Clinical Epidemiology

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ORIGINAL RESEARCH

Associations Between Estimated Pulse Wave Velocity and Five-Year All-Cause Mortality in Patients with Atherosclerotic Cardiovascular Disease with and without Standard Modifiable Risk Factors: Evidence From NHANES 1999-2016

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Aim: The study aimed to analyze the associations between estimated pulse wave velocity (ePWV) and 5-year mortality in atherosclerotic cardiovascular disease (ASCVD) patients with and without standard modifiable risk factors (SMuRFs), which included smoking status, hypertension, diabetes, and hypercholesterolemia.

Methods: The present retrospective cohort study utilized data from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2016. Patients with ASCVD who completed both the questionnaire survey and serum testing were included. Patients were categorized into the ≥1 SMuRF group if they had at least one SMuRF, while those without any SMuRFs were classified into the SMuRF-less group. The ePWV, which was calculated using the age and mean blood pressure, was evenly divided into three categories: low (Q1), medium (Q2), and high (Q3). Multivariable weighted Cox proportional-hazard regression analyses were utilized to explore the risk factors associated with 5-year mortality in patients with and without SMuRFs. And restricted cubic spline curve (RCS) was used to assess their nonlinear correlation.

Results: A total of 1901 patients with ASCVD were included in the study. For the patients in ≥1 SMuRF group, the Q3 group included patients who were older, with a higher proportion of males, more comorbidities, and a lower body mass index than the Q1 group ($P<0.05$). The Cox proportional-hazard regression model results revealed, the Q3 group had a higher risk of 5-year mortality than the Q1 group [hazard ratio (HR) 4.30, 95% confidence interval (CI) (2.66, 6.95), $P<0.001$]. RCS demonstrated a linear trend between high level of ePWV and decreased risks of mortality. Similar results were observed in the SMuRF-less group [HR 10.62, 95% CI (1.22, 92.06), $P=0.032$].

Conclusion: A high level of ePWV signified a higher risk of 5-year mortality in ASCVD patients with and without SMuRFs.

Keywords: atherosclerotic cardiovascular disease, standard modifiable risk factors, estimated pulse wave velocity, all-cause mortality

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is caused by plaque buildup in arterial walls and refers to conditions that include coronary artery disease (CAD) and stroke, and it remains a leading cause of the global burden of morbidity and mortality.[1–3] The prevention and treatment of cardiovascular disease has always been in the spotlight. The Framingham Heart

Received: 1 February 2024
Accepted: 16 May 2024
Published: 28 May 2024

Study (FHS) first described four standard modifiable risk factors (SMuRFs), including smoking status, hypertension, diabetes, and hypercholesterolemia.[4] This milestone research has enhanced primary healthcare for patients with ASCVD, emphasizing the identification and management of SMuRFs as effective measures for improving prognosis.[5] In 2021, modifiable risk factors recommended by the European Society of Cardiology (ESC) in patients with ASCVD were defined as high nonHDL-cholesterol, high blood pressure, cigarette smoking, and diabetes. The systematic coronary risk estimation 2 (SCORE 2) and SCORE 2-older persons risk charts have been designed to assess the risk of fatal and non-fatal (myocardial infarction, stroke) cardiovascular disease, based on age, sex, nonHDL-cholesterol, blood pressure and smoking status.[6] Most cardiovascular disease cases and mortality can be attributable to these common SMuRFs globally.[7] However, even with stringent control of these factors, cardiovascular disease remains a leading cause of mortality worldwide.[8] This suggests that there may be potential risk factors that are currently unknown affecting the prognosis of cardiovascular diseases.

Recent studies have revealed a significant proportion of patients without any SMuRFs (SMuRF-less) in clinical practice.[9] The ASCVD patients with SMuRF-less have similar risk of future adverse cardiovascular events and mortality with those with ≥1 SMuRF.[10,11] And many of them are not aware that their underlying coronary atherosclerosis had occurred until a heart attack occurs.[12] Although these patients are traditionally perceived as low-risk groups, face a worse prognosis with a higher mortality rate compared to those with at least one SMuRF (≥1 SMuRF), particularly in patients with CAD.[13] The increase in the number of ASCVD patients with SMuRFs-less and their high mortality may be attributed to the currently unidentified risk factors. It is urgent to find a new biomarker to effectively identify the prognosis of patients at high risk, providing an evidence-based foundation for subsequent treatment and prevention strategies.

Arteriosclerosis plays a crucial role in the occurrence and progression of ASCVD.[14] Early vascular aging is considered a significant contributor to arteriosclerosis and an independent predictor of future cardiovascular events in patients with ASCVD.[15,16] Carotid-femoral pulse wave velocity (cfPWV), which is measured using specialized equipment, is the gold standard for assessing vascular stiffness and aging.[17] However, due to equipment and location limitations, estimated pulse wave velocity (ePWV) has emerged as a more cost-effective and readily available alternative for measuring vascular aging using age and mean arterial blood pressure (MAP) equations. The ePWV has been shown to have similar predictive value for arterial stiffness with that of cfPWV, making it a reasonable substitute.[18,19] Previous studies have demonstrated that ePWV independently predicted cardiovascular events and all-cause mortality in individuals beyond the Framingham Risk Score.[20] Nevertheless, the associations between ePWV and mortality in ASCVD patients with and without SMuRF remains unclear, particularly in terms of the potential clinical predictive value in the relatively low-risk patients with ASCVD in SMuRFs-less.

Therefore, the present study aimed to investigate the relationship between ePWV and 5-year mortality in patients with ASCVD with or without SMuRFs using nationally representative data provided by the National Health and Nutrition Examination Survey (NHANES).

Methods

Data Source and Study Population

NHANES database is a population-based cross-sectional survey program carried out by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS). Initiated in 1999 and conducted every 2 years, the program aims to assess the health and nutritional status of both adults and children in the United States. Through interview surveys, physical examinations, and laboratory tests, this study collects detailed demographic information and conducts long-term follow-ups. On the NHANES homepage, all the data were freely available and with unrestricted re-use permitted via an open license (http://www.cdc.gov/nchs/nhanes.htm). All NHANES protocols have received approval from the NCHS Ethics Committee (National Center for Health Statistics, 2012) and written informed consent has been obtained from all participants. This study was exempted from approval by the Institutional Review Board of 920th Hospital of Joint Logistics Support Force, PLA, as the use of deidentified and open access data does not constitute human subject research.

The present study collected population data between 1999 and 2016 from the NHANES. Patients with ASCVD were defined as individuals whose responses in the NHANES questionnaire indicated a "yes" to either of the following questions: "Has a doctor or other health professional ever told you that you had stroke?", "Has a doctor or other health professional ever told you that you had a heart attack also called myocardial infarction?", "Has a doctor or other health

professional ever told you that you had coronary heart disease?" and "Has a doctor or other health professional ever told you that you had angina also called angina pectoris?". This method of identifying patients with ASCVD has been adopted in previous studies.[21–24] The data for 5168 patients with ASCVD were analyzed in NHANES (Figure 1). The analysis excluded 2042 patients with incomplete medical histories and 65 patients lacking ePWV records, ultimately including 1901 patients with ASCVD with complete data.

Definition of ≥1 SMuRF and SMuRF-Less

SMuRF refers to the presence of at least one of the following conditions: current smoking status (whose responses in the NHANES questionnaire indicated a "Every day"or 'Some days' to the questions: Do you now smoke cigarettes?), hypertension (having a previous diagnosis of hypertension, previous or ongoing antihypertensive pharmacotherapy?), diabetes (has a doctor or other health professional ever told you that you had diabetes?), and hypercholesterolemia (previous or ongoing oral low-density lipoprotein cholesterol (LDL-C)-lowering treatment, LDL-C concentration of ≥3.5 mmol/L, or total cholesterol concentration of ≥5.5 mmol/L).[13] SMuRF-less was defined as the absence of any of these SMuRFs.

Calculation of ePWV

The ePWV was calculated based on the patient's age and mean blood pressure (MBP) using the following equation:[18]

$$\mathrm{ePWV} = 9.587 - 0.402 \times \mathrm{age} + 4.560 \times 10^{-3} \times \mathrm{age}^2 - 2.621 \times 10^{-5} \times \mathrm{age}^2 \times \mathrm{MBP} + 3.176 \times 10^{-3} \times \mathrm{age} \times \mathrm{MBP} - 1.832 \times 10^{-2} \times \mathrm{MBP}$$

In the NHANES, each participant's systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times, and the mean of these three measurements was used to calculate the final SBP and DBP values. MBP was then calculated as DBP+0.4 (SBP-DBP).[25] The collected ePWV values were divided into three equal categories and categorized as low (Q1), medium (Q2), and high (Q3).

The Collection of Survival Data

The NCHS has linked data collected from several NCHS population surveys with death certificate records from the National Death Index (NDI). We used the International Classification of Diseases 10th Revision to determine the all causes mortality (010).[26] The definition of all-cause mortality included all kinds of deaths which derived from NDI data

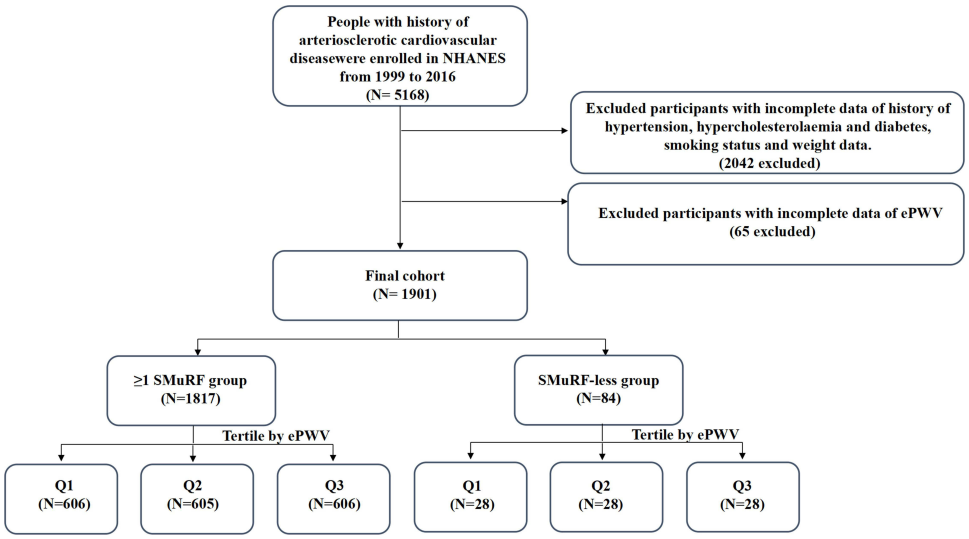

Figure 1 The flow chart of inclusion and exclusion.
Abbreviations: ePWV, estimated pulse wave velocity; SMuRF, standard modifiable risk factor; Q1, low ePWV group; Q2, medium ePWV group; Q3, high ePWV group.

(coding by International Classification of Diseases). Our study's primary endpoint was 5-year all-cause mortality. The 5-year mortality information from the NHANES updated until 2021. Thus, patients with ASCVD enrolled after 2016 were excluded due to lack of 5-year mortality information.

Assessment of Covariates

In the population data obtained from NHANES between 1999 and 2016, baseline information collected from family interviews and physical examinations included age, sex (male/female), race (non-hispanic white/other), smoking status (no, former, current), body mass index (BMI; calculated as weight divided by height), and blood pressure. Medical history data obtained from questionnaire surveys included status information for hypertension (yes or no), diabetes mellitus (yes or no), hypercholesterolemia (yes or no), congestive heart failure (yes or no), stroke (yes or no), cancer (yes or no), and chronic obstructive pulmonary disease (COPD) (yes or no). Please refer to the NHANES Laboratory Testing Manual (http://www.cdc.gov/nchs/nhanes.htm) for detailed guidelines and methods related to the applicable laboratory data. The collected laboratory examination data included levels of total cholesterol (TC), LDL-C, high-density lipoprotein-cholesterol (HDL-C), white blood cells (WBCs), and C-reactive protein (CRP). These covariates were selected because they were considered clinically relevant as confounders in the association between cardiovascular and metabolic outcomes.

Statistical Analysis

Statistical analyses in the present study were performed using IBM SPSS Statistics (v26.0; IBM, Armonk, NY) and R (Version 4.3.0) software packages. All statistical procedures were conducted following the guidelines outlined by the CDC. Due to the complex, stratified, multi-stage sampling design of NHANES, appropriate sample weights were applied based on the NCHS analysis guidelines. This ensured that the samples was nationally representative. Weighted samples reflected the characteristics of the US population, while unweighted samples showed the characteristics of the registered population. Continuous variables with a normal distribution were presented as the mean [standard deviation (SD)], while those without a normal distribution were described as the median [interquartile range (IQR)]. Weighted Student's *t*-test, weighted Wilcoxon rank sum test, and weighted chi-square test were used to evaluate baseline and ePWV characteristics at different levels. Univariable and multivariable weighted Cox proportional-hazard regression analyses were utilized to explore the associations between ePWV and five-year mortality in patients with ASCVD in the ≥1 SMuRF and SMuRF-less groups. Weighted Kaplan-Meier analysis was used to examine the difference in 5-year mortality among patients in the ≥1 SMuRF and SMuRF-less groups across various levels of ePWV. Weighted Cox proportional hazards regression models with restricted cubic splines and smooth curve fitting (penalized spline method) were conducted to explore association between ePWV and all-cause mortality in patients in the ≥1 SMuRF and SMuRF-less groups. If the relationship was nonlinear, we estimate the threshold value by trying all possible values and choosing the threshold point with the highest likelihood. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

The flow chart for inclusion and exclusion criteria was shown in Figure 1. A total of 1901 patients with ASCVD with complete data from NHANES were analyzed in the present study, including 1817 patients with ≥1 SMuRF and 84 patients with SMuRF-less. Table 1 showed the characteristics of the total ASCVD population included in the study. The mean age of these patients was 66.75±12.61 years, and most of them were male (58.1%) and non-hispanic white (58.3%). The mean value of BMI was 29.76 ±6.64kg/m^2, and the mean value of ePWV was 10.55±2.19. After assigning statistical weights, the total number of patients with ASCVD in the US was 16,583,797, including 15,811,897 patients with ≥1 SMuRF and 771,900 patients with SMuRF-less (Supplementary Table 1).

Clinical Characteristics of Patients with ASCVD in ≥1 SMuRF and SMuRF-Less Groups at Different ePWV Levels

Table 2 showed the clinical characteristics of patients with ASCVD who were divided into three equal groups based on their ePWV levels in the ≥1 SMuRF and SMuRF-less groups. Our results showed that in the ≥1 SMuRF group, compared with the low ePWV (Q1) group, the high ePWV (Q3) group were older (78.11±4.92 vs 54.57±9.88, P<0.001) and had a higher proportion of male (58.3% vs 52.8%, P=0.001), higher percentage of non-Hispanic white individuals (70.1% vs 49.5%, P<0.01), lower BMI values (27.94±5.21 vs 31.18±7.58, P<0.01), higher HDL-C levels (1.36±0.43 vs 1.25±0.40, P<0.01), and higher percentage of those with cancer history (29.5% vs 12.1%, P<0.001). In addition, in the SMuRF-less group, the Q3 group was older (80.25±4.42 vs 38.36±10.38, P<0.001) and had a higher proportion of male (78.6% vs 28.6%, P<0.001), higher percentage of non-Hispanic white individuals (82.1% vs 50%, P=0.025), lower BMI values (24.58±4.59 vs 27.55±4.90, P=0.003), and higher percentage of those with COPD history (17.9% vs 0%, P=0.023) than the Q1 group. There was no statistically significant difference in other parameters across these groups (P>0.05). Similar results were still observed in the weighted data analysis (Supplementary Table 2).

The Associations Between ePWV and 5-Year Mortality in Patients with ASCVD in ≥1 SMuRF and SMuRF-Less Groups

In the restricted cubic spline model, a linear trend was observed between higher ePWV and increased risks of all-cause mortality among patients with ASCVD in ≥1 SMuRF (Figure 2A) and SMuRF-less groups (Figure 2B). It revealed that higher levels of ePWV was associated with an increased risk of 5-year mortality among patients with ASCVD both in ≥1 SMuRF and SMuRF-less groups.

Table 1 Characteristics of the Study Patients

Variable	Total (N=1901)
Age (mean (SD))	66.75 (12.61)
Sex, n (%)	
Female	796 (41.9)
Male	1105 (58.1)
BMI (mean (SD))	29.76 (6.64)
Race, n (%)	
Non-Hispanic White	1108 (58.3)
Other	793 (41.7)
ePWV (mean (SD))	10.55 (2.19)
Congestive heart failure, n (%)	403 (21.5)
Stroke, n (%)	715 (37.7)
Cancer, n (%)	378 (19.9)
COPD, n (%)	239 (12.6)
TC (mean (SD))	4.79 (1.20)
LDL-C (mean (SD))	2.73 (1.00)
HDL-C (mean (SD))	1.31 (0.41)
WBC (mean (SD))	7.21 (3.47)
CRP (mean (SD))	0.58 (1.05)
SMuRF	
≥1 SMuRF	1817 (95.6)
SMuRF-less	84 (4.6)

Abbreviations: BMI, body mass index; ePWV, estimated pulse wave velocity; COPD, chronic obstructive pulmonary disease; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; WBC, white blood cell; CRP, C-reactive protein; SMuRF, standard modifiable risk factor.

Table 2 The Associations Between ePWV and Characteristics of the Study Patients in the ≥1 SMuRF and SMuRF-Less Cohort

Variable	Total (N=1817)	≥1 SMuRF			P value	Total (N=84)	SMuRF-less			P value
		Q1 (N=606)	Q2 (N=605)	Q3 (N=606)			Q1 (N=28)	Q2 (N=28)	Q3 (N=28)	
Age (mean (SD))	67.05 (12.17)	54.57 (9.88)	68.48 (6.49)	78.11 (4.92)	<0.001	60.11 (18.85)	38.36 (10.38)	61.71 (7.13)	80.25 (4.42)	<0.001
Sex, n (%)					0.001					<0.001
Female	761 (41.9)	286 (47.2)	222 (36.7)	253 (41.7)		35 (41.7)	20 (71.4)	9 (32.1)	6 (21.4)	
Male	1056 (58.1)	320 (52.8)	383 (63.3)	353 (58.3)		49 (58.3)	8 (28.6)	19 (67.9)	22 (78.6)	
BMI (mean (SD))	29.86 (6.66)	31.18 (7.58)	30.40 (6.51)	27.94 (5.21)	<0.001	27.44 (5.84)	27.55 (4.90)	29.97 (6.69)	24.58 (4.59)	0.003
Race, n (%)					<0.001					0.025
Non-Hispanic White	1056 (58.1)	300 (49.5)	331 (54.7)	425 (70.1)		52 (61.9)	14 (50.0)	15 (53.6)	23 (82.1)	
Other	761 (41.9)	306 (50.5)	274 (45.3)	181 (29.9)		32 (38.1)	14 (50.0)	13 (46.4)	5 (17.9)	
Congestive heart failure, n (%)	392 (21.9)	129 (21.5)	136 (22.8)	127 (21.4)	0.801	11 (13.1)	2 (7.1)	5 (17.9)	4 (14.3)	0.481
Stroke, n (%)	682 (37.7)	228 (37.7)	212 (35.2)	242 (40.1)	0.204	33 (39.3)	12 (42.9)	10 (35.7)	11 (39.3)	0.861
Cancer, n (%)	365 (20.1)	73 (12.1)	113 (18.7)	179 (29.5)	<0.001	13 (15.5)	3 (10.7)	3 (10.7)	7 (25.0)	0.233
COPD, n (%)	233 (12.8)	76 (12.5)	94 (15.5)	63 (10.4)	0.027	6 (7.1)	0 (0.0)	1 (3.6)	5 (17.9)	0.023
TC (mean (SD))	4.81 (1.22)	4.89 (1.24)	4.77 (1.21)	4.75 (1.21)	0.123	4.54 (0.55)	4.41 (0.70)	4.57 (0.47)	4.63 (0.42)	0.278
LDL-C (mean (SD))	2.73 (1.02)	2.80 (1.01)	2.71 (1.01)	2.68 (1.03)	0.111	2.63 (0.49)	2.53 (0.52)	2.68 (0.48)	2.68 (0.46)	0.438
HDL-C (mean (SD))	1.31 (0.41)	1.25 (0.40)	1.32 (0.39)	1.36 (0.43)	<0.001	1.37 (0.42)	1.44 (0.48)	1.28 (0.34)	1.39 (0.42)	0.354
WBC (mean (SD))	7.23 (3.51)	7.35 (2.14)	7.05 (2.40)	7.29 (5.17)	0.305	6.68 (2.14)	6.71 (1.93)	6.18 (2.24)	7.14 (2.19)	0.244
CRP (mean (SD))	0.56 (0.94)	0.64 (1.16)	0.55 (0.86)	0.48 (0.76)	0.061	0.94 (2.24)	0.86 (1.73)	0.93 (1.95)	1.02 (2.88)	0.970

Abbreviations: BMI, body mass index; ePWV, estimated pulse wave velocity; COPD, chronic obstructive pulmonary disease; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; WBC, white blood cell; CRP, C-reactive protein; SMuRF, standard modifiable risk factor. Bold values represent significant p values.

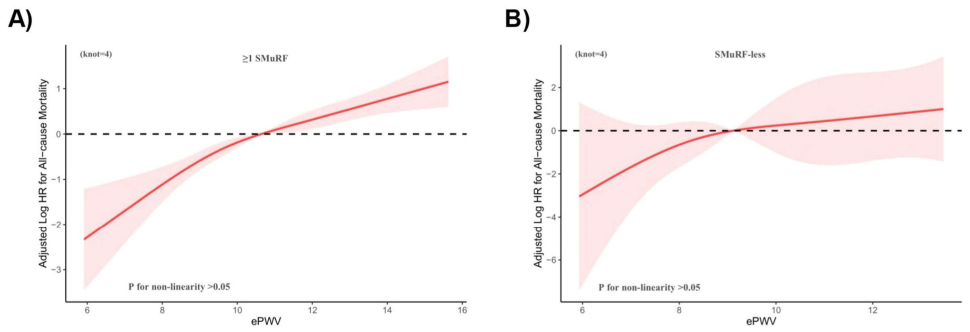

Figure 2 Association between ePWV and 5-year all-cause mortality in ASCVD patients with ≥1 SMuRF (**A**) and SMuRF-less (**B**). The solid line and red area represent the estimated values and their corresponding 95% CIs, respectively. (ePWV, estimated Pulse Wave Velocity; SMuRFs, Standard modifiable risk factors).

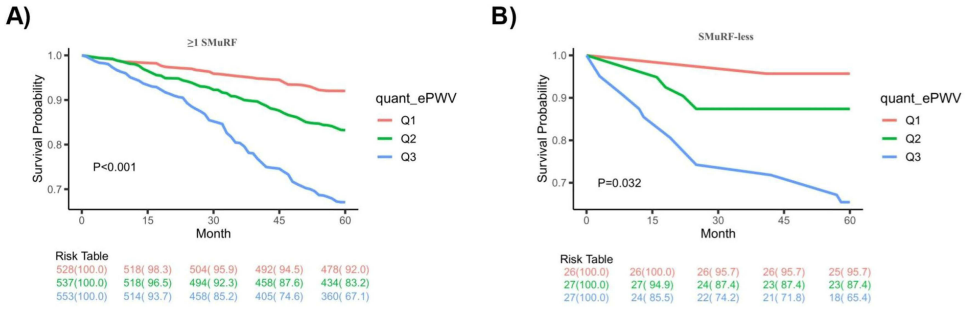

Figure 3 In the ≥1 SMuRF (**A**) and SMuRF-less groups (**B**), the 5-year all-cause mortality for different groups based on the level of ePWV. (ePWV, estimated Pulse Wave Velocity; SMuRFs, Standard modifiable risk factors).

Kaplan-Meier analysis revealed significant differences in the 5-year mortality between the Q3 and Q1 group among patients with ASCVD in the ≥1 SMuRF group (P<0.001; Figure 3A). It revealed a decreasing trend in 5-year all-cause mortality among patients with ASCVD with an increase in ePWV. Similar results were observed in patients with ASCVD in the SMuRF-Less group (P=0.032; Figure 3B).

In ASCVD patients with ≥1 SMuRF, univariable Cox proportional-hazard regression analysis (Crude model) revealed that higher level of ePWV (hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.29–1.47, P<0.001) were associated with the 5-year mortality. The Q3 group exhibited a significantly higher five-year mortality risk than the Q1 group (P<0.001). After adjusting for race and BMI (Model 1), the Q3 group had a higher five-year all-cause mortality risk than the Q1 group (P<0.001). After adjusting for race, BMI, congestive heart failure, stroke and cancer (Model 2), the Q3 group still showed a significantly higher five-year mortality risk than the Q1 group (P<0.001) (Table 3).

In ASCVD patients with SMuRF-less, univariable Cox proportional-hazard regression analysis (Crude model) indicated that higher level of ePWV (HR 1.44, 95% CI 1.16–1.80, P=0.001) were associated with the five-year mortality. The Q3 group had a significantly higher five-year mortality risk than the Q1 group (P=0.028). After adjusting for race and BMI (Model 1), the Q3 group had a higher five-year all-cause mortality risk than the Q1 group (P=0.032). Even after adjusting for race, BMI, congestive heart failure, stroke and cancer (Model 2), the Q3 group continued to exhibit a higher 5-year mortality risk than the Q1 group (P=0.032) (Table 3).

Discussion

In the present study, ePWV was independently associated with 5-year all-cause mortality in patients with ASCVD regardless of the presence of SMuRFs. Moreover, the 5-year all-cause mortality increased as the ePWV level increased. Our findings had important clinical significance because they described a convenient, practical, and superior index for assessing arterial stiffness. The higher ePWV level still signified a poorer 5-year all-cause mortality, particularly for

Table 3 Unadjusted and Adjusted Cox Proportional Regression Model of ePWV with 5-Year Mortality in the Patients with ≥1 SMuRF and SMuRF-Less

	Crude Model		Model 1		Model 2	
Character	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
≥1 SMuRF						
ePWV	1.38 (1.29,1.47)	<0.001	1.38 (1.29,1.48)	<0.001	1.35 (1.25,1.45)	<0.001
ePWV (Tertile)						
Q1	ref	ref	ref	ref	ref	ref
Q2	2.20 (1.34,3.63)	0.002	2.38 (1.43,3.97)	<0.001	2.33 (1.38,3.94)	0.001
Q3	4.79 (3.11,7.37)	<0.001	4.80 (3.04,7.58)	<0.001	4.30 (2.66,6.95)	<0.001
SMuRF-less						
ePWV	1.44 (1.16,1.80)	0.001	1.43 (1.12,1.83)	0.004	1.54 (1.05, 2.26)	0.026
ePWV (Tertile)						
Q1	ref	ref	ref	ref	ref	ref
Q2	3.12 (0.35,28.22)	0.310	2.24 (0.20,24.59)	0.509	2.57 (0.23,29.10)	0.446
Q3	9.71 (1.28,73.62)	0.028	7.74 (1.19,50.38)	0.032	10.62 (1.22,92.06)	0.032

Notes: Crude model: univariable model; Model 1 adjusted for race, BMI; Model 2 adjusted for race, BMI, congestive heart failure, stroke, cancer. Bold values represent significant p values.

Abbreviations: BMI, body mass index; ePWV, estimated pulse wave velocity; SMuRF, standard modifiable risk factor; HR, Hazard ratio; CI, Confidence interval.

patients with ASCVD in the SMuRF-less group who were traditionally considered to be at low risk. Such patients required a similar level of attention in clinical practice in order take the necessary secondary prevention measures.

With the advancements in modern medical technology, a considerable number of patients with early-stage ASCVD have been detected. Based on the modifiable risk factors of ASCVD (smoking status, hypertension, diabetes, and hypercholesterolemia), the risk charts have been developed for the early prevention and future risk assessment of ASCVD, including the Framingham General Cardiovascular Risk Score (FGCRS) in the United States, the SCORE 2 in Europe and China's Prediction for ASCVD Risk model (China-PAR), etc.[27] They all indicated that the presence of more SMuRFs in patients with ASCVD indicated a higher health risk in the future. However, there was a lack of effective methods for predicting future cardiovascular risk in individuals without SMuRF. A study based on 14 international randomized clinical trials of coronary heart disease (CHD) revealed that around 90% of patients with CHD had at least one SMuRF,[5] which was broadly consistent with the present research findings (95.6%). However, recent research has identified an increasing trend in the proportion of SMuRF-less patients with CAD in recent years, which can possibly be attributed to the advancements in medical care and heightened public health awareness.[9] Our results showed that older male were more likely to have a high level of ePWV, particularly among those with SMuRF-less. It indicated that older male may have a higher cardiovascular risk in future even without any traditional risk factors. This was consistent with the results of a community survey in China.[28]

Arteriosclerosis causes irreversible cardiovascular damage over time and has risk factors similar to ASCVD.[29] Increased arterial stiffness has been shown to predict future cardiovascular events and improve cardiovascular risk stratification.[30] Previous studies have found that SMuRF-less patients with CAD had a similar progression of coronary artery calcification and a higher incidence of major adverse cardiovascular events (MACEs) and mortality than those with ≥1 SMuRF.[31,32] Therefore, the traditional risk assessment methods for ASCVD may miss the diagnosis of high risk patients. Several previous studies recommend incorporating ePWV as a noninvasive biomarker to assess atherosclerosis into existing cardiovascular risk prediction models in order to enhance their accuracy.[18,33,34] The present study found that ePWV was an independent predictor of all-cause mortality over the course of 5 years in ASCVD patients with ≥1 SMuRF and SMuRF-less. These findings were consistent with those described in the study by Chen et al, which included patients with CAD.[35] The present study was also in line with the findings described in the study by Laugesen et al, which analyzed patients with stable angina undergoing elective coronary angiography.[36] These researches suggested that high levels of ePWV were associated with a poorer prognosis. Our

study further confirmed the importance of ePWV in detecting prognosis of cardiovascular disease. However, our study focused more on patients with SMuRF-less at a relatively lower-risk, and aimed to identify potential indicators beyond SMuRFs used to predict mortality of patients with SMuRF-less. Measure should be taken towards identifying individuals at increased cardiovascular risk in the asymptomatic subclinical stages to prevent the progression of disease.[37] The present study revealed that an elevated level of ePWV had higher risk of the 5-year all-cause mortality in ASCVD patients with SMuRFs-less, similar results were observed in ASCVD patients with ≥1 SMuRF. Therefore, even in the absence of traditional risk factors, ePWV can be used to assess risk stratification in ASCVD patients in clinical practice. This provides an efficient and convenient means of risk assessment for individual patients, clinicians, healthcare policy makers, and society to reduce the future burden of cardiovascular disease.

Despite its significant findings, there were still some limitations in the present study. First, the analysis results only suggested an association between ePWV and the overall mortality rate in patients with ASCVD with or without SMuRFs. Further prospective data are needed to validate this causal relationship. Second, the present study was designed to assess fatal events. Therefore, the effect of ePWV on non-fatal MACEs and other prognostic events was not examined. Third, Atherosclerosis was an inflammatory disease of blood vessels, and although our study compared the difference of CRP at different ePWV levels, the high sensitivity CRP seems to be a more effective predictor of pathological PWV values.[38] Fourth, the present study data were derived from the NHANES database of American adults. Whether the study results are applicable to other populations with different economic and geographic characteristics requires further research to evaluate. Finally, despite the adjustment for relevant confounding factors, the possibility of unadjusted potential confounders that might be correlated remains. For example, lifestyle (sedentary lifestyle, physical activity, diet, pressure), social background, family history, noise pollution and chronic kidney disease have all been reported to be associated with the development of atherosclerosis.[39,40] Therefore, studies with larger sample sizes and more variables are necessary for further research to establish the relationship between ePWV and all-cause mortality in patients with ASCVD with or without SMuRFs.

Conclusion

In conclusion, elevated level of ePWV predicted a higher 5-year all-cause mortality in patients with ASCVD regardless of the presence of SMuRFs. Patients with SMuRF-less, who were at a relatively low risk in the current prognostic risk stratification of ASCVD, should be carefully monitored for their ePWV levels. It can identify the population at high risk early and utilize necessary treatment strategies to improve their prognosis.

Abbreviations

ePWV, estimated Pulse Wave Velocity; ASCVD, Atherosclerotic cardiovascular disease; SMuRFs, Standard modifiable risk factors; MBP, Mean blood pressure; HR, Hazard ratio; CI, Confidence interval; RCS, restricted cubic spline curve.

Data Sharing Statement

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

All NHANES protocols have received approval from the NCHS Ethics Committee (National Center for Health Statistics, 2012) and written informed consent has been obtained from all participants. This study was exempted from approval by the Institutional Review Board of 920th Hospital of Joint Logistics Support Force, PLA, as the use of deidentified and open access data does not constitute human subjects research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Science and Technology Department of Yunnan Province (202101AY070001-030) and the 920th Hospital of Joint Logistics Support Force, PLA (2020YGD11).

Disclosure

The authors report no conflicts of interest in this work.

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