Journal of Geriatric Cardiology | JGC
LETTER TO THE EDITOR
J Geriatr Cardiol 2025; 22(11): 941–947

Association between arterial stiffness and geriatric status: results of cross-sectional study

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https://doi.org/10.26599/1671-5411.2025.11.001

Arterial stiffness is considered an important indicator reflecting age-related changes in the vascular wall[1] and the risk of developing comorbidities,[2] primarily cardiovascular diseases.[3] Cardiovascular diseases remain the leading cause of death worldwide. Many factors influence the rate of arterial aging. Research results have confirmed that arterial wall stiffness increases with an increasing number of risk factors,[4] as each of them acts independently through various mechanisms, adversely affecting the structure and function of the cardiovascular system.[5] In recent decades, most countries in the world have seen a progressive increase in the number of older adult and senile individuals, which is exponential in nature, leading to an increase in the prevalence of frailty and other geriatric syndromes (GS). Frailty syndrome is one of the key GS. Frailty is characterized by an age-related decrease in the physiological reserve and functions of many body systems, which increases the vulnerability of the older adult' s organism to the action of endo- and exogenous factors, and is also accompanied by a high risk of adverse outcomes, loss of autonomy and death.[6]

Over the past 20 years, many methods have been developed for preliminary examination of patients to assess the presence of frailty, for which a connection with the adverse effect on the health of older people has been confirmed.[7] Most of these methods are either tools for determining the "frailty" phenotype with a predominant assessment of motor activity indicators that affect the overall assessment of frailty, or tools for determining the "frailty index" that assess the presence of comorbidities, social factors, functional indicators and cognitive functions.[8] Since short and easy-to-use screening tools are most applicable in clinical practice, several methods for rapid preliminary assessment of frailty have been developed and approved for use.[7,9–12] In Russia, the "Vozrast ne pomekha" questionnaire was created to identify signs of frailty, the validity of which was confirmed. It is recommended to use this questionnaire for preliminary examination of patients 60 years and older who have sought medical care in outpatient or inpatient facilities, in order to identify GS and determine tactics for their management.[13,14] Arterial stiffness is measured using the cardio-ankle vascular index (CAVI), which reflects the rigidity of the walls of the aorta, femoral and tibial arteries. When calculating CAVI, the pulse wave velocity between the arm and ankle and the level of systolic blood pressure (BP) are considered. This approach ensures the independence of the CAVI indicator from the BP level,[15] which is especially important when examining patients who have BP fluctuations, as well as in the presence of masked hypertension or the use of antihypertensive drugs.[16] There is increasing evidence of common pathophysiological links between frailty and atherosclerosis, primarily inflammation.[17] The purpose of this study was to evaluate the AS indicator in patients over 60 years old both in the presence of frailty and in its absence.

The study included patients 60 years and older who did not have hemodynamically significant vascular lesions caused by atherosclerosis, as well as indications in the anamnesis of previous complications of cardiovascular disease (CVD), performed revascularization, the presence of aortic aneurysm and sensory or cognitive impairments. The study was approved by the Local Ethics Committee of the Russian Gerontological Research

and Clinical Center, the Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation (protocol No. 25 dated June 17, 2019). Before inclusion in the study, all patients signed informed consent. Based on a preliminary assessment using the "Vozrast ne pomekha" questionnaire, patients were assigned to one of three groups: a group without signs of frailty with a score of 0-2 points; a group with signs of frailty with a score of 5–7 points and a group with indeterminate results with a score of 3–4 points. Additionally, a short battery of tests was used to measure the level of physical functioning (SPPB) and based on the results obtained, patients were assigned to one of three groups: a group with pre-frailty 8–9 points, a group with frailty at 7 or fewer points and a group without frailty 10-12 points according to SPPB. The study included 150 patients aged 60 to 101 years, mean age 75.5 ± 7.0 years, 87% women, 50 patients in each group. All patients underwent a general clinical examination, as well as biochemical blood tests and assessment of arterial wall stiffness with determination of CAVI using volumetric sphygmometry (VaSera-VS-1500, FUKUDA DENSHI, Japan). Inclusion criteria: men and women aged 60 years and older who agreed to sign voluntary informed consent to participate in the study. Exclusion criteria: history of myocardial infarction, acute cerebrovascular accident, transient ischemic attack, myocardial revascularization or revascularization of any other localization, aortic aneurysm; presence of stenoses and occlusions of lower limb arteries, as well as diagnostically significant atherosclerosis of brachiocephalic arteries according to ultrasound examination; pulmonary embolism in history, thromboangiitis; Raynaud's disease, angiitis; presence of permanent atrial fibrillation; presence of acute or exacerbation of chronic diseases at the time of the study; severe sensory impairments (deafness and blindness). In all cases, anamnesis collection, review of medical records, physical examination, and assessment of CVD risk factors (smoking, low physical activity, abdominal obesity, obesity, diabetes mellitus, dyslipidemia, hyperglycemia) were performed. Measurements included body mass, height, BMI calculation (kg/m^2), waist, arm and calf circumference, and triplicate blood pressure measurements using the Korotkoff method with calculation of the arithmetic mean of the second and third measurements. A patient was considered a smoker if they smoked at least one cigarette daily. Physical activity was deemed low if moderate-intensity activity lasted less than 150 minutes per week or vigorous aerobic physical activity less than 75 minutes per week (walking at medium or high pace). Blood samples were collected from all patients to evaluate biochemical parameters (creatinine, total protein, fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)). Instrumental assessment of arterial wall stiffness was conducted using volumetric sphygmometry (VaSera-VS-1500 device, FUKUDA DENSHI, Japan) with determination of the CAVI. A CAVI value of 9.0 units or higher was considered pathological.

Results are presented as mean ± SD for quantitative indicators or as *n* (%) for qualitative indicators. Quantitative indicators were compared between groups using analysis of variance or the Kruskal-Wallis test for scores. Qualitative indicators were compared between groups using Fisher's exact test. In case of rejection of the null hypothesis of no differences between groups, pairwise comparisons were performed using Tukey's test or Dunn's test for score evaluations, as well as Fisher's exact test with Holm's correction for multiple comparisons for qualitative variables. Results were considered statistically significant at $P < 0.05$. Statistical analysis was performed using Statistica 10 (StatSoft Inc., USA) and R 3.6.2 (R Core Team, 2019).

The study included 150 patients aged 60 to 101 years, mean age 75.5 ± 7.0 years, 87% women. Patients were divided into 3 groups: without frailty s, with pre-frailty, and with frailty (mean age 73.6 ± 6.2; 76.6 ± 8.1 and 76.2 ± 6.2 years). In the first stage, a comparative analysis of main clinical characteristics, anthropometric and hemodynamic parameters, and CVD risk factors was conducted in the general and three designated patient groups (Table 1).

The patient groups were comparable in terms of age, anthropometric parameters, proportion of patients with low physical activity, systolic and diastolic blood pressure levels, and laboratory indicators, with the exception of the proportion of patients with hypercholesterolemia: the proportion of patients with hypercholesterolemia in the frailty group was lower compared to the group of patients without frailty. The proportion of smokers in the groups of patients with frailty and pre-frailty was lower compared to the group of patients without frailty.

Among the main chronic non-communicable diseases (NCDs), ischemic heart disease (IHD), chronic heart failure (CHF), and diabetes mellitus (DM) were the most

Table 1 Clinical characteristics of study participants.

Characteristics	Total sample	Without frailty, (1)	Pre-frailty, (2)	Frailty, (3)	*P*	P_{1-3}	P_{2-3}	P_{1-2}
Age, yrs	75.5 ± 7.0	73.6 ± 6.2	76.6 ± 8.1	76.2 ± 6.2	0.07			
Women	131	41	45	45	0.42			
Height, cm	157.4 ± 8.0	157.9 ± 7.5	157.1 ± 8.5	157.1 ± 8.0	0.81			
Weight, kg	69.9 ± 13.6	71.2 ± 12.8	68.1 ± 14.5	70.3 ± 13.5	0.50			
BMI, kg/m^2	28.1 ± 5.2	28.4 ± 4.6	27.4 ± 5.0	28.5 ± 5.9	0.52			
Body mass								
Deficit	2 (4%)	0	0	2 (4%)				
Norm	37 (25%)	10 (20%)	12 (24%)	15 (30%)	0.27			
Excessive	59 (39%)	20 (40%)	28 (56%)	11 (22%)				
Obesity	52 (35%)	20 (40%)	10 (20%)	22 (44%)				
Waist circumference, cm	93.7 ± 15.8	92.8 ± 13.7	93.3 ± 13.7	95 ± 19.7	0.78			
*Abdominal obesity	111 (74%)	40 (80%)	38 (76%)	33 (66%)	0.29			
Low level of physical activity	117 (78%)	37 (74%)	37 (74%)	43 (86%)	0.18			
Smoking	22 (15%)	15 (30%)	4 (8%)	3 (6%)	0.002	0.01	0.72	0.02
Duration of AH, years	20.3 ± 13.1	15.4 ± 12.9	20.7 ± 12.9	23.7 ± 12.7	0,05			
SBP, mmHg	143.9 ± 22.6	142.4 ± 22.6	147.9 ± 22.1	141.7 ± 23.0	0.32			
DBP, mmHg	82.9 ± 11.9	85.8 ± 10.8	81.6 ± 11.5	81.5 ± 12.9	0.12			
HR, beats/min	71.3 ± 9.3	70.2 ± 9.2	70.7 ± 8.6	72.9 ± 11.2	0.34			
TC, mmol/L	5.5 ± 1.2	5.7 ± 1.0	5.3 ± 1.5	5.3 ± 1.3	0.16			
LDL, mmol/L	3.1 ± 1.1	3.3 ± 1.0	3.1 ± 1.2	3.0 ± 1.1	0.30			
HDL, mmol/L	0.96 ± 0.55	1.49 ± 0.35	1.41 ± 0.40	1.64 ± 0.78	0.17			
Triglycerides, mmol/L	0.90 ± 0.67	1.41 ± 0.57	1.49 ± 0.71	1.44 ± 0.75	0.84			
Creatinine, mmol/L	53.6 ± 20.0	84.2 ± 19.0	87.8 ± 17.4	90.3 ± 22.6	0.26			
Total protein, g/L	46.0 ± 5.6	72.7 ± 4.4	73.3 ± 5.7	72.9 ± 6.4	0.87			
Glucose, mmol/L	3.7 ± 1.8	5.9 ± 1.7	5.8 ± 1.5	6.1 ± 2.0	0.65			
Glucose 5.6–6.9 mmol/L	36 (24%)	12 (24%)	9 (18%)	15 (30%)	0.39			
Total cholesterol ≥ 5,0 mmol/L	91 (61%)	39 (78%)	26 (52%)	26 (52%)	0.01	0.03	1	0.34
HDL ≥ 3.0 mmol/L	73 (49%)	30 (60%)	24 (49%)	19 (38%)	0.10			

Data are presented as mean ± SD or *n* (%). *Waist circumference ≥ 80 cm in women and 94 cm in men. AH: arterial hypertension; BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; HR: heart rate; LDL: low-density lipoprotein; SBP: systolic blood pressure; TC: cholesterol. *P* when comparing three groups of patients, P_{1-3} when comparing groups of patients with and without frailty, P_{2-3} when comparing groups of patients with frailty and pre-frailty, P_{1-2} when comparing groups of patients without frailty and pre-frailty.

common in all three patient groups (Figure 1).

The mean number of chronic non-communicable diseases (NCDs) in the group of patients without frailty was 1.0 ± 1.1, in the group of patients with pre-frailty −1.7 ± 1.1, and in the group of patients with frailty −1.5 ± 1.1 (P_{1-3} = 0.08, P_{2-3} = 1, P_{1-2} = 0.02; P_{1-3} when comparing groups of patients with and without frailty, P_{2-3} when comparing groups of patients with frailty and pre-frailty, P_{1-2} when comparing groups of patients without frailty and with pre-frailty). In the assessment of vascular wall stiffness using volumetric sphygmometry, the CAVI in the overall group was 9.8 ± 1.4 units. In the group of patients with frailty, the CAVI was 10.4 ± 1.7 units, in the group of patients with pre-frailty −9.8 ± 1.3 units, and in the group of patients without frailty −9.4 ± 1.0 units (P_{1-3} = 0.0007, P_{2-3} = 0.06, P_{1-2} = 0.36; P_{1-3} when comparing groups of patients with and without frailty, P_{2-3} when comparing groups of patients with frailty and pre-frailty, P_{1-2} when comparing groups of patients without frailty and with pre-frailty). The differences in CAVI reached statistical significance only when comparing groups of patients with and without frailty (Figure 2).

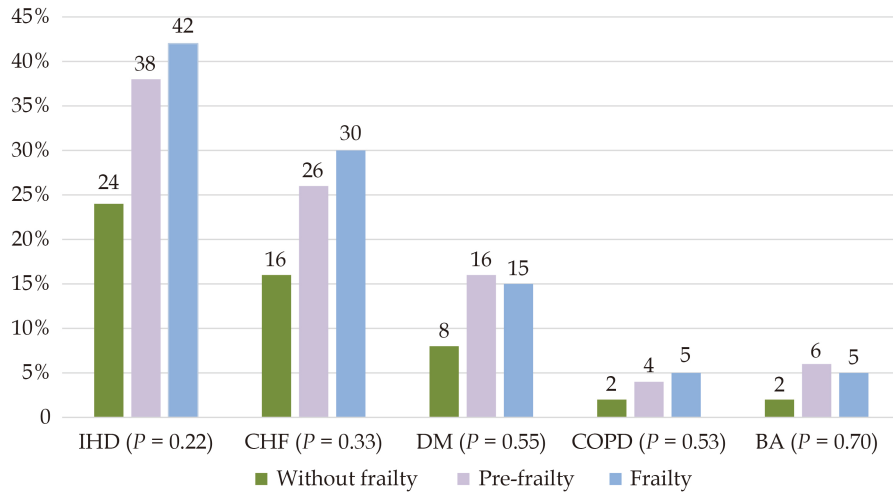

Figure 1 Prevalence of chronic non-communicable diseases in comparison groups. BA: bronchial asthma; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; IHD: ischemic heart disease.

Overall, when analyzing data from all participants, a statistically significantly higher CAVI was found in patients with low physical activity compared to patients with normal physical activity levels, as well as in the group of patients without frailty; in groups of patients with pre-frailty and frailty, the increase in CAVI did not reach statistical significance. In the group of patients with frailty, CAVI was statistically significantly higher in patients with normal waist circumference and BMI < 25 kg/m^2. In the group of patients with pre-frailty, no statistically significant differences in CAVI were found depending on cardiovascular disease risk factors. In the group of patients without frailty, an increase in CAVI was found in patients with BMI ≥ 25 kg/m^2, with diabetes mellitus, with total cholesterol levels of 5.0 mmol/L or higher, and with glycemia of 5.6–6.9 mmol/L. Notably, there was a divergent relationship between CAVI and BMI in patients without frailty and patients with frailty: in the group of patients without frailty and BMI ≥ 25 kg/m^2, a higher CAVI was observed, in contrast to the group of patients with frailty, who, conversely, had a higher vascular wall stiffness index with BMI < 25 kg/m^2 (Figure 3).

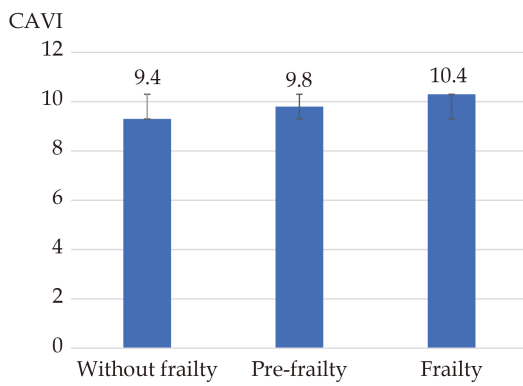

Figure 2 Mean values and standard deviations of the cardio-ankle vascular index. Correlation analysis revealed the following associations between CAVI and cardiovascular disease risk factors: in the group of patients with frailty and pre-frailty, CAVI had a statistically significant correlation with BMI (r = –0.416 and –0.343, respectively; P = 0.003 and 0.015 respectively). In the group of patients without frailty, CAVI showed a direct correlation with total blood cholesterol concentration (r = 0.322, P = 0.022). A comparative analysis of CAVI depending on the presence or absence of cardiovascular disease risk factors in groups of patients without frailty, with pre-frailty, with frailty, and in the overall patient group is presented in Table 2.

A two-way analysis of variance was performed, including the factors "patient group" and BMI, and their interaction (Table 3).

The relationship between AS and the severity of risk factors for CVD complications remains a subject of intensive study. At the same time, there is limited data on the association between AS and GS, primarily frailty. Sampaio, *et al*.[18] suggested that muscle blood supply decreases with age and that this was associated with the degree of arterial wall stiffness. Hemodynamic dysfunction may cause muscle mass reduction. This can cause deficit of body mass, results of dynamometry, and ultimately to a decline in the physical functioning of the elderly, which is a key component of frailty. In this study statistically significant difference in CAVI between groups of patients without frailty and patients with frailty was found (9.4 ± 1.0 units and 10.4 ± 1.7 units respectively, P = 0.0007). Aging is accompanied by significant changes in body composition and loss of muscle

Table 2 Comparative analysis of the CAVI depending on cardiovascular risk factors.

Characteristics	Total sample		Without frailty		Pre-frailty		Frailty	
Smoking	9.7 ± 1.4	$P = 0.42$	9.4 ± 1.0	$P = 0.79$	9.23 ± 0.62	$P = 0.33$	11.8 ± 2.1	$P = 0.28$
Non-smokers	9.8 ± 1.4		9.9 ± 1.4		9.4 ± 0.9		10.3 ± 1.6	
physical activity less 150 min/week	10.0 ± 1.4	$P < 0.0001$	9.7 ± 0.9	$P < 0.0001$	9.9 ± 1.4	$P = 0.19$	10.5 ± 1.7	$P = 0.31$
Physical activity at least 150 min/week	9.1 ± 0.9		8.5 ± 0.5		9.3 ± 0.9		9.7 ± 1.3	
waist circumference* above normal	9.7 ± 1.2	$P = 0.10$	9.5 ± 1.1	$P = 0.20$	9.6 ± 1.0	$P = 0.25$	9.9 ± 1.4	$P = 0.01$
waist circumference normal	10.4 ± 1.9		10.4 ± 1.9		9.2 ± 0.6		11.6 ± 1.9	
BMI ≥ 25 kg /m^2	9.7 ± 1.2	$P = 0.05$	9.5 ± 1.0	$P = 0.005$	9.6 ± 1.3	$P = 0.08$	9.9 ± 1.4	$P = 0.006$
BMI <25 kg /m^2	10.4 ± 1.7		8.8 ± 0.3		10.3 ± 1.3		11.3 ± 1.8	
DM$^+$	10.2 ± 1.2	$P = 0.16$	10.2 ± 0.5	$P = 0.04$	10.4 ± 1.4	$P = 0.21$	9.9 ± 1.3	$P = 0.55$
DM$^-$	9.8 ± 1.4		9.3 ± 1.0		9.6 ± 1.2		10.4 ± 1.7	
TC ≥ 5.0 mmol/L	9.8 ± 1.3	$P = 0.86$	9.6 ± 0.9	$P = 0.002$	9.7 ± 1.4	$P = 0.84$	10.3 ± 1.8	$P = 0.56$
TC, norm	9.8 ± 1.4		8.6 ± 0.8		9.8 ± 1.2		10.5 ± 1.6	
LDL ≥ 3.0 mmol/L	9.7 ± 1.3	$P = 0.86$	9.6 ± 1.0	$P = 0.06$	9.6 ± 1.4	$P = 0.53$	10.1 ± 1.4	$P = 0.73$
LDL, norm	9.9 ± 1.4		9.1 ± 0.8		9.8 ± 1.2		10.4 ± 1.7	
Glucose 5.6–6.9 mmol/L	9.8 ± 0.9	$P = 0.40$	9.8 ± 0.7	$P = 0.02$	10.1 ± 0.7	$P = 0.12$	9.7 ± 1.2	$P = 0.08$
Glucose norm, mmol/L	9.8 ± 1.5		9.3 ± 1.0		9.7 ± 1.4		10.6 ± 1.8	

Data are presented as mean ± SD. *Waist circumference ≥ 80 cm in women and 94 cm in men. BMI: body mass index; DM: diabetes mellitus; TC: cholesterol; LDL: low-density lipoprotein.

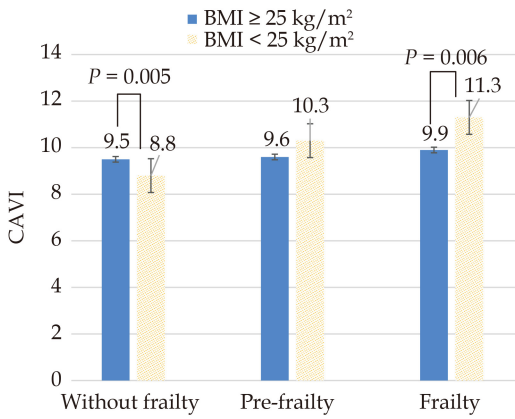

Figure 3 CAVI in patients with BMI ≥ 25 kg/m^2 and in patients with BMI < 25 kg/m^2. BMI: body mass index; CAVI: cardio-ankle vascular index.

Table 3 Results of analysis of variance on the relationship between body mass index and frailty syndrome with the cardio-ankle vascular index.

Effects	*F*	*P*
Patient group	11.8	< 0.0001
BMI	4.0	0.04
Patient group × BMI	6.8	0.002

BMI: body mass index. Thus, in the analysis of variance, the relationship of BMI, patient group, as well as their interaction with the AS index proved to be statistically significant.

mass.[19] Lv, *et al.*[20] found consistent inverse relationships between BMI and all-cause mortality. Our results provide additional evidence for the obesity paradox among the elderly. In the group of patients with frailty and pre-frailty, no correlations with traditional CVD risk factors were found; conversely, it was noted that in the frailty group, the arterial wall stiffness parameter was higher with BMI < 25 kg/m^2 compared to patients with BMI ≥ 25 kg/m^2 ($P = 0.006$) and higher in the absence of abdominal obesity ($P = 0.01$). Although obesity has been considered a risk factor for adverse health outcomes in the general population, emerging data have shown that overweight or obesity may be associated with a reduced risk of mortality in older adults. A J-shaped relationship between BMI and mortality is currently reported in the 50–71 age group.[21]

This study revealed an inverse relationship between AS indicators and BMI ($P = 0.003$). A relationship was also established not only between AS and BMI or a specific patient group, but also the dependence of such a relationship on these indicators (i.e., on BMI and the specific group respectively). Higher BMI is usually associated with better nutritional status, muscle mass, and skeletal muscle, rather than simply fat mass, which contributes to maintaining functioning and activity in eld-

erly and senile individuals. It is known that people with obesity and higher fitness have a reduced risk of all-cause mortality, risk of CVD complications, and metabolic diseases.[22] Physical exercises in the form of strength and aerobic exercises, including high-intensity interval training, increase muscle strength and are significantly associated with a reduced risk of all-cause mortality in older adults.[23,24] In conclusion, in older population,high AS can be considered as a risk factor for the development of geriatric syndromes associated with frailty. In the future it may be reasonable to consider weight loss as a possible negative factor in older people, and possible preventive role of optimal BMI or even mild obesity for maintaining independence in individuals in this age group.

DISCLOSURE

Competing Interests

The authors declare no conflict of interest.

Informed Consent

All participants of the study provided informed consent to take part in this study.

Ethical considerations

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by The Local Ethics Committee of the Russian Gerontology Research and Clinical Centre (Protocol #25, 17 June 2019).

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Please cite this article as: Luzina AV, Eruslanova KA, Gilyarevsky SR, Runikhina NK, Kotovskaya YV, Tkacheva ON. Association between arterial stiffness and geriatric status: results of cross-sectional study. *J Geriatr Cardiol* 2025; 22(11): 941–947. DOI: 10.26599/1671-5411.2025.11.001