0140-6736(12)62167-9).
- Ramsay SE, Arianayagam DS, Whincup PH, Lennon LT, Cryer J, Papacosta AO, Iliffe S, Wannamethee SG. Cardiovascular risk profile and frailty in a population-based study of older British men. *Heart*. 2015;101(8):616–22. <https://doi.org/10.1136/heartjnl-2014-306472>.
- Fontana L, Addante F, Copetti M, Paroni G, Fontana A, San Carlo D, Pellegri F, Ferrucci L, Pilotto A. Identification of a metabolic signature for multidimensional impairment and mortality risk in hospitalized older patients. *Aging Cell*. 2013;12(3):459–66. <https://doi.org/10.1111/acer.12068>.
- Xue Q, Qin MZ, Jia J, Liu JP, Wang Y. Association between frailty and the cardio-ankle vascular index. *Clin Interv Aging*. 2019;14:735–42. <https://doi.org/10.2147/CIA.S195109>. PMID:31114178.

29. Campana EMG, Inuzuka S. Vascular aging and arterial stiffness in older adults. *Int J Cardiovasc Sci.* 2020;33(4):357–9. <https://doi.org/10.36660/ijcs.20200132>.
30. Laurent S, Boutouyrie P. Arterial stiffness and hypertension in the elderly. *Front Cardiovasc Med.* 2020;7: 544302. <https://doi.org/10.3389/fcvm.2020.544302>.
31. Santillo E, Migale M, Balestrini F. Frailty and flow-mediated dilation: a pilot study in hospitalized elderly. *J Curr Res Sci Med.* 2016;2:92–7. <https://doi.org/10.4103/2455-3069.198368>.
32. Higashi Y, Kihara Y, Noma K. Endothelial dysfunction and hypertension in aging. *Hypertens Res.* 2012;35(11):1039–47. <https://doi.org/10.1038/hr.2012.138>.
33. Benjamin EJ, Larson MG, Keyes MJ, Mitchell GF, Vasani RS, Keaney JF Jr, Lehman BT, Fan S, O'Leary DH, Vita JA. Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study. *Circulation.* 2004;109(5):613–9. <https://doi.org/10.1161/01.CIR.0000112565.60887.1E>.
34. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med.* 2007;167(7):635–41. <https://doi.org/10.1001/archinte.167.7.635>.

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