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Association between hemoglobin, albumin, lymphocyte, and platelet scores and all-cause and cardiovascular mortality among adults with atherosclerotic cardiovascular disease in the United States

An analysis of NHANES

Yanan Zou, MM[a], Jing Cong, MM[a], Jixin Fu, MD[b], Xiao Yang, MM[a,*]

Abstract

Atherosclerotic cardiovascular disease (ASCVD) remains the foremost cause of mortality in the United States. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score, a straightforward and economical indicator, combines inflammatory and nutritional status. However, its association with ASCVD incidence and long-term mortality is uncertain. We conducted a cross-sectional study using US National Health and Nutrition Examination Survey data from 1999 to 2020, with mortality data collected until December 31, 2019, via the National Death Index. Weighted multivariable logistic regression was employed to assess the association between HALP scores and ASCVD prevalence. Kaplan–Meier analyses and weighted multivariate-adjusted Cox analyses were utilized to examine the relationship between HALP scores and all-cause and cardiovascular disease (CVD) mortality among patients with ASCVD. Restricted cubic spline curve (RCS) analysis was used to identify nonlinear relationships, and multisubgroup and sensitivity analyses were conducted to ensure the robustness of the results. This cohort study comprised 41,147 participants, including 4047 with ASCVD (prevalence: 7.7%). Over a median follow-up of 85 (49, 131) months, 1726 deaths occurred among patients with ASCVD, with 575 attributed to CVD. Multivariable-adjusted modeling showed no association between HALP score and ASCVD incidence. However, multivariable-adjusted Cox regression and RCS analyses revealed a nonlinear relationship between HALP scores and all-cause mortality and CVD mortality in patients with ASCVD (all P for nonlinearity < 0.001). Higher HALP scores were significantly associated with reduced all-cause and CVD mortality in patients with ASCVD (all P for trend < 0.05). Our results indicate a significant nonlinear association between HALP scores and all-cause as well as cardiovascular mortality in patients with ASCVD. Higher HALP scores are linked to decreased all-cause mortality and CVD mortality.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, HALP score = hemoglobin, albumin, lymphocyte, and platelet score, HR = hazard ratio, NHANES = National Health and Nutrition Examination Survey, RCS = restricted cubic spline curve.

Keywords: all-cause mortality, atherosclerotic cardiovascular disease, cardiovascular disease mortality, HALP score, National Health and Nutrition Examination Survey

1. Introduction

Despite considerable advancements in therapeutic strategies and drug development, atherosclerotic cardiovascular disease (ASCVD), encompassing coronary artery disease and stroke, remains a leading global cause of mortality.[1,2] In the United States, ASCVD maintains its status as the primary cause of death, with 163.6 deaths per 100,000 individuals in 2019.[3] Globally, ASCVD accounts for approximately 17.9 million deaths annually, with myocardial infarction (MI) and stroke contributing to 85% of fatalities.[4] Ischemic heart disease and

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The datasets generated during and/or analyzed during the current study are publicly available.

The studies involving human participants were reviewed and approved by The National Center for Health Statistics (NCHS) Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

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[a] Department of Anesthesiology, Weihai Central Hospital, Qingdao University, Weihai, Shandong, China, [b] Department of Gastrointestinal Surgery, Weihai Central Hospital, Qingdao University, Weihai, Shandong, China.

** Correspondence: Xiao Yang, Department of Anesthesiology, Weihai Central Hospital, Qingdao University, No. 3, Mishandong Road Xi, Wendeng District, Weihai, Shandong 264200, China (e-mail:714447609@qq.com).*

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stroke collectively claim over 14 million lives yearly.[4] Known factors influencing ASCVD development and prognosis include age, family history of cardiovascular disease (CVD), obesity, hypertension, smoking, poor dietary habits, physical inactivity, hypercholesterolemia, and diabetes mellitus.[5–7] Nevertheless, emerging evidence suggests that individuals lacking traditional risk factors remain vulnerable to ASCVD, underscoring the urgency of identifying novel predictors for disease onset and progression.[8–10]

The inflammatory response and immune cells are fundamental components in the pathophysiology of atherosclerosis and its associated ischemic cardiovascular complications.[11] Macrophages, pivotal in acute coronary atherosclerosis, sustain local inflammation, promote plaque formation, and facilitate thrombosis across various vascular beds.[12] Elevated granulocyte counts correlate with heightened ASCVD risk and arterial calcification volume in the general population,[13] highlighting the inflammatory nature of ASCVD progression. However, chronic inflammation exacerbates proteolysis, reduces albumin levels, and induces insulin resistance, appetite suppression, impaired nutrient absorption, and subsequent weight loss.[14–16] Thus, both inflammatory and nutritional statuses play pivotal roles in assessing ASCVD development and prognosis.

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score, introduced by Chen et al[17] in 2015, initially aimed to forecast the prognosis of patients with gastric cancer, reflecting both inflammatory and nutritional status. Since its inception, the HALP score has garnered attention for its potential in predicting prognosis across various diseases. Recent research identified the HALP score as an independent prognostic factor in unresectable esophageal squamous cell carcinoma[18] and as a valuable marker for predicting overall survival in metastatic patients with non-small-cell lung cancer.[19] Moreover, it has been linked independently to cardiovascular and all-cause mortality in the general population.[20] Given the pivotal role of inflammatory and nutritional status in ASCVD development and progression, investigating the association between HALP scores and ASCVD morbidity and long-term mortality is crucial for patient management and treatment.

The objective of this study was to explore the correlation between the HALP score and the risk of all-cause and CVD mortality in patients with ASCVD. Our goal is to establish the HALP score as a valuable predictor and provide substantial insights for the treatment and management of patients with ASCVD.

2. Materials and methods

2.1. Study population

The National Health and Nutrition Examination Study (NHANES) is a cross-sectional study conducted by the National Center for Health Statistics, a division of the Centers for Disease Control and Prevention.[21] Utilizing a nationally representative stratified multistage random sample design, NHANES collects essential physiological, physical examination, and healthcare data for the US population. Ethical approval for all surveys was granted by the National Center for Health Statistics Ethics Review Board, with all participants providing informed consent. Since all data were deidentified and publicly available, ethical approval from the review board of the Weihai Central Hospital was not required. For further details, visit https://www.cdc.gov/nchs/nhanes.

In this cohort study, we analyzed data from NHANES spanning 10 cycles from 1999 to 2018, encompassing a total of 101,316 participants. We excluded individuals under the age of 20 (n = 46,235). In addition, data lacking complete blood counts and serum albumin were excluded (n = 5457). Participants lacking information on ASCVD, including coronary heart disease, angina pectoris, MI, and stroke, were also excluded (n = 3). Pregnant individuals, those without follow-up information, and participants lacking relevant covariates (age, sex, race, and body mass index [BMI]) were also excluded (n = 8474). Consequently, our final analysis comprised 41,147 individuals (Fig. 1).

2.2. Definition of HALP score

In NHANES, blood samples are collected at mobile examination centers and subsequently analyzed in laboratories. Key components contributing to the HALP score encompass hemoglobin, serum albumin, lymphocytes, and platelets. Hemoglobin, lymphocyte, and platelet levels are assessed utilizing a blood analysis device (UniCel DxH 800 analyzer), while serum albumin concentrations are determined using Roche modular P and Roche Cobas 6000 chemistry analyzers. The HALP score calculation formula is hemoglobin (g/L) × albumin (g/L) × lymphocytes (10^9/L)/ platelets (10^9/L).[20,22]

2.3. Diagnosis of ASCVD

The outcome of our study was ASCVD, which is defined as at least 1 diagnosis of coronary artery disease, angina, heart attack, or stroke, according to the 2013 American College of Cardiology and American Heart Association Guidelines for Blood Cholesterol Treatment to Reduce Atherosclerotic Cardiovascular Risk in Adults.[23] To assess ASCVD status, we utilized the NHANES multiple choice questionnaire (MCQ160C/MCQ160D/MCQ160E/MCQ160F), which queried participants with: "Has a doctor or other health professional ever told you that you have coronary heart disease/angina/heart attack/stroke?." Individuals responding affirmatively to at least 1 of these questions were classified as having ASCVD.

2.4. Assessment of mortality

Mortality data up to December 31, 2019, were sourced from the NHANES Public Use Linked Mortality File. Causes of death were documented using the International Statistical Classification of Diseases, 10th edition (ICD-10) codes.[24] We examined both all-cause mortality and mortality attributable to CVD (ICD-10: I00-I09, I11, I13, I20-I51). The follow-up period spanned from the date of initial diagnosis to either the date of death or the study's endpoint on December 31, 2019, whichever occurred first.

2.5. Assessment of covariates

Our study's covariates encompassed age (years), sex (male or female), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other race), education (less than high school, high school, or more than high school), marital status (married/cohabiting, widowed/divorced/separated, or never married), and BMI categorized as <18.5, 18.5 to 25.0, 25.0 to 29.9, or >29.9 kg/m^2.[25] Income was determined using the poverty income ratio, classified as ≤1.0, 1.1 to 3.0, and >3.0 based on US Department of Health and Human Services recommendations. Smoking status delineated never smokers (<100 cigarettes smoked in their lifetime), current smokers, and former smokers (>100 cigarettes smoked, with cessation).[26] Drinking status was dichotomized as nondrinker or drinker (≥12 drinks in a year). Physical activity was quantified in metabolic equivalent minutes of moderate to vigorous exercise per week according to World Health Organization guidelines.[27] Diabetes mellitus was defined by self-report, physician diagnosis, or glycated hemoglobin ≥ 6.5% or fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L). Hypertension status was determined by medication use or self-reported diagnosis. In addition, complete blood count parameters, serum albumin levels, high-density lipoprotein cholesterol, and total cholesterol levels were extracted from the database.

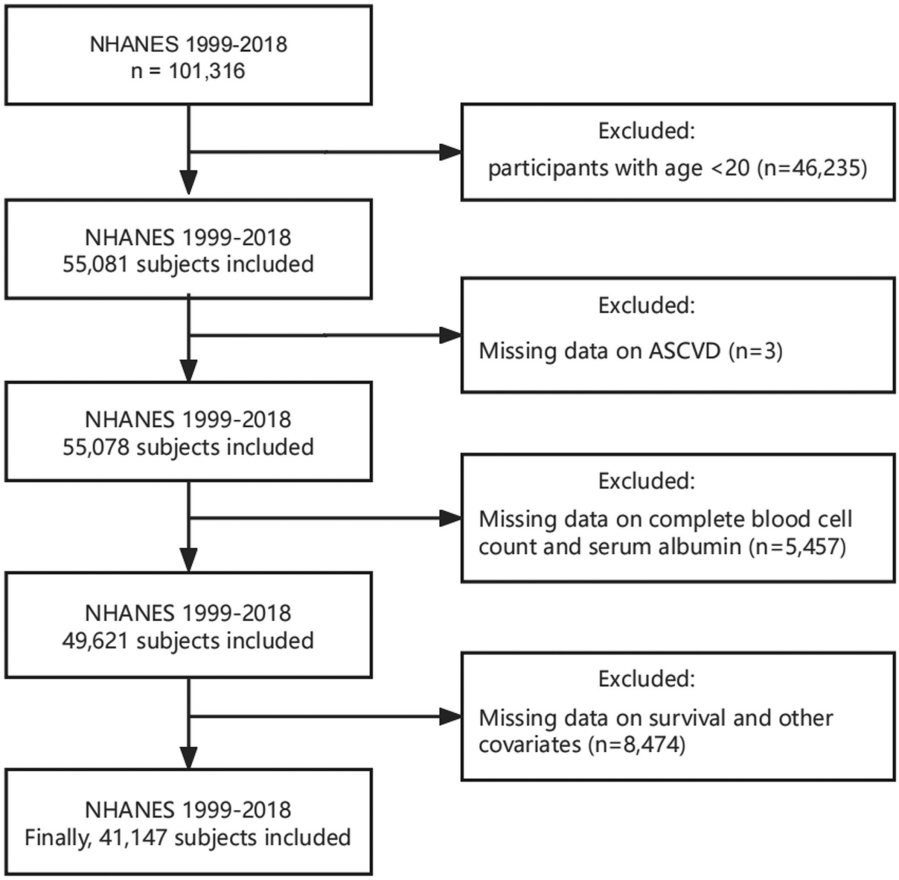

Figure 1. Flowchart of study design. NHANES = National Health and Nutrition Examination Survey.

2.6. Statistical analysis

Because HALP scores were derived from four laboratory parameters, we utilized the 2-year cycle of mobile examination center exam weights (wtmec2yr) for weighted statistical analysis. Continuous data were summarized as medians (interquartile range) and compared using the nonparametric Wilcoxon rank-sum test or independent samples *t* test, as appropriate. Categorical variables were presented as percentages (%) and evaluated using the χ^2 test or Fisher exact test, as appropriate.

Weighted logistic regression analyses were employed to assess the association between HALP scores and ASCVD incidence, presented as adjusted odds ratios with 95% confidence intervals (CIs). In addition, weighted Cox regression analyses were conducted to evaluate the relationship between HALP score and all-cause mortality as well as CVD mortality in patients with ASCVD, expressed as adjusted hazard ratios (HRs) with corresponding 95% CIs. Three models were utilized to ensure robustness: model 1, unadjusted; model 2, adjusted for age, sex, and race; and model 3, further adjusted for education level, poverty income ratio, physical activity, drinking and smoking status, BMI, self-reported diabetes, and hypertension.

We employed restricted cubic spline regression analysis to explore the nonlinear relationship between HALP scores and all-cause mortality and CVD mortality among patients with ASCVD. Knots were positioned at the 5th, 35th, 65th, and 95th percentiles for each exposure variable. In addition, Kaplan–Meier analyses were conducted to evaluate the survival correlation between HALP scores and both all-cause mortality and CVD mortality in patients with ASCVD. Furthermore, subgroup analyses were performed based on age, sex, BMI index, smoking status, self-reported hypertension, and self-reported diabetes.

We also conducted several sensitivity analyses to validate our results. Initially, we adjusted for antihypertensive and lipid-lowering medications to mitigate potential biases. Second, to address reverse causality bias, we excluded participants who died within the initial 2 years of follow-up. Lastly, to minimize the impact of cancer mortality on outcomes, individuals with a history of cancer at baseline were also excluded from the analysis.

3. Results

3.1. Baseline characteristics

Our study comprised 41,147 individuals, representing 17.03 million noninstitutionalized US residents. Table 1 presents the baseline characteristics and weighted estimates of the study population. Among them, 3786 individuals had ASCVD, ranging in age from 20 to 85 years, with a mean age of 49.35 ± 18.07 years. The racial distribution was as follows: non-Hispanic White (76%), non-Hispanic Black (10%), Mexican American (4.2%), other Hispanic (3.1%), and other (6.1%). Patients with ASCVD were predominantly older women, with lower education and income levels, higher rates of divorce, and higher prevalence of smoking and alcohol consumption. In addition, they exhibited higher BMI and waist circumference, lower physical activity, and increased prevalence of comorbid hypertension or diabetes mellitus. Notably, patients with ASCVD had lower high-density lipoprotein cholesterol and significantly higher total cholesterol compared with non-ASCVD individuals. Moreover, the median (P25, P75) values of hemoglobin, serum albumin, lymphocyte counts, platelet counts, and HALP scores in patients with ASCVD were 14.13 (13.21, 14.91), 4.20 (4.00, 4.40), 1.80 (1.52, 2.41), 232 (195, 281), and 50 (37, 65), respectively, all notably lower than those of non-ASCVD participants. Significant differences in HALP scores and related parameters were observed between ASCVD and non-ASCVD participants ($P < .05$).

Table 1

Baseline characteristics of adults in NHANES 1999 to 2018.

Characteristics	Overall, *N* = 41,147 (100%)	ASCVD		*P* value
		No, *N* = 37,100 (92%)	Yes, *N* = 4047 (7.7%)	
Sex (%)				<.001
Female	21,321 (52%)	19,592 (53%)	1729 (46%)	
Male	19,826 (48%)	17,508 (47%)	2318 (54%)	
Age (%)				<.001
20–35 years	10,755 (28%)	10,665 (30%)	90 (2.9%)	
35–60 years	16,789 (48%)	15,871 (49%)	918 (29%)	
60+ years	13,603 (25%)	10,564 (21%)	3039 (68%)	
Race/ethnicity (%)				<.001
Non-Hispanic White	18,621 (69%)	16,297 (68%)	2324 (76%)	
Non-Hispanic Black	8344 (11%)	7548 (11%)	796 (10%)	
Mexican American	7034 (8.3%)	6594 (8.6%)	440 (4.2%)	
Other race – including multiracial	3700 (6.9%)	3470 (7.0%)	230 (6.1%)	
Other Hispanic	3448 (5.2%)	3191 (5.4%)	257 (3.1%)	
Education level (%)				<.001
Below high school	10,803 (17%)	9371 (16%)	1432 (26%)	
High school	9553 (24%)	8547 (23%)	1006 (27%)	
Above high school	20,791 (59%)	19,182 (61%)	1609 (46%)	
Marital status (%)				<.001
Married/cohabiting	24,982 (64%)	22,697 (65%)	2285 (61%)	
Widowed/divorced/separated	9006 (18%)	7512 (17%)	1494 (33%)	
Never married	7159 (17%)	6891 (18%)	268 (6.3%)	
Family PIR (%)				<.001
≤1.0	7781 (13%)	6929 (13%)	852 (15%)	
1.1–3.0	19,182 (40%)	17,013 (39%)	2169 (50%)	
>3.0	14,184 (47%)	13,158 (48%)	1026 (35%)	
Smoking status (%)				<.001
Never smoker	22,341 (54%)	20,800 (55%)	1541 (37%)	
Former smoker	10,124 (25%)	8485 (23%)	1639 (40%)	
Current smoker	8682 (22%)	7815 (21%)	867 (23%)	
Drinking status (%)				<.001
Drinker	5339 (11%)	4708 (11%)	631 (15%)	
Nondrinker	35,808 (89%)	32,392 (89%)	3416 (85%)	
BMI (%)				<.001
Underweight (kg/m^2)	665 (1.6%)	605 (1.7%)	60 (1.4%)	
Normal (kg/m^2)	11,532 (29%)	10,662 (30%)	870 (21%)	
Overweight (kg/m^2)	13,928 (34%)	12,545 (34%)	1383 (34%)	
Obese (kg/m^2)	15,022 (35%)	13,288 (35%)	1734 (44%)	
Age (years)	46.0 (33.0–59.0)	44.0 (32.0–57.0)	66.0 (56.0–76.0)	<.001
Family PIR	3.00 (1.50–5.00)	3.09 (1.53–5.00)	2.21 (1.23–4.05)	<.001
BMI (kg/m^2)	28 (24–32)	28 (24–32)	29 (25–34)	<.001
Waist circumference (cm)	97 (87–108)	97 (86–108)	104 (95–115)	<.001
Self-reported hypertension (%)	14,226 (31%)	11,300 (27%)	2926 (70%)	<.001
Self-reported diabetes (%)	6102 (11%)	4668 (9.1%)	1434 (31%)	<.001
MET (min/wk)	1960 (0–5460)	2100 (0–5460)	1400 (0–4714)	<.001
Hemoglobin (g/dL)	14.28 (13.30–15.40)	14.42 (13.41–15.42)	14.13 (13.21–14.91)	<.001
Albumin (g/dL)	4.30 (4.10–4.50)	4.30 (4.10–4.50)	4.20 (4.00–4.40)	<.001
Platelet count (10^9/L)	245 (201–292)	242 (213–293)	232 (195–281)	<.001
Lymphocyte count (10^9/L)	2.01 (1.62–2.50)	2.03 (1.72–2.50)	1.80 (1.52–2.41)	<.001
HDL-C (mg/dL)	51 (41–63)	51 (41–62)	46 (35–55)	<.001
Total cholesterol (mg/dL)	194 (168–222)	190 (168–222)	198 (170–226)	.002
HALP score	51 (39–65)	51 (39–65)	50 (37–65)	.025
HALP score classification				.004
Tertile 1	13,579 (31%)	12,115 (31%)	1464 (34%)	
Tertile 2	13,578 (34%)	12,310 (34%)	1268 (32%)	
Tertile 3	13,990 (35%)	12,675 (35%)	1315 (34%)	

Continuous variables are described as medians (interquartile ranges). Categorical variables are presented as numbers (percentages). *N* reflect the study sample while percentages reflect the survey-weighted.

ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, HALP score = hemoglobin, albumin, lymphocyte, and platelet score, HDL-C = high-density lipoprotein cholesterol, MET = metabolic equivalent, NHANES = National Health and Nutrition Examination Survey, PIR = poverty income ratio.

3.2. Association between HALP score and ASCVD prevalence

The association between HALP scores and ASCVD prevalence is detailed in Table 2. In the crude model, higher HALP scores were significantly associated with reduced ASCVD prevalence, with an odds ratio of 0.86 (95% CI: 0.79–0.93; *P* for trend < .001) for the highest tertile compared with the lowest tertile. However, the significant association between HALP scores and ASCVD incidence disappeared in the multivariable-adjusted models 1 and 2, where *P* for trend was > .05 for both.

3.3. Association between HALP score and mortality

Following a median follow-up of 85 (49, 131) months, 1726 (42.65%) of the 4047 patients with ASCVD succumbed to

all-cause mortality, with 575 (14.21%) attributed to CVD. Notably, higher HALP scores were consistently linked to reduced all-cause mortality among patients with ASCVD across both crude and multivariable-adjusted models (all *P* for trend < .05). Specifically, HRs and 95% CIs for the highest tertile compared with the lowest tertile were HR = 0.56 (0.48–0.66), HR = 0.66 (0.56–0.79), and HR = 0.62 (0.52–0.74), respectively. Similarly, elevated HALP scores were significantly associated with lower CVD mortality in patients with ASCVD in both crude and multivariable-adjusted models (all *P* for trend < .05), with HRs and 95% CIs for the highest tertile compared with the lowest tertile of HR = 0.61 (0.49–0.76), HR = 0.69 (0.55–0.87), and HR = 0.66 (0.53–0.83), respectively (Table 3).

Furthermore, we conducted a comprehensive evaluation of the long-term survival association between HALP scores and both all-cause and CVD mortality in patients with ASCVD using Kaplan–Meier analysis. Illustrated in Figure 2, the Kaplan–Meier curves demonstrate a consistent trend: lower HALP scores correlate with diminished long-term survival among patients with ASCVD, evident in both all-cause mortality and CVD mortality (all *P* < .0001).

3.4. Restricted cubic spline analysis

After adjusting for multiple potential confounders, we utilized weighted RCS analysis to explore the nonlinear relationships between HALP scores and all-cause mortality as well as CVD mortality among patients with ASCVD. As depicted in Figure 3, our analysis revealed significant nonlinear associations between HALP scores and both endpoints (all *P* for nonlinearity < .001). Notably, the probability of all-cause mortality steadily declined, reaching a nadir at a HALP score of 80.43, before rising with higher HALP scores.

3.5. Subgroup analyses and sensitivity analyses

To further evaluate the robustness of the relationship between HALP score and all-cause mortality and CVD mortality in patients with ASCVD, subgroup analyses were conducted based on sex, age, BMI, smoking status, self-reported hypertension, and self-reported diabetes. Results indicated that the association between HALP score and mortality outcomes was more pronounced in patients over 60 years old, those with higher BMI, and those with comorbid hypertension or diabetes mellitus (Table 4). Moreover, no statistically significant interaction *P* values were observed.

In sensitivity analyses, we first adjusted for the use of antihypertensive and lipid-lowering medications, revealing consistent associations between higher HALP scores and reduced all-cause and CVD mortality across both crude and multivariable-adjusted models 1 and 2 (Tables S1 and S2, Supplemental Digital Content, https://links.lww.com/MD/O857). Second,

Table 2

Logistic regression analysis between HALP score and prevalence of ASCVD among adults in NHANES 1999 to 2018.

	HALP score			
	Tertile 1	Tertile 2	Tertile 3	*P* for trend
Range	<41.81	41.81–58.23	>58.23	
Crude	1.00 (Reference)	0.85 (0.79–0.92)	0.86 (0.79–0.93)	<.001
Model 1	1.00 (Reference)	0.98 (0.90–1.07)	1.08 (0.99–1.17)	.077
Model 2	1.00 (Reference)	0.97 (0.89–1.05)	0.98 (0.90–1.07)	.8

Data are presented as OR (95% CI). Model 1 was adjusted as age (continuous), MET (continuous), sex (male or female), and race/ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other). Model 2 was adjusted as model 1 plus education level (below high school, high school, or above high school), family poverty income ratio (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker and drinker), smoking status (never smoker, former smoker, or current smoker), BMI (<18.5, 18.5–25.0, 25.0–29.9, or >29.9), self-reported diabetes (yes or no), and self-reported hypertension (yes or no).

ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, CI = confidence interval, HALP score = hemoglobin, albumin, lymphocyte, and platelet score, MET = metabolic equivalent, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio.

Table 3

Cox regression analysis between HALP score with all-cause and cardiovascular disease mortality among ASCVD in NHANES 1999 to 2018.

	HALP score			
	Tertile 1	Tertile 2	Tertile 3	*P* for trend
All-cause mortality				
No. deaths/total	741/1464	503/1268	482/1315	
Crude	1.00 (Reference)	0.64 (0.55–0.75)	0.56 (0.48–0.66)	<.001
Model 1	1.00 (Reference)	0.69 (0.58–0.81)	0.66 (0.56–0.79)	<.001
Model 2	1.00 (Reference)	0.67 (0.56–0.81)	0.62 (0.52–0.74)	<.001
Cardiovascular disease mortality				
No. deaths/total	260/1464	161/1268	154/1315	
Crude	1.00 (Reference)	0.67 (0.54–0.83)	0.61 (0.49–0.76)	<.001
Model 1	1.00 (Reference)	0.72 (0.58–0.90)	0.69 (0.55–0.87)	.001
Model 2	1.00 (Reference)	0.72 (0.58–0.90)	0.66 (0.53–0.83)	<.001

Data are presented as HR (95% CI). Model 1 was adjusted as age (continuous), MET (continuous), sex (male or female), and race/ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other). Model 2 was adjusted as model 1 plus education level (below high school, high school, or above high school), family poverty income ratio (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker and drinker), smoking status (never smoker, former smoker, or current smoker), BMI (<18.5, 18.5–25.0, 25.0–29.9, or >29.9), self-reported diabetes (yes or no), and self-reported hypertension (yes or no).

ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, CI = confidence interval, HALP score = hemoglobin, albumin, lymphocyte, and platelet score, HR = hazard ratio, MET = metabolic equivalent, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio.

upon excluding ASCVD participants who died within the first 2 years of follow-up, similar results were observed (Table S3, Supplemental Digital Content, https://links.lww.com/MD/O857). Finally, after excluding participants with a history of cancer at baseline, repeated Cox regression models continued to demonstrate a significant association between higher HALP scores and decreased all-cause and CVD mortality (Table S4, Supplemental Digital Content, https://links.lww.com/MD/O857).

4. Discussion

We conducted a comprehensive cross-sectional study to investigate the association between HALP scores and ASCVD prevalence and long-term mortality in the noninstitutionalized US population from 1999 to 2018. Our findings revealed no significant association between HALP score and ASCVD prevalence after adjusting for multiple confounders. However, higher HALP scores were significantly linked to lower all-cause and CVD mortality in patients with ASCVD. This association remained robust across subgroup and sensitivity analyses. Our results underscore the potential of the HALP score as a valuable prognostic indicator for patients with ASCVD, offering critical insights for their management and treatment.

The pathogenesis of ASCVD is heavily influenced by inflammation, as supported by abundant evidence.[28–35] Initially, macrophage subpopulations infiltrate early arterial lesions, evolving into foam cells, a pivotal step in disease progression.[36] Concurrently, neutrophils and lymphocytes (T and B cells) play critical roles in plaque fate, impacting susceptibility to rupture.[37–39] Once immune cells breach the vascular wall, they release diverse mediators that compromise plaque stability. These include oxidative stress generation, matrix

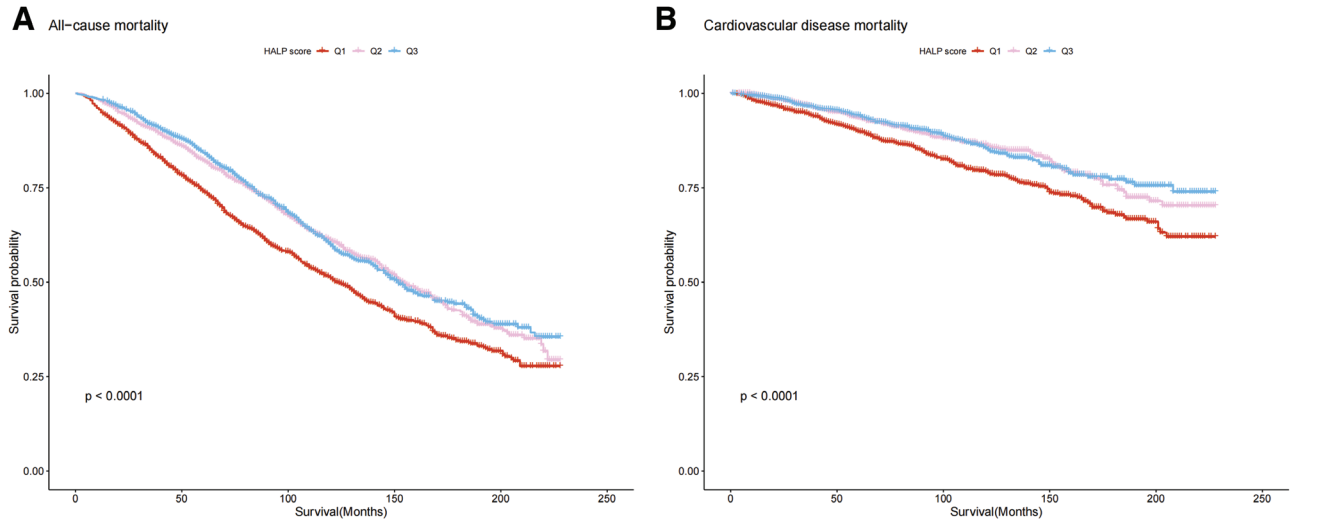

Figure 2. Kaplan–Meier survival survival estimates between HALP scores and all-cause mortality (a) and cardiovascular disease mortality (b) in patients with ASCVD. ASCVD = atherosclerotic cardiovascular disease, HALP score = hemoglobin, albumin, lymphocyte, and platelet score.

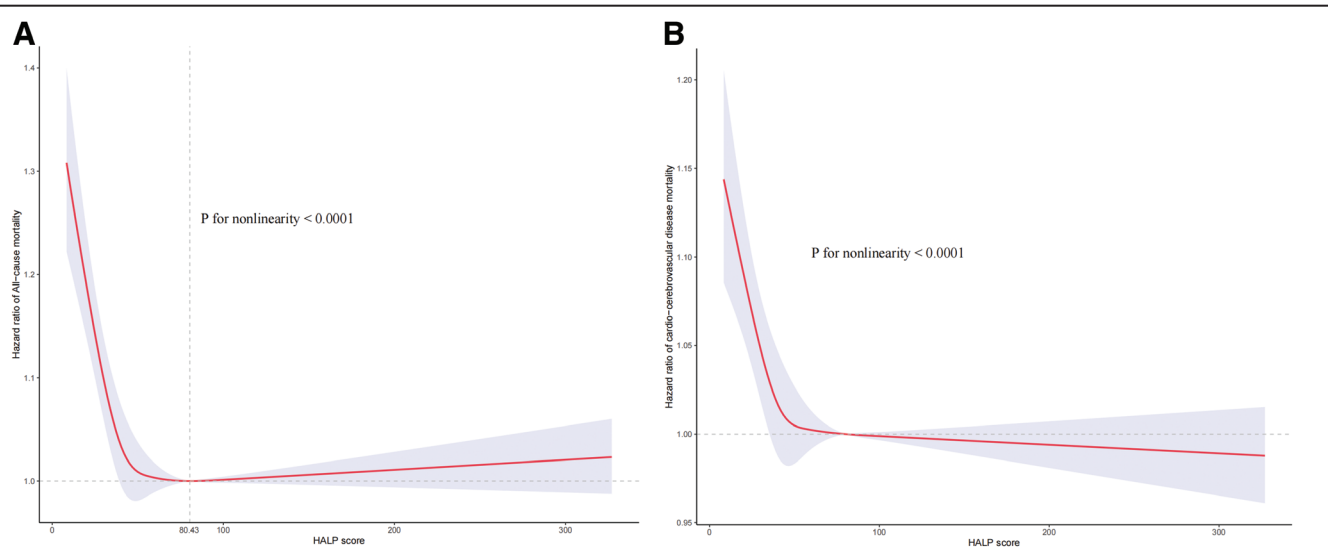

Figure 3. Restricted cubic spline analysis to assess the association between HALP score and all-cause mortality (a) and cardiovascular disease mortality (b) in patients with ASCVD. Adjusted for age (continuous), MET (continuous), sex (male or female), ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black or other), education level (below high school, high school, or above high school), family poverty income ratio (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker and drinker), smoking status (never smoker, former smoker, or current smoker), BMI (<18.5, 18.5–25.0, 25.0–29.9, or >29.9), self-reported diabetes (yes or no), and self-reported hypertension (yes or no). ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, HALP score = hemoglobin, albumin, lymphocyte, and platelet score, MET = metabolic equivalent.

degradation by collagenases (e.g., metalloproteinases and fibroblast-activating proteins), and the migration and proliferation of vascular smooth muscle cells. In addition, leukocytes may polarize toward an anti-inflammatory phenotype or deposit collagen, further influencing plaque stability.[40–43] Notably, inflammatory mediators also play a pivotal role in triggering the latest and severe thrombotic complication of atherosclerosis: plaque rupture or erosion, leading to MI and ischemic stroke.[44,45] Subsequent studies have explored the correlation between various proinflammatory mediators – including cytokines (interleukins and tumor necrosis factor α), adhesion molecules (intercellular adhesion molecule 1 and vascular cell adhesion molecule 1), and acute phase reactants (C-reactive protein, fibrinogen) – and ASCVD.[46–49] However, the outcomes have been less than satisfactory.[50,51] Given that prolonged chronic inflammation invariably results in decreased albumin levels and worsened nutritional status, it appears more rational to evaluate the prognosis of patients with ASCVD by considering both inflammatory and nutritional statuses.

The HALP score, derived from HALP levels, serves as a comprehensive indicator reflecting both the inflammatory and nutritional status of individuals. Notably, each constituent biomarker – hemoglobin, albumin, lymphocyte, and platelet levels – has demonstrated associations with CVD risk and prognosis. Hemoglobin concentrations, whether low or high, are linked to increased CVD risk and mortality,[52] while low serum albumin levels correlate with elevated risks of heart failure, hypertension, coronary artery disease, and stroke.[53] Hyperlipidemia exacerbates CVD risk and mortality and accelerates platelet turnover, making platelet counts valuable predictors of CVD risk and prognosis.[54] Furthermore, lymphocyte counts inversely correlate with inflammation, with reduced counts indicating heightened cardiovascular risk and mortality.[55,56] Given these insights, the HALP score emerges as a valuable tool for prognostication in patients with ASCVD.

While the HALP score is widely utilized for risk assessment and prognosis across various CVDs, certain areas remain contentious. Research indicates that higher HALP scores correlate

Table 4

Subgroup analysis of HALP score with all-cause and cardiovascular disease mortality among ASCVD in NHANES 1999 to 2018.

	HALP score				
	Tertile 1	Tertile 2	Tertile 3	*P* for trend	*P* for interaction
All-cause mortality					
Age (years)					.405
<60	1.00 (Reference)	0.75 (0.48–1.18)	0.68 (0.44–1.06)	.2	
>60	1.00 (Reference)	0.62 (0.52–0.75)	0.56 (0.47–0.68)	<.001	
Sex					.602
Male	1.00 (Reference)	0.72 (0.56–0.91)	0.61 (0.49–0.77)	<.001	
Female	1.00 (Reference)	0.61 (0.46–0.80)	0.63 (0.46–0.86)	<.001	
BMI					.420
<25.0	1.00 (Reference)	0.65 (0.43–0.96)	0.63 (0.42–0.95)	.033	
25.0–29.9	1.00 (Reference)	0.80 (0.59–1.10)	0.68 (0.50–0.92)	.044	
29.9	1.00 (Reference)	0.64 (0.49–0.84)	0.67 (0.51–0.88)	.002	
Smoke					.807
Yes	1.00 (Reference)	0.71 (0.57–0.89)	0.67 (0.54–0.84)	<.001	
No	1.00 (Reference)	0.61 (0.45–0.83)	0.55 (0.40–0.77)	<.001	
Diabetes					.200
Yes	1.00 (Reference)	0.55 (0.41–0.73)	0.55 (0.42–0.73)	<.001	
No	1.00 (Reference)	0.77 (0.61–0.98)	0.71 (0.55–0.90)	.012	
Hypertension					.415
Yes	1.00 (Reference)	0.67 (0.54–0.82)	0.58 (0.47–0.72)	<.001	
No	1.00 (Reference)	0.76 (0.52–1.11)	0.89 (0.61–1.29)	.4	
Cardiovascular disease mortality					
Age (years)					.632
<60	1.00 (Reference)	0.53 (0.26–1.06)	0.38 (0.19–0.77)	.023	
>60	1.00 (Reference)	0.71 (0.56–0.89)	0.66 (0.52–0.83)	<.001	
Sex					.980
Male	1.00 (Reference)	0.72 (0.54–0.96)	0.65 (0.49–0.86)	.007	
Female	1.00 (Reference)	0.72 (0.51–1.02)	0.68 (0.45–0.97)	.041	
BMI					.477
<25.0	1.00 (Reference)	0.80 (0.51–1.25)	0.84 (0.52–1.33)	.6	
25.0–29.9	1.00 (Reference)	0.89 (0.61–1.30)	0.82 (0.56–1.19)	.6	
29.9	1.00 (Reference)	0.58 (0.40–0.83)	0.56 (0.39–0.81)	.002	
Smoke					.544
Yes	1.00 (Reference)	0.71 (0.53–0.94)	0.73 (0.55–0.96)	.025	
No	1.00 (Reference)	0.73 (0.51–1.03)	0.55 (0.37–0.81)	.009	
Diabetes					.641
Yes	1.00 (Reference)	0.62 (0.43–0.88)	0.61 (0.43–0.87)	.006	
No	1.00 (Reference)	0.82 (0.61–1.090	0.78 (0.58–1.05)	.2	
Hypertension					.975
Yes	1.00 (Reference)	0.73 (0.56–0.94)	0.69 (0.54–0.90)	.007	
No	1.00 (Reference)	0.77 (0.48–1.22)	0.74 (0.46–1.19)	.4	

Data are presented as HR (95% CI), which was adjusted as age (continuous), MET (continuous), sex (male or female), race/ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other), education level (below high school, high school, or above high school), family poverty income ratio (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker and drinker), smoking status (never smoker, former smoker, or current smoker), BMI (<25.0, 25.0–29.9, or >29.9), self-reported diabetes (yes or no), and self-reported hypertension (yes or no). In addition, the corresponding subgroup analyses require the exclusion of the corresponding variables (e.g., age subgroup analyses require the exclusion of age).

ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, CI = confidence interval, HALP score = hemoglobin, albumin, lymphocyte, and platelet score, HR = hazard ratio, MET = metabolic equivalent, NHANES = National Health and Nutrition Examination Survey.

with reduced stroke risk,[22] whereas low HALP scores are linked to exacerbated cognitive symptoms in patients with acute ischemic stroke.[57] Nonetheless, the HALP score falls short in predicting the early or late prognosis of patients with acute heart failure.[58] Our cohort study extensively investigated the relationship between HALP scores, ASCVD incidence, and long-term mortality using the NHANES database. In the crude model, we found that HALP scores were negatively correlated with ASCVD incidence. However, after adjusting for key covariates, including physical inactivity, smoking, hypertension, and diabetes,[5] this correlation was no longer significant, highlighting the need for further validation of HALP scores in predicting ASCVD incidence. Importantly, we identified a significant nonlinear relationship between HALP scores and both all-cause and cardiovascular mortality in patients with ASCVD. Subgroup analyses revealed that HALP scores were particularly effective predictors of mortality in individuals over 60 years old, with higher BMI, and with comorbid hypertension or diabetes mellitus.

In our study, we observed a nonlinear relationship between HALP scores and all-cause mortality in patients with ASCVD, with the lowest mortality rate at a HALP level of 80.43. Given that HALP is derived from hemoglobin, albumin, lymphocyte count, and platelet count, previous studies support the presence of nonlinear associations between these components and mortality. For instance, a study involving 170,078 men and 122,116 women found a U- or J-shaped association between hemoglobin concentration and CVD mortality.[52] Similarly, Tsai et al[59] reported a U-shaped relationship between platelet count and CVD mortality in an elderly population. We hypothesize that a similar nonlinear relationship between hemoglobin levels, platelets, and all-cause mortality may underlie the observed pattern between HALP scores and mortality in patients with ASCVD. However, further studies are needed to confirm this hypothesis.

Our study offers several notable strengths. First, we utilized data spanning 10 cycles from 1999 to 2018 in the NHANES database, providing a robust analysis over an extensive timeframe with a large sample size, thereby enhancing the confidence level of our findings. Second, the HALP score employed in our study serves as a comprehensive indicator, capturing both the inflammatory and nutritional status of individuals, thereby offering more nuanced insights compared with single inflammatory markers. To our knowledge, our study represents the first cohort investigation into the association between the HALP score and the incidence as well as long-term mortality of ASCVD. Lastly, we employed a range of analytical methods, including subgroup analysis, sensitivity analysis, RCS analysis, and Kaplan–Meier analysis, ensuring the rigor and credibility of our findings.

Nevertheless, it is important to acknowledge the limitations of our study. First, reliance on self-reported data in the NHANES database introduces the potential for recall bias. Second, the diagnosis of ASCVD relied on a questionnaire-based approach, which may lack the precision of objective diagnostic criteria, potentially resulting in misdiagnosis or underdiagnosis. Third, despite adjusting for known factors such as age, gender, and smoking status, there could still be unidentified confounding variables influencing our results. Lastly, the HALP score, derived from a single complete blood count parameter and serum albumin measurement, may not fully capture the overall health status of participants.

5. Conclusion

We conducted a comprehensive nationwide survey among noninstitutionalized adults in the United States to investigate the correlation between HALP scores and ASCVD incidence and long-term mortality. Our analysis revealed a significant nonlinear association between HALP scores and both all-cause and CVD mortality among ASCVD individuals, indicating that higher HALP scores were linked to lower mortality rates. Thus, the HALP score emerges as a valuable and cost-effective tool for identifying high-risk individuals within the ASCVD population. Our findings offer valuable insights for enhancing the management of patients with ASCVD.

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Author contributions

Conceptualization: Yanan Zou, Jixin Fu, Xiao Yang.
Methodology: Yanan Zou, Jixin Fu.
Writing—original draft: Yanan Zou, Jing Cong.
Formal analysis: Jing Cong.
Writing—review & editing: Jixin Fu, Xiao Yang.
Data curation: Xiao Yang.

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