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Aortic pulse wave velocity predicts cardiovascular mortality among middle-aged metabolic syndrome subjects without overt cardiovascular disease

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Abstract

Background The objective of this cohort study was to assess the predictive value of main arterial markers for cardiovascular death in middle-aged subjects with metabolic syndrome (MetS).

Methods This prospective longitudinal study analyzed data from 5829 metabolic syndrome subjects without overt cardiovascular disease aged between 40 and 64 years and enrolled in the Lithuanian High Cardiovascular Risk primary prevention program. Initial assessment comprised the evaluation of aortic pulse wave velocity (aPWV), carotid intima-media thickness (cIMT), carotid stiffness index, cardio-ankle vascular index (CAVI), ankle-brachial index (ABI), aortic augmentation index adjusted for a heart rate of 75 bpm (AIXHR75), and endothelium-dependent flow-mediated dilatation (FMD).

Results During the mean follow-up period of 6.35 ± 2.99 years, 170 subjects (2.9%) had died, with 41 out of these deaths (24.1%) related to cardiovascular causes. Cox proportional hazard regression analysis revealed associations between cardiovascular deaths and increases in aPWV (HR 1.34, 95% CI 1.14–1.58, $p < 0.001$), CAVI (HR 1.28, 95% CI 1.09–1.50, $p = 0.002$), and cIMT (HR 1.004, 95% CI 1.001–1.006, $p = 0.003$), as well as a decrease in ABI (HR 0.020, 95% CI 0.001–0.359, $p = 0.008$). However, after adjustment for age and gender, only aPWV remained a statistically significant predictor. Common survival tree analysis foregrounded the predictive significance of C-reactive protein (CRP), as the primary variable associated with an increased risk of cardiovascular death, followed by aPWV and smoking as secondary and tertiary variables. The analysis also demonstrated sex-related differences: in women, the primary predictive variable was aPWV, whereas in men, CRP was identified as the primary variable, followed by CAVI and cIMT.

Conclusions The findings of this study suggest that, among the markers of subclinical arterial damage, an increase in both aPWV and CAVI has a statistically significant predictive value for cardiovascular mortality in the middle-aged subjects with MetS. However, only aPWV demonstrated predictive value that was independent of age and gender.

Keywords Pulse wave velocity, Carotid intima-media thickness, Endothelial function, Aortic stiffness, Cardiovascular mortality, Metabolic syndrome

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Background

During recent years, atherosclerotic cardiovascular disease (CVD) has caused an increasing number of deaths and its prevalence is predicted to reach 23.6 million deaths yearly by 2030 [1–3]. Despite advancements in treatment and preventive measures, particularly in high-income countries like the United States, where there has been a decrease in CVD related deaths, CVD remains the primary cause of death worldwide [2, 4]. Moreover, age-standardized CVD mortality continues to rise even in high-income nations [2]. Lithuania follows this trend, with CVD being the leading cause of death among both males and females for many years. According to the latest data from the Institute of Hygiene of Lithuania, CVD accounted for almost half of all deaths (52.5%) in 2022, which is a 4.3% increase compared to 2021 [5]. This significant burden of CVD has economic implications, with related costs estimated to increase by 183 billion dollars in the United States from 2015 to 2035 [6]. Such statistics underscore the importance of appropriate risk assessment and prevention strategies for CVD.

Metabolic syndrome (MetS) represents a prevalent cluster of cardiometabolic risk factors among adults, imposing significant costs on public health systems worldwide [7]. The risk factors associated with MetS undeniably contribute to an elevated risk for the development of various chronic diseases, such as type 2 diabetes mellitus and CVD [8]. Data from the National Heart, Lung, and Blood Institute (NHLBI) indicates that metabolic syndrome affects approximately one-third of adults in the United States [9]. Despite a decline in the MetS prevalence in Lithuania from 2009 to 2017, the presence of MetS among Lithuanians remains substantial, with rates as high as 30% [10].

As shown by the MARE consortium, the presence of MetS is associated with subclinical vascular damage [11, 12]. Other studies have also demonstrated that assessing arterial stiffness in different populations may help identify subjects at increased cardiovascular risk [13–15]. However, there are very few longitudinal studies in the middle-aged MetS subjects without overt cardiovascular disease, and the scientific community is still debating which markers of subclinical arterial damage have higher predictive value for cardiovascular (CV) risk in this population [11, 13].

Our study aims at filling this lacuna, examining the predictive value of several markers of early arterial aging and atherosclerosis for CV mortality. Our study analyzed the database that was compiled at the Vilnius University Hospital Santaros Klinikos, as part of the ongoing nation-wide Funding Program for the Screening and Preventive Management of the High Cardiovascular Risk Individuals (LitHiR program). The program commenced in Lithuania in 2006 and aims at reducing the prevalence of cardiovascular risk factors, lowering cardiovascular mortality, and increasing accessibility to early diagnostics [16]. In addition to the standard anthropometric and cardiac evaluation and lab tests, the database at Vilnius University Hospital Santaros Klinikos also features a comprehensive assessment of subclinical markers of arterial aging and atherosclerosis, as described below.

Methods

Subjects and study design

A total of 5829 subjects with metabolic syndrome were enrolled in a cohort study. All subjects were recruited from a single specialized healthcare center, Vilnius University Hospital Santaros Klinikos, as part of the LitHiR program. The LitHiR program aimed to recruit both women (aged 50–65 years old) and men (aged 40–55 years old) without a history of cardiovascular disease [16].

The exclusion criteria were as follows:

- Proven (clinically evident) coronary heart disease (CHD), including myocardial infarction or unstable angina, angina on effort with positive stress test results, coronary pathology identified on coronaroangiography or multi-slice computed tomography angiography, coronary artery bypass grafting, or angioplasty, as well as acute coronary events in the past;
- Proven cerebrovascular disease, comprising acute cerebrovascular events in the past or proven stenosis in the carotid arteries;
- Proven peripheral artery disease, encompassing acute ischemic syndrome, proven chronic ischemia in limbs, and aortic aneurism;
- End-stage oncological disease;
- Any other end-stage somatic disease.

Subjects diagnosed with metabolic syndrome following the initial assessment were referred to Vilnius University Hospital Santaros Klinikos for further evaluation. Metabolic syndrome was diagnosed according to the revised National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) definition [17], wherein the presence of three or more of the following criteria established the diagnosis:

- Waist circumference ≥ 102 cm for men, ≥ 88 cm for women;
- Triglyceride level ≥ 1.7 mmol/l;
- High-density lipoprotein cholesterol level < 1.03 mmol/l for men, < 1.29 mmol/l for women;
- Blood pressure ≥ 130/85 mmHg or ongoing antihypertensive treatment for a subject with a history of arterial hypertension;

- Fasting plasma glucose level ≥ 5.6 mmol/l.

The prospective longitudinal study was conducted in accordance with the principles of the Declaration of Helsinki, received approval from the Regional Ethics Committee (Permission No. 2019/3-1104-603) and the need to obtain informed patient consent was waived.

Clinical assessment

Before inclusion in the study, all subjects underwent physical examination, during which anthropometric data were recorded, including height in meters, weight in kilograms, waist circumference in centimeters, and body mass index (BMI), calculated as weight divided by the square of height. Cardiovascular risk factors such as smoking, familial cardiovascular disease, and arterial hypertension were assessed. Smoking was defined as smoking at least one cigarette per day, and familial CVD was considered if CV events had occurred among first-degree relatives (men ≤ 45 years, women ≤ 55 years old). Additionally, all subjects underwent a 12-lead electrocardiogram, with heart rate recorded, and blood pressure measurement. Blood pressure was measured, using an oscillometric semiautomatic device (Schiller Argus VCM) with a standard bladder (12–13 cm long and 35 cm wide), validated with a standardized mercury sphygmomanometer. Blood pressure was measured twice on the right arm after 5 min of rest, with the higher value being recorded. Mean arterial pressure was automatically calculated using the applanation tonometry system (SphygmoCor System) by obtaining the total area under the pressure curve and dividing this value by the duration of the time interval.

Additionally, a venous blood sample was collected after a 12-hour fast for the evaluation of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels. Glycated hemoglobin, fasting plasma glucose, and insulin levels were also assessed, along with plasma glucose and insulin levels after an oral glucose tolerance test.

The assessment of arterial markers

Arterial markers of subclinical atherosclerosis were assessed for all subjects using non-invasive means, which involved measuring endothelial function, arterial stiffness, wave reflection parameters, and wall parameters of the common carotid artery. Subjects were instructed to abstain from smoking and physical activity for at least 2 h before the examination. Vascular assessment was conducted after the subjects had rested for 10 min in a supine position.

Endothelial function was assessed using the endothelium-dependent flow-mediated dilatation (FMD) test, performed with a high-resolution ultrasound system equipped with a 12 MHz linear-array transducer and echo-tracking mode (Prosound α-10, Aloka, Japan) on the brachial artery. The diameter of the brachial artery was measured twice: first at rest and then after 5 min of ischemia introduced by inflating a pneumatic tourniquet placed on the forearm to 100 mmHg above the systolic blood pressure. Endothelium-dependent vasodilatation was automatically calculated as the maximum change in arterial diameter from the baseline during the first two minutes of the post-occlusive reactive hyperemia.

To evaluate arterial stiffness and wave reflection parameters the following tests were conducted:

- Pulse wave velocity (PWV) and wave reflection were assessed using an applanation tonometry system (SphygmoCor, AtCor Medical, version 8.0, Sydney, Australia) with a high-fidelity micromanometer (Millar Instruments, Houston, Texas). This system was placed on the skin surface at the projection of the carotid and femoral arteries to obtain pulse pressure wave curves. Brachial blood pressure was recorded, and the direct distance between the common carotid artery and the femoral artery was measured. This data, together with the simultaneously recorded electrocardiogram, enabled the system to compute the main parameter of arterial stiffness, aortic (carotid–femoral) pulse-wave velocity (aPWV) [18, 19].
- The ankle-brachial index (ABI) and cardio-ankle vascular index (CAVI) were measured using the VaSera VS-1000 (Fukuda Denshi Co. Ltd., Tokyo, Japan). After the subject had been stabilized in the supine position for 5 min, blood pressure at the posterior tibial and brachial arteries was measured. ABI was calculated as the ratio between systolic blood pressure measured at the ankle and systolic blood pressure measured in the arm. A value less than 0.9 was interpreted as indicating lower-limb arterial occlusion while the value greater than 1.3 was interpreted as indicative of lower-extremity arterial calcification and stiffness, with values in between interpreted as normal.
- Four blood pressure cuffs were placed on the four extremities to evaluate the CAVI. Electrocardiography electrodes were attached to both arms, and a microphone was positioned on the sternum in the second intercostal space. After the subject had been stabilized in the supine position for 10 min, electrocardiography and phonocardiography were monitored. CAVI was calculated using Bramwell-Hill's equation [20]: $\mathrm{CAVI} = \mathrm{a}*\frac{2\rho}{\Delta \mathrm{P}}*\ln\left(\frac{\mathrm{Ps}}{\mathrm{Pd}}\right)*\mathrm{PWV}^2 + \mathrm{b}$, where 'Ps' represents systolic blood pressure; 'Pd' represents diastolic blood pressure; 'ΔP' represents the

difference between systolic and diastolic blood pressure; 'PWV' represents the cardio-ankle pulse wave velocity; 'ρ' represents blood viscosity; and 'a' and 'b' are constants used for converting the CAVI value to a value obtained using the Hasegawa method.

Common carotid intima-media thickness (cIMT), cross-sectional carotid artery distensibility (both measured in μm), and the nondimensional index Quality Carotid Stiffness of the common carotid artery were assessed using high-resolution echo-tracking technology (Art. Lab, Esaote Europe B.V., Maastricht, the Netherlands). Measurements were taken 1 cm proximal to the carotid bifurcation along a 4 cm arterial segment. Quality Carotid Stiffness and cIMT were measured on both the right and left sides of the common carotid artery, and mean values of these measurements were used in the statistical analysis [21].

Follow-up and clinical outcomes

All the subjects were followed up for cardiovascular death for an average of 6.35±2.99 years. Outcome data were retrieved from the Lithuanian National Death Registry. CV death was defined as death caused by myocardial infarction or stroke (including both ischemic and hemorrhagic strokes), or sudden cardiac death.

Statistical analysis

Statistical analysis was conducted using *jamovi*, and the R statistical computing environment (version 4.2.3; R Core Team 2023). If not indicated otherwise, continuous variables are presented as medians along with interquartile ranges, instead of mean values with standard deviations, to account for the large dataset lacking evidence of normal distribution, as well the presence of numerous outliers.

The Shapiro–Wilk test was employed to assess normality. Continuous variables were compared using the Wilcoxon rank-sum test, while categorical variables were compared using the χ2-test or Fisher's exact test, as appropriate.

The Cox regression model was utilized to compute both unadjusted and adjusted relative risks for CV death during follow-up, estimated as the hazard ratio (HR) with the corresponding 95% confidence interval (CI). Schoenfeld's residuals were employed to evaluate the proportional hazard assumption. The weighted predictive mean matching method was employed for imputing missing values. Furthermore, two-level survival trees were constructed to identify the main predictive variables. In order to identify sets of variables having the optimal predictive value, survival tree analysis utilizes recursive binary partitioning of a predefined covariate space. These variables are referred to as "nodes". In order to distinguish the highest homogeneity of observations cut-off points for all "nodes" are estimated.

All p-values were 2-tailed, and the level of significance was set at 0.05.

Results

Baseline characteristics

The mean age of the enrolled subjects was 52.9±6.47 years, with 42.5% (2475) men and 57.5% (3354) women. All subjects were followed up for cardiovascular death for an average of 6.35±2.99 years. During the follow-up period, 170 (2.9%) subjects had died, out of which 41 (24.1%) were CV deaths.

The relationship between traditional CV risk factors and cardiovascular death

The univariate comparison of the baseline characteristics between groups of subjects with and without cardiovascular death revealed statistically significant differences in the medians of waist circumference (109 [IQR 105–118] vs. 104 [IQR 98–111], $p=0.001$), C-reactive protein level (2.90 [IQR 1.45–5.60] vs. 1.90 [IQR 1.01–3.70], $p=0.015$), high-density lipoprotein cholesterol level (1.05 [IQR 0.90–1.31] vs. 1.16 [IQR 0.99–1.37], $p=0.021$), and mean blood pressure (110 [IQR 97.7–116.0] vs. 102 [IQR 95.0-109.0], $p=0.003$). Additionally, statistically significant differences were observed between different levels of smoking ($p=0.001$) and the presence of diabetes mellitus ($p=0.018$). However, no statistically significant differences were found between subjects with and without cardiovascular death when analyzing other parameters such as age, body mass index, total cholesterol level, and fasting glucose level (Table 1).

The relationship between arterial markers and cardiovascular death

The comparison of arterial markers between subjects with and without CV death revealed statistically significant differences in the medians of aPWV (9.40 [IQR 8.70–10.40] vs. 8.40 [IQR 7.50–9.40], $p<0.001$), CAVI (8.10 [IQR 7.00-9.40] vs. 7.70 [IQR 6.80–8.60], $p=0.015$), ABI (1.06 [IQR 0.98–1.12] vs. 1.10 [IQR 1.03–1.15], $p=0.006$), and cIMT (708 [IQR 643–758] vs. 664 [IQR 599–736], $p=0.013$). However, these differences were not statistically significant for the medians of augmentation index adjusted for heart rate of 75 bpm ($p=0.544$), carotid stiffness index ($p=0.775$), and flow-mediated dilatation ($p=0.747$) (Table 2).

Cox proportional hazard regression analysis

Cox proportional hazard regression analysis demonstrated that a one-unit increase in aortic pulse wave velocity (adjusted for mean arterial blood pressure,

Table 1 Baseline characteristics and their distribution between groups of subjects with and without cardiovascular death

Characteristic	Total (*n* = 5829)	CV Death (+) (*n* = 41)	CV Death (-) (*n* = 5788)	*p*
Age, years, median [IQR]	53.0 [49.0;58.0]	53.0 [49.0;58.0]	53.0 [49.0;58.0]	0.667
BMI, kg/m^2, median [IQR]	31.6 [28.9;34.7]	32.0 [29.9;36.2]	31.6 [28.9;34.7]	0.271
Waist circumference, cm, median [IQR]	105 [99;111]	109 [105;118]	104 [98;111]	**0.001**
TC, mmol/l, median [IQR]	6.19 [5.36;7.10]	6.36 [5.61;7.53]	6.19 [5.36;7.10]	0.190
LDL-C, mmol/l, median [IQR]	4.01 [3.24;4.78]	4.43 [3.54;4.99]	4.00 [3.24;4.78]	0.116
HDL-C, mmol/l, median [IQR]	1.16 [0.99;1.37]	1.05 [0.90;1.31]	1.16 [0.99;1.37]	**0.021**
Triglycerides, mmol/l, median [IQR]	1.88 [1.37;2.57]	2.14 [1.56;2.89]	1.88 [1.37;2.57]	0.109
Fasting serum glucose, mmol/l, median [IQR]	6.02 [5.65;6.55]	6.28 [5.76;7.21]	6.02 [5.65;6.54]	0.131
CRP, mg/l, median [IQR]	1.90 [1.02;3.71]	2.90 [1.45;5.60]	1.90 [1.01;3.70]	**0.015**
Creatinine, µmol/l, median [IQR]	70.0 [63.0;78.0]	72.0 [68.0;80.0]	70.0 [63.0;78.0]	0.051
GFR, ml/min/1.73m^2, median [IQR]	94.8 [85.3;101.0]	98.8 [84.9;103.0]	94.8 [85.3;101.0]	0.470
Smoking, n (%)				**0.001***
never smoked	4017 (68.9%)	18 (43.9%)	3999 (69.1%)	
quit smoking	400 (6.9%)	2 (4.9%)	398 (6.9%)	
< 10 cigarettes/d.	641 (11.0%)	7 (17.1%)	634 (11.0%)	
≥ 10 cigarettes/d.	768 (13.2%)	14 (34.1%)	754 (13.0%)	
	3 no value		3 no value	
Mean BP, mmHg, median [IQR]	102 [95.0;109.0]	110 [97.7;116.0]	102 [95.0;109.0]	**0.003**
AH, n (%)				0.368*
no	442 (7. %)	1 (2.4%)	441 (7.6%)	
yes	5387 (92.4%)	40 (97.6%)	5347 (92.4%)	
Familial CHD, n (%)				0.754**
no	3600 (62.1%)	24 (58.5%)	3576 (62.1%)	
yes	2195 (37.9%)	17 (41.5%)	2178 (37.9%)	
	34 no value		34 no value	
DM, n (%)				**0.018****
no	4746 (81.4%)	27 (65.9%)	4719 (81.5%)	
yes	1083 (18.6%)	14 (34.1%)	1069 (18.5%)	
Dyslipidemia, n (%)				-
no	0 (0%)	0 (0%)	0 (0%)	
yes	5829 (100%)	41 (100%)	5788 (100%)	

BMI – body mass index, TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, CRP – C-reactive protein, GFR – glomerular filtration rate, BP – blood pressure, AH – arterial hypertension, CHD – coronary heart disease, DM – diabetes mellitus, IQR – interquartile range. *p values* obtained using Wilcoxon rank-sum test, unless specified otherwise. *Fisher's exact test. **χ2-test

Table 2 Arterial markers and their distribution between groups of subjects with and without cardiovascular death

Characteristic	Total (*n* = 5829)	CV Death (+) (*n* = 41)	CV Death (-) (*n* = 5788)	*p*
aPWV, m/s, median [IQR]	8.40 [7.50;9.40]	9.40 [8.70;10.40]	8.40 [7.50;9.40]	**< 0.001**
AIXHR75, median [IQR]	24.0 [17.0;30.0]	22.0 [16.0;29.0]	24.0 [17.0;30.0]	0.544
CAVI, median [IQR]	7.70 [6.80;8.60]	8.10 [7.00;9.40]	7.70 [6.80;8.60]	**0.015**
cIMT, µm, median [IQR]	664 [600;737]	708 [643;758]	664 [599;736]	**0.013**
Carotid stiffness index, median [IQR]	4.10 [3.25;5.20]	3.95 [3.25;5.48]	4.10 [3.25;5.20]	0.775
ABI, median [IQR]	1.10 [1.03;1.15]	1.06 [0.98;1.12]	1.10 [1.03;1.15]	**0.006**
FMD, %, median [IQR]	2.59 [1.21;4.23]	2.46 [1.49;4.23]	2.59 [1.21;4.22]	0.747

aPWV – aortic pulse wave velocity, AIXHR75 – aortic augmentation index adjusted for heart rate of 75 bpm, CAVI – cardio-ankle vascular index, cIMT – carotid intima media thickness, ABI – ankle-brachial index, FMD – flow-mediated dilatation, IQR – interquartile range. *p values* obtained using Wilcoxon rank-sum test

age and gender) in subjects with MetS raises the risk of cardiovascular death by 37% (HR 1.370 [1.150–1.632], $p<0.001$; unadjusted HR 1.340 [1.138–1.578], $p<0.001$). Analyzing the relationship between CV deaths and other arterial markers revealed an increase in unadjusted risk by 28.2% for each extra unit of CAVI (HR 1.282 [1.092–1.504], $p=0.002$), an increase in unadjusted risk by 0.4% for each extra unit of cIMT (HR 1.004 [1.001–1.006], $p=0.003$), and an increase in risk by 1.4% for each decreased unit of ABI (HR 0.014 [0.001–0.183], $p=0.001$;

Table 3 The results of the Cox proportional hazard regression analysis on the significance of arterial markers and CRP for cardiovascular deaths

Marker	HR (95% CI)	*p*
aPWV (adjusted for mean arterial blood pressure)	1.340 (1.138–1.578)	**< 0.001**
aPWV (adjusted for mean arterial blood pressure, age, and gender)	1.370 (1.150–1.632)	**< 0.001**
AIXHR75	0.998 (0.970–1.027)	0.890
AIXHR75 (adjusted for age and gender)	1.019 (0.985–1.054)	0.281
CAVI	1.282 (1.092–1.504)	**0.002**
CAVI (adjusted for age and gender)	1.159 (0.990–1.358)	0.066
ABI	0.020 (0.001–0.359)	**0.008**
ABI (adjusted for age and gender)	0.014 (0.001–0.183)	**0.001**
Carotid stiffness index	1.079 (0.902–1.292)	0.405
Carotid stiffness index (adjusted for age and gender)	1.126 (0.928–1.365)	0.229
cIMT	1.004 (1.001–1.006)	**0.003**
cIMT (adjusted for age and gender)	1.003 (0.997–1.005)	0.052
FMD	1.001 (0.914 – 1.095)	0.991
FMD (adjusted for age and gender)	1.008 (0.939–1.082)	0.828
CRP	1.085 (1.047–1.125)	**< 0.001**
CRP (adjusted for age and gender)	1.085 (1.047–1.125)	**< 0.001**

aPWV – aortic pulse wave velocity, AIXHR75 – aortic augmentation index adjusted for heart rate of 75 bpm, CAVI – cardio-ankle vascular index, cIMT – carotid intima media thickness, ABI – ankle-brachial index, FMD – flow-mediated dilatation, CRP – C-reactive protein. *p values* obtained using Cox proportional hazard regression analysis

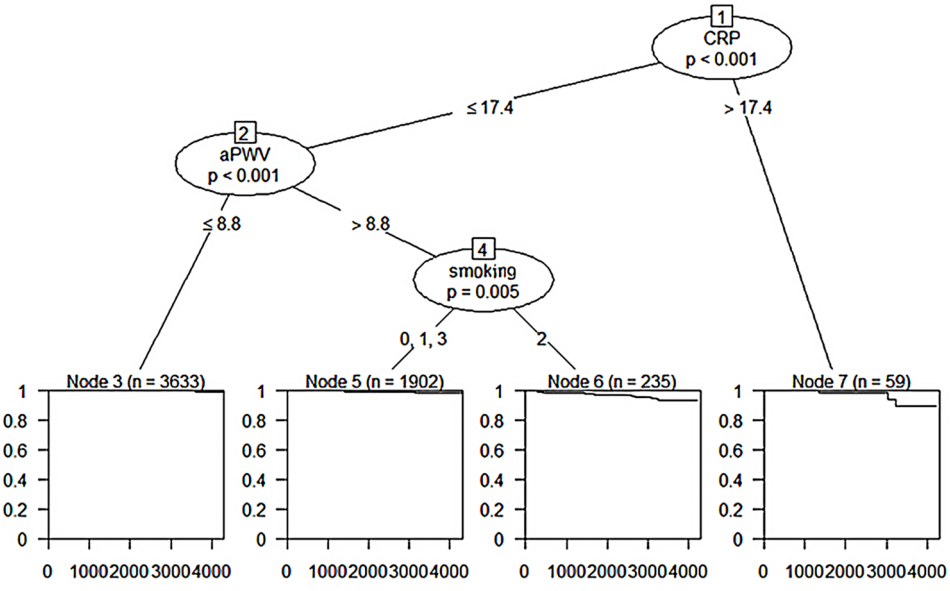

Fig. 1 Survival tree of all study participants (n – number of subjects in group, CRP – C-reactive protein, aPWV – aortic pulse wave velocity, smoking: 0 – no-smoker, 1 – <10 cigarettes per day, 2 – ≥10 cigarettes per day, 3 – quit smoking)

unadjusted HR 0.020 [0.001–0.359], $p=0.008$). Cox proportional hazard regression analysis showed no significant relationship between CV deaths and the following indices of subclinical arterial damage: AIXHR75, carotid stiffness index, and FMD (Table 3).

Survival tree analysis

Survival tree analysis revealed a slight variance in the main predictors of CV death when assessing both genders together and separately. The survival tree for all subjects showed CRP as the primary predictor (>17.4 mg/l, $p<0.001$), while aPWV was identified as the secondary predictor (>8.8 m/s, $p<0.001$), and smoking as the tertiary predictor (≥10 cigarettes/day, $p=0.005$) for lower survival rates (Fig. 1). Notably, after excluding outlier subjects with CRP levels exceeding 10 mg/l (269 subjects), aPWV emerged as the leading predictor of the CV death ($p=0.002$), followed by gender ($p=0.016$).

The survival tree for female subjects revealed a single statistically significant variable for predicting CV deaths

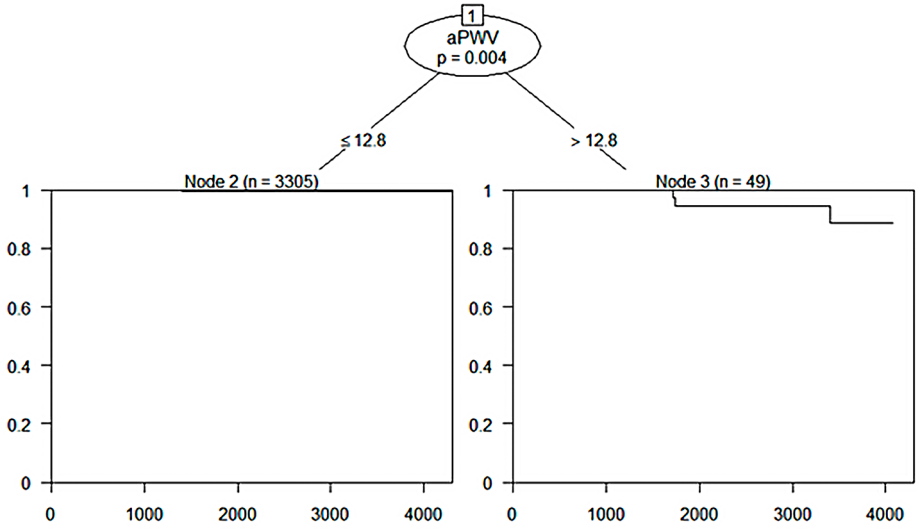

Fig. 2 Survival tree of female participants (n – number of subjects in group, aPWV – aortic pulse wave velocity)

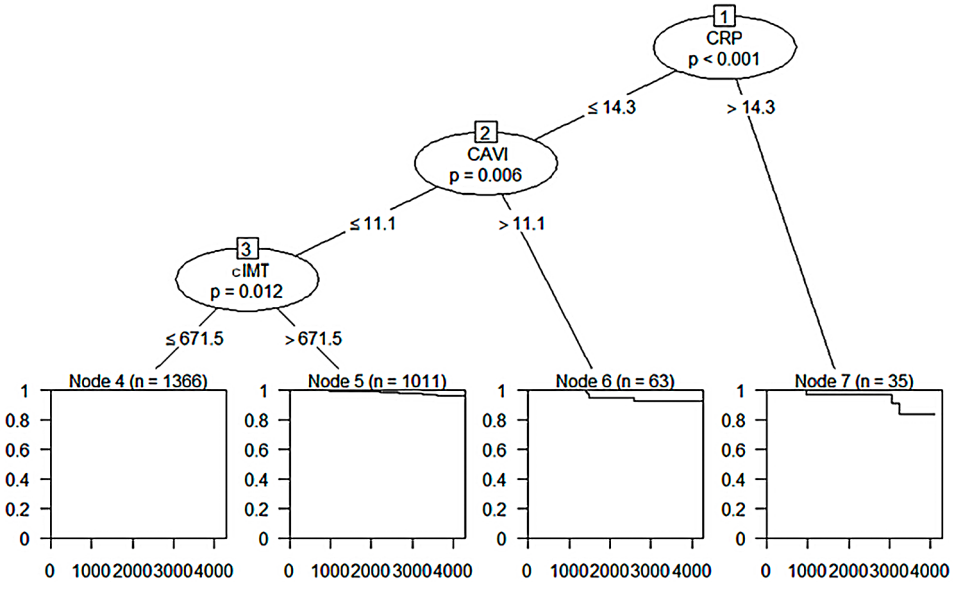

Fig. 3 Survival tree of male participants (n – number of subjects in group, CRP – C-reactive protein, CAVI – cardio-ankle vascular index, cIMT – carotid intima media thickness)

– aPWV (>12.8 m/s, $p=0.004$) (Fig. 2). In male subjects, we found a total of three predictive variables: the primary predictor for CV deaths was CRP (>14.3 mg/l, $p<0.001$), the secondary predictor was CAVI (>11.1, $p=0.006$), and the tertiary predictor was cIMT (>671.5 μm, $p=0.012$) (Fig. 3).

Discussion

The relationship between metabolic syndrome and increased mortality, particularly deaths caused by cardiovascular disease, has been identified for quite some time [22]. This association, coupled with the fact that metabolic syndrome can be diagnosed in almost one-third of the global population [9, 10, 23], underscores the importance of identifying specific predictors for cardiovascular mortality in this population. Among other predictors, the markers of subclinical arterial damage play an important role in assessing the risk of cardiovascular death in both subjects with cardiovascular disease and subjects without it. Furthermore, the predictive value of these markers is frequently shown to be independent of the traditional CV risk factors, such as blood pressure or cholesterol levels [24–26].

The American College of Cardiology Foundation and the American Heart Association currently does not recommend a routine evaluation of arterial stiffness in

asymptomatic subjects [27]. However, the latest guidelines from the European Society of Hypertension and the European Society of Cardiology now include the assessment of arterial stiffness [28]. One of the pivotal studies supporting these guidelines is the meta-analysis conducted by Vlachopoulos et al. [29], which revealed that the pooled relative risk of cardiovascular mortality for a 1 m/s increase in aortic PWV was 1.15 (95% CI: 1.09–1.21), corresponding to a 15% increase in risk. Over the past decade, numerous studies have demonstrated that aortic stiffness can be assessed using a variety of methodologies, but aPWV is currently considered to be the gold standard [19]. Several commercially available devices are accessible for evaluating aPWV in clinical settings, rendering it an appealing cardiovascular biomarker.

The results presented in this paper stand out among other studies conducted hitherto in two respects. Firstly, it provides a very comprehensive analysis, side-by-side assessing all relevant levels of subclinical arterial damage, from endothelial dysfunction to carotid wall morphology. Secondly, it is to date the largest longitudinal study of nearly 6000 middle-aged subjects with metabolic syndrome. It contributes to expanding the current state of knowledge, as most of the comparable studies analyzing the impact of arterial markers on predicting CVD death are smaller, predominantly enroll highrisk CVD populations in Asia, and focus on evaluating single arterial markers, frequently other than aPWV.

Furthermore, the other studies often fall short of demonstrating the predictive value of these markers independent of age and gender [30, 31]. For instance, Limpijankit et al. conducted a study in 2021 on CAVI as a predictor for cardiovascular events and deaths among subjects with metabolic syndrome. The results of their study revealed that MetS subjects with elevated CAVI face the highest risk of major cardiovascular events, such as myocardial infarction, stroke, or cardiovascular death, compared to subjects without MetS and those with MetS but within the normal CAVI range [30]. However, after adjusting for various risk factors, this difference became statistically insignificant ($p=0.48$). In the study by Okamoto et al., conducted in 2022, the value of CAVI was assessed for predicting cardiovascular events in subjects without established cardiovascular disease but with a number of risk factors. The results of the study indicated that the use of CAVI can enhance the prediction of cardiovascular events even after adjusting for covariates ($p=0.024$) [32]. Nevertheless, this study involved a cohort more than 13 times smaller than the cohort in the present study (5829 vs. 554 subjects), had a shorter median follow up period (6.35 vs. 4.3 years), and did not analyze the predictive value of other arterial markers, such as aPWV or cIMT. There are a few other studies examining the prognostic value of arterial stiffness in Asian population. However, they suffered from similar shortcomings, as they also assessed a single metric of arterial stiffness (CAVI) [31, 33].

Our study has affirmed the prognostic value of not only CAVI, but also of the carotid intima-media thickness for CVD, though not independently of age and gender. Carotid IMT has been proposed as a surrogate marker for coronary and peripheral artery disease, and it is recommended by guidelines for stratifying cardiovascular risk, particularly for subjects with intermediate risk [34, 35]. Other studies have also demonstrated the relationship between cIMT and increased CVD risk and mortality. For instance, a study by Timóteo et al., published in 2019, highlighted the positive effect of evaluating cIMT for subjects with hypertension, hyperlipidemia, and metabolic syndrome, as well as non-diabetic subjects, and revealed an association between increased cIMT and higher cardiovascular mortality ($p=0.084$) [36]. Similarly, a study by Wang et al., also published in 2019, demonstrated the relationship between cIMT and metabolic syndrome, as well as the association between metabolic syndrome and the increased risk for CVD mortality, independently of CVD risk factors among Chinese adults [37]. The present study complements these findings, showing that the predictive value of cIMT in the middle-aged white MetS subjects without overt CV disease is likely to be mediated by age and gender.

Finally, our finding that hsCRP was the primary predictive variable in the survival tree analysis (at least for men) aligns with earlier studies showing that inflammation plays a key role for developing subclinical arterial damage. For over two decades, there has been extensive discourse regarding the impact of inflammatory processes on the increase in cardiovascular risk and associated mortality. Numerous large-scale prospective trials, such as the Physicians' Health Study and the Women's Health Study, have shown that marginally elevated baseline levels of CRP in allegedly healthy individuals correlate with a 2-fold surge in the risk of future myocardial infarction. Notably, the prognostic efficacy of CRP remains independent from conventional risk factors, particularly elevated serum cholesterol [38–40]. Inflammatory processes disrupt the stability, rigidity, and elasticity of vascular walls, consequently impairing endothelial function and augmenting arterial stiffness [41]. Similarly, our study also revealed the association between CRP levels and CV survival rate. However, at least in subjects with CRP lower than 10 mg/l, aPWV remained the primary predictor of CV deaths.

While our study provides valuable findings, it also has some limitations. Drug usage was not taken into consideration, as all participants were part of a preventive program. Additionally, the number of events observed was limited.

Conclusions

The key contribution of this study lies in providing new evidence on predictive value of multiple arterial markers for cardiovascular mortality. It demonstrates that aPWV has an independent predictive value for CV deaths in white middle-aged MetS subjects without overt CV disease. To the best of our knowledge, it is the first follow-up study that assesses the predictive value of multiple arterial markers and affirms aPWV as the gold standard for assessing subclinical arterial damage in this population.

Abbreviations

ABI	Ankle-brachial index
AH	Arterial hypertension
AIXHR75	Aortic augmentation index adjusted for heart rate of 75 bpm
aPWV	Aortic pulse wave velocity
BMI	Body mass index
BP	Blood pressure
CAVI	Cardio-ankle vascular index
CHD	Coronary heart disease
CI	Confidence interval
cIMT	Carotid intima-media thickness
CV	Cardiovascular
CVD	Cardiovascular disease
CRP	C-reactive protein
DM	Diabetes mellitus
FMD	Flow-mediated dilatation
GFR	Glomerular filtration rate
HDL	C-high-density lipoprotein cholesterol
HR	Hazard ratio
IQR	Interquartile range
LDL	C-low-density lipoprotein cholesterol
LitHiR program	Lithuanian High Cardiovascular Risk primary prevention program
MetS	Metabolic syndrome
NCEP ATPIII	National Cholesterol Education Program Adult Treatment Panel III
PWV	Pulse wave velocity
TC	Tcholesterol

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Author contributions

A.J. and L.R. investigated, designed and directed the whole study. J.B. was involved in planning and supervised the work. A.J. and L.R. collaborated on writing the manuscript. R.P. performed all the calculations and statistical analysis and designed the figures. A.J., L.R. and J.B. performed a great part of the vascular measurements and supervised the vascular marker evaluation. All authors read and approved the final manuscript.

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Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki, received approval from the Regional Ethics Committee (Permission No. 2019/3-1104-603) and the need to obtain informed patient consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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