Journal of the American Heart Association

ORIGINAL RESEARCH

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

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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.[1] This VC-inducing effect is further compounded by the downregulation of calcification inhibitors, such as fetuin-A and matrix Gla protein, klotho, and osteoprotegerin.[2] 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.[3] 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

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For Sources of Funding and Disclosures, see page 11.

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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 prefrailty 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

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

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).[4] 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.[5] 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.[6] 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.[7] 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.[8,9] 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.[10] We also collected their spot urine

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 calcification[21] 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/m^2). 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 to data among those without prefrailty/frailty. This was followed by multiple logistic regression analyses with backward variable selection using 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.[26] 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,[27,28] a population at substantial risk of concurrently developing VC and frailty.[29] 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 0.1%; $P<0.001$), 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

	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	16 (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
Gout (%)	57 (5.0)	36 (5.6)	0.618	20 (5.6)	13 (5.4)	3 (6.4)	0.956
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)	2 (4.3)	0.533
Anxiolytics/sedatives/hypnotics (%)	208 (18.3)	165 (25.5)	0.001	83 (23.1)	65 (26.9)	17 (36.2)	0.001
Anthropometric 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/m^2	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±1.32	<0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2‡	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)

Table 1. (Continued)

	No AAC (n=1135)	With AAC (n=648)	*P* Value*	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.

data, AAC remained significantly associated with a high pre-frailty/frailty probability (OR, 10.9; 95% CI, 8.0–14.8), in a severity-dependent manner (Table 3). Finally, after adjusting for other geriatric phenotypes, AAC was still significantly associated with higher probability of bearing prefrailty or frailty (OR, 11.9; 95% CI, 7.9–15.4), in a severity-dependent manner (Table 3). The areas under the receiver operating characteristic curves of models 1, 2, 3, 4, 5, and 6 were 0.821 (95% CI, 0.794–0.849), 0.828 (95% CI, 0.802–0.854), 0.875 (95% CI, 0.854–0.897), 0.827 (95% CI, 0.8–0.854), 0.832 (95% CI, 0.806–0.859), and 0.876 (95% CI, 0.855–0.898), respectively (Figure 2). These findings suggested that the inclusion of laboratory data and other geriatric phenotypes successively improved model performance.

The association between the probability of frailty and AAC was more prominent when frailty was used as the dependent variable instead of using frailty or prefrailty as the dependent variable; AAC was associated with a significantly higher probability of frailty (OR, 67.7; 95% CI, 9.2–496.9; model 4), even after adjusting for laboratory data (model 5) and for laboratory data and geriatric phenotypes (model 6) (Table 3). We used variance-inflation factors to assess whether collinearity existed between these variables, and the variance-inflation factors of all included variables in models 4 to 6 were <2. The probability of frailty was associated with AAC in a severity-dependent manner (Table 3).

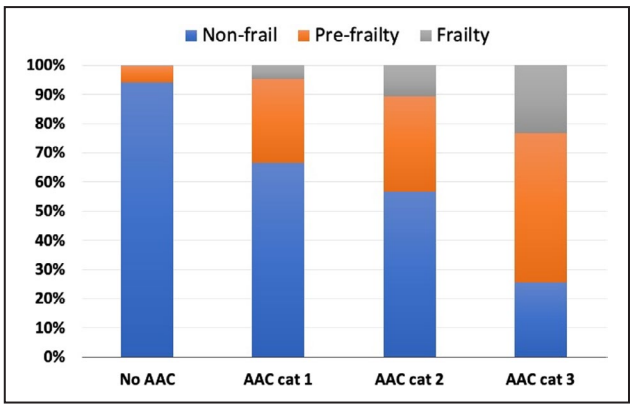

Figure 1. Distribution of different frailty statuses of participants without and with increasing AAC severity.
AAC indicates aortic arch calcification; and Cat, category.

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, 1.3–19.5) (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 2. Comparison of Clinical Features Between Older Adults With and Without Different Severities of Frailty

	No F/PF (n=1456)	With F/PF (n=327)	*P* Value*	PF (n=272)	F (n=55)	*P* Value†
Demographic profile						
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/m^2	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	5.6±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 m^2‡	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)

Table 2. (Continued)

	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 (25.1)	<0.001	65 (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.

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 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	11.0	7.9–15.4	<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	9.3	6.4–13.6	<0.001
Category 2	14.0	9.6–20.5	<0.001	13.5	9.2–19.6	<0.001	13.6	8.8–21	<0.001
Category 3	47.5	22.6–99.6	<0.001	45.1	21.2–96	<0.001	52.5	22.3–123.4	<0.001
	Model 4¶			Model 5#			Model 6‖		
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	62.2	8.4–462.5	<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	42.2	5.5–325.9	<0.001
Category 2	96.2	12.7–729.8	<0.001	100.3	13.1–766	<0.001	100.7	13.1–776.3	<0.001
Category 3	158.1	18.7–1333.6	<0.001	164.7	18.7–1447.8	<0.001	194.1	21.8–1726.9	<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.
‖Including model 5 variables and other geriatric phenotypes (anxiety, depression, insomnia, vision impairment, and cognitive impairment).
¶Including sociodemographic profile (age, sex, drinking and exercise history), comorbidity (cardiac disease), medications (hypnotics), anthropometric parameters (waist circumference, systolic/diastolic blood pressure, and pulse rate).
#Including model 4 variables and laboratory data (hemoglobin, estimated glomerular filtration rate, and proteinuric titer).
**Not including AAC status.

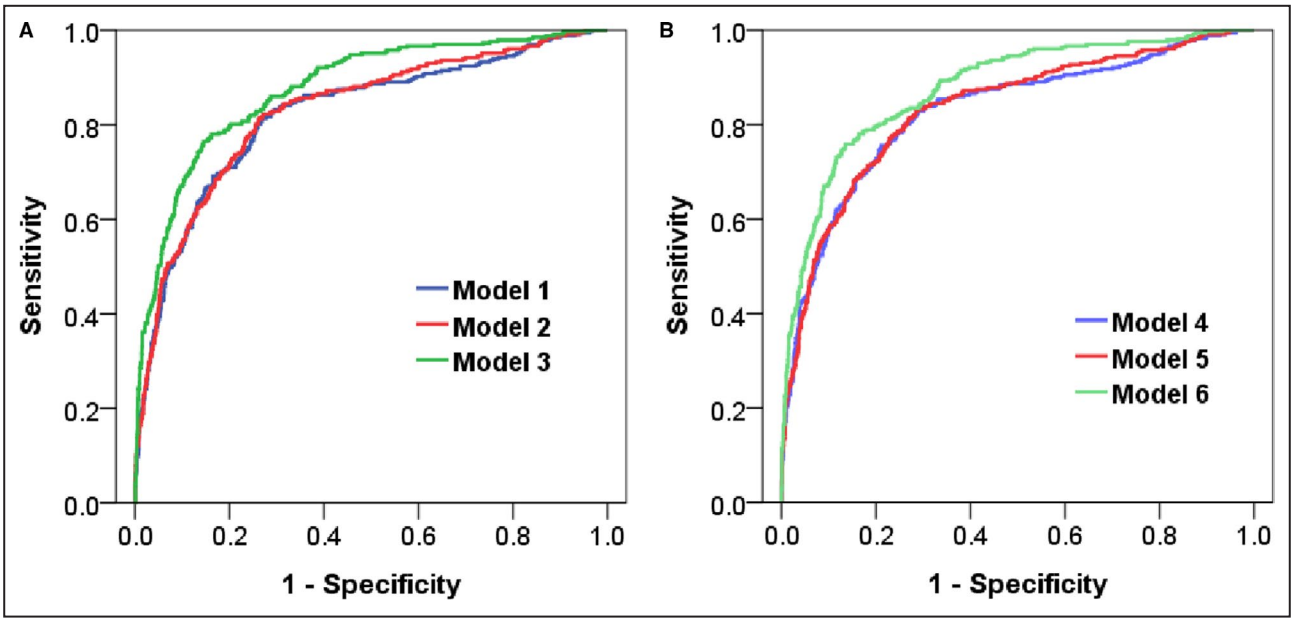

Figure 2. Receiver operating characteristic curves for the tested logistic regression models with prefrailty or frailty as the dependent variable.
A, AAC status; **B**, AAC categories. AAC indicates aortic arch calcification.

depending upon the measurement strategy and the study quality.[30] 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%.[31] 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.[32]

A prior review suggested that SOF might not accurately identify frailty in hospitalized patients because of their inability to complete physical tasks.[33] Similar risk is present when we apply other frailty instruments

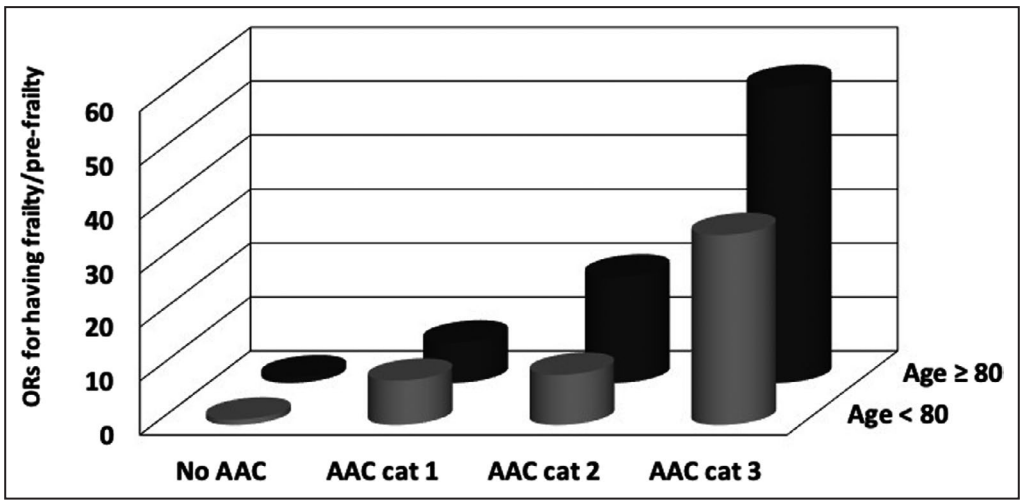

Figure 3. Probability of prefrailty or frailty among older adults based on age strata and AAC categories.
AAC indicates aortic arch calcification; Cat, category; and OR, odds ratio.

Table 4. Sensitivity Analysis Based on Abdominal Aortic Calcification Status

Outcomes	Model*		
	Odds Ratio	95% CI	*P* Value
Prefrailty or frailty as the dependent variable			
Abdominal aortic calcification status			
Absent	1	…	
Present	5.0	1.3–19.5	0.019

*Including age and sex.

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.[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.[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.[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.[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.[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.[39] In addition, the presence of AAC is frequently accompanied by calcification of other vascular beds, including intracranial arteries[40] and arteries supplying limbs.[41] Intracranial artery calcification of greater severity has

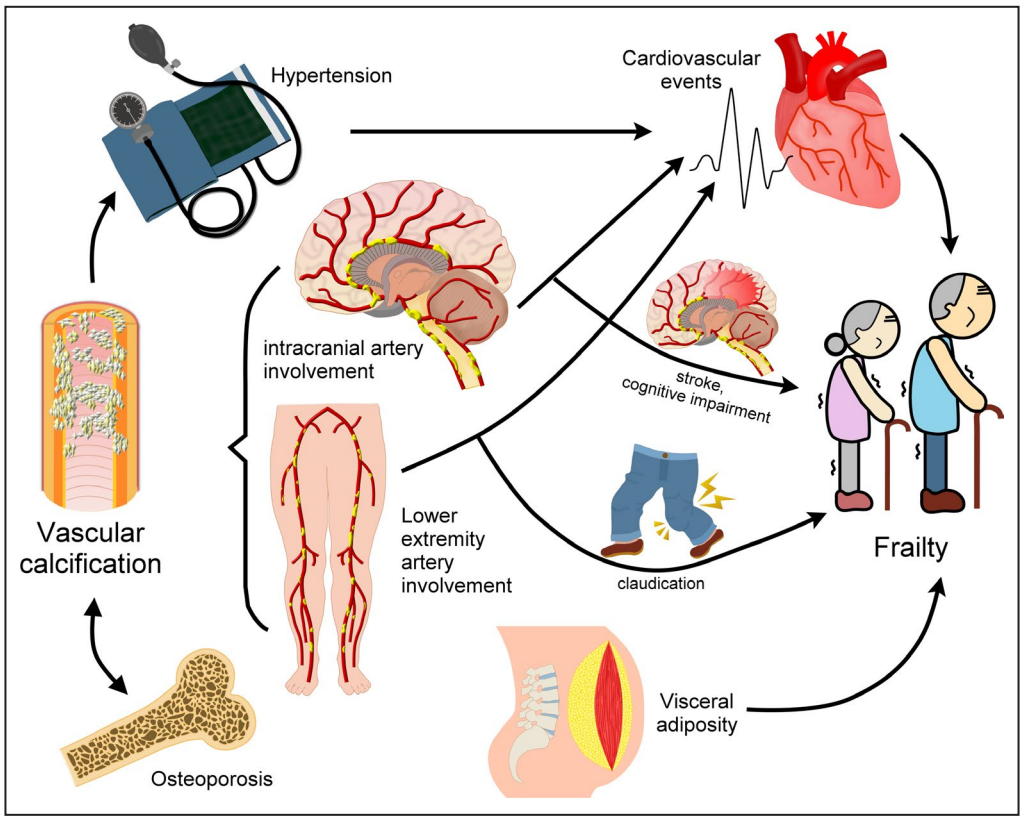

Figure 4. A putative diagram illustrating the potential mechanistic link between vascular calcification and frailty in older adults.

been shown to correlate with an increased posterior and anterior circulation blood flow velocity and resistance,[42] potentially compromising cortical perfusion and contributing to cognitive impairment as well as the risk of ischemic stroke and dementia.[43] 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.[44] Cognitive impairment, cerebrovascular accident, peripheral vascular disease, and limb claudication have all been reported to be independent risk factors for frailty among older adults.[45,46] 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,[47] and osteoporosis and fractures are established predecessors of frailty in these patients.[48] Finally, visceral adiposity and insulin resistance frequently coexist in patients with VC,[49] and these adverse metabolic phenotypes are also potential contributors to frailty in older adults.[8] 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.[50,51] 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,[17,18] 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,[33] 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,[52,53] poorly controlled DM, hypertension, and smoking,[54] in order to lower their subsequent risk of frailty. Finally, several promising treatments for VC, such as vitamin K and magnesium supplementation,[52] may be harnessed for the potential management of patients with VC-related frailty.

ARTICLE INFORMATION

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

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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 BeiHu Branch (10905) and Ministry of Science and Technology, Taiwan (MOST 108-2314-B-002-055- 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.

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