SCIENTIFIC Publishing Limited

ENT Updates

https://ojs.ukscip.com/index.php/ENTU

Article

Neutrophil-to-Lymphocyte Ratio and All-Cause and Heart Disease Mortality in Adults with Obstructive Sleep Apnea-Related Symptoms: A Population-Based Study

Fuke Wang [1], Shiping Sun [2], Chenxi Wang [3], Tian Lv [4,*], Junjian Dai [5,*] and Xiao Yu [6]

[1] Department of Critical Care Medicine, The Third Affiliated Hospital of Kunming Medical University, Cancer Hospital of Yunnan Province, Peking University Cancer Hospital, Kunming 650118, China; kmmc_wfk@163.com

[2] The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, Suzhou 215000, China; ssp113884@163.com

[3] Department of Hepatobiliary Oncology and Liver Transplantation, Zhongshan Hospital Affiliated to Fudan University, Shanghai 200032, China; wangchenxi0801@outlook.com

[4] Department of Neurology, Zhuji Affiliated Hospital of Wenzhou Medical University, Zhuji 311800, China

[5] Department of Neurosurgery, The First Affiliated Hospital of Kunming Medical University, Kunming 650118, China

[6] Department of Otolaryngology-Head and Neck Surgery, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200032, China; yuxiaoguagua123@sjtu.edu.cn

[*] Correspondence: Lt627756@wmu.edu.cn (T.L.); 20240807@kmmu.edu.cn (J.D.)

Received: 3 September 2026; **Revised:** 24 September 2026; **Accepted:** 4 November 2026; **Published:** 16 November 2026

Abstract: Obstructive sleep apnea (OSA) is associated with increased mortality risk, but the prognostic relevance of routinely available inflammatory biomarkers in adults with OSA-related symptoms remains incompletely characterized. This study aimed to compare hematological inflammatory indices in relation to all-cause and heart disease mortality among adults with OSA-related symptoms. Using National Health and Nutrition Examination Survey (NHANES) data from 2005–2008 and 2015–2018, we evaluated six inflammatory indices in relation to mortality using survey-weighted Cox regression, restricted cubic spline analyses, and time-dependent discrimination assessments. Primary association analyses modeled inflammatory indices continuously with effect estimates expressed per one standard deviation (SD) increase. The data-derived NLR (neutrophil-to-lymphocyte ratio) cutoff of 3.3 was examined exploratorily, with bootstrap resampling used to assess cutoff-selection stability. Among 4,559 adults with OSA-related symptoms, 452 deaths occurred, including 94 from heart disease. Each 1-SD increase in NLR was associated with higher all-cause mortality (adjusted Hazard Ratio (HR), 1.145; 95% Confidence Interval (CI), 1.050–1.248; $p = 0.002$). At 5 years, NLR showed greater discrimination than PIV (pan-immune-inflammation value) (ΔArea under the Curve (AUC), 0.064; $p = 0.007$), whereas its difference from SII (systemic immune inflammation index) was not statistically significant (ΔAUC, 0.034; $p = 0.238$). Adding NLR to the clinical model yielded limited incremental discrimination (ΔC-index, 0.002; $p = 0.060$). In an exploratory analysis, NLR ≥ 3.3 was associated with higher all-cause mortality (adjusted HR, 1.80; 95% CI, 1.34–2.41). The association between elevated NLR and heart disease mortality varied over follow-up (p for proportional hazards assumption <0.001), with exploratory analyses suggesting a stronger association beyond 5 years. Higher NLR was associated with all-cause mortality, while its association with heart disease mortality varied over time. Its incremental prognostic discrimination beyond clinical covariates was limited, and the data-derived cutoff of 3.3 remains exploratory.

Keywords: Obstructive Sleep Apnea; Neutrophil-to-Lymphocyte Ratio; All-Cause Mortality; Heart Disease Mortality; NHANES

1. Introduction

Obstructive sleep apnea (OSA) affects approximately 1 billion people worldwide and is associated with increased cardiovascular morbidity and mortality [1–3]. Identifying reliable prognostic biomarkers is therefore crucial. Inflammation plays a pivotal role in OSA pathogenesis [4]; however, effective biomarkers for predicting OSA prognosis remain lacking. The neutrophil-to-lymphocyte ratio (NLR), a readily available marker of systemic inflammation, has previously been associated with all-cause and cardiovascular mortality in the general population, including analyses of National Health and Nutrition Examination Survey (NHANES) data. However, its prognostic associations and comparative performance relative to other inflammatory indices among adults with OSA-related symptoms remain incompletely characterized [5–7]. This study therefore aimed to compare several inflammatory indices in relation to all-cause and heart disease mortality among adults with OSA-related symptoms, while additionally examining whether the NLR–mortality association differed according to OSA-related symptom status.

2. Methods

2.1. Study Population and Data Source

This study used data from four 2-year NHANES cycles: 2005–2006, 2007–2008, 2015–2016, and 2017–2018. These cycles included the sleep-questionnaire items required to construct the prespecified OSA-related symptom definition [8]. The 2009–2014 cycles were not included because the corresponding sleep questionnaires did not contain the complete set of symptom-frequency items required for this definition.

Among 39,722 participants in the four included cycles, 17,520 individuals aged <20 years were excluded. Of the remaining 22,202 adults, 74 were ineligible for mortality linkage, leaving 22,128 mortality-eligible participants. Among these, 6,421 met the questionnaire-based definition of OSA-related symptoms. We subsequently excluded 599 participants with missing laboratory measurements required to calculate the inflammatory indices, 481 with missing demographic or socioeconomic covariates, 731 with missing lifestyle or comorbidity covariates, and 51 with missing body mass index (BMI) data. The final complete-case analytical cohort consisted of 4,559 participants. The participant-selection process is shown in **Figure 1**.

2.2. Variables and Covariates

OSA-related symptom status was derived from three NHANES sleep-questionnaire domains: frequent snoring, recurrent snorting/gasping or breathing pauses during sleep, and excessive daytime sleepiness. Participants were classified as having OSA-related symptoms if they reported snoring on at least 3 nights per week, snorting/gasping or breathing pauses on at least 3 nights per week, or daytime sleepiness on 16–30 days per month despite approximately 7 or more hours of sleep on weekdays or workdays [9,10]. Equivalent response-frequency categories were applied across the 2005–2008 and 2015–2018 cycles to maintain a consistent symptom definition.

Inflammatory biomarkers followed the biomarkers of previous studies, including systemic immune inflammation index (SII), pan-immune-inflammation value (PIV), platelet–lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-albumin ratio (PAR). The calculation formulas for six inflammatory biomarkers were detailed in **Table S1** of **Supplementary Materials** [11–15].

Covariates included age, sex, race/ethnicity, educational attainment, marital status, poverty-to-income ratio (PIR), smoking status, alcohol consumption, body mass index (BMI), hypertension, diabetes, cancer, coronary heart disease (CHD), and stroke. BMI was calculated as measured weight in kilograms divided by measured height in meters squared (kg/m^2) [8,16,17]. Additional covariates were obtained to evaluate potential residual confounding in sensitivity analyses. Serum creatinine (LBXSCR, mg/dL) was obtained from the NHANES standard biochemistry profile. For the 2005–2006 cycle, serum creatinine values were standardized using the correction recommended by the National Center for Health Statistics (standardized creatinine = −0.016 + 0.978 × measured creatinine). Es-

timated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation without a race coefficient. Congestive heart failure was defined by an affirmative response to the question asking whether a doctor or other health professional had ever told the participant that they had congestive heart failure (MCQ160B). A self-reported physician diagnosis of chronic obstructive pulmonary disease (COPD) (MCQ160O) was available only in the 2015–2016 and 2017–2018 cycles. Because this variable was unavailable in the earlier cycles, an exploratory pulmonary disease proxy was constructed using self-reported physician-diagnosed emphysema (MCQ160G) or chronic bronchitis (MCQ160K), which were available across all four cycles. This proxy was not considered equivalent to confirmed COPD. Refused, don't know, and missing responses were treated as missing.

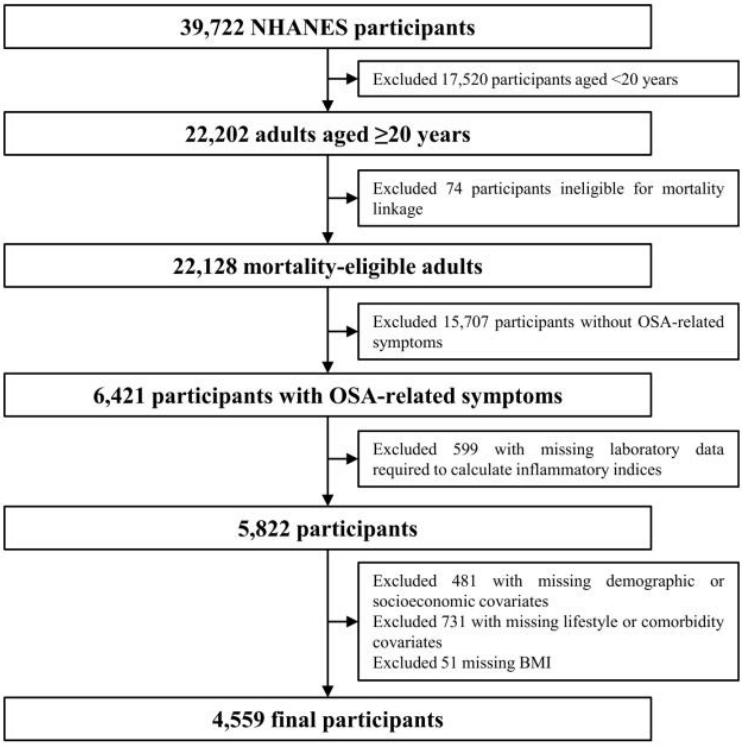


Figure 1. Flowchart of participant selection.

All-cause and cause-specific mortality: The study focused on all-cause mortality, heart disease mortality, and cancer mortality, as determined by the International Classification of Diseases, Tenth Revision (ICD-10). Cancer mortality was categorized as C00–C97, and heart disease mortality was defined by ICD-10 codes I00–I09, I11, I13, or I20–I51.

2.3. Statistical Analysis

NHANES sampling weights and design variables were incorporated throughout the analyses. Mobile Examination Center (MEC) sample weights (WTMEC2YR) were combined across the four survey cycles by dividing the original 2-year weights by four, while SDMVSTRA and SDMVPSU were used to retain the stratified, clustered sampling structure. Participants meeting the OSA-related symptom definition were analyzed as a survey subpopulation. Analyses were restricted to complete observations for the inflammatory indices and prespecified covariates. Multiple imputation was considered but not adopted because several missing measurements were components of the inflammatory exposures themselves and their imputation could modify the distributions of the derived indices. In the primary association analyses, all inflammatory indices were modeled continuously per one standard deviation (SD) increase. Dichotomization of NLR at the data-derived threshold of 3.3 was restricted to exploratory analyses. Three survey-weighted Cox models were specified: an unadjusted model; a model including age, sex, race/ethnicity, education, marital status, and PIR; and a fully adjusted model additionally including smoking, alcohol consumption, hy-

pertension, diabetes, cancer, coronary heart disease, stroke, and BMI. Survey-weighted comparisons were also performed between included and excluded participants to examine possible selection associated with complete-case analysis. Cause-specific mortality was analyzed with cause-specific Cox models, treating other causes of death as censored observations at the time of death. Proportional hazards were assessed using Schoenfeld residuals. Given the violation of this assumption for heart disease mortality, an exploratory time-varying coefficient cause-specific Cox model was fitted by splitting follow-up at 60 months. Separate NLR coefficients were estimated for the 0–60-month and >60-month intervals using start–stop survival data. Participants remaining at risk beyond 60 months contributed to the second interval, while competing deaths were censored at their occurrence. The model retained all Model 3 covariates and incorporated NHANES sampling weights, strata, and primary sampling units. Tied event times were handled using Efron's approximation. Interval-specific hazard ratios (HRs) were compared using a Wald test, and unweighted risk-set sizes and heart disease deaths were tabulated by NLR category. Because nonlinear associations were observed for some inflammatory indices, formal comparisons of time-dependent discrimination were based on biomarker risk scores derived from four-knot restricted cubic spline (RCS) models rather than on the raw biomarker values alone. Knots were placed at the 5th, 35th, 65th, and 95th percentiles. Time-dependent area under the receiver operating characteristic curve (AUC) values and pairwise differences in AUC were estimated at 5 and 10 years, with 95% confidence intervals (CIs) and two-sided *p* values obtained using 2,000 survey-design bootstrap replicates in which primary sampling units were resampled within strata. The incremental prognostic value of NLR beyond established clinical covariates was evaluated by comparing the fully adjusted clinical model with the same model additionally including standardized continuous NLR. Survey-weighted Harrell C-indices were calculated for both models, and the change in C-index (ΔC-index) was estimated. A category-free continuous net reclassification improvement (NRI) was additionally calculated at 5 years using inverse probability of censoring weighting. Confidence intervals were obtained using 500 survey-design bootstrap replicates with primary sampling units resampled within strata. Cutoff-selection stability was assessed using 2,000 survey-design bootstrap replicates, resampling primary sampling units within strata. In each replicate, the cutoff was re-estimated by maximizing the survey-weighted survival score statistic for all-cause mortality, requiring at least 10% of participants in each group. This procedure assessed cutoff variability, not predictive performance. Finally, to examine whether the association between NLR and mortality differed according to OSA-related symptom status, survey-weighted Cox models were fitted in the full eligible NLR analysis sample with an NLR × OSA-related symptom interaction term, adjusting for the covariates included in Model 3. To assess the robustness of the findings to potential reverse causation, three sensitivity analyses were conducted: (1) excluding deaths occurring within the first 2 years of follow-up; (2) excluding participants with baseline coronary heart disease, stroke, or cancer; and (3) excluding participants with extreme differential leukocyte counts. For the latter analysis, extreme counts were defined as neutrophil, lymphocyte, or monocyte values outside the 1st–99th percentile range of the analytical cohort. To further address potential confounding by renal dysfunction and heart failure, additional sensitivity analyses were performed by extending the fully adjusted model (Model 3). First, eGFR was incorporated as a continuous covariate, scaled per 10 mL/min/1.73 m^2. Second, eGFR and self-reported congestive heart failure were jointly included. An alternative specification using eGFR <60 mL/min/1.73 m^2 was also evaluated. Finally, an exploratory model further adjusted for self-reported emphysema or chronic bronchitis as a pulmonary disease proxy. This analysis was considered supplementary because the proxy does not provide a harmonized diagnosis of COPD. All additional Cox models incorporated the NHANES sampling weights, masked variance strata, and primary sampling units. Cause-specific Cox models were used for heart disease mortality, with deaths from competing causes censored at the time of death. Because the number of heart disease deaths was limited, subgroup analyses were considered exploratory. To reduce sparse-data bias and model overfitting, subgroup-specific cause-specific Cox models used a parsimonious adjustment set including age and sex, except for the variable used for stratification; models stratified by age were adjusted for sex only, and models stratified by sex were adjusted for age only. Stratum-specific HRs were not reported when fewer than five heart disease deaths occurred in a stratum. Interaction *p* values were obtained from survey-weighted Cox models containing multiplicative NLR × subgroup terms using the same reduced adjustment strategy. For age, interaction was evaluated using continuous age because the <40-year stratum contained only one heart disease death. All statistical analyses were executed using R software. A p-value < 0.05 was regarded as statistically significant.

3. Results

3.1. Study Population Characteristics

The final analytical cohort included 4,559 adults with OSA-related symptoms, representing approximately 52.04 million U.S. adults after application of the NHANES sampling weights. The median observed follow-up was 55 months (interquartile range, 35–147 months), corresponding to a total of 32,918 person-years of follow-up. During follow-up, 452 participants died, including 94 deaths from heart disease and 94 deaths from malignant neoplasms. Compared with surviving participants, those who died were substantially older and more frequently had lower educational attainment, lower poverty-to-income ratios, former or current smoking, hypertension, diabetes, cancer, coronary heart disease, and stroke (**Table 1**). The deceased group also had higher survey-weighted levels of SII, PIV, PLR, and NLR and lower LMR. In particular, mean NLR was 2.59 (SE, 0.09) among deceased participants compared with 2.14 (SE, 0.03) among survivors ($p < 0.001$). No significant between-group difference was observed for BMI or PAR. To assess potential selection related to the complete-case approach, we compared participants included in the final analytical cohort with those excluded because of missing analytical variables. Included participants were modestly younger (48.38 vs. 50.41 years, $p = 0.003$) and differed in race/ethnicity, educational attainment, PIR, alcohol consumption, cancer prevalence, and stroke prevalence. In contrast, no statistically significant differences were observed in sex, marital status, smoking status, BMI, hypertension, diabetes, or coronary heart disease (**Table S2**).

Table 1. Survey-weighted baseline characteristics of participants according to vital status.

Variable	Alive, n = 4,107	Death, n = 452	*p* Value
Age, years			<0.001
<40	1,267 (32.82%)	20 (7.17%)	
40–60	1,794 (47.10%)	101 (30.31%)	
>60	1,046 (20.08%)	331 (62.52%)	
Sex			0.090
Female	1,889 (45.23%)	166 (40.76%)	
Male	2,218 (54.77%)	286 (59.24%)	
Race/ethnicity			<0.001
Other race	800 (11.73%)	39 (6.01%)	
Non-Hispanic Black	844 (10.10%)	82 (9.04%)	
Mexican American	708 (8.23%)	35 (3.09%)	
Non-Hispanic White	1,755 (69.94%)	296 (81.87%)	
Education			<0.001
Less than high school	864 (12.98%)	180 (32.08%)	
High school	999 (26.48%)	119 (28.69%)	
College or above	2,244 (60.54%)	153 (39.23%)	
Marital status			<0.001
Never married	587 (13.32%)	25 (5.71%)	
Separated/widowed/divorced	785 (15.95%)	158 (33.76%)	
Married/living with partner	2,735 (70.73%)	269 (60.52%)	
PIR			<0.001
<1	746 (11.84%)	92 (15.27%)	
1–3	1,752 (34.87%)	246 (52.10%)	
>3	1,609 (53.29%)	114 (32.63%)	
Smoking			<0.001
Never	2,060 (50.19%)	144 (32.31%)	
Former	1,057 (26.45%)	187 (36.08%)	
Current	990 (23.36%)	121 (31.61%)	
Alcohol consumption			<0.001
Never	416 (7.21%)	64 (11.68%)	
Former	554 (11.95%)	178 (36.43%)	
Current	3,137 (80.84%)	210 (51.89%)	
Hypertension, yes	1,951 (43.87%)	327 (72.25%)	<0.001
Diabetes, yes	781 (14.42%)	170 (30.62%)	<0.001
Cancer, yes	338 (9.15%)	106 (22.28%)	<0.001
CHD, yes	156 (3.27%)	75 (14.70%)	<0.001
Stroke, yes	146 (2.64%)	67 (13.12%)	<0.001
BMI, kg/m^2	31.41 (0.16)	30.73 (0.47)	0.171
SII	554.38 (6.75)	636.54 (25.93)	0.002
PIV	332.64 (5.63)	403.55 (21.82)	<0.001
PLR	125.73 (0.98)	133.57 (3.44)	0.029
NLR	2.14 (0.03)	2.59 (0.09)	<0.001
LMR	4.05 (0.04)	3.68 (0.12)	0.002
PAR	6.16 (0.04)	6.12 (0.10)	0.698

Note: Values are presented as unweighted n (survey-weighted %) for categorical variables and survey-weighted mean (SE) for continuous variables. All estimates incorporated MEC examination weights, masked variance strata, and primary sampling units. BMI, body mass index; CHD, coronary heart disease; SII, systemic immune-inflammation index; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PAR, platelet-to-albumin ratio; PIR, poverty-to-income ratio.

3.2. Associations of Inflammatory Indices with All-Cause Mortality

To facilitate direct comparison across inflammatory indices measured on different scales, all six indices were standardized and analyzed per 1-SD increase. In the unadjusted model, higher PIV and NLR were significantly associated with all-cause mortality. After adjustment for demographic and socioeconomic characteristics, the association remained significant for NLR, whereas that for PIV was attenuated. In the fully adjusted model, which additionally accounted for smoking, alcohol consumption, hypertension, diabetes, cancer, coronary heart disease, stroke, and BMI, NLR remained independently associated with all-cause mortality (HR per 1-SD increase, 1.145; 95% CI, 1.050–1.248; $p = 0.002$). The fully adjusted associations for SII, PIV, PLR, LMR, and PAR did not reach statistical significance (**Table 2**). Additional sensitivity analyses were conducted to assess potential confounding by renal dysfunction and congestive heart failure (**Table S3**). After adjustment for eGFR, elevated NLR (≥3.3) remained associated with all-cause mortality (HR, 1.70; 95% CI, 1.36–2.13) and heart disease mortality (HR, 3.21; 95% CI, 1.77–5.82). Following joint adjustment for eGFR and heart failure, the corresponding associations remained positive for all-cause mortality (HR, 1.67; 95% CI, 1.33–2.10) and heart disease mortality (HR, 3.14; 95% CI, 1.72–5.74) among 4,553 participants, including 449 all-cause and 93 heart disease deaths. Similar findings were observed using an eGFR threshold of 60 mL/min/1.73 m^2 and after additional adjustment for an exploratory pulmonary disease proxy. These results suggest that the observed associations were not fully explained by the measured renal and cardiopulmonary covariates, although residual confounding cannot be excluded.

Table 2. Cox regression models for biomarkers and mortality.

Biomarker	Model 1 HR (95% CI)	*p* Value	Model 2 HR (95% CI)	*p* Value	Model 3 HR (95% CI)	*p* Value
SII	1.133 (0.902–1.424)	0.284	1.094 (0.949–1.262)	0.216	1.082 (0.973–1.203)	0.145
PIV	1.200 (1.026–1.404)	0.022	1.135 (0.998–1.291)	0.053	1.123 (0.997–1.264)	0.055
PLR	0.996 (0.683–1.453)	0.984	0.980 (0.767–1.254)	0.875	1.031 (0.788–1.348)	0.824
NLR	1.294 (1.171–1.430)	<0.001	1.180 (1.081–1.289)	<0.001	1.145 (1.050–1.248)	0.002
LMR	0.685 (0.404–1.161)	0.160	0.906 (0.591–1.390)	0.652	0.881 (0.578–1.343)	0.557
PAR	0.810 (0.469–1.400)	0.450	0.928 (0.601–1.432)	0.735	0.947 (0.642–1.398)	0.785

Note: HRs represent the change in mortality hazard per 1-SD increase in each inflammatory index. Model 1 was unadjusted. Model 2 adjusted for age, sex, race/ethnicity, education, marital status, and poverty-to-income ratio. Model 3 additionally adjusted for smoking status, alcohol consumption, hypertension, diabetes, cancer, coronary heart disease, stroke, and BMI. All Cox models incorporated the NHANES complex survey design.

Restricted cubic spline analyses further demonstrated significant overall associations of SII, PIV, and NLR with all-cause mortality (all *p* for overall association < 0.001). Evidence of nonlinearity was observed for SII (*p* for nonlinearity = 0.017) and NLR (*p* for nonlinearity = 0.021), whereas no statistically significant evidence of nonlinearity was observed for PIV (*p* for nonlinearity = 0.155) (**Figure S1a–c**).

Formal time-dependent discrimination analyses using flexible RCS-derived biomarker scores showed that NLR had the highest AUC estimates at both 5 and 10 years. At 5 years, the AUCs were 0.647 (95% CI, 0.605–0.689) for NLR, 0.612 (95% CI, 0.564–0.658) for SII, and 0.583 (95% CI, 0.539–0.624) for PIV. NLR showed significantly greater discrimination than PIV (ΔAUC, 0.064; 95% CI, 0.020–0.109; $p = 0.007$), whereas the difference between NLR and SII was not statistically significant (ΔAUC, 0.034; 95% CI, −0.022 to 0.088; $p = 0.238$). At 10 years, NLR showed significantly higher discrimination than both SII (ΔAUC, 0.054; 95% CI, 0.023–0.084; $p = 0.002$) and PIV (ΔAUC, 0.033; 95% CI, 0.003–0.063; $p = 0.036$) (**Table S4**).

The incremental prognostic value of NLR beyond the fully adjusted clinical model was modest. The survey-weighted C-index increased from 0.842 (95% CI, 0.824–0.867) to 0.844 (95% CI, 0.825–0.868) after addition of NLR, corresponding to a ΔC-index of 0.002 (95% CI, −0.000 to 0.004; $p = 0.060$). The 5-year continuous NRI was 0.295 (95% CI, 0.118–0.421), with the improvement arising predominantly from nonevent reclassification (**Table S5**). These findings suggest that NLR provided limited incremental improvement in overall discrimination beyond established clinical covariates.

3.3. Association of Elevated NLR with All-Cause and Cause-Specific Mortality

Using the data-derived NLR cut point of 3.3 for survival stratification, 4,102 participants were classified as having NLR < 3.3 and 457 as having NLR ≥ 3.3. During follow-up, 349 and 103 all-cause deaths occurred in the low- and high-NLR groups, respectively. The corresponding numbers of heart disease deaths were 64 and 30, and the numbers of cancer deaths were 81 and 13. Kaplan–Meier analysis demonstrated significantly poorer overall

survival among participants with NLR ≥ 3.3 than among those with NLR < 3.3 (log-rank $p < 0.001$; **Figure 2**).

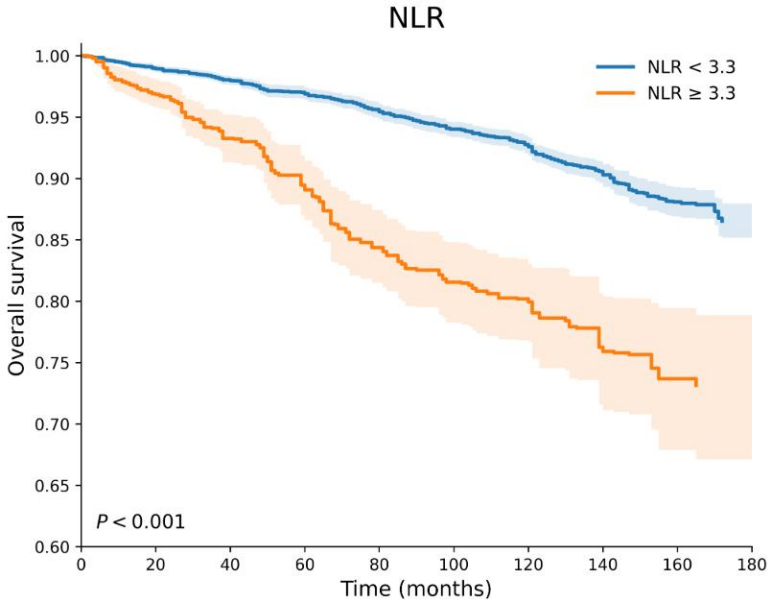


Figure 2. Kaplan–Meier survival curves according to neutrophil-to-lymphocyte ratio category. Participants were classified into lower- and higher-NLR groups using the X-tile-derived cutoff of 3.3. Overall survival differed significantly between the two groups (log-rank $p < 0.001$). Shaded areas represent 95% confidence intervals. NLR, neutrophil-to-lymphocyte ratio.

In the fully adjusted survey-weighted Cox model, NLR ≥ 3.3 was associated with an 80% higher hazard of all-cause mortality (HR, 1.80; 95% CI, 1.34–2.41). For heart disease mortality, the overall cause-specific HR was 3.22 (95% CI, 1.89–5.49), subject to the time-varying association described below. No statistically significant association was observed with cancer mortality (HR, 0.69; 95% CI, 0.39–1.22) (**Table 3**).

Table 3. Associations of elevated NLR with all-cause and cause-specific mortality.

Outcome	Events in NLR < 3.3, n = 4,102	Events in NLR ≥ 3.3, n = 457	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
All-cause mortality	349	103	2.62 (1.78–3.85)	1.94 (1.49–2.53)	1.80 (1.34–2.41)
Heart disease mortality	64	30	4.85 (2.45–9.59)	3.25 (1.99–5.32)	3.22 (1.89–5.49)
Cancer mortality	81	13	1.12 (0.55–2.27)	0.81 (0.39–1.68)	0.69 (0.39–1.22)

Note: NLR < 3.3 served as the reference group. Model 1 was unadjusted. Model 2 adjusted for age, sex, race/ethnicity, education, marital status, and poverty-to-income ratio. Model 3 additionally adjusted for smoking status, alcohol consumption, hypertension, diabetes, cancer, coronary heart disease, stroke, and BMI. Cause-specific Cox regression was used for heart disease and cancer mortality, with deaths from competing causes censored at the time of death. The overall HR for heart disease mortality summarizes the association across follow-up and should not be interpreted as constant over time because the proportional hazards assumption was violated. HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio.

Schoenfeld residual diagnostics showed no evidence of proportional hazards violations for all-cause ($p = 0.666$) or cancer mortality ($p = 0.672$), whereas the assumption was violated for heart disease mortality ($p < 0.001$). During the first 5 years, 41 heart disease deaths occurred (29 with NLR < 3.3 and 12 with NLR ≥ 3.3). Beyond 5 years, 2,063 participants remained at risk, with 53 subsequent heart disease deaths (35 and 18, respectively; **Table S6**). In the exploratory time-varying coefficient model, the adjusted HR was 1.33 (95% CI, 0.56–3.15) within 5 years and 6.76 (95% CI, 2.40–19.10) thereafter (p for interaction = 0.009). These findings indicate a stronger association beyond 5 years, although the interval-specific estimates were imprecise. The overall cause-specific HR of 3.22 (95% CI, 1.89–5.49) therefore summarizes the association across follow-up rather than representing a constant effect.

The principal findings were also robust in sensitivity analyses addressing potential reverse causation. After exclusion of deaths occurring within the first 2 years, NLR ≥ 3.3 remained associated with all-cause mortality (HR, 1.84; 95% CI, 1.32–2.56) and heart disease mortality (HR, 4.17; 95% CI, 2.11–8.26). Similar associations were observed after excluding participants with baseline coronary heart disease, stroke, or cancer (all-cause mortality: HR,

1.79; 95% CI, 1.13–2.85; heart disease mortality: HR, 3.31; 95% CI, 1.39–7.89) and after excluding participants with extreme differential leukocyte counts (all-cause mortality: HR, 1.73; 95% CI, 1.28–2.33; heart disease mortality: HR, 3.44; 95% CI, 1.97–6.00) (**Table S7**). Across 2,000 survey-design bootstrap replicates, the median selected NLR cutoff was 3.27 (interquartile range, 2.72–3.30). A cutoff of 3.30 was selected in 35.4% of replicates, while 67.5% yielded values between 3.20 and 3.30 (**Table S8**). These results characterize cutoff-selection variability rather than predictive validity.

In an additional analysis of the full eligible NLR sample, no statistically significant interaction was observed between NLR and OSA-related symptom status for either all-cause mortality (p for interaction = 0.193) or heart disease mortality (p for interaction = 0.846) (**Table S9**).

3.4. Exploratory Subgroup Analyses for Heart Disease Mortality

Exploratory subgroup analyses of heart disease mortality are presented in **Table 4**. Event counts were limited in several strata, including only one heart disease death among participants aged <40 years and three among never-married participants; therefore, HRs were not reported for these strata. Using parsimonious adjustment models, the magnitude and precision of the stratum-specific associations varied across subgroups. However, no statistically significant interaction was observed for age, sex, race/ethnicity, education, marital status, PIR, smoking status, or alcohol consumption (all p for interaction > 0.05), providing no evidence of effect modification by these characteristics.

Table 4. Exploratory subgroup analyses of the association between NLR ≥ 3.3 and heart disease mortality.

Subgroup	N	Heart Disease Deaths, n (NLR < 3.3/≥ 3.3)	Adjusted HR (95% CI)	*p* for Interaction
Age, years				0.724
<40	1,287	1 (1/0)	NE	
40–60	1,895	19 (14/5)	4.03 (0.73–22.19)	
>60	1,377	74 (49/25)	3.90 (2.02–7.55)	
Sex				0.279
Female	2,055	32 (27/5)	1.31 (0.33–5.25)	
Male	2,504	62 (37/25)	4.18 (1.88–9.33)	
Race/ethnicity				0.895
Other race	839	7 (6/1)	3.22 (0.05–226.96)	
Non-Hispanic Black	926	18 (14/4)	4.25 (1.17–15.44)	
Mexican American	743	10 (7/3)	5.44 (1.11–26.60)	
Non-Hispanic White	2,051	59 (37/22)	2.92 (1.40–6.12)	
Education				0.164
Less than high school	1,044	36 (26/10)	1.53 (0.30–7.92)	
High school	1,118	23 (11/12)	7.90 (2.64–23.69)	
College or above	2,397	35 (27/8)	1.92 (0.58–6.43)	
Marital status				0.263
Never married	612	3 (1/2)	NE	
Separated/widowed/divorced	943	35 (22/13)	5.17 (2.50–10.67)	
Married/living with partner	3,004	56 (41/15)	2.14 (0.91–5.00)	
PIR				0.478
<1	838	19 (18/1)	0.72 (0.10–5.46)	
1–3	1,995	56 (32/24)	4.62 (2.35–9.05)	
>3	1,726	19 (14/5)	1.76 (0.36–8.74)	
Smoking status				0.676
Never	2,204	27 (22/5)	2.80 (0.73–10.67)	
Former	1,244	45 (28/17)	2.35 (0.76–7.28)	
Current	1,111	22 (14/8)	4.49 (1.17–17.31)	
Alcohol consumption				0.246
Never	480	11 (8/3)	3.80 (0.38–38.46)	
Former	732	37 (29/8)	1.73 (0.59–5.03)	
Current	3,347	46 (27/19)	3.88 (1.54–9.73)	

Note: Hazard ratios compare NLR ≥ 3.3 with NLR < 3.3. Because of the limited number of heart disease deaths, subgroup analyses used parsimonious survey-weighted cause-specific Cox models to reduce sparse-data bias. Models were adjusted for age and sex, except for the stratifying variable; age-stratified models were adjusted for sex only, and sex-stratified models were adjusted for age only. Deaths from competing causes were censored at the time of death. Stratum-specific HRs were not reported when fewer than five heart disease deaths occurred. Interaction P values were obtained from survey-weighted models containing multiplicative interaction terms using the same reduced adjustment strategy. For age, interaction was evaluated using continuous age because only one heart disease death occurred among participants aged <40 years. NE, not estimable/reliably estimable because of sparse events; CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PIR, poverty-to-income ratio.

4. Discussion

In this population-based study, we compared inflammatory biomarkers associated with mortality among adults with OSA-related symptoms. Higher NLR was associated with increased all-cause and heart disease mortality, al-

though its incremental improvement in prognostic discrimination beyond established clinical covariates was limited. Importantly, these findings should not be interpreted as demonstrating that NLR is an OSA-specific prognostic marker or that its association with mortality is stronger in adults with OSA-related symptoms than in those without such symptoms. Rather, the contribution of this study lies in the comparative evaluation of routinely available inflammatory indices within a clinically relevant symptom-defined population.

Among NLR, SII, and PIV, NLR had the highest AUC point estimates at 5 and 10 years. However, its 5-year advantage over SII was not statistically significant, and adding NLR to the clinical model yielded minimal improvement in discrimination (ΔC-index, 0.002; $p = 0.060$). Thus, these findings do not establish consistent superiority over other inflammatory indices or meaningful incremental predictive value beyond established clinical covariates. Nevertheless, the observed mortality association is consistent with previous evidence linking NLR to adverse outcomes [18].

The additional sensitivity analyses provide further context for interpreting the observed associations. Renal dysfunction and congestive heart failure are clinically important potential confounders because both may influence systemic inflammatory markers and mortality risk. The persistence of the NLR–mortality associations after adjustment for eGFR and heart failure suggests that these measured conditions did not fully account for the observed relationships. However, this does not establish an independent causal effect of NLR or exclude residual confounding from disease severity and other unmeasured clinical factors. The exploratory adjustment for an emphysema/chronic bronchitis proxy provided a further assessment of pulmonary disease-related confounding, although this variable could not substitute for a consistently measured COPD diagnosis.

The association between NLR and cardiac death is of particular interest [19]. Previous NHANES-based research has also reported associations between elevated NLR and increased all-cause and cardiovascular mortality in the general US adult population [20]. In our study, we found that NLR was significantly associated with heart-related deaths in participants with OSA-related symptoms, while having no significant association with cancer-related deaths. A previous meta-analysis further demonstrated an association between OSA and elevated NLR, supporting the relevance of this inflammatory index in sleep-disordered breathing [21]. These findings suggest that the association between NLR and mortality in this cohort was more apparent for heart disease mortality than for cancer mortality; however, they do not establish cardiovascular specificity of NLR. Previous reviews have highlighted the association between OSA and cardiovascular diseases, including coronary artery disease, heart failure, and other cardiovascular complications [22,23]. Furthermore, OSA-related hypoxic burden and symptom subtypes have been associated with cardiovascular outcomes, suggesting heterogeneity in cardiovascular risk among affected individuals [24]. Given that OSA is closely linked to cardiovascular diseases, and chronic intermittent hypoxia and systemic inflammation are key drivers of endothelial dysfunction and atherosclerosis in OSA, NLR, as an inflammation-related biomarker, may reflect the inflammatory burden and subsequent cardiovascular risk in these patients. Scientific statements from the American Heart Association have further emphasized the multifactorial relationships between OSA, cardiovascular diseases, and cardiac arrhythmias, including the potential contributions of intermittent hypoxia, autonomic dysfunction, and systemic inflammation [25,26]. Because the NLR cutoff was derived and evaluated within the same cohort, the dichotomized hazard ratio may be subject to selection-related optimism. Bootstrap resampling assessed cutoff-selection stability rather than predictive validity. Therefore, continuous NLR remains the primary association measure, whereas the threshold of 3.3 should be considered exploratory pending external validation.

Our study has several strengths. We utilized a large-scale NHANES dataset with mortality linkage and accounted for the complex survey design. The comprehensive analytical framework, including Cox regression, time-dependent discrimination analyses, restricted cubic spline models, and sensitivity analyses, enabled a detailed evaluation of the associations and prognostic performance of multiple inflammatory indices.

Several features of the study constrain interpretation of the findings. The observational NHANES design does not permit causal attribution. Although additional sensitivity analyses accounted for eGFR and self-reported congestive heart failure, residual confounding related to disease severity and other unmeasured factors cannot be excluded. Self-reported physician-diagnosed COPD data were available only for the 2015–2016 and 2017–2018 NHANES cycles (**Table S10**). The exploratory pulmonary disease proxy, based on emphysema or chronic bronchitis, was not equivalent to a confirmed COPD diagnosis and therefore could not eliminate all chronic respiratory disease-related confounding. The analysis also relied on complete observations because several missing labora-

tory variables were direct components of the inflammatory indices, creating the possibility of selection related to missingness. The association between elevated NLR and heart disease mortality varied over follow-up, precluding interpretation of the overall HR as a constant effect. Although exploratory analyses suggested a stronger association beyond 5 years, these estimates were based on relatively few events. Moreover, all 53 heart disease deaths beyond 5 years occurred among participants from the 2005–2008 NHANES cycles, limiting temporal generalizability. Sparse events also constrained subgroup analyses. OSA-related symptom status was questionnaire-defined rather than polysomnography-confirmed, so the findings apply to a symptom-defined population. Finally, because follow-up differed markedly among NHANES cycles, longer-term discrimination estimates were informed mainly by participants enrolled in the earlier 2005–2008 cycles.

Overall, our findings support an association between elevated NLR and mortality among adults with OSA-related symptoms. However, the observational study design, residual confounding, and limited incremental prognostic discrimination warrant cautious interpretation.

5. Conclusion

Higher NLR was associated with all-cause mortality among adults with OSA-related symptoms, while its association with heart disease mortality varied over time. Its incremental prognostic discrimination beyond established clinical covariates was limited. The data-derived cutoff of 3.3 remains exploratory and requires external validation before clinical application.

Supplementary Materials

The supporting information can be downloaded at https://ojs.ukscip.com/uploads/2/asset-file/2026/11/asset-file_6fcfc858515f860da4a794dbeeaed7db.docx.

Author Contributions

Resources, validation, project administration, supervision, conceptualization, writing—review and editing, T.L., J.D. and X.Y.; writing—original draft, methodology, software, formal analysis, investigation, data curation, F.W., S.S. and C.W.; investigation, visualization, X.Y. and J.D. All authors have read and agreed to the published version of the manuscript.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Institutional Review Board Statement

The studies involving humans were approved by the National Center for Health Statistics' Research Ethics Review Board (Protocol #2024-01). The studies were conducted in accordance with the local legislation and institutional requirements.

Informed Consent Statement

The participants provided their written informed consent to participate in this study.

Data Availability Statement

All data used in the study can be obtained in the public database National Health and Nutrition Examination Survey (NHANES).

Acknowledgments

We thank the National Health and Nutrition Examination Survey participants and staff and the National Center for Health Statistics for their valuable contributions.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AI Use Statement

The authors declare that no artificial intelligence (AI) tools were used in the preparation of this manuscript.

References

1. Drager, L.F.; Togeiro, S.M.; Polotsky, V.Y.; et al. Obstructive sleep apnea: A cardiometabolic risk in obesity and the metabolic syndrome. *J. Am. Coll. Cardiol.* **2013**, *62*, 569–576. [CrossRef]
2. DiCaro, M.V.; Lei, K.; Yee, B.; et al. The Effects of Obstructive Sleep Apnea on the Cardiovascular System: A Comprehensive Review. *J. Clin. Med.* **2024**, *13*, 3223. [CrossRef]
3. Mazzotti, D.R.; Keenan, B.T.; Lim, D.C.; et al. Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes. *Am. J. Respir. Crit. Care Med.* **2019**, *200*, 493–506. [CrossRef]
4. Liu, X.; Ma, Y.; Ouyang, R.; et al. The relationship between inflammation and neurocognitive dysfunction in obstructive sleep apnea syndrome. *J. Neuroinflammation* **2020**, *17*, 229. [CrossRef]
5. Dentali, F.; Nigro, O.; Squizzato, A.; et al. Impact of neutrophils to lymphocytes ratio on major clinical outcomes in patients with acute coronary syndromes: A systematic review and meta-analysis of the literature. *Int. J. Cardiol.* **2018**, *266*, 31–37. [CrossRef]
6. Templeton, A.J.; McNamara, M.G.; Šeruga, B.; et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. *J. Natl. Cancer Inst.* **2014**, *106*, dju124. [CrossRef]
7. Song, M.; Graubard, B.I.; Rabkin, C.S.; et al. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. *Sci. Rep.* **2021**, *11*, 464. [CrossRef]
8. Yang, Z.; Lv, T.; Lv, X.; et al. Association of serum uric acid with all-cause and cardiovascular mortality in obstructive sleep apnea. *Sci. Rep.* **2023**, *13*, 19606. [CrossRef]
9. Sabanayagam, C.; Teppala, S.; Shankar, A. Markers of sleep disordered breathing and diabetes mellitus in a multiethnic sample of US adults: Results from the National Health and Nutrition Examination Survey (2005–2008). *Int. J. Endocrinol.* **2012**, *2012*, 879134. [CrossRef]
10. Zhang, Q.; Zhang, Q.; Li, X.; et al. Association of obstructive sleep apnea symptoms with all-cause mortality and cause-specific mortality in adults with or without diabetes: A cohort study based on the NHANES. *J. Diabetes* **2024**, *16*, e13538. [CrossRef]
11. Cao, Y.; Li, P.; Zhang, Y.; et al. Association of systemic immune inflammatory index with all-cause and cause-specific mortality in hypertensive individuals: Results from NHANES. *Front. Immunol.* **2023**, *14*, 1087345. [CrossRef]
12. Hsu, Y.-C.; Yang, Y.-Y.; Tsai, I.-T. Lymphocyte-to-monocyte ratio predicts mortality in cirrhotic patients with septic shock. *Am. J. Emerg. Med.* **2021**, *40*, 70–76. [CrossRef]
13. Ma, H.; Chen, J.; Zhan, X.; et al. Platelet-to-albumin ratio: A potential biomarker for predicting all-cause and cardiovascular mortality in patients undergoing peritoneal dialysis. *BMC Nephrol.* **2024**, *25*, 365. [CrossRef]
14. Xu, H.-B.; Xu, Y.-H.; He, Y.; et al. Association between admission pan-immune-inflammation value and short-term mortality in septic patients: A retrospective cohort study. *Sci. Rep.* **2024**, *14*, 15205. [CrossRef]
15. Zinellu, A.; Zinellu, E.; Mangoni, A.A.; et al. Clinical significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbations of COPD: Present and future. *Eur. Respir. Rev.* **2022**, *31*, 220095. [CrossRef]
16. Li, S.; Yang, Y.; Lin, M.; et al. Body Mass Index mediates the associations between dietary approaches to stop hypertension and obstructive sleep apnea among U.S. adults. *Front. Nutr.* **2024**, *11*, 1509711. [CrossRef]
17. National Center for Health Statistics. National Health and Nutrition Examination Survey 2017–2018 Data Documentation, Codebook, and Frequencies: Body Measures (BMX_J). Available online: https://www.cdc.gov/Nchs/Data/Nhanes/Public/2017/DataFiles/BMX_J.htm (accessed on 10 July 2026).
18. Buonacera, A.; Stancanelli, B.; Colaci, M.; et al. Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. *Int. J. Mol. Sci.* **2022**, *23*, 3636. [CrossRef]
19. Angkananard, T.; Anothaisintawee, T.; McEvoy, M.; et al. Neutrophil lymphocyte ratio and cardiovascular disease risk: A systematic review and meta-analysis. *BioMed Res. Int.* **2018**, *2018*, 2703518. [CrossRef]
20. Gu, L.; Xia, Z.; Qing, B.; et al. The core role of neutrophil–lymphocyte ratio to predict all-cause and cardio-

vascular mortality: A research of the 2005–2014 National Health and Nutrition Examination Survey. *Front. Cardiovasc. Med.* **2022**, *9*, 847998. [CrossRef]
21. Rha, M.S.; Kim, C.H.; Yoon, J.H.; et al. Association between the neutrophil-to-lymphocyte ratio and obstructive sleep apnea: A meta-analysis. *Sci. Rep.* **2020**, *10*, 10862. [CrossRef]
22. Li, Y.E.; Ren, J. Association between obstructive sleep apnea and cardiovascular diseases. *Acta Biochim. Biophys. Sin.* **2022**, *54*, 882–892. [CrossRef]
23. Khokhrina, A.; Andreeva, E.; Degryse, J.M. A systematic review on the association of sleep-disordered breathing with cardiovascular pathology in adults. *npj Prim. Care Respir. Med.* **2022**, *32*, 41. [CrossRef]
24. Trzepizur, W.; Blanchard, M.; Ganem, T.; et al. Sleep apnea-specific hypoxic burden, symptom subtypes, and risk of cardiovascular events and all-cause mortality. *Am. J. Respir. Crit. Care Med.* **2022**, *205*, 108–117. [CrossRef]
25. Yeghiazarians, Y.; Jneid, H.; Tietjens, J.R.; et al. Obstructive sleep apnea and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation* **2021**, *144*, e56–e67. [CrossRef]
26. Mehra, R.; Chung, M.K.; Olshansky, B.; et al. Sleep-disordered breathing and cardiac arrhythmias in adults: Mechanistic insights and clinical implications: A scientific statement from the American Heart Association. *Circulation* **2022**, *146*, e119–e136. [CrossRef]

Copyright © 2026 by the author(s). Published by UK Scientific Publishing Limited. This is an open access article under the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Publisher's Note: The views, opinions, and information presented in all publications are the sole responsibility of the respective authors and contributors, and do not necessarily reflect the views of UK Scientific Publishing Limited and/or its editors. UK Scientific Publishing Limited and/or its editors hereby disclaim any liability for any harm or damage to individuals or property arising from the implementation of ideas, methods, instructions, or products mentioned in the content.