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Association between inflammation indicators (MLR, NLR, SII, SIRI, and AISI) and erectile dysfunction in US adults: NHANES 2001–2004

Heng Liu[2†], Huqiang Dong[3†], Mixue Guo[4] and Hongping Cheng[1*]

Abstract

Background This study aimed to assess the relationship between multiple indicators of inflammation and erectile dysfunction through an analysis of data from the National Health and Nutrition Examination Survey (NHANES). This represents the first large-scale, cross-sectional investigation that explores this association by jointly analyzing various inflammatory markers.

Methods We performed a cross-sectional analysis with NHANES data from 2001 to 2004. Erectile dysfunction (ED) was evaluated through a self-reported questionnaire and testosterone levels, while inflammatory markers were derived from standard blood test parameters. Our approach included multivariate logistic regression, subgroup analyses, generalized additive modeling (GAM), and smoothed curve fitting to evaluate the link between inflammatory markers (NLR, MLR, SII, SIRI, AISI) and ED. Additionally, we utilized receiver operating characteristic (ROC) curves to determine the diagnostic utility of these markers, comparing their area under the curve (AUC) values.

Results A total of 3610 participants were included in this study, and the population-weighted ED patients were 18.91%. In the adjusted model, multiple logistic regression analysis showed a positive association between five inflammatory indicators (Ln-NLR, Ln-MLR, Ln-SII, Ln-SIRI, and Ln-AISI) and ED. Smoothed curve fitting showed a nonlinear positive correlation between the five inflammatory indicators and ED. Furthermore, subgroup analyses showed that this correlation was stronger in people older than 50 year. ROC curve analysis showed the highest diagnostic performance for the study outcome with MLR (AUC = 0.616, 95% CI: 0.5952–0.637), which was significantly better than SIRI, NLR, AISI, and SII.

Conclusion MLR is potentially more effective than other biomarkers (NLR, SIRI, AISI, SII) in predicting ED. Men with elevated MLR levels should be particularly aware of their increased risk of developing ED.

Keywords Inflammation, Indicator, Erectile dysfunction, NHANES, A cross-sectional study, ED

[†]Heng Liu and Huqiang Dong contributed equally to this work and share first authorship.

*Correspondence:
Hongping Cheng
936364147@qq.com
[1]Center of Health Administration and Development Studies, Hubei University of Medicine, Shiyan 442000, Hubei, China
[2]Department of Urology, Renmin Hospital, Hubei University of Medicine, Shiyan 442000, Hubei, PR China
[3]School of Public Health, Ningxia Medical University, Yinchuan 750004, Ningxia, China
[4]School of Basic Medical Sciences, Ningxia Medical University, Yinchuan 750004, Ningxia, China

Background

Male sexual dysfunction, often known as erectile dysfunction (ED), is characterized by changes in the erectile response's parts, which include both physiological and psychological elements [1]. Despite not being physically life-threatening, ED significantly lowers men's quality of life and their mental health [2]. By 2025, it is predicted that over 320 million men globally will be affected by this illness [3]. Although the exact causes of ED are unknown, a number of studies have suggested that a combination of vascular, neurological, and hormonal factors could be responsible [2, 4]. Erectile dysfunction in younger individuals might suggest an organic condition [5]. Furthermore, some research has shown a strong correlation between endothelial dysfunction indicators and inflammation in relation to the occurrence and severity of ED [5].

Among the indicators of inflammation, the Monocyte-to-Lymphocyte Ratio (MLR) has emerged as an important indicator of the combined inflammatory state and immune function [6]. This ratio is recognized as a chronic inflammatory state and has been thoroughly examined in several inflammation-related disorders, such as tuberculosis and cardiovascular disease [6, 7]. Research has indicated that the neutrophil-to-lymphocyte ratio (NLR) holds considerable predictive significance across a range of medical conditions [8, 9]. In addition, as indications for evaluating the local immune response and systemic inflammatory state [10, 11], the systemic immune-inflammatory index (SII) and the systemic inflammatory response index (SIRI) are based on the immune cell subpopulations and platelet counts [12]. The aggregate index of systemic inflammation (AISI) was originally designed to assess the inflammatory state of patients with idiopathic pulmonary fibrosis (IPF), and assesses the systemic inflammatory response primarily by reflecting the ratio of immune cell subpopulations (such as neutrophils, lymphocytes, and monocytes) to platelet counts [13]. Although it was initially applied in the study of pulmonary fibrosis, this inflammatory response is not only significantly present in IPF, but also plays an important role in many other diseases [14]. ED is closely associated with systemic chronic inflammation. Therefore, given that the pathomechanism of ED involves multiple inflammation-related factors, the application of the AISI index to ED patients could provide further insights into understanding the role of inflammatory responses in the disease and help identify potential therapeutic targets.

A growing body of evidence suggests that chronic inflammation plays a key role in the development of ED. In particular, some inflammatory markers (such as NLR, MLR, SII, SIRI) are closely associated with vascular endothelial dysfunction, which is recognized as one of the potential mechanisms leading to ED. Normally the vascular endothelium has anti-inflammatory properties, but in inflammatory states, endothelial function is impaired, leading to abnormal arterial function and affecting blood supply, which may trigger ED [15]. It has also been shown that levels of fibrinogen, a pro-inflammatory factor, are elevated in ED patients, especially in men with concomitant diabetes mellitus, which further reinforces the role of inflammation in ED [16]. In addition, angiotensin II exacerbates the inflammatory response by triggering oxidative stress, leading to local and systemic vascular inflammation, which not only affects penile blood flow, but may also trigger additional inflammatory responses on a systemic scale, further aggravating ED [17]. Thus, inflammation affects penile blood flow and function by impairing vascular endothelial function, elevating inflammatory factors, and increasing oxidative stress, ultimately leading to ED. Based on this, we hypothesized that these inflammatory markers are significantly and positively associated with the occurrence and severity of ED and may serve as potential predictors.

Therefore, this study aims to use data from the National Health and Nutrition Examination Survey (NHANES) to assess the relationship between various inflammatory variables and ED. The goal of this study is to identify a more practical and effective marker, aiming to provide new insights for the treatment of ED. Additionally, this approach seeks to uncover the role of inflammation in the development of ED, offering innovative strategies and evidence for clinical management and treatment.

Materials and methods

Data Availability

The NHANES database employs a complex, probability-based sampling design to assess the health and nutritional status of noninstitutionalized civilians in the United States through standardized interviews, physical examinations, and laboratory tests, thus ensuring representation from diverse populations. The data have been available for research since 1999 and are updated biennially. For this study, we collected data from two NHANES cycles (2001–2002 and 2003–2004), with additional information available on the NHANES website.

Study population

We selected datasets from two NHANES study cycles (2001–2002 and 2003–2004) for cross-sectional analyses because these where the only two cycles for which ED data were available. From 2001 to 2004, a total of 21,161 individuals participated in NHANES. The exclusion criteria were as follows: female (n=10,860); age<20 years (n=5,347); missing ED data (n=838); missing inflammatory index data (n=142); missing educational attainment data (n=2); missing marital status data (n=2); missing

Poverty Income Ratio (PIR) data ($n=208$); missing data on BMI ($n=94$); missing data on smoking ($n=4$); missing data on alcohol consumption ($n=2$); missing data on hypertension ($n=3$); missing data on diabetes mellitus ($n=32$); missing data on cardiovascular disease ($n=12$); and missing data on stroke ($n=5$). Finally, a total of 3,610 cases were included in this study. (Fig. 1)

Defining ED and inflammatory indicators

The interview takes place in a private room at the Medical Examination Center (MEC) with the administration method being an audio computer-assisted self-interview (ACASI). One item from the Massachusetts Male Aging Study was used to assess self-assessment of ED, which was intended to be the outcome variable. It read, "Many men experience problems with sexual intercourse." Regarding your ability to get and keep an erection powerful enough to engage in satisfying sexual activity, what would you say? "Usually able," "always or almost always able," "sometimes able," and "never able" were the available answers. Participants who indicated that they were "sometimes able" or "never able" to maintain an erection were classified as having ED in this analysis. Individuals who said that they were "usually able" or "always or almost always able" were not considered to have ED [5, 18].

Inflammation index measurement

The inflammatory markers assessed in this study—monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), and systemic inflammatory composite index (AISI)—were all derived from standard complete blood count (CBC) tests. As part of the NHANES protocol, blood samples were collected from participants by certified phlebotomists and processed in accredited laboratories. A complete blood count provides data on subtypes of white blood cells (WBCs), including neutrophils, lymphocytes, monocytes, and platelets. The reliability of these measurements is ensured by NHANES' rigorous quality control procedures, which encompass standardized laboratory protocols, utilization of validated equipment, and regular calibration checks. The formulas for calculating the ratios are as follows: Neutrophil-to-lymphocyte ratio (NLR) = neutrophil count (NC)/lymphocyte count (LC); Monocyte-to-lymphocyte ratio (MLR) = monocyte count (MC)/lymphocyte count (LC); Systemic immune-inflammation index (SII) = platelet count (PC) × neutrophil count (NC)/lymphocyte count (LC); Systemic inflammatory response index(SIRI) = neutrophil count(NC) × monocyte count(MC)/lymphocyte count(LC); Systemic inflammatory composite index(AISI) = neutrophil count(NC) × platelet count(PC) × monocyte count(MC)/lymphocyte(count LC)." [19, 20].

Covariates

In this study, the covariates included age, race, and race were categorized as follows: Mexican Americans, other Hispanics, non-Hispanic whites, non-Hispanic blacks, and other races. Education was categorized as below high school, high school graduate, and above high school. Marital status was classified into three categories: never married; married/living with a partner; and widowed/divorced/separated. The household income poverty rate (PIR) was stratified into three groups: <1.3 (low income), 1.3–3.5 (middle income), and >3.5 (high income). Body mass index (BMI) was divided into three classifications: <25 kg/m², 25–30 kg/m², and ≥30 kg/m². Smoking status was categorized as current smokers (≥100 cigarettes smoked in their lifetime) versus non-smokers (≤100 cigarettes or never smoked). A drinker was defined as an individual who has consumed at least 12 alcoholic beverages within any given year of their life. Diabetes diagnosis is based on one or more of the following criteria: confirmation by a doctor or healthcare professional; fasting blood glucose level of 126 mg/dL or higher; HbA1c percentage of 6.5% or greater; or use of diabetes medications, including insulin. High blood pressure is determined through any of the following methods: diagnosis by a doctor or healthcare professional; use of antihypertensive medications; or an average systolic blood pressure of at least 140 mmHg combined with a mean diastolic blood pressure of at least 90 mmHg. Stroke history is recorded as "yes" or "no." Cardiovascular disease encompasses conditions such as congestive heart failure, coronary artery disease, angina pectoris, and myocardial infarction.

We performed a sensitivity analysis by adding the ED diagnostic criteria and potential confounding variables. Additionally, we included male testosterone levels as part of the diagnosis of ED, defining individuals with testosterone levels below 2.3 ng/mL as ED patients [21, 22]. Based on previous studies, we further included some covariates, such as peripheral artery disease (PAD), metabolic syndrome, anxiety disorders, and depression. PAD was examined by trained health technicians in a mobile examination center. During the measurement, participants lay supine on an examination table. Systolic blood pressure was measured in the right arm (brachial artery) and at both ankles (posterior tibial artery). Systolic blood pressure was measured twice at each site for participants aged 40–59 years and once at each site for participants aged 60 years and older. ABPI was calculated automatically by a computer system and verified by NCHS. The presence of PAD was defined as an ankle-brachial blood pressure index (ABPI) ≤0.9 on the left or right [23, 24].

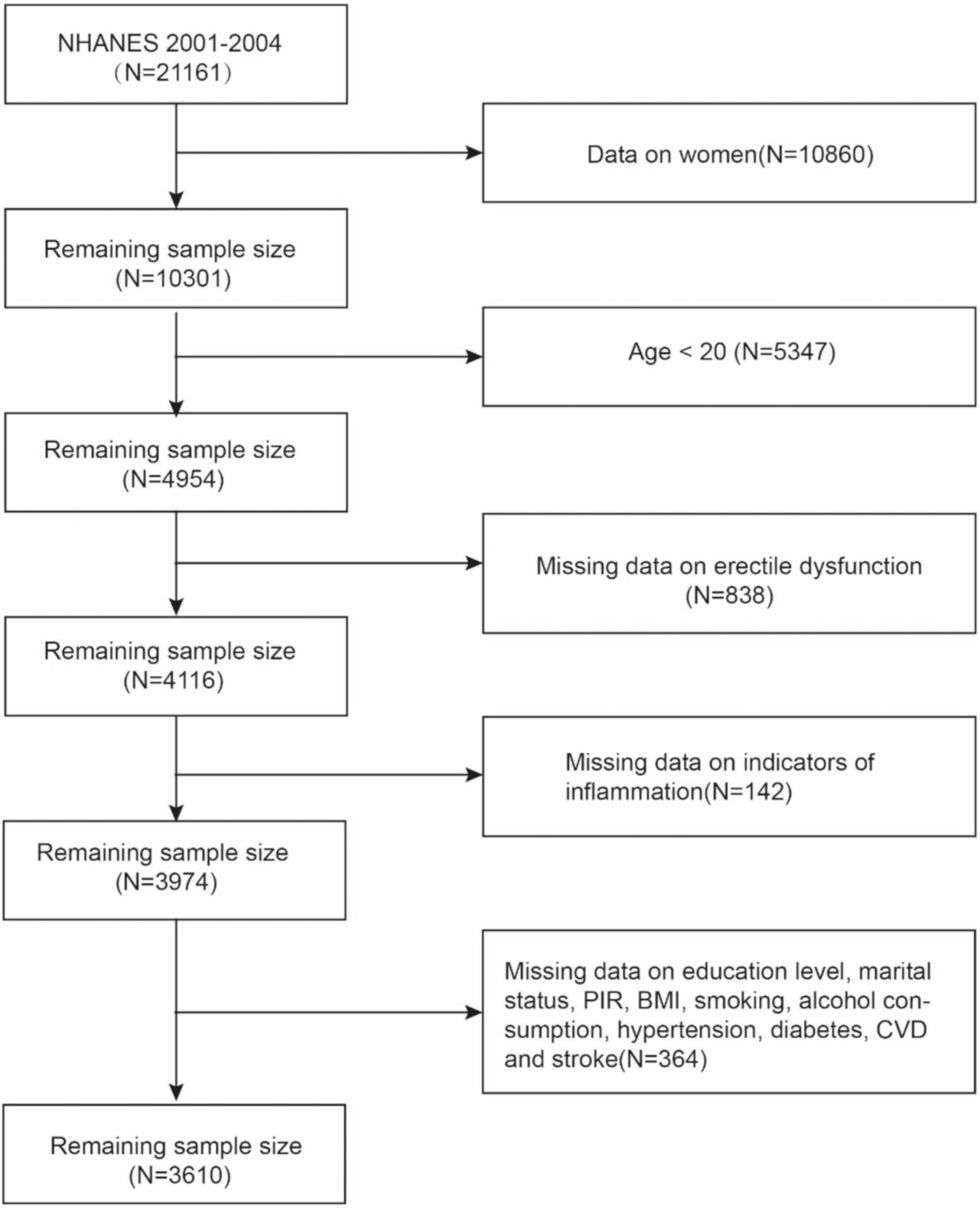

Fig. 1 Flow chart of the study

Anxiety and depression were assessed using questionnaires (CIQGAD) and (CIQDEP).

Statistical analysis

The multistage design of NHANES was considered in all statistical analyses. In the baseline characteristics table, continuous variables were reported as survey-weighted means (95% CI), and categorical variables as survey-weighted percentages (95% CI). We used weighted linear regression and weighted chi-square tests to assess differences between the ED and non-ED groups.

To explore the associations between five indicators of inflammation and the prevalence of ED, we employed three logistic regression models. Model 1 was unadjusted. Model 2 included adjustments for age, race, education, and marital status. Model 3 further incorporated BMI, PIR, smoking, alcohol consumption, diabetes, hypertension, cardiovascular disease, and stroke, building on Model 2. In the statistical analysis, we observed that the data for inflammation indicators were unevenly distributed and significantly skewed. Therefore, they were transformed using the natural logarithm (Ln-NLR, Ln-MLR, Ln-SII, Ln-SIRI, Ln-AISI) to better suit our statistical analysis. We performed weighted multivariate logistic regression to describe the relationship between inflammation indicators and ED, treating these indicators both as continuous variables and as categorical variables (trichotomies). We estimated trends by considering the trichotomies of inflammation indicators as continuous variables. Subsequently, we further analyzed the nonlinear associations between inflammatory indicators and ED prevalence using a generalized additive model (GAM) and smooth curve fitting. When nonlinear associations were observed, a two-segment linear regression model (segmented regression model) was fitted to each interval and compared to a single-linear model (non-segmented model) using a log-likelihood ratio test, with threshold effects calculated. Subsequently, subgroup analyses and interaction tests were performed on the potential confounders listed in the baseline table. Furthermore, we used receiver operating characteristic (ROC) curves to evaluate the diagnostic power of inflammatory markers (NLR, MLR, SII, SIRI, and AISI) for ED and compared the area under the curve (AUC) values. This study was statistically analyzed using R (http://www.r-project.org) and EmpowerStats (http://www.empowerstats.com), and the significance level was set at $P<0.05$.

Results

Baseline characteristics of the study population

A total of 3610 participants were enrolled in this study, representing a population-weighted prevalence of 18.91% (17.29%, 20.64%) among ED patients. Compared to non-ED patients, those with ED exhibited significantly higher levels of NLR, MLR, SII, SIRI, and AISI, with $p<0.001$. Additionally, the ED group showed a higher prevalence of factors such as age, BMI, marital status, smoking, diabetes, CVD, stroke, and hypertension. Conversely, they had significantly lower levels of alcohol consumption, educational level, and PIR. The differences between the groups were statistically significant ($p<0.001$). (Table 1)

For continuous variables: survey-weighted mean (95% CI), P-value was by survey-weighted linear regression. For categorical variables: survey-weighted percentage (95% CI), P-value was by survey-weighted Chi-square test.

Abbreviation: PIR, the ratio of income to poverty; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, system inflammation response index; AISI, aggregate index of systemic inflammation; CVD, cardiovascular disease;

Association between Inflammatory indicators and ED

Multiple logistic regression analyses revealed positive associations between the five inflammatory indicators and ED across both unadjusted and adjusted models (Table 2). After a full adjustment for covariates in Model 3, Ln-NLR, Ln-MLR, Ln-SII, Ln-SIRI, and Ln-AISI remained positively associated with ED, with adjusted odds ratios (OR) as follows: Ln-NLR: OR = 1.35, 95% CI: 1.09–1.68; Ln-MLR: OR = 1.50, 95% CI: 1.15–1.96; Ln-SII: OR = 1.21, 95% CI: 1.01–1.46; Ln-SIRI: OR = 1.23, 95% CI: 1.03–1.46; Ln-AISI: OR = 1.14, 95% CI: 0.99–1.33. We then categorized the continuous inflammation indicators into three groups. In Model 3, participants in the highest tertile of each indicator were significantly more likely to have ED compared to those in the lowest tertile, with all p-values for trend < 0.05. Furthermore, we explored the nonlinear relationship between these indicators and ED prevalence using generalized additive modeling (GAM) and smoothed curve fitting (as shown in Fig. 2). The analyses demonstrated a nonlinear positive correlation between the five inflammatory markers and ED prevalence, with all log-likelihood ratio test p-values < 0.05. (Table 3).

Subgroup analysis

To assess the consistency of the associations between five inflammatory indicators (Ln-NLR, Ln-MLR, Ln-SII, Ln-SIRI, and Ln-AISI) and ED prevalence across different populations, we conducted subgroup analyses. These analyses revealed that the positive association between Ln-NLR and ED prevalence was particularly strong in individuals aged over 50 years (OR = 2.12, 95% CI: 1.63–2.75) and in alcohol consumers (OR = 1.52, 95% CI: 1.11–2.07), with a significant interaction ($p<0.05$). Similarly, the association between Ln-MLR and ED prevalence was

Table 1 Baseline characteristics of study participants in NHANES 2001–2004, weighted

Characteristic	History of erectile dysfunction (ED)		*P*-value
	No	Yes	
Number (*n*)	2593	1017	
Age (years)	41.26 (40.65,41.87)	60.93 (59.89,61.97)	< 0.0001
NLR	2.18 (2.14,2.23)	2.55 (2.46,2.64)	< 0.0001
MLR	0.30 (0.29,0.30)	0.35 (0.33,0.36)	< 0.0001
SII	564.75 (550.29,579.21)	620.57 (589.43,651.70)	0.0043
SIRI	1.29 (1.25,1.32)	1.55 (1.48,1.63)	< 0.0001
AISI	337.73 (326.71,348.75)	385.64 (363.01,408.28)	0.0001
Race (%)			0.1747
Mexican American	8.05 (6.21,10.37)	6.94 (4.24,11.17)	
Other Hispanic	4.04 (2.57,6.30)	5.05 (2.17,11.33)	
Non-Hispanic White	74.04 (69.76,77.90)	77.11 (70.55,82.58)	
Non-Hispanic Black	9.59 (7.60,12.02)	8.21 (6.05,11.05)	
Other Race	4.29 (3.15,5.83)	2.68 (1.60,4.43)	
Education level (%)			< 0.0001
Less than high school	13.82 (12.37,15.42)	29.46 (25.15,34.17)	
High school	27.81 (25.42,30.34)	23.51 (20.38,26.95)	
More than high school	58.36 (55.59,61.09)	47.03 (43.09,51.02)	
Marital status (%)			< 0.0001
Never married	20.32 (17.78,23.12)	6.65 (4.80,9.13)	
Married/Living with a partner	69.25 (66.23,72.13)	77.62 (74.62,80.35)	
Widowed/divorced/Separated	10.43 (8.54,12.67)	15.74 (13.79,17.90)	
PIR (%)			< 0.0001
<1.3	15.63 (13.67,17.83)	18.64 (15.19,22.66)	
1.3–3.5	34.03 (31.47,36.69)	41.62 (37.65,45.70)	
≥3.5	50.33 (46.94,53.72)	39.75 (35.38,44.28)	
BMI (Kg/m^2)			0.0003
<25	30.53 (28.44,32.70)	24.49 (21.01,28.35)	
25–30	41.75 (39.51,44.02)	39.57 (35.83,43.44)	
≥30	27.73 (25.54,30.02)	35.94 (31.76,40.33)	
Smoking (%)			< 0.0001
No	45.36 (42.29,48.47)	30.48 (27.12,34.06)	
Yes	54.64 (51.53,57.71)	69.52 (65.94,72.88)	
Alcohol intake (%)			0.0039
No	15.56 (11.95,20.02)	19.81 (15.83,24.49)	
Yes	84.44 (79.98,88.05)	80.19 (75.51,84.17)	
Hypertension (%)			< 0.0001
No	71.31 (68.37,74.08)	41.89 (38.33,45.52)	
Yes	28.69 (25.92,31.63)	58.11 (54.48,61.67)	
Diabetes (%)			< 0.0001
No	94.24 (93.18,95.15)	72.00 (68.25,75.46)	
Yes	5.76 (4.85,6.82)	28.00 (24.54,31.75)	
CVD (%)			< 0.0001
No	95.39 (94.28,96.30)	77.48 (72.81,81.55)	
Yes	4.61 (3.70,5.72)	22.52 (18.45,27.19)	
Stroke (%)			< 0.0001
No	99.24 (98.68,99.56)	93.62 (91.76,95.08)	
Yes	0.76 (0.44,1.32)	6.38 (4.92,8.24)	

more pronounced in those aged over 50 years (OR = 2.66, 95% CI: 1.90–3.73) and in individuals with a PIR ≥ 3.5 (OR = 2.20, 95% CI: 1.48–3.28), also showing a significant interaction ($p < 0.05$). The relationship between Ln-SIRI and ED was stronger in the over-50 age group (OR = 1.76, 95% CI: 1.40–2.22) and among alcohol consumers (OR = 1.36, 95% CI: 1.06–1.76), with interaction p-values indicating significance ($p < 0.05$). However, the

Table 2 Multivariable logistic regression analyses for inflammatory indicators and ED, weighted

Index	Characteristic	Model 1		Model 2		Model 3	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Ln-NLR	Continuous	2.31 (1.95, 2.75)	< 0.001	1.43 (1.16, 1.77)	0.001	1.35 (1.09, 1.68)	0.007
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	1.27 (1.05, 1.54)	0.014	0.97 (0.77, 1.23)	0.829	0.92 (0.73, 1.16)	0.477
	Tertile 3	2.27 (1.89, 2.72)	< 0.001	1.39 (1.11, 1.75)	0.0045	1.31 (1.04, 1.65)	0.023
	P for trend		< 0.001		0.002		0.015
Ln-MLR	Continuous	3.25 (2.64, 4.02)	< 0.001	1.49 (1.15, 1.93)	0.003	1.50 (1.15, 1.96)	0.003
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	1.36 (1.12, 1.65)	0.002	0.94 (0.75, 1.18)	0.595	0.94 (0.74, 1.19)	0.593
	Tertile 3	2.36 (1.96, 2.83)	< 0.001	1.27 (1.01, 1.60)	0.041	1.27 (1.01, 1.61)	0.044
	P for trend		< 0.001		0.028		0.030
Ln-SII	Continuous	1.39 (1.20, 1.61)	< 0.001	1.25 (1.04, 1.49)	0.015	1.21 (1.01, 1.46)	0.041
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	1.11 (0.92, 1.33)	0.284	1.00 (0.80, 1.25)	0.981	1.03 (0.82, 1.30)	0.783
	Tertile 3	1.48 (1.24, 1.77)	< 0.001	1.35 (1.08, 1.68)	0.007	1.31 (1.05, 1.65)	0.019
	P for trend		< 0.001		0.005		0.017
Ln-SIRI	Continuous	1.85 (1.62, 2.11)	< 0.001	1.37 (1.16, 1.62)	< 0.001	1.23 (1.03, 1.46)	0.020
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	1.20 (0.99, 1.45)	0.065	0.90 (0.71, 1.13)	0.361	0.81 (0.64, 1.03)	0.083
	Tertile 3	2.37 (1.98, 2.84)	< 0.001	1.62 (1.30, 2.03)	< 0.001	1.44 (1.14, 1.82)	0.002
	P for trend		< 0.001		< 0.001		< 0.001
Ln-AISI	Continuous	1.36 (1.21, 1.53)	< 0.001	1.20 (1.04, 1.39)	0.014	1.14 (0.99, 1.33)	0.077
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	1.10 (0.92, 1.32)	0.302	0.93 (0.74, 1.17)	0.541	0.89 (0.71, 1.12)	0.327
	Tertile 3	1.60 (1.34, 1.91)	< 0.001	1.38 (1.11, 1.73)	0.005	1.28 (1.02, 1.62)	0.033
	P for trend		< 0.001		0.003		0.025

Model 1: no covariates were adjusted. Model 2: age, and race, education level, marital status were adjusted. Model 3: age, race, education level, marital status, PIR, BMI, smoking status, alcohol drinking status, diabetes status, hypertension status, CVD, and stroke were adjusted

associations between Ln-SII and Ln-AISI with ED prevalence did not show significant differences across the subgroups analyzed (p for interaction > 0.05). (Fig. 3)

ROC analysis

The accuracy of inflammatory markers (NLR, MLR, SII, SIRI, and AISI) in predicting ED was assessed by calculating AUC values (Fig. 4). We observed that among all the inflammatory markers, MLR had the highest AUC value in predicting ED. Table 4 shows that the difference in AUC values of inflammatory markers was statistically significant (all $p < 0.05$). This indicates that MLR may possess greater discriminatory power and accuracy compared to the other markers (NLR, SII, SIRI, and AISI) in predicting the risk of ED.

Sensitivity analysis

The sensitivity analysis showed that there was still a positive correlation between the inflammatory indicators and ED. In Model 3, for every one unit increase in Ln-MLR, the likelihood of ED increased by 45% (OR = 1.45, 95% CI: 1.11–1.89, $P = 0.0059$); for every one unit increase in Ln-NLR, the likelihood of ED increased by 33% (OR = 1.33, 95% CI: 1.07–1.65, $P = 0.0102$); for each unit increase in Ln-SII, the likelihood of ED increased by 20% (OR = 1.20, 95% CI: 1 0.00–1.45, $P = 0.0484$); for each unit increase in Ln-SIRI, the likelihood of ED increased by 22% (OR = 1.22, 95% CI: 1.02–1.44, $P = 0.0261$). (Table 5) (Table S1).

Discussion

Due to the complexity of the factors contributing to the development of ED, identifying key indicators for treatment is crucial. We discovered a strong correlation between MLR and the likelihood of ED in this study with 3670 individuals. Additionally, a greater incidence of ED was linked to raised levels of SII, NLR, PLR, and AISI. The associations between MLR and other inflammatory biomarkers did not show significant differences across the population, as evidenced by subgroup analyses and interaction tests. Based on ROC curve analysis, it seems that the MLR predicts ED more accurately than other indicators of inflammation. In conclusion, high levels of MLR should be closely monitored when assessing ED in adult men in the United States.

MLR serves as a comprehensive indicator of inflammatory status and immune function. This ratio has been extensively studied in various inflammation-related

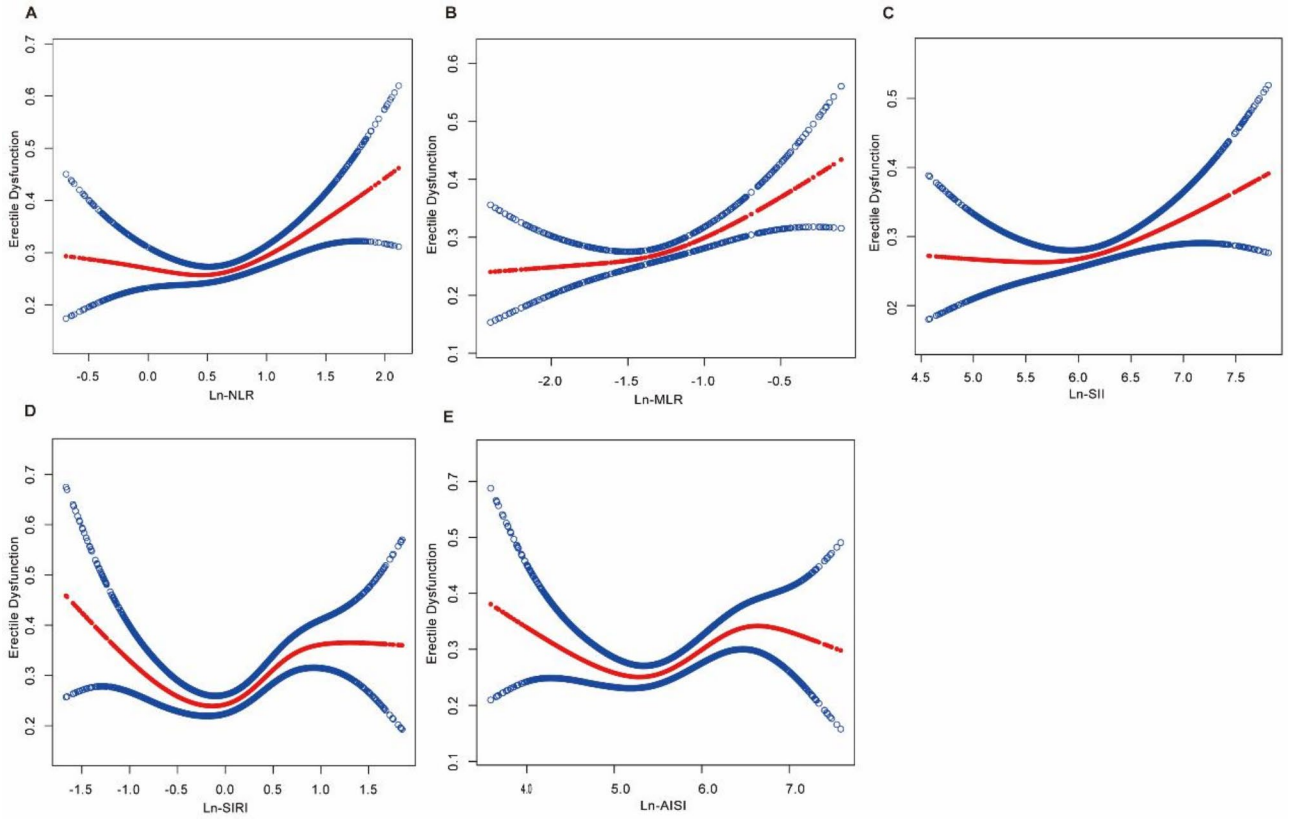

Fig. 2 Smooth Curve Fitting between Inflammatory Indicators and ED age, race, education level, marital status, PIR, BMI, smoking status, alcohol drinking status, diabetes status, hypertension status, CVD, and stroke were adjusted. **(A)** Ln-NLR and ED; **(B)** Ln-MLR and ED; **(C)** Ln-SII and ED; **(D)** Ln-SIRI and ED; **(E)** Ln-AISI and ED;

Table 3 Analysis of the threshold effect between inflammatory indicators and ED

Outcome: ED	**Ln-NLR**	**Ln-MLR**	**Ln-SII**	**Ln-SIRI**	**Ln-AISI**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Fitting by standard linear model	1.35 (1.09, 1.68)	1.50 (1.15, 1.96)	1.21 (1.01, 1.46)	1.23 (1.03, 1.46)	1.14 (0.99, 1.33)
P-value	0.007	0.003	0.041	0.020	0.077
Fitting by two-piecewise linear model					
Breakpoint(K)	0.58	-1.34	5.91	-0.2	5.25
OR1 < K	0.66 (0.40, 1.09)	0.83 (0.46, 1.50)	0.72 (0.44, 1.19)	0.49 (0.31, 0.77)	0.66 (0.45, 0.99)
	0.104	0.529	0.201	0.002	0.001
OR2 > K	2.00 (1.44, 2.80)	2.10 (1.40, 3.15)	1.49 (1.15, 1.93)	1.73 (1.37, 2.18)	1.41 (1.15, 1.74)
	< 0.001	0.001	0.003	< 0.001	0.004
Logarithmic likelihood ratio test P-value	0.002	0.031	0.029	< 0.001	0.004

age, race, education level, marital status, PIR, BMI, smoking status, alcohol drinking status, diabetes status, hypertension, CVD, and stroke were adjusted

diseases, including cancer, cardiovascular diseases, and tuberculosis. This metric effectively reflects both the immune response and the systemic inflammatory environment, making it a valuable tool in clinical and research settings [6, 7, 25]. Elevated MLR has also been associated with poor prognosis and disease progression in a variety of diseases [26, 27]. In a previous study, the risks of having ED increased by 160% for every unit rise in Ln-MLR. This increase may be the result of physiological changes related to aging that worsen the impact of lipid-related variables on erectile function [28, 29]. A continuous model with an odds ratio (OR) of 1.50 in the current study demonstrated a strong correlation between Ln-MLR and a higher risk of ED. We also looked at the connection between ED and other inflammatory biomarkers, utilizing ROC analysis to evaluate each one's predictive ability.

An increasing amount of research has looked into the diagnostic potential of different ED-related systemic inflammation biomarkers. NLR, recognized as a novel

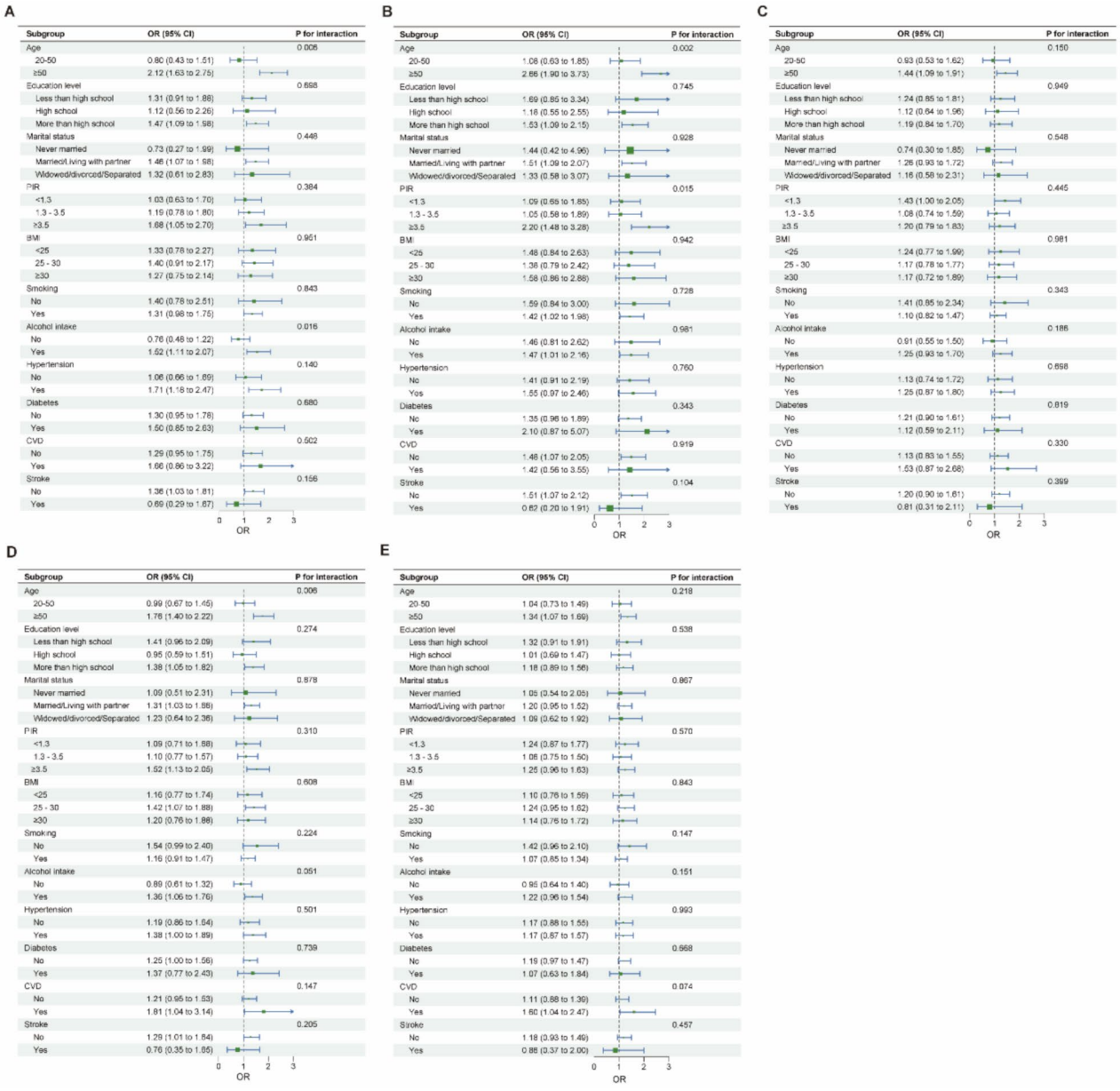

Fig. 3 Subgroup analysis for inflammatory indicators and ED, weighted. Note 1: The above model adjusted for age, gender, race, education level, Marital status, PIR, BMI, smoking status, alcohol drinking status, diabetes, hypertension, CVD, and stroke. Note 2: In each case, the model is not adjusted for the stratification variable. **(A)** Ln-NLR and ED; **(B)** Ln-MLR and ED; **(C)** Ln-SII and ED; **(D)** Ln-SIRI and ED; **(E)** Ln-AISI and ED;

marker of cellular immune activation, has garnered particular attention. In one such study, the ED population was divided into a subject group and a control group, revealing that NLR levels were significantly higher in the subject group compared to the control group. Additionally, a significant positive correlation was observed between NLR and ED for values greater than 1.52 [30]. In our study, Ln-NLR was significantly associated with ED, demonstrating that individuals in the highest tertile group exhibited a substantially increased risk of ED compared to controls. Additionally, Liu et al.'s multiple logistic regression investigation of the connection between SII and ED revealed no significant data [31]. On the other hand, Zhong's research revealed that ED patients had noticeably greater levels of SII than did non-ED patients. Additionally, elevated SII levels were recognized as an independent risk factor for ED, suggesting a different perspective from Liu et al.'s findings [32]. The institutional reasons for the discrepancies need to be further explored.

We also investigated the correlation between ED and two new composite indices, SIRI and AISI, which are

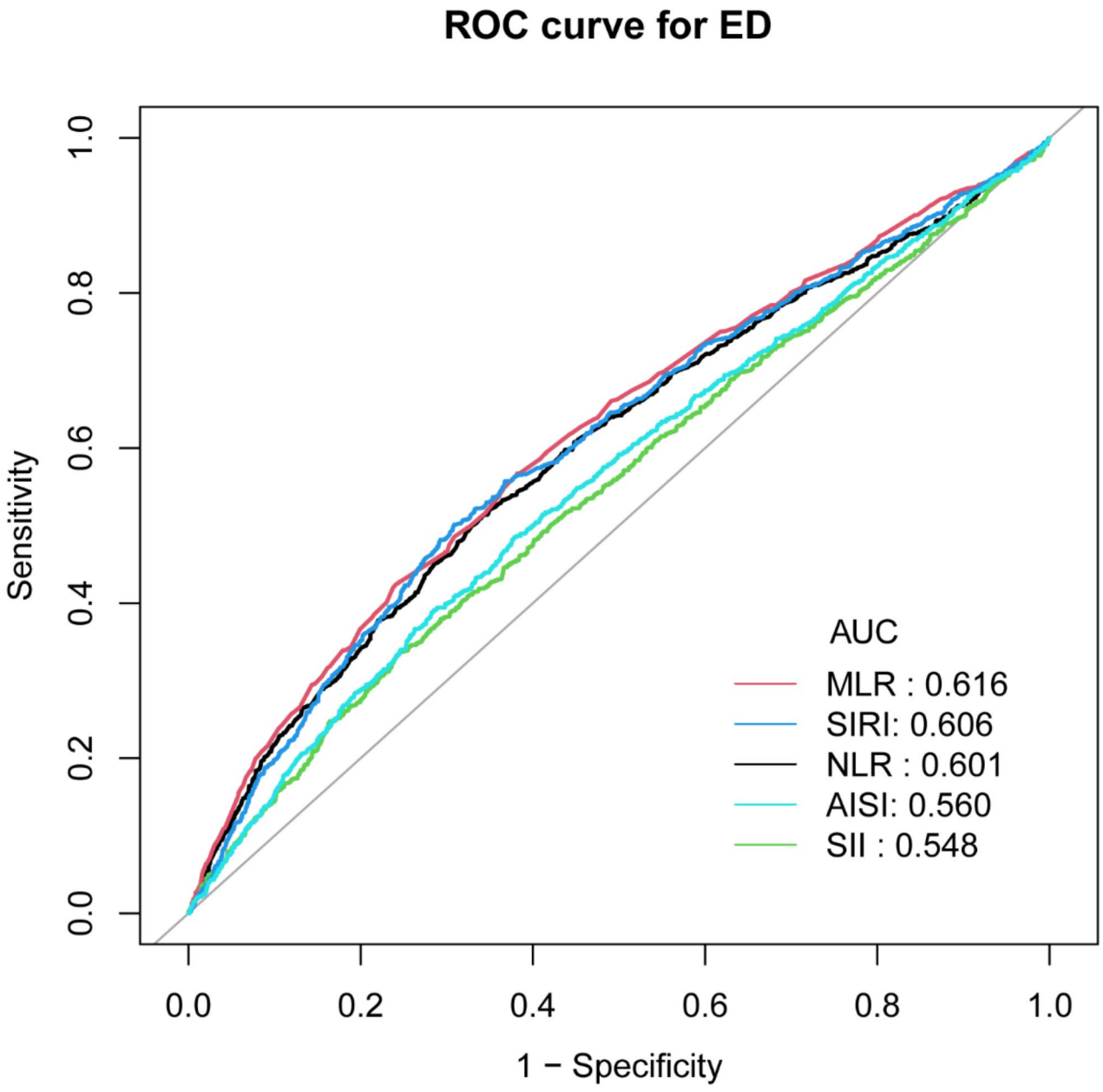

Fig. 4 ROC curves and the AUC values of the five inflammatory markers (NLR, MLR, SII, SIRI, and AISI) in diagnosing ED

Table 4 Comparison of AUC values between five indicators of inflammation

Test	[a]AUC	95%CI[b] low	95%CI upp	Best threshold	Specificity	Sensitivity	*p* for different in AUC
NLR	0.6008	0.5796	0.622	2.306	0.6707	0.5005	Reference
MLR	0.6161	0.5952	0.637	0.2968	0.6182	0.5674	< 0.001
SII	0.5479	0.5265	0.5692	659.6985	0.7547	0.3373	< 0.001
SIRI	0.6060	0.585	0.6269	1.3293	0.6911	0.5015	< 0.001
AISI	0.5598	0.5386	0.581	311.2153	0.6217	0.4848	< 0.001

[a]AUC: area under the curve

[b]95%CI: 95% confidence interval

Table 5 Sensitivity analysis between inflammatory markers and ED

Characteristic	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Ln-NLR	2.31 (1.95, 2.74)	< 0.0001	1.44 (1.17, 1.77)	0.0007	1.33 (1.07, 1.65)	0.0102
Ln-MLR	3.24 (2.63, 4.00)	< 0.0001	1.50 (1.16, 1.93)	0.0019	1.45 (1.11, 1.89)	0.0059
Ln-SII	1.39 (1.20, 1.61)	< 0.0001	1.24 (1.04, 1.49)	0.0164	1.20 (1.00, 1.45)	0.0484
Ln-SIRI	1.84 (1.61, 2.10)	< 0.0001	1.36 (1.15, 1.60)	0.0003	1.22 (1.02, 1.44)	0.0261
Ln-AISI	1.36 (1.21, 1.52)	< 0.0001	1.21 (1.05, 1.39)	0.0091	1.13 (0.98, 1.32)	0.0964

Model 1: No covariates were adjusted

Model 2: Adjusted for age, race, education level, and marital status

Model 3: Adjusted for age, race, education level, marital status, PIR, BMI, smoking status, alcohol consumption, diabetes status, hypertension status, CVD, stroke, Depression, anxiety, metabolic syndrome, and peripheral artery disease

linked to the interaction of thrombocytosis, inflammation, and immunity. These indices may offer new insights into the complex interplay between these physiological processes and ED [33]. SIRI includes both NLR and MLR. therefore, SIRI may be a more sensitive and useful biomarker of inflammation. a study by Lin et al. suggests that high levels of SIRI may increase the risk of ED in adult Americans [34]. In this investigation, the continuous model showed that the association between AISI and ED was not significant, with a p-value of 0.077. In terms of statistics, does not rule out the possibility that AISI and ED may not meaningfully correlate. Additionally, the combination of ROC found that the predictive performance of SIRI and AISI for ED seems to be poor. The many populations and geographical areas represented may have an impact on this. Additional prospective research is required to confirm our findings.

This study investigated the potential association between multiple inflammatory markers from routine blood tests (MLR, SIRI, NLR, AISI, SII) and the development of erectile dysfunction (ED). To the extent of our comprehension, few studies have explored the combined effect of these multiple inflammatory indicators on the occurrence of ED. Multivariate logistic regression analysis revealed that elevated levels of various inflammatory markers were associated with an increased incidence of ED. These associations remained significant even after adjusting for multiple covariates, suggesting that inflammation may play a crucial role in the pathophysiology of ED.

The benefits of utilizing MLR in disease prognosis prediction have been demonstrated by earlier research. Notably, MLR has been reported to serve as an independent predictive marker for the prognosis of patients with lung cancer who have undergone surgical treatment. This underscores its potential utility not only in the field of oncology but also in broader clinical applications [35]. In Wang's study, MLR was significantly superior to other inflammatory biomarkers in predicting prostate cancer [19]. By using ROC analysis, we were able to demonstrate that MLR was a more reliable inflammatory marker than other ones for predicting ED. The optimal diagnostic threshold for MLR was determined to be 0.2968, with a specificity of 0.6182 and a sensitivity of 0.5674. Additionally, a significant breakpoint was identified at -1.34 using a two-segment linear model to assess the threshold effect of Ln-MLR on ED. Above this threshold, the association became stronger and significant, with an adjusted odds ratio (OR) of 2.10. The log-likelihood ratio test further confirmed the presence of a threshold effect ($P=0.031$). This suggests that MLR levels above -1.34 may be strongly associated with identifying patients at a higher risk of ED and underscores the utility of MLR as a diagnostic marker in clinical settings.

An important factor in the onset and course of ED disease is inflammation [5, 19, 33]. Inflammation is recognized as an important factor in the pathogenesis of ED. Numerous investigations have demonstrated that experimental animals and people with ED both have increased amounts of inflammatory markers like TNF-α, IL-1β, and IL-6 [36]. In an environment predominantly characterized by a pro-inflammatory response, the bioavailability of nitric oxide is reduced, leading to impaired vasodilation. This disruption in nitric oxide availability is critical as it directly affects the vascular relaxation processes essential for proper blood flow and vascular health [37]. This injury, characterized by reduced blood flow to penile tissue, is primarily caused by endothelial dysfunction [38, 39].

Strength and limits

The research we conducted has a number of noteworthy advantages. First, we evaluated a large sample of 3610 participants, each providing comprehensive and clinically informative data. Data collection underwent rigorous quality assurance processes to ensure reliability. Although the sample size may seem modest, the participants represent a diverse cross-section of the U.S. population from 2001 to 2004, making our findings broadly applicable and representative. Second, we demonstrated a stronger correlation between MLR and ED compared to other inflammatory markers and highlighted the easy accessibility of MLR measurements.

However, there are several restrictions on our study. While we accounted for common comorbidities such as diabetes, cardiovascular disease, depression, anxiety, peripheral vascular disease, and hypertension, the NHANES dataset does not include specific data on neurological diseases, such as Parkinson's disease, dementia, or peripheral neuropathy. Similarly, certain potential endocrine disorders were not directly measured. The ED assessment was based on self-reported questionnaires and testosterone levels, which did not capture the duration of ED symptoms or related symptoms (such as reduced libido, ejaculatory dysfunction, or psychological factors). Furthermore, the NHANES dataset lacks complete information on illicit drug use or substance abuse during 2001–2004, which was not included in the study, potentially introducing confounding factors. Additionally, inflammatory markers were measured at a single time point, which may not accurately reflect chronic inflammation. Therefore, caution is warranted when inferring the relationship between inflammation and chronic conditions such as ED. Future research should employ repeated long-term measurements of inflammatory markers to more precisely determine the role of persistent inflammation in ED.

Conclusion

In conclusion, our results suggest that MLR may be superior to other inflammatory biomarkers (NLR, SII, AISI, and SIRI) in predicting erectile dysfunction (ED). U.S. adult men with elevated levels of these markers, particularly MLR, should be aware of their potential risk for ED.

Abbreviations

NHANES	National Health and Nutrition Examination Survey
MLR	Monocyte-to-lymphocyte ratio
NLR	Neutrophil-to-lymphocyte ratio
SII	Systemic immune-inflammatory index
SIRI	Systemic inflammatory response index
AISI	Aggregate index of systemic inflammation
ED	Erectile dysfunction
ACASI	Audio computer-assisted self-interview
MEC	Mobile Examination Center
GAM	Generalized additive model
ROC	Receiver operating characteristic
AUC	Area under the curve
PIR	Income to poverty ratio
CVD	Cardiovascular disease
BMI	Body mass index

Supplementary Information

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Supplementary Material 1

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Author contributions

CH, LH, and DH designed the research. LH, DH, and GM collected and analyzed the data, and drafted the manuscript. CH revised the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the NCHS Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

Competing interests

The authors declare no competing interests.

Conflict of interest

All authors declare that they have no competing financial interests.

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