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Combined impact of neutrophil-to-high-density lipoprotein cholesterol ratio (NHR) and cognitive function on all-cause mortality in older adults: a population-based study

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Abstract

Background The neutrophil-to-high-density lipoprotein cholesterol ratio (NHR) has emerged as a potential biomarker for chronic disease outcomes. Cognitive impairment is a major contributor to mortality in older adults. However, the combined effect of NHR and cognitive function on all-cause mortality remains unclear. This study aims to investigate the joint impact of NHR and cognitive impairment on all-cause mortality in this population.

Methods We analyzed participants in the National Health and Nutrition Examination Survey (NHANES) between 2011 and 2014. Participants were grouped according to NHR levels, DSST scores, and the combined NHR and DSST. Weighted Cox regression models assessed the association between NHR, cognitive impairment, and all-cause mortality. Weighted Kaplan-Meier curves estimated survival probabilities.

Results The study involved 1,486 participants (weighted sample was 54,078,084) aged 60 years and older, of whom 81.76% ($n=1,180$) survived and 18.24% ($n=306$) died by the end of follow-up. The median follow-up time was 78 months (IQR: 68–94). Weighted multivariable Cox regression revealed that high NHR (HR = 1.82, 95% CI: 1.21–2.74; $P=0.004$), cognitive impairment (HR = 1.87, 95% CI: 1.25–2.79; $P=0.002$), and the combination of high NHR and cognitive impairment (HR = 2.98, 95% CI: 1.45–6.14; $P=0.003$) were independently associated with higher all-cause mortality, after full adjustment in model 3. Kaplan-Meier curves revealed significant survival differences, with the highest survival rate in the NHR Low & Normal cognition and the lowest in the NHR High & Cognitive impairment ($P<0.001$).

Conclusions High NHR and cognitive impairment in aged 60 years and older have an increased risk of all-cause mortality. These findings underscore the importance of integrating both NHR and cognitive assessments in mortality risk evaluations, offering a potential strategy for early intervention in aging populations.

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Keywords Neutrophil-to-high-density lipoprotein cholesterol ratio (NHR), Cognitive impairment, All-cause mortality, Older adults, NHANES

Introduction

Cognitive impairment in older adults has become a significant public health challenge, especially given that aging is one of the primary risk factors for cognitive decline. Cognitive decline has emerged as a significant determinant of mortality among older adults. It is already well established that cognitive impairment and dementia are associated with increased risk of death [1, 2]. Specifically, cognitive decline often predicts adverse outcomes such as decreased functional independence, reduced quality of life, and heightened vulnerability to chronic diseases [3–5]. This relationship is particularly pronounced in aging populations, where the natural course of aging is compounded by underlying medical conditions, frailty, and inflammation [6]. Therefore, understanding the relationship between cognitive function and mortality in older adults is essential.

In recent years, the Neutrophil-to-High-Density Lipoprotein Cholesterol Ratio (NHR) has emerged as a novel biomarker of inflammation and cardiovascular risk. This ratio reflects the balance between neutrophil activity, which plays a role in inflammatory processes, and high-density lipoprotein cholesterol (HDL-C), which is known for its anti-inflammatory and protective effects [7, 8]. Studies indicate that an elevated NHR is a predictor of poor prognosis in several populations, including those with metabolic syndrome, cardiovascular diseases, diabetes, and cancer, and has been associated with increased mortality [9–11]. Increased NHR was also identified as a strong and independent predictor of all-cause mortality in the general population, further supporting its potential role in risk assessment [12]. However, the specific impact of NHR on all-cause mortality in older adults, especially in relation to cognitive function, remains poorly understood.

The NHR reflects systemic inflammation and lipid metabolism imbalance, while cognitive impairment is associated with neurodegeneration and neuroinflammation. Both elevated NHR and cognitive impairment are linked to poor health outcomes through inflammatory pathways. Although these factors are individually recognized as predictors of mortality, their potential synergistic effect remains unclear. Their coexistence may signify a higher-risk phenotype that warrants further investigation. However, few studies have explored their combined impact on health outcomes. Therefore, this study will utilize large-scale databases such as the National Health and Nutrition Examination Survey (NHANES) to explore the combined impact of NHR and cognitive function and on all-cause mortality in older adults. The findings aim to provide evidence on the association between NHR, cognitive function, and all-cause mortality, contributing to a better understanding of mortality risk in older adults. This may provide evidence for early risk assessment and intervention in clinical practice. Furthermore, understanding the interplay between these factors could inform public health strategies aimed at reducing mortality and improving the quality of life in aging populations.

Methods

Study population

NHANES is a large, complex, multistage survey of the noninstitutionalized U.S. population, conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS). Data used in this study were derived from a de-identified and publicly database (https://www.cdc.gov/nchs/nhanes/index.htm). The survey provides nationally representative estimates of health and nutritional status. The NHANES protocol was approved by the NCHS Research Ethics Review Board, and all participants provided informed consent. Data collection occurred through the Mobile Examination Center (MEC), which included face-to-face interviews, physical examinations, and laboratory tests. Our analysis focused on 3,632 participants aged 60 and older, selected from the 19,931 individuals who participated in NHANES between 2011 and 2014. We excluded participants with missing data, resulting in a final sample of 1,486 individuals. The participant selection process is illustrated in Fig. 1.

Baseline characteristics

Demographic, examination, laboratory and questionnaire data were downloaded from the NHANES website. Covariates considered include several demographic characteristics: sex, age (years), race, body mass index (BMI), family income (poverty income ratio, PIR), educational attainment (less than a high school education, some high school, high school graduate/General educational development (GED), some college or associate's degree, college graduate or more). Race was categorized as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black or other races. Smoking status was classified as never-smoker, former smoker or current smoker. Individuals were considered nondrinkers, 1 to < 5 drinks/month, 5 to < 10 drinks/month, or ≥ 10 drinks/month. Hypertension status was determined from a self-reported medical history of high blood pressure, antihypertensive medicine, or non-same-day randomized records of 3 times of systolic blood pressure ≥ 140 mmHg or diastolic

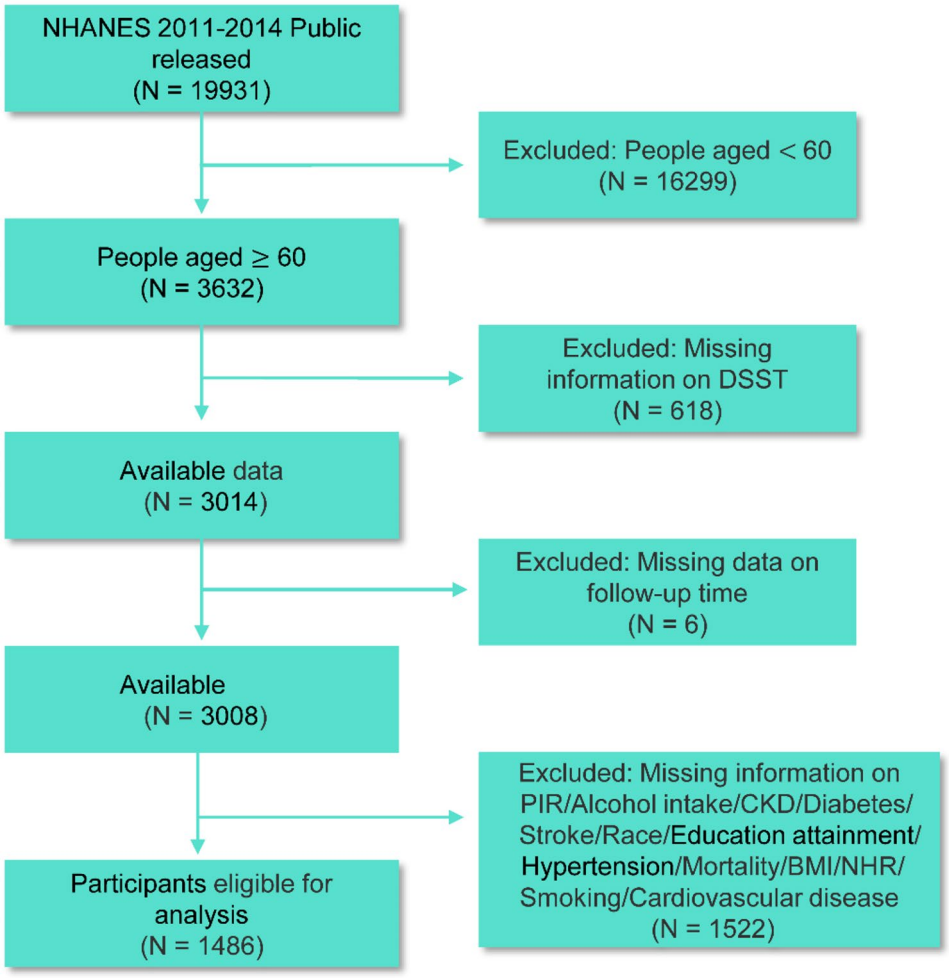

Fig. 1 Flowchart of participant selection from NHANES 2011–2014

blood pressure ≥ 90 mmHg [13]. Participants with diabetes were identified as having any of the following: hemoglobin A1C concentration ≥ 6.5% or a fasting plasma glucose level ≥ 126 mg/dL; for those who responded "yes" to the question: "Have you ever been told by a doctor that you have diabetes?", "Are you now taking insulin?", "Are you now taking diabetic pills to lower your blood sugar?" [14]. Creatinine, Neutrophil count and high-density lipoprotein cholesterol (HDL-C) were measured in the NHANES laboratory. Cardiovascular disease was defined as a self-reported diagnosis of heart failure, coronary heart disease, angina, heart attack. The eGFR was calculated from the serum creatinine (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Eq. 2009) [15]. Chronic kidney disease (CKD) is defined by eGFR < 60 mL/min/1.73 m^2.

Calculation of NHR

The NHR data used in this study were collected during the NHANES cycles from 2011 to 2014. Neutrophil counts were determined by total blood count using an automated blood analysis system and displayed as 10 ^ 3 cells / μL. HDL-C levels were assessed using an automatic device with venous blood samples obtained after 8-hour fasting. NHR is calculated as the neutrophil count (10^3 cells/μL) divided by the HDL-C level (mmol/L) [16]. The optimal cut-off value of NHR was 3.65 determined by the"surv_cutpoint" function in the "survminer" package [17]. Participants were categorized into NHR Low (< 3.65) and NHR High (≥ 3.65) as NHR group.

Calculation of cognitive function

Cognitive function was assessed using the Digit Symbol Substitution Test (DSST) for participants aged 60 and older from the NHANES 2011–2012 and 2013–2014 cycles. DSST evaluates important aspects of executive function, including processing speed, sustained attention, and working memory [18]. Participants match numerals to symbols based on a provided key, scoring one point for each correct match within 120 s, with a maximum score of 133, higher scores on these tests indicate better cognitive function, a result supported by extensive research

[19, 20]. There is no universally accepted "gold standard" for defining low cognitive performance using the DSST. Cognitive impairment was defined using the 25th percentile cut-off, consistent with previous research [21–23]. Participants scoring below this threshold in any of the three tests were classified as cognitively impaired. The DSST groups were then divided into normal cognition and cognitive impairment categories.

Mortality data

All-cause mortality refers to death from any cause were the primary outcomes. Mortality data were obtained by linking the study dataset with the National Death Index (NDI) through the Public-use Linked Mortality Files, available from the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/nchs/data-linkage/mortality.htm). Specifically, mortality outcomes were derived from the 2011–2014 NHANES public-use linked mortality files, with causes of death classified according to the International Classification of Diseases, Tenth Revision (ICD-10). Follow-up time was calculated from the date of interview to the date of death, or the end of follow-up (December 31, 2019), whichever came first [24].

Statistical analysis

NHANES utilized a complex, multistage, probability sampling design for representativeness of the US civilian non-institutionalized population. Sample weights, stratification, and clustering were incorporated in the analysis. A 2-year weight (wtsa2 year) was selected for the DSST score subsamples from the 2011–2012 and 2013–2014 cycles, with the final weight adjusted to 1/2 wtsa2 year for NHANES 2011–2014. Baseline characteristics were compared between the NHR and DSST groups, with continuous variables presented as medians (Q1, Q3) and categorical variables as counts (weighted percentages). Pearson's chi-square tests, with Rao & Scott adjustments for complex survey design, were used for categorical variables, and design-based Kruskal-Wallis tests for continuous variables. Log-rank and weighted Kaplan-Meier survival analyses were applied to compare survival probabilities. We created four subgroup (NHR Low & Normal cognition, NHR High & Normal cognition, NHR Low & Cognitive impairment, and NHR High & Cognitive impairment) to assess the combined effect of NHR and cognitive function on mortality using three weighted Cox regression models: Model 1 (unadjusted), Model 2 (adjusted for sex, age, race, education, PIR, alcohol intake, and smoking), and Model 3 (further adjusted for hypertension, diabetes, stroke, cardiovascular disease, BMI, and CKD) [25]. The NHR group, DSST group, and NHR & DSST group were analyzed separately in different models to assess their independent associations with all-cause mortality. Each model was adjusted for potential confounders as outlined. All analyses were conducted using R version 4.3.3, with statistical significance defined as $P < 0.05$.

Results

Baseline characteristics of the participants

A total of 1,486 participants aged 60 years and older were enrolled in this study from the NHANES 2011–2014 database. Based on the NHANES sampling design, the weighted data analysis provided a population estimate of 54,078,084, representing the US population aged 60 and older. By the end of follow-up, 81.76% ($n = 1,180$) survived, while 18.24% ($n = 306$) passed away. The median follow-up time was 78 months (IQR: 68–94) for the overall population, 81 months (IQR: 71–95) for the survivors, and 54 months (IQR: 32–72) for those who passed away.

In terms of NHR group, 33.16% of participants were in the NHR High group. The NHR High group had higher neutrophil counts, lower HDL-C levels, and higher NHR scores. The NHR High group also had a higher proportion of smokers, increased alcohol consumption, BMI ≥ 30, and higher rates of hypertension, diabetes, and cardiovascular disease ($P < 0.001$) (Table 1). Additionally, the NHR High group had lower DSST score and a higher all-cause mortality rate ($P < 0.001$).

In terms of cognitive function, 84.03% were in the normal cognition group and 15.97% in the cognitive impairment group (Table 2). The cognitive impairment group was older, with higher proportions in the 70–79 (36.21%) and ≥ 80 (33.63%) age groups ($P < 0.001$). Significant differences were found in race, education ($P < 0.001$), and smoking status ($P = 0.029$). Hypertension ($P = 0.001$), diabetes ($P = 0.002$), and cardiovascular disease ($P < 0.001$) were more common in this group, which also had a higher all-cause mortality rate.

Impact on all-cause mortality across different groups

Weighted Cox regression results are shown in Table 3. The NHR group, DSST group, and NHR & DSST group were examined separately across different models to evaluate their independent associations with all-cause mortality, with adjustments for potential confounders. Higher NHR and cognitive impairment were independently associated with increased mortality risk. After full adjustment in model 3, high NHR (HR = 1.82, 95% CI: 1.21–2.74, $P = 0.004$) remained significantly associated with higher mortality. Similarly, cognitive impairment (HR = 1.87, 95% CI: 1.25–2.79, $P = 0.002$) also remained significantly linked to higher mortality. The combination of high NHR and cognitive impairment showed the highest mortality risk (HR = 2.98, 95% CI: 1.45–6.14, $P = 0.003$), this finding is further supported by the weighted multivariable Cox regression analysis presented in Fig. 2.

Table 1 Characteristics of the participants based on NHR group

Characteristic	NHR Low *N* = 980 (66.84%)[1]	NHR High *N* = 506 (33.16%)[1]	*P* value[2]
Neutrophil count (1000 cells/uL)	3.40 (2.60, 4.00)	5.30 (4.50, 6.30)	< 0.001
HDL-C (mmol/L)	1.45 (1.27, 1.81)	1.06 (0.93, 1.24)	< 0.001
NHR	2.34 (1.67, 2.90)	4.76 (4.17, 5.87)	< 0.001
Sex			< 0.001
Female	548 (57.81%)	196 (40.52%)	
Male	432 (42.19%)	310 (59.48%)	
Age			0.12
60–69 years	501 (53.25%)	250 (50.49%)	
70–79 years	273 (26.44%)	152 (31.68%)	
≥ 80 years	206 (20.31%)	104 (17.83%)	
Race			0.12
Mexican American	81 (3.22%)	53 (4.31%)	
Other Hispanic	96 (3.58%)	61 (4.21%)	
Non-Hispanic White	448 (79.63%)	273 (79.85%)	
Non-Hispanic Black	256 (9.01%)	79 (5.82%)	
Other/multiracial	99 (4.56%)	40 (5.82%)	
Education attainment			< 0.001
Less Than 9th Grade	109 (5.59%)	66 (7.92%)	
9-11th Grade	143 (10.11%)	70 (12.72%)	
High School Graduate/GED	207 (18.10%)	148 (27.96%)	
Some College or AA degree	279 (33.14%)	145 (32.48%)	
College Graduate or above	242 (33.06%)	77 (18.91%)	
Alcohol intake			< 0.001
1–5 drinks/month	460 (46.77%)	291 (57.97%)	
5–10 drinks/month	43 (4.84%)	15 (2.79%)	
≥ 10 drinks/month	163 (20.63%)	42 (9.11%)	
Non-drinker	314 (27.75%)	158 (30.13%)	
Smoking			< 0.001
Current smoker	96 (7.36%)	96 (18.53%)	
Former smoker	356 (38.30%)	233 (48.23%)	
Never smoker	528 (54.34%)	177 (33.24%)	
BMI (kg/m^2)			< 0.001
< 30	631 (66.16%)	238 (42.55%)	
≥ 30	349 (33.84%)	268 (57.45%)	
Hypertension			< 0.001
No	301 (37.05%)	106 (20.84%)	
Yes	679 (62.95%)	400 (79.16%)	
Diabetes			< 0.001
No	610 (72.11%)	170 (38.84%)	
Yes	370 (27.89%)	336 (61.16%)	
PIR			0.005
≤ 1.3	284 (17.07%)	192 (25.84%)	
1.3 < to ≤ 3.5	411 (41.54%)	212 (44.28%)	
> 3.5	285 (41.38%)	102 (29.88%)	
Stroke			0.008
No	916 (94.60%)	455 (88.29%)	
Yes	64 (5.40%)	51 (11.71%)	
Cardiovascular disease			< 0.001
No	822 (84.19%)	353 (68.13%)	
Yes	158 (15.81%)	153 (31.87%)	
CKD			< 0.001
No	795 (81.98%)	341 (69.09%)	

Table 1 (continued)

Characteristic	NHR Low *N* = 980 (66.84%)[1]	NHR High *N* = 506 (33.16%)[1]	*P* value[2]
Yes	185 (18.02%)	165 (30.91%)	
DSST score	53 (42, 65)	48 (36, 57)	< 0.001
All-cause mortality			< 0.001
Alive	820 (86.43%)	360 (72.35%)	
Death	160 (13.57%)	146 (27.65%)	

[1]Median (Q1, Q3); n (weighted %)

[2]Design-based Kruskal Wallis test; Pearson's X^2: Rao & Scott adjustment

Abbreviation DSST, Digit Symbol Substitution Test; BMI, body mass index; PIR, Income to poverty ratio; HDL-C, High-density lipoprotein cholesterol; NHR, neutrophil count/ high-density lipoprotein cholesterol; CKD, Chronic kidney disease; GED, General educational development; AA, Associate of Arts

The forest plot (Fig. 2) illustrates the association between the NHR & DSST group and each risk factor with all-cause mortality, based on the weighted multivariable Cox regression analysis in the fully adjusted Model 3. Hazard ratio (HR) was calculated using weighted multivariable Cox regression, with NHR Low & normal cognition as the reference. NHR High & Normal cognition (HR = 2.12, 95% CI: 1.42–3.17, $P < 0.001$), NHR Low & Cognitive impairment (HR = 2.44, 95% CI: 1.46–4.08, $P < 0.001$), and NHR High & Cognitive impairment (HR = 2.98, 95% CI: 1.45–6.14, $P = 0.003$) all showed significantly higher mortality risk. Age was a significant risk factor, with those aged 70–79 (HR = 2.20, $P < 0.001$) and those aged 80 and older (HR = 5.01, $P < 0.001$). CKD (HR = 1.49, $P = 0.01$) increased mortality risk. However, a higher PIR > 3.5 was associated with reduced mortality (HR = 0.60, $P = 0.041$).

Kaplan-Meier survival curves for NHR and DSST

The weighted Kaplan-Meier survival curves were depicted in Fig. 3. The curves for the NHR group (Fig. 3A) illustrated those individuals with high NHR exhibited a significantly lower survival probability than those with low NHR ($P < 0.001$). The survival curves for the DSST group (Fig. 3B) indicated a significantly higher survival probability for individuals with normal cognition compared to those with cognitive impairment ($P < 0.001$). The combined analysis of NHR & DSST group (Fig. 3C) showed significant differences in survival probabilities ($P < 0.001$), with the highest survival in the NHR Low & normal cognition, the lowest in the NHR High & Cognitive impairment, and intermediate survival in the NHR High & Normal cognition and NHR Low & Cognitive impairment, with the former slightly higher.

Discussion

This study highlights the combined impact of NHR and cognitive function on all-cause mortality in older adults. Participants with cognitive impairment were older, had lower education levels, and higher rates of hypertension, diabetes, and cardiovascular disease, leading to higher mortality. Similarly, individuals with the high NHR had higher rates of smoking, BMI, hypertension, diabetes, and cardiovascular disease, with a higher mortality rate. Both high NHR and cognitive impairment were independently associated with increased mortality risk, with their combination showing the highest risk. Weighted multivariable Cox regression analysis confirmed the combined impact of NHR and cognitive function on mortality. Additionally, age and chronic kidney disease increased mortality risk, while a higher PIR > 3.5 was protective. Increasing age is associated with higher mortality risk due to the cumulative effects of age-related decline in physiological function, increased comorbidities, and reduced resilience to illness. Similarly, CKD increases mortality risk as it is often accompanied by deteriorating kidney function, metabolic imbalances, and a higher incidence of cardiovascular complications. In contrast, a higher PIR > 3.5 is protective, likely reflecting better socioeconomic status, which facilitates access to quality healthcare, healthier lifestyles, and lower levels of stress, ultimately contributing to a lower risk of death. The weighted Kaplan-Meier survival curves showed that the highest survival in the NHR Low & normal cognition, the lowest in the NHR High & Cognitive impairment. The findings indicate that the combination of high NHR and cognitive impairment significantly increases the risk of all-cause mortality in older adults, with the highest risk observed when both factors are present.

NHR, as an inflammatory marker, represents a risk factor for predicting mortality [26]. The "survminer: surv_cutpoint" package is widely used in survival prognosis analysis [17, 27]. This function employs the maximally selected rank statistics (also known as the maximization of the log-rank test statistic) to identify the cut-off that best separates the survival groups [28]. By calculating the optimal threshold, it ensures that the dichotomization of the continuous variable provides the most significant survival difference between the groups. This methodology is based on well-established statistical principles and has been widely used in survival analysis to define meaningful cut-offs for continuous variables. We used this method to determine a cutoff value of 3.65, dividing NHR into NHR group including NHR Low and NHR high.

Table 2 Characteristics of the participants based on cognitive function

Characteristic	Normal cognition *N* = 1080 (84.03%)[1]	Cognitive impairment *N* = 406 (15.97%)[1]	*P* value[2]
DSST score	54 (45, 65)	26 (21, 30)	< 0.001
Sex			0.5
Female	557 (51.67%)	187 (54.22%)	
Male	523 (48.33%)	219 (45.78%)	
Age			< 0.001
60–69 years	593 (56.54%)	158 (30.16%)	
70–79 years	291 (26.65%)	134 (36.21%)	
≥ 80 years	196 (16.80%)	114 (33.63%)	
Race			< 0.001
Mexican American	80 (2.49%)	54 (9.34%)	
Other Hispanic	81 (2.29%)	76 (11.65%)	
Non-Hispanic White	603 (84.42%)	118 (54.89%)	
Non-Hispanic Black	197 (5.53%)	138 (20.72%)	
Other/multiracial	119 (5.28%)	20 (3.40%)	
Education attainment			< 0.001
Less Than 9th Grade	37 (2.27%)	138 (27.96%)	
9-11th Grade	123 (8.99%)	90 (21.41%)	
High School Graduate/GED	258 (20.50%)	97 (25.96%)	
Some College or AA degree	362 (35.61%)	62 (18.78%)	
College Graduate or above	300 (32.64%)	19 (5.89%)	
Alcohol intake			< 0.001
1–5 drinks/month	533 (50.44%)	218 (50.75%)	
5–10 drinks/month	51 (4.72%)	7 (1.24%)	
≥ 10 drinks/month	173 (18.46%)	32 (8.12%)	
Non-drinker	323 (26.38%)	149 (39.89%)	
Smoking			0.029
Current smoker	122 (10.27%)	70 (15.23%)	
Former smoker	439 (42.42%)	150 (37.22%)	
Never smoker	519 (47.30%)	186 (47.55%)	
BMI (kg/m^2)			0.8
< 30	628 (58.14%)	241 (59.34%)	
≥ 30	452 (41.86%)	165 (40.66%)	
Hypertension			0.001
No	319 (33.88%)	88 (20.05%)	
Yes	761 (66.12%)	318 (79.95%)	
Diabetes			0.002
No	612 (63.81%)	168 (46.68%)	
Yes	468 (36.19%)	238 (53.32%)	
PIR			< 0.001
≤ 1.3	267 (15.19%)	209 (45.22%)	
1.3 < to ≤ 3.5	463 (42.36%)	160 (42.93%)	
> 3.5	350 (42.45%)	37 (11.85%)	
Stroke			0.003
No	1,015 (93.74%)	356 (86.00%)	
Yes	65 (6.26%)	50 (14.00%)	
Cardiovascular disease			< 0.001
No	874 (80.78%)	301 (68.78%)	
Yes	206 (19.22%)	105 (31.22%)	
CKD			< 0.001
No	865 (81.26%)	271 (59.00%)	
Yes	215 (18.74%)	135 (41.00%)	
Neutrophil count (1000 cells/uL)	3.80 (3.00, 4.80)	4.30 (3.30, 5.20)	0.007

Table 2 (continued)

Characteristic	Normal cognition *N* = 1080 (84.03%)[1]	Cognitive impairment *N* = 406 (15.97%)[1]	*P* value[2]
HDL-C (mmol/L)	1.34 (1.11, 1.66)	1.24 (1.06, 1.53)	0.022
NHR	2.85 (1.93, 3.96)	3.21 (2.38, 4.87)	0.003
NHR Group			0.047
NHR Low	728 (68.41%)	252 (58.59%)	
NHR High	352 (31.59%)	154 (41.41%)	
All-cause mortality			< 0.001
Alive	899 (85.20%)	281 (63.69%)	
Death	181 (14.80%)	125 (36.31%)	

[1]Median (Q1, Q3); n (weighted %)

[2]Design-based Kruskal Wallis test; Pearson's X^2: Rao & Scott adjustment

Table 3 Weighted multivariable Cox regression models to all-cause mortality

Characteristic	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95%CI)	*P* value
NHR Group						
NHR Low	Refence		Refence		Refence	
NHR High	2.31(1.62, 3.30)	< 0.001	2.25(1.55, 3.25)	< 0.001	1.82(1.21, 2.74)	0.004
DSST Group						
Normal cognition	Refence		Refence		Refence	
Cognitive impairment	2.91(1.90, 4.46)	< 0.001	2.24(1.51, 3.33)	< 0.001	1.87(1.25, 2.79)	0.002
NHR & DSST Group						
NHR Low & Normal cognition	Refence		Refence		Refence	
NHR High & Normal cognition	2.48(1.71, 3.58)	< 0.001	2.52(1.69, 3.77)	< 0.001	2.12(1.42, 3.17)	< 0.001
NHR Low & Cognitive impairment	3.37(2.07, 5.48)	< 0.001	2.75(1.67, 4.52)	< 0.001	2.44(1.46, 4.08)	< 0.001
NHR High & Cognitive impairment	5.54(2.99, 10.3)	< 0.001	4.29(2.25, 8.21)	< 0.001	2.98(1.45, 6.14)	0.003

HR = Hazard Ratio, CI = Confidence Interval

Model 1: no adjustment

Model 2: adjusted for Sex, Age, Race, Education attainment, PIR, Alcohol intake, Smoking

Model 3: adjusted for Model 2 plus Hypertension, Diabetes, BMI, Stroke, Cardiovascular disease, CKD

In previous studies, NHR is often divided into tertile or quartile for analysis [29, 30]. By selecting the optimal cutoff value using this method, the grouping boundaries can be determined based on the data itself, rather than a predefined standard, which helps provide more objective and practical results. Our study found that high NHR was significantly associated with all-cause mortality after full adjustment (HR = 1.82). Similarly, Jiang et al. [12] reported a 29% higher risk of all-cause mortality for participants in the highest tertile of NHR compared to the lowest tertile (HR = 1.29), while Chuang et al. [31] observed that the highest quartile of NHR was associated with an increased risk of all-cause mortality (HR = 1.48). In addition, a study by Wu et al. demonstrated that elevated NHR levels were independently associated with a 40% increased risk of all-cause mortality, further supporting the role of NHR as a predictor of mortality risk in older adults [32]. Similarly, Chen et al. found that higher NHR levels were significantly associated with an increased risk of in-hospital major adverse cardiac events (MACE) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (HR = 2.211, 95% CI: 1.092–4.479, $P = 0.027$), suggesting that NHR may serve as a valuable prognostic marker for predicting adverse outcomes in cardiovascular diseases [33]. Furthermore, a recent study by Ren et al. found that the diagnostic power of NHR was stronger in ST-segment elevated acute coronary syndrome (STE-ACS) patients compared to non-ST-segment elevated acute coronary syndrome (NSTE-ACS) patients ($P < 0.001$), highlighting the potential of NHR as a convenient and effective marker for predicting the presence, progression, and severity of acute coronary syndrome in type 2 diabetes mellitus (T2DM) patients [34]. These studies support NHR as a marker for all-cause mortality risk across different populations. Our study found that participants in the high NHR had higher rates of smoking, BMI ≥ 30, hypertension, diabetes, and cardiovascular disease. Other study had shown that high NHR was linked to the development of metabolic syndrome such as obesity, hypertension, and diabetes [35]. High NHR may thus be associated with the cumulative effects of chronic diseases. NHR independently predicted

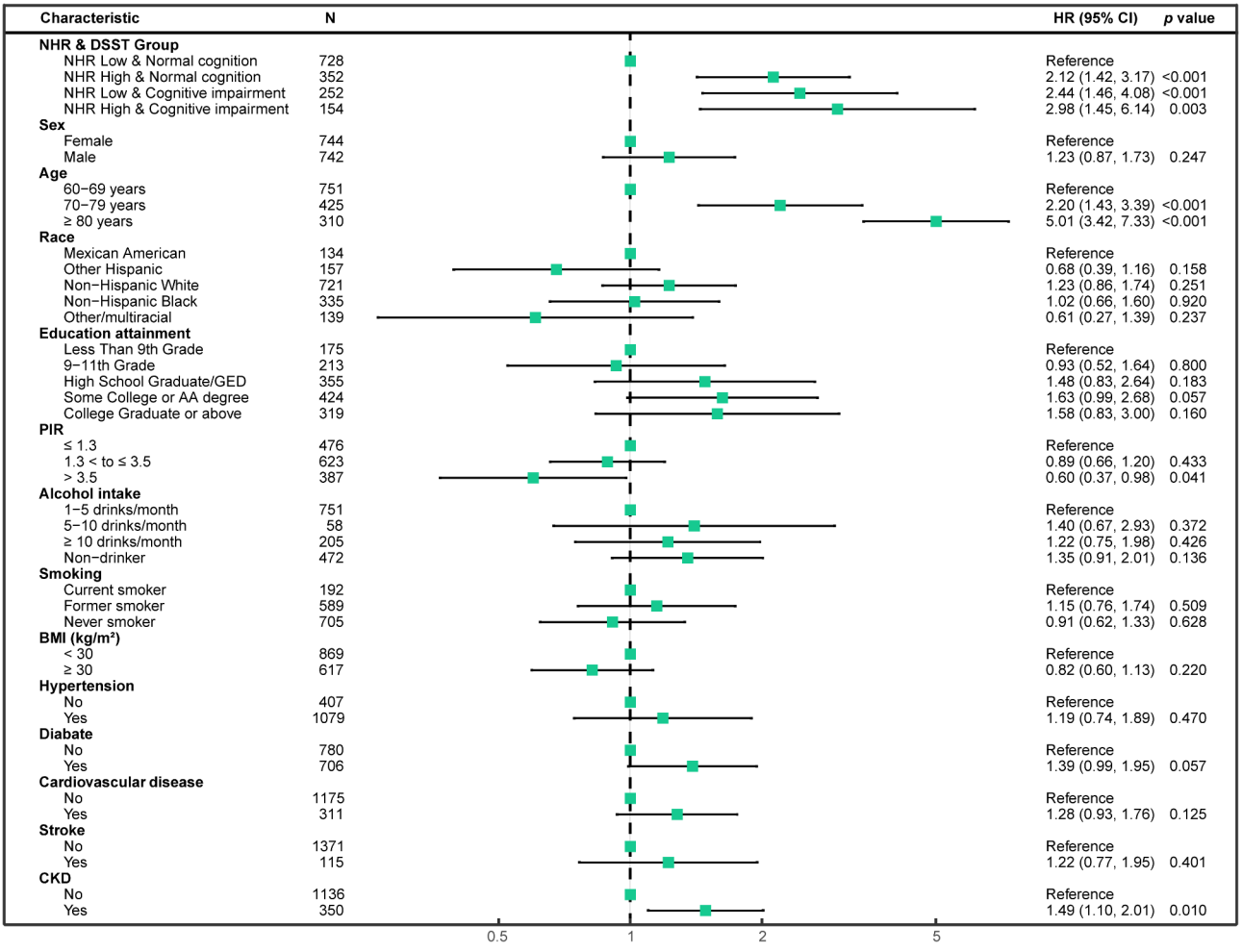

Fig. 2 Forest plot of the weighted multivariable Cox regression analysis for the association between characteristic groups and all-cause mortality

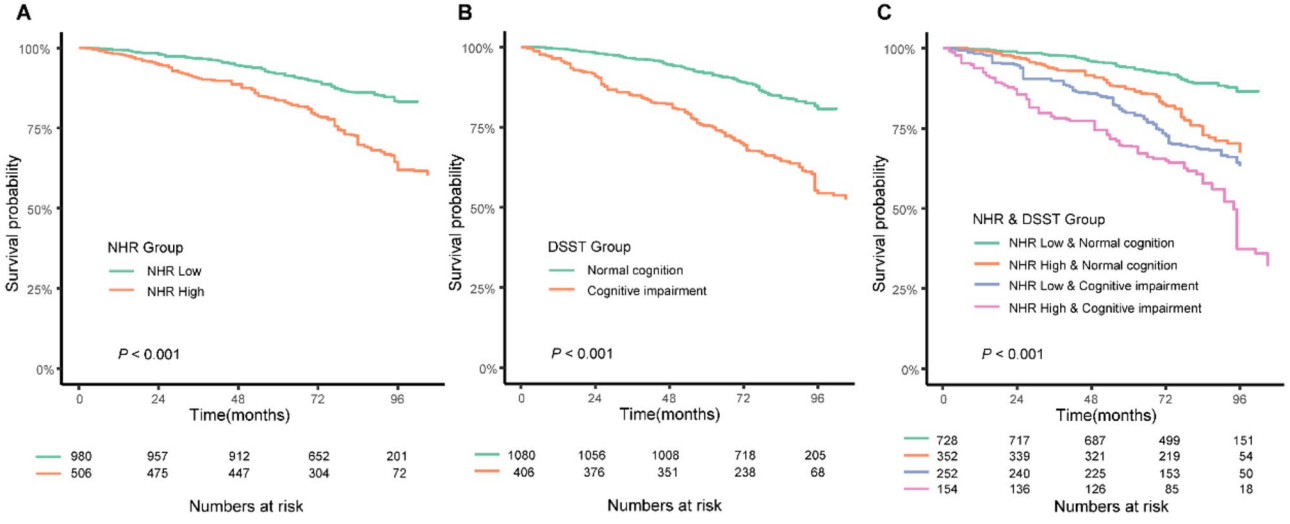

Fig. 3 Weighted Kaplan-Meier analyses by Log-rank for all-cause mortality. **A** NHR Group, **B** DSST Group, **C** NHR & DSST Group

all-cause mortality, with higher levels linked to increased risk.

DSST, a widely used tool for assessing cognitive function, has been linked to mortality in multiple studies [36–38]. In our study, cognitive impairment was defined using the 25th percentile cut-off, with 15.97% of older adults classified as impaired, aligning with previous reports estimating 10–20% of U.S. adults aged ≥ 65 having mild cognitive impairment [39]. Using the 25th percentile threshold offers a more reasonable method for estimating prevalence. Some studies have demonstrated a significant association between cognitive impairment and all-cause mortality. A population-based cohort study [40] found that in the 2002–2008 cohort, the risk of all-cause mortality due to cognitive impairment was 1.32 times higher, while in the 2008–2014 cohort, it was 1.26 times higher. Another study using data from the English Longitudinal Study of Ageing found that mild cognitive impairment was associated with a 1.40 times higher mortality risk, and moderate to severe cognitive impairment with a 2.49 times higher risk, compared to normal cognitive function [41]. In our study, after adjusting for confounders, the all-cause mortality risk was 1.87 times higher in the cognitive impairment group than in the normal cognition group, which reveals that impaired cognitive function is significantly linked to all-cause mortality in older adults, consistent with findings from other studies. Zhao et al. found that impairments in various cognitive subdomains, such as naming foods, registration, attention and calculation, copy figure, delayed recall, and language, were independently associated with increased mortality risk among participants [42]. Georgakis et al. reported that the coexistence of cognitive impairment (COGI) and depression increased all-cause and cardiovascular mortality risks by 66% and 72%, respectively, highlighting the synergistic impact of cognitive and mental health disorders on mortality outcomes [43]. These findings highlight the importance of early detection and management of cognitive impairment in the elderly to reduce mortality risk.

Our research provides new insights into the relationship between cognitive function and mortality by including the analysis of NHR. In our study, the results showed that the group with NHR Low & Normal cognition had the highest survival probability, while that with NHR High & Cognitive impairment had the lowest survival probability. This suggests that the combined effect of cognitive function and NHR is significant in predicting survival probability. Previous researches suggest that there is a close relationship between NHR and oxidative stress, as NHR reflects the activation state of neutrophils and the level of high-density lipoprotein cholesterol, which indirectly indicates the level of oxidative stress in the body [44, 45]. Meanwhile, numerous studies have shown that oxidative stress plays a key role in the onset and progression of cognitive impairment. It can damage the structure and function of neuronal cells, leading to pathological changes such as neuronal death, neurofibrillary tangles, and amyloid plaque deposition [46, 47]. Therefore, we infer that the combination of high NHR and cognitive impairment may exacerbate brain neurodegeneration through inflammation-induced oxidative stress, thereby increasing the risk of mortality. However, the specific mechanisms still need further research to be confirmed in the future.

Several limitations of this study should be acknowledged. First, although the study includes a relatively large sample size, the generalizability of our findings to other populations, particularly those outside the United States, is constrained. Second, the use of the DSST to assess cognitive function may not fully encompass the range of cognitive impairment. More comprehensive neuropsychological assessments would yield a clearer understanding of the relationship between cognitive decline and mortality. Third, while we adjusted for numerous confounders, residual confounding may still persist, especially concerning lifestyle factors and unmeasured variables such as physical activity and medication use. Fourth, the study did not account for potential variations in NHR levels over time, which may fluctuate due to acute infections, inflammatory conditions, or other transient factors. Finally, due to the limited sample size, we were unable to analyze the associations between NHR, DSST, and cause-specific mortality, which restricts our ability to determine whether the observed relationships are driven by specific disease processes, such as cardiovascular events or cancer.

Future research should address these limitations by employing longitudinal study designs that track individuals over extended periods. This approach would allow for a more accurate assessment of the temporal relationships between NHR, cognitive function, and mortality, thereby strengthening the evidence for causal inferences. Additionally, incorporating a broader range of neuropsychological tests into future studies would provide a more comprehensive evaluation of cognitive function, potentially revealing more detailed insights into how different cognitive domains interact with NHR to influence mortality. Conducting similar studies in diverse populations would enhance the generalizability of the findings. Finally, future research with larger sample sizes should investigate the associations between NHR, DSST, and cause-specific mortality to better understand the disease processes driving the observed relationships and to develop more precise risk stratification tools.

Conclusion

In conclusion, this study found that both high NHR and cognitive impairment are independently associated with an increased risk of all-cause mortality in older adults, with their combination further amplifying this risk. This underscores the importance of considering both cognitive function and NHR when assessing mortality risk in this population. The findings suggest that addressing both high NHR and cognitive impairment together is crucial for public health, and further studies are needed to confirm these results and explore effective prevention strategies.

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Author contributions
A.H. wrote the main manuscript text and performed the statistical analysis. K.Z. wrote the main manuscript text and prepared Figs. 1, 2 and 3. W.S. and X.L. collected the data. L.Z. and X.L. prepared Tables 1, 2, and 3. T.L. and F.C. designed the study, interpretation of the results, and critical revision of the manuscript. All authors reviewed the manuscript.

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Data availability
The datasets generated and analyzed during the current study are available in the National Health and Nutrition Examination Survey (NHANES), https://www.cdc.gov/nchs/nhanes/; Public-useLinked Mortality Files (https://www.cdc.gov/nchs/data-linkage/mortality.htm).

Declarations

Ethics approval and consent to participate
The survey protocol was approved by NCHS Ethics Review Board (https://www.cdc.gov/nchs/nhanes/irba98.htm), and all participants have written informed consent.

Competing interests
The authors declare no competing interests.

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