Plasma vascular adhesion protein-1 levels correlate positively with frailty severity in older adults

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Abstract
Geriatric frailty is associated with increased mortality and links to increased inflammatory activity. Vascular adhesion protein-1 (VAP-1) is important in inflammatory processes. This study investigates the relationship between plasma VAP-1 level and frailty in older adults. The cross-sectional study recruited community dwelling older adults from a hospital-based comprehensive geriatric assessment program. The demographic data, Fried Frailty Index, metabolic and inflammatory parameters were assessed.

A total of 151 participants (76 women, 50.3%) were included in the analysis, and the age (mean ± standard deviation) was 77.1 ± 6.1 years. The mean plasma VAP-1 level (ng/ml) was significantly different (P = .029) among different frailty groups (346.3 ± 86.5 in the robust older adults, 371.6 ± 107.9 in the pre-frail older adults, and 416.6 ± 141.1 in the frail older adults). Multivariate ordered logistic regression analysis also demonstrated that plasma VAP-1 levels were positively associated with frailty severity (P = .039). Analysis of the frailty components with plasma VAP-1 levels showed that the elderly who had “exhaustion” (P = .016) or “weakness” (P = .025) tended to have higher plasma VAP-1 levels.

The data support that VAP-1 might represent a potential plasma biomarker of frailty.

Abbreviations: CRP = C-reactive protein, TNF-α = tumor necrosis factor-α, VAP-1 = vascular adhesion protein-1.

Keywords: frailty, inflammation, vascular adhesion protein 1

1. Introduction

Frailty in older adults is associated with increased disability and mortality.[1,2] The concept of frailty, as proposed by Fried, is an accumulation of factors such as inadequate physical function, poor nutrition, and chronic illness.[3] The mechanism of frailty has been linked to immunosenescence and inflammation. The typical characteristics of an aging immune system includes the presence of low-grade inflammation as evidence by increased levels of dysregulated cytokines, such as tumor necrosis factor-α (TNF-α), C-reactive protein (CRP),[4–7] accompanied by impaired chemotaxis of neutrophil migration and systemic tissue damage. On the other hand, age-related adipose tissue dysfunction resulting in increased senescence-associated secretory phenotype and increased infiltrations of immune cells with oxidative stress also lead to metabolic disorders. As a result, chronic inflammation in frailty promotes an atherogenic profile and is related to degenerative disorders such as cardiovascular, renal, neuromuscular, and respiratory diseases.[8–11] Therefore, frailty during aging is a critical condition in the older adults.

Vascular adhesion protein-1 (VAP-1) is an amine oxidase which catalyzes the breakdown of primary amines to produce hydrogen peroxide, ammonia, and glycation end-products.[12,13] VAP-1 is also involved in leukocyte related inflammatory processes, and is mainly found in serum, smooth muscle, and endothelium. Moreover, VAP-1 in inflamed tissues is associated with leukocyte adhesion and migration through vascular endothelium to the tissues.[14,15] VAP-1-related production of reactive oxygen species and pro-inflammatory cytokines may lead to the development of atherosclerosis and arterial stiffness, hepatic fibrosis, amyloid beta-mediated vascular damage,
diabetic retinopathy, and hemorrhagic stroke.\(^{16,17}\) Furthermore, a previous study revealed that higher serum level of VAP-1 can predict higher cardiovascular and all cause mortality in diabetes patients.\(^{18}\)

Previous studies suggest that VAP-1 level increases with age, but its implications for frailty have not been well explored in older adults.\(^{17-21}\) Drawing on what existing understanding in the relationship between the inflammatory pathways with either frailty or serum VAP-1 level, we aim to investigate the link between geriatric frailty and plasma VAP-1 levels. We hypothesized that plasma VAP-1 levels increase with frailty in older adults.

### 2. Methods

#### 2.1. Subjects

From January 2007 to June 2008, older adults who had chronic diseases and visited their family physicians for follow-ups in a hospital-based program were recruited for a comprehensive geriatric assessment.\(^{22}\) Subjects were included for having geriatric indications, such as functional decline, with multiple comorbidities, and so on, as described in our previous study.\(^{23}\) Subjects who were bedridden, residing in nursing homes, with less than 6 months of life expectancy, or with severe hearing or communication impairment were excluded.

#### 2.2. Data collection

Experienced research nurses collected the data with a structured form including demographics, smoking habits, and medical histories, as well as recorded blood pressure and body mass index.\(^{22}\) The Frailty Index was assessed by a modified version of Fried’s criteria\(^{[3]}:\) “weight loss” was defined as self-reported, unintentional weight loss of more than 3 kgs or greater than 5% of the body weight in the previous year. Statements for assessing “Exhaustion” and “Low physical activity” were modified based on the Depression Scale of the Center for Epidemiological Studies and the Taiwan International Physical Activity Questionnaire—Short Form,\(^{26,27}\) respectively. The criteria for “Slow walking speed” and “Weakness” were not modified.\(^{[3]}\) Subjects were classified as “robust” for no positive component, “pre-frail” for 1 or 2 positive components, and “frail” for ≥3 positive components.\(^{[3]}\)

#### 2.3. VAP-1 measurement and biochemical assays

Blood samples were obtained from the antecubital vein of the subjects after an 8-hour fast for the measurement of the VAP-1 levels, complete blood count, and biochemical analyses. To measure the plasma levels of VAP-1, blood samples were immediately centrifuged and then frozen at -70°C until the analyses. Plasma VAP-1 levels were determined by commercial enzyme-linked immunosorbent assay kits (eBioscience, San Diego, CA). Plasma TNF-α levels were measured by commercial enzyme-linked immunosorbent assay kits (Assaypro LLC, Saint Charles, Missouri). Plasma CRP levels were measured by latex agglutination tests (Denka Seiken, Gosen, Niigata, Japan).

#### 2.4. Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the National Taiwan University Hospital (registration number: 200701017R), and written informed consent was obtained from all participants before their inclusion in the study. The items of the consent form explained the study aim, inclusion and exclusion criteria, procedures, harm and benefit, medical care, privacy and right, and withdrawal. All procedures were in accordance with the Helsinki Declaration. Potential participants who declined to participate or otherwise did not participate remained in the care of their family physicians and were not disadvantaged in any way.

### 2.5. Statistical analyses

To minimize possible statistic distortions by outliers, the subjects with VAP-1 levels of >95% or <5% were excluded from further analysis. The data for demographics, physical examinations, and laboratory tests of the study population were presented as mean ± standard deviation (continuous variables) or percentage (categorical variables). The analysis of variance or Kruskal Wallis tests were performed to test the mean differences between older adults with different frailty levels, and Chi-square tests or Fisher exact test were performed to test the differences in percentages. In addition, univariate and multivariable ordinal logistic regression were used to evaluate the association between frailty, VAP-1, and important covariates. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and a P value <.05 was considered statistically significant.

### 3. Results

#### 3.1. Study populations

A final of 151 older adults were included in the analyses after excluding 17 who had plasma VAP-1 levels within the highest and lowest 5% of the study population. The average age was 77.1 ± 6.1 years, and 76 (50.3%) were women. Their medication usage was summarized in Table 1, and the leading comorbidities were hypertension (84.8%), hyperlipidemia (62.3%), diabetes mellitus (43.1%), and coronary artery disease (31.8%). Assessed by frailty scoring, 41 (27.2%) older adults were robust, 79 (52.3%) were pre-frail, and 31 (20.5%) were frail. The waist circumference was 90.0 ± 10.2 cm; the body mass index was 25.1 ± 3.4 kg/m². The plasma VAP-1, TNF-α, and CRP levels were 374.0 ± 112.3 ng/mL, 43.5 ± 29.4 pg/mL, and 36.8 ± 43.4 nmol/L, respectively (Table 1). Other laboratory data are presented in Table 1.

Participants in the frail subgroup were significantly older than those in the robust and pre-frail subgroups (Table 2). The results of comorbidity and medication survey showed higher percentage of people in the frail group had stroke (41.9%), whereas, in the robust group, a higher percentage of people had hyperlipidemia (75.6%) and had statins implemented (51.2%). With regard to hemogram, hemoglobin level was significantly lower in the frail group (P = .002).

#### 3.2. Associations of VAP-1 and frailty

The plasma VAP-1 (ng/mL) levels in the robust, pre-frail, and frail subgroups were 346.3 ± 86.5, 371.6 ± 107.9, and 416.6 ± 141.1, respectively. The plasma VAP-1 levels were significantly different among the 3 subgroups (P = .029) (Table 2). Moreover, further analyses demonstrated the plasma VAP-1 levels rose progressively with frailty severity (P for trend = .0092) (Fig. 1).

The univariable and multivariable ordinal logistic regression analyses were used to explore the factors that may be correlated
with frailty severity (Table 3). Univariable analysis demonstrated that the severity of frailty was positively associated with age \((P=.002)\), stroke \((P=.005)\), hemoglobin \((P=.001)\), and plasma VAP-1 levels \((P=.009)\). The results also showed that frailty severity was negatively associated with ALT \((P=.045)\).

In multivariable regression analysis, stroke \((P=.011)\), and plasma VAP-1 levels \((P=.039)\) were independent factors influencing the severity of frailty.

We further analyzed the associations among frailty components and the plasma VAP-1 level by linear regression as demonstrated in Table 4. The results showed that older adults who had “exhaustion” \((P=.016)\) and “weakness” \((P=.025)\) tended to have higher plasma VAP-1 levels. In multivariable regression analysis, weakness \((P=.033)\) was the only independent frailty component influencing the plasma VAP-1 level.

### 4. Discussion

This study shows that the plasma level of VAP-1 is associated with geriatric frailty, and positively correlated with increase in the severity of frailty in the older adults. Furthermore, stroke, and plasma VAP-1 level were independent factors affecting frailty severity. Our findings brought new insights on the mechanism of frailty, and suggest that the VAP-1 could be a potential plasma biomarker of geriatric frailty and aging.

Frailty is believed to be the result of accumulated declines in multiple physiological systems, and efforts have been made to identify the underlying mechanism of frailty in the complex aging processes.\[^{[1,9]}\] Previous studies have shown that the aging process with the comorbidity of stroke cause declines of physiological function and are independent factors affecting frailty severity.\[^{[26]}\] Moreover, the link between inflammation, frailty, and aging is supported by previous research on lifelong cellular and molecular damage, sarcopenia, and genetic influencing factors during aging. The aging immune system may function inadequately during stress events, which may lead to disproportionate vulnerability in physical functions after stress events.\[^{[5]}\] Furthermore, acute medical illness such as stroke in older adults may present as syndromes including falls, immobility, pain, delirium and general weakness. These syndromes or atypical presentations of stroke could explain the finding that stroke is obviously associated with frailty.\[^{[126]}\] Although the differences of coronary artery disease among robust, pre-frail, and frail groups were not statistically different in the present study, the trend of incidences of coronary artery disease is different from that of stroke. The reason might be the lack of consensus on definition of frailty for patients at higher risk of poor outcomes and the brief indices of current operational definitions of frailty may not apply to numerous diseases.

Therefore, previous studies had suggested to develop a specific frailty index for patients with coronary artery disease.\[^{[27,28]}\]

We found in our study that the plasma VAP-1 level was elevated in older adults who were frail, even though TNF-\(\alpha\) and CRP levels were not. VAP-1 participates in the inflammation pathways by its enzymatic activity of producing reactive oxygen species such as hydrogen peroxide through catalyzing primary amines, and by its adhesive activity to influence leukocyte rolling and transmigration through endothelial cell monolayers.\[^{[20,29]}\]

VAP-1 also plays important roles in leukocyte migration, adipocyte function, and the regulation of glucose uptake. The activities of VAP-1 are known to change in various disorders such as DM, congestive heart failure, liver cirrhosis, and Alzheimer’s disease. For example, VAP-1 was found to promote leukocyte...

### Table 1

**Demographic data, physical examinations, and laboratory tests of the study participants \((N=151)\).**

| Variable                        | n (%) or Mean ± SD       |
|---------------------------------|--------------------------|
| Age (mean ± SD, yr)             | 77.1 ± 6.1               |
| Sex (female)                    | 76 (50.3%)               |
| Smoking status                  |                          |
| Never                           | 96 (63.6)                |
| Quitted                         | 48 (31.8)                |
| Smoking                         | 7 (4.6)                  |
| Comorbidity                     |                          |
| Hypertension                    | 128 (84.8)               |
| Hypertension diabetes mellitus  | 94 (62.3)                |
| Coronary artery disease         | 65 (43.1)                |
| Stroke                          | 48 (31.8)                |
| Frailty Score (Level)           |                          |
| 0 (Robust)                      | 41 (27.2)                |
| 1 (Pre-frail)                   | 47 (31.1)                |
| 2 (Pre-frail)                   | 32 (21.2)                |
| 3 (Frail)                       | 22 (14.6)                |
| 4 (Frail)                       | 9 (6.0)                  |
| 5 (Frail)                       | 0 (0.0)                  |
| Medication                      |                          |
| Aspirin                         | 64 (42.4)                |
| \(\beta\)-blockers              | 37 (24.5)                |
| Calcium channel blockers        | 71 (47.0)                |
| ACEIs or ARBs                   | 86 (57.0)                |
| Metformin                       | 39 (25.8)                |
| Sulfonylureas                   | 47 (31.1)                |
| Thiazolidinediones              | 11 (7.3)                 |
| Acarbose                        | 4 (2.7)                  |
| Repagipride                     | 4 (2.7)                  |
| Statins                         | 50 (33.1)                |
| Physical examination            |                          |
| Body mass index (kg/m²)         | 25.1 ± 3.4               |
| Waist circumference (cm)        | 90.0 ± 10.2              |
| ASMI (kg/m²)                    | 6.8 ± 1.1                |
| Fat mass percentage (%)         | 33.9 ± 8.2               |
| Laboratory tests                |                          |
| RBC (M/μL)                      | 4.4 ± 0.6                |
| Hb (g/dL)                       | 13.0 ± 1.6               |
| Platelet (K/μL)                 | 219.6 ± 68.1             |
| WBC (K/μL)                      | 6.5 ± 1.5                |
| Albumin (g/dL)                  | 4.6 ± 0.4                |
| Glucose AC (mmol/L)             | 6.5 ± 1.9                |
| Total-Cholesterol (mmol/L)      | 4.9 ± 0.9                |
| Triglyceride (mmol/L)           | 1.7 ± 1.0                |
| AST (μkat/L)                    | 0.4 ± 0.2                |
| ALT (μkat/L)                    | 0.4 ± 0.3                |
| BUN (mmol/L)                    | 7.4 ± 3.2                |
| Creatinine (μmol/L)             | 110.4 ± 48.6             |
| MDRD-simplify-GFR (mL/min/1.73 m²) | 57.5 ± 15.7   |
| Uric acid (μmol/L)              | 388.6 ± 96.0             |
| TNF-\(\alpha\) (pg/mL)         | 43.5 ± 29.4              |
| CRP (mg/L)                      | 36.8 ± 43.4              |
| VAP-1 (ng/mL)                   | 374.0 ± 112.3            |

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**References**

\[^{[1]}\] \[^{[9]}\] \[^{[26]}\] \[^{[5]}\] \[^{[27,28]}\] \[^{[20,29]}\]
recruitment to the liver through generating reactive oxygen species, and it also modulate the expression of profibrotic genes which link VAP-1 with hepatic fibrosis and inflammation.\textsuperscript{30-31} Serum VAP-1 is shown to be a novel marker for hyperglycemia-induced atherosclerosis, and retinal capillary endothelial cells are known to release VAP-1 which correlated with the levels of collagenases in the vitreous fluid of patients with proliferative diabetic retinopathy.\textsuperscript{32} Furthermore, Alzheimer’s disease patients with DM were found to have high VAP-1 with increased oxidative damage markers and glial activation in hippocampus which may contribute to vascular degeneration and severe disease progression.\textsuperscript{33} These evidences might explain that frailty appear to be associated with higher VAP-1.

On the other hand, frailty include the decline of many physiological systems, and 1 essential dimension of research is to find the key threshold of these cumulative changes.\textsuperscript{5} Since VAP-1 has been shown to be associated with the development of multiple diseases and is regarded as a useful prognostic biomarker for cardiovascular diseases, diabetes mellitus, arterial stiffness, hepatic fibrosis, amyloid beta-mediated vascular

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### Table 2

Comparisons among older adults with different frailty levels.

| Variable                      | Robust (n = 41) | Pre-Frail (n = 79) | Frail (n = 31) | P-value |
|-------------------------------|----------------|-------------------|---------------|---------|
| Age (mean ± SD, yr)\textsuperscript{a} | 74.8 ± 6.7\textsuperscript{a} | 77.5 ± 5.8         | 79.1 ± 5.0\textsuperscript{a} | .0135   |
| Sex (female)                 | 21 (51.2)      | 37 (46.8)         | 18 (58.1)     | .565    |
| Smoking status\textsuperscript{b} | 27 (65.0)      | 47 (59.9)         | 22 (71.0)     | .324    |
| Never                        |               |                   |               |         |
| Quitted                      | 11 (26.8)      | 30 (38.0)         | 7 (22.6)      |         |
| Smoking                      | 3 (7.3)        | 2 (2.5)           | 2 (6.5)       |         |
| Body mass index (mean ± SD, kg/m\textsuperscript{2}) | 24.9 ± 5.3     | 25.5 ± 5.6        | 24.5 ± 3.3    | .389    |
| Waist circumference (mean ± SD, cm) | 86.6 ± 9.4    | 90.9 ± 10.5       | 90.8 ± 10.1   | .222    |
| ASMI (kg/m\textsuperscript{2}) | 6.8 ± 1.0      | 6.9 ± 1.1         | 6.9 ± 0.9     | .000    |
| Fat mass percentage (%)      | 32.5 ± 8.5     | 34.1 ± 8.0        | 35.2 ± 8.4    | .362    |
| Comorbidity                  |               |                   |               |         |
| Hypertension                 | 37 (90.2)      | 66 (83.5)         | 25 (80.7)     | .484    |
| Hyperlipidemia               | 31 (75.6)      | 50 (63.3)         | 13 (41.9)     | .014\textsuperscript{c} |
| Diabetes mellitus            | 8 (19.5)       | 39 (49.4)         | 18 (11.9)     | .001\textsuperscript{c,d} |
| Coronary artery disease      | 12 (29.3)      | 30 (38.0)         | 6 (19.4)      | .155    |
| Stroke                       | 5 (12.2)       | 20 (25.3)         | 13 (41.9)     | .016\textsuperscript{c} |
| Medication                   |               |                   |               |         |
| Aspirin                      | 13 (31.7)      | 33 (41.8)         | 18 (58.1)     | .080    |
| β-blockers                   | 12 (29.3)      | 17 (21.5)         | 8 (25.8)      | .634    |
| CCBs                         | 19 (46.3)      | 40 (50.6)         | 12 (38.7)     | .527    |
| ACEIs or ARBs                | 23 (66.1)      | 43 (54.4)         | 20 (64.5)     | .625    |
| Metformin                    | 6 (14.6)       | 32 (26.6)         | 12 (38.7)     | .068    |
| Sulfonamides                 | 8 (19.5)       | 27 (34.2)         | 12 (38.7)     | .153    |
| Thiazolidinediones\textsuperscript{b} | 0 (0.00)      | 6 (7.6)           | 5 (16.1)      | .021    |
| Acardose\textsuperscript{b}  | 12 (29.3)      | 2 (2.5)           | 2 (6.5)       | .176    |
| Repaglinide\textsuperscript{b} | 0 (0.00)     | 3 (3.8)           | 1 (3.2)       | .535    |
| Statins                      | 21 (51.2)      | 25 (31.7)         | 4 (12.9)      | .003\textsuperscript{d} |
| Laboratory tests (mean ± SD) |               |                   |               |         |
| RBC (M\textsuperscript{3}/\mu L) | 4.5 ± 0.5      | 4.4 ± 0.6         | 4.2 ± 0.6     | .069    |
| Hb (g/dL)                    | 13.5 ± 1.2     | 13.1 ± 1.6        | 12.2 ± 1.7    | .002\textsuperscript{c,d} |
| Platelet (K/\mu L)\textsuperscript{c} | 212.5 ± 63.3   | 225.3 ± 71.3      | 214.9 ± 67.2  | .739    |
| WBC (K/\mu L)\textsuperscript{c} | 6.5 ± 1.2     | 6.4 ± 1.4         | 6.6 ± 1.9     | .668    |
| Albumin (g/dL)\textsuperscript{c} | 4.6 ± 0.2      | 4.6 ± 0.4         | 4.5 ± 0.3     | .003    |
| Glucose AC (mmol/L)\textsuperscript{a} | 6.1 ± 1.6     | 6.6 ± 2.1         | 6.7 ± 2.0     | .282    |
| Total-Cholesterol (mmol/L)\textsuperscript{a} | 5.0 ± 0.7     | 4.7 ± 0.9         | 5.0 ± 0.9     | .106    |
| Triglyceride (mmol/L)\textsuperscript{a} | 1.7 ± 0.7      | 1.6 ± 0.8         | 2.0 ± 1.7     | .544    |
| AST (\mukat/L)\textsuperscript{a} | 0.5 ± 0.2      | 0.4 ± 0.1         | 0.4 ± 0.4     | .045    |
| ALT (\mukat/L)\textsuperscript{a} | 0.5 ± 0.3      | 0.3 ± 0.1         | 0.4 ± 0.3     | .063    |
| BUN (mmol/L)\textsuperscript{a} | 6.4 ± 1.5      | 7.7 ± 3.9         | 8.0 ± 2.8     | .070    |
| Creatinine (\mumol/L)\textsuperscript{a} | 98.7 ± 25.4   | 115.3 ± 53.8      | 112.9 ± 55.2  | .250    |
| MDRD-simplify-GFR (mean ± SD, mL/min/1.73 m\textsuperscript{2}) | 62.1 ± 12.6    | 56.4 ± 17.1       | 54.6 ± 14.9   | .10     |
| Uric acid (\mumol/L)\textsuperscript{a} | 369.8 ± 70.6   | 402.7 ± 111.1     | 382.2 ± 86.7  | .348    |
| TNF-α (pg/mL)\textsuperscript{a} | 44.0 ± 26.4    | 43.1 ± 28.5       | 44.1 ± 35.7   | .981    |
| CRP (mg/L)\textsuperscript{a} | 38.1 ± 61.0    | 35.7 ± 32.6       | 37.6 ± 42.0   | .954    |
| VAP-1 (ng/mL)\textsuperscript{a} | 346.3 ± 86.5   | 371.6 ± 107.9     | 416.8 ± 141.1 | .029\textsuperscript{f} |

\textsuperscript{a}ACEIs = angiotensin-converting enzyme inhibitors, ALT = alanine aminotransferase, ARBs = angiotensin II receptor blockers, ASMI = appendicular skeletal muscle index, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CCBs = calcium channel blockers, CRP = C-reactive protein, Hb = hemoglobin, RBC = red blood cell, SD = standard deviation, TNF-α = tumor-necrosis factor alpha, VAP-1 = Vascular adhesion protein-1, WBC = white blood cell.
\textsuperscript{b}Kruskal Wallis test.
\textsuperscript{c}Fisher exact test.
\textsuperscript{d}Significant difference between the robust and frail groups after Bonferroni correction.
\textsuperscript{e}Significant difference between the pre-frail and frail groups after Bonferroni correction.
damage, and diabetic retinopathy, the systemic involvement of VAP-1 in the inflammation pathways has also made it a possible treatment target in the studies of several disorders. Our data supports that VAP-1 may be a more sensitive inflammatory marker than TNF-α and CRP in detecting geriatric frailty. The close link between frailty and VAP-1 suggests that VAP-1 may be a valuable diagnostic and prognostic biomarker which deserves future investigation for a better understanding of the inflammatory pathways that may lead to frailty.

There are 2 major limitations in the present study. First, the small sample size limits the power for further examination of the relationship between plasma VAP-1 levels with different components of frailty. However, since frailty is mixture of multiple domains of functional declines in older adults, the aim of the study to find the important role of VAP-1 in frailty is robustly identified. Second, the causal relationship of VAP-1 levels and frailty cannot be established in this cross-sectional study. Although our results demonstrated a link between plasma VAP-1 levels with frailty, further large-scale follow-up studies are needed to delineate the detailed mechanisms.

Plasma VAP-1 levels were demonstrated to be independently and positively correlated with the severity of frailty in older adults.

Table 3
Univariable and multivariable ordinal logistic regression analyses for frailty in overall participants (N = 151).

| Variable                      | Univariate | Multivariate |
|-------------------------------|------------|--------------|
|                              | OR         | 95% CI P-value | AOR 95% CI P-value |
| Age (yr)                      | 1.085      | 1.030–1.143 .002 | 1.056 0.996–1.121 .070 |
| Gender (male)                 | 1.150      | 0.626–2.112 .652 | 1.090 0.096–1.214 .292 |
| Smoking status                | 0.902      | 0.533–1.524 .699 | 1.090 0.618–1.099 .187 |
| Body mass index (mean±SD, kg/m²) | 0.990    | 0.906–1.082 .825 | 0.980 0.618–1.099 .825 |
| Waist circumference (cm)      | 1.022      | 0.992–1.054 .154 | 1.090 0.618–1.099 .187 |
| ASMI (kg/m²)                  | 0.824      | 0.618–1.099 .699 | 1.090 0.618–1.099 .187 |
| Fat mass percentage (%)       | 1.028      | 0.990–1.068 .148 | 1.028 0.990–1.068 .148 |
| Stroke                        | 2.867      | 1.367–5.927 .005 | 2.906 1.283–6.581 .011 |
| MDRD-simplify-GFR (mL/min/1.73 m²) | 0.980    | 0.900–1.001 .036 | 0.980 0.900–1.001 .036 |
| Glucose AC (mmol/L)           | 0.864      | 0.669–1.391 .846 | 0.864 0.669–1.391 .846 |
| Triglyceride (mmol/L)         | 1.234      | 0.901–1.692 .191 | 1.234 0.901–1.692 .191 |
| Hb (g/dL)                     | 0.700      | 0.565–0.868 .001 | 0.700 0.565–0.868 .001 |
| AST (μkat/L)                  | 0.670      | 0.146–3.075 .607 | 0.670 0.146–3.075 .607 |
| ALT (μkat/L)                  | 0.238      | 0.059–0.966 .045 | 0.238 0.059–0.966 .045 |
| VAP-1 (ng/mL)                 | 1.004      | 1.001–1.007 .009 | 1.004 1.001–1.007 .009 |

Fragility subgroups: robust, pre-frail, and frail.
Smoking status: never, former, and current.
ALT = alanine aminotransferase, AOR = Adjusted odds ratio, ASMI = appendicular skeletal muscle index, AST = aspartate aminotransferase, CI = Confidence interval, Hb = hemoglobin, OR = Odds ratio, SD = standard deviation, VAP-1 = Vascular adhesion protein-1.

MDRD (Modification of diet in renal disease):
MDRD-simplify-GFR (mL/min/1.73 m²) = 186 × [CRE]⁻¹.۱۵۴ × (age)⁻۰.۲۰۵ (if male).
MDRD-simplify-GFR (mL/min/1.73 m²) = 186 × [CRE]⁻¹.۱۵۴ × (age)⁻۰.۲۰۵ × 0.۷۴۲ (if female).

Table 4
Association between frailty components and vascular adhesion protein-1.

| Variable                      | Univariate | Multivariate |
|-------------------------------|------------|--------------|
|                              | Estimate   | SE P-value   | Estimate SE P-value |
| Weight loss (Yes vs No)       | 27.1194    | 32.6228 .4071 | 15.4136 21.7184 .4793 |
| Exhaustion (Yes vs No)        | 47.0448    | 19.3162 .0161 | 15.4136 21.7184 .4793 |
| Low physical activity (Yes vs No) | -30.1081 | 43.5524 .4904 | 15.4136 21.7184 .4793 |
| Slow walking speed (Yes vs No) | 34.5293    | 19.1859 .0739 | 15.4136 21.7184 .4793 |
| Weakness (Yes vs No)          | 42.0583    | 18.6043 .0252 | 46.1483 21.3520 .0327 |

Multivariable model was adjusted by exhaustion, weakness, age, stroke, Hb, and ALT.
SE = Standard Error.
adults, even after adjusting for age and other comorbidities. VAP-1 may be a plasma biomarker of geriatric frailty and play a role during the development of frailty. The underlying mechanisms warrant further investigation.

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Author contributions

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