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NPR is an independent risk factor for predicting all-cause mortality in patients with metabolic dysfunction-associated steatotic liver disease: evidence from NHANES 2007–2020

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Abstract

Background Neutrophil-associated inflammatory markers (NPR, NHR, SII, and SIRI) have been implicated in various metabolic diseases. However, studies on these markers with metabolic dysfunction-associated steatotic liver disease (MASLD) and advanced liver fibrosis (ALF), as well as their impact on all-cause mortality, remain limited.

Methods In this historical cohort study, data from 8051 adults aged 20 years and older were analysed. Weighted logistic regression was used to investigate the associations of neutrophil-associated inflammatory markers with MASLD and ALF. Nonlinear associations were described via restricted cubic spline regression. The diagnostic utility was assessed via receiver operating characteristic (ROC) curves. Furthermore, weighted Kaplan–Meier survival curves and Cox proportional hazards models were employed to assess all-cause mortality risk. Sensitivity analyses were employed to guarantee the robustness of the findings.

Results Following adjustment for confounding factors, there was a significant positive association between the ln-transformed NPR, NHR, SII, and SIRI and the risk of MASLD ($P < 0.001$). Conversely, an inverse association was noted between the ln-transformed SII, SIRI and ALF ($P < 0.05$). Nonlinear relationships were identified between ln-transformed NPR, NHR, and SIRI and the risk of MASLD ($P < 0.001$), as well as between ln-transformed NPR, SII, and SIRI and the risk of ALF ($P < 0.001$). Furthermore, the ln-transformed NHR (cut-off value: − 2.571) exhibited the highest diagnostic accuracy for MASLD (AUC 0.71, 95% CI = 0.70, 0.72), whereas the NPR (cut-off value: − 3.857) demonstrated the highest diagnostic value for ALF (AUC 0.73, 95% CI = 0.70, 0.75). The results of the present study revealed an independent association between the ln-transformed NPR and an elevated risk of all-cause mortality in subjects diagnosed with MASLD. Subgroup analyses highlighted the underrepresentation of neutrophil-associated inflammatory markers in lean individuals with MASLD and ALF (BMI < 25 kg/m^2).

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Conclusions Neutrophil-associated inflammatory markers are independently associated with MASLD and ALF. Specifically, the ln-transformed NHR and SII show promise as diagnostic markers for MASLD and ALF, respectively. Moreover, elevated ln-transformed NPR is independently associated with an increased risk of all-cause mortality in individuals with MASLD, highlighting the potential clinical relevance of these inflammatory markers in the context of steatotic liver disease.

Keywords Neutrophil, Inflammatory markers, Metabolic dysfunction-associated steatotic liver disease, Advanced liver fibrosis, Population-based study

Introduction

Once known as nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), which is typified by an excessive accumulation of fat in the liver, is thought to be the primary cause of chronic liver disease. The prevalence of MASLD is increasing quickly and is currently estimated to affect 38% of adults worldwide, with the leading cause of death being cardiovascular events [1]. The hepatic expression of metabolic syndrome is becoming more widely acknowledged, and it is tightly linked to a systemic immunoinflammatory state [2]. MASLD comprises a diverse spectrum of liver disorders, including simple steatosis and steatohepatitis, which can lead to advanced hepatic fibrosis (ALF), cirrhosis, and hepatocellular cancer [3]. Finding trustworthy biomarkers is essential for prognostic evaluation and early diagnosis, as it will slow the evolution of MASLD and its related morbidities.

ALF represents a critical juncture in the progression of chronic liver disease, resulting from prolonged and recurrent insults. The etiology of this damage is multifactorial, with potential origins including hepatotoxin exposure, metabolic disturbances associated with insulin resistance, persistent infections, and autoimmune disorders [4]. The hallmark of ALF is excessive extracellular matrix deposition, which results in architectural distortion and liver dysfunction [5]. MASLD represents the most common form of chronic liver disease and constitutes an important cause of ALF. ALF significantly elevates the risk of cardiovascular-related morbidity and mortality in MASLD patients, underscoring the need for early detection and intervention. Traditional methods for diagnosing ALF, such as liver biopsy, are invasive and carry potential risks [6]. Consequently, there is a pressing need for noninvasive biomarkers that can accurately reflect the fibrotic burden and predict clinical outcomes in patients with MASLD and ALF.

Neutrophils, which play pivotal roles in the innate immune response, are known to release inflammatory mediators that contribute to the progression of MASLD and the development of liver fibrosis [7]. Recent research has identified composite inflammatory markers related to neutrophils, including the neutrophil-to-platelet ratio (NPR), the neutrophil-to-high-density lipoprotein cholesterol (HDL-C) ratio (NHR), the systemic immune-inflammation index (SII) and the systemic inflammatory response index (SIRI). These indicators have shown promise in detecting systemic inflammation and have been connected to a variety of metabolic and cardiovascular illnesses [8]. However, their associations with MASLD and ALF remain underexplored, and existing studies have yielded inconsistent results.

The objective of this study was to elucidate the intricate relationships of neutrophil-associated inflammatory markers (NPR, NHR, SII, and SIRI) with MASLD and ALF, as well as their impacts on all-cause mortality. By employing a cohort study design and a sizeable, demographically representative sample from the general population, we aim to provide a comprehensive analysis of this association.

Materials and methods

Study population and mortality follow-up

We conducted a longitudinal cohort analysis utilizing data from the National Health and Nutrition Examination Survey (NHANES) spanning the years 2007–2020. The NHANES, managed by the National Center for Health Statistics, is a periodic cross-sectional survey that employs a multistage stratified probability cluster sampling design to accurately reflect the noninstitutionalized civilian population of the United States (https://www.cdc.gov/nchs/nhanes/index.htm). The survey collected comprehensive data on the prevalence of diseases, associated risk factors, and nutritional status through in-residence interviews and standardized clinical assessments, which included the collection of blood samples at ambulatory examination sites [9]. Over the course of the study period, a total of 66,148 participants engaged in six NHANES cycles. Exclusion criteria were applied, removing 26,932 individuals under the age of 20 years or those who were pregnant, 18,188 individuals with positive hepatitis B surface antigen or hepatitis C virus antibody tests, or missing data, and an additional 12,745 individuals with incomplete data on key covariates. Ultimately, the study population comprised 8,091 eligible participants. (Fig. 1).

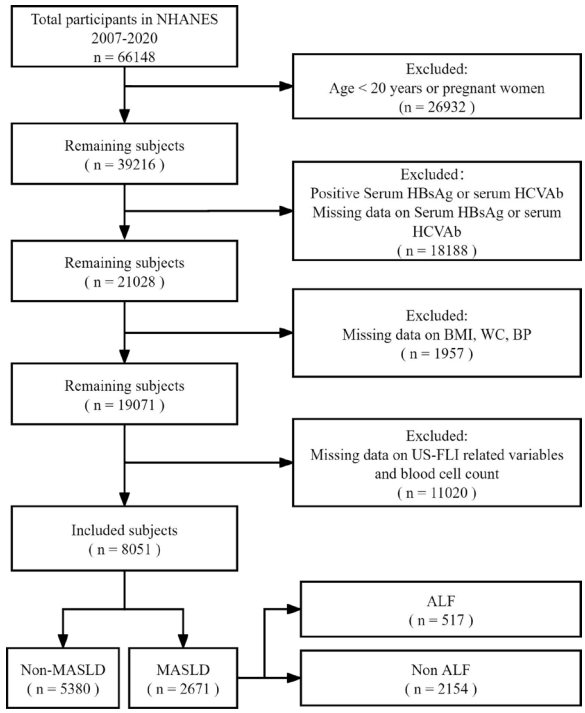

Fig. 1 Flow chat of the study participants. Abbreviations: NHANES, National Health and Nutrition Examination Survey; HBsAg, hepatitis B virus surface antigen; HCVAb, hepatitis C virus antibody; BMI, body mass index; WC, waist circumference; BP, blood pressure; US-FLI, U.S. fatty liver index; MASLD, metabolic dysfunction-associated steatotic liver disease; ALF, advanced liver fibrosis

Mortality outcomes for the participants were ascertained by merging NHANES data with the National Death Index (NDI), a publicly available resource (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). This integration facilitated the classification of participants into mortality status categories—deceased or alive—on the basis of NDI records [10]. The follow-up period was calculated from the NHANES examination date to either the date of death or, for survivors, December 31, 2019. Survival analyses were subsequently performed on the cohort with adequate follow-up data, with a focus on patients with MASLD.

Assessment of neutrophil-associated inflammatory markers

Neutrophil-associated inflammatory markers include the NPR, NHR, SII and SIRI. Table 1 shows the calculation methods and literature sources for these markers. Venous blood samples were obtained in the morning, following a minimum of 9 h of fasting overnight. Classified blood counts were measured on a Beckman Coulter DxH-800 analyser, and HDL-C concentrations were determined by precipitation or immunoassay on a Cobas 6000 chemistry analyser. The NHANES Laboratory Procedures Manual furnishes standardized protocols for the measurement of these biomarkers, accompanied by an exposition of the potential biases (https://www.cdc.gov/nchs/nhanes).

Assessment of MASLD and ALF

Since the 2007–2016 NHANES lacked data on liver ultrasound or transient elastography, the United States fatty liver index (US-FLI) was used to assess fatty liver status. The US-FLI was calculated via the following methodology [9]:

$$\mathrm{US-FLI} = (e^{y})/1 + e^{y}$$

In the formula, y = −0.8073*non-Hispanic black +0.3458*Mexican American +0.0093*age +0.6151*ln (GGT) +0.0249* waist circumference +1.1792*ln(insulin) +0.8242*ln(glucose) −14.7812. The values for 'non-Hispanic black' and 'Mexican American' are assigned as 1 if the participant belongs to that ethnicity and 0 if they do not belong to that ethnicity. In the absence of other liver diseases associated with the above factors, patients were considered to have fatty liver when the US-FLI score was ≥30.

MASLD is characterized by steatosis of the liver, and its diagnosis necessitates the fulfilment of at least one of the five established adult cardiometabolic criteria. These cardiometabolic risk factors are delineated as follows [3]: a) body mass index (BMI) ≥25 kg/m2 or waist

Table 1 Inflammatory markers about neutrophil

Inflammatory index	Formula	PMID
Neutrophil to platelet ratio, NPR	Neutrophil count (× 10^3cells/ul)/platelet count (× 10^3cells/ul)	38,129,626
Neutrophil to HDL cholesterol ratio, NHR	Neutrophil count(× 10^3cells/ul)/HDL cholesterol level(mg/dL)	36,057,713
Systemic immune-in-flammation index, SII	Platelet count (× 10^3cells/ul) × neutrophil count (× 10^3cells/ul)/lymphocyte count(× 10^3cells/ul)	36,189,280
Systemic inflammatory response index, SIRI	Neutrophil count (× 10^3cells/ul) × monocyte count(× 10^3cells/ul)/lymphocyte count(× 10^3cells/ul)	33,500,649

HDL-C, high density lipoprotein cholesterol

circumference ≥ 94 cm in males and 80 cm in females; b) fasting blood glucose ≥ 100 mg/dl or HbA1 C≥ 5.7% or diagnosed type 2 diabetes mellitus (T2DM) or treatment for T2DM; c) blood pressure ≥ 130/85 mmHg or treatment for hypertension; d) plasma triglyceride ≥ 150 mg/dl or treatment of hyperlipidemia; and e) plasma HDL-C < 40 mg/dl in males or < 50 mg/dl in females.

The diagnosis of ALF is contingent upon the concurrent presence of MASLD in conjunction with a NAFLD fibrosis score (NFS) ≥ 0.676 or a fibrosis-4 score (FIB-4) ≥ 2.67. NFS and FIB-4 were computed in the following manner [11]: NFS = − 1.675 + 0.037 * age (year) + 0.094 * BMI (kg/m^2) + 1.13 * hyperglycemia (yes = 1, no = 0) + 0.99 * AST/ALT—0.013 * platelet (× $10^3/mm^3$)—0.66 × blood albumin (g/dl); FIB-4 = age (year) × AST (U/L)/[platelet (× $10^3/mm^3$) × ALT (U/L) $^{1/2}$]. A higher NFS cut-off score of 0.676 facilitates the precise diagnosis of advanced fibrosis, with positive predictive values of 90% and 82% in the estimation and validation cohorts, respectively [12]. Concurrently, an FIB-4 score of 2.67 or greater has a positive predictive value of 80% for the presence of advanced fibrosis [13].

Covariates

In alignment with the extant literature and the insights derived from clinical practice, a comprehensive range of potential covariates has been included, including demographics, physical measurements, health-related behaviors, comorbidities and laboratory tests. The sociodemographic characteristics included age, sex, race, socioeconomic status and educational attainment. The physical measurements included BMI. The comorbidities included hypertension, hyperlipidaemia and T2DM. Health-related behaviors, including smoking status, were also considered. The laboratory test results reported were alanine aminotransferase levels and estimated glomerular filtration rates. A comprehensive account of the classification methodologies employed is provided in Supplementary Table 1.

Statistical analyses

We categorized all included participants into non-MASLD and MASLD groups and categorized MASLD patients into non-ALF and ALF groups. For descriptive statistical analyses, the median (interquartile range) was used to describe continuous variables, whereas frequencies (percentages) were used to describe categorical variables. In accordance with the analytical guidelines set forth by the NHANES, we employed sampling weights to derive national estimates that accurately reflect the relative proportions of various subgroups within the overall population of the United States. To facilitate the comparison of baseline information between groups, a weighted t test was employed for continuous variables, whereas a weighted chi-square test was used for classified information. Owing to the skewed distribution of neutrophil-associated inflammation markers, natural logarithms were performed to obtain an approximately normal distribution (Supplementary Fig. 1). Three weighted multivariate logistic regressions were employed to estimate independent associations between neutrophil-associated inflammatory indicators and both MASLD and ALF.

To investigate the putative nonlinear correlations between neutrophil-associated inflammatory markers and the risk of developing MASLD and ALF, we utilized restricted cubic spline (RCS) regression methodology. The comparative efficacy of the multivariate logistic regression framework versus RCS regression was evaluated through a likelihood ratio test. Furthermore, the optimal diagnostic threshold for neutrophil-associated inflammatory indices in the context of MASLD and ALF was determined by calculating the area under the receiver operating characteristic (ROC) curve. The participants were subsequently dichotomized on the basis of these inflammatory marker thresholds. To ascertain disparities in all-cause mortality between these two cohorts, the log-rank test was applied, complemented by Kaplan–Meier survival plots for graphical representation of survival discrepancies. The median follow-up period was computed via the reverse Kaplan–Meier technique. Additionally, we employed survey-weighted Cox proportional hazards models to ascertain the independent impact of neutrophil-associated inflammatory indices on all-cause mortality.

We also performed two sensitivity analyses to assess the robustness of our findings: 1) Subgroup analyses through multifactorial logistic regression analyses were employed to further explore the relationships between neutrophil-associated inflammatory markers and MASLD and ALF; 2) notably, subgroup examinations via survival analysis were not performed due to the limited number of participants with comprehensive follow-up data. Instead, we resort to unweighted multifactorial Cox proportional hazards regression to mitigate the potential for overadjustment bias stemming from sampling weights. All the statistical evaluations were carried out via R statistical software (version 4.2.1), with a two-tailed $P < 0.05$ deemed statistically significant.

Results

Population characteristics

Within the cohort of 8051 participants enrolled in this investigation, a total of 2671 individuals (33.2%) were diagnosed with MASLD, among whom 517 (19.4%) were identified as ALF cases. Due to the small sample size of MetALD (Metabolic-associated Alcoholic Liver

Table 2 Baseline characteristics of participants

Characteristics	Overall (n = 8051)	Non MASLD (n = 5380)	MASLD (n = 2671)	*P*	MASLD without ALF (n = 2154)	MASLD with ALF (n = 517)	*P*
Age, n (%)	39(29,53)	36(27,47)	45(34,60)	**< 0.001**	43(33,56)	66(55,74)	**< 0.001**
Gender, n (%)				**< 0.001**			**< 0.001**
Male	5,570(67.9%)	3,429(62.4%)	2,141(80.0%)		1,669(78.38%)	472(88.85%)	
Female	2,481(32.1%)	1,951(37.6%)	530(20.0%)		485(21.62%)	45(11.15%)	
Ethnicity, n (%)				**< 0.001**			**< 0.001**
Mexican American	1,260(9.8%)	633(7.4%)	627(15.0%)		560(16.50%)	67(6.90%)	
Non-Hispanic White	3,350(65.2%)	2,164(64.4%)	1,186(67.0%)		899(65.39%)	287(75.43%)	
Non-Hispanic Black	1,610(11.0%)	1,299(13.2%)	311(6.0%)		228(5.67%)	83(7.63%)	
Other Race	1,831(14.0%)	1,284(15.0%)	566(12%)		467(12.44%)	80(10.04%)	
PIR	3.0(1.4, 5.0)	3.1(1.5, 5.0)	2.7(1.4, 4.8)	**0.022**	2.73(1.31, 4.83)	2.72(1.61, 4.91)	0.3
Education, n (%)				**< 0.001**			0.9
Less than high school	1,813(15.7%)	1,061(13.7%)	752(20.0%)		616(20.13%)	136(19.10%)	
High school	1,791(21.9%)	1,176(21.2%)	615(23.4%)		490(23.34%)	125(23.57%)	
College or more	4,447(62.4%)	3,143(65.1%)	1,304(56.6%)		1,048(56.52%)	256(57.33%)	
Physical measurement							
BMI (kg/m^2)	27.6(24.0, 31.9)	25.7(22.9, 28.7)	32.9(29.4, 37.2)	**< 0.001**	32.6(29.2, 36.5)	36.0(30.8, 44.2)	< 0.001
Disorders or status							
Smoking, n (%)	3,687(44.99%)	2,324(42.71%)	1,363(50.03%)	**< 0.001**	1,050(48.26%)	313(59.92%)	< 0.001
T2DM, n (%)	1,258(10.89%)	426(4.91%)	832(24.13%)	**< 0.001**	558(19.71%)	274(48.93%)	< 0.001
Hypertension, n (%)	3,648(40.62%)	1,925(30.40%)	1,723(63.23%)	**< 0.001**	1,292(59.84%)	431(82.22%)	< 0.001
Hyperlipidemia, n (%)	4,703(57.13%)	2,686(48.84%)	2,017(75.44%)	**< 0.001**	1,627(75.90%)	390(72.89%)	0.3
Laboratory indicators							
ALT (U/L)	21(16, 29)	19(15, 25)	28(21, 38)	**< 0.001**	29(22, 39)	23(17, 30)	**< 0.001**
SCr (mg/dL)	0.88(0.74, 1.01)	0.87(0.73, 1.00)	0.90(0.77, 1.03)	**< 0.001**	0.88(0.76, 1.01)	1.01 (0.84, 1.21)	**< 0.001**
Neutrophil count (× 10^{3}cells/ul)	3.7(2.9, 4.8)	3.5(2.8, 4.5)	4.1(3.4, 5.2)	**< 0.001**	4.1(3.4, 5.2)	4.2(3.4, 5.2)	0.5
Monocyte count (× 10^{3}cells/ul)	0.5(0.4, 0.6)	0.5(0.4, 0.6)	0.6(0.5, 0.7)	**< 0.001**	0.6(0.5, 0.7)	0.6(0.5, 0.7)	0.4
HDL (mg/dL)	49(41, 59)	53(44, 63)	43(37., 49)	**< 0.001**	43(37, 49)	43(36, 50)	0.9
Neutrophil-associated inflammatory markers							
NPR	0.016 (0.013,0.021)	0.015 (0.012,0.020)	0.018 (0.014,0.023)	**< 0.001**	0.017 (0.014, 0.021)	0.024 (0.018, 0.031)	**< 0.001**
NHR	0.08(0.05, 0.10)	0.07(0.05, 0.09)	0.10(0.07, 0.13)	**< 0.001**	0.10(0.07, 0.13)	0.10(0.07, 0.13)	0.8
SII	440(323, 623)	421(310, 599)	484(355, 662)	**< 0.001**	494(362, 669)	442(306, 635)	**< 0.001**
SIRI	0.99(0.68, 1.41)	0.91(0.64, 1.32)	1.13(0.81, 1.61)	**< 0.001**	1.10(0.80, 1.56)	1.31(0.95, 2.00)	**< 0.001**

*Continuous variables are represented by Median (IQR)), while categorical variables are denoted by unweighted n (%). Bold values indicate statistical significance at $P<0.05$. **Abbreviation**: PIR, family poverty income ratio; BMI, body mass index; T2DM, type 2 diabetes mellitus; ALT, alanine aminotransferase; Scr, serum creatinin; HDL-C, high density lipoprotein cholesterol; NPR, neutrophil to platelet ratio; NHR, neutrophil to HDL-C cholesterol ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index

Table 3 The relationship between neutrophil-associated inflammatory index with the risk of MASLD and ALF

Characteristics (ln-transformed)	Model 1[1]		Model 2[2]		Model 3[3]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
MASLD						
NPR	2.58(2.10,3.04)	**< 0.001**	2.10(1.78,2.48)	**< 0.001**	1.63(1.35,1.97)	**< 0.001**
NHR	5.82(4.94,6.86)	**< 0.001**	5.74(4.83,6.83)	**< 0.001**	3.03(2.44,3.77)	**< 0.001**
SII	1.63(1.43,1.86)	**< 0.001**	1.59(1.38,1.83)	**< 0.001**	1.36(1.12,1.64)	**0.002**
SIRI	1.86(1.69,2.04)	**< 0.001**	1.52(1.37,1.69)	**< 0.001**	1.36(1.17,1.58)	**< 0.001**
ALF						
NPR	12.15(8.54,17.28)	**< 0.001**	9.91(6.80,14.44)	**< 0.001**	10.93(6.76,17.65)	**< 0.001**
NHR	1,04(0.73,1.48)	0.800	1.24(0.83,1.86)	0.300	0.58(0.32,1.03)	0.060
SII	0.66(0.51,0.86)	**< 0.001**	0.56(0.40,0.80)	**0.002**	0.22(0.11,0.45)	**< 0.001**
SIRI	1.98(1.56,2.51)	**< 0.001**	1.21(0.93,1.58)	0.200	0.72(0.53,0.98)	**0.040**

[1] The model 1 was not adjusted for any covariates

[2] The model 2 was adjusted for age, gender, and race

[3] The model 3 was adjusted for all covariates based on model 1

Bold values indicate statistical significance at $P<0.05$. MASLD, metabolic dysfunction-associated steatotic liver disease; ALF, advanced liver fibrosis; NPR, neutrophil to platelet ratio; NHR, neutrophil to HDL-C cholesterol ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index

Disease) in this study (only 59 out of 2671 MASLD patients), MetALD was not analyzed as a separate subgroup from MASLD. The delineation of demographic and clinical features distinguishing the four participant groups is shown in Table 2**.** Notably, in terms of neutrophil-associated inflammatory markers, participants with MASLD presented elevated NPR, NHR, SII and SIRI values than non-MASLD patients did ($P< 0.001$). Moreover, patients with ALF had higher NPRs and SIRIs but lower NHRs than did those without ALF ($P< 0.001$).

Independent associations between neutrophil-associated inflammatory markers and MASLD and ALF

The relationships between neutrophil-associated inflammatory markers and the risk of MASLD and ALF are delineated in Table 3. Through the employment of three distinct multivariate logistic regression models, which are incrementally adjusted for various potential confounders, we discerned a positive correlation between the natural logarithm transformations of NPR (OR = 1.63, 95% CI: 1.35–1.97), NHR (OR = 3.03, 95% CI: 2.44–3.77), SII (OR = 1.36, 95% CI: 1.12–1.64), and SIRI (OR = 1.36, 95% CI: 1.17–1.58) with the prevalence of MASLD ($P< 0.05$). Moreover, a significant positive association was detected between the NPR and the risk of ALF ($P< 0.001$, OR = 10.4, 95% CI: 6.50–16.5). In contrast, the SII and SIRI emerged as independent factors mitigating the risk of ALF development ($P< 0.001$, OR = 0.22, 95% CI: 0.11–0.45; $P< 0.05$, OR = 0.72, 95% CI: 0.53–0.98). Notably, the NPR was strongly associated with ALF compared with the other biomarkers under consideration.

Subgroup analyses were conducted to examine the relationships between neutrophil-associated inflammatory indices and the occurrence of MASLD and ALF, stratified by age, sex, race, BMI, smoking status, T2DM, hypertension, and hyperlipidemia. As detailed in Supplementary Table 2, the fully adjusted model indicated that the ln-transformed NHR remained positively correlated with the prevalence of MASLD across all the examined subgroups ($P< 0.05$). In contrast, elevated levels of ln-transformed NPR, SII, and SIRI were observed within specific subgroups of MASLD, including those aged 20–60 years, males, obese individuals, nonsmokers, non-T2DM patients, and nonhypertensive individuals. Additionally, the subgroup analyses revealed that, within the fully adjusted model, the ln-transformed NPR and SII were positively correlated with the incidence of ALF across all subgroups, except for those with a BMI less than 25 kg/m^2 (Supplementary Table 3). Our findings particularly underscore the underrepresentation of neutrophil-associated inflammatory markers in lean individuals with MASLD and ALF (BMI < 25 kg/m^2).

Nonlinear relationships between neutrophil-associated inflammatory markers and MASLD and ALF

A subsequent investigation was conducted to determine whether a nonlinear correlation exists between neutrophil-associated inflammatory markers and the risk of MASLD and ALF. As illustrated in Figs. 2 and 3, the

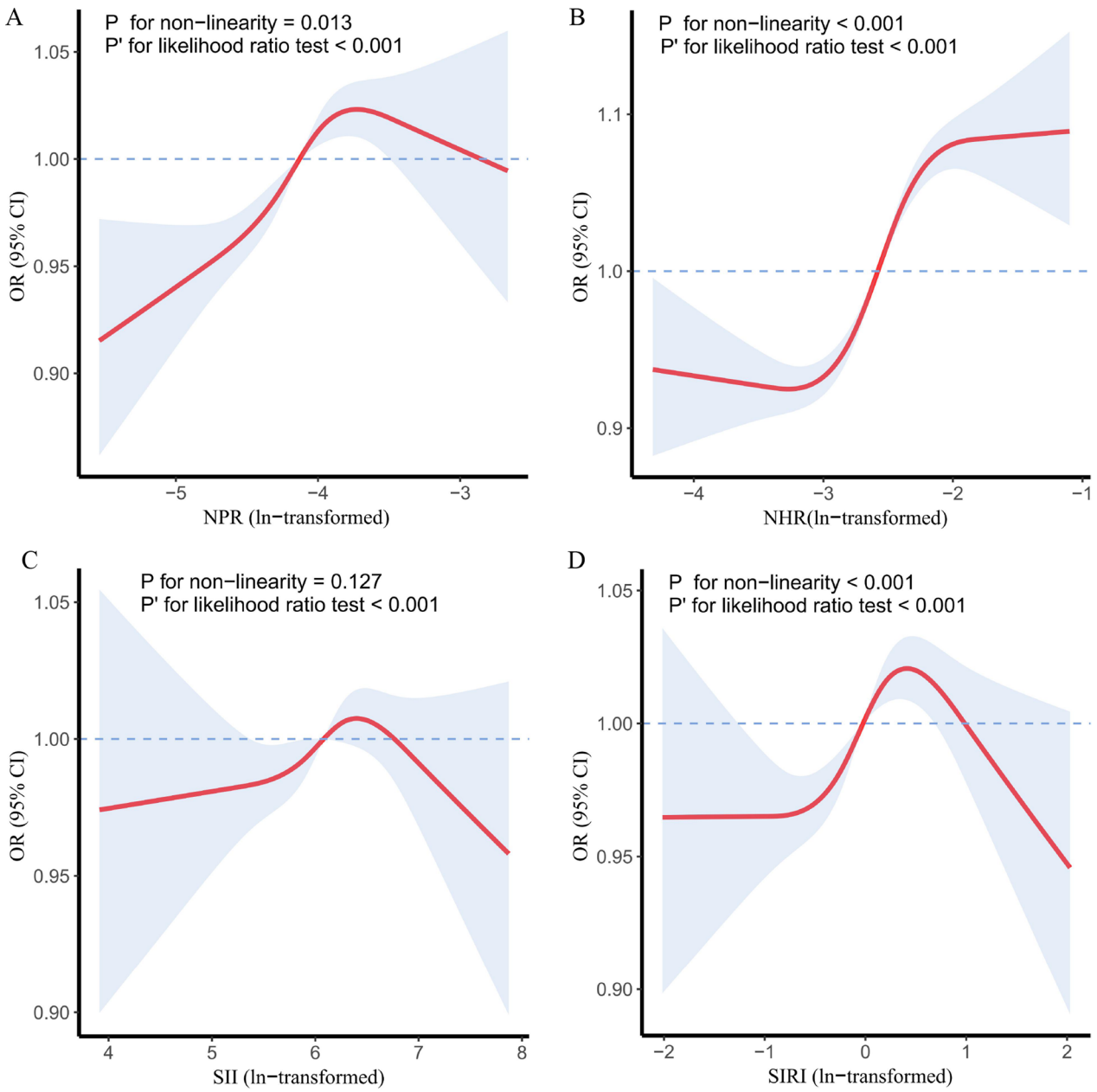

Fig. 2 Neutrophil-associated inflammatory markers with non-linear relationship to MASLD. **A** Restricted cubic spline for the association between NPR(ln-transformed) and MASLD. **B** Restricted cubic spline for the association between NHR (ln-transformed) and MASLD. **C** Restricted cubic spline for the association between SII (ln-transformed) and MASLD. **D** Restricted cubic spline for the association between SIRI (ln-transformed) and MASLD. Abbreviation: MASLD, metabolic dysfunction-associated steatotic liver disease; NPR, neutrophil to platelet ratio; NHR, neutrophil to HDL-C cholesterol ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index

results of fully adjusted RCS regression indicate a nonlinear relationship between NPR, NHR, SIRI and MASLD (*P* for nonlinearity < 0.05). Furthermore, there is a nonlinear relationship between the NPR, SII and SIRI (*P* for nonlinearity < 0.05). Moreover, the RCS regression demonstrated a superior fit to the data than the logistic regression did (*P* for likelihood ratio test < 0.001).

Diagnostic efficacy of neutrophil-associated inflammatory markers for MASLD and ALF

As shown in Fig. 4 and Table 4, the ln-transformed NHR (cut-off value: −2.571, sensitivity: 71.43%, specificity: 61.52%) had the highest area under the curve (AUC) (0.71, 95% CI = 0.70–0.72) for MASLD, which was significantly greater than that of the other inflammatory

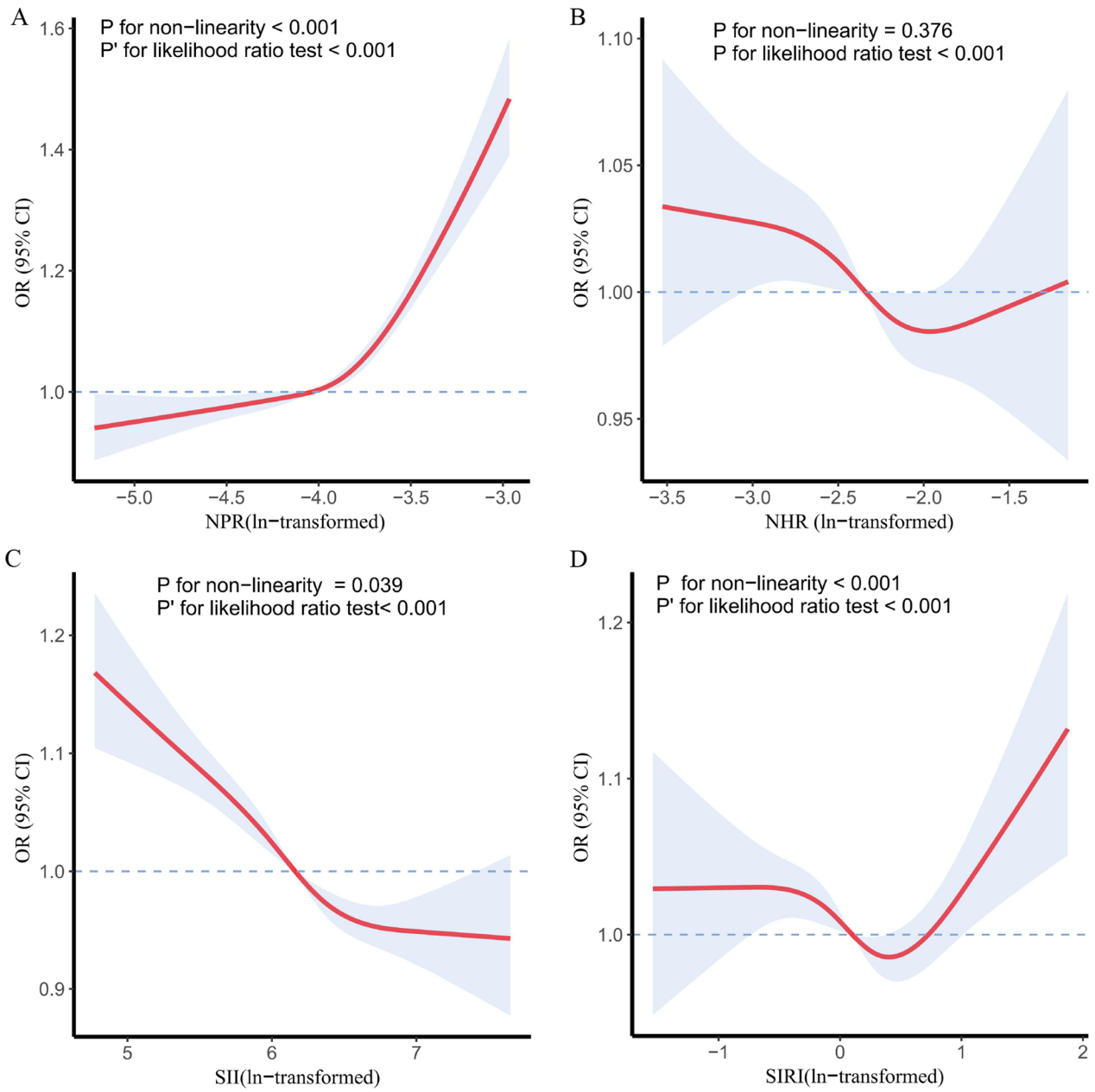

Fig. 3 Neutrophil-associated inflammatory markers with non-linear relationship to ALF. **A** Restricted cubic spline for the association between NPR (ln-transformed) and ALF. **B** Restricted cubic spline for the association between NHR (ln-transformed) and ALF. **C** Restricted cubic spline for the association between SII (ln-transformed) and ALF. **D** Restricted cubic spline for the association between SIRI (ln-transformed) and ALF. Abbreviation: ALF, advanced liver fibrosis; NPR, neutrophil to platelet ratio; NHR, neutrophil to HDL-C cholesterol ratio; SII, systemic immune-in-flammation index; SIRI, systemic inflammatory response index

markers ($P < 0.001$). Moreover, the ln-transformed NPR (cut-off value: −3.857, sensitivity: 62.28%, specificity: 74.56%) had the highest AUC (0.73, 95% CI = 0.70–0.75) for ALF, which was significantly greater than that of the other inflammatory markers ($P < 0.001$). Notably, the NHR exhibited the highest specificity but lowest sensitivity for the diagnosis of ALF.

Associations between neutrophil-associated inflammatory markers and all-cause mortality in MASLD and ALF patients

Among the 2671 patients with MASLD, 1894 had available follow-up data and were included in subsequent survival analyses, with a median follow-up period of 112 months (95% CI: 111–115 months). As illustrated

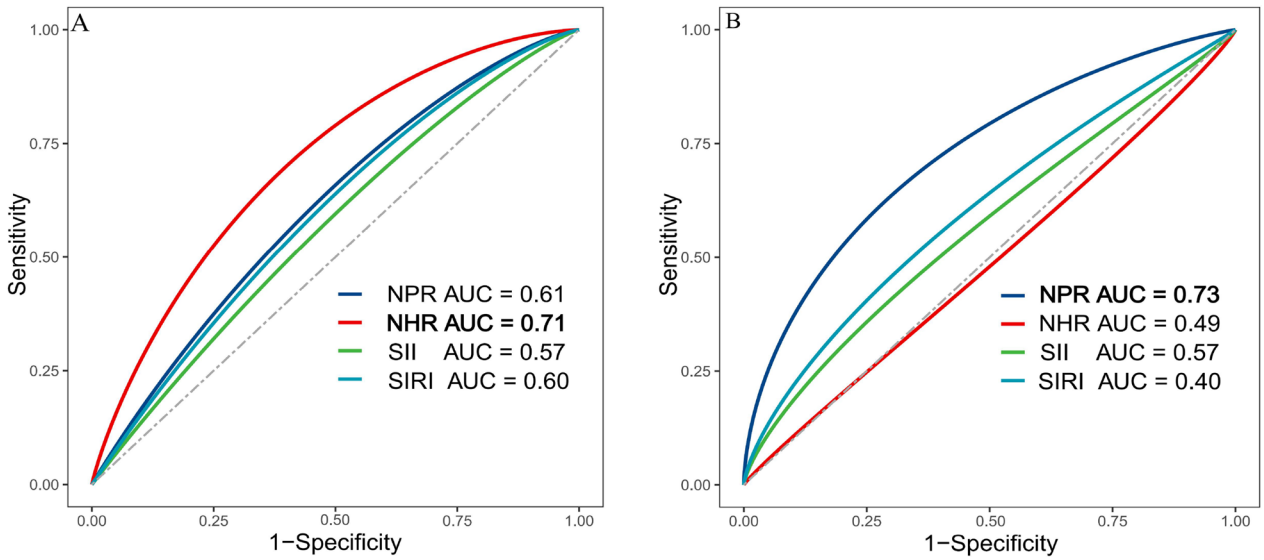

Fig. 4 ROC curves of ln-transformed inflammatory markers in MASLD and ALF. **A** ROC curves of neutrophil associated inflammatory markers (ln-transformed NPR, NHR, SII, SIRI) in MASLD. **B** ROC curves of neutrophil associated inflammatory markers (ln-transformed NPR, NHR, SII, SIRI) in ALF. Abbreviation: ROC, receiver operating characteristic curve; MASLD, metabolic dysfunction-associated steatotic liver disease; ALF, advanced liver fibrosis; NPR, neutrophil to platelet ratio; NHR, neutrophil to HDL-C cholesterol ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index

Table 4 The diagnostic efficacy of neutrophil-associated inflammatory markers for MASLD and ALF

Characteristics (ln-transformed)	AUC (95% CI)	Cut-off Value	Sensitivity	Specificity
MASLD				
NPR	0.61(0.60,0.62)	− 4.163	65.48%	52.49%
NHR	0.71(0.70,0.72)	− 2.571	71.43%	61.52%
SII	0.57(0.55,0.58)	5.892	71.88%	38.03%
SIRI	0.60(0.58,0.61)	− 0.092	65.14%	50.81%
ALF				
NPR	0.73(0.70,0.75)	− 3.857	62.28%	74.56%
NHR	0.49(0.46,0.51)	− 1.718	8.90%	93.13%
SII	0.57(0.54,0.60)	5.848	34.62%	77.21%
SIRI	0.60(0.58,0.63)	0.487	39.07%	79.34%

MASLD, metabolic dysfunction-associated steatotic liver disease; ALF, advanced liver fibrosis; NPR, neutrophil to platelet ratio; NHR, neutrophil to HDL-C cholesterol ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index

in Fig. 5, Kaplan–Meier survival curves revealed a significantly lower survival rate in the high NPR group than in the low NPR group (P for log-rank < 0.001). Similarly, a significant reduction in survival probability was observed in MASLD patients with higher SIRIs compared with those with lower SIRIs (P for log-rank < 0.001). In contrast, neither the NHR nor the SII had a significant effect on survival within the MASLD cohort (P for log-rank > 0.05). Consistent with these findings, unadjusted weighted Cox proportional hazards regression analyses yielded corresponding results (Table 5). Nevertheless, when we conducted a fully adjusted multivariate analysis, only elevated NPR were identified as independent predictors of all-cause mortality in the MASLD patient population ($P < 0.001$).

In the cohort of 517 patients who were diagnosed with MASLD and subsequently developed ALF, a total of 290 patients provided adequate follow-up data for survival analysis. During a median surveillance duration of 102 months (95% CI: 92–108 months), the weighted Kaplan–Meier survival curves failed to elicit any statistically significant discrepancies in all-cause mortality rates among the varying neutrophil-associated inflammatory index categories in the ALF cohort (P for log-rank > 0.05). This lack of significant difference was further substantiated by both univariate and multivariate weighted Cox regression analyses ($P > 0.05$).

To corroborate the robustness of our observations, sensitivity analyses were conducted employing unweighted Kaplan–Meier survival curves and Cox proportional hazards regression models (Supplementary Table 4). These sensitivity analyses, performed on the previously mentioned patient populations, confirmed the consistency of our primary analysis results.

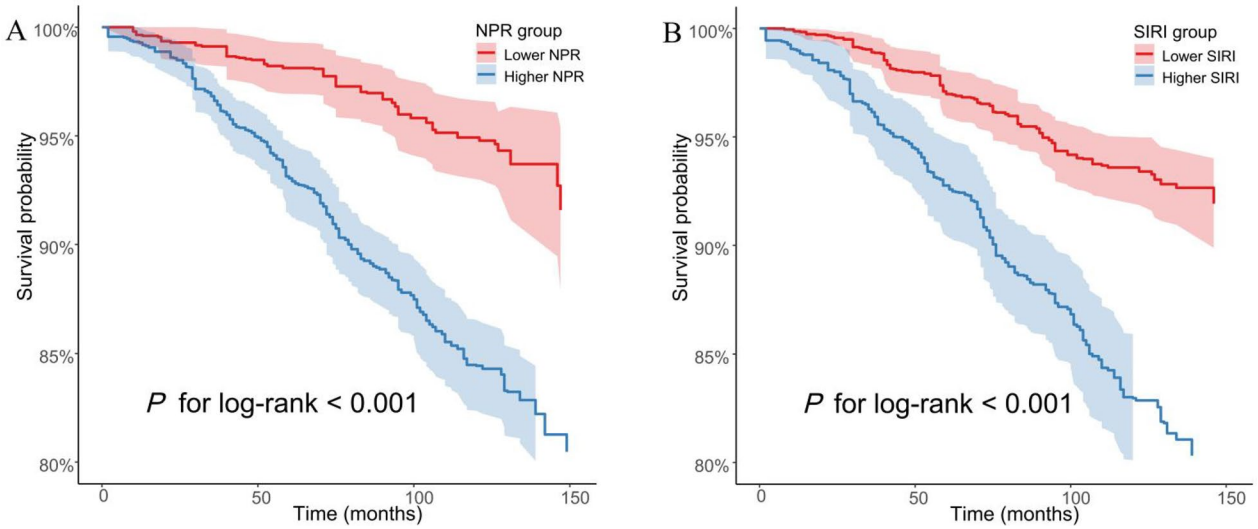

Fig. 5 Kaplan–Meier survival curves for all-cause mortality in MASLD (N = 1894). **A** Relationship between higher (> −4.163) and lower (≤ −4.163) ln-transformed NPR values with all-cause mortality in the MASLD group. **B** Relationship between higher (> −0.092) and lower (≤ −0.092) ln-transformed SIRI values with all-cause mortality in the MASLD group. Abbreviation: MASLD, metabolic dysfunction-associated steatotic liver disease; NPR, neutrophil to platelet ratio; SIRI, systemic inflammatory response index

Table 5 The relationship between neutrophil-associated inflammatory markers with the mortality of MASLD(N = 1894) and ALF(N = 290)

Characteristics (ln-transformed)	Model 1[1]		Model 2[2]		Model 3[3]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
MASLD						
NPR	3.10(2.16,4.45)	**< 0.001**	2.19(1.46,3.27)	**< 0.001**	1.98(1.32,2.96)	**< 0.001**
NHR	0.89(0.60,1.33)	0.573	1.06(0.73,1.55)	0.760	0.96(0.65,1.41)	0.829
SII	1.17(0.79,1.74)	0.441	1.14(0.77,1.71)	0.508	1.14(0.77,1.69)	0.527
SIRI	2.71(2.06,3.56)	**< 0.001**	1.51(1.04,2.19)	**0.029**	1.47(1.00,2.17)	0.052
ALF						
NPR	2.06(0.71,5.95)	0.181	1.64(0.54,4.99)	0.381	1.21(0.38,3.84)	0.748
NHR	0.85(0.40,1.79)	0.666	0.87(0.44,1.74)	0.703	1.15(0.46,2.89)	0.765
SII	0.85(0.51,1.40)	0.516	0.96(0.58,1.58)	0.865	1.60(0.76,3.39)	0.218
SIRI	1.48(0.90,2.45)	0.123	1.10(0.70,1.72)	0.681	1.55(0.73,3.28)	0.225

[1] The model 1 was not adjusted for any covariates

[2] Model 2 was adjusted for age, gender, and race

[3] Model 3 was adjusted for all covariates based on model 1

Bold values indicate statistical significance at $P<0.05$. MASLD, metabolic dysfunction-associated steatotic liver disease; ALF, advanced liver fibrosis; NPR, neutrophil to platelet ratio; NHR, neutrophil to HDL-C cholesterol ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index

Discussion

The present investigation was undertaken to elucidate the intricate relationships of neutrophil-associated inflammatory markers (NPR, NHR, SII, and SIRI) with MASLD and ALF, as well as their impact on all-cause mortality. The results of our investigation demonstrate that the ln-transformed NHR is more strongly correlated with MASLD than other biomarkers are. This finding is in accordance with the results of two previous small-scale cross-sectional studies, which established a correlation between elevated levels of NHR and an increased risk of MASLD [14, 15]. Furthermore, our analytical approach revealed that the ln-transformed NPR is more strongly associated with ALF than other biomarkers are. These findings suggest that elevated levels of NHR and NPR may be clinically relevant in the pathology of MASLD

and ALF, highlighting the pivotal role of neutrophils in the pathogenesis of these liver conditions. Additionally, our findings indicated that the ln-transformed NPR was positively correlated with all-cause mortality in patients with MASLD.

MASLD has emerged as the most prevalent liver disorder, with recent trend analyses indicating a significant increase in global prevalence, increasing from 21.9 to 37.3% between 1991 and 2019 [16]. MASLD encompasses a spectrum ranging from liver steatosis to progressive forms, such as MASH (metabolic dysfunction associated steatohepatitis), which is characterized by liver steatosis, hepatocellular death, immune cell accumulation and liver fibrosis [3]. Patients with MASLD are commonly associated with metabolic disorders, including hypertension, diabetes, and dyslipidemia [5]. The literature has shed light on the pivotal role of dysregulated hepatic immune activation in the pathogenesis and perpetuation of MASLD, which is also implicated in hypercoagulable states and dyslipidemia observed in the plasma [17, 18]. The assessment of neutrophil-associated inflammatory markers, which are frequently included in routine blood tests, offers an accessible method for the evaluation of the aforementioned abnormalities. For example, the neutrophil-to-lymphocyte ratio was identified as a significant and independent predictor of advanced inflammation and fibrosis [19]. Nevertheless, the existing body of research examining the relationships between these inflammatory biomarkers and MASLD, as well as ALF, remains limited. Our findings extend these observations by establishing, for the first time, a significant disparity in all-cause mortality between patients with higher and lower NPRs in the context of MASLD when the NPR is used as a categorical variable. This finding underscores the pivotal role of neutrophils and platelets, as key components, in immune-inflammatory and coagulation states throughout the course of MASLD.

The liver is widely acknowledged as a primary innate immune organ that harbors a diverse range of innate immune cells, including neutrophils, Kupffer cells and macrophages [20]. Among them, neutrophils are typically recruited to the damaged liver and serve as initial responders, clearing apoptotic hepatocytes [21]. In the context of MASLD, neutrophils have been identified as key mediators in the pathogenesis of liver steatosis, inflammation, and fibrosis due to their multifaceted roles [22]. The results of animal studies demonstrated that the removal of neutrophils by a specific antibody (1 A8 targeting the Ly6G molecule) led to a significant reduction in body weight, blood glucose levels and hepatic triglyceride accumulation in mice with MASLD [23]. Moreover, the absence of neutrophil chemotactic compounds (IL-8, IL-18, IL-17, CCL3, CCL4 and CXCL2) resulted in a reduction in the progression of liver fibrosis in mice [24].

The MASLD is characterized by the intracellular accumulation of lipotoxic lipids within hepatocytes, which in turn triggers the release of neutrophil chemoattractants such as TNF, IL-1β, and IL-6 [25]. These cytokines play crucial roles in modulating neutrophil activity and are instrumental in the pathogenesis of MASLD. This dysfunction subsequently allows for the infiltration of immune cells into the liver, including neutrophils, which in turn secrete serine proteases and cytokines. These mediators activate hepatic macrophages via a Toll-like receptor 4-dependent pathway [26]. Moreover, the release of signaling molecules from death receptors on hepatocytes, including TRAIL-R1, TRAIL-R2, and TNFR1, may contribute to the exacerbation of hepatocyte apoptosis and inflammation [27]. This activation cascade involves the production of mediators such as galectin-3, which stimulate the activation of hepatic stellate cells and result in excessive deposition of the extracellular matrix and collagen. Additionally, neutrophils are involved in the transition from MASLD to MASH by engaging in cross-talk with macrophages, which contributes to portal tract inflammation, endotoxemia, and insulin resistance [26, 28]. MASH represents a progressive stage of MASLD that markedly elevates the risk of end-stage liver disease and the occurrence of extrahepatic complications [3]. Consequently, neutrophil engagement in MASH markedly increases the incidence of end-stage liver disease and associated systemic disorders in patients with MASLD [29].

HDL-C is renowned for its role in reverse cholesterol transport, facilitating the removal of cholesterol from peripheral tissues [30]. Current evidence suggests that reduced HDL-C levels or impaired HDL functionality are linked to the development of MASLD [31]. Lipidomic research has revealed compositional changes in the serum HDL of MASLD patients, which correlate with hepatocyte ballooning [32]. HDL-C contributes to cholesterol metabolism by transferring cholesterol from arterial walls to the liver, potentially reducing atherosclerosis in MASLD patients. Moreover, HDL-C is involved in triglyceride metabolism, with lower plasma HDL-C levels inversely correlated with triglyceride levels. HDL-C also exhibits potent anti-inflammatory and antioxidant effects, inhibiting proinflammatory cytokines (e.g., TNF-α and IL-6) and reducing the expression of adhesive molecules [33]. Additionally, elevated plasma HDL-C levels have been shown to enhance the homeostasis model assessment of insulin resistance, indicating a reduction in insulin resistance [34]. Our research provides complementary evidence regarding the association between

low plasma HDL-C levels and MASLD. However, our subgroup analysis of MASLD patients with ALF revealed no significant difference in plasma HDL-C levels between those with and without ALF, suggesting that the relationship between HDL-C and the severity of liver fibrosis in MASLD warrants further exploration.

The findings of numerous studies have consistently demonstrated increased susceptibility to atherosclerosis and arteriovenous thrombosis in individuals suffering from MASLD. This elevated vulnerability is associated with abnormalities in coagulation factors, fibrinolytic activities, and dysfunction of the endothelium and platelets [35]. In the initial stages of MASLD, the PLT is identified as a marker of both coagulative and inflammatory processes [18]. A clinical investigation demonstrated that antiplatelet treatment could mitigate the severity of fatty liver disease, indicating that platelet aggregation is a probable therapeutic target for MASH [36]. In particular, recent studies suggest that lipopolysaccharide-induced platelet-associated intrahepatic thrombosis may be a mechanism involved in the hepatic inflammatory process [37]. The regular intake of aspirin has been associated with a reduction in the histological characteristics of MASLD and MASH, as well as a decreased likelihood of progression to severe fibrosis. Furthermore, platelets participate in the recruitment of immune cells through CD44 and GPIba, which contributes to the inflammatory environment [36]. In the context of MASLD, the interaction between platelet-derived growth factor-β (PDGF-β) and von Willebrand factor at the platelet surface has been implicated in the stimulation of hepatic stellate cell activation, thereby contributing to the exacerbation of liver fibrotic processes. Antiplatelet intervention or selective inhibition of PDGF-β may prove to be an effective means of reducing biliary fibrosis in patients with liver disease [38]. Nevertheless, the involvement of platelets in MASLD is multifaceted. In addition to promoting fibrosis, platelets can also repress the proliferation of hepatocellular carcinoma cells in NAFLD mice, a process mediated by P2Y12-dependent CD40L release [39]. This biphasic role of platelets, both in promoting fibrosis and inhibiting tumorigenesis, emphasizes the importance of a comprehensive understanding of platelet functionality within the framework of liver pathology. In the research, it was observed that NPR, rather than NHR, emerged as an independent risk factor for predicting all-cause mortality in MASLD patients. NPR, by incorporating both neutrophil and platelet counts, provides a composite measure that might better capture the balance between inflammatory and hemostatic activities in the body. In contrast, NHR that incorporates HDL levels may not reflect the inflammatory burden as directly as NPR does.

The present investigation presents preliminary evidence of the negative correlation between the SII, SIRI, and MASLD and ALF. Notably, recent findings have identified the SII as an independent predictor of hepatic steatosis and overall mortality in patients affected by MASLD [40]. Conversely, an analysis of the NHANES 2017–2020 dataset did not reveal a significant correlation between the SII and hepatic fibrosis, as determined by liver stiffness measurements via FibroScan. Importantly, this analysis did not adjust for body weight, which could have led to a type II error due to its potential as a confounding factor [41]. Lymphocytes included in the denominator of both the SII and the SIRI appear to contribute to fibrosis in MASLD patients, suggesting that lymphocytes participate in hepatic fibrosis in MASLD patients as chronic inflammatory cells. While our study suggests a promotional role of lymphocytes in liver fibrosis, it is important to acknowledge the complexity of lymphocyte subtypes. Further research is warranted to explore the specific subsets of lymphocytes that may be involved in the fibrotic process and to clarify their mechanisms of action.

The present investigation is distinguished by several noteworthy merits. Initially, the sample population was selected from a national survey encompassing adult residents of the United States, forming a prospective cohort study with a considerable sample size. Moreover, this research represents a pioneering endeavor to meticulously examine the relationships between neutrophil-associated inflammatory markers and MASLD, ALF, and overall mortality. Third, we employed multiple regression models, adjusting for various potential confounding factors, thereby confirming the independence of the correlations between the indices and the outcomes. Subsequently, exhaustive subgroup analyses and sensitivity assessments were executed to corroborate the reliability of the results and to delineate a more specific target demographic.

However, it is essential to recognize the limitations of this study. In the initial stages of the study, the diagnosis of MASLD and ALF was based on biochemical assessments rather than histological examination via liver biopsy. Moreover, the exclusion of participants with incomplete data during the analytical phase may have introduced selection bias. Additionally, the present study did not include an analysis of subjects under the age of 20. Another limitation arises from the inclusion of individuals with MetALD. Although only a small number of participants (59 out of 2671 MASLD patients) met the diagnostic criteria for MetALD, and therefore it was not feasible to form a separate subgroup for analysis, this aspect remains a potential confounding factor. MetALD, as a distinct subtype of MASLD, warrants further investigation, particularly as

its effects may differ from those of non-alcoholic forms of liver disease. Finally, while the analytical model incorporated a multitude of potential confounding variables, the presence of unascertained confounders remains an inevitable concern. Therefore, it is imperative that the inferences drawn from this investigation be regarded with a degree of circumspection. Subsequent studies should encompass a more extensive and varied patient population to corroborate and expand upon the current findings, thereby enhancing the validity and generalizability of the research outcomes. Despite its limitations and shortcomings, our study has considerable clinical significance. MASLD, as an underlying disease with a high prevalence, has a significant effect on the health of community populations. Neutrophil-associated inflammatory markers include several simple and effective hematological markers that can be used as direct and effective indicators for primary care physicians to assess MASLD and ALF. The study focused on two conditions: MASLD and ALF. A multicenter prospective cohort study in a subspecies population is anticipated to be conducted in the future. The objective of this study was to identify reliable and readily available hematological parameters for the follow-up of patients with MASLD through the routine testing of cell counts in patients'blood.

Conclusion

In summary, neutrophil-related inflammatory markers are significantly and independently linked to the presence of MASLD and ALF. Furthermore, our findings suggest that higher NPRs are independently correlated with an elevated risk of mortality from all causes in patients with MASLD. These findings underscore the potential importance of these inflammatory biomarkers in the clinical management of liver conditions.

Abbreviations

MASLD	Metabolic dysfunction-associated steatotic liver disease
ALF	Advanced liver fibrosis
NAFLD	Nonalcoholic fatty liver disease
NPR	Neutrophil-to-platelet ratio
HDL-C	High-density lipoprotein cholesterol
NHR	Neutrophil-to-HDL-C ratio
SII	Systemic immune-inflammation index
SIRI	Systemic inflammatory response index
NHANES	National Health and Nutrition Examination Survey
NDI	National death index
US-FLI	The United States fatty liver index
BMI	Body mass index
T2DM	Type 2 diabetes mellitus
MetALD	Metabolic-associated Alcoholic Liver Disease
NFS	NAFLD Fibrosis Score
FIB-4	Fibrosis-4 score
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
AUC	Area under the curve
MASH	Metabolic dysfunction associated steatohepatitis
PDGF-β	Platelet-derived growth factor-β

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12963-025-00378-w.

Additional file 1.

Acknowledgements

We sincerely thank the teams involved in the National Health and Nutrition Examination Survey for their valuable data provision.

Author contributions

Dan Ye (Conceptualization, Resources, Data Curation, Methodology, Formal Analysis, Investigation, Software, Writing—Original Draft Preparation, Visualization, Project Administration). Xueying Ji (Conceptualization, Resources, Methodology, Formal Analysis, Software, Writing—Original Draft Preparation, Visualization). Yiming Ma (Conceptualization,Resources,Data Curation, Methodology, Writing Original Draft, Visualization). Jiaheng Shi(Data Curation, Methodology, Investigation). Jiaofeng Wang(Data Curation, Methodology, Investigation). Jie Chen (Validation and Supervision). Xiaona Hu (Funding Acquisition, Writing—Review & Editing, Validation, Supervision, Project Administration). Zhijun Bao (Funding Acquisition, Writing—Review, Validation, Supervision).

Funding

This research was funded by the National Key R&D Program of China (2018YFC2002000), the National Natural Science Foundation of China (82071581), Shanghai Outstanding Young Medical Personnel Training Program & Excellence Project of the Shanghai Municipal Health Commission (20224Z0009), the Shanghai Municipal Health Commission (JKKPYL-2022–15), the Key Specialization Diseases Construction of Huadong Hospital (ZDZB2225) and the Key Discipline Projects of Huadong Hospital (LCZX2202).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

National Center for Health Statistics Ethics Review Board (Protocol #2005–06, Protocol #2011–17, Protocol #2018–01).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 3 December 2024 Accepted: 3 April 2025
Published online: 25 April 2025

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