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The Relation Between the Aggregate Index of Systemic Inflammation and the Mortality Rate of Cardiovascular Disease in the Elderly Population

ABSTRACT

Background: Cardiovascular disease (CVD) is a leading cause of death in older adults and is closely associated with inflammation. The aggregate index of systemic inflammation (AISI), a novel biomarker, may predict CVD mortality in this population. To analyze the association between AISI levels and CVD mortality in the older population.

Methods: This study was based on the National Health and Nutrition Examination Survey (NHANES) database. By constructing weighted Kaplan–Meier (K-M) survival curves and Cox proportional hazards models, the link between AISI levels and CVD mortality rate were analyzed in the elderly. The restricted cubic spline (RCS) was applied to elucidate the non-linear link. A random survival forest model was constructed to assess the predictive value of multiple variables.

Results: One thousand three hundred nineteen CVD death events were recorded. The weighted K-M survival curve manifested that the CVD mortality risk was considerably higher in the highest tertile group than in the lowest tertile. In the model with full adjustments, each one-unit increase in AISI was associated with a 1.52-fold higher risk of death (HR = 1.52, 95% CI: 1.30-1.76, $P < .001$), and a non-linear relationship was detected (P-nonlinear = .0001). When AISI was above the threshold of 263.43, the CVD mortality risk was significantly elevated (HR = 1.99, 95% CI: 1.59-2.49, $P < .001$). No significance was observed below this threshold. AISI had the highest predictive value for CVD mortality in the elderly.

Conclusion: The AISI is an effective indicator for predicting the CVD mortality risk in the elderly, especially when AISI reaches high levels.

Keywords: Aggregate index of systemic inflammation, cardiovascular disease mortality, elderly, National Health and Nutrition Examination Survey

ORIGINAL INVESTIGATION

INTRODUCTION

The health status and disease management of the elderly have become a focus of public health due to the growing worldwide aging population. Cardiovascular disease (CVD) contributes to the largest global death toll among the elderly,[1] causing widespread concern. As of 2019, the number of CVD patients in 204 countries and regions has climbed from 271 million in 1990 to 523 million, with an additional 6.5 million CVD deaths, making it a leading global cause of death.[2] Inflammation plays a central driving role in the occurrence and development of CVD, not only as a common pathological basis for various CVD,[3,4] but also as a key bridge connecting aging and CVD mortality risk. As age increases, the body's immune system gradually exhibits a chronic, low-grade activation state, known as inflammatory aging, characterized by a sustained increase in levels of inflammatory cells and mediators in peripheral blood.[5] This state can damage the vascular endothelial function, accelerate the process of atherosclerosis, and significantly increase the risk of CVD death.[6] Therefore, finding biomarkers that can reflect chronic low-grade inflammation is of great significance for CVD risk management in the elderly.

In recent years, the aggregate index of systemic inflammation (AISI) has received widespread attention as an emerging comprehensive inflammatory indicator, consisting of neutrophil count, platelet count, monocyte count, and lymphocyte

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count.[7] Compared to traditional inflammatory markers such as C-reactive protein (CRP) and white blood cell count, AISI may be able to more comprehensively evaluate the inflammatory status of the body. C-reactive protein can effectively reflect acute inflammatory response, but it is susceptible to interference from short-term infections and other factors.[8] White blood cell count is too general to distinguish specific components of the inflammatory response.[9] In contrast, AISI synchronously captures 3 interrelated pathophysiological networks: innate immunity (neutrophils, monocytes), adaptive immunity (lymphocytes), and thrombus inflammation interaction (platelets).

Therefore, the mechanism by which AISI affects CVD mortality may work synergistically through 3 core pathological pathways. Congenital immune overactivation (neutrophils and monocytes) directly leads to endothelial damage and progression of atherosclerosis.[10,11] Platelet-mediated thrombotic inflammatory cycle significantly increases the risk of acute occlusive events.[12] Lymphocytes can accelerate the formation of atherosclerotic lesions by affecting immune regulation.[13] The increase of AISI may reflect the triple hazards of pro-inflammatory, thrombotic, and immune imbalance, which together promote the occurrence of fatal CVD events. Moreover, a great positive linkage between AISI and the prevalence of hypertension has been discovered,[14] making AISI a new predictor of hypertension.[15] In addition, AISI can predict the mortality rate of stroke patients[16] and the mortality rate of patients with chronic obstructive pulmonary disease combined with COVID-19 infection.[17] However, AISI's role in predicting elderly people's CVD mortality has not been fully elucidated.

The objective of this study was to explore the link between AISI and CVD mortality in the elderly by analyzing a large sample size of data from the National Health and Nutrition Examination Survey (NHANES). Based on existing research progress, the hypothesis was proposed that there is an independent positive correlation between AISI and CVD mortality rate in the elderly population, and this correlation exhibits a non-linear threshold effect. It was intended to reveal the potential value of AISI in predicting CVD mortality in the elderly and provide a theoretical basis for future clinical applications.

HIGHLIGHTS

- This article reveals for the first time that there is a significant non-linear positive correlation between aggregate index of systemic inflammation (AISI) and the risk of cardiovascular disease (CVD) death in the elderly population, and the threshold point is determined to be 263.43.
- This article innovatively uses Cox regression and random survival forest models to mutually verify the reliability of AISI as an independent predictor of CVD mortality risk in the elderly population.
- The AISI has the potential to serve as a simple and easily accessible auxiliary tool for timely identification of high-risk CVD populations in the elderly population in clinical practice.

METHODS

Study Population from National Health and Nutrition Examination Survey

The population data used in this study were available through the NHANES database,[18] which is a publicly available, de-identified dataset. The NHANES is a comprehensive study conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) to examine the nutrition and health of the noninstitutionalized U.S. population through a multistage and stratified sampling method. All data were approved by the NCHS Ethics Review Committee; therefore, no additional ethical approval was required.

The link between AISI and CVD mortality in the elderly was probed using survey data from 10 cycles from 1999 to 2018 (n = 101 316). The exclusion criteria are as follows: (1) excluding participants younger than 60 (n = 82 229); (2) excluding participants with lacking or invalid AISI data (n = 2164); and (3) excluding participants with missing data on other covariate variables (n = 3401). A total of 13 522 elderly subjects were studied. The specific process of subject screening is displayed in Figure 1.

Independent Variable

The calculation of AISI was based on indicators in the whole blood cell count. The blood sampling followed the NHANES standardized protocol: venous blood samples were taken on an empty stomach for more than 8 hours and were collected at a mobile examination center. The complete blood cell count was measured using a Beckman Coulter automatic blood analyzer to ensure data reliability.[19]

AISI = neutrophil count × platelet count × monocyte count/lymphocyte count.[7]

Dependent Variable

The National Death Index records as of December 31, 2019 were the reference for us to determine the mortality outcomes. The underlying causes of mortality were assessed by the International Statistical Classification of Diseases, 10th Revision (ICD-10).

Variables

Covariates in this investigation included gender, body mass index (BMI), ethnicity, education level, poverty income ratio (PIR), red blood cell (RBC) count, diabetes, smoking, white blood cell (WBC) count, alcohol consumption, hypertension, hemoglobin, and mean RBC volume. Subjects fell into 3 distinct PIR categories: low income (PIR $\leq$ 1.3), moderate income (1.3 < PIR $\leq$ 3.5), and high income (PIR > 3.5).[20] Body mass index was calculated as weight (kg) divided by the square of height (m), and classified as obese (>30 kg/m^2), overweight (25-30 kg/m^2), and underweight/healthy weight (< 25 kg/m^2).[21] Smoking status was grouped into 3 groups based on the smoking history and current smoking behavior of the subjects: never smokers (reporting a total of less than 100 cigarettes smoked), former smokers (reporting a total of 100

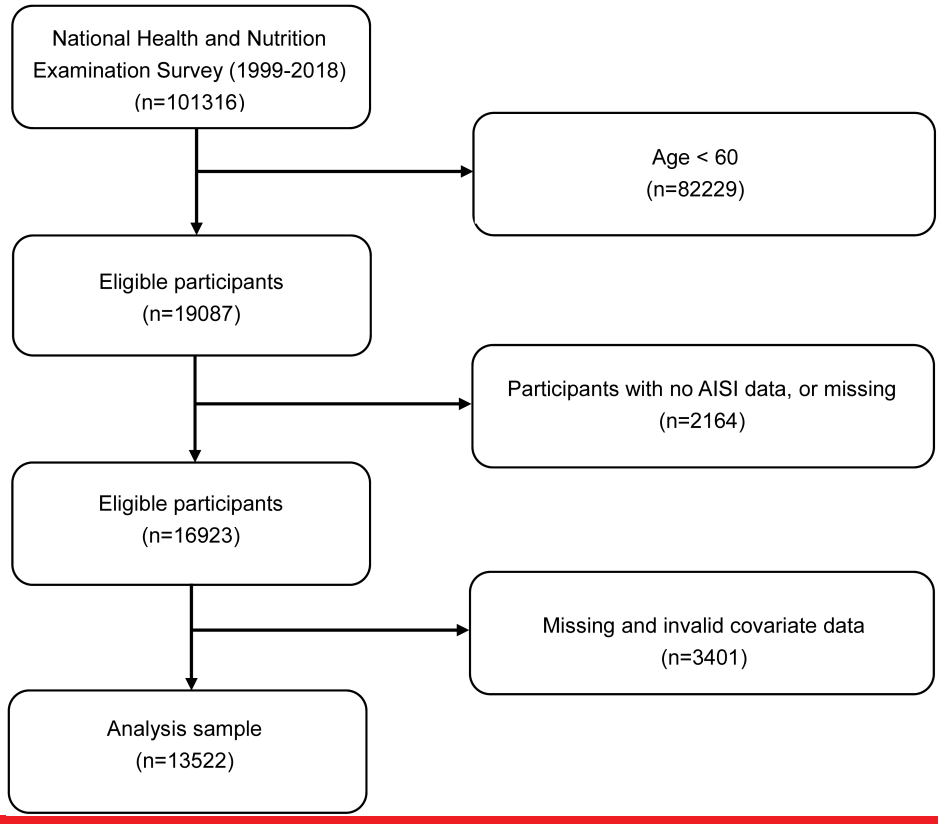

Figure 1. Flowchart of NHANES participant screening.

or more cigarettes smoked but currently not smoking), and current smokers (reporting a total of 100 or more cigarettes smoked and still smoking).[22] Drinking at least 12 drinks per year was defined as alcohol consumption.[23] Participants with diabetes were defined as having any of the following conditions: (1) glycated hemoglobin (HbA1C) concentration >6.5%; (2) fasting blood glucose level ≥126 mg/dL; (3) self-reported diabetes; and (4) currently taking antidiabetic medication to lower blood sugar.[24,25] High blood pressure was determined to be any of the following: (1) systolic blood pressure ≥ 140 mm Hg; (2) diastolic blood pressure ≥ 90 mm Hg; (3) self-reported hypertension; and (4) taking antihypertensive medication.[26]

Statistical Analysis

We completed all statistical analyses in this work by using R software (V4.4.1). The *tableone* package was employed to create the baseline table, which was based on the AISI-weighted tertile grouping and the characteristics of the total population. The sample size and its proportion [n (%)] were utilized to express the categorical variables in the statistical analysis, while the mean and standard deviation [mean (SD)] were utilized to express the continuous variables. Then, the continuous variable AISI with a non-normal distribution was logarithmically transformed for easy analysis.

The *jskm* package was utilized to plot the weighted Kaplan–Meier (K-M) survival curve based on the AISI weighted tertile grouping of subjects, describe the survival status of subjects, and evaluate the distinction between groups through the log-rank test. A Cox proportional hazard model was set up considering complex sampling by utilizing the *survey* package and the *survival* package, and the model was gradually adjusted to dig out the link between AISI and CVD mortality in the elderly. Based on biological relevance, variables were included and the variance inflation factor was calculated using the *car* package. The results were all <5, indicating no significant over-adjustment (Supplementary Table 1). Subgroup analysis was conducted based on stratification of gender, BMI, smoking, alcohol, diabetes, and hypertension to examine the independent effects of AISI. The crude model did not adjust for confounding factors. In Model 1, adjustments were added to gender, BMI, smoking, education level, PIR, race, and alcohol consumption. Model 2 had adjustments for all covariates (BMI, race, smoking, gender, education level, alcohol consumption, PIR, hypertension, WBC count, diabetes, hemoglobin, mean RBC volume, and RBC count). Furthermore, a trend test was launched to examine the linkage between the AISI-weighted tertiles and CVD mortality rates. If $P < .05$, statistical significance was indicated.

In the model with adjustment for all covariates, a restricted cubic spline (RCS) analysis was conducted by utilizing the *rms* package to illuminate the nonlinear relationship between AISI and CVD mortality in the elderly population. A 2-part linear regression model was set up to display threshold effects.

The *randomForestSRC* package was used to construct a random survival forest (RSF) model and evaluate the predictive value of multiple variables on CVD mortality in elderly individuals. The parameters were set to ntree = 1000 (number of trees), nodesize = 25 (minimum size of terminal nodes), splitrule = logrank (rule for survival splitting),

importance = TRUE (calculate variable importance), proximity = TRUE (calculate neighbor matrix), and cv = TRUE (cross-validation). The NHANES survey weights were normalized (weights = WEIGHT/mean (weight)) and incorporated into the model to consider complex sampling designs. The dataset was divided into a training set (70%) and a testing set (30%). The contribution of each variable was presented by utilizing the *ggRandomForests* package.

Time-dependent ROC curves were calculated using the *timeROC* package and the model's predictive accuracy was evaluated at different time points (3, 5, and 10 years). To quantify the incremental predictive value brought by incorporating AISI into the baseline model, prediction models were constructed with and without AISI. Further, the predictive performance of the 2 models were evaluated using the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) continuous models.[27]

Sensitivity analysis was conducted to ensure the robustness of the results: (1) As NHANES aims to represent the health status of the non-institutionalized American population, participants with acute or chronic inflammatory conditions were not excluded from this study. However, in order to assess the impact of related confounding factors, participants with hepatitis B virus infection, self-reported cancer, or rheumatoid arthritis were excluded, and 8632 participants were included for weighted Cox regression analysis. (2) After removing blood parameters, Model 3 was constructed for weighted Cox regression analysis. Model 3 adjusted for gender, race, BMI, educational level, PIR, smoking, drinking, diabetes, and hypertension.

RESULTS

Baseline Characteristics

To probe into the relationship between AISI and CVD mortality in the elderly, 13 522 samples from NHANES 1999-2018 were included. Of these, 1319 (8.5%) died from CVD. According to the AISI-weighted tertiles of the subjects, there were 364 deaths (6.5%) in Group T1, 413 deaths (7.9%) in Group T2, and 542 deaths (11.1%) in Group T3. Compared to participants in the lowest tertile of AISI, those with higher AISI were always male, former and current smokers, obese (BMI $\geq$ 30), and individuals with comorbidities such as diabetes and hypertension. Additionally, the levels of WBC count, RBC count, and hemoglobin in subjects with higher AISI were considerably higher than those in subjects with the lowest tertile (Table 1).

Relation Between Aggregate Index of Systemic Inflammation and Cardiovascular Disease Mortality in the Elderly

The weighted K-M survival curve manifested the survival probability trend in AISI-weighted tertile groups. The mortality risk was highest in the T3 group over time ($P < .001$), but no significant difference in the risk of CVD death between T1 and T2 was detected ($P = .180$) (Figure 2A). Next, the Cox proportional hazard model was utilized to further dissect the link between AISI and CVD mortality in the elderly. In the unadjusted model (Crude model), when the AISI variable increased by 1 unit, the risk of death increased by 1.60 times (HR = 1.60, 95% CI: 1.41-1.81, $P < .001$). In Model 1, adjustments were added to confounding factors, finding the significant trend (HR = 1.49, 95% CI: 1.31-1.69, $P < .001$). In Model 2 (all covariates adjusted), when the AISI variable increased by 1 unit, the risk of death increased by 1.52 times (HR = 1.52, 95% CI: 1.30-1.76, $P < .001$). The trend test demonstrated that among the 3 models, as the interquartile range of AISI increased, the CVD mortality risk in the elderly significantly elevated (Table 2). The results of subgroup analysis showed that after adjusting for all confounding variables, AISI was positively correlated with CVD mortality risk in the elderly population in all subgroups ($P < .005$), indicating that the independent effect of AISI was consistent and robust across different subgroups (Supplementary Table 2). The results of both sensitivity analyses showed that after adjusting for all confounding variables, AISI was still positively correlated with the risk of CVD mortality in the elderly population ($P < .05$) (Supplementary Tables 3 and 4).

Nonlinear Relationship Between Aggregate Index of Systemic Inflammation and Cardiovascular Disease Mortality Rate in the Elderly Population

Further, the threshold effect model was applied and RCS to probe into the nonlinear link between AISI and CVD mortality rate in the elderly, revealing a significant overall trend between AISI and the CVD mortality risk (P-overall <.0001). With increasing AISI, the CVD mortality risk in the elderly was greatly elevated. A non-linear link between AISI and CVD mortality in the elderly was detected (P-non-linear = .0001) (Figure 2B).

The threshold effect results implied no statistically significant link with the risk of CVD mortality in the elderly when AISI < 263.43 ($P = .6$). When AISI $\geq$ 263.43, a significant positive correlation with the risk of CVD mortality in elderly individuals was discovered (HR = 1.99, 95% CI: 1.59-2.49, $P < .001$). Furthermore, the Wald test revealed statistically significant differences between the 2 groups ($P < .001$) (Table 3).

Prognostic Value of Aggregate Index of Systemic Inflammation

We developed an RSF model to examine the value of AISI in predicting CVD mortality in the elderly. The results demonstrated that AISI was the most effective predictor of CVD mortality in the elderly compared to other variables (Figure 3A). Furthermore, the performance of RSF and Cox models was compared and evaluated using C-index: the C-index of RSF was 0.691, while that of the Cox model was 0.725. This indicates that the Cox model has slightly better overall discriminative ability than RSF, but RSF has more advantages in capturing nonlinear relationships and variable interactions.[28]

Subsequently, the predictive performance of the model was tested using the ROC curves. The model had AUC values of 0.729, 0.711, and 0.749 for predicting CVD mortality in elderly individuals at 3, 5, and 10 years, respectively, suggesting that the RSF model possessed good predictive ability (Figure 3B).

Table 1. Baseline Characteristics of Included Subjects

Characters	Total	T1 (<211.25)	T2 (211.25-365.14)	T3 (≥365.14)	*P*
Overall	13 522	4998 (33.3)	4314 (33.3)	4210 (33.3)	
Gender					<.001
Male	6809 (45.4)	2310 (40.0)	2149 (45.1)	2350 (51.0)	
Female	6713 (54.6)	2688 (60.0)	2165 (54.9)	1860 (49.0)	
Race					<.001
Mexican American	1967 (3.7)	766 (4.4)	680 (3.8)	521 (2.9)	
Other Hispanic	1003 (3.3)	434 (4.1)	309 (3.1)	260 (2.7)	
Non-Hispanic White	7239 (80.7)	1990 (72.6)	2450 (82.5)	2799 (87.0)	
Non-Hispanic Black	2518 (7.7)	1418 (12.9)	647 (6.2)	453 (4.1)	
Other race	795 (4.6)	390 (6.0)	228 (4.4)	177 (3.3)	
BMI (kg/m^2)					<.001
<25	3510 (26.0)	1309 (27.3)	1070 (24.3)	1131 (26.2)	
25-30	5115 (37.3)	1946 (39.3)	1640 (38.1)	1529 (34.5)	
>30	4897 (36.8)	1743 (33.4)	1604 (37.6)	1550 (39.3)	
Alcohol					.119
No	4454 (29.8)	1716 (30.8)	1428 (30.2)	1310 (28.4)	
Yes	9068 (70.2)	3282 (69.2)	2886 (69.8)	2900 (71.6)	
Smoke					<.001
Never	6448 (48.0)	2630 (53.9)	2049 (47.2)	1769 (43.0)	
Past	5357 (40.4)	1824 (37.5)	1740 (41.7)	1793 (42.1)	
Now	1717 (11.5)	544 (8.6)	525 (11.1)	648 (14.9)	
Education					.014
Less than high school	2424 (9.1)	935 (9.4)	813 (9.1)	676 (8.7)	
High school or equivalent	5221 (37.9)	1860 (35.2)	1640 (38.7)	1721 (39.9)	
College or above	5877 (53.0)	2203 (55.4)	1861 (52.2)	1813 (51.4)	
PIR					.001
Low	3848 (18.1)	1497 (18.5)	1186 (17.3)	1165 (18.3)	
Medium	5775 (41.8)	2029 (39.4)	1860 (40.8)	1886 (45.1)	
High	3899 (40.2)	1472 (42.0)	1268 (41.9)	1159 (36.6)	
Diabetes					<.001
No	9743 (76.5)	3635 (78.8)	3150 (77.8)	2958 (72.9)	
Yes	3779 (23.5)	1363 (21.2)	1164 (22.2)	1252 (27.1)	
Hypertension					<.001
No	2634 (22.1)	1070 (26.3)	833 (21.2)	731 (18.9)	
Yes	10 888 (77.9)	3928 (73.7)	3481 (78.8)	3479 (81.1)	
WBC (1000 cells/μL)	7.11 ± 3.42	6.09 ± 5.05	6.94 ± 1.53	8.31 ± 2.17	<.001
RBC (1000 cells/μL)	4.57 ± 0.48	4.53 ± 0.47	4.59 ± 0.46	4.60 ± 0.50	<.001
Hemoglobin (g/dL)	14.09 ± 1.40	13.97 ± 1.32	14.17 ± 1.36	14.14 ± 1.51	<.001
Mean cell volume (fL)	91.22 ± 5.11	91.33 ± 5.24	91.24 ± 4.88	91.08 ± 5.20	.136
CVD mortality					<.001
Alive	12 203 (91.5)	4634 (93.5)	3901 (92.1)	3668 (88.9)	
Deceased	1319 (8.5)	364 (6.5)	413 (7.9)	542 (11.1)	

n (%) represented the categorical variable and mean (sd) represented the continuous variable. n was unweighted. n (%), mean, and SD were weighted.
BMI, body mass index; CVD, cardiovascular disease; PIR, poverty-income ratio; RBC, red blood cell; WBC, white blood cell.

The Incremental Value of Aggregate Index of Systemic Inflammation Prediction Model

We used a weighted Cox model (Model 3) to construct models with and without AISI and evaluated predictive performance using Harrell's C-index and time-dependent AUC (3, 5, and 10 years). The results showed that the C-index of the model containing AISI was 0.741, which was higher than that of 0.733 in the model without AISI. The time-dependent AUC showed that the model containing AISI had better predictive performance at 3 years (0.765

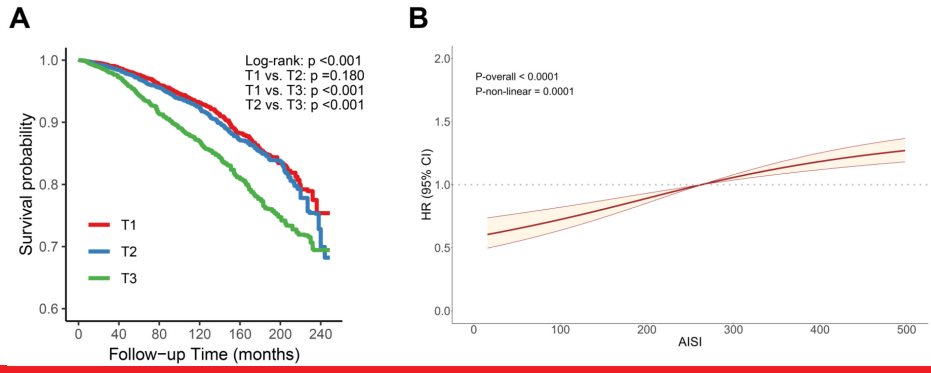

Figure 2. Weighted K-M survival curves (A) and RCS model (B) of AISI and CVD mortality in elderly individuals. The RCS model was adjusted for gender, race, BMI, education level, PIR, smoking, alcohol consumption, diabetes, hypertension, WBC count, RBC count, hemoglobin, and mean RBC volume. Take-home messages: (A) The highest CVD mortality risk in the T3 group; (B) A nonlinear increase in CVD mortality risk with rising AISI. AISI, aggregate index of systemic inflammation; CVD, cardiovascular disease; BMI, body mass index; PIR, poverty-income ratio; WBC, white blood cell; RBC, red blood cell.

Table 2. The Associations Between AISI and Cardiovascular Mortality in Elderly Individuals

	HR (95% CI), *P*		
Characteristic	**Crude Model**	**Model 1**	**Model 2**
CVD mortality			
AISI (continuous)	1.60 (1.41-1.81), <.001	1.49 (1.31-1.69), <.001	1.52 (1.30-1.76), <.001
AISI (categorical)			
T1	Ref.	Ref.	Ref.
T2	1.13 (0.95-1.35), .162	1.09 (0.92-1.29), .314	1.10 (0.93-1.31), .266
T3	1.81 (1.53-2.14), <.001	1.62 (1.36-1.93), <.001	1.58 (1.30-1.93), <.001
P for trend	<.001	<.001	<.001

The Crude model did not adjust for confounding factors. In Model 1, adjustments were made for gender, race, BMI, education level, PIR, smoking, and alcohol consumption. Model 2 had adjustments for all covariates, including gender, race, BMI, education level, PIR, smoking, alcohol consumption, diabetes, hypertension, WBC count, RBC count, hemoglobin, and mean RBC volume.
AISI, aggregate index of systemic inflammation; BMI, body mass index; CVD, cardiovascular disease; PIR, poverty-income ratio.

vs. 0.751), 5 years (0.757 vs. 0.745), and 10 years (0.753 vs. 0.747) (Figure 4).

In addition, the AISI model showed a statistically significant improvement in predictive ability compared to the baseline model (without AISI). The estimated value of IDI was greater than 0, and at 10 years, the model's integrated discriminative ability was improved by a net 1.5% (IDI = 0.015, $P < .001$). The estimated values of continuous NRI were between 0.160 and 0.178, and the *P*-values were significant (Supplementary Table 5). In summary, the IDI and NRI results clearly quantified and confirmed that AISI provides significant incremental predictive value independent of traditional risk factors, particularly in improving the accuracy of risk stratification.

DISCUSSION

In this nationally representative large-scale study, a significant positive relation between AISI and CVD mortality in the elderly population was revealed for the first time. The threshold effect analysis further demonstrated that when AISI reached or exceeded 263.43, the elderly had a considerably elevated risk of CVD mortality. In addition, the RSF model also verified AISI as a strong indicator for predicting CVD mortality in the elderly.

Mounting studies have revealed that chronic inflammation is essential for the pathogenesis of atherosclerosis and other CVDs.[3,4] Atherosclerosis is the leading cause of CVD worldwide.[29] In the initial stage of atherosclerosis, low-density lipoprotein cholesterol enters the subendothelial space, undergoes oxidation and aggregation, and the oxidative modification induces endothelial cells to express cell adhesion molecules, recruiting T lymphocytes and monocytes into the inflamed arterial wall.[30] Monocytes subsequently differentiate into macrophages and secrete pro-inflammatory

Table 3. Threshold Effect Analysis of AISI on CVD Mortality in Elderly Individuals

Outcomes	**HR (95% CI), *P***
AISI	
Cutoff	
<263.43	1.08 (0.80-1.46), .6
≥263.43	1.99 (1.59-2.49), <.001
P for Wald test	<.001

Adjustments were made for gender, race, BMI, education level, PIR, smoking, alcohol consumption, diabetes, hypertension, WBC count, RBC count, hemoglobin, and mean RBC volume.
AISI, aggregate index of systemic inflammation; BMI, body mass index; CVD, cardiovascular disease; PIR, poverty-income ratio.

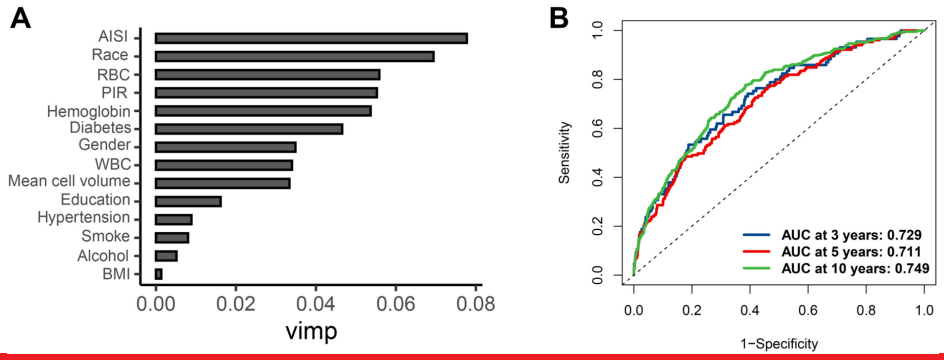

Figure 3. Prognostic value of AISI for CVD mortality in elderly individuals. (A) Prognostic value of AISI for CVD mortality in elderly individuals using the random survival forest model. (B) ROC curves of the random survival forest model. Take-home messages: (A) AISI is the best indicator for predicting CVD mortality risk; (B) The predictive model incorporating AISI exhibits strong predictive capability. AISI, aggregate index of systemic inflammation; CVD, cardiovascular disease; BMI, body mass index; PIR, poverty-income ratio; WBC, white blood cell; RBC, red blood cell.

cytokines (IL-12, IL-1α, IL-6, IL-1β, etc.), resulting in local inflammation, further boosting plaque formation and atherosclerosis.[31]

Inflammatory biomarkers are positively linked with the risk and mortality rate of CVD. A prospective study demonstrated that higher levels of CRP are associated with an elevated risk of heart failure in CVD patients.[32] Another Mendelian randomization study revealed that genetically determined elevated levels of CRP increase the risk of hypertension-related heart disease by 21%.[33] As an indicator of systemic inflammation, the neutrophil-to-lymphocyte ratio is remarkably positively associated with CVD mortality in patients with diabetes, rheumatoid arthritis, and hypertension.[25,34,35] Another marker of inflammation is the platelet-to-lymphocyte ratio (PLR), with high levels of PLR elevating the risks of all-cause mortality and CVD mortality in maintenance hemodialysis patients.[36] The AISI integrates multiple blood cell parameters related to inflammation, including neutrophils, platelets, monocytes, and lymphocytes, comprehensively reflecting the body's systemic inflammatory status, rather than relying solely on a single indicator. The AISI has been confirmed as an effective indicator for assessing cardiovascular risk in patients with acute coronary syndrome receiving percutaneous coronary intervention, with higher AISI levels closely linked with elevated cardiovascular event risk.[37] An elevated mortality rate in stroke patients has been revealed to be connected with high AISI.[16] Additionally, AISI is an essential predictor of restenosis and mortality following carotid endarterectomy.[38] The results coincided with the former findings that higher AISI levels significantly correlate with CVD mortality in the elderly.

It was considered that individuals with higher AISI levels often have more complications (such as diabetes and obesity), so the association between AISI and CVD mortality may be disturbed by such factors. To verify whether AISI has an independent predictive effect on comorbidities, a multicollinearity diagnosis was performed using the variance inflation factor, and the results confirmed that there was no serious collinearity issue between AISI and other comorbidities. Further subgroup analysis revealed that AISI maintained stable predictive ability in different clinical feature populations, supporting its robustness as an independent predictor.

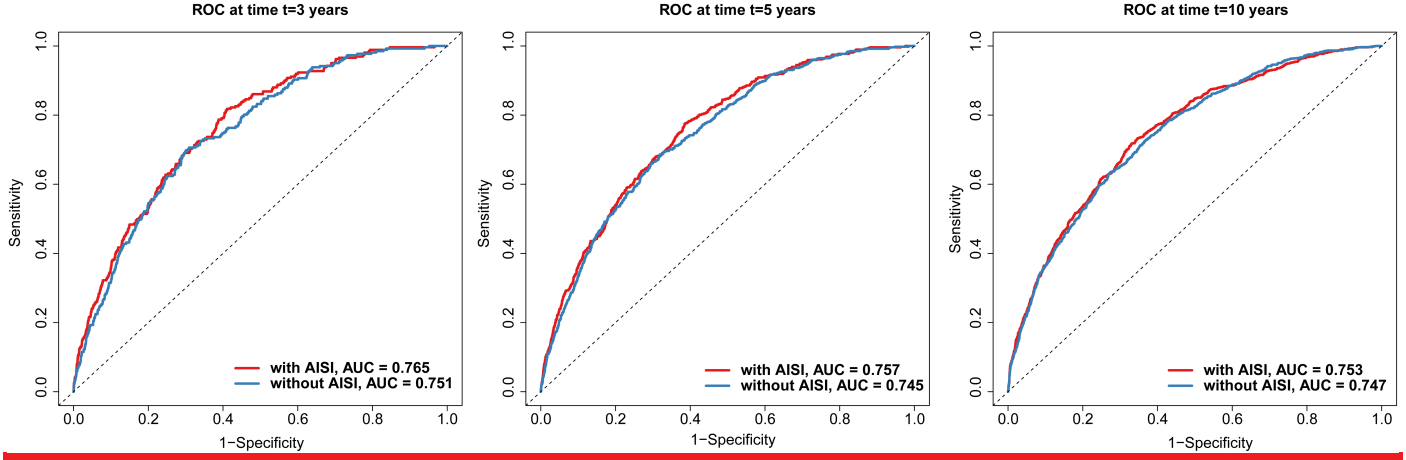

Figure 4. Prognostic value of AISI for CVD mortality in elderly individuals (Comparison between the model with AISI and the model without AISI). Take-home messages: The prediction model containing AISI has better predictive value. AISI, aggregate index of systemic inflammation; CVD, cardiovascular disease.

Based on the above analysis, AISI is not just a substitute indicator for known risk factors, but more likely an independent risk marker that can reflect the potential immune-inflammatory status of the body.

The threshold effect analysis uncovered that the CVD mortality in the elderly population significantly rose when AISI reached or exceeded 263.43 (HR = 1.99), indicating that for every unit increase in AISI, the relative risk of CVD occurrence increased by 99%. No significant statistical significance was detected below this threshold. This suggested that the CVD mortality rate in the elderly population significantly rose only when the inflammatory state reached a certain level. The weighted K-M survival curves also confirmed this finding, demonstrating a significantly elevated risk of CVD death only in the highest tertile (T3) group, with no obvious difference in CVD mortality risk observed between the T1 and T2 groups. These findings echo a former study revealing that as AISI exceeds 507.45, the mortality rate of stroke patients significantly rises with the increase of AISI values.[16] Therefore, the work further supported the potential value of AISI as an indicator for CVD mortality prediction in the elderly, especially in the presence of high inflammation. This suggests that AISI may serve as a practical risk assessment tool in clinical practice. Clinical doctors can use this threshold to quickly identify high-risk elderly patients with elevated inflammation levels and significantly increased CVD risk. However, it should be noted that the AISI cutoff value (263.43) can only be used for risk stratification and is not an accurate value for clinical decision-making. In addition, AISI also has the potential to optimize existing risk prediction models. Based on the results of the RSF model, AISI has been identified as an important variable for predicting CVD mortality in the elderly population. ROC curve and incremental predictive value analysis further indicated that incorporating AISI into the model significantly improves its predictive performance, which may lead to better management of CVD risk in the elderly. Most importantly, AISI can be calculated from routine blood tests. It can assist clinical doctors in assessing cardiovascular risk without the need for additional testing. It is low-cost and easy to operate, exhibiting outstanding advantages.

A hallmark of aging is systemic chronic inflammation, a phenomenon known as inflammation.[39] The factors secreted by senescent cells are collectively referred to as senescence-related secretory phenotypes, which not only accelerate the progression of chronic inflammation but also trigger senescence in normal cells.[40] Long-term inflammation can trigger fibrosis in the heart and blood vessels,[41,42] thereby elevating the risk of CVD. The growth in AISI may reflect this inflammatory aging state in the elderly, making AISI a strong predictor of CVD mortality risk. However, the predictive value of AISI in CVD mortality risk in other age groups has not been fully dissected, awaiting further studies in the future.

Although this study offered evidence supporting AISI as an indicator for predicting CVD mortality risk in the elderly, certain shortcomings persist. First, though this prospective cohort study had a large sample size and lasted for a long follow-up period, a causal relationship cannot be established due to the nature of observational studies. Individuals with preclinical or undiagnosed subclinical CVD may already have more severe systemic inflammatory states in their bodies, leading to elevated levels of AISI. In this case, the increase in AISI may be a result of potential CVD rather than the cause, which could affect the interpretability of the research results. Secondly, the research focuses on the elderly population in the United States, and caution should be exercised when generalizing the research results to other healthcare environments, younger populations, or populations in other countries, as there may be differences in lifestyle, access to medical resources, and disease prevalence among different regions or age groups. Thirdly, NHANES only provides a single record of laboratory blood cell count and cannot evaluate changes in AISI over time, which may not reflect the average level of long-term follow-up. In future research, measurements of AISI can be repeated at multiple time points to explore the relationship between the dynamic changes of AISI and the risk of CVD in elderly people. Lastly, although the independent predictive value of AISI has been validated through various statistical methods, there may still be other confounding factors that have not been considered, such as dietary details, genetic factors, etc., that may affect the results. Therefore, future large-scale clinical trials are recommended to validate the findings of this study.

CONCLUSION AND RECOMMENDATIONS

This study found that AISI is an independent predictor of CVD mortality risk in the elderly population, especially for those at high AISI levels (AISI $\geq$ 263.43). Therefore, AISI has the potential to serve as an objective and easily accessible auxiliary tool for the timely identification of high-risk populations in clinical practice, and can also be integrated into other CVD risk assessment models, which may optimize the predictive value of prediction models.

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Supplementary Table 1. VIF of variables for multivariate cox regression

Characters	VIF
AISI	1.074
Gender	1.162
Race	1.070
BMI	1.036
Education	1.101
PIR	1.066
Smoke	1.060
Alcohol	1.099
Diabetes	1.056
Hypertension	1.022
WBC	1.026
RBC	3.950
Hemoglobin	3.744
Mean cell volume	2.629

AISI, Aggregate index of systemic inflammation; BMI, Body Mass Index; PIR, Poverty-Income Ratio; WBC, White Blood Cell; RBC, Red Blood Cell; VIF, variance inflation factor.

Supplementary Table 2. Subgroup analysis based on stratifications of gender, BMI, smoking, alcohol, diabetes, and hypertension

	HR (95% CI), *P*
Participants	**Model 2**
Gender	
Male	1.51 (1.23-1.85), <0.001
Female	1.49 (1.23-1.80), <0.001
BMI	
<25	1.42 (1.15-1.75), <0.001
25-30	1.45 (1.17-1.79), <0.001
>30	1.74 (1.32-2.28), <0.001
Smoke	
No	1.49 (1.20-1.86), <0.001
Yes	1.49 (1.19-11.86), <0.001
Alcohol	
No	1.49 (1.18-1.89), <0.001
Yes	1.49 (1.22-1.83), <0.001
Diabetes	
No	1.42 (1.21-1.67), <0.001
Yes	1.73 (1.32-2.25), <0.001
Hypertension	
No	1.46 (1.04-2.04), 0.027
Yes	1.51 (1.29-1.77), <0.001

The model adjusted for gender, race BMI, educational level, PIR, smoking, drinking, diabetes, hypertension, white blood cell count, red blood cell count, hemoglobin and mean red blood cell volume. BMI, Body Mass Index; PIR, Poverty-Income Ratio.

Supplementary Table 3. The associations between AISI and cardiovascular mortality in elderly individuals (after excluding participants with hepatitis B virus infection, self-reported cancer, or rheumatoid arthritis)

	HR (95% CI), *P*		
Characteristic	**Crude model**	**Model 1**	**Model 2**
CVD mortality			
AISI (continuous)	1.45 (1.24-1.70), <0.001	1.35 (1.13-1.60), <0.001	1.37 (1.13-1.67), 0.002

The Crude model did not adjust for confounding factors; Model 1 adjusted for gender, race BMI, educational level, PIR, smoking and drinking; Model 2 adjusted for gender, race BMI, educational level, PIR, smoking, drinking, diabetes, hypertension, white blood cell count, red blood cell count, hemoglobin and mean red blood cell volume. Abbreviation: AISI, Aggregate index of systemic inflammation; BMI, Body Mass Index; PIR, Poverty-Income Ratio; CVD, Cardiovascular Disease.

Supplementary Table 4. The associations between AISI and cardiovascular mortality in elderly individuals (after removing blood parameters)

	HR (95% CI), *P*
Characteristic	**Model 3**
CVD mortality	
AISI (continuous)	1.47 (1.29-1.67), <0.001

Model 3 adjusted for gender, race BMI, educational level, PIR, smoking, drinking, diabetes, and hypertension. Abbreviation: AISI, Aggregate index of systemic inflammation; BMI, Body Mass Index; PIR, Poverty-Income Ratio; CVD, Cardiovascular Disease.

Supplementary Table 5. The incremental value of the AISI prediction model

Time Point	Metric	Point estimation	95% (CI)	*P*
3 years	IDI	0.007	[0.001, 0.011]	<0.001
	Continuous NRI	0.178	[0.033, 0.218]	<0.001
5 years	IDI	0.011	[0.001, 0.014]	<0.001
	Continuous NRI	0.172	[0.037, 0.214]	<0.001
10 years	IDI	0.015	[0.003, 0.020]	<0.001
	Continuous NRI	0.160	[0.031, 0.183]	<0.001

The Model adjusted for gender, race BMI, educational level, PIR, smoking, drinking, diabetes, and hypertension. Abbreviation: AISI, Aggregate index of systemic inflammation; IDI, Integrated Discrimination Improvement; NRI, Net Reclassification Improvement.