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The role of the advanced lung cancer inflammation index (ALI) in the risk of liver fibrosis and mortality among US adult MAFLD patients: a cross-sectional study of NHANES 1999–2018

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Abstract

Background Metabolic dysfunction-associated fatty liver disease (MAFLD) is a prevalent chronic liver disease globally, with inflammation and nutrition playing key roles in its progression. The Advanced Lung Cancer Inflammation Index (ALI) is a novel biomarker reflecting nutritional and inflammatory status. This study aims to explore the association between ALI and the risk of liver fibrosis and prognosis in MAFLD patients.

Methods This cross-sectional study analyzed NHANES data from the 1999–2018 on adult participants in the US. Weighted logistic regression assessed the association between ALI and liver fibrosis risk. Mortality outcomes, including all-cause, cardiovascular disease (CVD), and cancer mortality, analyzed using weighted Kaplan-Meier and Cox proportional hazards models. Restricted cubic splines (RCS) and threshold effect analyses were uesd to explore non-linear relationships. Receiver operating characteristic (ROC) curve evaluated the prognostic value of ALI, and stratified analyses examined subgroup differences.

Results A total of 6,858 MAFLD patients (mean age 51.38 ± 17.22 years, 54% male) were included. A non-linear relationship was found between ALI and liver fibrosis risk, with a threshold at 5.68, beyond which the risk increased significantly (OR = 2.35, 95% CI: 1.89–2.95). Stronger associations were observed in subgroups with central obesity and prediabetes (*P* for interaction < 0.05). ALI was inversely associated with all-cause mortality (HR = 0.64, 95% CI: 0.56–0.72) and CVD mortality (HR = 0.57, 95% CI: 0.46–0.65), but not cancer mortality. RCS analysis showed an L-shaped non-linear relationship with all-cause mortality (threshold at 5.36) and a linear relationship with CVD mortality. Low HDL cholesterol and excessive alcohol consumption influenced the association between ALI and all-cause mortality (*P* for interaction < 0.05). ALI demonstrated the highest predictive accuracy for CVD mortality.

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Conclusion ALI is associated with an increased risk of liver fibrosis and reduced all-cause and CVD mortality, highlighting its potential value in assessing MAFLD prognosis, particularly CVD-related mortality.

Keywords Advanced lung Cancer inflammation index (ALI), Metabolic dysfunction-associated fatty liver disease (MAFLD), Cross-sectional study, National health and nutrition examination survey (NHANES), All-cause mortality, Cardiovascular disease (CVD) mortality

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, affecting about 25% of adults [1, 2]. Characterized by hepatic steatosis, NAFLD is closely linked to metabolic syndrome, including obesity, insulin resistance, and dyslipidemia. Over half of NAFLD patients develop non-alcoholic steatohepatitis (NASH), which increases the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [1, 3]. However, the term "non-alcoholic" primarily defines the disease by exclusion, overlooking its metabolic driver. To better reflect disease pathogenesis, metabolic associated fatty liver disease (MAFLD) has been proposed [4]. While the nomenclature has shifted, the diagnostic criteria for MAFLD largely overlap with NAFLD and previous research on NAFLD remains broadly applicable to MAFLD [5]. By emphasizing metabolic dysfunction, MAFLD improves the identification of high-risk individuals [6], with patients exhibiting higher fibrosis scores, more comorbidities, and worse prognoses compared to NAFLD [7, 8]. In 2023, the new definition of metabolic dysfunction-associated steatotic liver disease (MASLD) was officially proposed. Similar to MAFLD, both definitions recognize metabolic dysfunction as a key driver of chronic liver disease. However, there is still no global consensus on which terminology is more appropriate [9]. Studies have reported that compared to MASLD, the diagnostic criteria for MAFLD are more conducive to disease risk stratification and management based on different metabolic characteristics [10].

Inflammation and nutritional status are critical factors influencing MAFLD progression. The liver, as an immunological organ enriched with immune cells, plays a central role in inflammation-driven disease progression [11, 12]. Systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), reflect immune imbalance and are predictive of liver fibrosis and adverse outcomes in MAFLD patients [13, 14]. Nutritional status, assessed by body mass index (BMI) and serum albumin, is another essential determinant of disease severity [15, 16]. Obesity and hypoalbuminemia have been associated with advanced fibrosis and poor prognosis in MAFLD, though further validation is required [17, 18].

However, most prior studies have focused solely on either nutrition or inflammation, such as the Systemic Inflammation Response Index (SIRI) [19], Triglyceride-Glucose Body Mass Index (TyG-BMI) [20, 21], and Neutrophil-to-Lymphocyte Ratio (NLR), failing to capture their combined impact on Metabolic Associated Fatty Liver Disease (MAFLD) prognosis. The Advanced Lung Cancer Inflammation Index (ALI), calculated from BMI, serum albumin, and NLR, reflects the interplay between nutrition and inflammation. Initially developed for prognostication in non-small cell lung cancer (NSCLC) [22], ALI has since demonstrated prognostic value in a range of inflammation-related conditions, including type 2 diabetes mellitus (T2DM) [23], gastrointestinal cancers [24], rheumatoid arthritis [25], HCC [26], and chronic obstructive pulmonary disease (COPD) [27]. Recent studies have highlighted the association between ALI and liver fibrosis in NAFLD patients [28]. However, with the evolving definition of NAFLD, the precise relationship between ALI and liver fibrosis or prognosis in MAFLD remains unclear. However, with the evolving definition of NAFLD, the precise relationship between ALI and liver fibrosis or prognosis in MAFLD remains unclear. Some evidence suggests that ALI is closely associated with key metabolic features defined by the MAFLD diagnostic criteria, including type 2 diabetes [29], hypertension [30], and overweight or obesity [31]. Nevertheless, further research is warranted to elucidate the prognostic value of ALI in this population.

The National Health and Nutrition Examination Survey (NHANES) is a large-scale, population-based cross-sectional study designed to assess the health and nutritional status of the US population. NHANES uses a multistage, stratified probability sampling approach to collect data through structured interviews, physical examinations, and laboratory tests. Using NHANES data, this study explored the association between the ALI and the risk of liver fibrosis in American adults with MAFLD. Additionally, it examined the relationships between ALI and all-cause, cardiovascular disease (CVD), and cancer mortality, providing new insights into the management of MAFLD patients.

Materials and methods

Study design and population

The NHANES protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and all participants provided written informed consent. For this study, we analyzed data from adults with MAFLD in NHANES between 1999 and 2018. Our exclusion criteria were as follows: (1) age under 18 years

($n = 42,112$); (2) participants with missing US Fatty Liver Index (USFLI) data or USFLI < 30 ($n = 52,247$); (3) missing ALI data ($n = 80$); (4) missing survival data($n = 7$); (5) failure to meet the remaining MAFLD diagnostic criteria, which require the presence of overweight/obesity, T2DM, or at least two metabolic abnormalities($n = 12$). A detailed description of the sample selection process is provided in Figure S1. All data used in this study were publicly available on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

Demographic characteristics

A total of 6,858 adult MAFLD patients from the United States were included in this study. The mean age of participants was 51.38 ± 17.22 years, with 54.3% female and 45.7% male. Non-Hispanic Whites accounted for 51.8%, followed by non-Hispanic Blacks (21.8%). Of the participants, 97% were overweight/obese, 81.3% had diabetes, and 66.7% had hypertension. Further details on the basic characteristics of the study population can be found in Table S1.

Diagnosis of MAFLD

According to the 2020 international expert consensus, the diagnosis of metabolic dysfunction-associated fatty liver disease (MAFLD) requires the presence of hepatic steatosis—confirmed by histological biopsy, imaging, or blood biomarkers—along with at least one of the following conditions: overweight/obesity, type 2 diabetes mellitus (T2DM), or metabolic dysregulation. Metabolic dysregulation is defined by the presence of at least two metabolic risk abnormalities, as specified in Table S2 [4]. However, the invasiveness of liver biopsy, the high cost of imaging, and the need for expert interpretation pose challenges for large-scale population studies. To overcome these limitations, the FLI, a widely used non-invasive tool, is commonly employed to assess hepatic steatosis [32, 33]. Given the diverse racial composition of the US population, the FLI has been further adapted using NHANES data to develop the USFLI [34]. The USFLI demonstrates good diagnostic performance for hepatic steatosis (as determined by ultrasound), with an area under the curve (AUC) of 0.80 (95% CI: 0.77–0.83). A threshold of USFLI ≥ 30 provides a sensitivity of 62% and a specificity of 88% for diagnosing fatty liver.

In this study, USFLI with a cutoff value of ≥ 30 was used as the diagnostic criterion for fatty liver. The USFLI is calculated using the following formula:

$$USFLI = \frac{\left(e^{-0.8073\times non-Hispanic\,black+0.3458\times Mexican\,American+0.0093\times age+0.6151\times \log_e GGT} +0.0249\times waist\,circumference+1.1792\times \log_e insulin +0.8242\times \log_e glucose -14.7812\right)}{\left(1+e^{-0.8073\times non-Hispanic\,black+0.3458\times Mexican\,American+0.0093\times age+0.6151\times \log_e GGT} +0.0249\times waist\,circumference+1.1792\times \log_e insulin +0.8242\times \log_e glucose -14.7812\right)}\times 100$$

Measurement of ALI

In this study, the ALI was the primary exposure variable. The ALI [35] was calculated using the formula: ALI = BMI × albumin (g/dL) / NLR. (NLR = Neutrophil counts/lymphocyte counts). Due to the lack of established threshold values for ALI, participants were categorized into four groups based on ALI quartiles (Quantile 1 [Q_1], Quantile 2 [Q_2], Quantile 3 [Q_3], and Quantile 4 [Q_4]), as done in previous studies [36]. Linear trend tests were then performed to better capture the relationship between different levels of ALI and health outcomes.

Definition of outcome variables

One of the primary outcomes of this study was the liver fibrosis risk. We used the Metabolic Dysfunction–Associated Fibrosis 5 (MAF-5) score [37] to assess the risk of liver fibrosis. The MAF-5 developed and validated using large datasets from NHANES and hospital populations, has demonstrated superior diagnostic performance compared to tools like the Fibrosis-4 (FIB-4) index and the Nonalcoholic Fatty Liver Disease Fibrosis Score (NFS). Based on thresholds identified in previous studies, participants were classified into three risk groups: low fibrosis risk (MAF-5 < 0), moderate risk (MAF-5: 0–1), and high fibrosis risk (MAF-5 ≥ 1) [37].

Another of the primary outcomes was the mortality outcomes including all-cause (010), CVD (054–068, 070), and cancer (019–043) mortality. These causes of death were identified using data from the NCHS [38], with follow-up until December 31, 2019. The ICD-10 codes of each mortality were detailed in Table S3.

Covariates

Based on previous studies [28, 36], we adjusted for covariates that may potentially influence ALI or MAFLD prognosis, including demographic factors, lifestyle behaviors, and health indicators. Demographic variables included age, sex, race/ethnicity, income-to-poverty ratio (PIR), education level, and marital status. In addition to commonly adjusted lifestyle factors such as smoking status, alcohol consumption, diabetes, and hypertension, we also included sedentary behavior and energy intake, as evidence suggests that a sedentary lifestyle and excessive nutrition contribute to NAFLD progression [39]. Furthermore, total cholesterol (TC), a lipid component closely linked to MAFLD [40], was also included as a covariate.

Age was categorized as follows: ≤19 years (adolescents), 20–39 years (young adults), 40–64 years (middle-aged adults), and ≥65 years (elderly). Race/ethnicity was divided into Mexican Americans, non-Hispanic whites, non-Hispanic blacks, and other race/ethnic groups. PIR was stratified into three levels: <1.3, 1.3–3.5, and >3.5. Education level was classified as below high school,

high school, and above high school. Marital status was grouped into three categories: Married/Living with a partner, Widowed/Divorced/Separated/Never married. BMI was categorized as non-overweight (BMI < 25) and overweight (BMI ≥ 25). Smoking status was classified as never smokers (fewer than 100 cigarettes in a lifetime), former smokers (at least 100 cigarettes but quit), and current smokers (at least 100 cigarettes and currently smoking). Alcohol consumption was defined as exceeding 3 drinks per day for women and 4 for men [41]. Diabetes was defined as a physician-diagnosed condition or a fasting blood glucose level ≥ 100 mg/dL or hemoglobin A1c ≥ 5.7%. Hypertension was diagnosed either by a physician or based on systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, based on multiple measurements. Sedentary behavior was assessed by self-reported physical activity or reporting more than 6 h of sedentary time daily [42]. Dietary energy intake was based on the average of two recall records or a single available measurement. TC was treated as a continuous variable in the analysis.

Statistical analysis

Baseline characteristics were analyzed using appropriate methods based on the distribution of the variables. Continuous variables with a non-normal distributions were expressed as Median (Interquartile Range), and statistical differences between groups were assessed using the weighted Kruskal-Wallis H test. Categorical variables were presented as frequency (percentage), with group comparisons conducted using the weighted chi-square test.

To investigate the association between ALI and the risk of liver fibrosis, both univariate and multivariate weighted logistic regression models were constructed. Results were presented as the odd ratio (OR) with a 95% confidence interval (CI). Model 1 was the unadjusted model; Model 2 adjusted for age, sex, and race/ethnicity; and Model 3 further additional covariates including PIR, education level, marital status, BMI, smoking status, alcohol consumption, diabetes, hypertension, physical inactivity, energy intake, and TC. Multicollinearity among variables was assessed using the variance inflation factor (VIF), and variables with a VIF > 10 were excluded. Weighted restricted cubic spline (RCS) models were employed to examine potential non-linear relationships between ALI and liver fibrosis risk, with threshold effect analysis used to identify inflection points.

Kaplan-Meier analysis was first performed to examine the relationship between ALI and each mortality outcome. Subsequently, weighted Cox proportional hazards models were applied, with results expressed as hazard ratios (HR) and 95% CI. Similarly, weighted RCS curves and threshold effect analysis were used to assess non-linear trends and identify inflection points.

To ensure the robustness of our findings, stratified analyses were conducted to evaluate potential interactions between ALI and key subgroups, including common demographic and lifestyle factors: age (< 60 years vs. ≥60 years), sex (male vs. female), smoking status (never smoker, ex-smoker, or current smoker), and excessive alcohol consumption (yes vs. no). Notably, patients with excessive alcohol intake were excluded from the NAFLD diagnosis, making it necessary to assess whether excessive alcohol consumption affects the study outcomes [1]. Furthermore, each diagnostic component of MAFLD, including diabetes, overweight/obesity, central obesity, hypertension, high triglycerides (TG), low high-density lipoprotein (HDL) cholesterol, prediabetes, insulin resistance (IR), and elevated C-reactive protein (CRP), was separately analyzed as a subgroup to clarify the impact of different metabolic abnormalities on the study results [4].

The predictive ability of ALI for liver fibrosis and mortality risk in MAFLD patients was assessed using receiver operating characteristic (ROC) curves and time-dependent ROC curves, with the area under the curve (AUC) as the evaluation metric. ALI was compared with other established predictors, including the TyG-BMI [20, 21], the SIRI [19], the Fib-4 [43], and the NFS [44], all of which have been previously demonstrated to be valuable in predicting MAFLD prognosis. Additionally, ROC analysis was performed to evaluate the predictive performance of each individual component of ALI (BMI, NLR, and albumin) in assessing MAFLD prognosis.

It is important to note that, during the regression analysis, the ALI was $\log_2$-transformed due to its right-skewed distribution. Missing data were handled using multiple imputation with the random forest method. All statistical analyses were performed using R software (version 4.4.1), with statistical significance defined as a two-sided P-value ≤ 0.05.

Results

Baseline characteristics of participants

Participants in the lower ALI quartile were more likely to be older, male, and either current or former smokers. They also had lower total energy intake, a lower prevalence of obesity/overweight, but a higher prevalence of diabetes, hypertension, and elevated CRP compared to those in the higher ALI quartile. Detailed baseline characteristics stratified by ALI quartile are presented in Table S4.

Association between ALI and liver fibrosis risk

Figure S2 illustrates that as ALI levels increased, the MAF-5 score also increased. Weighted logistic regression results (Table 1) confirmed a statistically significant

Table 1 Association between ALI and the risk of liver fibrosis

	Model 1		Model 2		Model 3	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Continous Log_2-ALI	1.37 (1.18, 1.58)	< 0.001	1.66 (1.43, 1.94)	< 0.001	1.70 (1.41, 2.05)	< 0.001
ALI quartiles						
Q_1	Reference		Reference		Reference	
Q_2	1.04 (0.79, 1.36)	0.800	1.19 (0.89, 1.59)	0.239	1.02 (0.72, 1.45)	0.916
Q_3	1.51 (1.14, 2.00)	0.005	1.93 (1.45, 2.59)	< 0.001	1.87 (1.34, 2.62)	0.003
Q_4	1.64 (1.17, 2.29)	0.005	2.38 (1.68, 3.36)	< 0.001	2.65 (1.76, 4.00)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	

Q_1: < 52.7 Q_2: [552.7, 72.4); Q_3: [72.4, 97.9); Q_4: >= 97.9; ALI: Advanced lung cancer inflammation index; OR (95% CI): Odd ratio (95% confidence interval); Model 1: No covariates were adjusted; Model 2: Adjusted age, sex and race/ethnicity; Model 3: Adjusted age, sex, race/ethnicity, PIR, education, marital status, BMI, smoking, alcohol, diabetes, hypertension, snulledentary behaviour, energy intake, and TC

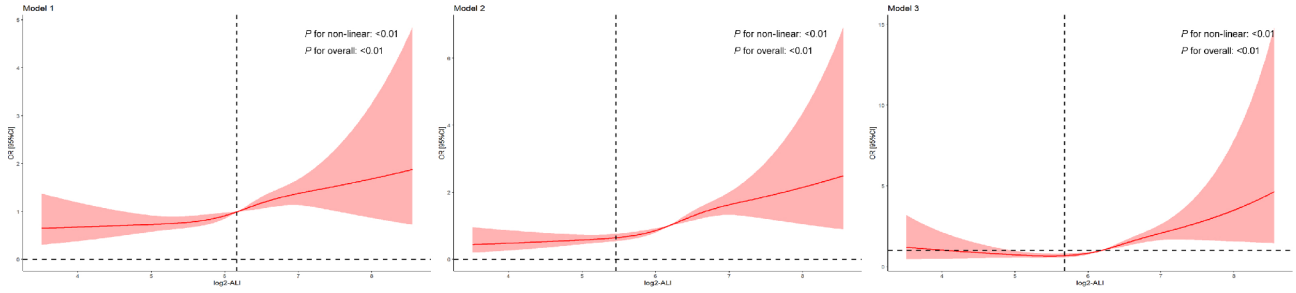

Fig. 1 Restrictive cubic spline fitting of the association between ALI and liver fibrosis. Model 1: No covariates were adjusted; Model 2: Adjusted age, sex and race/ethnicity; Model 3: Adjusted age, sex, race/ethnicity, PIR, education, marital status, BMI, smoking, alcohol, diabetes, hypertension, sedentary behaviour, energy intake, and TC; ALI: Advanced lung cancer inflammation index; OR (95% CI): Odd ratio (95% confidence interval); Liver fibrosis risk assessment using MAF-5, low risk vs. medium to high risk

Table 2 Threshold effect analysis between ALI and the risk of liver fibrosis

Inflection point	OR (95% CI)	*P*-value	*P* for Log-likelihood ratio
Model 1			0.177
< 6.16	1.38 (1.15, 1.65)	0.001	
>=6.16	1.79 (1.37, 2.38)	< 0.001	
Model 2			0.113
< 5.46	1.36 (0.95, 1.89)	0.082	
>=5.46	1.93 (1.62, 2.30)	< 0.001	
Model 3			< 0.001
< 5.68	1.01 (0.71, 1.43)	0.226	
>=5.68	2.35 (1.89, 2.95)	< 0.001	

Model 1: No covariates were adjusted; Model 2: Adjusted age, sex and race/ethnicity; Model 3: Adjusted age, sex, race/ethnicity, PIR, education, marital status, BMI, smoking, alcohol, diabetes, hypertension, sedentary behaviour, energy intake, and TC; OR (95%CI): Odd ratio (95% confidence interval)

positive association between ALI and liver fibrosis risk. In Model 3, compared to participants in the first ALI quartile, those in the fourth quartile had a higher risk of moderate-to-high liver fibrosis (OR: 2.56; 95% CI: 1.76, 4.00). The RCS curve (Fig. 1) revealed a non-linear relationship between ALI and liver fibrosis risk (*P* for non-linearity < 0.010), regardless of covariate adjustments. The RCS curve and segmented regression results (Table 2) identified an inflection point at 5.68, beyond which the relationship between ALI and liver fibrosis risk became statistically significant (OR: 2.35; 95% CI: 1.89, 2.95). This suggests that this threshold may represent a critical point for assessing MAFLD liver fibrosis progression. Stratified analyses (Figure S3) revealed significant interactions between ALI and central obesity (OR: 1.50; 95% CI: 1.26, 1.80), as well as between ALI and prediabetes (OR: 1.99; 95% CI: 1.49, 2.68), with *P* for interaction both < 0.05.

The relationship between ALI and all-cause, CVD, and cancer mortality

A total of 1182 participants (17.2%) died during the follow-up period, including 393 (5.7%) from CVD and 282 (4.1%) from cancer. Kaplan-Meier analysis and log-rank tests (Fig. 2) showed a significant association between higher ALI levels and reduced all-cause, CVD and cancer mortality ($P < 0.01$). Multivariable weighted Cox regression analysis further confirmed these associations. In the fully adjusted model (Table 3), higher ALI was significantly associated with lower all-cause mortality (HR: 0.53, 95% CI: 0.42–0.67) and CVD mortality (HR: 0.50, 95% CI: 0.33–0.75). However, no significant association was observed between ALI and cancer mortality after adjusting for covariates. RCS analysis (Fig. 3) demonstrated a significant L-shaped non-linear relationship between ALI and all-cause mortality (*P* for non-linearity < 0.05). A saturation effect was observed, with the inflection point occurring around an ALI value of 5.36 (Table 4). Beyond this threshold, the protective effect

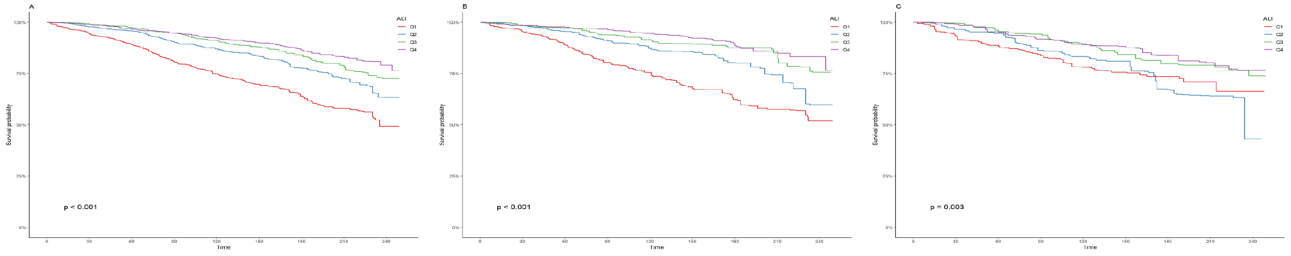

Fig. 2 Kaplan-Meier survival curves of ALI impact mortality in patients with NAFLD. (**A**): All-cause; (**B**): CVD; (**C**): Malignant neoplasms; ALI: Advanced lung cancer inflammation index; Q1: < 53.2; Q2: [53.2, 72.6); Q3: [72.6, 98.2); Q4: >= 98.2

Table 3 Relationship between ALI and All-cause, CVD and cancer mortality in patients with NAFLD

ALI	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality						
Continous Log_2-ALI	0.48 (0.43, 0.54)	< 0.001	0.60 (0.53, 0.68)	< 0.001	0.64 (0.56, 0.72)	< 0.001
Q_1	Reference		Reference		Reference	
Q_2	0.52 (0.43, 0.64)	< 0.001	0.61 (0.51, 0.75)	< 0.001	0.67 (0.55, 0.82)	< 0.001
Q_3	0.36 (0.29, 0.46)	< 0.001	0.52 (0.41, 0.66)	< 0.001	0.57 (0.42, 0.66)	< 0.001
Q_4	0.30 (0.24, 0.38)	< 0.001	0.47 (0.37, 0.59)	< 0.001	0.53 (0.42, 0.67)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	
CVD mortality						
Continous Log_2-ALI	0.41 (0.34, 0.49)	< 0.001	0.54 (0.44, 0.65)	< 0.001	0.57 (0.46, 0.69)	< 0.001
Q_1	Reference		Reference		Reference	
Q_2	0.452 (0.37, 0.73)	< 0.001	0.64 (0.45, 0.91)	0.014	0.68 (0.47, 0.99)	0.046
Q_3	0.32 (0.22, 0.49)	< 0.001	0.49 (0.33, 0.73)	< 0.001	0.53 (0.34, 0.81)	0.003
Q_4	0.24 (0.17, 0.36)	< 0.001	0.40 (0.28, 0.59)	< 0.001	0.50 (0.33, 0.75)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	
Cancer mortality						
Continous Log_2-ALI	0.63 (0.48, 0.83)	0.001	0.76 (0.57, 1.00)	0.051	0.80 (0.60, 1.06)	0.119
Q_1	Reference		Reference		Reference	
Q_2	0.89 (0.56, 1.40)	0.608	1.00 (0.63, 1.60)	0.999	0.99 (0.56, 1.55)	0.952
Q_3	0.52 (0.32, 0.83)	0.006	0.67 (0.41, 1.08)	0.102	0.72 (0.45, 1.14)	0.170
Q_4	0.49 (0.28, 0.83)	0.009	0.68 (0.40, 1.15)	0.151	0.74 (0.43, 1.26)	0.266
P for trend	0.001		0.074		0.165	

ALI: Advanced lung cancer inflammation index; Q_1: < 52.7 Q_2: [52.7, 72.4); Q_3: [72, 97.9); Q_4: >= 97.9; Model 1: No covariates were adjusted; Model 2: Adjusted age, sex and race/ethnicity; Model 3: Adjusted age, sex, race/ethnicity, PIR, education, marital status, BMI, smoking, alcohol, diabetes, hypertension, sedentary behaviour, energy intake, and TC; HR (95%CI): Hazard Ratio (95% confidence interval)

of increasing ALI on mortality plateaued, suggesting that 5.36 may represent a critical value for assessing the impact of nutritional and inflammatory status on prognosis. In contrast, ALI exhibited a linear dose-response relationship with CVD mortality (*P* for non-linear = 0.48). Stratified analysis (Fig. S4) showed significant interactions between ALI and excessive alcohol consumption (HR: 0.70; 95% CI: 0.54, 0.89), as well as between ALI and low HDL-cholesterol (OR: 0.51; 95% CI: 0.44, 0.57), with *P* for interaction both < 0.05.

ROC analysis of the predictive value of ALI for liver fibrosis risk and mortality

Table S5 presents the ROC analysis of ALI in predicting liver fibrosis risk and comparisons with other established indicators. The results indicate that when ALI is below 5.68, its predictive ability is relatively weak, further supporting the findings from the RCS analysis. However, when ALI exceeds 5.68, its predictive performance improves, with an AUC of 0.57 (95% CI: 0.54, 0.60), which is comparable to SIRI and NLR but inferior to TyG-BMI, Fib-4, NFS, and BMI.

Furthermore, Tables S6 and S7 provide the ROC analysis results for ALI in predicting all-cause and CVD mortality. When ALI is below 5.36, it demonstrates the highest predictive accuracy for 5-year all-cause mortality in MAFLD patients, with an AUC of 0.66 (95% CI: 0.60, 0.71), comparable to TyG-BMI, Fib-4, NFS, BMI, and albumin, and outperforming SIRI and NLR. However, when ALI exceeds 5.36, its predictive accuracy for all-cause mortality declines, aligning with the trends observed in the RCS analysis.

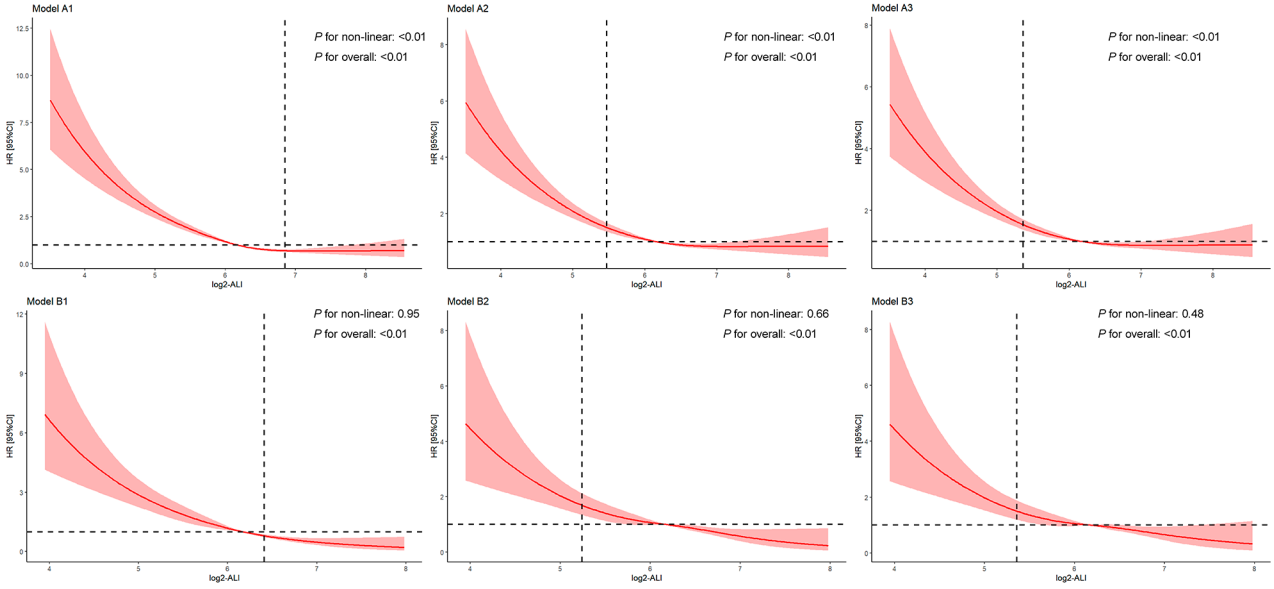

Fig. 3 Restrictive cubic spline fitting of the association between ALI and mortality in patients with NAFLD. (**A**): All-cause; (**B**): CVD; Model 1: No covariates were adjusted; Model 2: Adjusted age, sex and race/ethnicity; Model 3: Adjusted age, sex, race/ethnicity, PIR, education, marital status, BMI, smoking, alcohol, diabetes, hypertension, sedentary, behaviour, energy intake, and TC

Table 4 Threshold effect analysis of between ALI and All-cause mortality

Inflection point	HR (95% CI)	*P*-value	*P* for Log-likelihood ratio
All-cause mortality			
Model 1			< 0.001
< 6.85	0.49 (0.45, 0.53)	< 0.001	
>=6.85	1.33 (1.02, 1.72)	0.033	
Model 2			< 0.001
< 6.37	0.55 (0.49, 0.61)	< 0.001	
>=6.37	1.03 (0.85, 1.26)	0.749	
Model 3			< 0.001
< 5.36	0.42 (0.35, 0.51)	< 0.001	
>=5.36	0.79 (0.71, 0.88)	< 0.001	

HR (95%CI): Hazard Ratio (95% confidence interval); Model 1: No covariates were adjusted; Model 2: Adjusted age, sex and race/ethnicity; Model 3: Adjusted age, sex, race/ethnicity, PIR, education, marital status, BMI, smoking, alcohol, diabetes, hypertension, sedentary behavior, energy intake, and TC

Regarding CVD mortality, ALI exhibits moderate discriminative ability for 1-year (AUC: 0.70; 95% CI: 0.54, 0.85) and 3-year (AUC: 0.68; 95% CI: 0.60, 0.74) predictions in MAFLD patients. However, its performance in predicting 5-year and 10-year CVD mortality is inferior to that of Fib-4.

Discussion

This study, based on NHANES data from 1999 to 2018, included 6,858 MAFLD patients. The results indicated that when ALI levels exceed 5.68, the risk of liver fibrosis significantly increases. The relationship between ALI and liver fibrosis risk was more pronounced in subgroups with prediabetes and central obesity. However, ALI alone has limited predictive ability for liver fibrosis risk. ALI was significantly inversely associated with both all-cause mortality and CVD mortality, but no significant association was found with cancer mortality. Specifically, ALI showed an L-shaped non-linear relationship with all-cause mortality, with a saturation effect observed at a threshold of 5.36. Notably, low levels of HDL-cholesterol and excessive alcohol consumption may modulate the inverse relationship between ALI and mortality. Among the outcomes analyzed, ALI exhibited the highest AUC for predicting CVD mortality.

The development of liver fibrosis is the result of the gradual progression from steatosis and NASH to fibrosis. Consistent with previous studies, we also found a non-linear relationship between ALI and liver fibrosis [28]. However, our turning point was 5.68, which is lower than that reported in earlier research. This difference may be attributed to variations in the definitions of NAFLD and MAFLD, as well as differences in the populations included. This non-linear relationship suggests that liver fibrosis is the result of the complex interplay among nutritional status, inflammation, and metabolic factors. First, in our study, 97% of the patients were overweight or obese. Obesity induces hepatic fat accumulation, adipocyte dysfunction, and chronic low-grade metabolic inflammation, which accelerate fibrosis progression [45]. This hepatic inflammatory activity can be reflected by changes in NLR, particularly the activation of neutrophils, which play a key role in liver inflammation [46]. In the early stages of the disease, neutrophils may promote fibrosis by forming neutrophil extracellular traps (NETs). However, as liver fibrosis advances, excessive neutrophil

activation and the resulting inflammation may further impair liver function and hinder the liver's repair mechanisms [47]. Human serum albumin is a multifunctional protein with anti-inflammatory, antioxidant, and plasma oncotic pressure-regulating properties. Liver inflammation and obesity-induced adipose tissue inflammation and insulin resistance may lead to decreased albumin levels and impaired function [48, 49]. However, in the context of ALI, the decline in albumin levels may be masked by obesity. Moreover, we found that the positive association between ALI and liver fibrosis was more pronounced in subgroups with central obesity and prediabetes. Notably, not all obese individuals are at equal risk of developing liver disease. Visceral fat may be an independent factor influencing liver fibrosis in MAFLD. The biological mechanisms through which visceral fat promotes liver fibrosis are complex and may involve the secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and adipokines, as well as a higher lipolytic activity that releases large amounts of free fatty acids. These substances, upon entering the liver, can trigger oxidative stress and chronic inflammation [50, 51]. Although prediabetes represents a milder state of insulin sensitivity impairment and β-cell dysfunction, it contributes to insulin resistance, increased oxidative stress, and chronic inflammation, which are potential pathways leading to liver cancer and CVD [52, 53]. Early lifestyle and dietary interventions in individuals with central obesity and prediabetes are crucial for slowing the progression of MAFLD.

However, the predictive ability of ALI for liver fibrosis risk is limited. Our study suggests that BMI alone may have a stronger predictive value, indicating that BMI could be the dominant component in the relationship between ALI and liver fibrosis. In our study, the NFS demonstrated good accuracy, but previous studies have shown that NFS has false-negative rates of 2-4% and false-positive rates of 28-29% in the general population, making it unsuitable as a primary screening tool in general or high-risk populations [54]. Therefore, future research should focus on exploring the mechanisms underlying the interplay of nutrition and inflammation in the progression of liver fibrosis in MAFLD and finding more accurate nutritional-inflammatory markers to better assess disease progression.

We also found that increasing ALI levels are negatively correlated with all-cause mortality and CVD mortality. We believe this can be explained by several biological mechanisms. First, the "obesity paradox" may help explain the protective effect of obesity on mortality risk. The "obesity paradox" suggests that although obesity may increase disease risk, paradoxically, it is associated with lower mortality rates in certain chronic conditions [55]. A potential mechanism is that adipose tissue in obese individuals secretes beneficial metabolic products such as adiponectin, which may, to some extent, slow the progression of chronic inflammation, cellular damage, and metabolic dysregulation [56]. Second, similar to high BMI, high albumin levels also reflect the patient's potentially better nutritional status and immune function [57]. As mentioned earlier, albumin is a multifunctional plasma protein, with various roles including volume expansion, antioxidant activity, and regulation of inflammation. It is also often used as a treatment for decompensated cirrhosis and critically ill patients [58, 59]. Finally, Higher NLR reflects increased neutrophil activity, and the inflammatory mediators they release, such as TNF-α, IL-1β, and reactive oxygen species (ROS), can lead to endothelial dysfunction and vascular wall damage. In contrast, lymphocytes counteract atherosclerosis by producing anti-inflammatory cytokines (such as IL-10) and promoting inflammation resolution [60]. Therefore, a lower NLR may reduce the incidence of cardiovascular events in MAFLD patients, thereby lowering all-cause and CVD mortality [60, 61]. Additionally, our study found that the protective effect of ALI was more pronounced in subgroups with low HDL-cholesterol levels and those who did not engage in excessive alcohol consumption. We speculate that this relationship may be due to the inclusion of individuals with excessively high HDL-cholesterol levels. Studies have shown a U-shaped non-linear relationship between HDL-cholesterol levels and both all-cause mortality and cardiovascular event risk in T2DM patients. This may be related to the increase in HDL-cholesterol particle size and harmful subtypes, which have been associated with hypertension and a higher incidence of cardiovascular events [62]. Previous studies have indicated that excessive alcohol intake synergistically interacts with metabolic disorders, increasing the risk of all-cause, liver-related, and cancer-related mortality in MAFLD patients [63, 64]. Therefore, although the current definition of MAFLD no longer emphasizes alcohol consumption, assessing drinking history remains crucial.

Interestingly, we found that the relationship between ALI and all-cause mortality was nonlinear, whereas no such pattern was observed for CVD mortality. First, we speculate that this discrepancy may be due to the confounding effects of various causes of death within all-cause mortality. For example, our study found no significant association between ALI and cancer mortality. Patients with MAFLD complicated by cancer may be influenced by factors beyond nutrition and inflammation, such as age, hepatitis B virus infection, tumor type, size, and number [65]. Second, this nonlinear relationship may be attributed to the disruption of the previously maintained balance between nutrition and inflammation once ALI surpasses the threshold of 5.36. This disruption could be driven by factors such as excessive obesity [35]

or excessive suppression of inflammation [66], leading to the emergence of more comorbidities and affecting all-cause mortality.

In conclusion, the innovation of this study lies in its first-time demonstration of the relationship between ALI and both liver fibrosis and mortality in MAFLD patients. Our findings suggest that ALI may serve as a more suitable prognostic indicator rather than a predictor of liver fibrosis risk, particularly in assessing CVD mortality risk in MAFLD patients. Unlike traditional single inflammatory or nutritional markers, long-term monitoring of ALI in clinical practice can help clinicians comprehensively evaluate patients' nutritional and inflammatory status. For instance, patients with low ALI levels may benefit from a more detailed assessment of their nutritional and inflammatory conditions, with appropriate nutritional support and/or anti-inflammatory treatment. Conversely, excessively high ALI levels should prompt clinicians to consider the possibility of nutritional overload or excessive immune suppression. However, our study is an initial exploration of the relationship between ALI and prognosis, as well as its predictive capability. Further prospective validation in larger population samples is warranted to confirm our findings and to establish more precise ALI thresholds for clinical evaluation and management.

Strengths and limitations

This study has several strengths. First, it utilized a nationally representative sample, enhancing the generalizability of the results. Second, we adjusted for multiple confounders and conducted stratified analyses, which strengthened the robustness of our findings. Third, ALI, a simple and clinically accessible biomarker, has the potential to serve as a prognostic indicator for MAFLD.

However, this study also has some limitations. As a cross-sectional study with ALI measured only once, we cannot establish causality or assess its long-term effects on MAFLD outcomes. Future studies with larger prospective cohorts are needed to validate these findings. Additionally, to ensure data completeness, we excluded a substantial number of samples with missing values, which may have reduced the representativeness of the sample. Since this study was conducted using a U.S. adult population, further research is required to determine whether the findings can be generalized to broader geographical and demographic groups. Furthermore, to expend the sample size, we used non-invasive criteria for fatty liver diagnosis. Although the USFLI has demonstrated good diagnostic performance, its accuracy remains inferior to liver biopsy. Additionally, self-reported outcomes may introduce some subjective bias. Finally, although we have adjusted for many key covariates, there may still be unmeasured confounders, such as medication use and dietary habits, that could influence the study results.

Conclusion

This study revealed the relationship between ALI and the risk of liver fibrosis and prognosis in MAFLD patients, demonstrating a non-linear association between ALI and both liver fibrosis and all-cause mortality. ALI holds promise as a simple and cost-effective prognostic biomarker for MAFLD patients, aiding clinicians in assessing and monitoring nutritional and inflammatory status. However, larger-scale prospective studies are needed to validate and further explore these findings in the future.

Abbreviations

MAFLD	Metabolic dysfunction-associated fatty liver disease
ALI	Advanced Lung Cancer Inflammation Index
NHANES	National Health and Nutrition Examination Survey
CVD	Cardiovascular disease
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
HDL	High-density lipoprotein
NAFLD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
HCC	Hepatocellular carcinoma
NLR	Neutrophil-to-lymphocyte ratio
BMI	Body mass index
TyG-BMI	Triglyceride-glucose body mass index
SIRI	Systemic inflammation response index
MASLD	Metabolic dysfunction-associated steatotic liver disease
NSCLC	Non-small cell lung cancer
T2DM	Type 2 diabetes mellitus
COPD	Chronic obstructive pulmonary disease
NCHS	National Center for Health Statistics
USFLI	United States Fatty Liver Index
FLI	Fatty Liver Index
GGT	Gamma glutamyltransferase
Q_1	Quantile 1
Q_2	Quantile 2
Q_3	Quantile 3
Q_4	Quantile 4
MAF-5	Metabolic Dysfunction–Associated Fibrosis 5
FIB-4	Fibrosis-4 index
NFS	Nonalcoholic Fatty Liver Disease Fibrosis Score
PIR	Income-to-poverty ratio
TC	Total cholesterol
OR	Odd Ratio
CI	Confidence Interval
HR	Hazard Ratio
TG	Triglycerides
IR	Insulin resistance
CRP	C-reactive protein
AUC	Area under the curve
NETs	Neutrophil extracellular traps
ROS	Reactive oxygen species

Supplementary Information

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Supplementary Material 1

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Study concept and design: All the authors. Statistical analysis: Chunchun Yu, Lefu Chen, Wanting Hu, Xiong Lei, Xiling Liu, Zhixiao Xu, Chengshui Chen, Hongjun Zhao. Data analysis review: Chunchun Yu, Lefu Chen, Wanting Hu, Xiong Lei, Xiling Liu, Zhixiao Xu, Chengshui Chen, Hongjun Zhao. Critical revision of the manuscript for intellectual content: Chunchun Yu, Lefu Chen, Wanting Hu, Xiong Lei, Xiling Liu, Zhixiao Xu, Chengshui Chen, Hongjun Zhao. Supervision: Chunchun Yu, Lefu Chen, Wanting Hu, Xiong Lei, Xiling Liu, Zhixiao Xu, Chengshui Chen, Hongjun Zhao. All authors reviewed and edited the manuscript drafts, read, and agreed to the published version of the manuscript.

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Data availability
The data used in this study are publicly available as part of the NHANES, which is distributed and sponsored by the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and the Istanbul Declaration. NHANES was approved by the NCHS Ethics Review Board, and written informed consent was obtained from all participants.

Consent for publication
None.

Competing interests
The authors declare no competing interests.

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