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Frontiers in Preventive Medicine

Journal homepage: https://www.fpmjournal.org/

Original Research

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# Systemic Inflammatory Response Index (SIRI) is associated with all-cause mortality and cardiovascular mortality among individuals with Nonalcoholic Fatty Liver Disease (NAFLD): evidence from NHANES (1999-2018)

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ARTICLE INFO

*Article history:*
Received 08 December 2025
Accepted 21 December 2025

Keywords:
SIRI;
NAFLD;
NHANES;
Inflammation;
Mortality

ABSTRACT

**Background:** Nonalcoholic fatty liver disease (NAFLD) is an increasingly prevalent global health concern, with systemic inflammation significantly contributing to disease progression and related cardiovascular complications. The systemic inflammatory response index (SIRI), which combines neutrophil, monocyte, and lymphocyte counts, has been associated with negative outcomes in various diseases. Nevertheless, the connection between the SIRI and mortality in NAFLD patients has yet to be thoroughly investigated. **Objective:** This study aimed to examine the associations between the SIRI and all-cause and cardiovascular disease (CVD) mortality in a large cohort of NAFLD patients. **Methods:** Data were analyzed from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2018, including 5,179 individuals diagnosed with NAFLD. Kaplan-Meier (KM) survival curves, restricted cubic spline (RCS) analysis and Cox proportional hazard models were used to assess the relationship between the SIRI and mortality. Receiver operating characteristic (ROC) curves were used to explore the prognostic value of SIRI. Sensitivity analysis was performed to enhance the robustness of the results. **Results:** Over a median follow-up of 109 months, 898 participants died, 310 of whom died from CVD. Participants who experienced mortality had higher levels of SIRI in the baseline. KM survival analysis revealed that participants in the highest SIRI quartile (Q4) had significantly worse survival outcomes than those in Q1 (log-rank test, $P < 0.001$). The multivariable-adjusted Cox regression models demonstrated that higher SIRI levels were independently associated with increased risks of all-cause mortality (HR per unit increase = 1.20; 95% CI: 1.09-1.32) and CVD mortality (HR per unit increase = 1.17; 95% CI: 1.02-1.35). Compared with those SIRI levels in Q1, participants in Q4 had a 57% higher risk of all-cause mortality (HR = 1.57; 95% CI: 1.17-2.10) and an 81% greater risk of CVD mortality (HR = 1.81; 95% CI: 1.07-3.07) compared to those in Q1. ROC curve analysis yielded an area under the curve (AUC) of 0.622 for predicting all-cause mortality and 0.625 for predicting CVD mortality. **Conclusion:** The SIRI is a robust and independent predictor of all-cause and CVD mortality in NAFLD patients. These findings underscore the importance of systemic inflammation in NAFLD progression.



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ISSN: 3068-9376/ 
http://dx.doi.org/10.64904/fpm2026.01.003

## 1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has emerged as a major global health concern, with its prevalence rising dramatically from 25.5% before 2005 to 37.8% in 2016 or later, making it one of the most common liver disorders worldwide [1][2][3][4]. NAFLD encompasses a spectrum of liver conditions characterized by the excessive accumulation of fat in the liver in individuals who consume little to no alcohol and do not have other specific hepatic disorders [5][6]. The strong association between NAFLD and metabolic abnormalities, including obesity, type 2 diabetes, and dyslipidemia, has led to its classification as a multisystem disease with significant clinical implications [7]. Notably, NAFLD is associated with increased risks of both all-cause and cardiovascular disease (CVD) mortality, underscoring the critical need for effective risk stratification to guide patient management and improve long-term outcomes [8].

Systemic inflammation is a key driver of NAFLD pathogenesis and progression, playing a central role in the transition from simple steatosis to more severe stages, such as nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma [9][10]. Chronic low-grade inflammation contributes to both hepatic and extrahepatic complications and CVD, which is the leading cause of death among patients with NAFLD [11]. Understanding the inflammatory burden in these individuals is critical for predicting disease progression and guiding therapeutic interventions.

The systemic inflammatory response index (SIRI), a novel composite index, integrates three independent white blood cell subsets [12], which was initially used for the assessment of tumor prognosis [13]. Emerging evidence has demonstrated the predictive value of SIRI in unfavourable outcomes in acute coronary syndrome and cardiovascular event mortality [14][15]. More importantly, several recent findings have shown that SIRI is significantly associated with NAFLD, indicating a potential role of SIRI in NAFLD prognostic. Elevated SIRI levels have been reported to be associated with increased systemic inflammation, a key driver in NAFLD pathogenesis, and have been linked to the progression from simple steatosis to NASH and fibrosis [16]. Additionally, higher SIRI levels have been correlated with an increased risk of cardiovascular complications, which are common in NAFLD patients [17]. These findings indicate that SIRI reflects the inflammatory burden of NAFLD and may provide valuable insights into predicting disease progression and cardiovascular risk. However, the relationship between SIRI and mortality risk in NAFLD patients remains unexplored. Given the heterogeneity in the clinical course and outcomes of NAFLD, understanding how SIRI is associated with all-cause and CVD mortality in this population may provide novel insights into disease prognosis and identify potential targets for therapeutic intervention.

To assess the associations between the SIRI and both all-cause mortality and CVD mortality in a cohort of individuals with NAFLD, we utilized data from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2018. In the present study, we conducted a comprehensive analysis of SIRI levels in relation to mortality outcomes.

## 2. Methods

### *2.1. Study Design and Population*

This study utilized data from the NHANES, conducted by the National Center for Health Statistics (NCHS), to collect cross-sectional, nationally representative information on the health and nutritional status of the civilian, non-institutionalized population in the United States. Data were collected from ten NHANES cycles spanning from 1999 to 2018. The NHANES employs a complex, multistage probability sampling design to ensure a representative cohort. All study protocols received approval from the NCHS Research Ethics Review Board, and informed consent was obtained from all participants.

From the NHANES cycles between 1999 and 2018, individuals were initially screened based on the availability of data on demographic information, complications, anthropometrics, and laboratory measurements necessary for NAFLD patients. Eligible participants included those 18 years and older who exhibited no evidence of other liver diseases, including viral hepatitis, as indicated by a positive hepatitis B surface antigen or a positive hepatitis C virus antibody RNA. Additionally, individuals who consumed alcohol heavily, defined as consuming ≥4 drinks per day for men and ≥3 drinks per day for women, were also excluded. Furthermore, participants with cancer, rheumatic immune diseases, missing data for the SIRI index and those who were pregnant were excluded from the study. Finally, those lost to follow-up from 1999 to December 31, 2019, were also excluded from the final analysis (**Figure 1**).

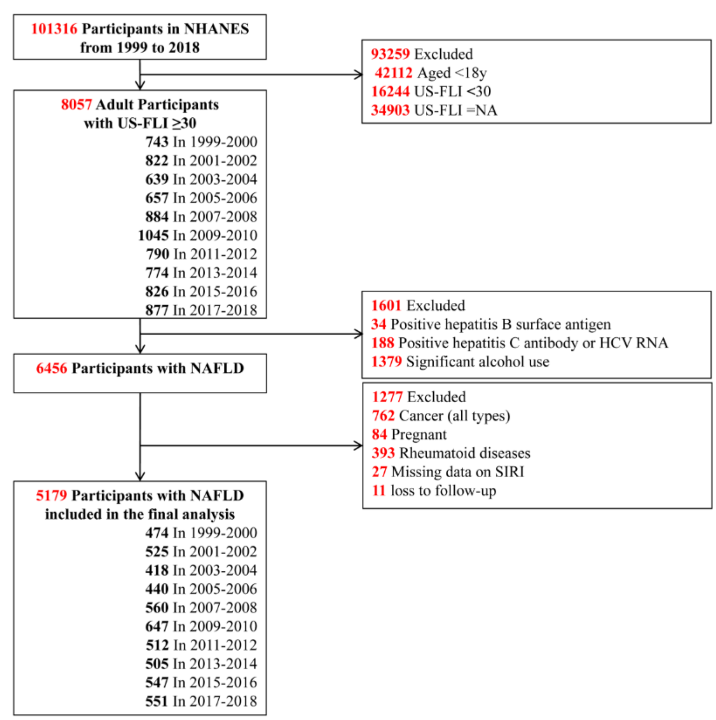


**Fig. 1 - Flowchart Illustrating Selection of the Study Population in NHANES From 1999 to 2018**

### *2.2. Definition of the SIRI and NAFLD*

The SIRI was assessed as both a continuous variable and a categorical variable as quartiles (Q1-Q4) to examine its relationship with mortality risk in NAFLD patients. SIRI is calculated based:

$$\text{SIRI}=\frac{\text{Neutrophil count}\times\text{Monocyte count}}{\text{Lymphocyte count}}$$

NAFLD was defined using the United States Fatty Liver Index (usFLI), a validated noninvasive scoring system developed to estimate the presence of hepatic steatosis in large epidemiological studies[18]. Individuals with an usFLI ≥30 were defined as NAFLD. The usFLI is calculated based on a combination of anthropometric and laboratory measures, as follows:

$$\text{usFLI} = \frac{e^y}{1+e^y} \times 100$$

y = (-0.8073 × non-Hispanic Black + 0.3458 × Mexican American) + (0.0093 × age) + (0.6151 × $\log_e$ γ glutamyltransferase) + (0.0249 × waist circumference) + (1.1792 × $\log_e$ insulin) + (0.8242 × $\log_e$ glucose) - 14.7812.

### *2.3. Outcome Measurements*

The primary outcomes of this study were all-cause mortality and CVD mortality, which were determined through linkage to the National Death Index(NDI)(https://ftp.cdc.gov/pub/Health_Statistics/NCHS/datalinkage/linked_mortality/), with follow-up extending to December 31, 2019. All-cause mortality encompassed deaths from any cause, while CVD mortality was identified using International Classification of Diseases, 10th Revision (ICD-10) codes, including I00-I09, I11, I13, I20-I51, and I60-I69, which correspond to various cardiovascular conditions such as hypertensive, ischemic, and cerebrovascular diseases [19].

### ***2.4.*** *Missing Data Handling*

In this study, multiple imputation was employed to address missing data for variables with less than 10% missing data, ensuring robust analysis and minimizing bias. The variable with the highest percentage of missing data was poverty (9.19%), followed by LDL (7.36%) and BMI (0.76%). Additional variables with missing values included AST (0.14%), ALT (0.12%), TG (0.08%), and HDL (0.02%), whereas other variables had no missing data. Multiple imputation by chained equations (MICE) was used to impute missing values, preserving relationships between variables. Five imputed datasets were generated for subsequent analysis, ensuring accuracy and reducing potential bias.

### *2.5. Covariate Assessment*

The covariates used in this study included age, sex, education, ethnicity, marital status, current smoking status, body mass index (BMI), waist circumference, poverty income ratio (PIR), diabetes (DM), hypertension, antidiabetic drugs, antihyperlipidemic drugs, antihypertensive drugs, glucose (Glu), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), estimated glomerular filtration rate (eGFR), lymphocyte count (LYM), monocyte count (Mono), neutrophil count (Neu), and platelet count (PLT).

Age was considered both as a continuous and categorical variable. As a categorical variable, it was grouped into three age ranges: 18-39 years, 40-59 years, and 60 years and older. Ethnicity was classified into four groups: non-Hispanic white, Mexican American, non-Hispanic black, and other races. Educational levels were divided into three categories: ≤high school, college, and >college. Current smoking status was defined as 100 cigarettes in a lifetime and smoke some days or every day now. BMI categories followed WHO guidelines: non-obese (< 30.0 kg/m$^2$) and obese (≥ 30.0 kg/m$^2$).

Diabetes was diagnosed on the basis of the following criteria: (1) doctor told you have diabetes; or (2) glycohemoglobin HbA1c(%) ≥ 6.5; or (3) fasting glucose (mmol/l) ≥ 7.0; or (4) random blood glucose (mmol/l) ≥ 11.1; or (5) two-hour OGTT blood glucose (mmol/l) ≥ 11.1; or (6) use of diabetes medi4cation or insulin. Hypertension was diagnosed on three separate occasions on the basis of the following criteria: (1) physician-diagnosed history; (2) use of hypertension medication; (3) systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

Medication use (antihypertensive, antidiabetic, or antihyperlipidemic drugs) was recorded based on participant self-reports. Key laboratory variables, such as Glu, HDL, LDL, TG, ALT, AST, LYM, Mono, Neu and PLT, were derived from NHANES laboratory data.

### ***2.6. Statistical Analysis***

In this study, we utilized data from the NHANES cohort from 1999 to 2018 (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx), incorporating sample weights, pseudo-primary sampling units (PSUs), and pseudo-strata (sdmvstra) to account for the complex, stratified, multistage sampling design used in NHANES. Following NHANES guidelines, sample weights were calculated as 2/10WTMEC4YR for the 1999-2002 cycles and 1/10WTMEC2YR for the 2003-2018 cycles. This approach ensured that our analyses accurately reflected population estimates while addressing the sampling design.

Continuous variables conforming to normal distribution were expressed as mean [standard error (SE)], and measurement data with skewed distribution were expressed as median [interquartile range (IQR)]. Categorical variables were described as frequencies and percentages (%). Analysis of variance (ANOVA) and tests were used for group comparisons.

Kaplan-Meier (KM) survival curves were generated to assess survival probabilities across stratified quartiles of the SIRI, and log-rank tests were conducted to evaluate the differences in survival among quartiles. The KM curves were plotted separately for all-cause mortality and CVD mortality, facilitating a direct comparison of cumulative survival rates over time among the different SIRI quartiles.

To evaluate the independent associations of SIRI with mortality outcomes, both linear and non-linear associations of SIRI with mortality outcomes were first examined with a restricted cubic spline (RCS) with 3 knots at the 10th, 50th and 90th percentiles fitted in the multivariable Cox regression model. Four models were constructed by adjusting several potential factors that might influence the results with respect to the SIRI and mortality outcomes: (1) The Crude Model included no covariate adjustments. (2) Model 1 was adjusted for age, sex, education, ethnicity, and poverty. (3) Model 2 was further adjusted for smoking status, BMI, hypertension, diabetes, and antidiabetic, antihyperlipidemic, and antihypertensive medications. (4) Model 3 was further adjusted for Glu, LDL, ALT, AST and eGFR. Furthermore, as a categorical variable, the independent associations of SIRI with hazard ratios (HRs) of mortality outcomes were determined with a multivariable Cox regression model adjusted for potential confounders as specified above. Hazard ratios and 95% confidence intervals (CIs) were calculated for continuous SIRI values and quartile-based categories.

Subgroup analyses were performed to assess potential interactions between SIRI and key demographic and clinical factors, attention was given to age (18-39, 40-59 and ≥ 60 years) [20], sex (female and male), hypertension (yes/no), and diabetes (yes/no), BMI (<30.0 kg/m$^2$ and ≥30.0 kg/m$^2$). Likelihood ratio tests were used to assess interactions with the stratification variables.

Two sensitivity analyses were conducted as follows: (1) participants with missing values for any covariates were excluded from a complete-case analysis, ensuring that the primary results were not biased by missing data; (2) participants who died within two years of follow-up were excluded to minimize potential reverse causation bias.

All the statistical analyses were performed using R 4.4.1, with statistical significance defined as a two-tailed *P*-value <0.05.

## 3. Results

### 3.1. Baseline Characteristics of the Study Population

This study included 5,179 participants with confirmed NAFLD (**Table 1**), with a mean age of 50.96 years, of whom 56.26% were male. Participants who experienced all-cause mortality were significantly older, with a mean age of 65.80 years compared to 48.72 years ($P < 0.0001$), and were more likely to be male. Similarly, those who died from CVD were older (mean age 66.83 vs. 50.21 years, $P < 0.0001$). The cohort had a high mean body mass index (BMI) of 34.10 kg/m²; however, BMI was lower among those who died (32.63 kg/m² vs. 34.32 kg/m², $P < 0.0001$). Comorbidities were more prevalent in participants who died for all-cause, with higher rates of diabetes (48.08% vs. 26.21%, $P < 0.0001$) and hypertension (73.01% vs. 51.73%, $P < 0.0001$) compared to survivors. This trend was consistent for CVD mortality, where diabetes (47.75% vs. 28.19%, $P < 0.0001$) and hypertension (78.21% vs. 53.40%, $P < 0.0001$) were also more common. The use of medication was greater among those who died, with increased use of antihypertensive, antidiabetic and antihyperlipidemic drugs.

**Table 1 - Baseline Characteristics of Participants With NAFLD in NHANES 1999 to 2018**

| Variables | Total (n=5179) | All-cause mortality | | | CVD mortality | | |
|---|---|---|---|---|---|---|---|
| | | No (n = 4281) | Yes (n = 898) | *P* value | No (n =4869) | Yes (n = 310) | *P* value |
| Age, y | 50.96(0.32) | 48.72(0.33) | 65.80(0.70) | < 0.0001 | 50.21(0.32) | 66.83(0.98) | < 0.0001 |
| BMI, kg/m$^2$ | 34.10(0.14) | 34.32(0.16) | 32.63(0.28) | < 0.0001 | 34.16(0.15) | 32.81(0.46) | 0.01 |
| Waist, cm | 112.96(0.32) | 113.07(0.35) | 112.23(0.65) | 0.25 | 112.96(0.34) | 112.92(1.10) | 0.97 |
| Poverty income ratio | 2.99(0.04) | 3.06(0.04) | 2.57(0.07) | < 0.0001 | 3.00(0.04) | 2.75(0.11) | 0.03 |
| Sex, n(%) | | | | 0.39 | | | 0.17 |
| Female | 2363(43.74) | 1996(44.00) | 367(42.01) | | 2243(43.95) | 120(39.26) | |
| Male | 2816(56.26) | 2285(56.00) | 531(57.99) | | 2626(56.05) | 190(60.74) | |
| Current Smoking, n(%) | | | | 0.02 | | | 0.13 |
| no | 4454(85.34) | 3690(85.86) | 764(81.88) | | 4185(85.54) | 269(81.11) | |
| yes | 725(14.66) | 591(14.14) | 134(18.12) | | 684(14.46) | 41(18.89) | |
| Level of education, n(%) | | | | < 0.0001 | | | < 0.001 |
| <=High school | 2969(46.07) | 2350(43.74) | 619(61.47) | | 2759(45.40) | 210(60.05) | |
| College | 1336(31.50) | 1148(32.17) | 188(27.02) | | 1278(31.86) | 58(23.75) | |
| >College | 874(22.44) | 783(24.09) | 91(11.51) | | 832(22.73) | 42(16.19) | |
| Ethnicity, n(%) | | | | < 0.0001 | | | 0.004 |
| Mexican American | 1415(11.55) | 1209(12.42) | 206( 5.80) | | 1348(11.82) | 67( 6.02) | |
| Non-Hispanic Black | 643( 6.46) | 537(6.47) | 106(6.38) | | 600(6.39) | 43(7.88) | |
| Non-Hispanic White | 2209(70.10) | 1703(68.73) | 506(79.20) | | 2038(69.75) | 171(77.57) | |
| Other Race | 912(11.88) | 832(12.38) | 80( 8.62) | | 883(12.04) | 29( 8.53) | |
| Marital, n(%) | | | | 0.05 | | | 0.08 |
| Married | 2947(61.41) | 2468(62.06) | 479(57.09) | | 2790(61.69) | 157(55.47) | |
| others | 2232(38.59) | 1813(37.94) | 419(42.91) | | 2079(38.31) | 153(44.53) | |
| DM, n(%) | | | | < 0.0001 | | | < 0.0001 |
| no | 3374(70.92) | 2936(73.79) | 438(51.92) | | 3220(71.81) | 154(52.25) | |
| yes | 1805(29.08) | 1345(26.21) | 460(48.08) | | 1649(28.19) | 156(47.75) | |
| Hypertension, n(%) | | | | < 0.0001 | | | < 0.0001 |
| no | 2326(45.47) | 2094(48.27) | 232(26.99) | | 2263(46.60) | 63(21.79) | |
| yes | 2853(54.53) | 2187(51.73) | 666(73.01) | | 2606(53.40) | 247(78.21) | |
| Antidiabetic drugs, n(%) | | | | < 0.0001 | | | < 0.0001 |
| no | 4165(83.48) | 3543(85.28) | 622(71.59) | | 3955(84.14) | 210(69.55) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| yes | 1014(16.52) | 738(14.72) | 276(28.41) | | 914(15.86) | 100(30.45) | |
| Antihyperlipidemic drugs, n(%) | | | | < 0.0001 | | | < 0.0001 |
| no | 3808(72.85) | 3254(75.07) | 554(58.15) | | 3624(73.76) | 184(53.73) | |
| yes | 1371(27.15) | 1027(24.93) | 344(41.85) | | 1245(26.24) | 126(46.27) | |
| Antihypertensive drugs, n(%) | | | | < 0.0001 | | | < 0.0001 |
| no | 4419(85.71) | 3785(88.27) | 634(68.75) | | 4212(86.72) | 207(64.50) | |
| yes | 760(14.29) | 496(11.73) | 264(31.25) | | 657(13.28) | 103(35.50) | |
| Glu, mmol/L | 6.30(0.04) | 6.17(0.04) | 7.15(0.14) | < 0.0001 | 6.27(0.04) | 7.10(0.21) | < 0.001 |
| HDL, mmol/L | 1.18(0.01) | 1.18(0.01) | 1.21(0.01) | 0.06 | 1.18(0.01) | 1.21(0.02) | 0.33 |
| LDL, mmol/L | 3.09(0.02) | 3.12(0.02) | 2.93(0.04) | < 0.0001 | 3.10(0.02) | 2.88(0.08) | 0.01 |
| TG, mmol/L | 2.02(0.03) | 2.01(0.03) | 2.07(0.06) | 0.37 | 2.02(0.03) | 2.06(0.08) | 0.65 |
| ALT, U/L | 32.27(0.67) | 32.64(0.36) | 29.86(4.34) | 0.52 | 32.64(0.70) | 24.55(0.96) | < 0.0001 |
| AST, U/L | 26.88(0.26) | 27.03(0.29) | 25.92(0.51) | 0.06 | 26.98(0.28) | 24.83(0.66) | 0.005 |
| eGFR, $ml\cdot min^{-1}\cdot(1.73m^2)^{-1}$ | 91.48(0.43) | 94.11(0.45) | 74.05(1.08) | < 0.0001 | 92.40(0.43) | 72.03(1.81) | < 0.0001 |
| LYM, 10^9/L | 2.12(0.01) | 2.14(0.01) | 2.00(0.04) | < 0.001 | 2.13(0.01) | 1.94(0.04) | < 0.0001 |
| Mono, 10^9/L | 0.58(0.00) | 0.57(0.00) | 0.62(0.01) | < 0.0001 | 0.57(0.00) | 0.61(0.02) | 0.06 |
| Neu, 10^9/L | 4.41(0.03) | 4.36(0.03) | 4.71(0.09) | < 0.001 | 4.39(0.03) | 4.70(0.11) | 0.01 |
| PLT, 10^9/L | 254.79(1.32) | 256.67(1.49) | 242.35(3.24) | < 0.001 | 255.45(1.37) | 240.95(5.27) | 0.01 |
| SIRI | 1.30(0.01) | 1.25(0.01) | 1.63(0.05) | < 0.0001 | 1.29(0.01) | 1.61(0.07) | < 0.0001 |
| SIRIQ4, n(%) | | | | < 0.0001 | | | < 0.0001 |
| Q1 | 1295(22.08) | 1153(23.35) | 142(13.67) | | 1249(22.59) | 46(11.28) | |
| Q2 | 1299(25.38) | 1126(26.53) | 173(17.76) | | 1246(25.88) | 53(14.87) | |
| Q3 | 1288(25.21) | 1053(25.08) | 235(26.07) | | 1197(24.99) | 91(29.98) | |
| Q4 | 1297(27.33) | 949(25.04) | 348(42.50) | | 1177(26.55) | 120(43.87) | |

Laboratory markers revealed worse metabolic and inflammatory profiles in participants who experienced all-cause and CVD mortality. Glucose levels were significantly elevated in both mortality groups (7.15 mmol/L vs. 6.17 mmol/L, $P < 0.0001$ for all-cause mortality; 7.10 mmol/L vs. 6.27 mmol/L, $P < 0.001$ for CVD mortality). Lipid profiles indicated LDL levels decreased in those who died (2.93 mmol/L vs. 3.12 mmol/L, $P < 0.0001$ for all-cause mortality; 2.88 mmol/L vs. 3.10 mmol/L, $P = 0.01$ for CVD mortality), while HDL levels showed no significant differences. The levels of liver function markers, including ALT and AST levels, were elevated among those who died.

Notably, inflammatory markers were also significantly greater in participants with primary outcomes, with elevated neutrophil and monocyte counts, contributing to higher SIRI values (1.63 vs. 1.25, $P < 0.0001$ for all-cause mortality; 1.61 vs. 1.29, $P < 0.0001$ for CVD mortality).

### *3.2. The association of SIRI and Mortality Outcomes*

During a median follow-up period of 109 months (interquartile range 57-164 months), 898 subjects died for any reason, and among them, 310 died from CVD. The Kaplan-Meier survival curves **(Figure 2)** revealed the potential association of SIRI with all-cause and CVD mortality stratified by SIRI quartiles. Resutls showed that participants in the highest SIRI quartile (Q4) exhibited significantly lower survival probabilities compared to those in the lower quartiles (Q1-Q3). The log-rank test confirmed significant differences in survival distributions across SIRI quartiles ($P < 0.001$ for both all-cause and CVD mortality). The curves suggest a dose-response relationship, with progressively shorter survival times associated with higher SIRI levels.

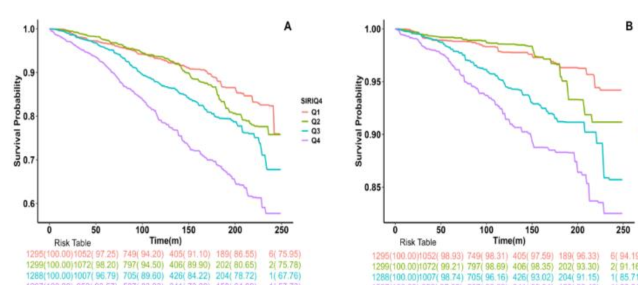


**Fig. 2 - Kaplan-Meier survival curve for All-Cause and CVD Mortality Among Individuals With NAFLD. (A) Kaplan-Meier survival curve for All-Cause Mortality; (B) Kaplan-Meier survival curve for CVD Mortality.**

In the RCS analysis, as a continuous variable, there was no evident nonlinear association between SIRI and all-cause mortality ($P = 0.342$ for nonlinear), but a nonlinear association with CVD mortality ($P = 0.022$ for nonlinear) (**Figure 3-4**). Nontheless, SIRI demonstrated a significant dose-response association with all-cause mortality (HR per unit increase = 1.20; 95% CI: 1.09-1.32) and CVD mortality (HR per unit increase = 1.17; 95% CI: 1.02-1.35) before and after multivariable adjusted ($P$ <0.05).

Furthermore, as a categorical variable, SIRI also demonstrated significant association with mortality outcomes. **Table 2** outlines the HRs for all-cause and CVD mortality across SIRI quartiles, adjusted for relevant covariates in sequential models. Higher SIRI quartiles were significantly associated with an increased risk of all-cause and CVD mortality. For all-cause mortality, individuals in the highest SIRI quartile (Q4) had a significantly increased risk in the fully adjusted model (Model 3), with an HR of 1.57 (95% CI: 1.17-2.10; *P* for trend <0.001) compared to those in the lowest quartile (Q1). Furthermore, SIRI as a continuous variable demonstrated a significant association with all-cause mortality (HR per unit increase = 1.20; 95% CI: 1.09-1.32). A similar pattern was observed for CVD mortality, where participants in the highest SIRI quartile (Q4) had an HR of 1.81 (95% CI: 1.07-3.07) compared to the lowest quartile, after full adjustment. The increasing trend in HRs across SIRI quartiles (*P* for trend <0.001 for all-cause mortality and *P* = 0.01 for CVD mortality) indicates that higher SIRI levels are associated with increased mortality risk.

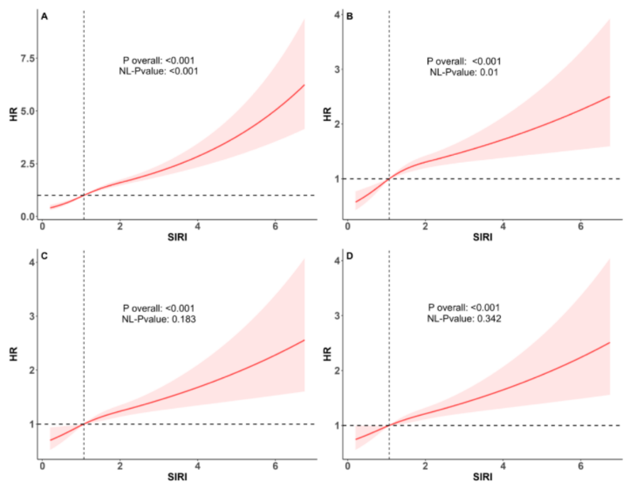


**Fig. 3 - Restricted cubic spline regression analysis for all-cause mortality among individuals with NAFLD. (A) Crudel model: Adjusted for none. (B) Model 1: Adjusted for age, sex, level of education, ethnicity and poverty. (C) Model 2: Adjusted for variables in Model 1 plus current smoking, BMI, hypertension, DM, antidiabetic drugs, antihyperlipidemic drugs and antihypertensive drugs. (D) Model 3: Adjusted for variables in Model 2 plus Glu, LDL, ALT, AST and eGFR. The RCS regression analysis employs the likelihood ratio test and the shaded area represents the 95% CI. NL-P value was obtained from the nonlinear test in RCS analysis. NL-P value indicates significance of non-linear relationships, while P overall assesses overall model significance.**

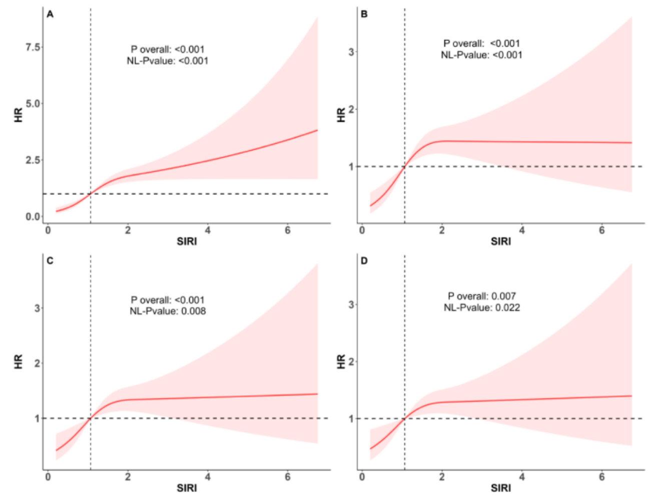


**Fig. 4 - Restricted cubic spline regression analysis for CVD mortality among individuals with NAFLD. (A) Crudel model: Adjusted for none. (B) Model 1: Adjusted for age, sex, level of education, ethnicity and poverty. (C) Model 2: Adjusted for variables in Model 1 plus current smoking, BMI, hypertension, DM, antidiabetic drugs, antihyperlipidemic drugs and antihypertensive drugs. (D) Model 3: Adjusted for variables in Model 2 plus Glu, LDL, ALT, AST and eGFR. The RCS regression analysis employs the likelihood ratio test and the shaded area represents the 95% CI. NL-P value was obtained from the nonlinear test in RCS analysis. NL-P value indicates significance of non-linear relationships, while P overall assesses overall model significance.**

**Table 2 - Hazard Ratios for All-Cause and CVD Mortality Among Participants with NAFLD in NHANES 1999 to 2018**

| NHANES Cohort | SIRI (continuous per 1 unit) | SIRI quartile | | | | |
|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | *P* for trend |
| **All-cause mortality** | | | | | | |
| **crude model[a]** | 1.46(1.35,1.58) | ref | 1.15(0.84,1.56) | 1.69(1.26,2.26) | 2.91(2.19,3.88) | <0.0001 |
| ***P* value** | <0.0001 | | 0.39 | <0.001 | <0.0001 | |
| **Model 1[b]** | 1.23(1.10,1.37) | ref | 1.08(0.81,1.43) | 1.44(1.09,1.89) | 1.88(1.42,2.49) | <0.0001 |
| ***P* value** | <0.001 | | 0.60 | 0.01 | <0.0001 | |
| **Model 2[c]** | 1.21(1.09,1.34) | ref | 1.08(0.81,1.43) | 1.34(1.00,1.79) | 1.64(1.22,2.19) | <0.001 |
| ***P* value** | <0.001 | | 0.60 | 0.05 | <0.001 | |
| **Model 3[d]** | 1.20(1.09,1.32) | ref | 1.07(0.81,1.43) | 1.27(0.94,1.72) | 1.57(1.17,2.10) | <0.001 |
| ***P* value** | <0.001 | | 0.62 | 0.11 | 0.002 | |
| **CVD mortality** | | | | | | |
| **crude model[a]** | 1.45(1.31,1.60) | ref | 1.16(0.70,1.90) | 2.35(1.48,3.72) | 3.61(2.25,5.80) | <0.0001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ***P* value** | <0.0001 | | 0.56 | <0.001 | <0.0001 | |
| **Model 1**[b] | 1.22(1.08,1.38) | ref | 1.10(0.67,1.79) | 1.96(1.25,3.08) | 2.36(1.45,3.85) | <0.0001 |
| ***P* value** | 0.002 | | 0.71 | 0.003 | <0.001 | |
| **Model 2**[c] | 1.19(1.04,1.36) | ref | 1.10(0.68,1.79) | 1.76(1.10,2.82) | 1.96(1.17,3.27) | 0.003 |
| ***P* value** | 0.01 | | 0.70 | 0.02 | 0.01 | |
| **Model 3**[d] | 1.17(1.02,1.35) | ref | 1.10(0.67,1.81) | 1.66(1.02,2.70) | 1.81(1.07,3.07) | 0.01 |
| ***P* value** | 0.03 | | 0.69 | 0.04 | 0.03 | |

[a]Crudel model: Adjusted for none. [b]Model 1: Adjusted for Age, sex, level of education, ethnicity and poverty.

[c]Model 2: Adjusted for variables in Model 1 plus current smoking, BMI, hypertension, DM, antidiabetic drugs, antihyperlipidemic drugs and antihypertensive drugs.

[d]Model 3: Adjusted for variables in Model 2 plus Glu, LDL, ALT, AST and eGFR.

### *3.3. The Prognostic Value of SIRI*

The receiver operating characteristic (ROC) curve serves as an essential instrument for assessing the performance of the SIRI as a prognostic diagnostic tool. **Figure 5** illustrates the ROC curve. The ability of the SIRI to predict all-cause mortality is represented by an area under the curve (AUC) value of 0.622 (95% CI: 0.601, 0.642). Similarly, in relation to CVD mortality, SIRI's predictive performance is characterized by an AUC of 0.625 (95% CI: 0.592, 0.657).

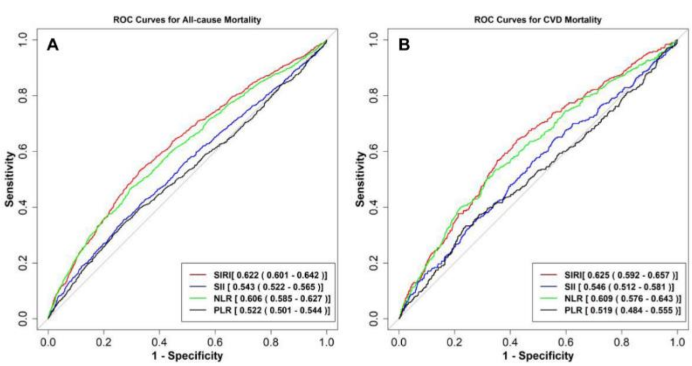


**Fig. 5 - The ROC value of SIRI, SII, NLR, and PLR in predicting outcomes in NAFLD patients. (A) ROC curve analysis of SIRI and all-cause mortality. The AUC of SIRI was 0.622. (B) ROC curve analysis of SIRI and CVD mortality. The AUC of SIRI was 0.625.**

### *3.4. **Subgroup and Sensitivity Analysis***

The associations between elevated SIRI and mortality outcomes varied across demographic and clinical subgroups. The strongest relationship between SIRI and all-cause mortality was observed in participants aged 40 to 59 years (HR: 1.51, 95% CI: 1.22-1.88, $P < 0.001$), with a similar trend noted for CVD mortality in this age group (HR: 1.34, 95% CI: 0.92-1.95, $P = 0.13$). Compared with females, males presented a slightly higher mortality risk associated with SIRI than females. Compared with nonhypertensive participants, hypertensive participants demonstrated a stronger relationship between SIRI and all-cause mortality (HR: 1.34, 95% CI: 1.22-1.47, $P < 0.001$) than those without hypertension (HR: 1.10, 95% CI: 0.93-1.30, $P = 0.35$), with a similar trend observed for CVD mortality in the same group. Participants with diabetes exhibited a lower risk of all-cause mortality (HR: 1.18, 95% CI: 1.03-1.35, $P = 0.02$) compared to non-diabetic participants (HR: 1.30, 95% CI: 1.14-1.49, $P < 0.001$). For CVD mortality, non-diabetic participants exhibited a significantly higher risk (HR: 1.38, 95% CI: 1.18-1.63, $P < 0.001$), with a borderline significant interaction ($P = 0.03$). Additionally, participants with a BMI <30 kg/m$^2$ displayed a more pronounced association between SIRI and mortality outcomes than those with a BMI ≥30 kg/m² **(Figure 6)**.

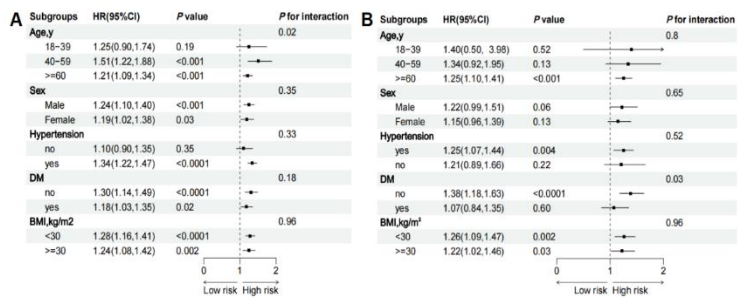


**Fig. 6 - Subgroup analysis and interaction analysis. (A) Subgroup analysis for the association between SIRI and all-cause mortality. (B) Subgroup analysis for the association between SIRI and cardiovascular mortality.**

Two sensitivity analyses were performed to ensure the robustness of the results. In the first analysis, participants with missing values for any covariates were excluded from the complete-case analysis. The findings remained consistent with those of the primary analysis, confirming that missing data did not bias the results. In the second analysis, participants who died within two years of follow-up were excluded to reduce the potential for reverse causation. After excluding early deaths, the associations between elevated SIRI and all-cause and CVD mortality remained significant, though slightly attenuated.

## 4. Discussion

This study demonstrated that the SIRI is a significant predictor of both all-cause and cardiovascular disease (CVD) mortality in individuals with nonalcoholic fatty liver disease (NAFLD). By analyzing data from the NHANES cohort (1999-2018), we observed a stepwise increase in mortality risk with higher SIRI levels, independent of traditional risk factors such as age, sex, BMI, diabetes, and medication use. These findings provide novel insights into the prognostic importance of systemic inflammation in NAFLD and suggest that SIRI, a readily available marker derived from routine blood counts, may serve as a valuable tool for risk stratification in clinical practice.

Numerous investigations have demonstrated that inflammation is crucial to hepatic steatosis and its prognosis. Researchers previously highlighted the potential of the SIRI, which is derived from white blood cell subsets [21], for identifying practical markers for risk stratification in NAFLD, making it an inexpensive and accessible marker that can be easily integrated into routine NAFLD assessments. Moreover, several studies have revealed a robust link between elevated SIRI and increased risks of stroke, myocardial infarction (MI), and all-cause mortality [22][23][24][25][26], underscoring the role of chronic low-grade inflammation in promoting cardiovascular complications and emphasizing that chronic inflammation is not only a hallmark of NAFLD but also contributes to its CVD comorbidities. In our study, we consistently demonstrated that individuals with NALFD in the highest quartile of SIRI had a 57% increased risk of all-cause mortality and an 81% increased risk of CVD mortality, even after adjusting for confounding variables, reinforcing systemic inflammation's role beyond traditional pathways. These findings underscore the crucial role that systemic inflammation plays in driving both liver disease outcomes and cardiovascular health, which is consistent with the growing recognition that inflammation is central to NAFLD progression from steatosis to nonalcoholic steatohepatitis (NASH) [27]. The increased mortality risk suggests that inflammation may mediate the progression from steatosis to advanced liver disease while concurrently promoting atherosclerosis and cardiovascular complications [28][29]. Most importantly, the associations between SIRI and mortality risk, including age, sex, hypertension, diabetes, and obesity, were consistent across subgroups. Thus, systemic inflammation, as captured by SIRI, serves as a valuable predictor of mortality in NAFLD patients.

Interestingly, the associations between SIRI and all-cause mortality and CVD mortality were more pronounced in participants without diabetes compared to those with diabetes. This differential effect could be explained by additional metabolic and inflammatory pathways present in patients with diabetes, such as chronic hyperglycemia, insulin resistance, and advanced glycation end-products, which may modulate the impact of SIRI on mortality outcomes [30]. The use of antidiabetic medications may provide additional benefits for NAFLD patients beyond glycemic control by improving hepatic lipid deposition, reducing inflammation, and attenuating fibrosis [31]. Indeed, studies have shown that certain antidiabetic agents, such as GLP-1 receptor agonists and SGLT2 inhibitors [32], not only improve insulin sensitivity but also have direct effects on hepatic steatosis and inflammation, leading to better overall outcomes in NAFLD patients [33][34]. Furthermore, the higher all-cause mortality in the 40-59 years age group associated with SIRI is noteworthy. Middle-aged individuals often experience the onset or peak of chronic conditions such as cardiovascular disease, diabetes, and NAFLD progression. Systemic inflammation can exacerbate these conditions at this stage, increasing mortality risk [35]. Additionally, lifestyle factors such as stress, poor diet, and physical inactivity, which are common in this age group, contribute to heightened inflammation. In other words, the increased mortality observed in this subgroup needs to be paid more attention to reduce the risk of adverse outcomes.

Our study has several notable strengths. First, this study is the first to demonstrate a significant association between SIRI and both all-cause and CVD mortality in individuals with NAFLD, thereby addressing a critical gap in the literature. Second, the analysis is based on data from the NHANES 1999-2018 cohort, which comprises a large and nationally representative sample, ensuring the robustness and generalizability of the findings. Third, the study incorporates extensive multivariable adjustments, subgroup analysis, and sensitivity analysis, further ensuring the robustness of the findings. However, some limitations are worth mentioning. First, the observational design prevents us from making definitive conclusions about causality, and the potential for residual confounding remains despite rigorous adjustments and sensitivity analysis performed by excluding participants who died within two years of follow-up. Second, SIRI was measured at baseline, and changes over time in inflammatory status were not accounted for, potentially affecting the associations observed. Third, NAFLD diagnosis was based on the usFLI, which, while validated in population studies, lacks the precision of imaging-based or histopathological assessments.

In summary, this study provides compelling evidence that higher SIRI levels are independently associated with increased risks of all-cause and CVD mortality in individuals with NAFLD. These findings underscore the critical role of systemic inflammation in NAFLD prognosis and highlight SIRI as a potentially valuable tool for risk stratification in this population. Future prospective studies and clinical trials are needed to validate the predictive utility of SIRI, explore its relationship with other inflammatory markers, and assess the impact of interventions targeting inflammation on mortality outcomes in NAFLD patients.

## Declaration

### *A.1. Availability of data and materials*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *A.2. Conflict of Interest*

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

### *A.3. Funding*

This work was financially supported by the Guangdong Basic and Applied Basic Research Fund Project (Regional Joint Fund-Youth Fund Project, 2019A1515110583) and Young Scientists Fund of the National Natural Science Foundation of China (82003455). The funders had no role in the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication.

### *A.4. Author Contributions*

YL conceived and designed the study, analyzed data and drafted the manuscript. FJ reviewed the manuscript. YF, YB were invloed in Methodology and checked the full data. All authors were involved in discussing and revising the paper and had final approval of the submitted versions. FJ is the guarantor of this work and, as such, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

### *A.5. Acknowledgements*

The authors gratefully acknowledge the support of the study participants, study staff, and partner organizations participating in the study survey.

## REFERENCES

[1] Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397(10290):2212-2224.

[2] Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11-20.

[3] Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7(9):851-861.

[4] Younossi ZM, Golabi P, Paik JM, et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77(4):1335-1347.

[5] Pouwels S, Sakran N, Graham Y, et al. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. BMC Endocr Disord. 2022;22(1):63.

[6] Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology. 2002;123(1):134-140.

[7] Zou J, Song Q, Shaw PC, et al. Tangerine Peel-Derived Exosome-Like Nanovesicles Alleviate Hepatic Steatosis Induced by Type 2 Diabetes: Evidenced by Regulating Lipid Metabolism and Intestinal Microflora. Int J Nanomedicine. 2024;19:10023-10043.

[8] Park CH, Lim H, Kim YN, et al. Non-alcoholic Fatty Liver Disease (NAFLD) and its association with kidney and cardiovascular outcomes in moderate to advanced chronic kidney disease. Am J Nephrol. 2024;1-23.

[9] Gong H, He Q, Zhu L, et al. Associations between systemic inflammation indicators and nonalcoholic fatty liver disease: evidence from a prospective study. Front Immunol. 2024;15:1389967.

[10] Tilg H, Adolph TE, Dudek M, et al. Non-alcoholic fatty liver disease: the interplay between metabolism, microbes and immunity. Nat Metab. 2021;3(12):1596-1607.

[11] Wong VW, Ekstedt M, Wong GL, et al. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol. 2023;79(3):842-852.

[12] Kivrak A, Yildirim A. Relationship between systemic inflammation indices and time of symptom onset in cardiac remodeling after first ST-segment elevation myocardial infarction. Kardiol Pol. 2023;81(9):886-894.

[13] Gu X, Han X, Shen Y, et al. Prognostic value of systemic inflammation response index in cancer patients treated with PD-1/PD-L1 immune checkpoint inhibitors. J Immunother Cancer. 2024;12(8):e008802.

[14] Liu Z, Ding Y, Liu J, et al. Predictive effect of the systemic inflammation response index (SIRI) on the efficacy and prognosis of neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer. BMC Surg. 2024;24:89.

[15] Dong W, Gong Y, Zhao J, et al. A combined analysis of TyG index, SII index, and SIRI index: positive association with CHD risk and coronary atherosclerosis severity in patients with NAFLD. Front Endocrinol (Lausanne). 2024;14:1281839.

[16] Sun W, Fang Y, Zhou B, et al. The association of systemic inflammatory biomarkers with non-alcoholic fatty liver disease: a large population-based cross-sectional study. Prev Med Rep. 2024;37:102536.

[17] Dong W, Gong Y, Zhao J, et al. A combined analysis of TyG index, SII index, and SIRI index: positive association with CHD risk and coronary atherosclerosis severity in patients with NAFLD. Front Endocrinol (Lausanne). 2023;14:1281839.

[18] Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Aliment Pharmacol Ther. 2015;41(1):65-76.

[19] Ebrahimi R, Yano EM, Alvarez CA, et al. Trends in Cardiovascular Disease Mortality in US Women Veterans vs Civilians. JAMA Netw Open. 2023;6(10):e2340242.

[20] Pan J, Zhou Y, Pang N, et al. Dietary Niacin Intake and Mortality Among Individuals With Nonalcoholic Fatty Liver Disease. JAMA Netw Open. 2024;7(2):e2354277.

[21] Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer. 2016;122(14):2158-2167.

[22] Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822-1832.

[23] Moore KJ. Targeting inflammation in CVD: advances and challenges. Nat Rev Cardiol. 2019;16(2):74-75.

[24] Zhao S, Dong S, Qin Y, et al. Inflammation index SIRI is associated with increased all-cause and cardiovascular mortality among patients with hypertension. Front Cardiovasc Med. 2022;9:1066219.

[25] Liu Z, Zheng L. Associations between SII, SIRI, and cardiovascular disease in obese individuals: a nationwide cross-sectional analysis. Front Cardiovasc Med. 2024;11:1361088.

[26] Jin Z, Wu Q, Chen S, et al. The Associations of Two Novel Inflammation Indexes, SII and SIRI with the Risks for Cardiovascular Diseases and All-Cause Mortality: A Ten-Year Follow-Up Study in 85,154 Individuals. J Inflamm Res. 2021;14:131-140.

[27] Schuster S, Cabrera D, Arrese M, et al. Triggering and resolution of inflammation in NASH. Nat Rev Gastroenterol Hepatol. 2018;15(6):349-364.

[28] Ismaiel A, Dumitrascu DL. How to Reduce Cardiovascular Risk in Nonalcoholic Fatty Liver Disease. Am J Ther. 2023;30(3):e242-e256.

[29] Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. J Hepatol. 2024;73(4):809-824.

[30] Gong M, Wen S, Nguyen T, et al. Converging Relationships of Obesity and Nonalcoholic Fatty Liver Disease With Incident Cardiovascular Disease and Mortality. J Am Heart Assoc. 2024;13(15):e036241.

[31] Zachou M, Flevari P, Nasiri-Ansari N, et al. The role of anti-diabetic drugs in NAFLD. Have we found the Holy Grail? A narrative review. Eur J Clin Pharmacol. 2024;80(1):127-150.

[32] Ong Lopez AMC, Pajimna JAT. Efficacy of sodium glucose cotransporter 2 inhibitors on hepatic fibrosis and steatosis in non-alcoholic fatty liver disease: an updated systematic review and meta-analysis. Sci Rep. 2024;14(1):2122.

[33] Luo C, Lin Y, Zhou W, et al. Survival advantage associated with metformin usage in hepatocellular carcinoma patients with diabetes mellitus receiving radical resection: a propensity score matching analysis. Eur J Gastroenterol Hepatol. 2020;32(8):1030-1035.

[34] Xu F, Li Z, Zheng X, et al. SIRT1 mediates the effect of GLP-1 receptor agonist exenatide on ameliorating hepatic steatosis. Diabetes. 2014;63(11):3637-3646.

[35] Hu Y, Yang Y, Gao Y, et al. The impact of chronic diseases on the health-related quality of life of middle-aged and older adults: the role of physical activity and degree of digitization. BMC Public Health. 2024;24(1):2335.