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ORIGINAL RESEARCH

Association of Prognostic Nutritional Index With Mortality in High-Risk OSA Individuals and with Disease Severity in Clinical OSA Patients

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Background: Obstructive sleep apnea (OSA) shows marked variability in cardiovascular and mortality risk. The Prognostic Nutritional Index (PNI), derived from serum albumin and lymphocyte count, reflects nutritional and inflammatory status, but its relevance in OSA populations remains unclear.

Methods: We analyzed 10,229 adults at risk for OSA from NHANES 2005–2008 and 2015–2018, with mortality follow-up through 2019 (median 5.08 years). Survey-weighted Cox models examined associations between PNI and all-cause and cardiovascular mortality. Dose-response relationships were assessed using restricted cubic splines, and discrimination was evaluated with time-dependent ROC analyses. Subgroup and sensitivity analyses assessed robustness. Additionally, 555 polysomnography-confirmed OSA patients were analyzed cross-sectionally to examine associations between PNI and disease severity.

Results: During follow-up, 1025 all-cause and 287 cardiovascular deaths occurred. Higher PNI was associated with lower all-cause (adjusted HR 0.59, 95% CI 0.47–0.75) and cardiovascular mortality (HR 0.57, 95% CI 0.36–0.89), with significant dose–response trends and nonlinear associations for all-cause mortality. Associations were consistent across subgroups and sensitivity analyses. PNI showed better discrimination for mortality than its individual components (12-month AUC 0.74). In the clinical cohort, higher PNI was associated with reduced odds of severe OSA (OR 0.864, 95% CI 0.833–0.896) and lower apnea-hypopnea index.

Conclusion: Lower PNI is independently associated with higher mortality risk among individuals at risk for OSA and with greater disease severity in confirmed OSA. These findings highlight the potential clinical relevance of nutritional and immune status in OSA populations. However, the temporal and causal relationships between PNI, OSA severity, and mortality require further investigation.

Keywords: prognostic nutritional index, obstructive sleep apnea, all-cause mortality, cardiovascular mortality, nutritional status, immune status, risk stratification

Introduction

Obstructive sleep apnea (OSA) is a common disorder of sleep in which the upper airway repeatedly collapses during the night. These recurrent episodes lead to reduced oxygen levels, disrupted sleep continuity, and alterations in normal circadian regulation.[1] It is estimated that OSA affects nearly 936 million individuals worldwide, among whom roughly 425 million have moderate to severe forms that warrant clinical intervention.[2] Large cohort studies have demonstrated strong associations between OSA and coronary heart disease,[3] atrial fibrillation,[4] cognitive decline,[5] and stroke,[6] as well as an increased risk of all-cause and cardiovascular mortality.[7,8] Adverse outcomes in OSA are primarily driven by mechanisms such as intermittent hypoxia, oxidative stress, systemic inflammation, blood pressure fluctuations, insulin resistance, endothelial dysfunction, and heightened sympathetic activity.[9] Given the central role of systemic inflammation and metabolic dysregulation in OSA-related complications, biomarkers integrating nutritional and immune status may provide additional prognostic value.

The prognostic nutritional index (PNI), derived from serum albumin concentration and lymphocyte count, was initially created to evaluate the nutritional and immune status of patients undergoing surgery.[10] Increasing evidence indicates that PNI is closely related to prognosis in a variety of conditions, including cancer,[11,12] chronic kidney disease,[13] and chronic heart

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failure.[14] By integrating information on nutritional status and systemic inflammation, PNI has demonstrated superior predictive performance for cardiovascular events and long-term mortality compared with its individual components.[15] However, whether PNI carries similar prognostic and disease-severity implications in OSA populations remains unclear.

In this study, we used a nationally representative cohort to examine the association between PNI and all-cause and cardiovascular mortality among individuals at risk for OSA. In an independent clinical cross-sectional cohort of polysomnography-confirmed OSA patients, we further evaluated the relationship between PNI and disease severity. We also explored potential nonlinear associations and compared the predictive performance of PNI with its individual components. Through these analyses, we aimed to clarify the clinical relevance of PNI in OSA populations and to provide evidence for risk stratification and future mechanistic research.

Methods

Study Population and Design

This study employed a two-stage design. First, a nationally representative cohort analysis based on the National Health and Nutrition Examination Survey (NHANES) was conducted to investigate the association between the PNI and long-term mortality outcomes among individuals at risk for OSA. Second, an independent hospital-based clinical cohort was used to further explore the association between PNI and objectively measured OSA severity in a polysomnography-confirmed population.

NHANES is a continuous, nationwide survey administered by the National Center for Health Statistics and is designed to assess the health conditions and dietary patterns of the U.S. population. Data are collected through interviews, standardized physical examinations, laboratory tests, and structured questionnaires using a complex multi-stage probability sampling design.

Participant data from the 2005–2008 and 2015–2018 NHANES cycles were combined, as both cycles included detailed survey items related to sleep disorders. Participants were classified as being at risk for OSA based on an affirmative response to any of the following three binary questions:[16] (1) snoring three or more nights per week; (2) gasping, snorting, or stopping breathing during sleep three or more nights per week; or (3) feeling excessively sleepy during the daytime on 16–30 days per month. Among 39,722 participants from these cycles, 11,717 met the symptom-based criteria for OSA risk. After excluding 1174 participants with missing serum albumin or lymphocyte counts that precluded calculation of the PNI, and 314 participants with missing follow-up or mortality information or who were younger than 18 years, a total of 10,229 adults with complete OSA risk and PNI data were included in the final analysis (Figure 1). It should be noted that NHANES does not include polysomnography data; therefore, OSA was not clinically diagnosed, and only symptom-defined OSA risk was assessed.

The external cohort was a hospital-based cross-sectional study consisting of consecutive adult patients who underwent full-night attended polysomnography at the Sleep Medicine Center of the Second Hospital of Shanxi Medical University between January 2022 and December 2023. OSA was diagnosed according to standard polysomnographic criteria, and disease severity was classified based on the apnea–hypopnea index (AHI), with mild OSA defined as an AHI of 5.0–14.9 events per hour, moderate OSA as an AHI of 15.0–29.9 events per hour, and severe OSA as an AHI of 30.0 events per hour or higher.

Inclusion criteria for the external cohort were a polysomnography-confirmed diagnosis of OSA and availability of baseline serum albumin and peripheral lymphocyte count measurements required for calculation of the PNI. Exclusion criteria included missing laboratory data required for PNI calculation or incomplete polysomnographic recordings. After excluding patients with missing serum albumin or PNI data, a total of 555 patients were finally included in the external cohort.

This hospital-based cohort employed a cross-sectional design and was used to examine the association between PNI and objectively measured OSA severity. Therefore, mortality follow-up was not included. As this study involved retrospective analysis of data collected during routine clinical care, did not include additional interventions or invasive procedures, and posed minimal risk to participants, the requirement for written informed consent was waived by the ethics committee. The research procedures were approved by the Ethics Committee of the Second Hospital of Shanxi

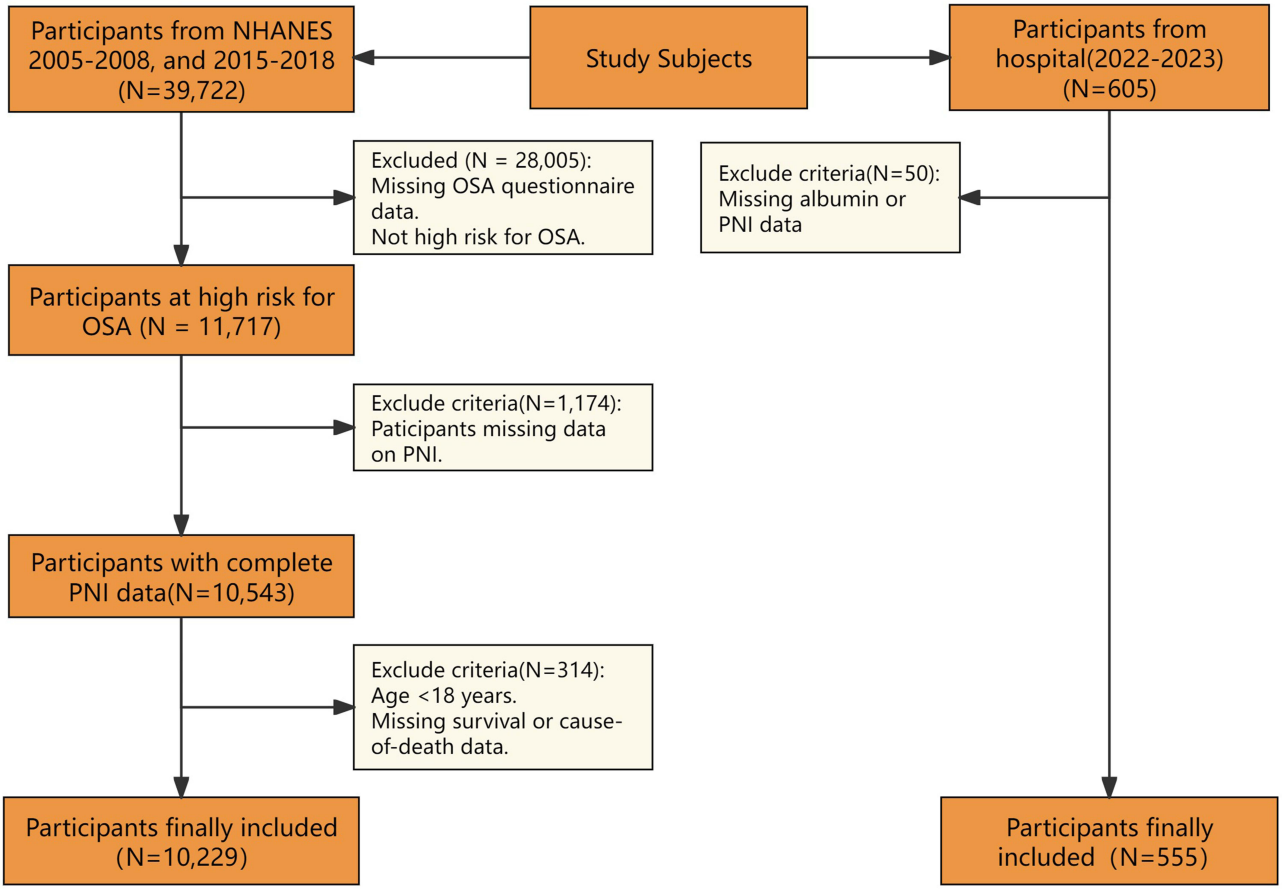

Figure 1 Flow diagram of participants selection. Flowchart illustrating the inclusion and exclusion criteria applied to derive the final analytic sample from the NHANES cohort and the clinical validation cohort.

Medical University (approval No. 2025YX385). All patient data were anonymized prior to analysis. Personal identifiers were removed, and data were accessed only by authorized study investigators for research purposes.

Exposure and Outcome Measures

PNI was the primary exposure variable in analyses evaluating its association with long-term mortality among individuals at risk for OSA. At baseline, PNI was derived using the formula: serum albumin (g/L) plus five times the lymphocyte count (10^9/L).[15] Information on vital status was extracted from the NHANES linked mortality database, which follows participants through probabilistic linkage with the National Death Index, with follow-up available through December 31, 2019. Causes of death were classified based on ICD-10 categories. Deaths from any source were considered all-cause mortality, while cardiovascular mortality included only fatalities attributed to cardiac or cerebrovascular disease.

Covariates of Interest

Covariates were derived from NHANES demographic, clinical, and laboratory data. Sociodemographic factors included age, gender, race/ethnicity (Mexican American, non-Hispanic Black, non-Hispanic White, Other Hispanic, or Other Races), marital status (Married or Living with a Partner, Never married, Widowed/Divorced/Separated), educational level (Above high school, Below high school, High school graduate), and poverty-to-income ratio (PIR: <1.3, 1.3–3.5, ≥3.5). Behavioral and comorbidity factors included smoking status (Former, Never, Current), alcohol use (Never, Former, Mild, Moderate, Heavy), diabetes, hypertension, hyperlipidemia, and cardiovascular disease, all based on self-reported diagnosis.

Additional covariates from physical examinations and laboratory assessments included body mass index (BMI) and biochemical markers: white blood cell (WBC), neutrophils (Neu), lymphocytes (Lym), hemoglobin (Hb), platelets (PLT),

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alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin (ALB), serum creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C).

For the clinical cross-sectional cohort, covariates included demographic parameters. These comprised sex, age, BMI, smoking history and alcohol use. Comorbid conditions included hypertension, diabetes, hyperlipidemia and cardiovascular disease. Due to differences in laboratory measurements between the NHANES and clinical cohorts, lipid-related covariates were selected based on availability within each dataset. Laboratory indicators included complete blood count, ALT, AST, ALB, BUN, Cr, UA, Triglycerides (TG) and HDL-C.

Statistical Analysis

All statistical analyses were performed using R (version 4.5.2). For the NHANES cohort, the complex survey design was accounted for by incorporating sample weights, stratification, and clustering. Continuous variables were reported as weighted means ± standard errors, and categorical variables as weighted percentages. Differences among PNI tertiles were evaluated using survey-weighted linear regression for continuous variables and Rao-Scott chi-square tests for categorical variables. Kaplan-Meier curves were generated to visualize variations in all-cause and cardiovascular mortality across PNI groups, with significance assessed using the Log rank test.

Among individuals at risk for OSA, the association between PNI and mortality was examined using survey-weighted Cox proportional hazards models. Three models were sequentially constructed: Model 1 was unadjusted; Model 2 adjusted for demographic variables (age, sex, race/ethnicity, marital status, education, and poverty-income ratio); Model 3 further included lifestyle factors, comorbidities, and laboratory measurements such as BMI, smoking, alcohol consumption, diabetes, hypertension, hyperlipidemia, cardiovascular disease, and biochemical markers. Restricted cubic spline models were applied to explore potential dose-response relationships. Subgroup and interaction analyses were conducted to evaluate effect modifications across key clinical strata. The predictive ability of PNI for mortality was assessed via ROC curves and compared with its individual components, serum albumin and lymphocyte count.

In the clinical cross-sectional study, mortality outcomes were unavailable. Continuous variables were described using mean ±standard deviation or median with interquartile range, and categorical variables as counts and percentages. Group differences across OSA severity levels were tested using ANOVA, Kruskal–Wallis, or chi-square/Fisher exact tests as appropriate. Logistic regression models assessed the association between PNI and severe OSA, using sequential adjustment: Model 1 unadjusted; Model 2 adjusted for age and sex; Model 3 additionally controlled for BMI, lifestyle factors, comorbidities, and laboratory parameters. Multivariable linear regression was employed to examine the relationship between PNI and AHI with the same set of covariates. ROC analyses evaluated the discriminative performance of PNI for identifying severe OSA compared with serum albumin and lymphocyte counts. Additional subgroup and sensitivity analyses were performed according to symptom-based OSA phenotypes and alternative STOP-defined high-risk criteria to evaluate the robustness of the findings.[17] STOP criteria include Snoring, Tiredness, Observed apnea, and high blood Pressure. In the sensitivity analysis, high-risk OSA was defined as ≥2 of the following: habitual snoring (≥5 nights/week), observed apnea during sleep (≥5 nights/week), excessive daytime sleepiness (16–30 times/month), or hypertension (self-reported physician diagnosis or blood pressure ≥140/90 mmHg).

The sample size for the NHANES cohort was determined by the survey design of the publicly available database. For the clinical cohort (n = 555), post hoc power analysis indicated a statistical power > 0.99, demonstrating adequate power. All statistical tests were two-sided, and P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics According to PNI Tertiles

A total of 10,229 participants at risk for OSA were included and stratified into tertiles based on the PNI: T1 (lowest), T2 (middle), and T3 (highest) (Table 1). Participants in the lowest PNI tertile were generally older and more often female, whereas those in the highest tertile were younger and predominantly male. The mean ages across tertiles were 53.61 ±0.51, 48.32±0.43, and 43.40±0.39 years, and male proportions were 45.43%, 54.26%, and 63.70% (P<0.001). Racial composition varied modestly, with a higher proportion of non-Hispanic Black participants in T1 (13.44%). Participants

Table 1 Demographic and Clinical Characteristics According to PNI Tertiles Among Participants at High Risk of OSA

Variables	Total (n=10,229)	T1 (Lowest) (n=3536)	T2 (Middle) (n=3583)	T3 (Highest) (n=3110)	*P*
Age (years)	48.43±0.33	53.61±0.51	48.32±0.43*	43.40±0.39*†	<0.001
BMI (kg/m2)	30.67±0.11	31.76±0.18	30.34±0.16*	29.95±0.19*	< 0.001
Gender (%)					<0.001*†
Male	5516(54.48)	1623(45.43)	1948(54.26)	1945(63.70)	
Female	4713(45.52)	1913(54.57)	1635(45.74)	1165(36.30)	
Race (%)					<0.001*
Mexican American	1866(9.04)	543(7.53)	711(9.63)	612(9.90)	
Non-Hispanic Black	2158(10.83)	888(13.44)	724(10.48)	546(8.60)	
Non-Hispanic White	4113(66.93)	1458(67.09)	1388(66.21)	1267(67.55)	
Other Hispanic	1071(5.69)	342(5.18)	393(5.89)	336(5.98)	
Other Races	1021(7.51)	305(6.75)	367(7.78)	349(7.96)	
Marital status (%)					<0.001*†
Married/Living with Partner	6592(68.52)	2201(67.26)	2361(69.95)	2030(68.23)	
Never married	1595(14.26)	464(11.05)	540(13.36)	591(18.42)	
Widowed/Divorced/Separated	2042(17.22)	871(21.69)	682(16.68)	489(13.35)	
Education level (%)					0.698
Above high school	4969(57.28)	1698(56.57)	1767(58.14)	1504(57.05)	
Below high school	2746(16.88)	965(17.58)	957(16.43)	824(16.68)	
High school graduate	2514(25.84)	873(25.85)	859(25.43)	782(26.27)	
PIR (%)					0.711
<1.3	3028(19.86)	1084(20.48)	1030(19.05)	914(20.13)	
1.3–3.5	3051(43.15)	1007(42.12)	1108(44.16)	936(43.08)	
≥3.5	4150(36.99)	1445(37.40)	1445(36.79)	1260(36.79)	
Smoking status (%)					< 0.001*†
Former	2658(26.70)	1073(30.76)	906(25.67)	679(23.79)	
Never	5229(49.94)	1848(53.30)	1880(51.33)	1501(45.09)	
Current	2342(23.36)	615(15.94)	797(23.01)	930(31.12)	
Alcohol use (%)					< 0.001*†
Former	2065(17.30)	839(19.95)	675(16.42)	551(15.62)	
Heavy	2108(21.92)	570(16.89)	736(20.92)	802(28.00)	
Mild	3236(35.25)	1131(36.59)	1174(36.75)	931(32.30)	
Moderate	1485(16.11)	497(15.31)	538(16.89)	450(16.08)	
Never	1335(9.42)	499(11.26)	460(9.02)	376(8.01)	
Diabetes (%)					< 0.001*†
IFG/IGT	982(10.35)	381(12.85)	380(11.28)	221(6.84)	
No	6978(72.45)	2224(65.97)	2458(72.95)	2296(78.33)	
Yes	2269(17.21)	931(21.18)	745(15.77)	593(14.83)	
Hypertension (%)					< 0.001*
No	5440(56.64)	1678(51.18)	1950(58.04)	1812(60.53)	
Yes	4789(43.36)	1858(48.82)	1633(41.96)	1298(39.47)	
Hyperlipidemia (%)					0.596
No	2577(25.50)	923(25.09)	881(25.04)	773(26.40)	
Yes	7652(74.50)	2613(74.91)	2702(74.96)	2337(73.60)	
CVD (%)					< 0.001*†
No	8578(88.16)	2783(82.71)	3091(89.88)	2704(91.69)	
Yes	1651(11.84)	753(17.29)	492(10.12)	406(8.31)	

Notes: Continuous variables were compared using weighted linear regression models, and categorical variables were compared using the Rao-Scott chi-square test. Data are presented as mean ± standard error (SE) for continuous variables and as n (%) for categorical variables. All analyses accounted for the complex, multistage probability sampling design of NHANES. *p < 0.05 compared with T1 (lowest) group. †p < 0.05 compared with T2 (lowest) group.

Abbreviations: BMI, body mass index; PIR, poverty-to-income ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CVD, cardiovascular disease.

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with lower PNI were also more likely to be widowed, divorced, or separated, while education level and poverty-income ratio did not differ significantly (both $P > 0.05$).

Lifestyle and comorbidity profiles differed significantly across PNI tertiles. Current smoking and heavy alcohol consumption increased progressively from T1 to T3 (both $P<0.001$), whereas former smokers and drinkers were more prevalent in T1. Cardiometabolic comorbidities, including diabetes, hypertension, and cardiovascular disease, were more frequent in the lowest PNI tertile (all $P < 0.001$), while hyperlipidemia rates were comparable. BMI also varied significantly across tertiles ($P < 0.001$).

Overall, lower PNI values corresponded to an older age, female predominance, higher comorbidity burden, and less favorable lifestyle, reflecting a more vulnerable clinical phenotype among individuals at risk for OSA.

Laboratory and Metabolic Characteristics Across PNI Tertiles

Laboratory assessments demonstrated distinct patterns across PNI tertiles (Table 2). Higher PNI was associated with increased lymphocyte count, hemoglobin, and serum albumin (all $P < 0.001$), underscoring PNI as an integrated indicator of nutritional and immune function. WBC, neutrophil, and platelet counts showed modest increases, while creatinine and BUN were slightly elevated in T1, suggesting an association between low nutritional status and subclinical renal impairment. Liver enzymes (ALT, AST) and uric acid increased with PNI, whereas HDL-C decreased (all $P < 0.01$). These findings indicate that higher PNI reflects better metabolic and immune resilience, whereas low PNI is linked to less favorable biochemical profiles.

Association Between PNI Levels and Mortality in Individuals at Risk for OSA

Over a median follow-up of 5.08 years, there were 1025 deaths from all causes, including 287 due to cardiovascular events. Kaplan-Meier analysis revealed a clear gradient in survival across PNI tertiles (Figure 2), with patients in the lowest tertile (T1) exhibiting markedly higher all-cause mortality than those in T2 and T3 (log-rank P < 0.001). In survey-weighted Cox proportional hazards models (Table 3), when PNI was entered into the model as an exposure variable, individuals in the highest tertile (T3) had significantly lower risks of both all-cause mortality (HR 0.34, 95% CI 0.28–0.41) and cardiovascular mortality (HR 0.23, 95% CI 0.17–0.30) in the unadjusted analysis. These inverse

Table 2 Laboratory and Metabolic Profiles According to PNI Tertiles Among Participants at High Risk of OSA

Variables	Total (n=10,229)	T1 (Lowest) (n=3536)	T2 (Middle) (n=3583)	T3 (Highest) (n=3110)	*P*
WBC (10^9/L)	7.52±0.03	6.71±0.05	7.36±0.06*	8.52±0.07*†	< 0.001
Neu (10^9/L)	4.46±0.03	4.24±0.05	4.41±0.05*	4.73±0.04*†	< 0.001
Lym (10^9/L)	2.21±0.01	1.68±0.01	2.11±0.01*	2.86±0.03*†	< 0.001
Hb (g/dL)	14.44±0.04	13.90±0.04	14.52±0.05*	14.88±0.04*†	< 0.001
PLT (10^9/L)	258.52±1.09	249.34±1.96	258.28±1.46*	267.91±1.69*†	< 0.001
ALT (U/L)	26.85±0.22	24.20±0.33	27.06±0.44*	29.24±0.38*†	< 0.001
AST (U/L)	25.34±0.18	24.57±0.32	25.26±0.31	26.20±0.25*	< 0.001
ALB (g/L)	42.16±0.08	39.32±0.09	42.42±0.07*	44.69±0.08*†	< 0.001
BUN (mg/dL)	13.97±0.11	14.65±0.18	13.77±0.15*	13.50±0.14*	< 0.001
Cr (μmol/L)	79.44±0.41	81.12±0.98	78.12±0.38*	79.20±0.43	0.004
UA (μmol/L)	333.09±1.23	324.73±2.59	331.37±1.71	343.29±1.95*†	< 0.001
TC (mg/dL)	195.03±0.78	190.91±1.37	194.79±0.91*	199.38±1.20*†	< 0.001
HDL (mg/dL)	51.32±0.27	53.31±0.43	51.32±0.37*	49.33±0.43*†	< 0.001

Notes: Continuous variables were compared across PNI tertiles using weighted linear regression. Data are presented as mean ± standard error (SE). Analyses accounted for the complex sampling design of NHANES. *p < 0.05 compared with T1 (lowest) group. †p < 0.05 compared with T2 (lowest) group.

Abbreviations: WBC, white blood cell count; Neu, neutrophils; Lym, lymphocytes; Hb, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, serum albumin; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol.

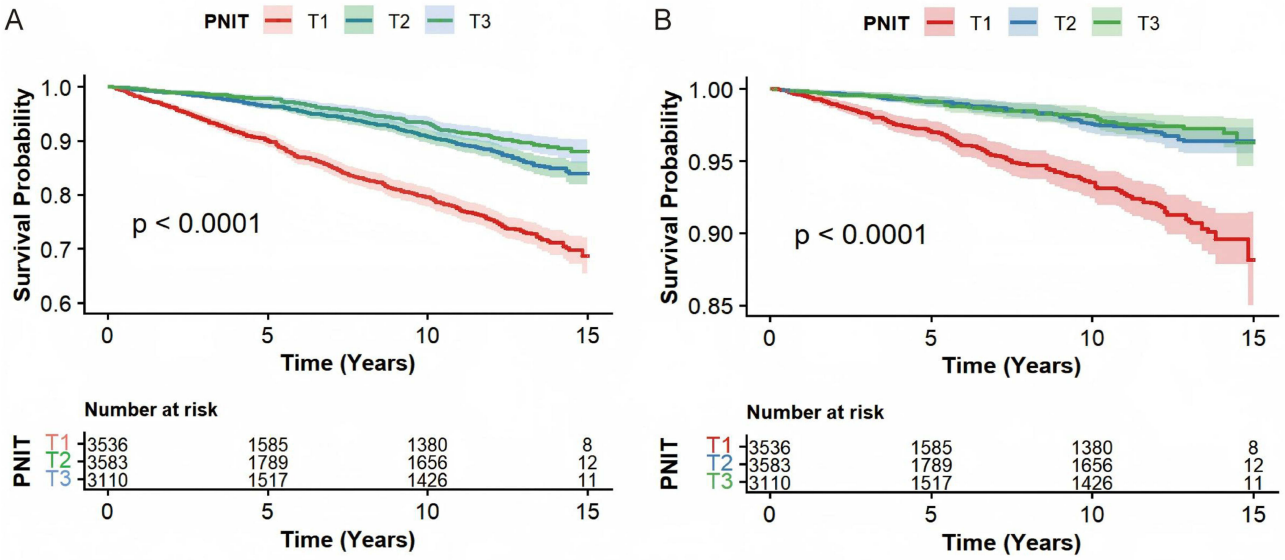

Figure 2 Kaplan-Meier survival curves stratified by tertiles of the prognostic nutritional index (PNI) among individuals at risk for obstructive sleep apnea. (**A**) All-cause mortality. (**B**) Cardiovascular mortality. Patients were categorized into three PNI tertiles: T1 (lowest), T2 (middle), and T3 (highest). Log rank test results are presented for comparisons among groups. Shaded areas represent 95% confidence intervals.

associations persisted after full adjustment for demographic, socioeconomic, lifestyle, comorbidities, and laboratory parameters (Model 3), with HRs of 0.59 (95% CI 0.47–0.75) for all-cause and 0.57 (95% CI 0.36–0.89) for cardiovascular mortality (both $P < 0.01$). A dose-response relationship was observed (P for trend < 0.05), indicating that lower PNI independently predicts higher mortality risk among individuals at risk for OSA.

PNI Predictive Performance for Mortality

ROC curve analyses were conducted to assess the ability of PNI to predict mortality among individuals at risk for OSA, compared with its individual components, lymphocyte count and serum albumin (Figure 3). For all-cause mortality, PNI

Table 3 Association Between PNI and All-Cause and Cardiovascular Mortality Among Participants at High Risk of OSA

Exposure	Outcome	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
PNI (continuous)	Cardiovascular mortality	0.43(0.36,0.52)	<0.001	0.68(0.54,0.84)	<0.001	0.68(0.53,0.89)	0.005
PNI tertile							
T1 (lowest)		Reference		Reference		Reference	
T2 (middle)		0.41(0.27,0.62)	<0.001	0.68(0.44,1.03)	0.070	0.72(0.47,1.10)	0.130
T3 (highest)		0.23(0.17,0.30)	<0.001	0.55(0.40,0.76)	<0.001	0.57(0.36,0.89)	0.010
P for trend		<0.001		<0.001		0.012	
PNI (continuous)	All-cause mortality	0.57(0.46,0.72)	<0.001	0.84(0.65,1.08)	0.180	0.62(0.53,0.73)	<0.001
PNI tertile							
T1 (lowest)		Reference		Reference		Reference	
T2 (middle)		0.44(0.37,0.53)	<0.001	0.66(0.53,0.82)	<0.001	0.66(0.53,0.83)	<0.001
T3 (highest)		0.34(0.28,0.41)	<0.001	0.70(0.57,0.86)	<0.001	0.59(0.47,0.75)	<0.001
P for trend		<0.001		<0.001		<0.001	

Notes: Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between PNI (continuous and tertiles) and mortality outcomes among participants at high risk of OSA. Model 1 was unadjusted; Model 2 and Model 3 were progressively adjusted for demographic and clinical covariates. P for trend was calculated across tertiles (T1 as reference). High-risk OSA was defined as an affirmative response to any of the following self-reported symptoms: habitual snoring ≥3 nights per week; gasping, snorting, or stopping breathing during sleep ≥3 nights per week; or excessive daytime sleepiness occurring on 16–30 days per month.

Abbreviations: PNI, prognostic nutritional index; HR, hazard ratio; CI, confidence interval; OSA, obstructive sleep apnea.

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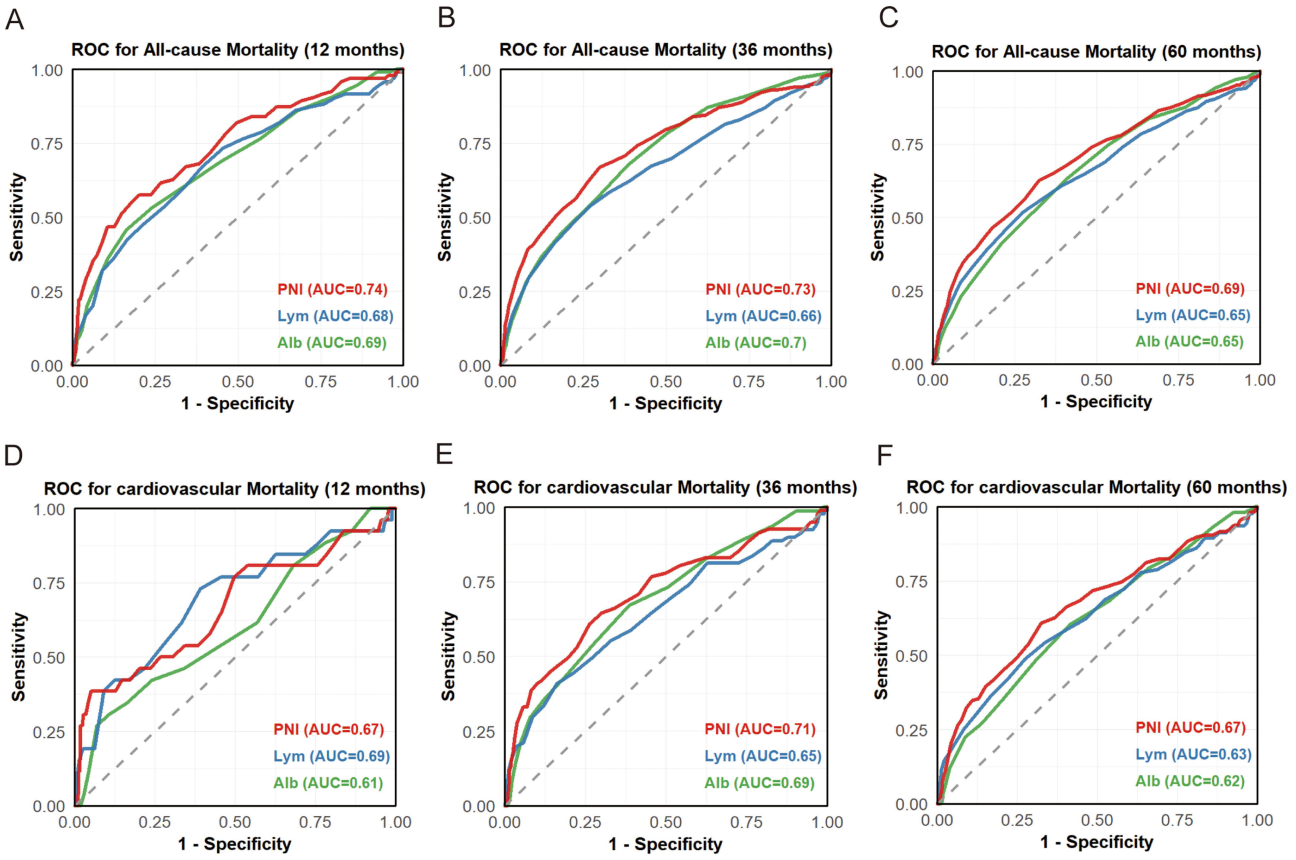

Figure 3 Receiver operating characteristic curves of the prognostic nutritional index (PNI) for predicting mortality among individuals at risk for obstructive sleep apnea (OSA). PNI, serum albumin, and lymphocyte count were assessed for predicting all-cause mortality at 12, 36, and 60 months (**A**–**C**) and cardiovascular mortality at 12, 36, and 60 months (**D**–**F**). Area under the curve (AUC) values for each biomarker at corresponding time points are presented in the figure.

demonstrated higher AUCs at 12, 36, and 60 months (0.74, 0.73, and 0.69, respectively), exceeding those of albumin and lymphocyte count (0.65–0.70). A similar trend was seen for cardiovascular mortality, with PNI showing superior discrimination at all time points (0.67, 0.71, and 0.67). These findings suggest that PNI is a more comprehensive and robust predictor of long-term mortality risk in individuals at risk for OSA than its individual components.

Nonlinear Relationship Between PNI and Mortality

Restricted cubic spline models were applied to investigate possible nonlinear associations between PNI and mortality outcomes (Figure 4). For cardiovascular mortality, an overall significant association was detected (P-overall<0.01), although the test for non-linearity approached but did not reach significance (P-nonlinear=0.051). The risk of cardiovascular death decreased with rising PNI and plateaued at higher levels.

In contrast, for all-cause mortality, both overall and nonlinear associations were statistically significant (P-overall<0.001; P-nonlinear<0.001). The risk declined sharply with increasing PNI up to a threshold, beyond which it stabilized. These findings suggest that inadequate nutritional status-reflected by low PNI-marks a high-risk state for mortality among individuals at risk for OSA.

Subgroup and Sensitivity Analyses

Subgroup analyses showed that the inverse association between PNI and both all-cause and cardiovascular mortality was generally consistent across major clinical strata (Figure 5). Although the associations did not reach statistical significance within every individual subgroup, the direction of effect was largely uniform. Significant interactions were observed for hyperlipidemia status in both outcomes (P for interaction = 0.002 for all-cause mortality and 0.007 for cardiovascular mortality), with a stronger

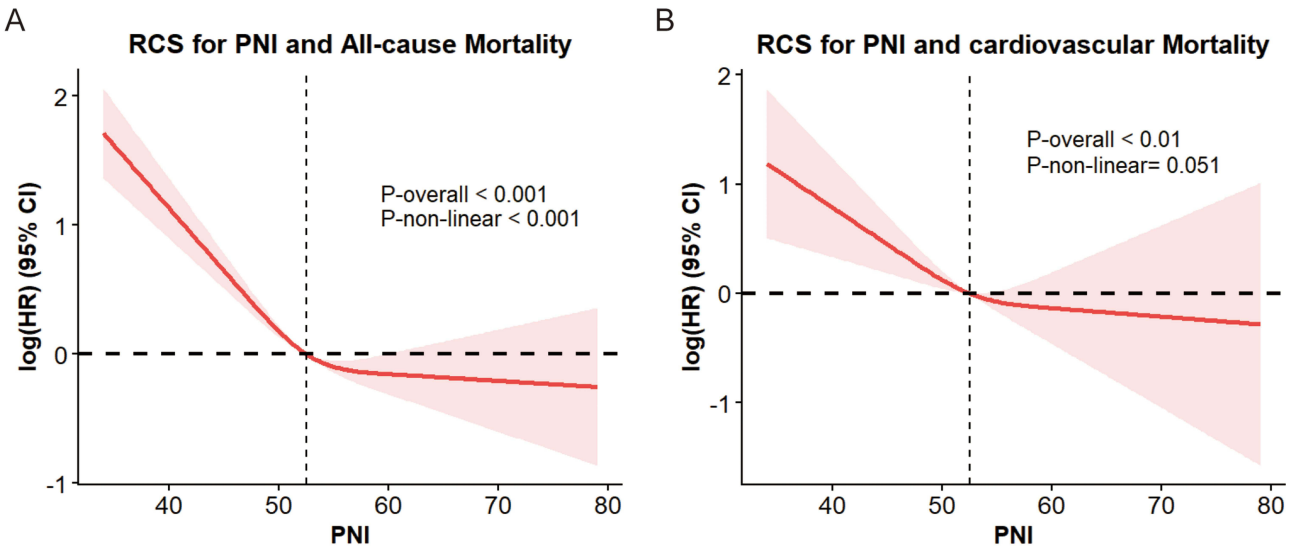

Figure 4 Restricted cubic spline analyses of the association between the prognostic nutritional index (PNI) and mortality among individuals at risk for obstructive sleep apnea. (**A**) All-cause mortality. Both the overall association (*P* for overall association < 0.001) and the non-linear association (*P* for non-linearity < 0.001) were statistically significant. (**B**) Cardiovascular mortality. The overall association was statistically significant (*P* for overall association < 0.01), whereas the test for non-linearity was not significant (*P* for non-linearity = 0.051).

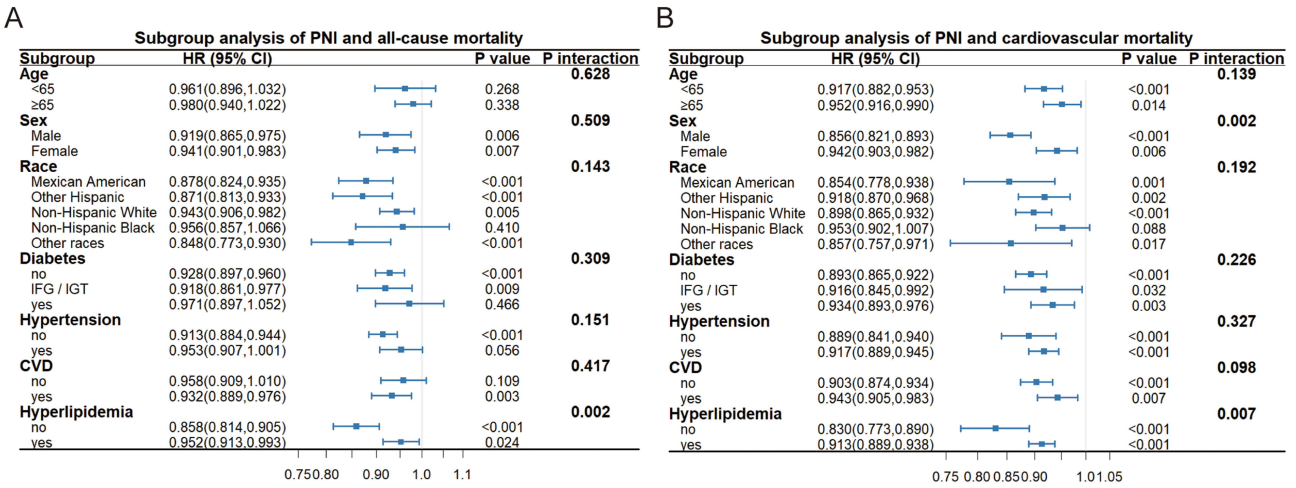

Figure 5 Subgroup analyses of the association between the prognostic nutritional index (PNI) and mortality among individuals at risk for obstructive sleep apnea. Forest plots display the associations between PNI and (**A**) all-cause mortality and (**B**) cardiovascular mortality across prespecified subgroups. Effect estimates are presented with corresponding 95% confidence intervals.

inverse association among individuals without hyperlipidemia. In addition, a significant interaction by sex was identified for cardiovascular mortality (*P* for interaction = 0.002). No other significant interactions were detected.

When stratified by sleepy and snoring status (Table 4), the inverse association between PNI and all-cause mortality persisted among non-sleepy individuals as well as among those reporting snoring. No significant interaction effects were identified for sleepy or snoring status, indicating a stable association across symptom-defined subgroups. After excluding individuals presenting with isolated sleepy symptoms (Table S1), higher PNI continued to be independently associated with lower risks of both all-cause and cardiovascular mortality in fully adjusted models. The dose-response relationship across PNI tertiles remained evident.

Sensitivity analyses using STOP-defined high risk of OSA (Table S2) yielded similar findings. In the fully adjusted model, higher PNI was independently associated with lower all-cause mortality, with a significant trend across tertiles. For cardiovascular mortality, the direction of association remained inverse, although statistical significance was attenuated after full adjustment.

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Table 4 Association Between PNI and All-Cause Mortality Stratified by Sleepy and Snoring Status Among Participants at High Risk of OSA

Subgroup	HR (95% CI)	*P* value	*P* for Interaction
Sleepy status			0.235
Non-sleepy	0.924(0.883,0.968)	0.001	
Sleepy	0.971(0.915,1.031)	0.331	
Snoring status			0.685
Non-snore	0.951(0.867,1.043)	0.283	
Snore	0.931(0.894,0.970)	<0.001	

Notes: Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality per 1-unit increase in PNI among participants at high risk of OSA. Models were fully adjusted for demographic and clinical covariates as described in Table 3. P for interaction was calculated using multiplicative interaction terms. High-risk OSA was defined as an affirmative response to any of the following self-reported symptoms: habitual snoring ≥3 nights per week; gasping, snorting, or stopping breathing during sleep ≥3 nights per week; or excessive daytime sleepiness occurring on 16–30 days per month.
Abbreviations: PNI, prognostic nutritional index; HR, hazard ratio; CI, confidence interval; OSA, obstructive sleep apnea.

Baseline Characteristics in the Clinical Cross-Sectional Study

A total of 555 participants were analyzed (Table S3). Age and sex distributions were comparable across OSA severity categories. BMI showed a positive trend with increasing OSA severity ($P < 0.001$). In contrast, lymphocyte counts and serum albumin levels declined as severity increased (both $P < 0.001$), while BUN, uric acid, total cholesterol, and ALT levels rose. PNI values decreased with higher OSA severity ($P < 0.001$), reflecting progressively poorer nutritional and immune status in patients with severe OSA.

Association Between PNI and OSA Severity

Binary logistic regression was performed to evaluate the association between PNI and OSA severity (Table 5). In the unadjusted analysis, higher PNI was associated with lower likelihood of severe OSA (OR 0.874, 95% CI 0.846–0.903, $P < 0.001$). This inverse relationship remained consistent after adjusting for age and sex, and further controlling for BMI, lifestyle, comorbidities, and laboratory variables (Model 3) had little effect (OR 0.864, 95% CI 0.833–0.896, $P < 0.001$). ROC curve analysis indicated that PNI effectively distinguished severe OSA, surpassing its individual components such as serum albumin and lymphocyte count, highlighting its value as a composite predictor (Figure 6).

Linear Regression Analysis of PNI and AHI

Linear regression was conducted to examine the relationship between PNI and OSA severity, measured by AHI (Figure 7). After adjusting for age, sex, BMI, lifestyle factors, comorbidities, and laboratory indicators, PNI remained a significant negative predictor of AHI (β= −1.789, 95% CI:-2.039 to −1.539, $P < 0.001$), indicating that each 1-unit increase in PNI was associated with an average decrease of approximately 1.79 events per hour in AHI. Age and BMI showed modest associations with AHI, whereas other covariates were not statistically significant.

Table 5 Association Between PNI and Severe OSA in the Clinical Validation Cohort

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
PNI	0.874(0.846–0.903)	< 0.001	0.867(0.839–0.897)	< 0.001	0.864(0.833–0.896)	< 0.001

Notes: Binary logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between PNI and severe OSA. Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was further adjusted for body mass index, lifestyle factors, comorbidities, and laboratory variables.
Abbreviations: PNI, prognostic nutritional index; OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval.

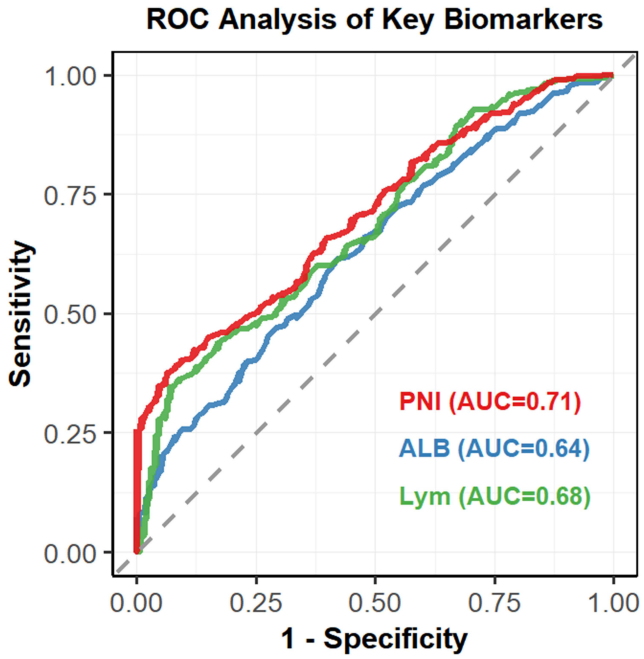

Figure 6 Receiver operating characteristic (ROC) curves of the prognostic nutritional index (PNI), serum albumin (ALB), and lymphocyte count (Lym) for predicting severe obstructive sleep apnea. PNI, ALB, and Lym were evaluated for their discriminative performance in detecting severe obstructive sleep apnea. Corresponding area under the curve (AUC) values are shown.

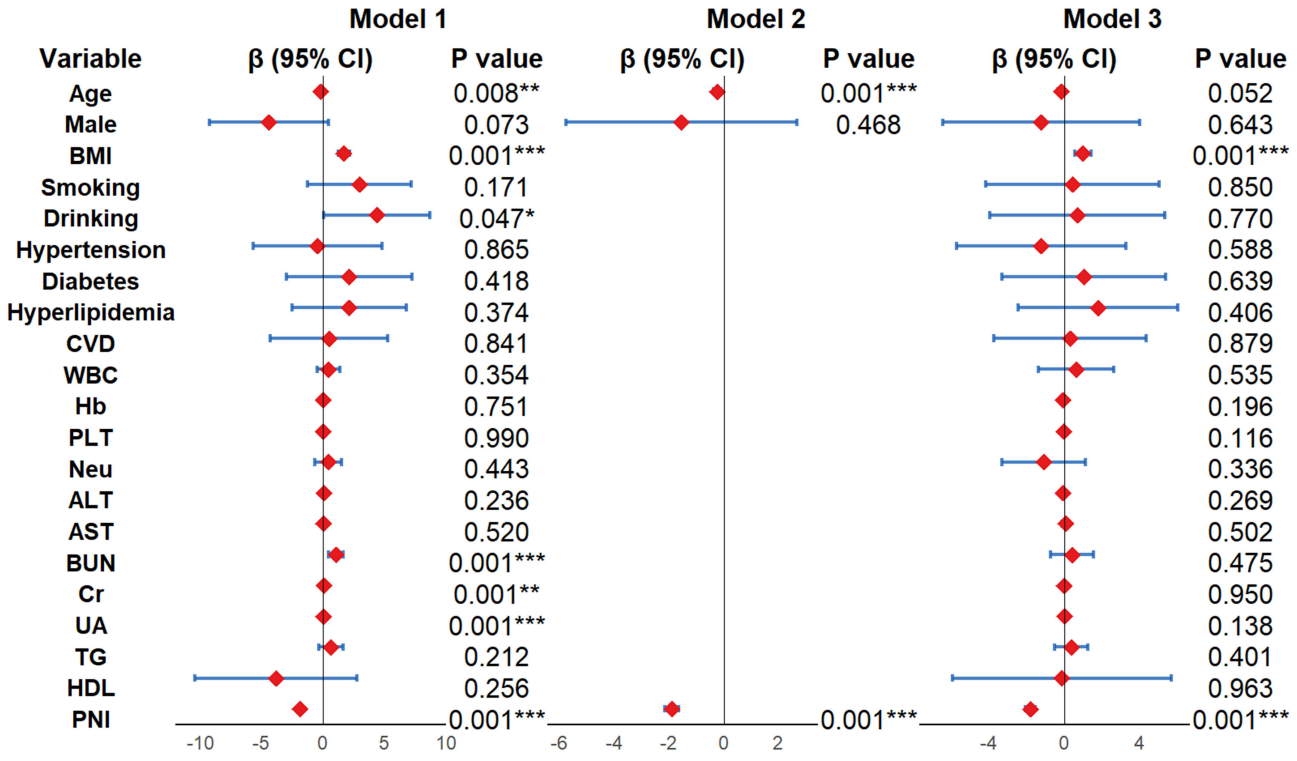

Figure 7 Linear regression analysis of the association between the prognostic nutritional index (PNI) and the apnea hypopnea index (AHI). Linear regression was performed to evaluate the association between PNI and AHI. Three models were applied: Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, further adjusted for BMI, smoking, alcohol consumption, hypertension, diabetes, hyperlipidemia, cardiovascular disease (CVD), white blood cell count (WBC), hemoglobin (Hb), platelet count (PLT), neutrophil count (Neu), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), triglycerides (TG), and high-density lipoprotein cholesterol (HDL). *P < 0.05, **P < 0.01, ***P < 0.001.

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Discussion

This study assessed the prognostic value of PNI in individuals at risk for OSA within a nationally representative cohort, together with findings from an independent clinical cross-sectional study. Within the NHANES cohort, lower PNI was significantly associated with higher all-cause and cardiovascular mortality among participants classified as being at risk for OSA based on symptom criteria and these associations remained robust after multivariable adjustment. Furthermore, PNI demonstrated better predictive performance than its individual components, serum albumin and lymphocyte count, indicating its utility as a comprehensive marker of nutritional and immune status. In the clinical cross-sectional study, although mortality outcomes were not available, lower PNI was associated with more severe OSA, higher AHI, and adverse laboratory profiles, providing independent support for the link between nutritional/immune status and OSA severity in polysomnography-confirmed patients. Importantly, the association between PNI and mortality remained consistent across symptom-defined phenotypes, including sleepy and non-sleepy OSA risk profiles, and after excluding individuals with isolated excessive daytime sleepiness. Similar findings were observed when high OSA risk was defined using STOP criteria, supporting the robustness of the results across alternative symptom-based definitions.

Our results align with previous studies. In a large cohort study by Zhou et al, individuals in the highest PNI quartile had a 73% lower risk of all-cause mortality compared with those in the lowest quartile, and this reduction remained approximately 60% after multivariable adjustment.[15] A longitudinal study in frail older adults further demonstrated that each one unit increase in PNI was associated with an approximate twelve percent decrease in all cause mortality risk.[18] Comparable associations have been observed in populations with diabetes and nonalcoholic fatty liver disease,[19,20] collectively highlighting that PNI captures the interplay between nutritional status and systemic inflammation, serving as a robust prognostic marker across diverse chronic conditions. Importantly, evidence in clinically confirmed OSA has been scarce; this study extends the application of PNI to the field of sleep disorders, demonstrating association with mortality risk in a population at risk for OSA and its relationship with disease severity in a clinically confirmed cohort.

The biological basis linking low PNI to increased mortality in OSA may involve nutrition, immune function, and systemic inflammation. Intermittent hypoxia in OSA induces oxidative stress and activates inflammatory pathways such as NF-κB and HIF-1α, leading to elevated cytokines including IL-6 and TNF-α.[21–23] These changes promote immune cell apoptosis and reduce peripheral lymphocyte counts. Albumin, a negative acute-phase reactant, is suppressed under chronic inflammation and oxidative stress[24] and the metabolic dysregulation, adipose-tissue inflammation, and impaired nutrient utilization commonly observed in OSA further decrease circulating albumin levels.[25,26] Reduced albumin not only reflects diminished nutritional reserves but also weakens antioxidant defenses, increases vascular permeability, and contributes to endothelial dysfunction and oxidative injury, thereby promoting atherosclerosis and cardiovascular events.[27] Lymphopenia, another key component of the PNI, indicates impaired immune competence and heightened systemic stress and has been linked to persistent inflammation, infection susceptibility, organ injury, and adverse cardiovascular outcomes.[28,29] Consistent with these biological alterations, previous studies have shown significant inverse correlations between PNI and inflammatory markers such as CRP and IL-6,[30] reinforcing its role as an integrated indicator of inflammatory activity and immune status. These mechanisms may help explain the association between low PNI and increased mortality among individuals at risk for OSA, as well as its relationship with disease severity in polysomnography-confirmed patients.

In subgroup analyses, we observed that sex and hyperlipidemia modified the prognostic effect of PNI. The inverse association between PNI and cardiovascular mortality was stronger in men and weaker in women, which contrasts with conventional expectations. Postmenopausal women are generally considered at higher cardiovascular risk due to estrogen decline and lipid metabolic disturbances, which would suggest a stronger protective effect of PNI; however, estrogen deficiency-related dyslipidemia and chronic inflammation may attenuate this effect in women.[31–33] In men, distinct lipid metabolic patterns and immune responses may enhance the predictive value of PNI.[34–36] Lipid status also modified these associations: in individuals without hyperlipidemia, PNI demonstrated a clearer protective effect with stronger inverse correlations with all-cause and cardiovascular mortality, whereas in those with hyperlipidemia, this relationship was attenuated, indicating that dyslipidemia may diminish the prognostic utility of PNI.[36] These findings underscore that sex and lipid metabolism interact with nutritional and immune status, affecting the prognostic performance of PNI in individuals at risk for OSA.

From a clinical perspective, PNI is simple, low-cost, and derived from routine laboratory tests, allowing early identification of high-risk individuals with OSA risk or confirmed OSA, and potential timely nutritional or anti-

inflammatory interventions. Its integration of nutrition and inflammation provides advantages over single biochemical markers for risk assessment.

Key strengths of this study include the inclusion of a nationally representative cohort, the incorporation of an independent clinical cross-sectional cohort to provide complementary evidence from a different clinical perspective, and stepwise adjustment for multiple covariates, which together enhance the robustness and generalizability of the results. However, several limitations should be acknowledged. From a causal inference perspective, PNI may not simply represent an adjustment variable and could lie along the potential pathway linking OSA to mortality. Therefore, its causal role cannot be definitively established in this observational study. In addition, OSA was not confirmed by polysomnography in NHANES. Instead, participants were classified as being at risk for OSA using symptom-based criteria, which may introduce misclassification bias. Because classification required only a single affirmative response to any of the symptom questions, the prevalence of individuals at risk for OSA may have been overestimated. To address this concern, we conducted sensitivity analyses using the STOP criteria to define high OSA risk. The associations between higher PNI and lower all-cause mortality remained significant after full adjustment, and the inverse association with cardiovascular mortality persisted in direction, although statistical significance was attenuated. These findings support the robustness of the observed associations across alternative symptom-based definitions. Accordingly, findings from the national cohort reflect associations among individuals at risk for OSA rather than clinically diagnosed OSA patients. Furthermore, because corresponding symptom variables were not systematically collected in the clinical cohort, we were unable to assess the agreement between symptom-defined OSA and AHI-defined OSA. This difference in definitions should be considered when interpreting the results.

Future research should evaluate whether improving nutritional and inflammatory status can reduce mortality risk in OSA and explore the combined predictive performance of PNI with other metabolic and inflammatory markers. Understanding the interaction between nutrition, inflammation, and intermittent hypoxia may facilitate more precise risk stratification and targeted interventions in patients with OSA.

Conclusions

Among individuals at risk for obstructive sleep apnea identified using symptom-based criteria, low PNI independently predicted higher risks of all-cause and cardiovascular mortality. Additionally, in the clinical cross-sectional cohort, lower PNI was closely associated with greater OSA severity. These findings highlight PNI not only as a reflection of nutritional and immune status but also as a potential biomarker for risk stratification and early intervention, offering a promising tool to guide precise management and improve outcomes in OSA patients.

Generative AI Statement

The authors confirm that this manuscript was prepared entirely without the use of generative artificial intelligence tools.

Data Sharing Statement

The NHANES data used in this study are publicly available from the National Center for Health Statistics website (https://www.cdc.gov/nchs/nhanes/). The hospital-based clinical cohort data used in this study are available from the corresponding author upon reasonable request.

Ethics Statement

The NHANES study was approved by the National Center for Health Statistics Ethics Review Board, and all participants or their guardians provided written informed consent. The clinical cohort was approved by the Ethics Committee of the Second Hospital of Shanxi Medical University, where written consent was waived in accordance with national and institutional regulations.

Author Contributions

Yan Li: conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, writing-original draft and Writing-review & editing. Shudan Deng: investigation, data curation, formal analysis, visualization, and writing-review & editing.
Lu Zhai: investigation, resources, data curation, and writing-review & editing.
LiMantian Wang: investigation, validation, data curation, and writing-review & editing.
Lu Zhang: methodology, formal analysis, visualization, and writing-review & editing.
Bomeng Zhao: investigation, resources, validation, and writing-review & editing.
Huiyan Niu: project administration, supervision, resources, and writing-review & editing.
Xiaoling Gao: conceptualization, funding acquisition, supervision, project administration, and writing-review & editing.

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no financial or commercial interests that might have influenced the study design, execution, or interpretation.

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