Vascular Calcification as an Underrecognized Risk Factor for Frailty in 1783 Community-Dwelling Elderly Individuals

Szu-Ying Lee, MD; Chia-Ter Chao, MD, PhD; Jenq-Wen Huang, MD, PhD; Kuo-Chin Huang, MD, PhD

BACKGROUND: Vascular calcification (VC) is associated with high morbidity and mortality among older adults, a population that exhibits a higher tendency for developing frailty at the same time. Whether VC serves as a risk factor for the development of frailty in this population remains unclear.

METHODS AND RESULTS: We analyzed a prospectively assembled cohort of community-dwelling older adults between 2014 and 2017 (n=1783). Frailty and prefrailty were determined on the basis of the Study of Osteoporotic Fractures criteria, and VC was measured using semiquantitative aortic arch calcification (AAC) and abdominal aortic calcification scoring. We conducted multiple logistic regression with prefrailty or frailty as the dependent variable, incorporating sociodemographic profiles, comorbidities, medications, laboratory data, AAC status/severity, and other geriatric phenotypes. Among all participants, 327 (18.3%) exhibited either prefrailty (15.3%) or frailty (3.1%), and 648 (36.3%) exhibited AAC. After adjusting for multiple confounders, we found that AAC incidence was associated with a substantially higher probability of prefrailty or frailty (odds ratio [OR], 11.9; 95% CI, 7.9–15.4), with a dose-responsive relationship (OR for older adults with AAC categories 1, 2, and 3 was 9.3, 13.6, and 52.5, respectively). Similar association was observed for older adults with abdominal aortic calcification (OR, 5.0; 95% CI, 1.3–19.5), and might be replicable in another cohort of patients with end-stage renal disease.

CONCLUSIONS: Severity of VC exhibited a linear positive relationship with frailty in older adults. Our findings suggest that a prompt diagnosis and potential management of VC may assist in risk mitigation for patients with frailty.

Key Words: aortic calcification ■ chronic kidney disease ■ chronic kidney disease-mineral bone disorder ■ end-stage renal disease ■ frailty ■ prefrailty ■ vascular calcification

Vascular calcification (VC) denotes the ectopic deposition of calcium-containing minerals within the vascular wall. The pathogenesis of VC has been shown to involve the active secretion of osteoid-like matrices from transdifferentiated resident vascular smooth muscle cells, triggered by metabolically noxious stimuli, inflammatory cytokines, milieu of oxidative stress, and excessive inorganic phosphate. This VC-inducing effect is further compounded by the downregulation of calcification inhibitors, such as fetuin-A and matrix Gla protein, klotho, and osteoprotegerin. The presence of VC, whether in the form of coronary artery, thoracic, or abdominal aortic calcification (AbAC), has been reported to be a predictor of an increased overall and cardiovascular mortality in general and at-risk populations, including individuals of advanced age or with chronic kidney disease. Therefore, potential VC inhibitors are eagerly awaited in the hope of reversing vascular dysfunction and lowering the risk of cardiovascular events in affected individuals. However, a complete understanding of the pathological consequences caused by VC remains to be explored.

Frailty, as a geriatric phenotype, describes the adverse health influence introduced by the accumulation...
Frailty and Vascular Calcification

of subclinical deficits and the vulnerability to external or endogenous stressors, leading to negative patient outcomes. Frailty is measurable using the concept of frailty index (rated by multidimensional checklists across the biological, psychological, and sociological spectrum) or frail phenotype (rated by physical performances). Older adults are particularly susceptible to developing this syndrome; the presence of frailty has been repeatedly shown to elevate the risk of subsequent fall episodes, hospitalization, functional impairment, and mortality among the affected people. The putative pathogenesis of frailty can be complex; several age-associated phenomena have been responsible for the development of frailty in older adults, including impaired brain neuronal plasticity, endocrinological aberrations, chronic inflammation, and a diverse spectrum of tissue-specific epigenetic changes. Dysfunctional central nervous system and musculoskeletal degeneration are traditionally regarded as pivotal pathological events during the course of frailty; however, the contribution of a disturbed cardiovascular system has gradually been uncovered. Studies addressing the relationship between cardiovascular disorders and frailty mostly focus on cardiac diseases and atherosclerosis, but very few researchers have examined the role of VC in the pathogenesis of frailty, and its milder form, prefrailty. It is still unclear if VC serves as a risk factor for frailty in older adults. We hypothesized that VC might be a significant factor associated with prefrailty as well as frailty in the geriatric population. We investigated this association using a prospectively assembled cohort of community-dwelling older adults.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request subject to the approval of the local institution and the administrative authority.

Ethical Approval

The protocol of this study was approved by the institutional review board of National Taiwan University Hospital (No. 201802088RINC and 201403006RINB), and it adhered to the guidelines of the Declaration of Helsinki. Informed consent was deemed unnecessary by the board because this was a retrospective analysis of prospectively collected data.

Participant Enrollment and Procedures

The procedures for identifying participants have been described in detail previously. In brief, community-dwelling older adults (defined as those aged ≥65 years) participating in their annual health examination program between 2014 and 2017 were identified and included in this study. Patients without available chest posteroanterior film were excluded. After inclusion, we collected basic information from these patients, including sociodemographic parameters (age, sex, history of smoking or alcohol consumption, and whether they regularly exercised or not), comorbidities (hypertension, diabetes mellitus [DM], hyperlipidemia, hyperuricemia or gout, and cardiac diseases), and use of chronic medications. Patients subsequently underwent physical examination along with assessment of anthropometric parameters, including body height/body weight, waist circumference, blood pressure, and pulse rate. Body mass index was calculated using the formula body weight in kilograms divided by the square of body height in meters. The included participants also underwent blood tests for assessing hemogram; serum biochemistry, involving nutrition [albumin], inflammation [globulin], and lipid profile [cholesterol and triglyceride]; fasting glucose; uric acid; and renal function. Their estimated glomerular filtration rate was calculated on the basis of Modification of Diet in Renal Disease formula. We also collected their spot urine CLINICAL PERSPECTIVE

What Is New?

• Among a group of older adults with 36.3% having aortic arch calcification, we showed that the presence of aortic arch calcification or abdominal aortic calcification independently correlated with an increased risk of prefraility or frailty, with a dose-responsive relationship.

• The relationship between aortic arch calcification and frailty could be replicable in another group of patients with end-stage renal disease.

What Are the Clinical Implications?

• Vascular calcification might serve not only as an indicator of frailty risk in patients at risk of developing frailty but also as a potential therapeutic target for those with vascular calcification-related frailty.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| AAC          | aortic arch calcification |
| AbAC         | abdominal aortic calcification |
| DM           | diabetes mellitus |
| ESRD         | end-stage renal disease |
| OR           | odds ratio |
| SOF          | Study of Osteoporotic Fracture |
| VC           | vascular calcification |

CLINICAL PERSPECTIVE

What Is New?

• Among a group of older adults with 36.3% having aortic arch calcification, we showed that the presence of aortic arch calcification or abdominal aortic calcification independently correlated with an increased risk of prefraility or frailty, with a dose-responsive relationship.

• The relationship between aortic arch calcification and frailty could be replicable in another group of patients with end-stage renal disease.

What Are the Clinical Implications?

• Vascular calcification might serve not only as an indicator of frailty risk in patients at risk of developing frailty but also as a potential therapeutic target for those with vascular calcification-related frailty.
under fasting status and sent it for semiquantitative dipstick analysis of proteinuria (0–4).

Patients were instructed to respond to questionnaires involving the assessment of several geriatric phenotypes, including anxiety, depression,11 insomnia,12 sensory dysfunction in the form of visual impairment, and cognitive impairment. For the assessment of anxiety, participants were asked whether they had excessive and persistent anxiety-related symptoms, such as nervousness, restlessness, impending danger, etc., that disturbed their life. They were classified as having depression if diagnosed by a psychiatrist or if they were exhibiting a depressive mood, presenting with anhedonia, which interfered with their daily activities. Insomnia was recognized if the patients complained of difficulty in falling asleep, early awakening, daytime sleepiness, etc., that influenced their concentration or memory. Visual impairment was confirmed based on self-reported symptoms. This information was supplemented by input from their caregivers to verify their responses. For cognitive impairment, we used the AD8 questionnaire for screening; AD8 is a highly sensitive 8-item short screening questionnaire for informants, aiming to uncover those with an impaired daily function secondary to cognitive changes on a chronic basis.13 Any participant with an AD8 score of 2 or higher was categorized as positive for cognitive impairment according to the original construct.14

Assessment of Aortic Arch Calcification
We assessed the severity of aortic arch calcification (AAC) on a posteroanterior chest film to gauge the extent of VC as described previously.15,16 Patients were categorized as being without AAC, or with category 1, 2, and 3 AAC if they did not have any calcification, had speckles/fragments of calcifications, had sheet-like calcifications involving less than half of the arch, and had nearly circumferential arch calcifications, respectively. A graphical illustration of this AAC categorization system can be found in our previous work.17,18 The interpretation of AAC was made by 2 researchers (C.T.C., S.Y.L.), and the agreement rate was higher than 90%. Differences in interpretation findings were resolved by another researcher (J.-W.H.). Previous literature has shown that AAC severity is associated with the risk of cardiovascular events among various populations, including those with end-stage renal disease (ESRD),19 advanced age or stroke,20 and the extent of AAC correlates closely with that of coronary artery calcification21 and AbAC.15

Strategies for Measuring Frailty
In this study, we assessed frailty using the SOF (Study of Osteoporotic Fractures) scheme.22 The SOF scheme screens for frailty based on 3 criteria: unintentional weight loss-related malnutrition, compromised mobility including difficulty rising from a chair repetitively by oneself, and the presence of subjective fatigue/exhaustive sensation. We further operationalized 2 of the 3 parameters using available variables, as described previously.9 Malnutrition was substituted by the presence of hypoalbuminemia (<3.5 g/dL) or underweight (body mass index <18.5 kg/m²). Indeed, hypoalbuminemia, underweight, and weight loss have been shown to correlate closely with each other,23,24 and all these factors exhibit significant associations with adverse health outcomes in older adults, serving as meaningful surrogates of malnutrition. Compromised mobility was identified if patients had poor lower extremity strength, represented by repetitive episodes of falling during the preceding months.25 Subjective fatigue sensation was obtained from direct inquiry of one’s energy status (low energy or not). According to the original scheme, patients with 1 criterion and at least 2 positive criteria were classified as prefrailty and frailty, respectively.

Statistical Analysis
Continuous variables were expressed as mean with SDs, and categorical variables were expressed as numbers with percentages. The normalcy of continuous variables was tested using the Kolmogorov–Smirnov test. We compared normally distributed and nonnormally distributed continuous variables using the Student t test and Mann–Whitney U test, respectively, and categorical variables were compared using the chi-square test. For comparison between more than 2 groups, we used 1-way ANOVA. Because we aimed to examine the relationship between VC and the probability of prefrailty or frailty, we first evaluated the differences between patients with and without AAC and between those with different severities of AAC. We then conducted univariate analysis by comparing clinical characteristics, physical parameters, and laboratory data among those with prefrailty/frailty as the dependent variable, incorporating variables with \( P < 0.05 \) in univariate analyses. We tested 3 regression models a priori. In model 1, we included only sociodemographic variables and physical parameters, whereas models 2 and 3 included laboratory data and laboratory data/geriatric phenotypes, respectively. Areas under the receiver operating characteristic curves were used to estimate the performance of the regression models. We further examined whether age modified the relationship between frailty and the presence of AAC by dividing patients into different age
subgroups. All statistical analyses were performed using SPSS version 19, and a *P*<0.05 was deemed statistically significant.

Sensitivity analyses were also undertaken to confirm the validity of our findings. We collected lateral lumbar spine X-ray of all participants whenever available on enrollment and examined whether they exhibited AbAC. The severity of AbAC was rated based on the well-established 24-point Kaupilla score. Clinical variables were compared between those with and without AbAC and with prefrailty or frailty, followed by multiple logistic regression analyses with prefrailty/frailty as the dependent variable.

### Validation Study

A validation study was conducted in an independent cohort. We examined the association between frailty and AAC using a previous ESRD cohort, a population at substantial risk of concurrently developing VC and frailty. Associations between the severity of frailty, assessed using the Fatigue, Resistance, Ambulation, Illness, and Loss of Weight (FRAIL) scale (0–5, higher scores denoting greater severity), and AAC categories in these patients with ESRD were examined.

### RESULTS

A total of 2932 older adults were initially selected during the study period, and 1149 individuals were excluded because of their absence of chest X-ray examination findings, and thus, 1783 individuals were included in this study. There were no differences in demographic features between the excluded and the enrolled participants. Among the 1783 community-dwelling older adults, 648 (36.3%) had AAC, among whom 55.4%, 37.3%, and 7.3% had category 1, 2, and 3 AAC, respectively (Table 1). The participants with AAC had significantly higher age (*P*<0.001), prevalence of comorbidities (hypertension, DM, and cardiac diseases), and probability to receive comorbidity-directed medications as well as sedatives/hypnotics. Participants with AAC were less likely to exercise (*P*<0.001), had significantly lower body weight, body mass index, serum albumin (*P*<0.001), and hemoglobin but higher globulin (*P*=0.036), urea nitrogen (*P*<0.001), creatinine (*P*<0.003), and urine protein levels (*P*<0.001). These discrepancies in clinical characteristics, physical parameters, and laboratory data between participants with and without AAC intensified when we compared those with a lower and a higher AAC category (Table 1). Participants with AAC were more likely to exhibit multiple geriatric phenotypes, including depression, anxiety, sleep disturbance, and visual and cognitive impairment (Table 1).

Participants with AAC exhibited a significantly higher prevalence of frailty (with versus without, 8.4% versus 1%; *P*<0.001), prefrailty (31.8% versus 5.8%, *P*<0.001), and a higher number of positive SOF items (0.49 versus 0.06 items, *P*<0.001). Similarly, a progressive increase in the prevalence of frailty (category 1 versus 2 versus 3 AAC, 4.7% versus 10.7% versus 23.4%; *P*<0.001) and prefrailty (28.7% versus 32.6% versus 51.1%, *P*<0.001), and the number of positive SOF items (0.38 versus 0.55 versus 1.02, *P*<0.001) was observed with increasing AAC severity (Figure 1).

### Comparison Between Older Adults With and Without Prefrailty/Frailty and With Different Frailty Severities

Among all participants, 327 (18.3%) had either prefrailty (15.3%) or frailty (3.1%) (Table 2). Univariate analyses showed that participants with prefrailty or frailty had significantly higher age (*P*<0.001); were more likely to have DM (*P*<0.001) and receive antidiabetic medications (*P*=0.002); and lower body weight, body mass index, and systolic and diastolic blood pressure. Those with prefrailty or frailty also had significantly lower serum albumin (*P*<0.001), hemoglobin (*P*<0.001), cholesterol (*P*=0.005), and triglycerides (*P*=0.049) and higher urea nitrogen (*P*<0.001), creatinine (*P*=0.002), and urine protein (*P*<0.002) levels (Table 2). The differences between participants with and without prefrailty or frailty became more significant with increasing severity of frailty. It is also clear that older adults with prefrailty or frailty were more likely to exhibit other geriatric phenotypes, including depression, anxiety, sleep disturbance, and visual and cognitive impairment (all *P*<0.001) (Table 2).

Older adults with prefrailty or frailty exhibited a significantly higher prevalence of AAC (with versus without, 79.5% versus 26.6%; *P*<0.001). Furthermore, a progressive increase in the prevalence of AAC (frailty versus prefrailty, 98.2% versus 75.7%; *P*<0.001) was observed with rising frailty severity.

### Investigation of Association Between AAC and Frailty

We conducted multiple logistic regression analyses with prefrailty or frailty as the dependent variable, adjusting for 3 different sets of confounders in models 1, 2, and 3. Model 1 revealed that the presence of AAC was significantly associated with a higher probability of prefrailty or frailty among older adults (odds ratio [OR], 11.4; 95% CI, 8.4–15.5) (Table 3). This probability increased with increase in AAC severity (OR, 8.4, 14.0, and 47.5, for categories 1, 2, and 3 AAC, respectively) (Table 3). In model 2, additionally including laboratory
Table 1. Comparison of Clinical Features Between Older Adults With and Without Different Severities of Aortic Arch Calcification

| Category | No AAC (n=1135) | With AAC (n=648) | P Value* | Category 1 (n=359) | Category 2 (n=242) | Category 3 (n=47) | P Value† |
|----------|----------------|-----------------|----------|-------------------|-------------------|-----------------|----------|
| Demographic profile | | | | | | | | |
| Age, y | 71.9±6.1 | 76.7±7.1 | <0.001 | 74.8±6.7 | 78.1±6.4 | 82.2±7.8 | <0.001 |
| Sex (male) | 513 (45.2) | 275 (42.4) | 0.278 | 155 (43.2) | 98 (40.5) | 22 (46.8) | 0.555 |
| Lifestyle factors | | | | | | | | |
| Smoking (%) | 62 (5.5) | 24 (3.7) | 0.098 | 18 (4.5) | 7 (4.5) | 1 (2.1) | 0.281 |
| Drinking (%) | 292 (25.7) | 127 (19.6) | 0.004 | 79 (22.0) | 43 (17.8) | 5 (10.6) | 0.006 |
| Regular exercise (%) | 1030 (90.8) | 545 (84.1) | <0.001 | 314 (87.5) | 201 (83.1) | 30 (63.8) | <0.001 |
| Comorbidities | | | | | | | | |
| Hypertension (%) | 498 (43.9) | 361 (55.7) | <0.001 | 181 (50.4) | 147 (60.7) | 33 (70.2) | <0.001 |
| Diabetes mellitus (%) | 129 (11.4) | 109 (16.8) | 0.002 | 48 (13.4) | 49 (20.3) | 12 (25.5) | <0.001 |
| Hyperlipidemia (%) | 185 (16.3) | 120 (18.5) | 0.223 | 58 (16.2) | 54 (22.3) | 8 (17.0) | 0.146 |
| Prior cardiac diseases (%) | 214 (18.9) | 168 (25.9) | <0.001 | 92 (25.6) | 64 (26.5) | 12 (25.5) | 0.006 |
| Chronic medications | | | | | | | | |
| Antihypertensives (%) | 453 (39.9) | 339 (52.3) | <0.001 | 167 (46.5) | 140 (57.9) | 32 (68.1) | <0.001 |
| Antidiabetics (%) | 118 (10.4) | 96 (14.8) | 0.009 | 40 (11.1) | 45 (18.6) | 11 (23.4) | <0.001 |
| Antilipemics (%) | 129 (11.4) | 92 (14.2) | 0.078 | 40 (11.1) | 46 (19.0) | 6 (12.8) | 0.010 |
| Urate-lowering medicine (%) | 33 (2.9) | 27 (4.2) | 0.154 | 14 (3.9) | 11 (4.6) | 1 (2.1) | 0.333 |
| Anthropic parameters | | | | | | | | |
| Body height, cm | 158.5±8.2 | 156.9±8.4 | <0.001 | 157.5±8.2 | 156.3±8.7 | 155.5±8.7 | <0.001 |
| Body weight, kg | 60.5±10.2 | 58.1±10.7 | <0.001 | 58.3±10.2 | 58.3±11.1 | 55.2±11.7 | <0.001 |
| Body mass index, kg/m² | 24.0±3.3 | 23.5±3.7 | 0.003 | 23.4±3.5 | 23.8±3.7 | 22.7±4.2 | 0.004 |
| Waist circumference, cm | 83.2±8.9 | 83.2±9.9 | 0.975 | 82.5±9.8 | 84.3±9.8 | 82.9±11.1 | 0.127 |
| Systolic BP, mm Hg | 126.6±16.2 | 128.5±17.3 | 0.020 | 127.3±16.9 | 129.8±17.6 | 130.7±18.0 | 0.023 |
| Diastolic BP, mm Hg | 69.1±10.9 | 66.9±11.5 | <0.001 | 67.5±11.2 | 66.2±11.6 | 65.8±13.6 | <0.001 |
| Pulse rate, /min | 70.3±10.6 | 70.3±10.9 | 0.954 | 69.8±10.9 | 70.3±10.8 | 74.1±11.4 | 0.091 |
| Laboratory data | | | | | | | | |
| Albumin, g/dL | 4.3±0.2 | 4.2±0.3 | <0.001 | 4.3±0.3 | 4.2±0.3 | 4.1±0.4 | <0.001 |
| Globulin, g/dL | 2.76±0.36 | 2.80±0.42 | 0.036 | 2.8±0.4 | 2.8±0.4 | 2.8±0.6 | 0.179 |
| Hemoglobin, mg/dL | 13.6±1.3 | 13.2±1.5 | <0.001 | 13.3±1.3 | 13.1±1.4 | 12.4±2.3 | <0.001 |
| Platelet, K/μL | 210.4±52.3 | 207.5±61.1 | 0.279 | 207.1±65.7 | 209.8±55.3 | 199.3±52.7 | 0.469 |
| Leukocyte, K/μL | 5.5±1.5 | 5.7±1.6 | 0.090 | 5.6±1.6 | 5.7±1.5 | 6.2±2.3 | 0.016 |
| Urea nitrogen, mg/dL | 16.6±5.2 | 18.1±7.6 | <0.001 | 17.0±5.1 | 18.4±7.7 | 25.2±15.7 | <0.001 |
| Creatinine, mg/dL | 0.86±0.44 | 0.93±0.6 | 0.003 | 0.87±0.29 | 0.94±0.66 | 1.42±0.32 | <0.001 |
| Estimated glomerular filtration rate, mL/min per 1.73 m² | 87.0±21.2 | 82.0±23.5 | <0.001 | 85.2±22.9 | 81.0±22.4 | 63.5±25.6 | <0.001 |
| Total cholesterol, mg/dL | 183.9±31.6 | 181.6±34.4 | 0.155 | 182.7±34.2 | 182.2±33.5 | 169.8±38.6 | 0.034 |
| Triglyceride, mg/dL | 118.2±58.0 | 117.5±66.8 | 0.817 | 115.1±63.2 | 119.1±66.8 | 126.1±89.5 | 0.640 |
| Glucose, mg/dL | 99.7±18.4 | 100.3±19.1 | 0.466 | 98.3±15.5 | 102.6±22.3 | 103.5±24.8 | 0.024 |
| Uric acid, mg/dL | 5.8±1.3 | 5.8±1.5 | 0.191 | 5.8±1.4 | 5.9±1.7 | 6.1±1.5 | 0.365 |
| Dipstick urine protein titer (0≈4+) | 0.10±0.33 | 0.20±0.51 | <0.001 | 0.14±0.41 | 0.24±0.57 | 0.40±0.78 | <0.001 |
| Geriatric phenotypes | | | | | | | | |
| Depression (%) | 56 (4.9) | 73 (11.3) | <0.001 | 36 (10.0) | 32 (13.2) | 5 (10.6) | <0.001 |
| Anxiety (%) | 74 (6.5) | 87 (13.4) | <0.001 | 38 (10.6) | 37 (15.3) | 12 (25.5) | <0.001 |
| Insomnia/sleep disturbance (%) | 173 (15.2) | 128 (19.8) | 0.019 | 61 (17.0) | 58 (24.0) | 9 (19.2) | 0.012 |

(Continues)
Frailty and Vascular Calcification

In addition, we examined whether AAC interacted with other known risk factors of prefrailty/frailty. Age was found to be an important modifier of the influence of AAC on prefrailty/frailty (Figure 3); we revealed that advanced age (≥80 years) significantly accentuated the risk for prefrailty/frailty even among those with different severities of AAC. The frailty risk significantly increased with rising AAC severity (age <80 versus ≥80 years, for category 1, OR, 7.5 versus 8.2; for category 2, OR, 9.3 versus 19.7; for category 3, OR, 35.2 versus 54.9) (Figure 3).

Sensitivity Analysis
Among the 1783 participants, lateral lumbar spine films were available for only 116 (6.5%) participants, and 48.3% patients had AbAC. Older adults with AbAC exhibited significantly higher age (*P*<0.001); higher prevalence of DM (*P*=0.004), frailty (*P*=0.035), and prefrailty (*P*=0.015); higher urea nitrogen (*P*=0.008) and creatinine (*P*=0.001) levels; and more positive SOF items (*P*=0.001) than those without. Participants with prefrailty or frailty also exhibited significantly higher prevalence of AbAC (*P*=0.001) and higher Kauppila score (*P*=0.006) than those without. Multiple logistic regression analysis with prefrailty or frailty as the dependent variable showed that AbAC was associated with a significantly higher probability of prefrailty/frailty (OR, 5.0; 95% CI, 5.0–19.5) (Table 4), supporting the validity of our original findings.

Validation of the Study Findings
We examined whether AAC was associated with frailty in an independent cohort of patients with ESRD (n=42), among whom 19.0%, 54.8%, 21.4%, and 4.8% did not have AAC or had category 1, 2, and 3 AAC, respectively. We discovered that the FRAIL scores increased successively with higher AAC severity (for no AAC or category 1, 2, and 3 AAC, mean FRAIL scores: 1.63, 0.78, 1.89, and 2.00, respectively; *P*=0.032 using 1-way ANOVA). The prevalence of prefrailty (FRAIL scores 1–2) or frailty (scores >2) also correlated with AAC severity (for no AAC or category 1, 2, and 3 AAC, prevalence: 75%, 43%, 89%, and 100%, respectively; *P*=0.046 using 1-way ANOVA).

Table 1. (Continued)

| Category | No AAC (n=1135) | With AAC (n=648) | Category 1 (n=359) | Category 2 (n=242) | Category 3 (n=47) | P Value† |
|----------|----------------|-----------------|-------------------|-------------------|-----------------|---------|
| Visual impairment (%) | 101 (8.9) | 99 (15.3) | <0.001 | 42 (11.7) | 46 (19.0) | 11 (23.4) | <0.001 |
| Cognitive impairment (%) | 83 (7.3) | 123 (19.0) | <0.001 | 45 (12.5) | 57 (23.6) | 21 (44.7) | <0.001 |

AAC indicates aortic arch calcification; and BP, blood pressure.
*Compared using the Student *t* test or chi-square test as appropriate.
†Compared between no VC, category 1, 2, and 3 VC groups using the 1-way ANOVA.
‡Based on the Modification of Diet in Renal Disease formula.

Figure 1. Distribution of different frailty statuses of participants without and with increasing AAC severity.
AAC indicates aortic arch calcification; and Cat, category.
| Demographic profile | No F/PF  
(n=1456) | With F/PF  
(n=327) | \( P \) Value* | PF (n=272) | F (n=55) | \( P \) Value† |
|---------------------|-----------|-------------|--------------|-----------|---------|-------------|
| Age, y              | 73.1±6.5  | 75.9±7.9    | <0.001       | 75.2±7.6  | 79.5±8.5 | <0.001      |
| Sex (male)          | 656 (45.1)| 132 (40.4)  | 0.123        | 112 (41.2)| 20 (36.4)| 0.246       |
| Lifestyle factors   |           |             |              |           |         |             |
| Smoking (%)         | 76 (5.2)  | 10 (3.1)    | 0.099        | 9 (3.3)   | 1 (1.8)  | 0.230       |
| Drinking (%)        | 360 (24.7)| 59 (18.0)   | 0.01         | 52 (19.1)| 7 (12.7) | 0.022       |
| Regular exercise (%)| 1322 (90.8)| 253 (77.4) | <0.001       | 221 (81.3)| 32 (58.2)| <0.001      |
| Comorbidities       |           |             |              |           |         |             |
| Hypertension (%)    | 707 (48.6)| 152 (46.5)  | 0.498        | 125 (46.0)| 27 (49.1)| 0.726       |
| Diabetes mellitus (%)| 175 (12.0)| 63 (19.3)   | <0.001       | 56 (20.6)| 7 (12.7) | 0.001       |
| Hyperlipidemia (%)  | 249 (17.1)| 56 (17.1)   | 0.992        | 46 (16.9)| 10 (18.2)| 0.974       |
| Prior cardiac diseases (%)| 301 (20.7)| 81 (24.8)   | 0.103        | 63 (23.2)| 18 (32.7)| 0.076       |
| Gout (%)            | 75 (5.2)  | 18 (5.5)    | 0.795        | 15 (5.5)  | 3 (5.5)  | 0.076       |
| Chronic medications |           |             |              |           |         |             |
| Antihypertensives (%)| 657 (45.1)| 135 (41.3)  | 0.207        | 110 (40.4)| 25 (45.5)| 0.357       |
| Antidiabetics (%)   | 158 (10.9)| 56 (17.1)   | 0.002        | 51 (18.8)| 5 (9.1)  | 0.001       |
| Antilipemics (%)    | 178 (12.2)| 43 (13.2)   | 0.647        | 37 (13.6)| 6 (10.9) | 0.773       |
| Urate-lowering medicine (%)| 47 (3.2)  | 13 (4.0)    | 0.498        | 10 (3.7) | 3 (5.5)  | 0.637       |
| Anxiolytics/sedatives/hypnotics (%)| 272 (18.7)| 101 (30.9) | <0.001       | 78 (28.7)| 23 (41.8)| <0.001      |
| Anthropometric parameters |           |             |              |           |         |             |
| Body height, cm     | 158.1±8.2 | 157.1±8.8   | 0.066        | 157.7±8.5| 154.4±9.8| 0.005       |
| Body weight, kg      | 60.4±9.8  | 56.0±12.1   | <0.001       | 56.7±11.6| 52.4±14.0| <0.001      |
| Body mass index, kg/m²| 24.1±3.1 | 22.6±4.2    | <0.001       | 22.7±4.0 | 21.8±4.9 | <0.001      |
| Waist circumference, cm| 83.6±8.7 | 81.3±11.2   | <0.001       | 81.4±10.7| 80.7±13.2| <0.001      |
| Systolic BP, mm Hg   | 128.2±16.5| 123.1±16.6  | <0.001       | 123.1±16.3| 123.3±18.0| <0.001      |
| Diastolic BP, mm Hg  | 69.0±11.1 | 65.2±11.0   | <0.001       | 65.3±11.0| 64.9±11.0| <0.001      |
| Pulse rate, /min     | 70.1±10.7 | 71.0±10.9   | 0.190        | 70.5±10.5| 73.2±12.4| 0.108       |
| Laboratory data      |           |             |              |           |         |             |
| Albumin, g/dL        | 4.3±0.2   | 4.2±0.3     | <0.001       | 4.2±0.3  | 4.0±0.4  | <0.001      |
| Globulin, g/dL       | 2.8±0.4   | 2.8±0.5     | 0.161        | 2.8±0.4  | 2.9±0.6  | 0.045       |
| Hemoglobin, mg/dL    | 13.5±1.3  | 12.9±1.5    | <0.001       | 13.0±1.5| 12.2±1.4 | <0.001      |
| Platelet, K/μL       | 209.6±52.4| 208.4±68.4  | 0.726        | 208.5±70.4| 208.0±58.1| 0.939       |
| Leukocyte, K/μL      | 5.6±1.5   | 5.5±1.6     | 0.554        | 5.8±1.6 | 5.5±1.7  | 0.815       |
| Urea nitrogen, mg/dL | 16.9±5.3  | 18.3±9.2    | <0.001       | 17.7±8.3| 21.2±12.7| <0.001      |
| Creatinine, mg/dL    | 0.87±0.4  | 0.97±0.8    | 0.002        | 0.92±0.55| 1.18±1.43| <0.001      |
| Estimated glomerular filtration rate, mL/min per 1.73 m²| 85.9±21.6| 82.3±24.4 | 0.008        | 82.9±22.9| 79.3±31.2| 0.016       |
| Total cholesterol, mg/dL| 184.1±32.0| 178.5±35.1 | 0.005        | 178.7±33.9| 177.0±40.8| 0.018       |
| Triglyceride, mg/dL  | 119.3±60.4| 111.9±64.8  | 0.049        | 113.3±66.3| 105.1±56.6| 0.097       |
| Glucose, mg/dL       | 100.0±17.9| 99.5±21.7   | 0.688        | 99.7±21.4| 98.5±23.3| 0.843       |
| Uric acid, mg/dL     | 5.8±1.4   | 5.7±1.6     | 0.548        | 5.8±1.5 | 5.6±1.8  | 0.618       |
| Dipstick urine protein titer (0~4+) | 0.12±0.38| 0.20±0.51 | 0.002        | 0.17±0.47| 0.33±0.67| <0.001      |
| Geriatric syndromes  |           |             |              |           |         |             |
| Depression (%)       | 62 (4.3)  | 67 (20.5)   | <0.001       | 48 (17.7)| 19 (34.6)| <0.001      |
| Anxiety (%)          | 84 (5.8)  | 77 (23.6)   | <0.001       | 59 (21.7)| 18 (32.7)| <0.001      |
| Insomnia/sleep disturbance (%)| 205 (14.1)| 96 (29.4)   | <0.001       | 75 (27.6)| 21 (38.2)| <0.001      |

(Continues)
DISCUSSION

In the current study, we harnessed a large prospectively assembled cohort of older adults to examine the association between VC and frailty. Through extensive adjustment for clinical variables, laboratory profiles, and various geriatric phenotypes, we showed that VC, whether in the form of AAC or AbAC, exhibited a significantly positive correlation with the presence of prefrailty or frailty among these older adults. Similar relationship was also evident in populations with ESRD. We believe that VC may be an underrated risk factor of frailty in multiple at-risk populations, and interventions directed toward VC are expected to ameliorate or attenuate frailty in the future.

The prevalence of prefrailty and frailty in our patients is relatively lower than that reported previously. A systematic review and meta-analysis estimated the prevalence of frailty was around 12% to 17%.

### Table 2. (Continued)

| Outcomes                  | No F/PF (n=1456) | With F/PF (n=327) | P Value* | PF (n=272) | F (n=55) | P Value† |
|---------------------------|------------------|-------------------|----------|------------|----------|----------|
| Visual impairment (%)     | 118 (8.1)        | 82 (26.1)         | <0.001   | 66 (23.9)  | 17 (30.9) | <0.001   |
| Cognitive impairment (%)  | 95 (6.5)         | 111 (33.9)        | <0.001   | 84 (30.9)  | 27 (49.1) | <0.001   |

BP indicates blood pressure; F, frailty; and PF, prefrailty.
*Compared using the Student t test or chi-square test as appropriate.
†Compared between no VC, category 1, 2, and 3 VC groups using the 1-way ANOVA.
‡Based on the Modification of Diet in Renal Disease formula.

### Table 3. Multiple Logistic Regression With Having Different Severities of Frailty as the Dependent Variable

| Outcomes                  | Model 1* | Model 2† | Model 3‡ |
|---------------------------|----------|----------|----------|
|                           | OR 95% CI | P Value  | OR 95% CI | P Value  | OR 95% CI | P Value  |
| Prefrailty or frailty vs no frailty as the dependent variable |          |          |          |
| AAC status§              |          |          |          |
| Absent                   | 1        | ...      | 1        | ...      | 1        | ...      |
| Present                  | 11.4     | 8.4–15.5 | <0.001   | 10.9     | 8.0–14.8 | <0.001   |
| AAC category **          |          |          |          |
| Absent                   | 1        | ...      | 1        | ...      | 1        | ...      |
| Category 1               | 8.4      | 5.9–11.8 | <0.001   | 8.2      | 5.8–11.6 | <0.001   |
| Category 2               | 14.0     | 9.6–20.5 | <0.001   | 13.5     | 9.2–19.6 | <0.001   |
| Category 3               | 47.5     | 22.6–99.6| <0.001   | 45.1     | 21.2–96  | <0.001   |
| Frailty vs prefrailty or no frailty as the dependent variable |          |          |          |
| AAC status§              |          |          |          |
| Absent                   | 1        | ...      | 1        | ...      | 1        | ...      |
| Present                  | 67.7     | 9.2–496.9| <0.001   | 65.1     | 8.8–479.9| <0.001   |
| AAC category **          |          |          |          |
| Absent                   | 1        | ...      | 1        | ...      | 1        | ...      |
| Category 1               | 44.0     | 5.8–334.6| <0.001   | 42.7     | 5.6–325.8| <0.001   |
| Category 2               | 96.2     | 12.7–729.8| <0.001 | 100.3     | 13.1–766 | <0.001   |
| Category 3               | 158.1    | 18.7–1333.6| <0.001 | 164.7     | 18.7–1447.8| <0.001 |

AAC indicates aortic arch calcification; and OR, odds ratio.
*Including sociodemographic profile (age, sex, drinking and exercise history), comorbidity (diabetes mellitus), medications (antidiabetics and hypnotics), anthropometric parameters (waist circumference and systolic/diastolic blood pressure).
†Including model 1 variables and laboratory data (hemoglobin, total cholesterol, triglycerides, estimated glomerular filtration rate, and proteinuric titer).
‡Including model 2 variables and other geriatric phenotypes (anxiety, depression, insomnia, vision impairment, and cognitive impairment).
§Not including AAC category.
**Not including AAC status.
depending upon the measurement strategy and the study quality. However, another study suggested that the prevalence of frailty varies depending on the country, ranging from 3.9% in China to more than 50% in Cuba, whereas the prevalence of prefrailty ranged between 13% and 71%. Therefore, our findings of frailty (3.1%) and prefrailty (15.3%) prevalence are compatible with those reported by others but fall toward the lower end of the data range. This could be attributed to our frailty screening approach (physical phenotype instead of frailty index), the East Asian population origin, and the high proportion of participants with a habit of regular exercise (80–90%) (Table 1). Nonetheless, we believe that our results are applicable to other geriatric populations of different ethnicities, because the risk of prefrailty/frailty posed by VC is prominent and persists despite the adjustment for multiple interfering factors. The prevalence of AAC in our study was also similar to that reported previously among older adults of similar ethnicity.

A prior review suggested that SOF might not accurately identify frailty in hospitalized patients because of their inability to complete physical tasks. Similar risk is present when we apply other frailty instruments...
containing physical measurement, such as Fried’s frailty phenotype, to patients with acute illnesses. However, in this study, we enrolled older adults from the community setting without obvious acute illnesses. Consequently, we believe that the accuracy of SOF to identify frailty in our participants remains fair, in light of others’ findings.\textsuperscript{34,35}

Very few studies have addressed the association between VC and frailty, and the available studies focused on the relationship of frailty with either atherosclerosis or vascular aging. Using the keywords “frailty” or “prefrailty” and “vascular calcification” or “aortic calcification” in PubMed and MEDLINE, we found only 2 original investigations directly comparing the prevalence of VC between frail and nonfrail elderly individuals.\textsuperscript{36,37} Idoate et al focused on the influence of frailty on VC at different anatomical sites in nonagenarians. They discovered that, among 42 patients, coronary artery calcium scores based on computed tomography did not differ between those with and without frailty.\textsuperscript{36} They also reported that the mean thoracic, abdominal aortic, iliac, and femoral artery calcium levels were higher in frail older adults than those in nonfrail ones, but the differences in calcium levels were significant only for femoral artery calcification.\textsuperscript{37} Their findings suggested that VC tends to be more severe among those with frailty than those without. Our findings greatly extended the existing knowledge by showing the risk of frailty conferred by VC in older adults based on a larger contemporary cohort. Another study examined the relationship between coronary artery calcium scores and frailty among men infected with HIV; however, they reported neutral results.\textsuperscript{38}

The potential contribution of VC to the pathogenesis of frailty can be conceivable from multiple perspectives. VC, in the form of AAC, inevitably leads to hypertension due to vascular stiffening and impaired aortic compliance; hypertension has been shown to be an important risk factor for frailty in older adults.\textsuperscript{39} In addition, the presence of AAC is frequently accompanied by calcification of other vascular beds, including intracranial arteries\textsuperscript{40} and arteries supplying limbs.\textsuperscript{41} Intracranial artery calcification of greater severity has

![Figure 4](image_url)

**Figure 4.** A putative diagram illustrating the potential mechanistic link between vascular calcification and frailty in older adults.
been shown to correlate with an increased posterior and anterior circulation blood flow velocity and resistance, potentially compromising cortical perfusion and contributing to cognitive impairment as well as the risk of ischemic stroke and dementia. Lower extremity arterial calcification, including iliac and femoropopliteal calcification, is frequently accompanied by a higher plaque burden and perfusion insufficiency, leading to ischemic ulcers, adverse limb events, and cardiovascular mortality. Cognitive impairment, cerebrovascular accident, peripheral vascular disease, and limb claudication have all been reported to be independent risk factors for frailty among older adults. Furthermore, VC has been shown to be associated with a deranged calcium/phosphate metabolism and decreased bone mineral density with fractures in the geriatric population, and osteoporosis and fractures are established predecessors of frailty in these patients. Finally, visceral adiposity and insulin resistance frequently coexist in patients with VC, and these adverse metabolic phenotypes are also potential contributors to frailty in older adults. A brief summary diagram is shown in Figure 4.

Our study had strengths and limitations. The size of the cohort we used to conduct these analyses was large enough to permit comprehensive adjustment for confounders, and the graded association between AAC and frailty remains valid in another ESRD cohort as well. Importantly, this observation is not affected by age per se, comorbidities such as DM, participants’ renal function, and other geriatric phenotypes, suggesting that VC can be a previously underrated risk factor for frailty in older adults. However, there were limitations to our findings. This was a cross-sectional study, and a causal inference between VC and frailty cannot be confirmed. We did not perform dual-energy X-ray absorptiometry to measure bone mineral density or body adiposity; therefore, these variables were unavailable for the mechanistic analysis, despite that VC has been experimentally and clinically shown to correlate with osteoporosis. For the determination of VC, we used standardized posteroanterior chest images instead of computed tomography, because the latter examination incurred excessive radiation exposure and was inconvenient for routine application. Nonetheless, the AAC grading structure has been widely explored in previous literature and also by us previously, supporting the reliability of our findings.

**CONCLUSIONS**

In conclusion, we found that AAC exhibited a dose-dependent relationship with frailty, and similar findings were observed using AbAC for subanalysis and replicable in another cohort of patients with ESRD. Our findings are expected to shed light on the influence of VC on the risk of frailty in the following aspects: first, because VC is truly an underappreciated risk factor for frailty in older adults and those with ESRD, it may be worthwhile to screen patients with VC using frailty-screening instruments such as SOF index, FRAIL scale, or Fried’s frail phenotype, although the threshold of VC severity above which frailty screening should commence remains to be determined. Second, we can consider reducing patient exposure to known predisposing factors of VC, such as hypercalcemia, hyperphosphatemia, and warfarin use in those with ESRD, poorly controlled DM, hypertension, and smoking, in order to lower their subsequent risk of frailty. Finally, several promising treatments for VC, such as vitamin K and magnesium supplementation, may be harnessed for the potential management of patients with VC-related frailty.

**ARTICLE INFORMATION**

Received April 28, 2020; accepted August 10, 2020.

**Affiliations**

From the Nephrology Division, Department of Internal Medicine, National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan (S.-Y.L., J.-W.H.); Nephrology Division, Department of Internal Medicine (C.-T.C., K.-C.H.) and Geriatric and Community Medicine Research Center (C.-T.C., K.-C.H.), National Taiwan University Hospital BeiiHu Branch, Taipei, Taiwan; and Graduate Institute of Toxicology, National Taiwan University College of Medicine, Taipei, Taiwan (C.-T.C.).

**Acknowledgments**

We are grateful to the Second Core Laboratory, Department of Medical Research of National Taiwan University Hospital and the Genomic Research and Precision Medicine Center of National Taiwan University College of Medicine for their technical input.

Study design: Lee, Chao, J.-W. Huang; Data analysis: Lee, Chao, J.-W. Huang; Article drafting: Chao, J.-W. Huang, K.-C. Huang; All authors approved the final version of the manuscript.

**Sources of Funding**

The study is financially sponsored by National Taiwan University Hospital BeiiHu Branch (10905) and Ministry of Science and Technology, Taiwan (MOST 108-2314-B-002-056- and MOST 109-2314-B-002-193-MY3). The sponsors have no role in the study design, data collection, analysis, and result interpretation of this study.

**Disclosures**

None.

**REFERENCES**

1. Chao C-T, Yeh H-Y, Tsai Y-T, Chuang P-H, Yuan T-H, Huang J-W, Chen H-W. Natural and non-natural antioxidative compounds: potential candidates for treatment of vascular calcification. *Cell Death Discov*. 2019;5:145.
2. Moe SM, Reslerova M, Ketteler M, O’Neill K, Duan D, Koczman J, Westenfeld R, Jahnen-Dechent W, Chen NX. Role of calcification in dates for treatment of vascular calcification. *Kidney Int*. 2005;67:2295–2304.
3. Chen J, Budoff MJ, Reilly MP, Yang W, Rosas SE, Rahman M, Zhang X, Roy JA, Lustigova E, Nessel L, et al. Coronary artery calcification and risk of cardiovascular disease and death among patients with chronic kidney disease. *JAMA Cardiol*. 2017;2:635–643.
4. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuño R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019;394:1376–1386.

5. Hoogendijk EO, Alfaro J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet. 2019;394:1365–1375.

6. Brivio P, Paladini MS, Racagni G, Fliva MA, Calabrese F, Molteni R. From healthy aging to frailty: in search of the underlying mechanisms. Curr Med Chem. 2019;26:3685–3701.

7. Nadruz W Jr, Kitzman D, Windham BG, Kucharska-Newton A, Butler K, Palta P, Griswold ME, Wagenknecht LE, Heiss G, Solomon LD, et al. Cardiovascular dysfunction and frailty among older adults in the community: the ARIC study. J Gerontol A Biol Sci Med Sci. 2017;72:958–964.

8. Chao C-T, Lee Y-H, Li C-M, Han D-S, Huang J-W, Huang K-C. Advanced Age and chronic kidney disease modify the association between metabolic syndrome and frailty among community-dwelling elderly. Rejuvenation Res. 2019. Oct 1 [epub ahead of print]. DOI: 10.1089/rej.2019.2202.

9. Chao CT, Lee YH, Yang KC, Peng J-K, Li C-M, Chen S-I, Han D-S, Huang J-W. Impact of self-report and eGFR-based chronic kidney disease on the risk of chronic kidney disease-related complications and geriatric syndromes in community-dwelling older adults. Kidney Blood Press Res. 2018;43:1908–1918.

10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med. 1999;130:461–470.

11. Kienzschmieder C, Kennedy C J. Depression and anxiety in late life: diagnostic insights and therapeutic options. Mt Sinai J Med. 2011;78:527–545.

12. Vaz Fragoso CA, Gill TM. Sleep complaints in community-living older persons: a multifactorial geriatric syndrome. J Am Geriatr Soc. 2007;55:1853–1866.

13. Hendry K, Green C, McShane R, Noel-Storr AH, Stott DJ, Anwer S, McShane R. Frailty and subclinical aortic valve calcification in chest X-ray. J Atheroscler Thromb. 2009;16:256–264.

14. Bannas P, Jung C, Blanke P, Treszl A, Derlen T, Adam G, Bley TA. Severe aortic arch calcification depicted on chest radiography strongly suggests coronary artery calcification. Eur Radiol. 2013;23:2652–2657.

15. Hashimoto H, Iijima K, Hashimoto M, Son B-K, Ota H, Ogawa S, Eto M, Akishita M, Ouchi Y. Validity and usefulness of aortic arch calcification as a novel marker of cardiovascular disease in a variety of healthcare settings. Cochrane Database Syst Rev. 2019;3:CD011121.

16. Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JP, Storandt M, Morris JC. The AD8: a brief informant interview to detect dementia. Neurology. 2005;65:559–564.

17. Hendry K, Green C, McShane R, Noel-Storr AH, Stott DJ, Anwer S, McShane R. Undernutrition at baseline and subsequent mortality and mortality over a 1-year period in older adults receiving Medicare home health services. J Am Med Dir Assoc. 2011;12:287–294.

18. van Stijn MFM, Korkic-Halilovic I, Bakker MS, van der Ploeg T, van Leeuwen PA, Houdijk AP. Preoperative nutrition status and postoperative outcome in elderly general surgery patients. J Parenter Enteral Nutr. 2013;37:57–63.

19. Chao CT, Lee Y-H, Chang P-Y, He Y-T, Leng R-S, Lai C-F, Chiang C-K, Huang J-W, Huang S-J. Simple self-report FRALL scale might be more closely associated with dialysis complications than other frailty screening instruments in rural chronic dialysis patients. Nephrology. 2015;20:321–328.

20. Chao C-T, Huang J-W, Chiang C-K, Hung KY. Applicability of laboratory deficit-based frailty index in predominantly older patients with end-stage renal disease under chronic dialysis: a pilot test of its correlation with survival and self-reported instruments. Nephrology. 2020;25:73–81.

21. Wu PY, Chao C-T, Chan D-C, Huang J-W, Hung K-Y. Contributors, risk associates, and complications of frailty in patients with chronic kidney disease: a scoping review. Ther Adv Chronic Dis. 2019;10:2040622319880382.

22. O’Caoimh R, Galluzzo L, Rodriguez-Laso A, van der Heyden J, Ranhoff AH, Lamprini-Koula M, Custin M, Lopez-Samaniego L, Caracillon-Bentata L, Kennedy S, et al. Prevalence of frailty at population level in European ADVANCE Joint Action Member States: a systematic review and meta-analysis. Ann Intern Med. 2018;54:226–238.

23. Sirirawandha DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. BMJ Open. 2018;8:e018195.

24. Jiang CQ, Xu L, Lam TH, Thomas GN, Zhang WS, Cheng KK, Schooling CM. Alcohol consumption and aortic arch calcification in an older Chinese sample: the Guangzhou Biobank Cohort Study. Int J Cardiol. 2013;164:349–354.

25. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. Eur J Intern Med. 2016;31:3–10.

26. Boulou C, Salameh P, Barberge-Gateau P. Malnutrition and frailty in community-dwelling older adults living in a rural setting. Clin Nutr. 2016;35:138–143.

27. Cable N, Hyoshi A, Kondo N, Aida J, Sjöqvist H, Kondo K. Identifying frail-related biomarkers among community-dwelling older adults in Japan: a research example from the Japanese Gerontological Evaluation Study. Biomed Res Int. 2018;2018:5382948.

28. Idofe F, Cadore EL, Casas-Herrero A, Zambomb-Ferraresi F, Marcellan T, de Gordoa AR, Rodriguez-Manas L, Bastarriza G, Marques MC, Martinez-Velilla N, et al. Adipose tissue compartments, muscle mass, muscle fat infiltration, and coronary calcium in institutionalized frail nonagenarians. Eur J Radiol. 2015;25:2163–2175.

29. Idofe F, Cadore EL, Casas-Herrero A, Zambomb-Ferraresi F, Martinez-Velilla N, Rodriguez-Manas L, Battaro M, Ramirez-Velez R, Izquierdo M. Noncoronary vascular calcification, bone mineral density, and muscle mass in institutionalized frail nonagenarians. Rejuvenation Res. 2017;20:298–308.

30. Korada SKC, Zhao D, Tibaukau M, Brown TT, Jacobson LP, Guellar E, Bolan RK, Paella FJ, Margolick JB, Martinson JJ, et al. Frailty and subclinical coronary atherosclerosis: the multicenter AIDS Cohort Study (MACS). Atherosclerosis. 2017;266:240–247.

31. Aprahamian I, Sasaki E, dos Santos MF, Izbicki R, Puigrossi RC, Biella MM, Borges AC, Sassaaki MM, Torres LM, Fernandez LS, et al. Hypertension and frailty in older adults. J Clin Hypertens (Greenwich). 2018;20:186–192.

32. Yamada S, Hashimoto K, Ogata H, Watanabe Y, Oshima M, Miyake H. Calcium at orifices of aortic arch branches is a reliable and significant marker of chronic kidney disease: a 25-year follow-up study. Arch Gerontol Geriatr. 1997;32:245–250.

33. Hendriks EJE, Beulen JW, de Jong PA, van der Schouw YT, Sun W-N, Wright CM, Criqui MH, Allison MA, Ix JH.Calcification of the splenic, iliac, and breast arteries and risk of all-cause and cardiovascular mortality. Atherosclerosis. 2017;258:120–127.

34. Wilk J, Wu L, Wang L, Zhong J, Ko J, Shi L, Soo Y, Leung T, Wong KS, Abrego J, Chen X. Impact of intracranial artery calcification on cerebral hemodynamic changes. Neuroradiology. 2018;60:357–363.

35. Kao H-W, Liou M, Chung H-W, Liu H-S, Tsai P-H, Chiang S-W, Chou M-C, Peng G-S, Huang G-S., Hsu H-I, et al. High agatston calcium score of intracranial carotid artery: a significant risk factor for cognitive impairment. Medicine (Baltimore). 2015;94:e1546.
44. Okuno S, Iida O, Shiraki T, Fujita M, Masuda M, Okamoto S, Ishihara T, Nanto K, Kanda T, Takahara M, et al. Impact of calcification on clinical outcomes after endovascular therapy for superficial femoral artery disease: assessment using the peripheral artery calcification scoring system. J Endovasc Ther. 2016;23:731–737.

45. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment—a review of the evidence and causal mechanisms. Ageing Res Rev. 2013;12:840–861.

46. Lin C-H, Chou C-Y, Liu C-S, Huang C-Y, Li T-C, Lin C-C. Association between frailty and subclinical peripheral vascular disease in a community-dwelling geriatric population: Taichung Community Health Study for Elders. Geriatr Gerontol Int. 2015;15:261–267.

47. Figueiredo CP, Rajamannan NM, Lopes JB, Caparbo VF, Takayama L, Kuroishi ME, Oliveira IS, Menezes PR, Scazufca M, Bonfa E, et al. Serum phosphate and hip bone mineral density as additional factors for high vascular calcification scores in a community-dwelling: the São Paulo Ageing & Health Study (SPAH), Bone. 2013;52:354–359.

48. Chao C-T, Wang J, Huang J-W, Chan D-C, Hung K-Y, Chen K-L. Chronic kidney disease–related osteoporosis is associated with incident frailty among patients with diabetic kidney disease: a propensity score–matched cohort study. Osteoporos Int. 2020;31:699–708.

49. Shang X, Scott D, Hodge A, Khan B, Khan N, English DR, Giles GG, Ebeling PR, Sanders KM. Adiposity assessed by anthropometric measures has a similar or greater predictive ability than dual-energy X-ray absorptiometry measures for abdominal aortic calcification in community-dwelling older adults. Int J Cardiovas Imaging. 2016;32:1451–1460.

50. Hofbauer LC, Brueck CC, Shanahan CM, Schoppe M, Dobnie H. Vascular calcification and osteoporosis—from clinical observation towards molecular understanding. Osteoporos Int. 2007;18:251–259.

51. Zhang Y, Feng B. Systematic review and meta-analysis for the association of bone mineral density and osteoporosis/osteopenia with vascular calcification in women. Int J Rheum Dis. 2017;20:154–160.

52. Ruderman I, Holt SG, Hewitson TD, Smith ER, Toussaint ND. Current and potential therapeutic strategies for the management of vascular calcification in patients with chronic kidney disease including those on dialysis. Semin Dial. 2018;31:487–499.

53. Poterucha TJ, Goldhaber S. Warfarin and vascular calcification. Am J Med. 2016;129:635.e1–635.e4.

54. Vos A, Kockelkoren R, de Vis JB, van der Schouw YT, van der Schaaf I, Velthuis BK, Mali WP, de Jong PA. Risk factors for atherosclerotic and medial arterial calcification of the intracranial internal carotid artery. Atherosclerosis. 2018;276:44–49.