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Associations between systemic inflammatory biomarkers and metabolic dysfunction associated steatotic liver disease: a cross-sectional study of NHANES 2017–2020

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Abstract

Background Metabolic dysfunction-associated steatotic liver disease (MASLD) is a primary cause of chronic liver disease, with potential progression to cirrhosis and hepatocellular carcinoma (HCC). Although systemic inflammatory biomarkers are associated with liver diseases, their specific role in MASLD remains unclear. This study examines the association between systemic inflammatory biomarkers and MASLD.

Methods This cross-sectional study enrolled 6613 adults aged 20 years or older from the National Health and Nutrition Examination Survey (NHANES) spanning from 2017 to March 2020. Among these participants,, 34.67% were aged 40–59 years, 50.85% were female, and 63.26% were Non-Hispanic White. We investigated 10 inflammatory biomarkers: ALI, SIRI, SII, SIPS, IBI, NLR, PLR, CAR, LMR, and PNI. Logistic regression models were performed to assess the linear association between systemic inflammatory biomarkers and MASLD. Restricted cubic spline (RCS) regression was employed to explore potential nonlinear relationships between biomarkers and MASLD risk. Additionally, subgroup analyses were conducted to examine the influence of various demographic and clinical characteristics on the observed associations.

Results After adjusting for key confounders, NLR and PLR exhibited negative association with MASLD risk, while ALI, CAR, and PNI exhibited the opposite association ($P < 0.05$). Most biomarkers, including ALI, SIRI, IBI, CAR, LMR, and PNI, exhibited significant non-linear correlations with MASLD ($P < 0.05$). Subgroup analyses revealed substantial age-related differences in the association between ALI and MASLD risk, as well as varying relationships between PNI and MASLD risk across various cardiovascular outcomes ($P < 0.05$).

Conclusion Systemic inflammatory biomarkers are significantly associated with MASLD risk. Large-scale prospective studies are warranted to confirm these findings and elucidate the underlying mechanisms.

Keywords Metabolic dysfunction associated steatotic liver disease (MASLD), Systemic inflammatory biomarkers, NHANES, Population-based study

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Introduction

Metabolic dysfunction associated steatotic liver disease (MASLD), formerly termed as non-alcoholic fatty liver disease (NAFLD), was officially renamed in June 2023 [1]. In the United States, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is notably high, affecting 29.8 – 45.2% of the population [2–4]. In the United Kingdom and Asia, the prevalence of MASLD is approximately 30.5–32.95% [5, 6]. Meanwhile, its incidence is rising due to the increasing rates of obesity and diabetes [7, 8]. It is estimated that the global prevalence of MASLD may reach 55.4% by 2040 if current trends continue [9]. MASLD is characterized by hepatocyte steatosis and excludes the influence of viruses, alcohol, and autoimmune factors. It is accompanied by cardiometabolic risk factors, including high body mass index (BMI) and diabetes [10]. The specific pathogenesis of MASLD remains largely unknown; however, complex regulation of lipid metabolism, involving membrane transport proteins, metabolic enzymes, and transcription factors, are believed to play a critical role in its development [11]. Approximately 20% of individuals with MASLD may progress to metabolic dysfunction-associated steatohepatitis (MASH), which can lead to cirrhosis and hepatocellular carcinoma (HCC), posing a significant public health risk [12]. While liver biopsy is the gold standard for the diagnosis of MASLD [13], its invasiveness extremely limits its clinical application. Therefore, there is an urgent need to discover novel and reliable biomarkers for the diagnosis and monitoring of MASLD.

Inflammation represents the body's innate response to tissue injury or infection [14], leading to the release of various inflammatory mediators. Persistent inflammation can lead to chronic systemic inflammatory changes [15], exacerbating tissue damage. Systemic inflammation is widely recognized as a key pathophysiological mechanism in liver steatosis [16]. Systemic inflammatory biomarkers such as the systemic immune inflammation index (SII), systemic inflammation response index (SIRI), and lymphocyte-to-monocyte ratio (LMR) were obviously increased in NAFLD and closely related with NAFLD risk [17–19]. Nonetheless, as a newly raised conception, the specific mechanism of MASLD remains elusive.

National Health and Nutrition Examination Survey (NHANES) (www.cdc.gov/nchs/nhanes) is designed to assess the health and nutritional status of adults and children in the United States. The survey is distinctive in that it incorporates both physical examinations and interviews. Several cross-sectional, nationally representative health examination surveys are part of the NHANES program. Questions about demographics, health insurance status, dietary habits, acute and chronic medical issues, mental health, and prescription drug use are all included in the health interview. Exam components can change between survey cycles but typically include blood pressure, dental exams, vision, hearing, dermatology, fitness, balance and strength testing, respiratory testing, taste and smell, and body measurements (weight, height, skin folds, body composition scans). Hematology, organ and endocrine function (e.g., thyroid, kidney), environmental exposure, dietary biomarkers, metabolic and cardiovascular health, and infectious disease are some laboratory components. The extensive data provided by NHANES makes it an ideal resource for studying the relationship between systemic inflammatory biomarkers and MASLD.

This study aimed to comprehensively investigate the association between systemic inflammatory biomarkers—including the advanced lung cancer inflammation index (ALI), Scottish inflammatory prognostic score (SIPS), inflammatory burden index (IBI), platelet-to-lymphocyte ratio (PLR), C-reactive protein-to-albumin ratio (CAR), prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), as well as SIRI, SII, and LMR—and the risk of MASLD.. Employing a cross-sectional study design from the NHANES, we utilized a substantial and representative sample from the national population to conduct a comprehensive analysis, to investigate the association of these markers with MASLD risk.

Methods

Survey description

The data for this study were retrospectively collected from NHANES, a biannual, cross-sectional survey designed to monitor the health and nutritional status of the non-institutionalized, civilian U.S. population. Using a multistage probability sampling approach, NHANES gathers data through interviews and physical examinations, adhering to standardized protocols. All procedures were conducted in compliance with relevant guidelines and regulations.

Inclusion and exclusion criteria

A total of 15,560 participants from NHANES 2017 to March 2020 were initially included in this study. Among this cohort, 6328 individuals aged 20 years or older were considered for further analysis. Stringent exclusion criteria were applied to ensure the precision and credibility of the findings. Initially, individuals who were expecting mothers were omitted. Subsequently, participants with incomplete elastography examination data or missing information on education, marital status, smoking habits, white blood cell (WBC) count, monocyte (MONO) count, neutrophil (NEU) count, lymphocyte (LYM) count, platelet (PLT) count, albumin (ALB) level, BMI, and C-reactive protein (CRP) were excluded. Finally,

individuals diagnosed with hepatitis (including hepatitis B virus (HBV), hepatitis C virus (HCV), autoimmune hepatitis) or liver cancer were excluded from the analysis. Consequently, the study included a total of 6613 participants (Fig. 1).

Assessment of MASLD

Steatotic liver disease (SLD) was defined by a median controlled attenuated parameter (CAP) of ≥ 285 dB/m, with optimal sensitivity and specificity determined using the Youden's index in liver ultrasound transient elastography examination, as previously reported [20, 21]. Alcohol consumption was assessed using specific questions from the dataset: ALQ130 (Average alcoholic drinks/day in past 12 months), ALQ121 (How often drink alcoholic beverage in past 12 months), ALQ142 (Days have 4 or 5 drinks in past 12 months), ALQ280 (Times 8+ drinks in 1 day in past 12 months), and ALQ290 (Times 12+ drinks in 1 day in past 12 months), to calculate weekly intake. Participants with a weekly alcohol intake of less than 140g for females or 210g for males were classified as light alcohol consumers. MASLD was defined as SLD combined with light alcohol use and at least one of the following cardiometabolic risk factors [22]: (1) BMI ≥ 25 kg/m^2 or waist circumference > 94 cm (for males) and 80 cm (for females). (2) Fasting serum glucose ≥ 5.6 mmol/L, or 2-hour post-load glucose levels ≥ 7.8 mmol/L, or HbA1c ≥ 5.7%, or presence of type 2 diabetes, or undergoing treatment for type 2 diabetes. (3) Blood pressure ≥ 130/85 mmHg or specific antihypertensive drug treatment. (4) Plasma triglycerides ≥ 1.70 mmol/L or receiving lipid-lowering treatment. (5) Plasma HDL-cholesterol ≤ 1.0 mmol/L (for males) and ≤ 1.3 mmol/L (for females) or undergoing lipid-lowering treatment.

Calculation of systemic inflammatory biomarkers

Systemic inflammatory biomarkers were calculated using the following formulas:

1. ALI = BMI ∗ ALB(g/dl) ∗ LYM count/NEU count;

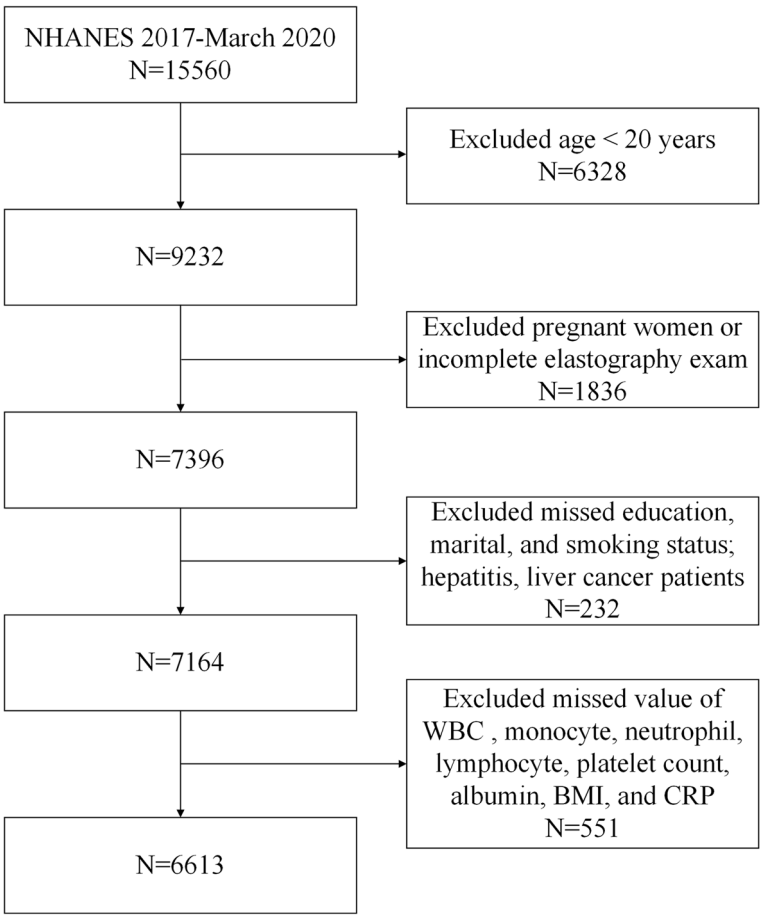

Fig. 1 Flow chart of participants selection

2. SIRI = MONO count ∗ NEU count/LYM count;
3. SII = PLT ∗ NEU count/LYM count;
4. IBI = CRP(mg/L) ∗ NEU count/LYM count;
5. NLR = NEU count/LYM count;
6. PLR = PLT count/LYM count;
7. CAR = CRP/ALB;
8. LMR = LYM count/MONO count;
9. PNI = (ALB(g/dl) ∗ 10) + (LYM count ∗ 5);
10. SIPS = ALB level score(> 3.5g/dl, 0; ≤ 3.5g/dl, 1) + NEU count score($\leq 7.5 \times 10^9$/l, 0; $> 7.5 \times 10^9$/l, 1) .

Sociodemographic data

Sociodemographic variables, including age, gender, race, marital status, education level, family poverty income ratio (PIR), and smoking status, were analyzed in this study. Age was categorized into three groups: 20–39 years, 40–59 years, and ≥60 years. Gender was classified as males or females. Race was classified into five groups according to the NHANES survey framework: Non-Hispanic White, Non-Hispanic Black, Mexican American, Non-Hispanic Asian, and Other Race. The PIR was categorized into three groups: low (≤1.3), medium (1.3-3.5), and high (>3.5). Education level was classified into three categories: less than high school, high school or equivalent, and some college or higher. Smoking status was determined based on NHANES survey queries, with participants categorized as smokers if they had smoked at least 100 cigarettes during their lifetime and further classified as current, former, or never smokers.

Clinical variables

For clinical variables, BMI categories were defined as follows: normal weight (<25.0 kg/m^2), overweight (25.0-30.0 kg/m^2), and obese (>30.0 kg/m^2). Diabetes was comprehensively defined to include the use of oral hypoglycemic agents, insulin, or self-reported history of diabetes. Hypertension was diagnosed if systolic blood pressure was ≥135 mmHg or diastolic blood pressure was ≥85 mmHg, or if there was a self-reported history of hypertension or use of antihypertensive medication. Hyperlipidemia was identified by triglyceride levels ≥ 1.7 mmol/L or a history of lipid-lowering medication. Cardiovascular outcomes were defined as a reported history of heart failure, coronary heart disease, angina pectoris, or myocardial infarction.

Statistical analysis

The sample size was calculated using the epiR package (2.0.75) [23], applying the function epi.sssimpleestb() to estimate the required sample size based on a MASLD prevalence of 30% [5, 6] and an allowable error of 0.025 [24]. The calculated sample size was 1,291, which is considerably smaller than the actual sample size used in our study. Continuous variables are presented as means (standard deviation), and categorical variables are reported as frequencies (percentages). Weighted t-tests were used for continuous variables and weighted chi-square tests were employed for categorical variables to compare baseline characteristics between groups. These weighted tests account for the complex survey design of the NHANES data, ensuring accurate representation of the population. Continuous systemic inflammatory biomarkers (ALI, SIRI, SII, IBI, NLR, PLR, CAR, LMR, PNI) were stratified into quartiles (Q1, Q2, Q3, and Q4) for analysis. This stratification enables the examination of potential dose-response relationships. Multifactorial logistic regression analyses to assess the impact of these biomarkers on MASLD risk. For both continuous and categorical (quartile) variables, the lowest quartile (Q1) served as the reference group. The results are presented as odds ratios (OR) with 95% confidence intervals (CI). A trend test was conducted to detect any linear trend in MASLD risk across the quartiles of biomarkers.

To control for potential confounding variables, three logistic regression models were constructed. The variables included were selected based on their established influence on metabolic dysfunction and liver health. In Model 1 (unadjusted), the crude associations were examined. In Model 2, adjustments were made for age, gender, and race, as these demographic factors are known to influence liver disease and inflammatory markers. Model 3 included additional adjustments for education, PIR, marital status, smoking, BMI, diabetes, and cardiovascular outcomes, as these are important lifestyle and health-related factors that may confound the relationship between systemic inflammatory biomarkers and MASLD. By adjusting for these variables, we aimed to isolate the effect of inflammatory biomarkers on MASLD risk, accounting for factors that influence both the biomarkers and the disease. To explore potential nonlinear relationships between systemic inflammatory biomarkers and MASLD risk, restricted cubic spline (RCS) regression was used. This method allows for the flexible modeling of relationships without assuming linearity. Threshold analysis was performed to identify any specific points at which the relationship between biomarkers and MASLD risk changes. Furthermore, to examine whether this relationship was modified by age, gender, BMI, hypertension, hyperlipidemia, and cardiovascular outcome, interaction analyses and subgroup analyses were conducted in continuous variables.

All data analyses were performed using R software (https://www.r-project.org/; version 4.3.2). $P < 0.05$ was considered statistically different.

Results

Population characteristics

The study included 6,613 participants, with their demographic characteristics detailed in Table 1. Among these, 34.67% were aged 40-59 years, 50.85% were female, and 63.26% were Non-Hispanic White. The prevalence of MASLD was 35.78%. Notably, individuals with MASLD comprised the highest proportion in the 40-59 age group (38.73%), with a higher male proportion (56.47%), lower educational attainment, and a higher prevalence of diabetes, hypertension, hyperlipidemia, and cardiovascular outcomes compared to those without MASLD. Significant differences were observed in most of the systemic inflammatory biomarkers, namely ALI, SIRI, SII, SIPS, IBI, PLR, and CAR between the MASLD and non-MASLD groups ($P< 0.05$). Similar results were obtained when these continuous variables were stratified into quartiles. Furthermore, hepatic function indices (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and individual components of systemic inflammatory biomarkers, namely NEU, LYM, MONO, ALB, and CRP, showed significant differences between the MASLD and non-MASLD groups ($P < 0.05$). Figure 2 illustrates the distribution of MASLD patients categorized by SIPS and the quartiles of continuous systemic inflammatory biomarkers. Elevated quartiles of ALI, SIRI, IBI, NLR, and CAR were correlated with a heightened MASLD prevalence, while increased SIPS levels and quartiles of PLR were associated with a lower prevalence. It is important to note that the columns of the SIPS differed significantly from those of other biomarkers due to its nature as a categorical variable with values of 0, 1, and 2. Conversely, quartiles of SII, LMR, and PNI exhibited similar proportions of MASLD.

Association of inflammatory biomarkers with MASLD risk

We subsequently explored the association between the risk of MASLD and systemic inflammatory biomarkers, which revealed significant variances between the MASLD and non-MASLD groups. These biomarkers included ALI, SIRI, SII, IBI, NLR, PLR, CAR, and SIPS (Table 2). Three models were constructed, with adjustments for various confounding variables to assess this relationship. After controlling for age, gender, race, education, marital status, smoking, PIR, BMI, diabetes, and cardiovascular outcomes (model 3), significant associations were found between MASLD risk and NLR (OR = 0.893, 95% CI: 0.806–0.8062, $P = 0.035$) and PLR (OR = 0.997, 95% CI: 0.997–1.000, $P = 0.048$). Additionally, significant associations were observed when ALI (OR = 1.604, 95% CI: 1.072–2.402, $P = 0.031$), CAR (OR = 2.013, 95% CI: 1.079–3.755, $P = 0.030$), and PNI (OR = 1.708, 95% CI: 1.161–2.512, $P = 0.018$) were stratified into quartiles, demonstrating a progressive increase in MASLD risk in the highest quartile group (Q4) (P for trend < 0.05).

Furthermore, we examined the roles of components of systemic inflammatory biomarkers (Supplementary Table 1). After adjusting for relevant confounders (Model 3), we found significant positive associations between stratified LYM (OR = 1.843, 95% CI: 1.283–2.646, $P = 0.009$) and CRP (OR = 2.072, 95% CI: 1.151–3.730, $P = 0.026$) levels and MASLD risk, revealing a progressive increase in MASLD risk in the highest quartile (Q4) compared to Q1 (P for trend < 0.05).

Dose–response of systemic inflammatory biomarkers and MASLD risk

To enhance the robustness of our findings, we further analyzed non-linear relationships between continuous systemic inflammatory biomarkers and MASLD risk using RCS regression model, adjusting for key confounders (Model 3). Significant non-linear associations were identified for ALI, SIRI, IBI, CAR, LMR, and PNI with MASLD risk (P-non-linear < 0.05, Fig. 3), while no significant non-linear correlations were observed for SII, NLR, or PLR (P-non-linear > 0.05). Notably, inflection points were identified for ALI, SIRI, IBI, CAR, and LMR at values of 115.196, 2.232, 20.136, 2.086, and 5.520, respectively. For ALI, values below 115.196 showed a positive association with MASLD risk, with each unit increase corresponding to a 0.001-fold increase in risk, whereas values above this threshold were inversely associated with MASLD risk, with each additional unit corresponding to a 0.0001-fold decrease in risk. Similar trends were observed for SIRI, IBI, CAR, and LMR. For PNI, inflection points at 47.232 and 57.111 were identified. Between these values, each unit increase in PNI was associated with a 0.009-fold increase in MASLD risk. Outside this range, the relationship weakened, with a 0.003-fold increase in risk below 47.232 and a 0.0002-fold increase above 57.111. Overall, the majority of systemic inflammatory biomarkers exhibited non-linear relationships with MASLD risk, indicating that their effects vary at different levels of exposure.

Subgroup analyses

To further investigate the relationship between systemic inflammatory biomarkers and MASLD risk, subgroup analyses were performed considering age, gender, BMI, diabetes, hypertension, and cardiovascular outcomes (Fig. 4). In the fully adjusted model (Model 3), a significant interaction was observed between ALI and age groups regarding MASLD risk ($P = 0.048$), even after adjusting for key covariates including age. Participants aged 20–39 showed a significant increase in MASLD risk with higher ALI levels, whereas those over 60 did

Table 1 Characteristics of the study population

Characteristic	Overall, *N* = 6613 (100.00%)[a]	Non-MASLD, *N* = 4247 (64.22%)[a]	MASLD, *N* = 2366 (35.78%)[a]	*P* Value[2]
Age				<0.001
20-39 years	2,072(36.91%)	1,552(41.87%)	520(27.68%)	
40-59 years	2,249(34.67%)	1,339(32.49%)	910(38.73%)	
≥60 years	2,292(28.42%)	1,356(25.64%)	936(33.59%)	
Gender				<0.001
Female	3,391(50.85%)	2,323(54.78%)	1,068(43.53%)	
Male	3,222(49.15%)	1,924(45.22%)	1,298(56.47%)	
Race				<0.001
Non-Hispanic White	2,300(63.26%)	1,440(63.51%)	860(62.80%)	
Non-Hispanic Black	1,646(10.49%)	1,182(11.87%)	464(7.94%)	
Non-Hispanic Asian	804(5.77%)	547(6.14%)	257(5.09%)	
Mexican American	832(8.78%)	414(6.82%)	418(12.43%)	
Other Race	1,031(11.70%)	664(11.66%)	367(11.74%)	
Marital status				<0.001
Married/Living with partner	3,911(62.74%)	2,389(59.47%)	1,522(68.81%)	
Widowed/Divorced/Separated	1,412(17.70%)	909(18.09%)	503(16.98%)	
Never married	1,290(19.56%)	949(22.44%)	341(14.21%)	
Education				0.001
Less than high school	1,199(10.58%)	745(10.49%)	454(10.74%)	
High school or equivalent	1,562(26.00%)	985(24.11%)	577(29.53%)	
Some college or more	3,852(63.42%)	2,517(65.40%)	1,335(59.73%)	
PIR				0.400
Low income	1,604(20.56%)	1,026(20.32%)	578(21.00%)	
Medium income	2,175(38.19%)	1,390(37.33%)	785(39.79%)	
High income	1,500(41.25%)	970(42.35%)	530(39.21%)	
Smoking				0.003
Now	1,129(15.50%)	786(16.87%)	343(12.95%)	
Former	1,555(25.94%)	896(23.88%)	659(29.78%)	
Never	3,929(58.56%)	2,565(59.25%)	1,364(57.27%)	
BMI				<0.001
Normal weight	1,676(26.19%)	1,559(38.11%)	117(3.99%)	
Overweight	2,155(32.42%)	1,498(35.74%)	657(26.26%)	
Obese	2,782(41.39%)	1,190(26.15%)	1,592(69.75%)	
Diabetes				<0.001
No	5,579(88.31%)	3,834(94.03%)	1,745(77.67%)	
Yes	1,034(11.69%)	413(5.97%)	621(22.33%)	
Hypertension				<0.001
No	4,265(70.83%)	3,020(78.68%)	1,245(56.23%)	
Yes	2,348(29.17%)	1,227(21.32%)	1,121(43.77%)	
Hyperlipidemia				<0.001
No	4,754(74.22%)	3,310(80.43%)	1,444(62.67%)	
Yes	1,859(25.78%)	937(19.57%)	922(37.33%)	
Cardiovascular outcome				<0.001
No	6,102(93.58%)	3,965(94.92%)	2,137(91.07%)	
Yes	511(6.42%)	282(5.08%)	229(8.93%)	
ALT (U/L)	18.00 (13.00, 26.00)	16.00 (13.00, 23.00)	23.00 (17.00, 32.00)	<0.001
AST (U/L)	19.00 (16.00, 24.00)	19.00 (16.00, 23.00)	20.00 (17.00, 25.00)	<0.001
WBC (1000 cell/mL)	6.90 (5.70, 8.40)	6.70 (5.50, 8.16)	7.40 (6.20, 8.90)	<0.001
NEU (1000 cell/mL)	4.00 (3.10, 5.10)	3.80 (3.00, 4.90)	4.30 (3.40, 5.40)	<0.001

Table 1 (continued)

Characteristic	Overall, *N* = 6613 (100.00%)[a]	Non-MASLD, *N* = 4247 (64.22%)[a]	MASLD, *N* = 2366 (35.78%)[a]	*P* Value[2]
LYM (1000 cell/mL)	2.10 (1.70, 2.60)	2.00 (1.60, 2.50)	2.20 (1.80, 2.70)	<0.001
MONO (1000 cell/mL)	0.50 (0.50, 0.70)	0.50 (0.40, 0.60)	0.60 (0.50, 0.70)	<0.001
PLT (1000 cell/mL)	240 (206, 281)	239 (205, 279)	242 (208, 283)	0.200
CRP (mg/L)	1.8 (0.8, 4.1)	1.3 (0.6, 3.2)	2.9 (1.3, 5.8)	<0.001
ALB (g/dL)	4.10 (3.90, 4.30)	4.10 (3.90, 4.40)	4.10 (3.90, 4.30)	<0.001
ALI	63.10 (45.65, 84.42)	58.09 (43.11, 79.45)	69.51 (52.26, 91.24)	<0.001
ALI.quantile.var				<0.001
Q1	1,594 (25.03%)	1,200 (29.75%)	394 (16.25%)	
Q2	1,620 (24.97%)	1,086 (25.89%)	534 (23.27%)	
Q3	1,528 (25.01%)	934 (23.22%)	594 (28.35%)	
Q4	1,871 (24.98%)	1,027 (21.14%)	844 (32.13%)	
SIRI	1.06 (0.73, 1.54)	1.00 (0.69, 1.47)	1.15 (0.79, 1.67)	<0.001
SIRI.quantile.var				<0.001
Q1	1,973 (25.01%)	1,373 (27.76%)	600 (19.89%)	
Q2	1,599 (25.00%)	1,026 (25.92%)	573 (23.29%)	
Q3	1,490 (24.99%)	935 (23.92%)	555 (26.98%)	
Q4	1,551 (25.00%)	913 (22.40%)	638 (29.84%)	
SII	462.02 (336.00, 639.88)	454.69 (331.72, 634.16)	483.83 (350.80, 650.57)	0.040
SII.quantile.var				0.100
Q1	1,927 (25.07%)	1,277 (26.08%)	650 (23.19%)	
Q2	1,590 (24.95%)	1,048 (25.63%)	542 (23.68%)	
Q3	1,561 (25.00%)	972 (23.98%)	589 (26.91%)	
Q4	1,535 (24.98%)	950 (24.31%)	585 (26.23%)	
SIPS				0.020
0	6,054 (92.91%)	3,932 (93.75%)	2,122 (91.35%)	
1	527 (6.72%)	296 (5.93%)	231 (8.20%)	
2	32 (0.37%)	19 (0.32%)	13 (0.45%)	
IBI	3.40 (1.43, 8.53)	2.46 (1.16, 6.63)	5.68 (2.53, 11.66)	<0.001
IBI.quantile.var				<0.001
Q1	1,663 (25.00%)	1,336 (31.55%)	327 (12.82%)	
Q2	1,608 (25.01%)	1,097 (27.75%)	511 (19.91%)	
Q3	1,680 (25.00%)	968 (21.08%)	712 (32.27%)	
Q4	1,662 (24.99%)	846 (19.62%)	816 (35.00%)	
NLR	1.92 (1.47, 2.54)	1.89 (1.43, 2.50)	1.95 (1.52, 2.60)	0.056
NLR.quantile.var				0.034
Q1	1,956 (25.01%)	1,315 (26.70%)	641 (21.87%)	
Q2	1,583 (25.05%)	996 (24.32%)	587 (26.40%)	
Q3	1,534 (25.01%)	965 (24.80%)	569 (25.42%)	
Q4	1,540 (24.93%)	971 (24.19%)	569 (26.31%)	
PLR	116.67 (93.11, 145.29)	118.82 (95.26, 149.44)	112.07 (89.40, 138.37)	<0.001
PLR.quantile.var				<0.001
Q1	1,745.00 (25.01%)	1,021.00 (22.82%)	724.00 (29.10%)	
Q2	1,652.00 (25.05%)	1,041.00 (24.64%)	611.00 (25.81%)	
Q3	1,571.00 (25.00%)	1,017.00 (25.41%)	554.00 (24.24%)	
Q4	1,645.00 (24.94%)	1,168.00 (27.13%)	477.00 (20.85%)	
CAR	0.43 (0.19, 1.00)	0.32 (0.15, 0.76)	0.70 (0.32, 1.47)	<0.001
CAR.quantile.var				<0.001
Q1	1,553 (25.02%)	1,292 (32.81%)	261 (10.50%)	
Q2	1,595 (24.99%)	1,060 (26.10%)	535 (22.93%)	

Table 1 (continued)

Characteristic	Overall, $N = 6613$ (100.00%)[a]	Non-MASLD, $N = 4247$ (64.22%)[a]	MASLD, $N = 2366$ (35.78%)[a]	*P* Value[2]
Q3	1,676 (24.99%)	997 (22.16%)	679 (30.26%)	
Q4	1,789 (25.00%)	898 (18.93%)	891 (36.30%)	
LMR	3.80 (3.00, 4.76)	3.80 (3.00, 4.80)	3.80 (3.00, 4.75)	0.300
LMR.quantile.var				>0.900
Q1	1,727(28.064%)	1,130(27.733%)	597(28.680%)	
Q2	1,440(22.770%)	901(22.981%)	539(22.376%)	
Q3	1,575(24.196%)	1,036(24.098%)	539(24.379%)	
Q4	1,871(24.970%)	1,180(25.187%)	691(24.566%)	
PNI	51.50 (48.50, 55.00)-51.5 (48.5, 55.0)-52.0 (48.5, 55.0)	51.5 (48.50, 55.00)-51.5 (48.5, 55.0)-52.0 (48.5, 55.0)	51.50 (48.50, 55.00)-51.5 (48.5, 55.0)-52.0 (48.5, 55.0)	0.200
PNI.quantile.var				0.800
Q1	1,873 (25.89%)	1,249 (26.25%)	624 (25.22%)	
Q2	1,618 (24.20%)	1,055 (24.51%)	563 (23.62%)	
Q3	1,711 (26.16%)	1,100 (25.94%)	611 (26.58%)	
Q4	1,411 (23.74%)	843 (23.30%)	568 (24.57%)	

Abbreviation: *ALT* Alanine Aminotransferase, *AST* Aspartate Aminotransferase, *WBC* White blood cell, *NEU* Neutrophil, *LYM* Lymphocyte, *PLT* Platelet, *ALB* Albumin, *BMI* Body mass index, *CRP* C-reactive protein, *ALI* Advanced lung cancer inflammation index, *SIRI* Systemic inflammation response index, *SII* Systemic immune inflammation index, *SIPS* Scottish inflammatory prognostic score, *NLR* Neutrophil to lymphocyte ratio, *LMR* Lymphocyte to monocyte ratio, *IBI* Inflammatory burden index, *PLR* Platelet-to-lymphocyte ratio, *CAR* C-reactive protein to albumin ratio, *PNI* Prognostic nutritional index

[a] n (unweighted) (%); Median (IQR)

[2] chi-squared test with Rao & Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples

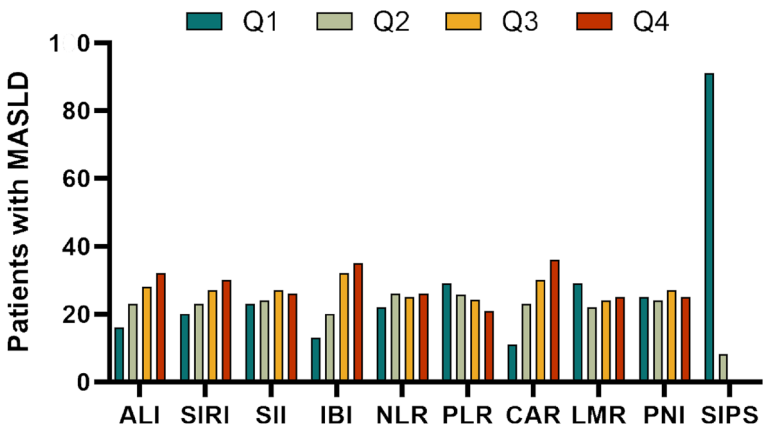

Fig. 2 Proportion of MASLD patients by quartiles of systemic inflammatory biomarkers

not exhibit such association. Additionally, the association between PNI and MASLD risk varied significantly depending on the presence of cardiovascular outcomes ($P = 0.006$). Specifically, after adjusting for vital covariates including cardiovascular outcomes, individuals without cardiovascular diseases exhibited an increasing MASLD risk with higher PNI levels, while those with cardiovascular outcomes did not demonstrate such an association. In contrast, SIRI, SII, IBI, NLR, PLR, CAR, and LMR exhibited consistent effects on MASLD risk in different age, gender, BMI, diabetes, hypertension, and cardiovascular outcomes ($P > 0.05$).

Discussion

As a nascent concept, the associations between MASLD and systemic inflammatory biomarkers have received limited investigation. In this study, we comprehensively investigated the association between a broad range of systemic inflammatory biomarkers and MASLD through an analysis of the NHANES database. Our findings demonstrated a statistically significant correlation between

Table 2 The relationship between inflammatory markers and the risk of MASLD

Markers	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
ALI	c					
ALI (Quartile)						
Q1	Ref		Ref		Ref	
Q2	1.646 (1.245, 2.176)	0.001**	1.810 (1.363, 2.404)	< 0.001***	1.302 (0.942, 1.799)	0.086
Q3	2.237 (1.768, 2.830)	< 0.001***	2.598 (2.077, 3.249)	< 0.001***	1.716 (1.270, 2.318)	0.008**
Q4	2.784 (2.177, 3.560)	< 0.001***	3.633 (2.730, 4.834)	< 0.001***	1.604 (1.072, 2.402)	0.031*
P for trend		< 0.001***		< 0.001***		0.016*
SIRI	1.200 (1.087, 1.324)	< 0.001***	1.126 (1.022, 1.239)	0.019*	0.988 (0.880, 1.108)	0.799
SIRI (Quartile)						
Q1	Ref		Ref		Ref	
Q2	1.255 (1.010, 1.559)	0.042*	1.189 (0.935, 1.512)	0.146	0.880 (0.593, 1.305)	0.418
Q3	1.574 (1.233, 2.010)	< 0.001***	1.482 (1.142, 1.923)	0.006**	0.925 (0.595, 1.439)	0.649
Q4	1.860 (1.478, 2.341)	< 0.001***	1.624 (1.269, 2.077)	< 0.001***	0.934 (0.586, 1.490)	0.707
P for trend		< 0.001***		< 0.001***		0.797
SII	1.000 (1.000, 1.000)	0.300	1.000 (1.000, 1.000)	0.420	1.000 (0.999, 1.000)	0.149
SII (Quartile)						
Q1	Ref		Ref		Ref	
Q2	1.039 (0.863, 1.252)	0.672	1.034 (0.844, 1.266)	0.732	0.909 (0.654, 1.263)	0.465
Q3	1.262 (1.000, 1.593)	0.050	1.284 (1.001, 1.647)	0.049	0.928 (0.627, 1.374)	0.626
Q4	1.213 (0.958, 1.537)	0.104	1.215 (0.951, 1.553)	0.112	0.764 (0.558, 1.046)	0.076
P for trend		0.054		0.053		0.096
IBI	1.006 (0.998, 1.013)	0.120	1.005 (0.997, 1.013)	0.178	1.000 (0.995, 1.004)	0.847
IBI(Quartile)						
Q1	Ref		Ref		Ref	
Q2	1.765 (1.319, 2.360)	< 0.001***	1.620 (1.180, 2.224)	0.005**	1.181 (0.778, 1.794)	0.330
Q3	3.766 (2.741, 5.173)	< 0.001***	3.701 (2.549, 5.373)	< 0.001***	1.797 (1.016, 3.179)	0.046*
Q4	4.390 (3.001, 6.420)	< 0.001***	4.576 (2.940, 7.124)	< 0.001***	1.502 (0.820, 2.750)	0.135
P for trend		< 0.001***		< 0.001***		0.084
NLR	1.020 (0.953, 1.091)	0.556	0.971 (0.911, 1.035)	0.339	0.893 (0.806, 0.989)	0.035*
NLR(Quartile)						
Q1	Ref		Ref		Ref	
Q2	1.326 (1.079, 1.628)	0.009**	1.279 (1.046, 1.565)	0.020*	1.124 (0.835, 1.514)	0.336
Q3	1.252 (0.980, 1.599)	0.070	1.192 (0.933, 1.523)	0.146	0.933 (0.653, 1.332)	0.616
Q4	1.328 (1.043, 1.690)	0.023*	1.125 (0.879, 1.442)	0.325	0.755 (0.493, 1.155)	0.140
P for trend		0.048*		0.503		0.067
PLR	0.996 (0.994, 0.998)	< 0.001***	0.996 (0.994, 0.998)	< 0.001***	0.997 (0.994, 1.000)	0.048*
PLR(Quartile)						
Q1	Ref		Ref		Ref	
Q2	0.822 (0.710, 0.950)	0.010*	0.835 (0.716, 0.972)	0.023*	0.839 (0.633, 1.110)	0.157
Q3	0.748 (0.569, 0.983)	0.038*	0.764 (0.573, 1.018)	0.064	0.813 (0.453, 1.457)	0.380
Q4	0.603 (0.488, 0.745)	< 0.001***	0.586 (0.461, 0.744)	< 0.001***	0.696 (0.472, 1.025)	0.060
P for trend		< 0.001***		< 0.001***		0.099
CAR	1.168 (1.041, 1.312)	0.010*	1.189 (1.036, 1.365)	0.017*	1.022 (0.933, 1.119)	0.580
CAR(Quartile)						
Q1	Ref		Ref		Ref	
Q2	2.745 (2.002, 3.764)	< 0.001***	2.631 (1.880, 3.681)	< 0.001***	1.696 (1.047, 2.747)	0.038*
Q3	4.266 (2.879, 6.321)	< 0.001***	4.331 (2.838, 6.611)	< 0.001***	2.192 (1.184, 4.058)	0.024*
Q4	5.991 (3.881, 9.248)	< 0.001***	6.815 (4.125, 11.259)	< 0.001***	2.013 (1.079, 3.755)	0.036*

Table 2 (continued)

Markers	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
P for trend		< 0.001***		< 0.001***		0.030*
PNI	1.003 (0.993, 1.012)	0.592	1.007 (0.986, 1.030)	0.485	1.017 (0.968, 1.069)	0.427
PNI(Quartile)						
Q1	Ref		Ref		Ref	
Q1	1.003 (0.766, 1.314)	0.981	1.044 (0.775, 1.406)	0.762	1.127 (0.692, 1.837)	0.534
Q2	1.067 (0.813, 1.400)	0.627	1.179 (0.874, 1.590)	0.258	1.340 (0.843, 2.131)	0.155
Q3	1.098 (0.888, 1.358)	0.372	1.272 (1.013, 1.596)	0.040*	1.708 (1.161, 2.512)	0.018*
P for trend		0.335		0.034*		0.007**
SIPS						
0	Ref		Ref		Ref	
1	1.419 (1.096, 1.837)	0.010*	1.502 (1.168, 1.931)	0.003**	0.911 (0.602, 1.379)	0.589
2	1.423 (0.505, 4.015)	0.488	1.464 (0.487, 4.406)	0.474	0.295 (0.021, 4.097)	0.286

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

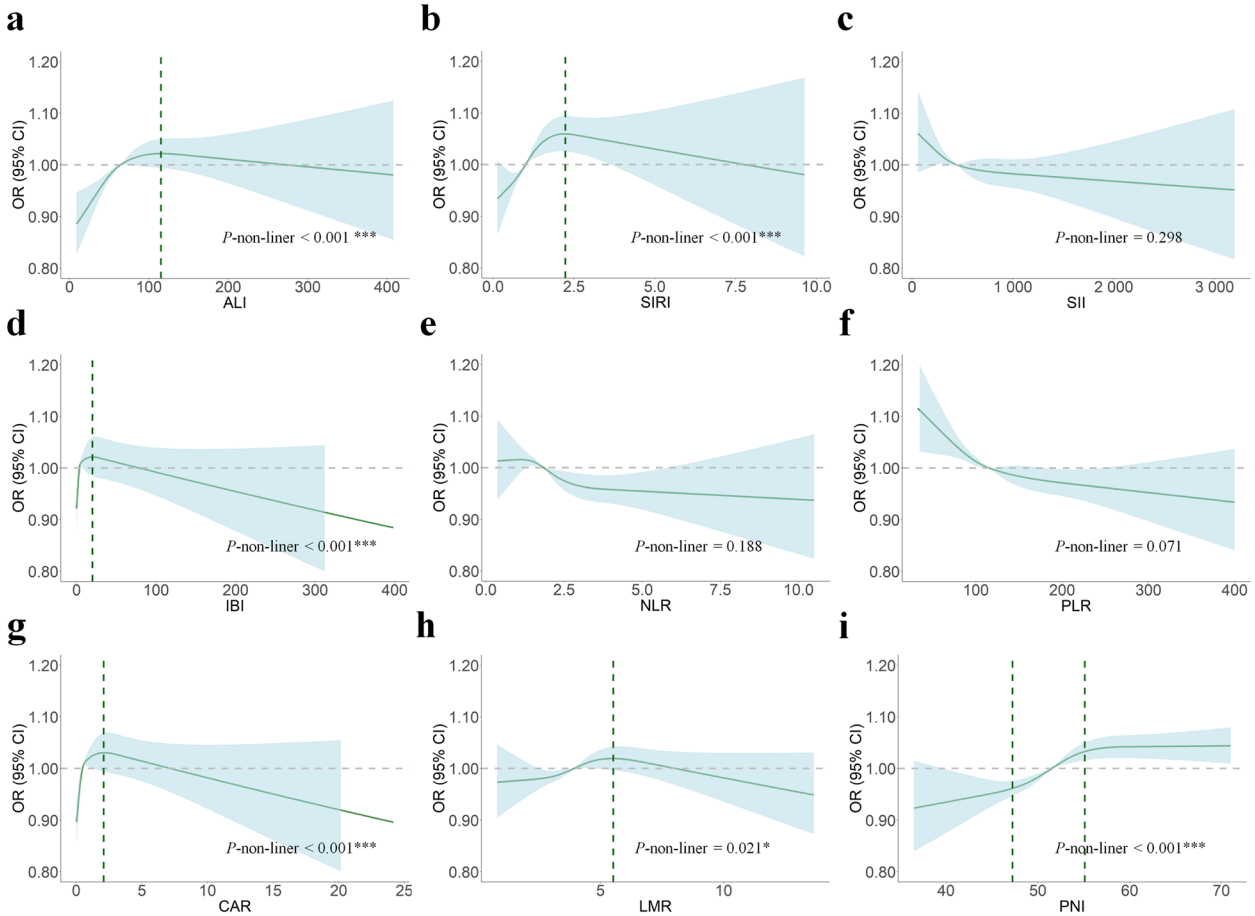

Fig. 3 Dose–response of continuous systemic inflammatory biomarkers and MASLD risk. ***: $P < 0.001$; **: $P < 0.01$; *: $P < 0.05$

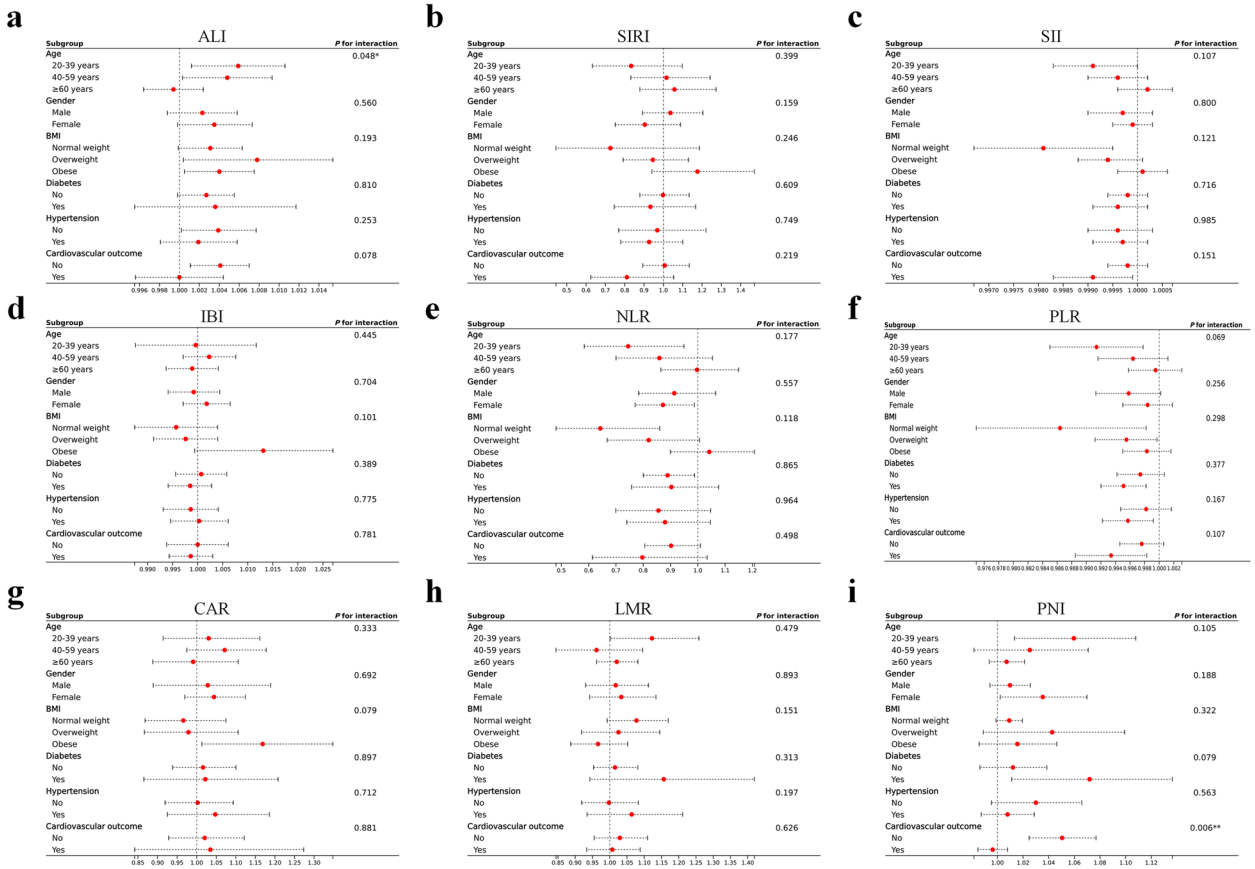

Fig. 4 Subgroup analyses of continuous systemic inflammatory biomarkers and MASLD risk. ***: $P < 0.001$; **: $P < 0.01$; *: $P < 0.05$

NLR, PLR, stratified ALI, CAR, PNI, and MASLD. Specifically, elevated NLR and PLR levels were associated with a reduced risk of MASLD, consistent with previous studies [25, 26]. Conversely, higher ALI, CAR, and PNI values were associated with an elevated risk of MASLD. Additionally, we observed a nonlinear dose–response relationship for most biomarkers, including ALI, SIRI, IBI, LMR, PNI, and MASLD. These results underscore the vital roles of inflammatory biomarkers in MASLD.

The systemic inflammatory biomarkers included in this study are known to be associated with the risk of various diseases. For instance, ALI, which reflects both inflammation and nutritional status, has been shown to be a prognostic indicator in heart failure [27], asthma [28], and various cancer [29–31]. Similarly, SIPS, derived from ALB (≥35 g/L) and NEU ($<7.5 \times 10^9$/L), which indicates a better nutritional state and lower inflammation, has been associated with survival outcomes in non-small cell lung cancer (NSCLC) [32, 33] and HCC [34]. Both NLR and PLR, which reflect systemic inflammation, have been associated with the risk of acute kidney injury [35], myocardial infarction [36], and rheumatoid arthritis [37]. In our study, we observed a significant correlation between the risk of MASLD and various systemic inflammatory biomarkers, underscoring the necessity for further investigation.

The specific mechanisms of these inflammatory markers remain largely unknown. In our study, NLR and PLR, composed by NEU/LYM and PLT/LYM respectively, were negatively correlated with MASLD risk. Mechanically, NEU can modulate the progression of inflammation through the expression of myeloperoxidase (MPO), which inhibits the initiation of the adaptive immune response by suppressing T cell proliferation, cytokine production, and the T helper 1 (Th1)/T helper 2 (Th2) cell ratio, thereby exerting anti-inflammatory effects in MASLD [38–40]. PLT can influence immune responses through direct interactions with NEU and the release of soluble mediators, such as chemokines, angiogenic factors, and growth factors [41]. Additionally, PLT modulate the function of liver sinusoidal endothelial cells by stimulating the secretion of hepatocyte growth factor (HGF) from hepatic stellate cells [42, 43] . As to LYM, which encompasses T cells, B cells, and natural killer (NK) cells, plays crucial roles in immunity. LYM may promote MASLD through activation of CD4 and CD8 T cells via

antigen presentation and by secreting cytokines such as interlukin-6 (IL-6) and tumor necrosis factor (TNFα), thereby faciliating the development of inflammation [44] . These findings may elucidate the anti-MASLD roles of NLR and PLR.

In contrast, ALI, CAR, and PNI were found to exert pro-MASLD roles in this study, with these indices being composed of ALB, BMI, CRP, LYM, and NEU. Elevated ALB levels are associated with increased insulin resistance, a key driver in the development of MASLD, potentially promoting hepatic fat deposition [45]. Conversely, ALB deficiency may reduce plasma free fatty acid concentrations, thereby decreasing hepatic steatosis and inflammation [46]. This suggests that higher ALB levels, central to both ALI and PNI, may contribute to an increased risk of MASLD. Additionally, BMI is a critical promoter of MASLD, with overweight and obese individuals comprising 96% of the total MASLD patients in our study. Furthermore, CRP can recognize microorganisms and apoptotic cells via phosphocholine binding [47], promoting the phagocytosis of phosphorylated substances by activating the classical complement pathway [48]. CRP may exert a stronger pro-inflammatory role than ALB in MASLD, contributing to the positive CAR-MASLD relationship.

In addition to systemic inflammation biomarkers, their components, namely NEU, LYM, PLT, MONO, ALB, and CRP, which collectively contributed to the inflammatory cascade, were predominantly differentiated expressed in MASLD and non-MASLD groups in our study, underscoring the critical role of inflammation in MASLD. Moreover, ALT and AST levels were notably elevated in MASLD patients, indicating hepatocyte damage and dysfunction caused by inflammation and steatosis.

Further subgroup analyses revealed notable differences in the relationship between ALI and MASLD risk across different age groups. This may be due to ALI being more reflective of inflammation related to nutritional status and body weight, both of which are significantly affected by age-related changes. However, other systemic inflammatory biomarkers may represent more consistent systemic inflammation, which does not fluctuate significantly with age, leading to no significant differences across age groups. Moreover, the associations between PNI and MASLD risk varied significantly across different cardiovascular outcome states. This may be attributed to the components of PNI, ALB and LYM, which may more sensitively reflect the state of cardiovascular diseases more sensitively, consistent with previous reports [49–51].

Several limitations should be considered when interpretating our results. First, due to the cross-sectional design of NHANES, we were unable to establish causal relationships between systemic inflammatory biomarkers and MASLD. To address this limitation, future research should consider conducting longitudinal studies or randomized controlled trials that can assess temporal associations and potential causal pathways. Second, as liver ultrasound transient elastography data were available only for NHANES from 2017 to March 2020, our study sample was relatively small. Therefore, expanding the study to include a larger sample size and a longer follow-up period would help validate our findings and enhance the generalizability of the results. Finally, despite careful adjustment for key covariates, residual confounding remains a potential concern. Future studies should aim to incorporate additional covariates not unavailable in NHANES, such as genetic predispositions or more detailed clinical data, to mitigate the risk of residual confounding. Moreover, incorporating dynamic biomarker measurements over time will help clarify their role in MASLD progression and provide a more comprehensive understanding of their impact on disease outcomes.

Our study has several strengths. While previous studies have examined the roles of some biomarkers in the context of liver disease, this study uniquely investigates a broad range of inflammatory markers and their non-linear relationships with MASLD risk. Additionally, the incorporation of inflection points in biomarkers such as ALI, SIRI, IBI, and PNI represents a novel approach in understanding how these biomarkers interact with MASLD across different thresholds. The use of NHANES data enables access to a large, nationally representative sample, enhancing the generalizability of the findings. Furthermore, systemic inflammatory biomarkers such as NLR, PLR, ALI, CAR, and PNI could serve as non-invasive tools for early MASLD screening and risk stratification. These biomarkers may also help monitor disease progression and assess treatment response, offering a less invasive alternative to liver biopsy. Future research should focus on validating their clinical utility and exploring their role in personalized management of MASLD.

Conclusions

Our study demonstrates significant associations between systemic inflammatory biomarkers and MASLD risk in U.S. adults. Elevated ALI, CAR, and PNI, along with decreased NLR and PLR, are robust predictors of increased MASLD risk, highlighting their potential as prognostic tools. While causality cannot be inferred from this cross-sectional analysis, these results provide a foundation for future longitudinal research to validate and expand upon these findings

Abbreviations

MASLD	Metabolic dysfunction associated steatotic liver disease
HCC	Hepatocellular carcinoma
NHANES	National health and nutrition examination survey
NAFLD	Non-alcoholic fatty liver disease
BMI	Body mass index
MASH	Metabolic dysfunction-associated steatohepatitis
HCC	Hepatocellular carcinoma
SII	Systemic immune inflammation index
SIRI	Systemic inflammation response index
LMR	Lymphocyte-to-monocyte ratio
ALI	Advanced lung cancer inflammation index
SIPS	Scottish inflammatory prognostic score
IBI	Inflammatory burden index
PLR	Platelet-to-lymphocyte ratio
CAR	C-reactive protein-to-albumin ratio
PNI	Prognostic nutritional index
NLR	Neutrophil-to-lymphocyte ratio
NCHS	National Center for Health Statistics
WBC	White blood cell
MONO	Monocyte
NEU	Neutrophil
LYM	Lymphocyte
PLT	Platelet
ALB	Albumin
CRP	C-reactive protein
HBV	Hepatitis B virus
HCV	Hepatitis C virus
SLD	Steatotic liver disease
CAP	Controlled attenuated parameter
PIR	Poverty income ratio
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
MAFLD	Metabolic dysfunction-associated fatty liver disease
MPO	Myeloperoxidase
Th1	T helper 1
Th2	T helper 2
HGF	Hepatocyte growth factor
NK	Natural killer
IL-6	Interlukin-6
TNFα	Tumor necrosis factor α

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03625-4.

Supplementary Material 1.

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Authors' contributions
Q.X and S.S wrote the main manuscript text. J.NZ, F.YF and Y.GD. performed the analysis and interpretation of data. L.DH.reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data of this research originate from the National Health and Nutrition Examination Surveys (NHANES): https://www.cdc.gov/nchs/nhanes/index.htm, which are publicly available.

Declarations

Ethics approval and consent to participate
The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Review Board of the National Center for Health Statistics (NCHS). Written informed consent was obtained from all patients included in the study.

Consent for publication
Not Applicable

Competing interests
The authors declare no competing interests.

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