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Dietary habits in liver health and disease: preclinical and clinical studies

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Dietary habits in liver health and disease: preclinical and clinical studies

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Table of contents

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Editorial: Dietary habits in liver health and disease: preclinical and clinical studies

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Editorial on the Research Topic
Dietary habits in liver health and disease: preclinical and clinical studies

The intricate relationship between dietary habits and liver health has become a rapidly growing field of research, especially in light of the worldwide increase in chronic liver disease (CLD) (1). The liver is the central organ responsible for regulating metabolism, detoxification, and modulating the immune system and is also susceptible to nutrients (2). Understanding how diet influences liver function and pathology is crucial for developing effective strategies to prevent and treat liver disease. This research theme combines preclinical and clinical investigations that examine the impact of dietary patterns, nutrients, and metabolic indicators on liver health, offering new insights for researchers and clinicians.

The increasing prevalence of non-alcoholic fatty liver disease (NAFLD) worldwide, now often referred to as metabolic dysfunction-associated steatotic liver disease (MASLD), underscores the critical role of diet in liver pathology. NAFLD is driven by increasing obesity and diabetes and can lead to more serious conditions such as fibrosis, cirrhosis, and hepatocellular carcinoma (3). The economic impact is substantial, necessitating a coordinated global effort to address the growing burden of CLD (4).

Recent research has focused on identifying specific dietary components and patterns that contribute to the development of liver disease. For example, the impact of pro-inflammatory diets on the risk of CLD has been studied in detail. A comprehensive analysis of data from the UK Biobank cohort revealed a significant association between a higher Dietary Inflammatory Index (DII), which indicates a more inflammatory dietary pattern, and an increased risk of CLD. This robust finding, consistent with various demographic and lifestyle factors, strongly suggests that adopting anti-inflammatory dietary patterns may be a critical strategy to mitigate the global burden of CLD (Pan et al.).

In addition to general dietary patterns, the role of specific food categories, such as ultra-processed foods (UPF), has received increasing attention. A cross-sectional analysis of 4,992 adults from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 cycle showed that higher UPF consumption was significantly associated with increased liver fat accumulation, as measured by the controlled attenuation parameter (CAP). These results underscore the deleterious impact of UPF on liver steatosis, particularly in individuals who are overweight or have increased waist circumference (Song et al.).

The interaction between diet, metabolic health, and liver function extends deep into the realm of insulin resistance (IR). IR is a well-established factor in the pathogenesis

of NAFLD and its progression to liver fibrosis. Yang et al. confirm a significant association between various IR indexes and liver fibrosis in NAFLD patients. In particular, the triglyceride glucose-waist to height ratio (TyG-WHtR) has been shown to be a prominent predictor of liver fibrosis, even after adjustment for covariates. This work highlights the potential of incorporating IR indexes into routine clinical practice for early risk assessment and timely interventions to prevent the progression of fibrosis.

In addition, the broader concept of cardiovascular health, as the Life's Essential 8 (LE8) construct from the American Heart Association, has been linked to liver function. A cross-sectional study using data from the NHANES 2007–2018 cycle revealed that higher LE8 scores are associated with better liver function, particularly with lower levels of liver enzymes, including ALT, ALT/AST ratio, ALP, and GGT (Liang et al.). This association exhibits non-linear patterns and is more pronounced in younger individuals. These findings suggest that comprehensive interventions to improve cardiovascular health, which include a balanced diet, regular physical activity, and other lifestyle factors, may also benefit liver health.

The impact of nutritional interventions also extends to specific clinical contexts, such as postoperative care for patients with colorectal cancer (CRC). Malnutrition is common in CRC patients, hindering recovery and increasing the risk of complications. Research has shown that early postoperative administration of dietary fiber significantly improves immune function, reduces inflammation, and improves the nutritional status in CRC patients (Ji et al.). This evidence highlights the importance of tailoring nutritional support strategies, including dietary fiber, to achieve optimal patient outcomes. Machine learning models have also been successfully used to predict the impact of dietary fiber on immune function and inflammatory responses. Important predictors, such as procalcitonin (PCT), prealbumin (PAB), albumin (ALB), and interleukin-1 (IL-1), were identified (Ji et al.).

Finally, the role of trace elements in liver health, which is influenced by dietary intake and environmental exposure, is also gaining increasing attention. For example, He et al. have examined the association between serum manganese (Mn) levels and NAFLD. The results indicate that higher serum Mn levels are associated with an increased risk of NAFLD, with sex-specific differences in the dose-response relationship. This study emphasizes the importance of further investigating the intricate relationship between trace elements, environmental factors, and CLD pathogenesis, to develop sex-specific prevention strategies.

In summary, there is consistent and converging evidence that provides a substantial amount of relevant new data on the role of diet composition, dietary patterns, and the benefits of dietary interventions to liver health and disease. Despite the extensive literature available on this important topic, the papers published in this Research Topic demonstrate that some gaps still exist in various aspects of the complex area of diet's influence on liver function, which remain to be clarified and better understood. After reading this volume, readers will have a clearer understanding of topics such as the impact of inflammatory diets, the role of specific sugars, the importance of IR markers, the wide-ranging benefits of cardiovascular health metrics, and the nuanced effects of trace minerals, reinforcing the understanding that dietary habits are a cornerstone in the prevention and treatment of liver disease.

Author contributions

EP: Conceptualization, Writing – original draft, Writing – review & editing. CF-S: Writing – original draft, Writing – review & editing.

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.

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Association between changes in body composition and progression of liver fibrosis in patients with type 2 diabetes mellitus

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Aim: The correlation between type 2 diabetes mellitus (T2DM) and the occurrence of liver fibrosis is well-established. However, the longitudinal association between body composition and liver fibrosis progression in patients with T2DM remains incompletely explored.

Methods: Total of 390 patients with T2DM underwent body composition assessments, followed by a median duration of 2.13 years. The calculated parameters included body mass index (BMI), fat mass index (FMI), trunk fat mass index (TFMI), appendicular skeletal muscle mass index (ASMI), muscle/fat mass ratio (M/F) and appendicular skeletal muscle mass/trunk fat mass ratio (A/T). Liver fibrosis was evaluated through liver stiffness measurement (LSM). Patients were classified according to BMI and body composition, followed by a comprehensive investigation into the impact of body composition changes on liver fibrosis outcomes.

Results: Among 72 patients with incident advanced liver fibrosis at readmission, ΔBMI, ΔFMI and ΔTFMI increased, while ΔM/F and ΔA/T decreased. Individuals who kept obese had a dramatically elevated hazard of incident advanced liver fibrosis compared to those who kept non-obese, with an adjusted odds ratio of 3.464. When TFMI heightened, the hazard of incident advanced liver fibrosis was 3.601 times higher compared to the decreased group. Additionally, individuals in increased ASMI and A/T groups showed a slight advantage in preventing incident advanced liver fibrosis compared to the stable groups.

Conclusion: Stable obesity was associated with a greater hazard of liver fibrosis advancement, and an increase in TFMI may promote the progression of liver fibrosis. Maintaining a balanced muscle/fat ratio appeared to help prevent the progression.

KEYWORDS

body composition, body mass index, liver fibrosis progression, type 2 diabetes mellitus, muscle fat ratio

1 Introduction

Researchers have emphasized the significance of liver fibrosis severity as a pivotal determinant of long-term prognosis, exhibiting strong correlations with both hepatic and extra-hepatic events as well as mortality (1, 2). Relevant studies have previously established a robust correlation between type 2 diabetes mellitus (T2DM) and the initiation as well as progression of liver fibrosis (3, 4). The underlying pathological mechanism suggests that elevated blood glucose levels play a direct role in inducing hepatotoxicity, leading to hepatocellular injury and eventual mortality. Therefore, the assessment of liver fibrosis progression in individuals with T2DM holds significant importance. Although the assessment of liver fibrosis staging relies on liver biopsy as the gold standard (5), its limitations encompass exorbitant expenses, invasiveness, and suboptimal adherence. Consequently, the recent recommendation is to employ non-invasive methodologies such as ultrasound transient elastography (TE) (6).

The weight change serves as an indicator of an individual's lifelong trajectory toward optimal health (7, 8). The weight fluctuations observed in individuals with T2DM are influenced by multiple factors. Relevant investigations have indicated that the underlying mechanisms contributing to the adverse effects of weight fluctuations across different life stages may exhibit variations (7, 9). For instance, initial weight gain primarily arises from lipid accumulation (10–12), while it is frequently attributed to a decline in muscle mass over time (13, 14). Importantly, even when body weight remains stable, the distribution of adipose tissue and muscle mass can vary significantly. Notably, recent research has established a significant association between sarcopenia and non-alcoholic fatty liver disease (NAFLD), which is one of the major risks of liver fibrosis (15). The association between the two has been further substantiated by another study, independent of obesity and insulin resistance (16). The study findings also indicated that an increased risk of liver fibrosis progression was associated with both weight gain and obesity (17).

When assessing T2DM patients during subsequent visits, it is crucial to acknowledge that changes in weight may not serve as the exclusive indicator of liver fibrosis. In spite of numerous researches conducted on the correlation between fluctuations in body weight and the development of liver fibrosis among adults (18–22), the impact of changes in body composition on the prognosis of liver fibrosis in patients with T2DM remains unknown. Furthermore, the majority of researches have utilized cross-sectional methodologies, and a longitudinal cohort study that is pertinent to this topic remains absent. We hoped to compare the frequency of incident advanced liver fibrosis and non-advanced liver fibrosis in patients with T2DM at baseline and readmission, and further explore potential body composition parameters that may contribute to preventing advanced liver fibrosis progression.

2 Materials and methods

2.1 Study population

This was a retrospective cohort study conducted in the Department of Infectious Diseases, the Third Affiliated Hospital of Sun Yat-sen University. We systematically selected 1,280 participants by recruiting every third hospitalized patient from April 1, 2013, to March 30, 2024. After the preliminary assessment, 507 individuals participated in subsequent phase of the study. Those lacking comprehensive data were omitted from the examination. Ultimately, the sample size was narrowed down to 390 participants, comprising 200 males and 190 females. The sample size achieved sufficient power to detect the expected differences with the given effect size. The median follow-up duration was 2.13 years. The study flowchart is displayed in Figure 1.

Inclusion criteria: (1) Aged ≥45 years who satisfied the 2021 American Diabetes Association diagnostic standards for T2DM and were experiencing antidiabetic drug treatment (23); (2) Had complete data on body composition and liver stiffness assessment; (3) Understood the study's purpose and voluntary participation.

Exclusion criteria: (1) Declined participation; (2) Had other types of diabetes; (3) Critically ill patients who had ketoacidosis, hyperosmotic nonketotic coma, cirrhosis, chronic viral hepatitis (including hepatitis B and C virus infection), infectious illnesses, malignant tumors or autoimmune disease, etc.; (4) Had muscle loss due to poisoning, drug abuse or anti-inflammatory or hormone drugs uses; (5) History of severe cardiovascular diseases; (6) History of metabolic disorders affecting nutritional status; (7) Excessive alcohol intake (men >140 g/week; women >70 g/week) (24); (8) Tested positive for autoantibodies associated with diabetes and hepatic disorders; (9) Athletes or pregnant women.

2.2 Data collection

Experienced physicians obtained comprehensive clinical data from all participants, including gender, age, disease course, and family history, etc. To guarantee the precision and legitimacy of the data, patient's identification number and admission number were securely obtained, and medical records were reviewed. Measured the individual's weight and height in the morning (model: RGZ-120-RT). After a 15-min rest, blood pressure and body mass index (BMI) was measured. BMI = weight (kg) / height^2 (m^2). The waist to hip ratio (WHR) = waist circumference (cm) / hip circumference (cm). BMI ≥28 was Obesity (25).

The venous blood samples were collected following a 10-h fasting. The concentrations of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT) and creatinine (Cr) were measured using Siemens ADVIA 2400 automatic biochemical analyzer. Additionally, C-reactive protein (CRP) levels, platelet counts (PLT), international normalized ratio (INR) values for prothrombin time, albumin (ALB) levels and fasting plasma glucose (FPG) concentrations were determined. The estimated glomerular filtration rate (eGFR) = 186× (serum Cr [μmol/L]/88.41)–1.154 × age–0.203 (×0.742 female) (12). High-performance liquid chromatography (VARIANTII; Bio-Rad, CA, United States) was used to determine glycosylated hemoglobin (HbA1c) levels.

2.3 Liver fibrosis assessment

Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were obtained for each patient using available

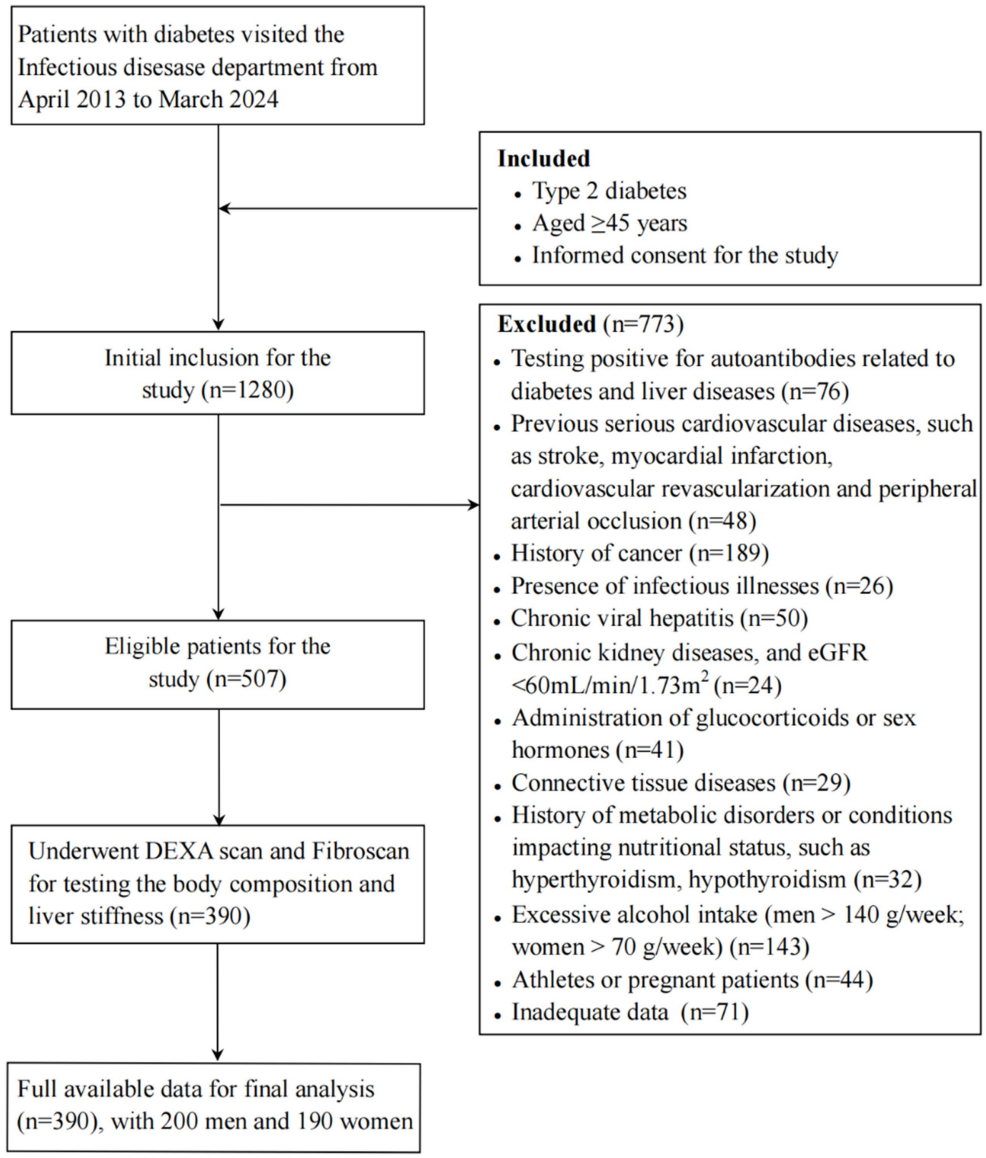

FIGURE 1
Study flowchart Note: eGFR, estimated glomerular filtration rate; DEXA, dual-energy X-ray absorptiometry.

TE evaluation (FibroScan; Echosens®™, Echosens, Paris, France). The intra- and inter-assay coefficients of variation for FibroScan were 0.78 and 0.83%, respectively. LSM scores were evaluated for the detection of liver fibrosis. To estimate reliability, we computed the ratio of the LSM interquartile range (IQR) to its median. LSM must be at least 10 kPa with a success rate of at least 60%, and a ratio of IQR to median LSM should not be exceed 30%. The validity of CAP is only confirmed when the corresponding LSM meets these criteria.

LSM < 8.2 kPa was defined as F0. The presence of significant fibrosis (≥F1) was indicated by a median LSM value of ≥8.2 kPa, while advanced fibrosis (F2) and cirrhosis (F3) were indicated by LSM values of ≥9.7 kPa and ≥ 13.6 kPa, respectively (6). Newly occurring F2 and F3 grades of liver fibrosis at readmission was referred to as incident advanced liver fibrosis (incident F2-3). A transition from F2 to either F0 or F1 was defined as incident non-advanced liver fibrosis (incident F0-1). Patients with cirrhosis at baseline have been excluded from this study.

2.4 Body composition examination

Dual-energy X-ray absorptiometry (DEXA, American GELUNAR Company, Prodigy Type) was utilized to assess body composition. The whole-body fat mass index (FMI) = whole-body fat mass (kg)/height^2 (m^2); whole-body muscle mass index (MMI) = muscle mass (kg)/height^2 (m^2); trunk fat mass index (TFMI) = trunk fat mass (kg)/height^2 (m^2); appendicular skeletal muscle mass index (ASMI) = appendicular skeletal muscle mass (kg)/height^2 (m^2). M/F = whole-body muscle mass (kg)/whole-body fat mass (kg); A/T = appendicular skeletal muscle mass (kg)/trunk fat mass (kg). The change value represented the disparity between measurements at

baseline and readmission. The adjustment of annual change rates based on the duration of follow-up in years. The intra- and inter-assay coefficients of variation for DEXA were 0.64 and 0.80%, respectively.

2.5 Grouping criteria

We assessed BMI and body composition indexes at baseline and readmission. The patterns of BMI change were categorized into four groups: stable non-obese (<28 kg/m^2), weight losing (baseline ≥28 kg/m^2 and readmission <28 kg/m^2), weight gaining (baseline <28 kg/m^2 and readmission ≥28 kg/m^2), and stable obese (≥28 kg/m^2) (8).

Changes in body composition were quantified by the differences between baseline and readmission measurement values of BMI (ΔBMI), FMI (ΔFMI), MMI (ΔMMI), M/F (ΔM/F), TFMI (ΔTFMI), ASMI (ΔASMI) and A/T (ΔA/T). A previous investigation revealed that patients in the intervention group exhibited a significant increase of approximately 3% in leg muscle mass compared to those without any special intervention. Therefore, we established 3% as the threshold value. The body composition indexes were categorized as decreasing, stabilizing, and increasing according to ΔFMI, ΔMMI, ΔM/F, ΔTFMI, ΔASMI, and ΔA/T < −3%, −3 to 3, and > 3%, respectively (26).

2.6 Statistical analysis

SPSS for Windows (version 25.0) was utilized for statistical analysis, and $p < 0.05$ indicated significance. We specified the primary outcomes of interest for our study and established the desired significance level ($\alpha = 0.05$) and power ($1\text{-}\beta = 0.80$), which is commonly accepted in clinical research. Suitable sampling weight analysis was added in analysis. When the information is not collected, information is lost after being collected, and the information is collected, identified as incorrect, and deleted, the data was identified as missing. Inserted techniques such as multiple imputations were chosen to minimize bias and maintain the integrity of the dataset. Continuous variables were presented as means with standard deviations (SDs) or medians with IQRs, evaluating group differences using an independent sample t-test or non-parametric test. Categorical variables were presented as frequencies and percentages, evaluating group differences using χ^2 test. Pearson's correlation coefficient was employed to assess univariate association between body composition and LSM. Bivariate logistic regression was conducted to investigate the association between weight change patterns and the occurrence of advanced liver fibrosis, with odds ratios (ORs) and 95% confidence intervals (CIs) being reported. Binary logistic regression analyzed the correlations between ΔFMI, ΔMMI, ΔM/F, ΔTFMI, ΔASMI, ΔA/T and incident advanced liver fibrosis, with adjusted findings presented as OR and 95% CI.

3 Results

3.1 Patient characteristics

The median duration of follow-up for the 390 readmitted individuals (200 men and 190 women) was 2.13 years, and with an average age of 61.02 ± 12.05 years. Patients with advanced liver fibrosis and non-advanced liver fibrosis at baseline were separately compared (Table 1). Statistically significant differences were observed in LSM, CAP, duration, DBP, TC, TG, ALT, AST, ALB levels and the prevalence of obesity among patients at baseline and readmission. At readmission, patients in advanced liver fibrosis group demonstrated a decrease in FMI and TFMI, while the M/F and A/T increased ($p < 0.05$; Supplementary Table S1).

Among 39 patients (30.2%) diagnosed with advanced liver fibrosis at baseline, a transition to the F0-1 stage was observed at readmission. In these cases, no significant changes were observed in body composition. Among those diagnosed with non-advanced liver fibrosis at baseline, 27.6% (72/261) progressed to the F2-3 stage. There was a significant increase in ΔBMI, ΔFMI and ΔTFMI, and a significant reduction in ΔM/F and ΔA/T levels compared to those maintained non-advanced liver fibrosis at readmission (Table 2).

3.2 Correlation of weight change patterns with liver fibrosis outcomes

Univariate correlation analysis demonstrated that ΔBMI was positively correlated with ΔLSM among patients at baseline, regardless of liver fibrosis grade ($r = 0.160$ and 0.158, respectively, $p < 0.01$; Supplementary Table S2). To further explore the effect of different BMI trends on the outcome of liver fibrosis, we categorized readmitted patients into four groups according to weight change patterns and used binary regression analysis.

After adjusting for all covariates, the stable obese group with non-advanced liver fibrosis at baseline exhibited a significantly higher risk of incident F2-3 (OR = 3.464; 95% CI = 1.989–4.735). Conversely, among patients with advanced liver fibrosis at baseline, the stable obese group demonstrated the lowest risk of incident F0-1 (OR = 0.352; 95% CI = 0.137–0.562; Table 3).

3.3 Binary logistic regression analysis of body composition changes and liver fibrosis outcomes

Among individuals with advanced liver fibrosis at baseline, all body composition metrics were significantly correlated with ΔLSM except for ΔM/F (Supplementary Table S2). Although a positive association between ΔBMI and ΔLSM was identified, contrasting results were found for muscle and fat. Specifically, ΔFMI and ΔTFMI were positively correlated with ΔLSM, while ΔMMI, ΔASMI and ΔA/T were negatively correlated with ΔLSM. Furthermore, among the fat mass metrics, ΔTFMI exhibited the most powerful relationship with ΔLSM ($r = 0.276$, $p = 0.004$; Supplementary Table S2). Similarly, we performed binary regression analysis in order to further investigate the effect of body composition changes on liver fibrosis outcomes.

After adjusting for confounders, the increased FMI group showed a significantly greater risk of incident F2-3 compared to the decreased group ($p < 0.001$; Figure 2). This trend was also observed in TFMI ($p < 0.05$). When FMI and TFMI increased, the risk of incident F2-3 was 3.618 and 3.601 times higher, respectively, in comparison to the decreased group (FMI: OR = 3.618, 95% CI = 1.794–5.739, $p < 0.001$; TFMI: OR = 3.601, 95% CI = 1.462–5.870, $p = 0.002$). Additionally, the

TABLE 1 Comparison of characteristics between baseline and readmitted subjects.

Variables	Advanced liver fibrosis at baseline(n=129)	Readmitted patients(n = 129)	p	Non-advanced liver fibrosis at baseline(n=261)	Readmitted patients(n = 261)	p
Duration (years)	6.97 ± 6.36	8.56 ± 6.95	**<0.001**	8.65 ± 6.88	9.49 ± 7.21	**0.014**
Male (n, %)	66(51.2)	/	/	134(51.3)	/	/
BMI (kg/m^2)	25.83 ± 3.20	26.31 ± 8.77	0.053	22.86 ± 3.03	23.01 ± 3.52	0.078
WHR	84.32 ± 9.95	91.62 ± 8.97	**<0.001**	82.07 ± 9.34	89.70 ± 10.43	**<0.001**
SBP (mmHg)	137.14 ± 19.30	135.04 ± 20.43	**0.026**	138.61 ± 20.05	138.55 ± 21.59	0.952
DBP (mmHg)	81.42 ± 11.29	77.81 ± 10.95	**<0.001**	77.98 ± 10.45	75.94 ± 10.90	**<0.001**
Obesity (n, %)	41(31.8)	46(35.7)	**0.012**	23(8.8)	27(10.3)	**0.023**
HT (n, %)	12(9.3)	17(13.2)	0.179	31(11.9)	33(12.6)	0.129
Current smoking (n, %)	48(37.2)	51(39.5)	0.541	25(9.6)	29(11.1)	0.421
Alcoholic consumption (n, %)	56(43.4)	43(33.3)	0.365	37(14.2)	34(13.0)	0.190
Antidiabetic treatments						
Drug naive, n (%)	34(26.4)	33(25.6)	0.122	66(25.3)	45(17.2)	**0.021**
Insulin, n (%)	40(31.0)	45(34.9)	0.239	87(33.3)	72(27.6)	**0.018**
Secretagogues, n (%)	23(17.8)	21(16.3)	0.340	45(17.2)	43(16.5)	0.098
Metformin, n (%)	49(38.0)	60(46.5)	**0.005**	65(24.9)	50(19.2)	**0.010**
TZDs, n (%)	33(25.6)	45(34.9)	**0.013**	38(14.6)	41(15.7)	0.078
AGIs, n (%)	41(31.8)	30(23.3)	**0.041**	42(16.1)	39(14.9)	0.061
DPP-4Is, n (%)	32(24.8)	28(21.7)	0.088	44(16.9)	40(15.3)	0.054
SGLT-2Is, n (%)	28(21.7)	34(26.4)	0.120	54(20.7)	59(22.6)	0.103
GLP-1RAs, n (%)	20(15.5)	24(18.6)	0.051	50(19.2)	52(19.9)	0.198
Statin use, n (%)	67(51.9)	51(39.5)	**0.039**	88(33.7)	96(36.8)	0.135
Biochemical data						
TC (mmol/L)	4.92 ± 1.29	4.73 ± 1.23	**<0.001**	4.68 ± 1.44	4.34 ± 1.20	**0.003**
TG (mmol/L)	2.25 ± 2.15	1.30 ± 0.82	**<0.001**	2.22 ± 1.89	1.49 ± 1.05	**<0.001**
HDL-c (mmol/L)	1.28 ± 0.41	1.14 ± 0.31	**<0.001**	1.01 ± 0.27	1.13 ± 0.38	**<0.001**
LDL-c (mmol/L)	2.99 ± 1.10	2.90 ± 1.02	0.085	2.73 ± 1.01	2.84 ± 1.00	**0.021**
ALT (U/L)	25.00(18.00–38.25)	20.00(14.00–31.00)	**<0.001**	21.00(15.00–31.00)	17.00(12.00–24.00)	**<0.001**
AST (U/L)	21.00(17.00–28.00)	20.00(16.00–27.00)	**<0.001**	21.00(17.00–26.00)	19.00(15.00–25.00)	**<0.001**
GGT (U/L)	32.00(22.00–54.00)	24.00(17.00–40.00)	**<0.001**	27.00(18.00–44.00)	20.00(14.00–35.00)	**<0.001**
Cr (umol/L)	76.26 ± 37.82	74.73 ± 32.96	0.287	67.18 ± 31.45	66.04 ± 55.27	0.174
eGFR (ml/min/1.73m^2)	97.50 ± 20.88	96.26 ± 25.23	0.743	92.26 ± 25.66	86.05 ± 33.61	0.211
PLT (10^9/L)	226.33 ± 71.85	223.17 ± 82.01	0.393	250.28 ± 72.37	246.81 ± 84.43	0.374
Prothrombin time, INR	0.98 ± 0.02	0.96 ± 0.21	0.261	0.93 ± 0.10	0.94 ± 0.06	0.369
ALB (g/L)	4.03 ± 0.47	3.75 ± 0.57	**<0.001**	4.00 ± 0.41	3.83 ± 0.50	**<0.001**
CRP (mg/L)	8.13(5.32–12.69)	7.23(4.65–11.82)	0.081	4.43(2.65–7.39)	5.50(3.15–9.47)	0.165
FPG (mmol/L)	6.25 ± 1.96	6.31 ± 3.97	0.761	6.35 ± 1.93	6.31 ± 2.90	0.658
HbA1c (%)	9.40 ± 2.41	9.61 ± 2.91	0.118	9.00 ± 2.19	9.05 ± 2.55	0.795
Liver measurement						
LSM (kPa)	8.36 ± 3.50	7.63 ± 2.90	**<0.001**	4.67 ± 2.14	5.28 ± 1.25	**<0.001**
CAP (dB/m)	289.54 ± 81.74	276.98 ± 75.49	**0.013**	247.85 ± 71.56	257.29 ± 73.12	**<0.001**

Data are presented as mean ± SD, number (%), or median (interquartile range). BMI, body mass index; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; PLT, platelet; INR, international normalized ratio; ALB, albumin; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; LSM, liver stiffness measurement; CAP, controlled attenuation parameter. Bold values represents as $p < 0.05$.

TABLE 2 Body composition changes in incident F0-1/F2-3 subjects.

Body composition variables	Advanced liver fibrosis at baseline(n = 129)			Non-advanced liver fibrosis at baseline(n = 261)		
	Incident F0-1(n = 39)	Advanced liver fibrosis (n = 90)	p	Incident F2-3(n = 72)	Non-advanced liver fibrosis(n = 189)	p
ΔBMI (kg/m^2)	0.31(−0.75–1.42)	0.67(−0.29–3.49)	0.092	0.46(−0.46–1.55)	−0.33(−1.31–0.62)	**0.006**
ΔFMI (kg/m^2)	0.29(−0.36–1.16)	0.69(−0.19–1.83)	0.163	0.66(−0.20–1.53)	−0.07(−0.67–0.67)	**0.006**
ΔMMI (kg/m^2)	0.14(−0.58–0.92)	0.08(−0.56–0.57)	0.674	−0.08(−0.67–0.55)	0.36(−0.41–0.84)	0.224
ΔM/F (%)	−0.10(−0.57–0.20)	−0.28(−0.65–0.11)	0.248	−0.09(−0.34–0.08)	0.12(−0.14–0.37)	**0.037**
ΔTFMI (kg/m^2)	0.09(−0.27–0.69)	0.60(−0.19–1.41)	0.052	0.53(−0.12–1.25)	−0.02(−0.5–0.42)	**0.010**
ΔASMI (kg/m^2)	0.21(−0.30–0.49)	−0.01(−0.27–0.26)	0.119	−0.04(−0.43–0.26)	0.03(−0.23–0.37)	0.229
ΔA/T (%)	−0.03(−0.33–0.14)	−0.23(−0.67–0.06)	0.102	−0.09(−0.24–0.05)	0.06(−0.13–0.26)	**0.022**

Data are presented as median (interquartile range). BMI, body mass index; FMI, fat mass index; MMI, muscle mass index; M/F, muscle/fat mass ratio; TFMI, trunk fat mass index; ASMI, appendicular skeletal muscle mass index; A/T, appendicular skeletal muscle mass/trunk fat mass ratio. Bold values represents as $p < 0.05$.

TABLE 3 Association of weight changes with incident liver fibrosis risk among readmitted patients.

Incident F2-3 among non-advanced liver fibrosis at baseline	Weight change patterns			
	Stable non-obese (reference)	Weight loss	Weight gain	Stable obese
Events/total	25/110	23/88	12/24	12/39
unadjusted	1.000	0.812(0.504–1.238)	2.029(1.052–3.013)*	4.942(2.701–7.144)*
Model 1	1.000	0.860(0.317–1.376)	1.519(1.002–2.070)*	3.277(1.545–5.054)*
Model 2	1.000	0.870(0.168–1.313)	2.065(1.550–2.563)*	3.464(1.989–4.735)*
Incident F0-1 among advanced liver fibrosis at baseline				
Events/total	13/41	18/43	2/19	6/26
unadjusted	1.000	1.804(1.217–2.475)*	1.734(0.692–2.742)	0.560(0.236–0.960)*
Model 1	1.000	1.100(0.374–2.036)	0.942(0.814–1.989)	0.586(0.358–0.794)*
Model 2	1.000	0.609(0.166–1.106)	0.681(0.063–1.252)	0.352(0.157–0.562)*

Data are presented as OR (95% CI). Model 1: adjusted for age, gender; Model 2: adjusted for age, gender, obesity, hypertension, ΔSBP, ΔDBP, ΔWHR, ΔTG, ΔTC, ΔHDL-c, ΔLDL-c, ΔALT, ΔAST, ΔGGT, ΔALB, drug use. OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALB, albumin. *$p < 0.05$.

increased MMI group appeared to have a slight advantage in preventing incident F2-3 compared to the stable group. This trend was also evident for the ASMI and A/T.

However, among individuals with non-advanced liver fibrosis at baseline, only ΔFMI was significantly correlated with ΔLSM (Supplementary Table S2). Moreover, the increased FMI group exhibited a significantly lower probability of incident F0-1 than the decreased group after adjusting for confounders ($p = 0.014$; Supplementary Figure S1).

4 Discussion

This study investigated the association between body composition changes and the outcome of liver fibrosis in a cohort of 390 patients with T2DM. Our findings indicated that middle-aged and elderly readmitted patients with T2DM who have incident advanced liver fibrosis tended to have higher BMI, FMI, and TFMI values, while M/F and A/T values were lower. Those who maintained stable obesity exhibited the highest risk of developing incident advanced liver fibrosis among non-advanced at baseline. Furthermore, subregional analysis demonstrated that non-advanced liver fibrosis patients at baseline with significant changes in FMI and TFMI were prone to develop incident advanced liver fibrosis. Conversely, Increased MMI, ASMI and A/T reduced the risk of developing incident advanced liver fibrosis. These findings highlight the potential of optimizing weight management strategies as a means of mitigating the risk of liver fibrosis in patients with T2DM.

Patients with T2DM who had advanced liver fibrosis at baseline exhibited more severe lipid metabolism disorders compared to non-advanced liver fibrosis adults, characterized by elevated TC and TG levels. Reaching the cirrhosis stage is uncommon for mild fibrosis (F1), which is generally recognized as an initial phase of NAFLD (27). However, in the context of obesity and T2DM, a considerable number of patients with fibrosis may exhibit heightened susceptibility to accelerated disease progression toward more severe liver pathology (28, 29). In addition to obesity status, there is growing research interest in investigating correlation between weight fluctuations and their impact on health outcomes, given the prevalent occurrence of weight changes throughout adulthood (30, 31). The finding of a large prospective cohort study revealed that both obesity and weight gain were positively associated with liver fibrosis progression (17). Our

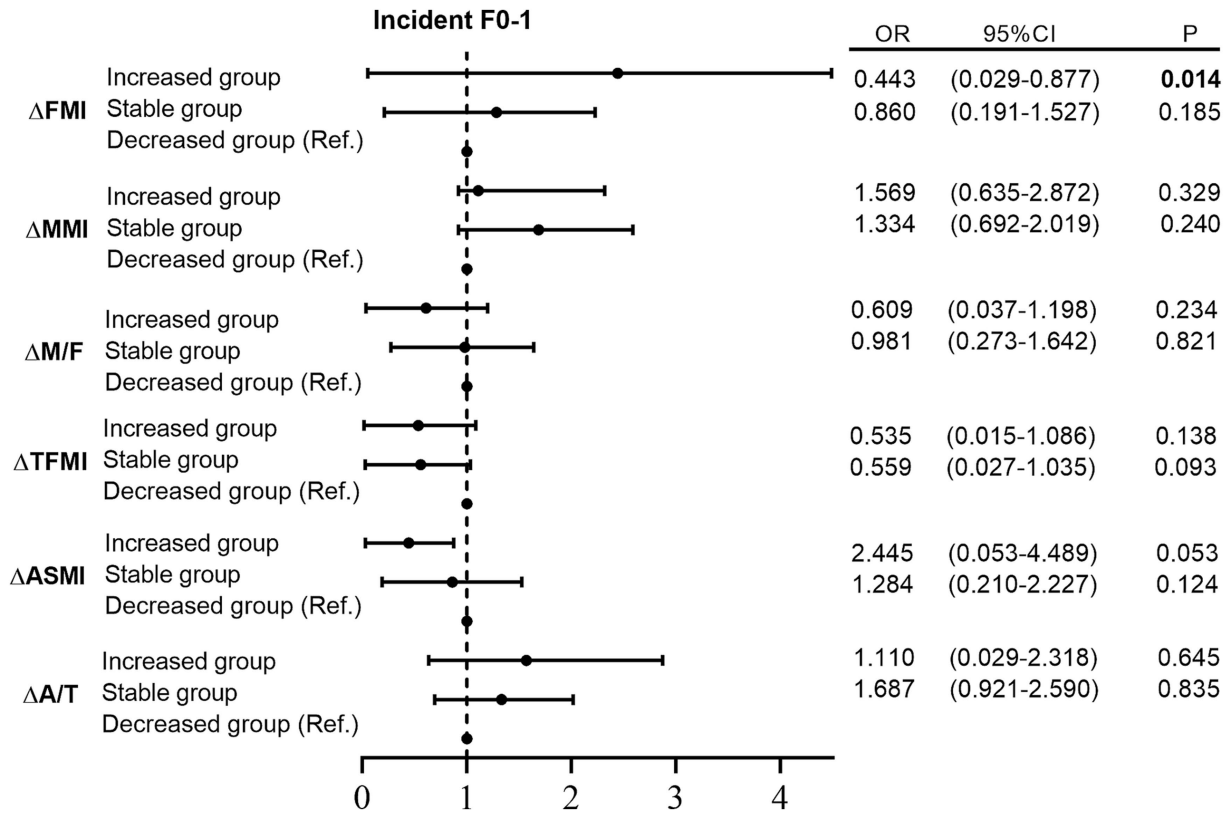

FIGURE 2
Binary logistic regression analysis between different trends of body composition and incident liver fibrosis Note: adjusted for age, gender, obesity, hypertension, drug use, ΔSBP, ΔDBP, ΔWHR, ΔTG, ΔTC, ΔHDL-c, ΔLDL-c, ΔALT, ΔAST, ΔGGT, and ΔALB. SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALB, albumin; FMI, fat mass index; MMI, muscle mass index; M/F, muscle/fat mass ratio; TFMI, trunk fat mass index; ASMI, appendicular skeletal muscle mass index; A/T, appendicular skeletal muscle mass/trunk fat mass ratio.

findings consistently highlight that stable obese individuals with T2DM face the highest risk of incident advanced liver fibrosis, underscoring the vulnerability of obese and diabetic patients and emphasizing the need for more vigilant screening measures. Elevated intrahepatic triglycerides resulting from excessive delivery of FFAs to the liver and musculoskeletal tissue contribute to fat accumulation in the liver, promoting hepatic fibrotic lesions (32). Hence, controlling weight gain emerges as a crucial strategy for reducing the risk of liver fibrosis.

Sarcopenia and NAFLD often coexist and may worsen chronic inflammation and oxidative stress linked to obesity (33). The novel results of our study demonstrated that increased ASMI and A/T over time were beneficial for preventing the progression of advanced liver fibrosis, regardless of baseline ASMI and A/T. Skeletal muscle is acknowledged as an endocrine organ to release various myokines including irisin and interleukin-6 (34, 35). Exercise is known to stimulate the release of healthy myokines and promote muscle hypertrophy. Irisin, stimulated by exercise, activates peroxisome proliferator activated receptor α signaling and is pivotal in fatty acid β-oxidation in the liver, resulting in improvements in hepatic steatosis and insulin sensitivity accompanied by the upregulation of fibroblast growth factor 21 (36, 37). Therefore, skeletal muscle could potentially influence the development or amelioration of liver fibrosis by releasing favorable myokines. Furthermore, insufficient muscle mass leads to physical disability which reduces energy expenditures, increases the risk of obesity, and contributes to hepatic steatosis (15). When categorized based on A/T trends, the findings revealed that individuals with a decreased muscle/fat ratio exhibited increased susceptibility to incident advanced liver fibrosis, even if they were non-advanced at baseline.

Chronic inflammation could serve as a crucial connection between decreased muscle mass and liver fibrosis (38). Growth differentiation factor (GDF-15), an inflammatory and sarcopenic biomarkers, was found to be associated with hepatitis and liver fibrosis in NAFLD (39). Consequently, elevated GDF-15 level may potentially influence the development of sarcopenia and the occurrence of advanced liver fibrosis. Moreover, lower serum vitamin D levels may lead to decreased muscle mass and incident advanced liver fibrosis because vitamin D deficiency is correlated to both sarcopenia and NAFLD (40).

Reduced muscle mass and increased adiposity are significant independent contributors for the pathogenesis of diabetes. Investigations have demonstrated that each one SD increase in BMI among Asians is associated with a 1.52–1.59 times higher likelihood of developing diabetes (41). However, the progression of liver fibrosis varies among individuals due to multiple factors. We observed that patients who

experienced weight gain or remained stable obese group exhibited a significantly higher risk of incident advanced liver fibrosis compared to the stable non-obese group. Additionally, the increased MMI group appeared to slightly more favorable in preventing advanced liver fibrosis when compared with the stable group. Similar trends were observed in ASMI and A/T, suggesting that changes in BMI alone may not accurately reflect changes in liver fibrosis among patients with T2DM.

The main strength of this study lies in its design as a cohort study with a substantial number of participants. We also excluded individuals with irregular thyroid function and chronic kidney diseases, which were linked to the advancement of NAFLD or sarcopenia (42, 43). Furthermore, data on the correlation between changes in body composition and incident advanced liver fibrosis at baseline and readmission is a novel contribution to the filed. However, there are several limitations needed to consider. Firstly, despite being a retrospective study, the relatively short follow-up period in our study may have limited the ability to thoroughly assess the relationship between long-term changes in body composition and the outcome of advanced liver fibrosis. Extending the follow-up time could offer more robust insights into these relationships. And the findings are associative and not causal. Secondly, the study population primarily consisted of middle-aged and elderly individuals from a single center. This may restrict the applicability of the results to other age groups. And missing data may bias the results. Thirdly, this study lacks mechanistic insight. However, following publications describing novel interactions between liver fibrosis and energy metabolism through experimental studies and transgenic models, it becomes imperative to validate these hypotheses in relevant human populations *in vivo*. Fourthly, we did not utilize other non-invasive markers like Fibrosis 4 score (FIB-4) for liver fibrosis diagnosis due to the limited number of liver fibrosis events observed. The use of such an index might resulted in overlooking many liver fibrosis events. Instead, we diagnosed incident advanced liver fibrosis using LSM rather than liver biopsy. Although liver biopsy serves as the gold standard (44, 45), conducting invasive test in a large population-based investigation was impractical. Furthermore, while we made adjustments for known confounders in our analyses, there may be unmeasured variables that could still influence the observed associations. We recommend that future research should aim to include a more comprehensive assessment of these confounders and consider longitudinal data to better capture the dynamic relationships between these factors.

5 Conclusion

We observed that persistent obesity and weight accumulation were associated with an elevated hazard of incident advanced liver fibrosis in adults with T2DM. Additionally, an increased TFMI may promotes the progression of liver fibrosis, while maintaining a balanced muscle/fat ratio could contribute to preventing advanced liver fibrosis progression.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This research received ethical approval from the Ethics Committee at the Third Affiliated Hospital of Sun Yat-sen University.

Author contributions

YL: Writing – original draft, Methodology, Data curation, Conceptualization. ZL: Writing – review & editing, Methodology, Data curation. XL: Writing – review & editing, Validation, Data curation. YC: Writing – review & editing, Conceptualization.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1476467/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Binary logistic regression analysis between different trends of body composition and incident F0-1.

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Glossary

T2DM	type 2 diabetes mellitus
BMI	body mass index
FMI	fat mass index
MMI	muscle mass index
TFMI	trunk fat mass index
ASMI	appendicular skeletal muscle mass index
M/F	body muscle mass / body fat mass
A/T	appendicular skeletal muscle mass /trunk fat mass
TE	transient elastography
LSM	liver stiffness measurement
CAP	controlled attenuation parameter
IQR	interquartile range
NAFLD	nonalcoholic fatty liver disease
WHR	waist to hip ratio
TC	total cholesterol
TG	triglyceride
HDL-c	high-density lipoprotein cholesterol
LDL-c	low-density lipoprotein cholesterol
ALT	alanine aminotransferase
AST	aspartate aminotransferase
GGT	γ-glutamyl transferase
Cr	creatinine
CRP	C-reactive protein
PLT	platelet
INR	international normalized ratio
ALB	albumin
FPG	fasting plasma glucose
eGFR	estimated glomerular filtration rate
HbA1c	glycosylated hemoglobin
SBP	systolic blood pressure
DBP	diastolic blood pressure
DEXA	dual-energy X-ray absorptiometry
SDs	standard deviations
ORs	odds ratios
CIs	confidence intervals
GDF-15	growth differentiation factor
FIB-4	fibrosis 4 score

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U-shaped association of serum vitamin A concentrations with all-cause mortality in patients with NAFLD: results from the NHANES database prospective cohort study

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Background: Previous studies have demonstrated a significant association between serum vitamin A concentration and non-alcoholic fatty liver disease (NAFLD) development. However, the long-term prognostic implications of serum vitamin A in patients with NAFLD remain underexplored. This study aims to investigate whether there exists a correlation between serum vitamin A concentrations and overall mortality among subjects diagnosed with NAFLD.

Methods: To investigate the association between serum vitamin A concentrations and NAFLD outcomes, we conducted prospective cohort studies using data from the 1999–2006 and 2017–2018 National Health and Nutrition Examination Survey (NHANES). We utilized a multivariate Cox regression model to explore the relationship between serum vitamin A levels and all-cause mortality. Survival curves related to serum vitamin A were constructed using the Kaplan–Meier method. Additionally, the restricted cubic splines (RCS) method was applied to examine potential nonlinear relationships between serum vitamin A concentrations and all-cause mortality of NAFLD.

Results: Over a median follow-up period of 10.3 years, a total of 1,399 all-cause deaths were recorded. The weighted average concentration of serum vitamin A was 61.48 ± 0.37 μg/dL. After adjusting for potential confounders, a significant U-shaped relationship was identified between serum vitamin A concentrations and the risk of all-cause mortality in NAFLD patients. This relationship was particularly pronounced in men and elderly individuals aged 60 to 85.

Conclusion: Our study reveals a significant non-linear relationship between serum vitamin A concentrations and the risk of all-cause mortality in patients with NAFLD. These findings underscore the importance of monitoring and maintaining optimal serum vitamin A levels to potentially improve survival outcomes in NAFLD patients.

KEYWORDS

serum vitamin A, all-cause mortality, NAFLD, NHANES, nonlinear

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) affects approximately 30% of the global population and represents a significant global public health concern due to its increasing prevalence (1, 2). It is defined by fat accumulation in hepatocytes without secondary hepatic steatosis causes, such as excessive alcohol consumption, viral hepatitis, or genetic disorders (3). NAFLD encompasses a spectrum of hepatic damage, ranging from simple steatosis to more severe conditions such as non-alcoholic steatohepatitis (NASH), with or without fibrosis, cirrhosis, and hepatocellular carcinoma (4). Despite its global prevalence, the precise mechanisms underlying the onset and progression of NAFLD remain poorly understood. The multiple parallel hit hypothesis states that NAFLD develops through complex interactions involving insulin resistance, adipokine secretion, oxidative stress, lipid peroxidation, mitochondrial damage, endoplasmic reticulum stress, intestinal microbiota, innate immunity, genetics, and epigenetic mechanisms (4). Oxidative stress and inflammation are believed to play critical roles in the transition from steatosis to NASH (5–7).

Patatin-like Phospholipase Domain Containing 3 (PNPLA3) is a multifunctional enzyme that acts as a triglyceride hydrolase, retinyl esterase, and acetyl-CoA-independent transacylase and promotes the release of retinol from lipid droplets (8–10). Pirazzi et al. reported that PNPLA3 can specifically hydrolyze retinyl palmitate in human hepatic stellate cells (HSCs), with this enzymatic activity significantly reduced in the PNPLA3-I148M variant (11). Other studies indicate that the PNPLA3-I148M variant may lead to lower serum retinol levels in patients with NAFLD, accompanied by hepatic accumulation of retinyl esters and triglycerides (4). Recent genetic studies have demonstrated that the PNPLA3-I148M variant is an independent risk factor for the development and severity of liver fibrosis, regulating the activity of HSCs and leading to a pro-inflammatory and pro-fibrotic phenotype (12). Vitamin A, a vital fat-soluble vitamin essential for human physiology, plays a crucial role in several physiological processes such as vision, cell proliferation, and differentiation, immune regulation, embryogenesis, glucose, and lipid metabolism. Approximately 60–95% of the body's vitamin A is stored in the form of retinyl esters in HSCs (9, 10). Previous studies have suggested that vitamin A and its metabolites may have therapeutic potential for liver diseases (9, 13). Therefore, we hypothesized that there might be a connection between serum vitamin A levels and NAFLD. Lotfi et al. found that higher vitamin A intake was associated with a lower risk of developing NAFLD (14). Mazidi et al. observed that a higher quartile of serum retinol was associated with a reduced risk of NAFLD (15). Furthermore, several studies have indicated a positive correlation between serum vitamin A levels and the severity of NAFLD (16, 17). However, the relationship between serum vitamin A levels and the long-term prognosis of patients with NAFLD remains insufficiently explored. Based on these findings, we investigated the relationship between serum vitamin A concentrations and all-cause mortality in a nationally representative sample of American NAFLD patients.

2 Materials and methods

2.1 Study design and subjects

The data utilized in this study were obtained publicly from the National Health and Nutrition Examination Survey (NHANES) database. NHANES is a nationwide survey and examination program conducted by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC) in the United States since 1999. All data were collected through household interviews, mobile examinations, and laboratory tests. All participants provided written informed consent. NHANES interviews gather data on demographic characteristics, dietary intake, physical examinations, and laboratory tests to assess disease prevalence, risk factors, and nutritional status among the non-institutionalized civilian population of the United States. For more information on NHANES, please refer to the relevant website.[1]

Data for this study were obtained from the NHANES conducted during 1999–2006 and 2017–2018. Due to the absence of abdominal ultrasound data in the NHANES database, the United States Fatty Liver Index (US FLI) was employed to diagnose NAFLD (18). To ensure the reliability of the study, participants were excluded based on the following criteria: (1) individuals under 18 years of age ($N = 22{,}248$); (2) those with missing serum vitamin A data ($N = 3{,}492$); (3) individuals with missing mortality rate data ($N = 48$), and (4) individuals meeting criteria such as excessive alcohol consumption (men >3 drinks/day, women >2 drinks/day), positive hepatitis B or C status, missing US FLI components, or US FLI ≤30 ($N = 18{,}803$) (18, 19). After applying these exclusion criteria, the final study population comprised 6,137 NAFLD participants. Figure 1 outlines the detailed flowchart illustrating the participant selection process.

2.2 Serum vitamin A

Serum samples in this study were collected, processed, and stored according to standardized protocols. Comprehensive details of all assay procedures can be accessed on the official NHANES website. Serum vitamin A concentrations were quantified using high-performance liquid chromatography and photodiode array detection. To explore the association between various serum vitamin A concentrations and all-cause mortality rates among NAFLD patients, the concentrations were divided into four groups by the quartile values: Q1 [0.7, 46.1], Q2 (46.1, 56.8], Q3 (56.8, 69.2], and Q4 (69.2, 185] μg/dL.

2.3 Non-alcoholic fatty liver disease

Liver biopsy is recognized as the gold standard for diagnosing NAFLD; however, its use is restricted due to its invasiveness and high cost. Consequently, the improved US FLI and the Fibrosis4 (FIB4) scores were employed to assess NHANES in this study. The US FLI has demonstrated predictive capabilities for hepatic steatosis. US FLI >30 is used to define NAFLD (18). The Fibrosis-4 score (FIB4 score) is employed to evaluate the risk of advanced fibrosis, with a threshold set at 2.67 (20).

The formulas are as follows:

$$\text{US FLI} = \left(e^{-0.8073 \times \text{non-Hispanic black} + 0.3458 \times \text{Mexican American} + 0.0093 \times \text{age} + 0.6151 \times \ln(\text{GGT}) + 0.0249 \times \text{waist circumference} + 1.1792 \times \ln(\text{insulin}) + 0.8242 \times \ln(\text{glucose}) - 14.7812}\right) / \left(1 + e^{-0.8073 \times \text{non-Hispanic black} + 0.3458 \times \text{Mexican American} + 0.0093 \times \text{age} + 0.6151 \times \ln(\text{GGT}) + 0.0249 \times \text{waist circumference} + 1.1792 \times \ln(\text{insulin}) + 0.8242 \times \ln(\text{glucose}) - 14.7812}\right) \times 100$$ (18, 21).

1 https://www.cdc.gov/nchs/nhanes/index.htm

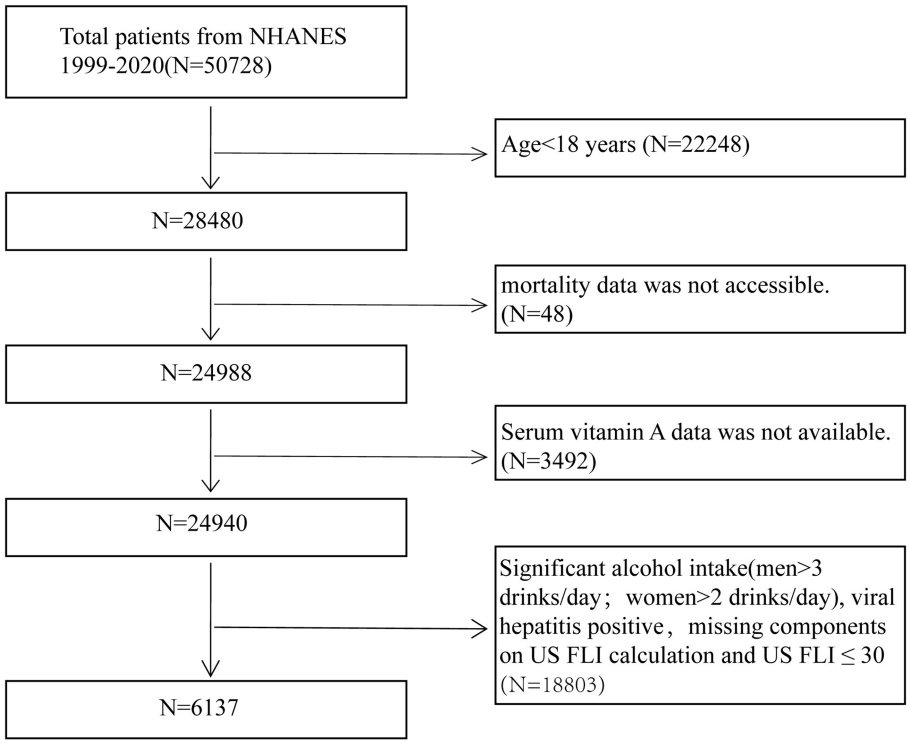

FIGURE 1
Flow-chart of the study samples.

FIB4 score = Age (year) × AST (IU/L)/(platelet count (109/L) × square-root of ALT (IU/L)) (22).

2.4 The mortality data

The mortality data utilized in this study were linked to the National Death Index (NDI), a comprehensive database maintained by the NCHS that covers all deaths in the United States. Each participant's follow-up time was from the survey date until their date of death or until December 31, 2019. Detailed mortality data in this study can be accessed through the NHANES Public-Use Linked Mortality Files, available at the following web address: https://www.cdc.gov/nchs/data-linkage/mortality-public.htm.

2.5 Covariates

Covariates associated with NAFLD include age, sex, race, glycated hemoglobin A1c (HbA1c), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT, uric acid, high-density lipoprotein (HDL), low-density lipoprotein (LDL), alkaline phosphatase (ALP), serum cholesterol, serum triglycerides, and energy intake. Race was classified into four groups: non-Hispanic White, non-Hispanic Black, Mexican American, and other races. Body mass index (BMI) was categorized into 3 groups: <25 kg/m^2 (normal), 25–30 kg/m^2 (overweight), and ≥ 30 kg/m^2 (obesity) (23, 24). Smoking behavior was classified as current, former, and never smokers. Drinking behavior was categorized into five groups: (1) never drinkers, (2) mild drinkers (<2 drinks/day for females, <3drinks/day for males), (3) moderate drinkers (≥2 drinks/day for females, ≥3drinks/day for males, or binge drinking ≥2 days/month), (4) heavy drinkers (≥3 drinks/day for females, ≥4 drinks/day for males, or ≥ 4 drinks on a single occasion for females, ≥5 drinks for males), and (5) those with unavailable drinking data (25). Participants' physical activity levels were categorized into four groups according to the 2018 Physical Activity Guidelines for Americans: low (<500 metabolic equivalent (MET) – minutes per week), moderate (≥500 to <1,000 MET-minutes per week), high (≥1,000 to <1,500 MET-minutes per week), and very high (≥1,500 MET-minutes per week) (26). Diabetes was diagnosed using predefined criteria, including self-report, current use of anti-diabetic medications, HbA1c levels≥6.5%, or fasting blood glucose (FPG) ≥ 126 mg/dL (7 mmol/L) (27). Hypertension was defined as the existence of one of the following conditions: (1) self-reported hypertension, (2) current use of antihypertensive medications, or (3) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg (28). Hyperlipidemia was diagnosed if participants met any of the following conditions: (1) triglycerides (TG) ≥150 mg/dL, (2) total cholesterol (TC) ≥ 200 mg/dL, (3) low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL, (4) high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL for males and < 50 mg/dL for females, or (5) receipt of lipid-lowering medication (29).

2.6 Statistical analysis

This study's analyses adhered to the NHANES guidelines and utilized a non-random, stratified sampling design. Continuous

variables were presented as weighted means ± standard error (SE) and were examined using weighted linear regression models. Categorical variables were reported as percentages ± SE and were analyzed using weighted Rao-Scott chi-square tests. The multivariate Cox regression analysis was conducted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality in NAFLD patients based on serum vitamin A levels. Three models were developed, each adjusting for different potential confounders: Model 1 without adjustments, Model 2 adjusting for sex, age, and race, and Model 3 further adjusting for BMI, smoking behavior and drinking behavior, physical activity level, energy intake, CRP, diabetes status, and hypertension status. Stratified analyses and interaction tests were performed based on various factors including age groups (18–39, 40–59, 60–85 years), sex (male/female), BMI (<25 kg/m^2 or ≥ 25 kg/m^2, <30 kg/m^2 or ≥ 30 kg/m^2), diabetes status, hypertension status, and advanced fibrosis status. The association between serum vitamin A levels and survival was illustrated using Kaplan–Meier curves, with comparisons conducted using the log-rank test. Restricted cubic spline (RCS) curves with four nodes (5th, 35th, 65th, and 95th percentiles) were utilized to display the potential non-linear relationships between serum vitamin A levels and all-cause mortality in NAFLD patients. p-values ≤ 0.05 were considered statistically significant. Statistical analyses were conducted using the R software (version 4.2.0).

3 Results

3.1 Basic characteristics of study participants

Table 1 presents the baseline characteristics of the entire study population. The mean age of participants was 50 ± 0.39 years old. The average follow-up period was 10.3 years, culminating in 1399 cases of all-cause mortality. The weighted mean concentration of serum vitamin A was 61.48 ± 0.37 μg/dL. Participants with NAFLD were predominantly obese men, of non-Hispanic white race, with a history of non-smoking or former smoking and mild drinking behavior. Baseline data distribution varied significantly among groups. Compared to those with low serum vitamin A levels, participants with higher levels were more likely to be male, overweight (25–30 kg/m^2), non-Hispanic White, and have a history of smoking or mild alcohol consumption. Higher serum vitamin A levels were also associated with a greater incidence of hypertension and hyperlipidemia. Additionally, this group showed other metabolic disturbances, including elevated serum ALT, GGT, uric acid, LDL, cholesterol, and triglycerides, while observing an opposing trend for ALP and CRP levels.

Subsequently, we examined whether there were differences in the severity of liver fibrosis among the four groups, determined by a FIB-4 score. We categorized liver fibrosis into two classifications: non-advanced (≤ 2.67) and advanced (> 2.67). The majority of patients with NAFLD had non-advanced liver fibrosis. The highest proportion of advanced liver fibrosis occurred in patients with low serum vitamin A levels ($p < 0.05$).

3.2 Association between serum vitamin A level and all-cause mortality

The study utilized three Cox regression models to explore the independent effect of serum vitamin A levels on all-cause mortality in patients with NAFLD. As illustrated in Table 2, Model 1 revealed a significant association between serum vitamin A levels and an increased risk of all-cause mortality. Specifically, NAFLD patients in the highest serum vitamin A quartile (Q4) exhibited a greater risk of all-cause mortality compared to those in the lowest quartile (Q1). However, after adjusting for relevant variables (Models 2 and 3), serum vitamin A levels were significantly linked to a decreased risk of all-cause mortality among NAFLD patients. Notably, in Model 3, the group with moderate serum vitamin A levels (Q2) had the lowest mortality risk compared to Q1 (HR = 0.633, 95% CI = 0.456–0.880). The groups with higher serum vitamin A levels (Q3 and Q4) also had lower mortality risks than Q1, with Q3 showing HR = 0.727, 95% CI = 0.541–0.976, and Q4 showing HR = 0.663, 95% CI = 0.499–0.880. However, the trend test was insignificant (p for trend = 0.077), suggesting a potential nonlinear relationship between serum vitamin A levels and all-cause mortality.

3.3 Subgroup analysis

To further elucidate the complex relationship between serum vitamin A levels and all-cause mortality in NAFLD patients, stratified analyses and interaction tests were performed based on sex, age, BMI, diabetes status, hypertension status, and advanced fibrosis status. Details are presented in Table 3. This study demonstrated consistent results when stratified by BMI, diabetes, hypertension, and advanced fibrosis (p for interaction >0.05). However, significant interactions were observed when stratified by sex and age (p for interaction <0.05), indicating a more pronounced correlation between serum vitamin A levels and all-cause mortality in male and elderly NAFLD patients. Consequently, a thorough examination of the relationship between serum vitamin A and all-cause mortality was conducted across different sex and age categories. Supplementary Tables S1, S2 demonstrate that these associations remain generally consistent among the elderly (60–85 years) and male populations. Additionally, we conducted a Kaplan–Meier analysis on elderly (aged 60–85) and male NAFLD patients, revealing that those in the Q2 group had the lowest risk of all-cause mortality (Log-rank $p < 0.05$), consistent with the Cox regression results (Figure 2).

3.4 Dose–response relationship between serum vitamin A levels and all-cause mortality in NAFLD patients

Figure 3 vividly illustrates the dose–response relationship between serum vitamin A levels and all-cause mortality in NAFLD patients. A notable U-shaped association was identified by applying the RCS model with comprehensive adjustment for all variables (p for non-linearity <0.001, p for overall <0.001), with a crucial threshold identified at 64.5 μg/dL.

TABLE 1 Baseline characteristics of participants according to serum vitamin A concentrations.

Character	Serum vitamin A concentrations (ug/dL)					*p* value
	Total	Q1 [0.7,46.1]	Q2 (46.1,56.8]	Q3 (56.8,69.2]	Q4 (69.2,185]	
Number of participants	6,137 (100)	1,538 (25.06)	1,532 (24.96)	1,534 (25.00)	1,533 (24.98)	
Age (year)	50 (0.39)	44 (0.60)	47 (0.60)	51 (0.63)	55 (0.52)	< 0.0001
BMI (kg/m^2)	31.53 (0.12)	33.88 (0.28)	32.44 (0.21)	31.17 (0.19)	29.66 (0.16)	< 0.0001
HbA1c	5.67 (0.02)	5.75 (0.04)	5.63 (0.03)	5.67 (0.04)	5.65 (0.03)	0.12
ALT (U/L)	27 (0.55)	25 (0.82)	27 (0.54)	28 (0.58)	29 (1.74)	0.03
AST (U/L)	25 (0.23)	23 (0.74)	24 (0.44)	25 (0.45)	25 (0.29)	0.12
GGT (U/L)	33 (0.62)	29 (1.18)	31 (1.18)	32 (1.06)	37 (1.12)	< 0.0001
CRP (mg/L)	0.54 (0.02)	0.86 (0.05)	0.63 (0.05)	0.46 (0.02)	0.39 (0.02)	< 0.0001
Uric acid (mg/dL)	6 (0.03)	5 (0.05)	6 (0.04)	6 (0.04)	6 (0.04)	< 0.0001
HDL (mg/dL)	49 (0.23)	49 (0.46)	48 (0.42)	48 (0.42)	50 (0.41)	< 0.0001
LDL (mg/dL)	122 (0.78)	115 (1.45)	122 (1.53)	125 (1.25)	125 (1.56)	< 0.0001
ALP (U/L)	76 (0.46)	83 (1.09)	76 (0.81)	75 (0.79)	71 (0.83)	< 0.0001
Serum triglyceridel (mg/dL)	167 (2.66)	125 (3.67)	150 (4.33)	169 (2.66)	207 (6.04)	< 0.0001
Serum Cholesterol (mg/dL)	203 (1.02)	189 (1.70)	198 (1.67)	206 (1.52)	215 (1.85)	< 0.0001
Energy intake (kcal/d)	2,180 (18)	1,987 (37)	2,222 (33)	2,202 (39)	2,245 (35)	< 0.0001
Serum VA (μg/dL)	61.48 (0.37)	38.67 (0.20)	51.82 (0.12)	62.82 (0.12)	82.47 (0.43)	< 0.0001
FLI	70.04 (0.39)	70.66 (0.72)	70.67 (0.67)	70.04 (0.74)	69.11 (0.74)	0.39
FIB4 score	1.02 (0.01)	0.90 (0.03)	0.94 (0.02)	1.06 (0.02)	1.12 (0.02)	< 0.0001
Sex						< 0.0001
Male	53.51 (0.02)	30.93 (1.79)	50.43 (1.49)	58.74 (1.56)	65.22 (1.29)	
Female	46.49 (0.02)	69.07 (1.79)	49.57 (1.49)	41.26 (1.56)	34.78 (1.29)	
Race						< 0.0001
Non-Hispanic White	70.83 (0.03)	47.07 (2.36)	67.50 (1.96)	75.81 (1.91)	83.74 (1.44)	
Non-Hispanic Black	11.06 (0.01)	22.40 (1.91)	11.79 (1.19)	8.52 (0.89)	5.75 (0.64)	
Mexican American	7.53 (0.01)	15.08 (1.54)	8.65 (1.01)	6.12 (0.83)	3.21 (0.42)	
Other	10.58 (0.01)	15.44 (1.90)	12.06 (1.35)	9.54 (1.28)	7.30 (1.06)	
BMI category						< 0.0001
<25	8.30 (0.01)	4.23 (0.67)	5.31 (0.83)	8.07 (1.00)	13.55 (1.16)	
≥25, <30	39.81 (0.02)	26.36 (1.56)	36.69 (1.69)	42.65 (1.79)	48.13 (1.82)	
≥30	51.88 (0.02)	69.40 (1.64)	58.00 (1.78)	49.29 (1.83)	38.32 (1.66)	
Physical activity						0.09
Mild	32.08 (0.01)	38.63 (2.22)	39.01 (1.83)	45.93 (2.16)	41.60 (1.86)	
Moderate	14.59 (0.01)	16.99 (1.66)	20.22 (1.62)	17.53 (1.59)	20.41 (1.53)	
High	6.89 (0.01)	9.40 (1.14)	8.22 (1.00)	8.57 (1.06)	9.65 (1.06)	
Very high	23.40 (0.01)	34.97 (2.34)	32.55 (1.92)	27.96 (1.91)	28.35 (1.51)	
Smoking behavior						< 0.0001
Current smoke	16.00 (0.01)	18.02 (1.66)	17.99 (1.41)	15.49 (1.18)	13.57 (1.11)	
Ever smoke	30.38 (0.01)	18.85 (1.94)	27.92 (1.55)	32.13 (1.58)	37.95 (1.71)	
Never smoke	51.86 (0.02)	60.35 (2.35)	51.17 (1.76)	51.23 (1.82)	47.75 (1.50)	
Not recorded	1.76 (0.00)	2.78 (0.38)	2.91 (0.40)	1.16 (0.23)	0.72 (0.17)	
Dinking behavior						< 0.0001
Never drunk	11.90 (0.01)	15.10 (0.97)	13.66 (1.49)	10.24 (1.46)	9.98 (0.85)	
Mild drunk	41.36 (0.02)	30.12 (1.89)	38.41 (1.79)	44.58 (1.97)	47.80 (1.90)	

(Continued)

TABLE 1 (Continued)

Character	Serum vitamin A concentrations (ug/dL)					*p* value
	Total	Q1 [0.7,46.1]	Q2 (46.1,56.8]	Q3 (56.8,69.2]	Q4 (69.2,185]	
Moderate drunk	15.70 (0.01)	17.91 (1.53)	17.09 (1.46)	13.52 (1.11)	15.19 (1.29)	
Heavy drunk	1.19 (0.00)	0.31 (0.10)	0.82 (0.34)	1.02 (0.28)	2.19 (0.50)	
Not recorded	29.86 (0.01)	36.56 (1.84)	30.02 (1.73)	30.63 (1.64)	24.85 (1.49)	
Hypertension						< 0.0001
No	51.65 (0.02)	62.90 (1.85)	58.13 (1.72)	49.19 (1.96)	41.55 (1.84)	
Yes	48.35 (0.02)	37.10 (1.85)	41.87 (1.72)	50.81 (1.96)	58.45 (1.84)	
Diabetes						0.25
No	80.57 (0.03)	80.31 (1.22)	84.24 (1.16)	82.62 (1.65)	81.15 (1.29)	
Yes	17.48 (0.01)	19.69 (1.22)	15.76 (1.16)	17.38 (1.65)	18.85 (1.29)	
Hyperlipidemia						< 0.0001
No	16.15 (0.01)	24.88 (1.49)	20.43 (1.48)	15.53 (1.20)	7.74 (1.04)	
Yes	83.85 (0.03)	75.12 (1.49)	79.57 (1.48)	84.47 (1.20)	92.26 (1.04)	
FIB4 score						0.02
≤ 2.67	97.88 (0.03)	97.17 (0.51)	98.75 (0.27)	98.27 (0.32)	98.51 (0.34)	
> 2.67	1.74 (0.00)	2.83 (0.51)	1.25 (0.27)	1.73 (0.32)	1.49 (0.34)	

Data are expressed as weighted proportions ± Standard Error (SE) for categorical variables and as weighted means ± SE for continuous variables. Linear regression and Rao-Scott chi-square test were used to compare groups. BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GGT, gamma-glutamyl transferase; CRP, C-reactive protein; ALP, alkaline phosphatase; FLI, fat liver index; FIB4 score, Fibrosis-4 scores; Serum VA, Serum Vitamin A.

TABLE 2 HRs (95% CIs) for all-cause mortality according to serum vitamin A concentrations among participants.

Serum VA (per SD increase) (μg/dL)	Model 1 OR (95% CI)	*p* value	Model 2 OR (95% CI)	*p* value	Model 3 OR (95% CI)	*p* value
Q1 [0.7,46.1]	Reference		Reference		Reference	
Q2 (46.1,56.8]	0.835 (0.643,1.084)	0.175	0.619 (0.497,0.771)	<0.0001	0.633 (0.456,0.880)	0.006
Q3 (56.8,69.2]	1.230 (0.963,1.570)	0.097	0.668 (0.543,0.821)	<0.001	0.727 (0.541,0.976)	0.034
Q4 (69.2,185]	1.485 (1.181,1.868)	<0.001	0.648 (0.529,0.794)	<0.0001	0.663 (0.499,0.880)	0.004
p for trend		<0.0001		0.006		0.077

Model 1: no covariates were adjusted; Model 2: Age, sex, and race were adjusted; Model 3: Adjusted for age, sex, race, BMI, smoking behavior, drinking behavior, physical activity, energy intake, CRP, diabetes, and hypertension status. Abbreviations: HRs, hazard ratios; 95%CI, 95% confidence interval; BMI, body mass index; CRP, C-reactive protein.

4 Discussion

This study employed a prospective cohort design to investigate the relationship between serum vitamin A levels and all-cause mortality in NAFLD patients. The results revealed a U-shaped association between serum vitamin A concentrations and all-cause mortality, indicating that excessively low and high vitamin A levels increase mortality risk. This relationship was particularly pronounced among elderly individuals (aged 60–85) and males. To our knowledge, this is the first study to examine the association between serum vitamin A levels and all-cause mortality in the NAFLD population.

Current research on serum vitamin A levels and mortality rates largely focuses on pediatric populations, with less emphasis on studies involving adults. Abhishek Goyal et al. employed Cox regression analysis to reveal a substantial correlation between serum vitamin A levels and all-cause mortality in the overall population. Their findings indicate a noticeable reduction in mortality risk from Q2 to Q4 in comparison to the initial quintile Q1, while Q5 demonstrates a relative escalation in mortality risk (30). However, they did not conduct an in-depth analysis. An additional investigation discovered a strong correlation between reduced serum retinol levels and heightened occurrences of liver fibrosis and liver-related mortality within a cohort of American adults. For individuals with chronic liver disease (CLD), those in the lowest retinol category exhibited a significantly increased HR for liver-related mortality, reaching 7.76 (95% CI, 1.19–50.5) compared to the highest retinol group. However, no significant difference was observed in all-cause mortality (31). To date, there are no reported clinical studies on the relationship between serum vitamin A levels and all-cause mortality in the NAFLD population. Our study is the first to identify a U-shaped association between serum vitamin A levels and all-cause mortality in individuals with NAFLD.

We conducted stratified analyses to further identify subgroups of NAFLD patients for whom serum vitamin A levels are most strongly associated with all-cause mortality. The results revealed that sex and age are significant influencing factors. Specifically, the association between serum vitamin A levels and the risk of all-cause mortality is more pronounced in elderly individuals (aged 60–85) and males.

TABLE 3 Associations between serum vitamin A and all-cause mortality in NAFLD participants, stratified by age, sex, BMI, diabetes status, hypertension status, and advanced fibrosis status.

Subgroup	Q1 [0.7,46.1]	Q2 (46.1,56.8]	Q3 (56.8,69.2]	Q4 (69.2,185]	*p* for trend	*p* for interaction
Sex						0.005
Male	Reference	0.452 (0.280,0.728)	0.765 (0.512,1.144)	0.587 (0.394,0.873)	0.387	
Female	Reference	0.935 (0.615,1.423)	0.599 (0.390,0.922)	0.795 (0.559,1.131)	0.162	
Age						0.018
18–39	Reference	0.500 (0.094, 2.661)	1.128 (0.266, 4.787)	1.219 (0.250, 5.940)	0.481	
40–59	Reference	0.430 (0.203,0.913)	1.044 (0.607,1.794)	0.670 (0.346,1.296)	0.978	
60–85	Reference	0.647 (0.444,0.943)	0.590 (0.417,0.836)	0.617 (0.430,0.884)	0.052	
BMI						0.375
< 25	Reference	1.028 (0.427,2.475)	0.893 (0.389,2.051)	0.626 (0.283,1.384)	0.075	
≥ 25, <30	Reference	0.670 (0.419,1.072)	0.736 (0.504,1.073)	0.685 (0.488,0.963)	0.211	
≥ 30	Reference	0.621 (0.393,0.980)	0.809 (0.534,1.228)	0.750 (0.483,1.166)	0.594	
Diabetes status						0.345
No	Reference	0.610 (0.415,0.896)	0.700 (0.513,0.955)	0.573 (0.430,0.765)	0.002	
Yes	Reference	0.784 (0.411,1.497)	0.886 (0.450,1.743)	1.086 (0.568,2.073)	0.414	
Hypertension status						0.275
No	Reference	0.524 (0.300,0.916)	0.703 (0.419,1.180)	0.498 (0.287,0.865)	0.073	
Yes	Reference	0.705 (0.475,1.047)	0.744 (0.513,1.081)	0.761 (0.540,1.071)	0.428	
Advanced fibrosis						0.719
No (FIB4 score ≤ 2.67)	Reference	0.645 (0.445,0.936)	0.737 (0.517,1.050)	0.696 (0.500,0.969)	0.217	
Yes (FIB4 score>2.67)	Reference	1.110 (0.417,2.953)	1.388 (0.636,3.032)	0.956 (0.342,2.676)	0.855	

Adjusted for age, sex, race, BMI, smoking behavior, drinking behavior, physical activity, energy intake, CRP, diabetes status, and hypertension status, except the variable itself. Abbreviations: 95%CI, 95% confidence interval; BMI, body mass index; CRP, C-reactive protein; FIB4 score, Fibrosis-4 scores.

Previous studies have suggested that NAFLD may be more severe in older populations. For instance, Mazen Noureddin et al. found a significant increase in the prevalence and severity of NAFLD among participants aged 60 or older (32). Frith et al. also observed higher rates of fibrosis and cirrhosis in elderly NAFLD patients (33). Pegah et al.'s study showed a common occurrence of NAFLD in older adults, associated with increased mortality risk in individuals aged 60–74 with NAFLD (29). Furthermore, Sun Q et al. noted that lower serum retinol levels (<50 μg/dL) were linked to increased mortality among participants aged 60 years and older with prediabetes and diabetes, potentially attributed to the increased susceptibility to malnutrition in older age, underscoring the importance of adequate vitamin A intake for nutritional enhancement (34). However, the specific relationship between serum vitamin A levels and all-cause mortality risk in older adults requires further investigation. Additionally, male predominance in NAFLD prevalence over females is believed to be influenced by the protective effects of estrogen in premenopausal women (2, 5). Several studies have underscored estrogen's significant roles in antioxidative, anti-inflammatory, anti-apoptotic, and potential anti-fibrotic processes (5, 35–37). However, there have been no definitive reports on the relationship between serum vitamin A levels and all-cause mortality rates among different sexes. Although the exact mechanisms of these results remain unclear, clinical health management should pay particular attention to serum vitamin A levels in older adults (aged 60–85 years) and male populations.

The potential mechanisms underlying the relationship between serum vitamin A levels and all-cause mortality rates in NAFLD patients remain unclear. Oxidative stress, characterized by an imbalance between the generation of reactive oxygen species (ROS) and the clearance capacity of antioxidant systems such as superoxide dismutase and catalase, is believed to play a crucial role (4). Vitamin A exerts significant antioxidant effects in liver diseases and plays a critical role in controlling cell growth and differentiation (4, 16). It can inhibit the production of pro-inflammatory cytokines in macrophages, reduce inflammatory responses, suppress hepatocyte transformation, and inhibit liver cancer cell proliferation (38–41). Our findings showed that advanced liver fibrosis was most prevalent among patients with low serum vitamin A levels. Similarly, Song J et al. found that individuals with CLD who had the lowest retinol levels were significantly more likely to develop fibrosis and liver-related mortality compared to those with higher levels (31). A possible explanation for this is that the depletion of vitamin A may lead to oxidative stress-mediated damage observed in advanced liver disease. After liver injury, HSCs become activated and transform from vitamin A-rich, quiescent cells into proliferative and fibrogenic myofibroblasts. These activated cells produce excessive extracellular matrix, leading to liver fibrosis. Concurrently, there is a loss of characteristic perinuclear lipid droplets containing retinol (vitamin A), possibly leading to a loss of the ability of HSCs to store vitamin A (7, 11). However, our study revealed a U-shaped relationship between serum vitamin A levels and all-cause mortality in NAFLD patients. This may be due to excessive vitamin A metabolism, which could lead to an over-release of retinol-binding protein (RBP)/retinol complexes, thereby increasing lipid accumulation in liver cells and contributing to NAFLD progression.

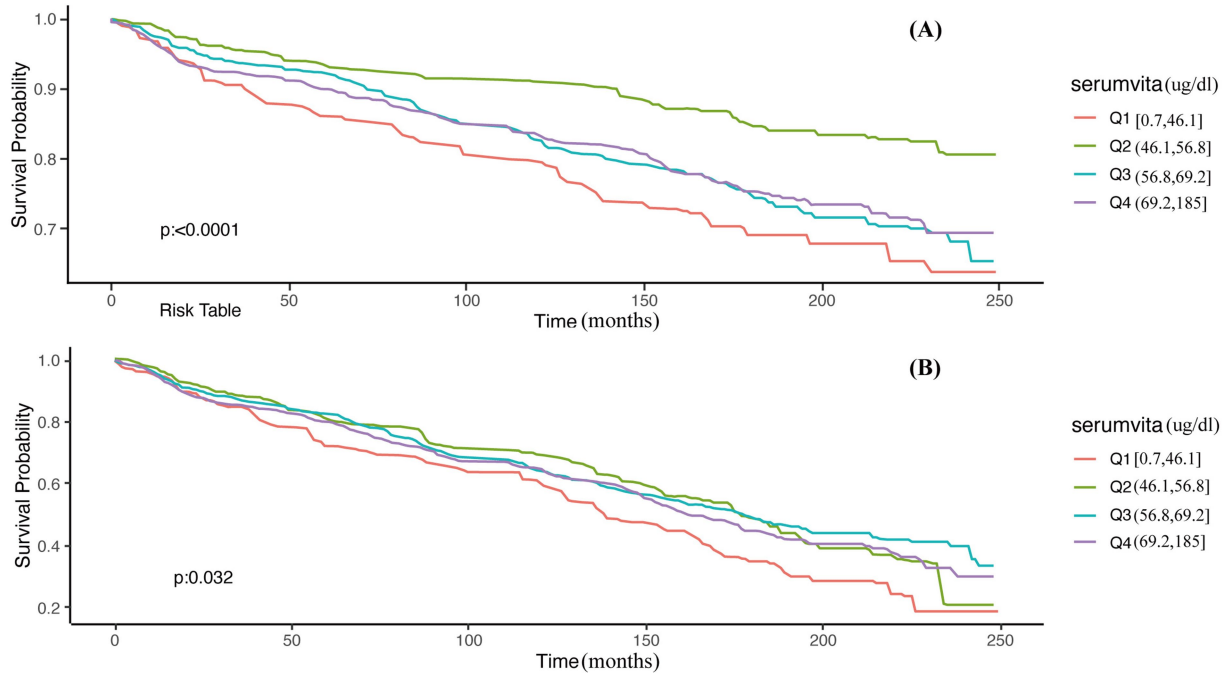

FIGURE 2
Unadjusted Kaplan–Meier survival curves for all-cause mortality among serum vitamin A. **(A)** Males; **(B)** 60–85 years.

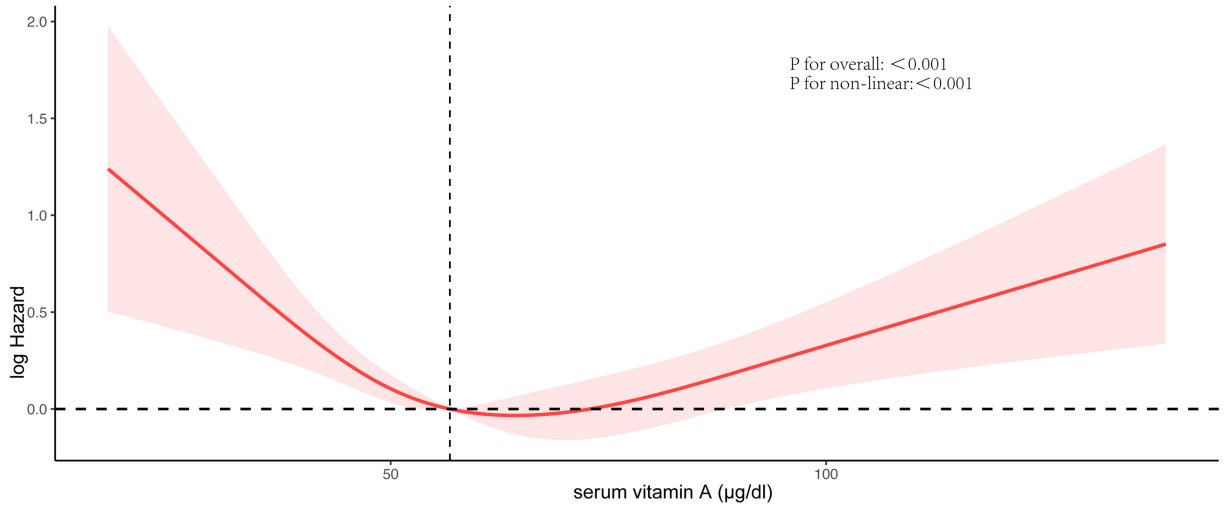

FIGURE 3
Association between serum vitamin A concentrations and all-cause mortality. Red solid lines and red dotted lines, respectively, represent restricted cubic spline models and 95%CI. Models were adjusted by age, race, BMI, smoking behavior, drinking behavior, physical activity, energy intake, C-reactive protein, diabetes status, and hypertension status.

Moreover, excessive antioxidants might inhibit the induction of antioxidant defenses and the necessary pro-oxidative signals for tissue adaptation (16), potentially explaining why higher serum vitamin A levels are linked to increased all-cause mortality in NAFLD patients. Therefore, determining the most appropriate serum vitamin A levels is crucial.

Nevertheless, this study is subject to several limitations. Firstly, all measurements were conducted at baseline, and participants' lifestyles and dietary habits may have changed during the long-term follow-up period, potentially affecting unmeasured variables that could influence the study outcomes. Secondly, we utilized the US FLI to assess hepatic steatosis and the FIB-4 score to evaluate hepatic fibrosis, which is not considered the gold standard for diagnosing NAFLD. Furthermore, despite adjusting for relevant covariates that could influence all-cause mortality rates, we cannot exclude the possibility of residual or unmeasured confounding factors affecting the study results. Lastly, there is a possibility that recall bias influenced self-reported data.

5 Conclusion

This study systematically investigated the association between serum vitamin A levels and all-cause mortality among NAFLD patients for the first time. The findings reveal a U-shaped correlation between serum vitamin A concentration and the risk of all-cause mortality among NAFLD patients in the United States. This finding offers new insights into the health management of patients with NAFLD, indicating that monitoring serum vitamin A levels may be important in clinical practice, particularly for men and older adults aged 60 and above, to reduce the risk of all-cause mortality.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HL: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. JY: Writing – original draft, Data curation. YD: Writing – original draft, Conceptualization, Investigation. WK: Data curation, Writing – original draft. GQ: Supervision, Writing – review & editing. YX: Supervision, Writing – review & editing, Formal analysis, Funding acquisition, Software.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1467659/full#supplementary-material

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Glossary

NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
NAFLD	Non-alcoholic fatty liver disease
CDC	Centers for Disease Control and Prevention
NDI	National Death Index
CLD	Chronic liver disease
NASH	Non-Alcoholic Steatohepatitis
RCS	Restricted cubic spline
ROS	Reactive oxygen species
FIB4 score	Fibrosis-4 score
PNPLA3	Patatin-like Phospholipase Domain Containing 3
HbA1c	Glycated hemoglobin A1c
CRP	C-reactive protein
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
ALP	Alkaline phosphatase
BMI	Body mass index
MET	Metabolic equivalent
FPG	Fasting blood glucose
TG	Triglycerides
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
SE	Standard Error
OR	Odds ratio

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Body composition differences in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease

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Background: Although body composition (BC) has been associated with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), there is little evidence of differences in BC in patients with MASLD regarding body mass index (BMI). The aim of this study was to determine differences in BC in terms of BMI and metabolic comorbidities in patients with MASLD.

Materials and methods: It is a cross-sectional study with patients who attended the check-up unit. Liver steatosis was evaluated by controlled attenuation parameter, and patients were classified into five groups according to BMI, presence of MASLD, and metabolic characteristics: <25 kg/m^2 non-MASLD; <25 kg/m^2-MASLD; Overweight-MASLD; Metabolically Healthy Obese (MHO)-MASLD; and Metabolically Unhealthy Obese (MUO)-MASLD. BC was assessed by bioelectrical impedance and a Bioimpedance Vectorial Analysis (BIVA) was carried out. Differences in BC were analyzed by a One-Way ANOVA test. Univariate and multivariate analyses were performed for factors associated with abnormal BC.

Results: A total of 316 patients were included. 59% ($n = 189$) were male, with a mean age of 49 ± 10 years. Fat% significantly higher according to BMI was not different between BMI <25 kg/m^2-MASLD and Overweight-MASLD groups. Skeletal muscle mass (SMM) was significantly lower in obesity groups with respect to overweight and normal weight groups ($p < 0.05$); however, no differences were observed in the post-hoc analysis. Extracellular Water/Intracellular Water ratio was significantly higher in the MHO-MASLD group and MUO-MASLD group compared with the BMI <25 kg/m^2 non-MASLD group and with the BMI <25 kg/m^2-MASLD group. Abnormal Waist Circumference (WC) and liver steatosis were independent factors associated with abnormal BC.

Conclusion: BC in MASLD patients varies according to BMI increase; changes could be explained by loss of SMM and not necessarily by the presence of metabolic abnormalities. High WC and the presence of steatosis are independent factors associated with altered BC.

KEYWORDS

steatosis, liver, body composition, obesity, muscle mass

1 Introduction

Metabolic diseases have been related to the body composition (BC) pattern, which is defined as the combination of variables that describe an individual's distribution of fat and/or muscle, quantifying *in vivo* the body components, the quantitative relationships between the components, and their quantitative changes related to influential factors (1).

It is well known that due to the increase in the prevalence of obesity and diabetes mellitus (DM), other metabolic diseases have also increased; one of the most important is Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), which nowadays is the most important chronic liver disease and one of the major indication for liver transplant worldwide, with an estimated prevalence of 30% (2, 3).

The inflammatory factors are one of the most important players in the relationship between metabolic diseases and BC (4). In MASLD patients, changes in BC are related to insulin resistance (IR), increase of lipolysis, and fatty acids accumulation in liver tissue (5); moreover, alterations in BC have been associated with an increased risk of presence and progression of MASLD (6–8).

In MASLD patients, BC assessment is important since it is associated with hepatic fat percentage and progression of liver disease (9, 10). Altered BC, characterized by high-fat tissue and low muscle mass, has been related to functional performance and metabolic comorbidities in patients with MASLD, especially in those with DM and cardiovascular diseases, which also get worse with fat tissue increase (10).

Whereas the Dual Energy X-ray Absorptiometry (DEXA) is the reference method for BC assessment (11), the Bioelectrical Impedance Analysis (BIA) has shown good concordance with DEXA, and it has been proposed as a good method of BC assessment in obese patients in whom the physiological and hydration conditions could interfere with measurement reliability (5, 12, 13). BIA is a noninvasive and relatively available method for BC analysis based on measuring resistance (R) and reactance (Xc), which allows to determine the fat and muscle percentage and hydration state through bioelectrical impedance vector analysis (BIVA) (14, 15).

While the relationship between changes in BC and the presence of liver steatosis has been established, there is little evidence about the characteristics of BC in patients with MASLD and differences related to body mass index (BMI); therefore, the aim of this study was to determine differences in BC according to BMI and metabolic comorbidities in patients with MASLD.

2 Materials and methods

2.1 Study population

This prospective study was carried out at the Medica Sur Clinic & Foundation check-up unit from March 2023 to January 2024, including patients between 18 and 70 years old. Demographic variables, hereditary family history, and pathological personal history of chronic degenerative diseases were collected as part of the check-up evaluation. We excluded patients with previous diagnoses of other liver diseases, such as viral hepatitis (hepatitis B or C virus infection), autoimmune hepatitis, hereditary diseases, liver cirrhosis, and those with hepatotoxic drugs treatment; laboratory tests and medical history confirmed the absence of these criteria during the check-up. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Medica Sur (2021-EXT-638).

2.2 Anthropometric and biochemical metabolic assessment

Anthropometric parameters of waist circumference (WC), weight, and height were collected; BMI was calculated as weight (kg)/height (m)^2, and overweight was determined as BMI ≥25 kg/m2. Laboratory studies included blood count, blood chemistry, lipid profile, and liver function tests taken from blood samples after fasting for at least 8–12 h. Metabolic syndrome criteria were defined according to the Adult Treatment Panel III (16). Patients with obesity were divided into Metabolically Healthy Obesity (MHO; BMI ≥30 kg/m^2 and one metabolic syndrome criteria) and Metabolically Unhealthy Obesity (MUO; BMI ≥30 kg/m^2 and ≥2 metabolic syndrome criteria) (17).

2.3 MASLD diagnosis

MASLD was determined according to the definition criteria (3). Hepatic steatosis (dB/m) and liver fibrosis (skPa) were determined by transient elastography (TE; FibroScan®, Echosens™, 502 Touch, Paris, France) with Controlled Attenuation Parameter (CAP), with fasting for at least 4 h. It was performed by a single expert operator, using M or XL probe according to the manufacturer's instructions and following the reliability criteria (IQR-CAP <40 and IQR-kPa <30) Patients whose studies did not meet the reliability criteria were excluded, as well as patients with F4 liver fibrosis according to TE (≥12 kPa). Steatosis determination was established according to Sirli et al.'s cut-off, being steatosis ≥263 dB (18). Once TE confirmed steatosis, MASLD was diagnosed if the patient had at least one of the cardiometabolic criteria (BMI ≥25 kg/m^2; WC >94 (M) and >88 (F), fasting glucose ≥100 mg/dl or HbA1c ≥5.7% or DM or DM treatment, blood pressure ≥ 130/85 mmHg or antihypertensive treatment, and HDL < 40 (M) and < 50 (F) or lipid-lowering treatment). Patients with significant alcohol consumption [>140 g (F) and > 210 g (M)] referred in the medical record of the check-up were excluded.

Patients were classified into five groups according to BMI, the presence of MASLD, and metabolic abnormalities: BMI <25 kg/m^2 non-MASLD, BMI <25 kg/m^2-MASLD, overweight-MASLD, MHO-MASLD, and MUO-MASLD.

2.4 Body composition assessment

BC was analyzed by BIA by recording R and Xc using a four-terminal, single-frequency impedance analyzer (model Quantum IV-BIA; RJL-System, Detroit, MI, USA). BIA was conducted according to manufacturer's recommendations. BC components (phase angle (PA), mass and percentages of fat, skeletal muscle mass

(SMM), total body water (TBW), intracellular water (ICW), and extracellular water (ECW)) were calculated using the manufacturer's software using the Mexican Adults equation set. Additionally, the ECW/ICW ratio was calculated. Body fluid variation was assessed by BIVA, according to Piccoli et al. (19), with the RXc graphic method, which analyzes the R and Xc values adjusted by height. BIVA graphics were generated using the Mexican population references (20).

2.5 Statistical analysis

Data distribution was determined by the Kolmogorov–Smirnov test. Then, continuous variables are reported as median and standard deviation, whereas categorical variables are expressed as percentages and frequencies. Differences in BC components were analyzed by one-way ANOVA test with Bonferroni post-hoc. First, we analyzed BC differences among all groups and then only in MASLD groups. Bivariate and multivariate analyses were carried out in these patients to determine the independent factors related to abnormal BC, with a percentile 75 of ECW/ICW ratio (≥0.95), and BIVA analysis as reference. A p-value <0.05 was considered statistically significant. All statistical analyses were conducted using the statistics program SPSS v20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

3 Results

A total of 316 patients were included: BMI <25 kg/m^2 non-MASLD (n = 70), BMI <25 kg/m^2-MASLD (n = 36), overweight-MASLD (n = 70), MHO-MASLD (n = 70), and MUO-MASLD (n = 70). 59.6% (n = 189) were male with a mean age of 49 ± 10 years; at the time of evaluation, 6.9% (n = 22) had a known diagnosis of DM and 16.7% (n = 53) had a known diagnosis of high blood pressure. Concerning metabolic risks, a decreased High-density Lipoprotein (HDL) level was the most prevalent (38.2%, n = 121), followed by abnormal triglycerides (34.1%, n = 108), and glucose impairments (28.1%, n = 89). The mean of dB/m was 287.9 ± 55.2; meanwhile, the mean of kPa was 3.7 ± 0.8. 1.2% (n = 4) of patients have significant fibrosis (8.0–11.9 kPa). General characteristics of patients are presented in Table 1.

Regarding the analysis of BC differences among all groups (Table 2), R and Xc show significant differences ($p \leq 0.0001$), and PA did not show differences among groups. As expected, Fat% was significantly increased in terms of BMI ($p \leq 0.0001$); however, in post-hoc analysis, Fat% was not different between the BMI <25 kg/m^2-MASLD (34.9 ± 6.7%) and Overweight-MASLD (36.5 ± 6.3%) groups. SMM% was significantly lower in obesity groups with respect to overweight and normal weight groups ($p < 0.05$); no significant differences were observed among overweight and normal weight groups. Despite the differences among all groups ($p \leq 0.001$), no significant differences were observed between

TABLE 1 General characteristics of patients.

Characteristic	All patients (n = 316)	BMI <25 kg/m^2 non-MASLD (n = 70)	BMI <25 kg/m^2-MASLD (n = 36)	Overweight-MASLD (n = 70)	MHO-MASLD (n = 70)	MUO-MASLD (n = 70)	p*
	n (%), μ ± SD	n (%), μ ± SD	n (%), μ ± SD	n (%), μ ± SD	n (%), μ ± SD	n (%), μ ± SD	
Male	59.6 (189)	43.7 (31)	55.6 (20)	62.9 (44)	64.3 (45)	70 (49)	0.01
Age (years)	49.2 ± 10.5	49.1 ± 12.6	50.8 ± 9.3	50.2 ± 10	48.3 ± 9.9	48.5 ± 10.1	0.68
DM	6.9 (22)	1.4 (1)	-	11.4 (8)	7.1 (5)	11.4 (8)	0.03
Dyslipidemia	18.6 (59)	9.9 (7)	19.4 (7)	34.3 (24)	11.4 (8)	18.6 (13)	0.002
HT	16.7 (53)	1.4 (1)	5.6 (2)	24.3 (17)	22.9 (16)	24.3 (17)	≤0.001
BMI kg/m^2	28.4 ± 5.0	22.3 ± 1.8	23.7 ± 1.0	27.8 ± 1.3	32.6 ± 2.3	33.4 ± 3.2	≤0.001
WC cm	98.2 ± 15.0	81.2 ± 12.6	88.7 ± 6.7	97.2 ± 7.6	109.3 ± 9.5	110.3 ± 9.2	≤0.001
SBP mmHg	118.9 ± 16.7	107.7 ± 12.8	114.9 ± 16.9	116.8 ± 14.8	122.2 ± 14.6	131.4 ± 14.6	≤0.001
DBP mmHg	76.8 ± 10.8	69.0 ± 8.4	75.8 ± 9.5	75.1 ± 9.9	79.4 ± 10.1	84.4 ± 9.2	≤0.001
Fasting glucose mg/dl	95.9 ± 18.8	88.7 ± 12.5	95.6 ± 10.8	96.3 ± 13.9	91.1 ± 8.6	107.7 ± 30.4	≤0.001
Triglycerides mg/dl	143.0 ± 90.9	88.0 ± 40.1	178.8 ± 132.2	144.4 ± 68.7	113.9 ± 39.3	208.4 ± 110.1	≤0.001
HDL mg/dl	48.8 ± 13.7	57.0 ± 13.9	50.5 ± 14.3	49.6 ± 13.0	49.2 ± 11.1	38.3 ± 9.3	≤0.001
HbA1C %	5.4 ± 0.7	5.2 ± 0.5	5.4 ± 0.4	5.3 ± 0.8	5.5 ± 0.3	5.8 ± 1.0	≤0.001
CRP mg/L	3.0 ± 3.9	1.7 ± 3.6	1.9 ± 2.3	2.7 ± 2.5	4.3 ± 5.4	4.0 ± 3.7	≤0.001
dB/m	287.9 ± 55.2	206.0 ± 25.7	287.9 ± 25.2	306.8 ± 31.2	312.3 ± 32.4	327.9 ± 38.3	≤0.001
skPa	4.1 ± 1.0	3.7 ± 0.8	4.3 ± 1.4	3.9 ± 0.7	4.1 ± 1.0	4.6 ± 1.1	≤0.001

BMI, Body Mass Index; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MHO, Metabolically Healthy Obesity; MUO, Metabolically Unhealthy Obesity; DM, Diabetes Mellitus; HT, Hypertension; WC, Waist Circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HDL, High-Density Lipoprotein; HbA1C, Glycosylated hemoglobin; CRP, C-Reactive Protein.

*p-value represents the comparison among groups.

TABLE 2 Differences in body composition components among groups.

Component	BMI <25 kg/m² non-MASLD (*n* = 70)	BMI <25 kg/m²-MASLD (*n* = 36)	Overweight-MASLD (*n* = 70)	MHO-MASLD (*n* = 70)	MUO-MASLD (*n* = 70)	*p**
	μ ± SD, %	μ ± SD, %	μ ± SD, %	μ ± SD, %	μ ± SD, %	
Resistance Ω	598.3 ± 67.9	597.4 ± 77.4	525.4 ± 63.6	501.8 ± 69.3	482.9 ± 535.3	**≤0.001**
Reactance Ω	65.3 ± 8.7	66.4 ± 7.3	59.7 ± 6.5	57.5 ± 7.8	55.5 ± 6.8	**≤0.001**
PA °	6.2 ± 0.9	6.4 ± 0.8	6.5 ± 0.7	6.5 ± 0.7	6.6 ± 0.7	0.09
Fat kg	19.6 ± 5.2	23.7 ± 4.9	28.6 ± 6.4	38.7 ± 12.3	38.7 ± 7.4	**≤0.001**
Fat %	31.5 ± 7.8	34.9 ± 6.7	36.5 ± 6.3	40.6 ± 8.1	40.3 ± 6.0	**≤0.001**
TBW kg	32.4 ± 6.2	33.5 ± 5.9	38.1 ± 7.2	41.3 ± 8.4	42.6 ± 8.1	**≤0.001**
TBW %	51.6 ± 5.1	48.7 ± 4.8	47.5 ± 5.3	43.6 ± 6.7	44.0 ± 4.6	**≤0.001**
ICW kg	17.9 ± 4.2	18.5 ± 4.0	20.7 ± 4.6	21.9 ± 5.2	22.9 ± 5.2	**≤0.001**
ICW %	28.2 ± 4.1	26.8 ± 4.0	25.8 ± 4.1	23.2 ± 4.7	23.5 ± 3.4	**≤0.001**
ECW kg	14.5 ± 2.2	14.5 ± 3.3	17.3 ± 2.7	19.4 ± 3.6	19.8 ± 3.2	**≤0.001**
ECW %	23.0 ± 2.1	21.8 ± 1.3	21.5 ± 1.5	20.4 ± 2.2	20.5 ± 1.3	**≤0.001**
SMM kg	20.3 ± 5.3	21.1 ± 4.8	24.3 ± 5.1	27.0 ± 6.4	27.7 ± 6.4	**≤0.001**
SMM %	31.9 ± 5.7	30.7 ± 5.3	30.2 ± 4.4	28.4 ± 5.0	28.6 ± 4.2	**≤0.001**
ECW/ICW	0.82 ± 0.10	0.80 ± 0.17	0.85 ± 0.10	0.90 ± 0.11	0.89 ± 0.11	**≤0.001**

BMI, Body Mass Index; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MHO, Metabolically Healthy Obesity; MUO, Metabolically Unhealthy Obesity; PA, Phase Angle; TBW, Total Body Water; ICW, Intracellular Water; ECW, Extracellular Water; SMM, Skeletal Muscle Mass.
**p*-value represents the comparison among groups. Bold values represents *p*-values <0.05.

BMI <25 kg/m² groups with (32.4 ± 6.2 kg) or without MASLD (33.5 ± 5.9 kg), and Overweight MASLD (38.1 ± 7.2 kg) compared to MHO-MASLD group (41.3 ± 8.4 kg) regarding water-related components. ECW was significantly higher according to BMI increase; however, no differences were observed according to metabolic health or unhealth in obesity groups. ECW/ICW ratio was significantly higher in the MHO-MASLD group and MUO-MASLD group compared with the BMI <25 kg/m² non-MASLD group ($p = 0.001$ and $p = 0.02$, respectively), and with the BMI <25 kg/m²-MASLD group ($p = 0.001$ and $p = 0.01$, respectively; Figure 1D).

Once again, only in MASLD groups ($n = 246$) all components showed differences in the One-way ANOVA test, except PA, where differences in BC were analyzed. Fat% was higher according to BMI; however, there was no difference between the BMI <25 kg/m²-MASLD group and the Overweight-MASLD group (34.9 ± 6.7% vs. 36.5 ± 6.3%, $p = 1.00$), nor between the MHO-MASLD group and the MUO-MASLD group (40.6 ± 8.1 vs. 40.3 ± 6.0%, $p = 1.00$) in post-hoc analysis. SMM% was significantly different among groups ($p = 0.01$), being higher in BMI <25 kg/m²-MASLD group and Overweight-MASLD group than in Obesity Groups (30% vs. 28%), but no significant differences were observed in post-hoc analysis (Figure 1A).

ICW was significantly higher only among the BMI <25 kg/m²-MASLD and MHO-MASLD (18.5 ± 4.0 kg vs. 21.9 ± 5.2 kg, $p = 0.003$) and MUO-MASLD groups (18.5 ± 4.0 kg vs. 22.8 ± 5.0, $p = 0.0002$; Figure 1B). Instead, ECW was significantly different among all groups, increasing in terms of BMI, but once again, without difference in obesity groups (Figure 1C). When the ECW/ICW ratio was analyzed, we observed an increase according to BMI; however, the BMI <25 kg/m²-MASLD group only showed significant differences with MHO-MASLD and MUO-MASLD groups (0.80 ± 0.1 vs. 0.90 ± 0.1, $p = 0.005$, and 0.80 ± 0.1 vs. 0.89, $p = 0.04$, respectively), whereas the Overweight-MASLD group only showed differences with the MHO-MASLD group (0.85 ± 0.1 vs. 0.90 ± 0.1, $p = 0.04$; Figure 1D).

The differences in water components were confirmed with the BIVA qualitative analysis. According to the RXc point graphic and tolerance ellipses, with the increase of BMI, the points were situated in vectors that represent more fluids but not necessarily in those that represent fewer lean tissues (21, 22) (Figure 2). Regarding the BIVA tissue classification, normal tissue was majorly prevalent in the BMI <25 kg/m² non-MASLD (70.4%, $n = 50/70$) group, BMI <25 kg/m²-MASLD (83.3%, $n = 30/36$) group, and Overweight-MASDL (70%, $n = 49/70$) group; however, it was decreased in the MHO-MASLD (51.4%, $n = 36/70$) group and MUO-MASLD (45.7%, $n = 32/70$) group. The prevalence of sarcopenia-cachexia tissue was higher in BMI <25 kg/m² groups (20%), and lower in Overweight-MASLD (4.2%, $n = 3$) group, MHO-MASLD group, and MUO-MASLD group (2.9%, $n = 2$, both). Conversely, overhydration was higher in Overweight-MASLD (17.1%, $n = 12$) group, MHO-MASLD (35.7%, $n = 25$) group, and MUO-MASLD (37.1%, $n = 26$) group. In the BMI <25 kg/m² non-MASLD group, only 7% ($n = 5$) presented overhydration, and it was not present in the BMI <25 kg/m²-MASLD group (Figure 3).

Factors associated with abnormal BC were analyzed, according to the ECW/ICW ratio and the BIVA tissue classification. In all patients ($n = 316$), female sex, abnormal WC, abnormal HDL levels, and the presence of liver steatosis were independent factors associated with abnormal BC, according to ECW/ICW ratio (Table 3); as for BIVA, female sex [OR 3.3 CI95% (1.9–5.5), $p \leq 0.001$] and abnormal WC [OR 2.2 CI95% (1.3–3.9), $p \leq 0.001$] were independently associated with abnormal BC (Table 3). We performed the bivariate and multivariate analyses adjusting by sex, and then the abnormal WC and the presence of

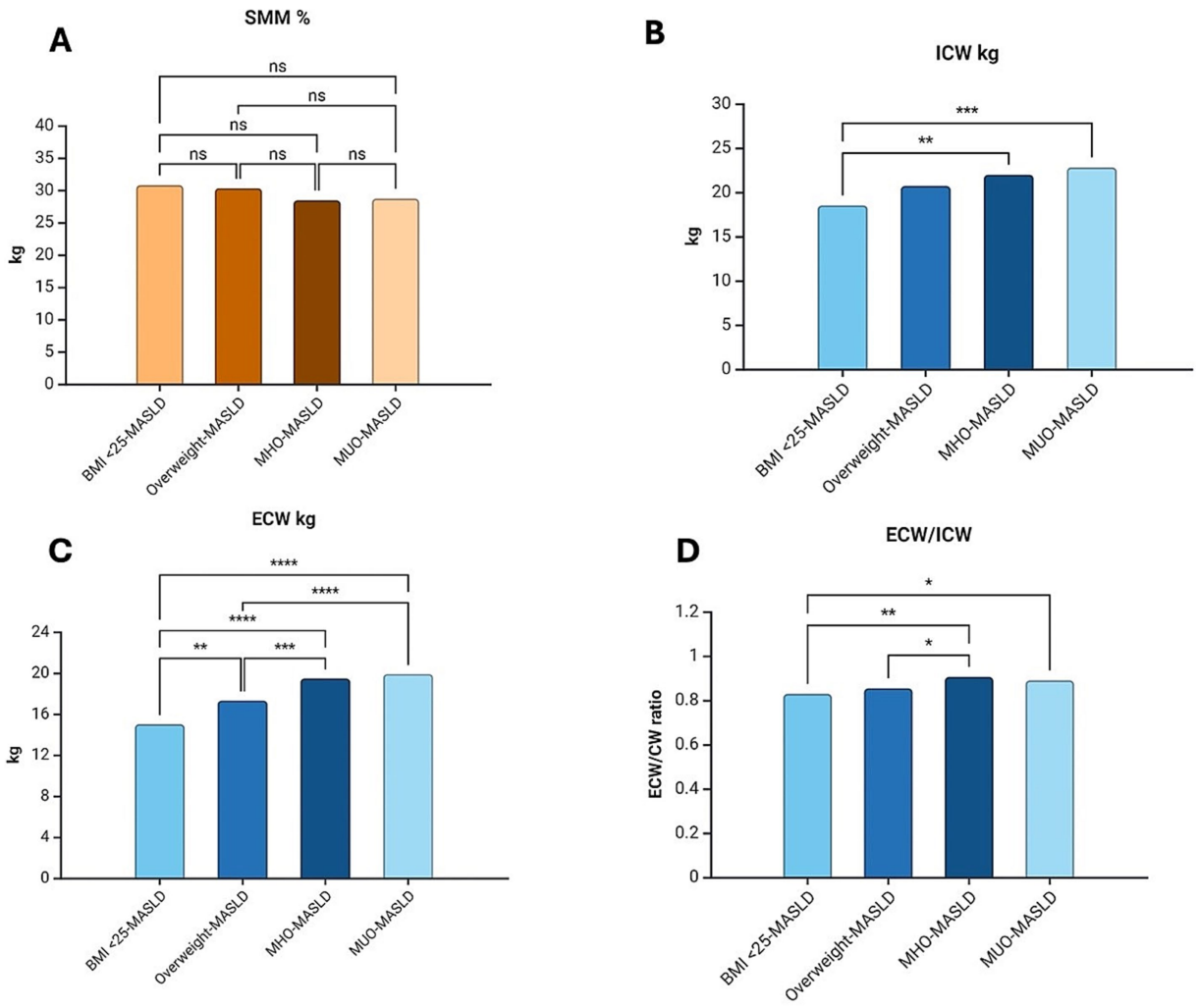

FIGURE 1
Comparison of body composition components among groups. (A) SMM showed differences in the comparison of all groups; however, although SMM showed lower values, differences were not observed in a *post hoc* analysis. (B) ICW (kg) was significantly higher when the BMI < 25-MASLD group was compared with obesity-MASLD groups. (C) ECW (kg) did not show significant differences in obesity groups. (D) ECW/ICW ratio shows differences among the BMI < 25-MASLD group and the obesity groups and between overweight and MHO-MASDL groups. SMM, Skeletal Muscle Mass; BMI, Body Mass Index; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MHO, Metabolically Healthy Obesity; MUO, Metabolically Unhealthy Obesity; ICW, Intracellular Water; ECW, Extracellular Water; ns non-significative; *; **; ***; **** $p < 0.05$. Created with BioRender.com

liver steatosis maintained the independent association with abnormal BC, according to ECW/ICW ratio (Table 4); as for BIVA, only abnormal WC [OR 2.7 CI95% (1.4–5.2), $p = 0.003$] was independently associated with abnormal BC (Table 4). When these analyses were carried out, only in MASLD groups, female sex, and abnormal WC were independent factors associated with abnormal BC in both criteria (data not shown); in adjusted analysis by sex, abnormal WC maintained the independent association with BIVA [OR 4.3 CI 95% (1.8–10.1), $p = 0.001$] as reference, but abnormal WC only showed association in bivariate analysis [OR 3.6 CI 95% (1.8–7.3), $p = 0.001$] with ECW/ICW ratio as reference.

4 Discussion

The evidence of alterations in body composition in the MASLD scenario is scarce. In our study, changes in BC in patients with MASLD were observed, with significant differences compared to healthy patients (BMI < 25 kg/m^2 and non-MASLD). As expected, Fat%, TBW, and ECW/ICW ratio were increased according to BMI increase, and conversely, SMM was decreased. However, significant differences were not observed among all groups and in MASLD groups in post-hoc analysis.

Fat accumulation is now considered a major risk factor for mortality, independent of obesity (23). A significant increase in Fat% has been observed in patients with MASLD and BMI < 25 kg/m^2; this has been observed in the United States population by Mainous III et al. (24) and in the Rotterdam cohort (OR 1.77, $p \leq 0.05$) (25). In our population, we observed a significant difference in the increase of Fat% in patients with BMI <25 kg/m^2, being higher in those with MASLD. The prevalence of MASLD in patients with BMI <25 kg/m^2 is relatively low; in our population, we previously reported a prevalence of 7.9% (26), even though the BMI < 25 kg/m^2-MASLD group is smaller than the other groups. One of the strengths of our study is the inclusion and comparison of this group of patients with other MASLD phenotypes,

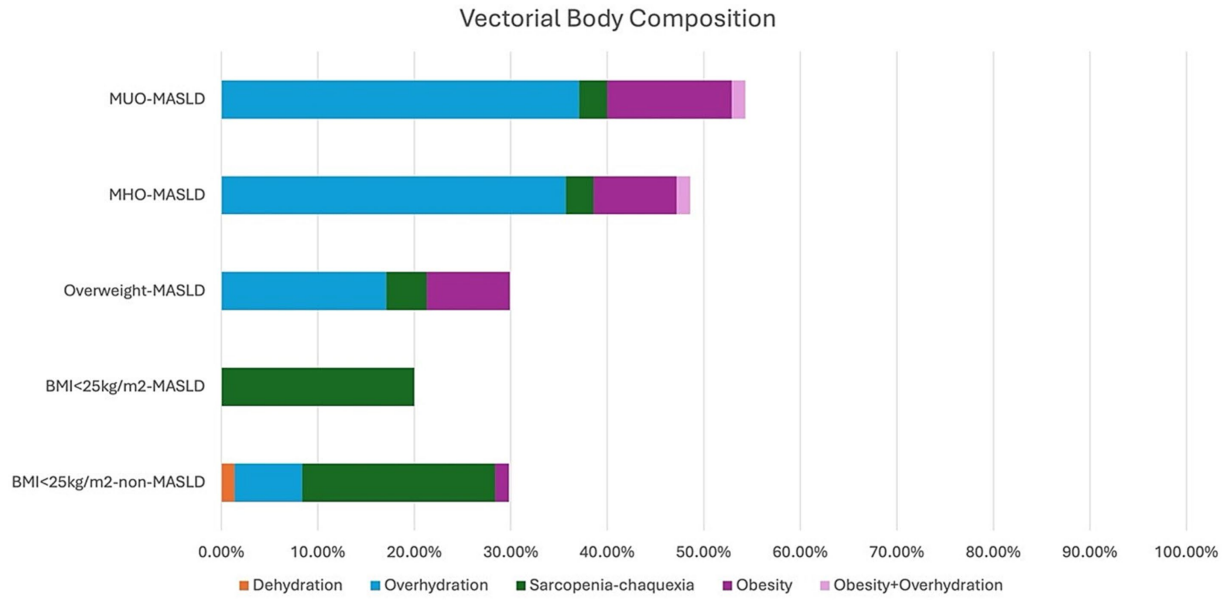

FIGURE 2
Bioimpedance Vectorial Analysis in each group. Graphic representation of body composition in each group, for male and female patients, according to tolerance ellipses for the Mexican population. BMI, Body Mass Index; MASLD, Metabolic dysfunction-associated Steatotic Liver Disease; MHO, Metabolically Healthy Obesity; MUO, Metabolically Unhealthy Obesity; Xc, Reactance; H, Height.

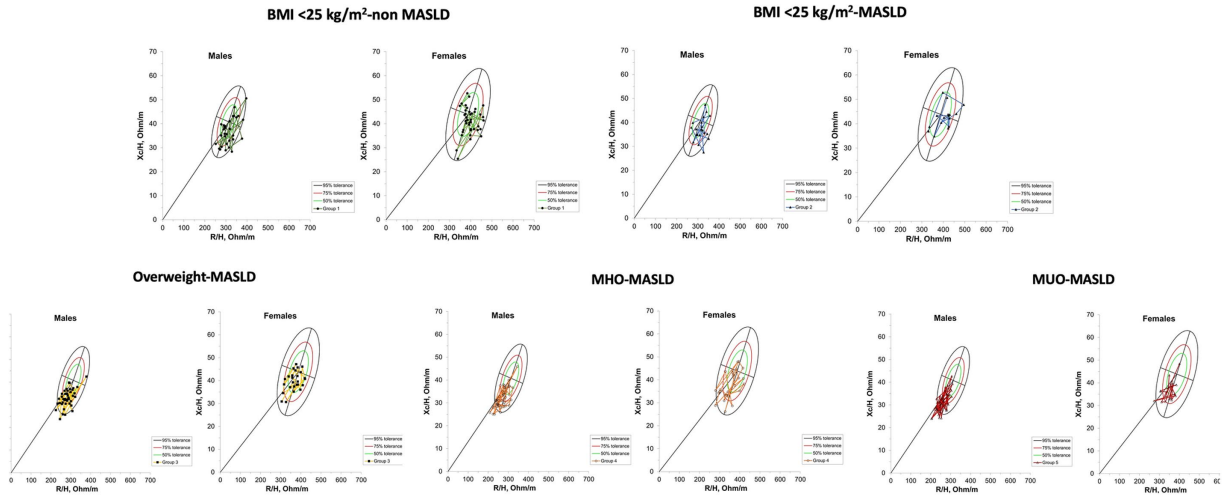

FIGURE 3
Classification of patients according to Bioimpedance Vectorial Analysis. BMI, Body Mass Index; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MHO, Metabolically Healthy Obesity; MUO, Metabolically Unhealthy Obesity.

taking their low prevalence into account. BC assessment could be an early detection tool in these patients in whom MASLD is not an initial clinical suspicion. Another strength of this study is the BIVA analysis, which is the qualitative point of view of BC. As far as we know, it has not been evaluated in patients with MASLD. According to our results, changes observed in BC are consistent with BIVA in overhydration and lean mass tissue terms, according to the tolerance ellipses and BIVA tissue classification (Figures 2, 3).

Abdominal fat accumulation seems to be a better indicator of MASLD than BMI or the presence of obesity (27). In our study, we observed a significant increase in Fat% in both BMI <25 kg/m^2 and overweight/obese patients. On the other hand, WC was an independent factor associated with altered BC in all patients and also when only MASLD patients were analyzed, without differences among the number of comorbidities in obese patients.

Sarcopenia increases in MASLD and is considered a progression factor independent of obesity and IR. Muscle strength was not evaluated in our study, so we cannot use the sarcopenic obesity concept (decreased muscle mass, increased fat, and decreased muscle strength) (28). We refer to myopenia instead, which exclusively refers to low muscle mass (23); in obese patients, it will be *myopenic obesity.*

TABLE 3 Univariate and multivariate analysis for abnormal body composition according to ECW/ICW > 0.95 and BIVA.

Factor	Univariate		Multivariate	
	OR (CI 95%)	*p*	OR (CI 95%)	*p*
ECW/ICW >0.95				
Female	14.2 (7.1–28.4)	**≤0.001**	78.0 (30.7–198.0)	**≤0.001**
WC	2.2 (1.4–3.6)	**≤0.001**	2.8 (1.0–7.3)	**0.03**
Abnormal HDL	1.5 (1.1–2.2)	**0.018**	2.3 (1.1–5.1)	**0.02**
HbA1c ≥5.6%	1.6 (1.0–2.1)	0.063		
Liver steatosis	2.1 (1.1–3.9)	**0.006**	4.0 (1.3–11.9)	**0.01**
BIVA				
Female	2.2 (1.5–3.1)	**≤0.001**	3.3 (1.9–5.5)	**p ≤ 0.001**
WC	1.7 (1.2–2.4)	**0.001**	2.2 (1.3–3.9)	**p ≤ 0.001**
HT history	1.3 (0.9–1.8)	0.08		
Abnormal AT	1.5 (1.1–2.0)	**0.02**		

ECW/ICW, Extracellular Water–Intracellular Water ratio; BIVA, Bioimpedance Vectorial Analysis; WC, Waist Circumference > 88 cm in women and > 102 in men; HDL, High-Density Lipoprotein < 50 in women and < 40 in men; HbA1c, Glycosylated Hemoglobin; HT, Hypertension. Bold values represents *p*-values <0.05.

TABLE 4 Univariate and multivariate analysis for abnormal body composition according to ECW/ICW > 0.95 and BIVA, adjusted by sex.

Factor	Univariate		Multivariate	
	OR (CI 95%)	*p*	OR (CI 95%)	*p*
ECW/ICW >0.95				
WC	2.8 (1.8–4.3)	**≤0.001**	4.5 (1.5–12.9)	**0.005**
Abnormal BP	1.5 (1.2–2.0)	**0.050**		
Abnormal HDL	1.4 (1.1–1.9)	**0.006**		
HbA1c >5.6%	1.3 (1.0–1.7)	0.069		
Liver steatosis (>263 dB/m)	3.4 (1.9–6.1)	**≤0.001**	3.9 (1.2–12.4)	**0.017**
BIVA				
WC	1.9 (1.3–2.8)	**≤0.001**	2.7 (1.4–5.2)	**0.003**
HT history	1.3 (0.9–1.8)	0.09		
Abnormal HDL	1.4 (1.0–1.8)	**0.02**		

ECW/ICW, Extracellular Water–Intracellular Water ratio; BIVA, Bioimpedance Vectorial Analysis; WC, Waist Circumference > 88 cm in women and > 102 in men; BP, Blood pressure; HDL, High-Density Lipoprotein < 50 in women and < 40 in men; HbA1c, Glycosylated Hemoglobin; HT, Hypertension. Bold values represents *p*-values <0.05.

In patients with MASLD, a decrease in SMM has been associated with BMI, Fat Mass Index, and WC, with significant differences regarding sex, majorly attributed to hormones. Onishi et al. (10) evaluated the associated factors to SMM decrease in patients with MASLD, finding that BMI, Fat-free mass Index, and WC were independent associated factors. However, the study was conducted in an Asian population with a different BMI cut-off to determine overweight. Despite this, our results confirm that SMM is significantly lower in patients with MASLD according to BMI increase; however, despite detecting a trend, no significant differences were observed in terms of BMI classification or the presence of comorbidities in obese patients in a post-hoc analysis. Statistical significance could be lost since our study universe corresponds to an open-apparently healthy population that attended a check-up unit with an overall mean age (49.2 ± 10.5) and stage of liver steatosis (287.9 ± 55.2) in which significant muscle loss is not expected. However, this observed trend is clinically significant for early recognition of decreased SMM.

As for water measurements, we observed a significant decrease in the TBW percentage, according to BMI increase (Table 2). TBW percentage has been observed to reflect higher levels of adiposity, and this could affect the reliability of measurements of fat-free mass. However, this could produce a clinical underestimation of obesity if only TBW is considered for body composition assessment (20). Therefore, the evaluation of TBW components is a more reliable measurement, especially in obese patients, since one of the characteristics of obesity is an alteration in fluid regulation; changes in ECW and ICW have been attributed to the high proportion of ECW in adipose tissue, the relationship of ECW with chronic inflammation (29), obesity-related edema, and hormonal responses to fat tissue, leading to a primary deficiency in hemodynamic fluid regulation that could not be reversible in morbid obesity (30, 31).

The increase in water components of BC at the expense of increased fat could be the explanation for the difficulty of muscle mass recovery, even in lean patients; moreover, this fluid alteration seems to persist after weight loss becomes irreversible (30, 32).

Although it is interesting to highlight that the ECW/ICW ratio has demonstrated to be an overload water marker and, even more, a mortality marker in populations different than ours and in cardiovascular risk populations (15, 33–37), there is no evidence of this ratio in MASLD patients. However, different studies (33, 36, 37) show that this ratio could be an early marker of muscle mass and function loss. In our study, this ratio was higher in patients with BMI >25 kg/m^2; therefore, if we evaluate it with SMM percentage, even if no statistical difference was observed, it could be considered an early marker of sarcopenia.

Regarding PA, Chen et al. (38) observed that it is lower in patients with MASLD compared to non-MASLD patients. When the analysis was adjusted by BMI, sex, and comorbidities, PA was associated with MASLD risk; however, this association was not observed in patients with BMI >30 kg/m^2. The authors concluded that PA could be an indicator in MASLD management limited to overweight patients.

Abnormal BC has been established as a risk factor and as an indicator for the presence of liver steatosis (8, 39). According to our results, liver steatosis is an independent factor associated with altered BC when it is defined by the ECW/ICW ratio in multivariate analysis. Therefore, changes in BC seem to be one more factor affected by MASLD development.

From the anthropometric point of view, the assessment of MASLD patients would need deeper indicators than BMI, including BC analysis, which seems to be a tool for patients' diagnosis, classification, muscle mass measurement, and follow-up. Improvement of BC has been related to a decrease in liver fat content in patients with MASLD (40). Currently, there is insufficient evidence to assess whether newest treatments that have demonstrated to reverse steatosis or fibrosis also impact BC. Although weight loss is the cornerstone of MASLD treatment, it is important to evaluate whether treatment schemes could have a "negative" impact on BC, especially in those patients with increased Fat% and decreased SMM in whom weight loss without improvement or maintenance of SMM could remain a risk for metabolic and cardiovascular mortality, despite weight loss.

5 Conclusion

BC in MASLD patients varies according to BMI increase; changes could be explained by loss of SMM and not necessarily by the presence of metabolic abnormalities. High WC and the presence of steatosis are independent factors associated with altered BC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Medica Sur S.A.B de C.V. Ethics in Human Research Committe. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KB-C: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. MB-A: Data curation, Writing – original draft. RC-R: Data curation, Writing – original draft. MR-O: Data curation, Resources, Writing – original draft. MU: Resources, Supervision, Writing – review & editing. IL-M: Conceptualization, Formal analysis, Methodology, Writing – review & editing. EJ-H: Conceptualization, Formal analysis, Methodology, Writing – review & editing.

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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.

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Association of dietary inflammatory index with sarcopenia in patients with Metabolic dysfunction-associated fatty liver disease: a cross-sectional study

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Background: Sarcopenia is a common complication of fatty liver, and sarcopenia increases the risk of advanced liver fibrosis in patients with Metabolic dysfunction-associated fatty liver disease (MAFLD). Chronic inflammation is the crucial link between sarcopenia and fatty liver. An anti-inflammatory diet is expected to be an essential measure to prevent sarcopenia in patients with fatty liver, and the dietary inflammatory index (DII) is a crucial tool for assessing the inflammatory potential of diets. However, the relationship between DII and sarcopenia in patients with fatty liver is unclear.

Objective: This study investigated the correlation between the dietary inflammatory index (DII) and sarcopenia in patients with Metabolic dysfunction-associated fatty liver disease (MAFLD).

Methods: Data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES) 2017–2018, with 917 patients with MAFLD participating in the study. Participants were divided into three groups based on DII tertiles: group T1 ($n = 305$), group T2 ($n = 306$), and group T3 ($n = 306$), and binary logistic regression was used to assess the relationship between DII and sarcopenia with stratified analyses based on the weights recommended by the NHANES and multivariate linear regression was used to evaluate the association of DII with total appendicular lean mass.

Results: After adjusting for all confounders, DII was significantly and positively associated with the risk of sarcopenia in women [OR: 1.61, 95% CI: (1.226, 2.06), $p < 0.001$]. The risk of sarcopenia was higher in the T3 group compared to the T1 group [OR: 4.04, 95% CI: (1.66, 9.84), $p = 0.002$]. DII was negatively associated with appendicular lean mass adjusted for body mass index in both men and women.

Conclusion: DII was significantly associated with the risk of sarcopenia in female patients with MAFLD, with higher DII scores related to a higher risk of sarcopenia. Higher DII scores related to a higher risk of sarcopenia in men with significant fibrosis.

KEYWORDS

dietary inflammatory index, Metabolic dysfunction-associated fatty liver disease, sarcopenia, NHANES, diet

1 Introduction

Metabolism-associated fatty liver disease (MAFLD), a new diagnostic definition proposed in 2020 by an international panel of experts from 22 countries, emphasizes the metabolic dysregulation that accompanies fatty liver disease, previously known as non-alcoholic fatty liver disease (NAFLD), a leading cause of chronic liver disease worldwide, the prevalence of which has been increasing (1, 2). Sarcopenia is a progressive and generalized skeletal muscle disease involving accelerated loss of muscle mass and function (3). Globally, sarcopenia poses a huge challenge to human healthcare. Studies have shown that people with MAFLD are at higher risk of developing sarcopenia (4, 5). And sarcopenia increases the risk of advanced liver fibrosis and mortality in people with MAFLD (6–8). Therefore, prevention of sarcopenia in patients with MAFLD is essential.

It has been shown that MAFLD is associated with a systemic inflammatory response and that patients with MAFLD have elevated serum levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), CC chemokine ligand 2 (CCL2), CC chemokine ligand 19 (CCL19) (9). Meanwhile, systemic chronic low-grade inflammation is involved in the development of sarcopenia (10). Given the link between inflammation and MAFLD and sarcopenia, anti-inflammatory interventions are expected to prevent sarcopenia in patients with MAFLD, and diet is one of the most important measures to control systemic inflammation. Diet is involved in inflammation, and dietary components such as total fat, trans fat, carbohydrate, and cholesterol can promote inflammation, and based on this, previous studies have developed the Dietary Inflammation Index (DII) for assessing the inflammatory potential of diets, with a high DII score being a marker of a pro-inflammatory diet and a lower DII score representing an anti-inflammatory diet (11). Studies have shown that the risk of sarcopenia increases as the DII increases (12). However, no studies have investigated the relationship between DII and sarcopenia in patients with MAFLD.

This study aimed to examine the correlation between DII levels and the risk of sarcopenia in patients with MAFLD, thereby providing a valuable reference for the prevention and management of sarcopenia in patients with MAFLD.

2 Methods

2.1 Study population

The National Health and Nutrition Examination Survey (NHANES) is the most in-depth survey administered by the National Center for Health Statistics (NCHS) to assess the health and nutritional status of adults and children in the United States. The NHANES surveys approximately 5,000 individuals annually in 15 different counties across the country in a two-year cycle, and the study cohort is representative of the entire U.S. population through a sample-weighted analysis. This study is based on data from the 2017 to 2018 NHANES, a cycle that included participants' vibration-controlled transient elastography (VCTE) data used to define MAFLD. The Research Ethics Review Board of the National Center for Health Statistics approved the NHANES study. All participants provided informed consent. According to a large meta-analysis, a controlled attenuation parameter (CAP) of ≥248 dB/m (AUC: 0.823, Sensitivity: 0.688, Specificity: 0.822) was used as the threshold for the diagnosis of hepatic steatosis (13). And a median liver stiffness of ≥8.2 kPa was used to significant fibrosis (14). According to the European Association for the study of the Live (EASL) Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis, CAP≥275 dB/m might be used to diagnose steatosis (15). Therefore, we also conducted an analysis using the CAP ≥275 dB/m (Supplementary materials). Of the 9,254 participants, those who were not older than 18 years, pregnant, those with missing dietary data used to calculate DII, those with missing CAP data and CAP less than 248 dB/m, those with missing dual-energy X-ray data used to measure skeletal muscle mass, those who did not meet the diagnosis of MAFLD and those with missing data on relevant covariates were excluded, and finally, a total of 917 participants were enrolled in the study (Figure 1).

2.2 Definition of MAFLD

Based on the presence of imaging evidence of hepatic steatosis in combination with one of the following three conditions: overweight or obesity (defined as BMI ≥25 kg/m^2 in Caucasians or BMI ≥23 kg/m^2 in Asians), type 2 diabetes mellitus, and metabolic dysfunction. Metabolic dysfunction was defined as the presence of at least two of the following risk factors for metabolic abnormalities: (1) waist circumference ≥ 102 cm in Caucasian men and ≥ 88 cm in women (or ≥ 90 cm in men and ≥ 80 cm in women in Asians); (2) blood pressure ≥ 130/85 mmHg or specific drug treatment; (3) triglyceride (TG) ≥1.7 mmol/L or specific drug treatment; (4) high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L in men and HDL-C < 1.3 mmol/L in women or specific drug treatment; (5) prediabetes; (6) homeostasis model assessment of insulin resistance score (HOMA-IR) ≥2.5; and (7) high-sensitivity C-reactive protein (hs-CRP) >2 mg/L (1).

2.3 Definition of sarcopenia

According to the National Institutes of Health recommendations for determining the presence of sarcopenia, appendicular lean mass adjusted for body mass index (ALM_{BMI}) is used. ALM_{BMI} = appendicular lean mass (kg)/body mass index (kg/m^2), with males <0.789 and females <0.512 considered to have sarcopenia (16). The appendicular lean mass of the extremities was measured by dual-energy X-ray absorptiometry (DXA) whole-body scanning, which was obtained on a Hologic Discovery A optical densitometer (Hologic, Inc., Bedford, Massachusetts) using the Apex 3.2 software version. Trained and certified radiologic technologists perform DXA examinations and more detailed information on the DXA examination program is documented on the NHANES.[1] In the NHANES files "DXDLLLE," "DXDRLLE," "DXDLALE" and "DXDRALE," the specific values of limb lean body mass are recorded.

1 https://www.cdc.gov/nchs/nhanes/index.htm

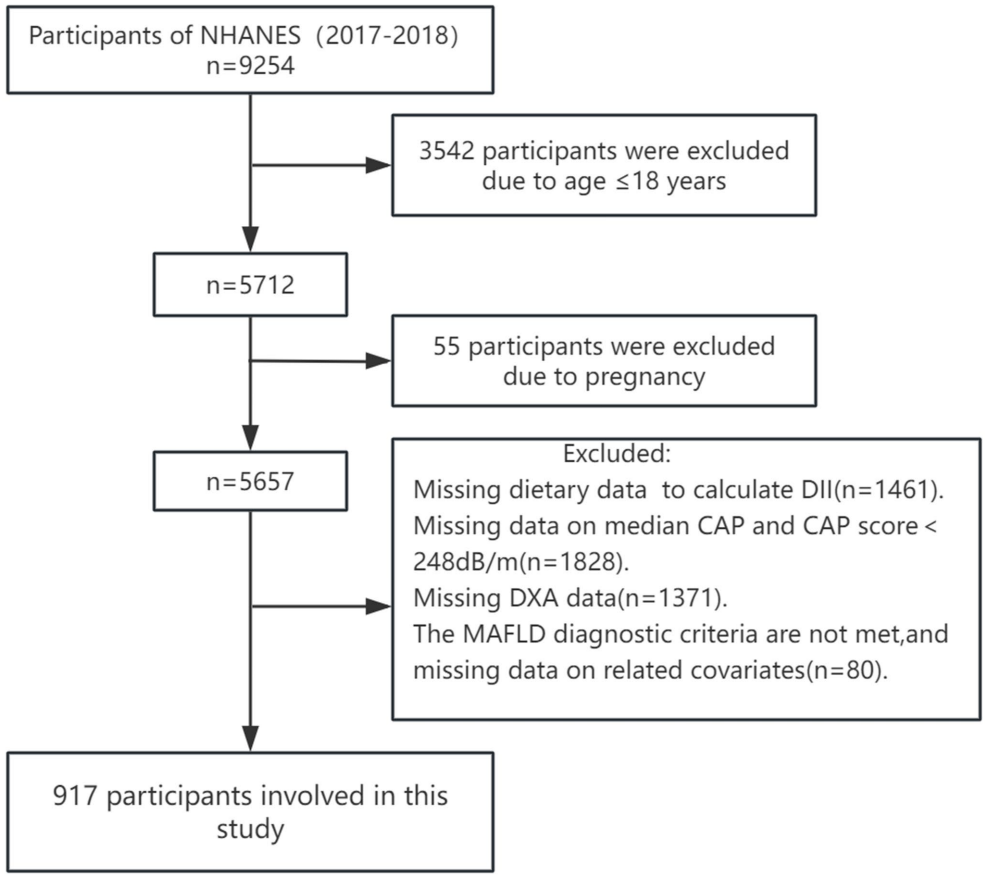

FIGURE 1
Flow chart of the study.

2.4 Calculation of DII

Daily intakes of dietary components in the NHANES database are obtained from 24-h dietary recall interview, and in this study, the average of two 24-h dietary data was used to calculate the DII. The specific calculation methodology is reported in detail elsewhere (11). In the present study, we used 28 different dietary components to estimate DII, including energy, protein, carbohydrate, dietary fiber, vitamins A, B1, B2, B6, B12, C, D, total fat, total saturated fatty acids, total monounsaturated fatty acids, total polyunsaturated fatty acids, n-3 fatty acids, n-6 fatty acids, cholesterol, vitamin E, β-carotene, niacin, folate, magnesium, iron, zinc, selenium, caffeine and alcohol.

2.5 Variables

Variables included in this study were gender, age, race, smoking, body mass index (BMI), Alcohol intake, Significant fibrosis, diabetes, cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and glycosylated hemoglobin (HbA1c). Race was categorized as Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, non-Hispanic Asian, and other races, BMI was weight (kg)/height (m) squared, and smoking was defined as smoking more than 100 cigarettes in one's lifetime, which was obtained from a questionnaire. The methods of testing TC, TG, HDL-C, and HbA1c are described in detail on the official NHANES website. Diabetes mellitus was defined as "your doctor has told you that you have diabetes mellitus," or a fasting blood glucose ≥7.0 mmol/L or a random blood glucose ≥11.1 mmol/L or an HbA1c >6.5%, or taking hypoglycemic medication to lower blood glucose or using insulin.

2.6 Statistical methods

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as frequencies and weighted percentages, and weighted linear regression models (for continuous variables), as well as weighted chi-square tests (for categorical variables), were utilized to compare the differences between the two groups. Binary logistic regression was used to analyze the relationship between DII and sarcopenia. Model 1 was unadjusted for variables; model 2 was adjusted for age, race, and BMI; and model 3 was adjusted for age, race, BMI, Alcohol intake, smoking, significant fibrosis, diabetes, TC, TG, HDL-C and HbA1c. In addition, analyses were stratified by age, BMI, and significant fibrosis. Multivariate linear regression was used to estimate the relationship between DII and ALM_{BMI}. Data were analyzed using the R package, EmpowerStats, and Stata, and $p < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics of participants

In this study, 917 patients with MAFLD were enrolled with a weighted mean age of 42.58 years and a prevalence of sarcopenia of 13.07%. Participants were categorized into three groups based on DII tertiles: group T1 ($n = 305$), group T2 ($n = 306$), and group T3 ($n = 306$). There was a statistically significant difference in mean age between the three groups (T1: 44.56 ± 11.10 vs. T2: 41.86 ± 11.57 vs. T3: 41.24 ± 12.24, $p < 0.001$). In addition, participants with higher DII were more likely to be female (T1: 26.89% vs. T2: 54.12% vs. T3: 63.85%, $p < 0.001$), have a higher prevalence of diabetes mellitus (T1: 13.07% vs. T2: 12.29% vs. T3: 21.24%, $p = 0.004$), and a higher BMI (T1: 31.43 ± 5.67 vs. T2: 32.58 ± 6.55 vs. T3: 34.21 ± 6.94, $p < 0.001$), higher TC (T1: 4.84 ± 0.88 vs. T2: 5.08 ± 0.98 vs. T3: 5.21 ± 1.19, $p = 0.009$), lower alcohol intake (T1: 15.08 ± 24.75 vs. T2: 8.82 ± 24.59 vs. T3: 6.19 ± 14.46, $p < 0.001$), lower ALM_{BMI} (T1: 0.84 ± 0.17 vs. T2: 0.75 ± 0.18 vs. T3: 0.70 ± 0.17, $p < 0.001$). In these three groups, there were no statistical differences in smoking ($p = 0.056$), TG ($p = 0.904$), HDL-C ($p = 0.941$), HbA1c ($p = 0.168$), prevalence of significant fibrosis ($p = 0.262$) and prevalence of sarcopenia ($p = 0.111$). Detailed information is shown in Table 1. In female participants, we observed that DII was significantly higher in sarcopenia patients than in non-sarcopenia patients ($p < 0.001$), whereas there was no statistically significant difference in males ($p = 0.568$) (Table 2).

3.2 The association between DII and sarcopenia

The association between DII and the risk of prevalence of sarcopenia in NAFLD was analyzed using binary logistic regression models (Table 3). When DII was used as a continuous variable, it was significantly and positively associated with the risk of sarcopenia in women [model 1: odds ratio (OR): 1.42, 95% CI: (1.13, 1.78), $p = 0.002$]. This relationship remained statistically significant after adjusting for confounders [Model 2: OR: 1.57, 95% CI: (1.24, 1.99), $p < 0.001$. Model 3: OR: 1.62, 95% CI: (1.27, 2.08), $p < 0.001$]. In contrast, men had no significant correlation ($p > 0.05$). When DII was used as a categorical variable, in women, the T3 group had a higher risk of sarcopenia than the T1 group [Model 1: OR: 2.55, 95% CI: (1.09, 5.99), $p = 0.031$]. After adjusting for age, race, and BMI, the T3 group still exhibited a higher risk of sarcopenia [Model 2: OR: 3.95, 95% CI: (1.65, 9.46), $p = 0.002$]. After adjusting for age, race, BMI, Alcohol intake, smoking, significant fibrosis, diabetes, TC, TG, HDL-C and HbA1c, the association between DII and the risk of developing sarcopenia did not change [model 3: OR: 4.02, 95% CI: (1.64, 9.82), $p = 0.002$]. In men, a higher risk of prevalence of sarcopenia in the T2 group than in the T1 group was observed only in Model 2 and Model 3 [Model 2: OR: 2.48, 95% CI: (1.03, 5.96), $p = 0.042$. Model 3: OR: 2.87, 95% CI: (1.11, 7.41), $p = 0.030$].

3.3 Subgroup analysis

In a stratified analysis according to age (women: P for interaction = 0.938, men: P for interaction = 0.822), BMI (women: P for interaction = 0.357, men: P for interaction = 0.08) were stratified, and the risk of prevalence of DII and sarcopenia among MAFLD patients did not change. The association did not change and still showed a significant positive correlation between DII and the risk of sarcopenia in women, whereas in men, there was no significant correlation. However, after stratifying the participants according to significant fibrosis, higher DII scores related to a higher risk of sarcopenia in men with significant fibrosis [OR: 3.42, 95% CI: (1.08, 10.83), P for interaction = 0.033], and no significant difference among women (P for interaction = 0.580) (Figure 2).

3.4 The association between DII and ALM_{BMI}

As shown in Table 4, multivariate linear regression analysis showed that DII was negatively associated with ALM_{BMI} in both men and women [women: Model 1: β: −0.008, 95% CI: (−0.014, −0.003), $p = 0.004$. Model 2: β: −0.007, 95% CI: (−0.012, −0.002), $p = 0.010$; men: Model 1: β: −0.007, 95% CI: (−0.013, −0.001), $p = 0.042$. Model 2: β: −0.007, 95% CI: (−0.013, −0.001), $p = 0.049$] (Table 4).

4 Discussion

A total of 917 patients with MAFLD were included in this study, which showed that higher DII was significantly associated with the risk of developing sarcopenia in women, whereas no association was found in men. After stratification according to age and BMI, the association between DII and sarcopenia in patients with MAFLD was unchanged. However, after stratification according to significant fibrosis, higher DII scores related to a higher risk of sarcopenia in men with significant fibrosis, and no significant difference among women. These findings suggest that an anti-inflammatory diet may be an effective measure to prevent sarcopenia in patients with MAFLD.

Chronic low-grade inflammation throughout the body is a contributing factor to many chronic non-communicable diseases, and daily diet can influence the level of inflammation in the body. Poor dietary habits may promote the development of chronic inflammation, which in turn affects people's health. The Mediterranean diet, which is rich in fruits, vegetables, whole grains, and olive oil, is considered an anti-inflammatory dietary pattern, and studies have shown that the Mediterranean diet reduces the level of inflammation in the body (17, 18). Meanwhile, the Mediterranean diet may positively affect biochemical parameters and fatty liver index in individuals with NAFLD (19). On the contrary, a diet high in fructose and fat may increase the level of inflammation in the organism (20). Experimental animal studies have shown that a high fructose diet for 8–12 weeks causes mice to develop fatty liver, with increased disease progression with longer exposure (21). A 6-week fructose-restricted diet (<7.5 g/meal and < 10 g/day) reduces intrahepatic lipid content (22). Therefore, a rational dietary profile can help to reduce the level of body inflammation. Currently, no one diet is the key for the treatment MAFLD, personalized approach maybe. DII can quantify diet-mediated inflammation and be used to assess the impact of dietary inflammation on disease. Studies have shown that higher DII is associated with the risk of developing several chronic diseases, including tumors (23–25), cardiovascular disease (26), Diabetes mellitus (27), Osteoporosis (28). The large prospective study by Petermann-Rocha et al. demonstrated

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TABLE 1 The baseline characteristics of participants (weighted).

Variable	Total (n = 917)	T1 group (n = 305)	T2 group (n = 306)	T3 group (n = 306)	p-value
Age (years)	42.58 ± 11.72	44.56 ± 11.10	41.86 ± 11.57	41.24 ± 12.24	<0.001
Gender, n (%)					<0.001
Male	452 (52.09)	211 (73.11)	137 (45.88)	104 (36.15)	
Female	465 (47.91)	94 (26.89)	169 (54.12)	202 (63.85)	
Race/ethnicity, n (%)					0.003
Mexican American	185 (14.30)	76 (18.80)	63 (12.58)	46 (11.33)	
Other Hispanic	93 (8.69)	37 (10.56)	25 (6.88)	31 (8.65)	
Non-Hispanic White	268 (54.56)	70 (47.43)	92 (59.14)	106 (57.25)	
Non-Hispanic Black	162 (9.65)	38 (6.77)	55 (9.04)	69 (13.43)	
Non-Hispanic Asian	155 (6.74)	66 (8.30)	53 (6.65)	36 (5.14)	
Other Race	54 (6.07)	18 (8.15)	18 (5.71)	18 (4.20)	
Smoking, n (%)					0.056
Yes	345 (41.86)	106 (37.99)	113 (40.63)	126 (47.39)	
No	572 (58.14)	199 (62.01)	193 (59.37)	180 (52.61)	
Diabetes, n (%)					0.004
Yes	178 (15.39)	51 (13.07)	56 (12.29)	71 (21.24)	
No	739 (84.61)	254 (86.93)	250 (87.71)	235 (78.76)	
Significant fibrosis, n (%)					0.262
Yes	116 (12.26)	39 (11.99)	40 (10.31)	37 (14.65)	
No	801 (87.74)	266 (88.01)	266 (89.69)	269 (85.35)	
Alcohol intake (g)	10.12 ± 22.27	15.08 ± 24.75	8.82 ± 24.59	6.19 ± 14.46	<0.001
BMI, (Kg/m^2)	32.71 ± 6.49	31.43 ± 5.67	32.58 ± 6.55	34.21 ± 6.94	<0.001
TC (mmol/L)	5.03 ± 1.02	4.84 ± 0.88	5.08 ± 0.98	5.21 ± 1.19	0.009
TG (mmol/L)	1.84 ± 1.87	1.79 ± 1.56	1.86 ± 1.71	1.88 ± 2.34	0.904
HDL-C (mmol/L)	1.27 ± 0.34	1.26 ± 0.32	1.28 ± 0.36	1.26 ± 0.34	0.941
HbA1c (%)	5.78 ± 1.10	5.68 ± 0.92	5.93 ± 1.28	5.76 ± 1.08	0.168
ALM_{BMI}	0.77 ± 0.18	0.84 ± 0.17	0.75 ± 0.18	0.70 ± 0.17	<0.001
Sarcopenia, n (%)					0.111
No	770 (86.93)	266 (90.12)	255 (85.79)	249 (84.73)	
Yes	147 (13.07)	39 (9.88)	51 (14.21)	57 (15.27)	

Mean ± standard deviation was used to describe continuous variables, and unweighted frequencies and weighted percentages were used to describe categorical variables. p-values were calculated using weighted linear regression models for continuous variables and weighted chi-square tests for categorical variables.

that DII levels are associated with NAFLD severity (29). In addition, a cohort study found that high DII was significantly related to the incidence of NAFLD (30). However, the relationship between DII and sarcopenia in patients with fatty liver disease remains understudied. We associated DII with sarcopenia in patients with MAFLD and found that female patients with higher DII were more likely to develop sarcopenia. Previous studies have shown that higher DII is associated with an elevated risk of sarcopenia in patients with hypertension, asthma, chronic kidney disease, and Crohn's disease, both in men and women (31–34). Our study showed this relationship only in women. This may be related to estrogen levels in female patients, which decrease as women age leading to muscle atrophy (35). However, in subgroup analyses stratified by significant fibrosis, we found that male patients with significant fibrosis are a particular population and that the higher the DII score, the higher the risk of sarcopenia in male patients with significant hepatic fibrosis. This finding has significant implications for the prevention and treatment of sarcopenia. We also analyzed the relationship between DII and appendicular lean mass. We found that DII was negatively associated with appendicular lean mass adjusted for body mass index. More high-quality studies in different subgroups still need to be added in the future to confirm the relationship between DII and sarcopenia in patients with MAFLD.

A chronic inflammatory state usually accompanies patients with MAFLD. In sarcopenia, the major pro-inflammatory cytokines include TNF-α, IL-6, and interleukin-1 (IL-1) (36). Chronic inflammation may be an essential factor in the development of sarcopenia in patients with MAFLD. Therefore, the mechanism by which a pro-inflammatory diet leads to the development of sarcopenia in patients with MAFLD may be related to inflammatory factors. Controlling the pro-inflammatory diet in patients with MAFLD may

TABLE 2 Comparison of DII by sarcopenia subgroups (weighted).

Variable	Women			Men		
	Non-sarcopenia	Sarcopenia	*p*-value	Non-sarcopenia	Sarcopenia	*p*-value
DII	1.42 ± 1.58	2.21 ± 1.51	<0.001	0.33 ± 1.84	0.46 ± 1.882	0.568

TABLE 3 The association between DII and sarcopenia (weighted).

Variable	Model 1		Model 2		Model 3	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Women						
Continuous DII	1.42 (1.13, 1.78)	0.002	1.57 (1.24, 1.99)	<0.001	1.62 (1.27, 2.08)	<0.001
Categorical DII						
T1 group	1.00 (reference)		1.00 (reference)		1.00 (reference)	
T2 group	1.54 (0.62, 3.80)	0.348	1.84 (0.69, 4.92)	0.219	1.64 (0.59, 4.60)	0.344
T3 group	2.55 (1.09, 5.99)	0.031	3.95 (1.65, 9.46)	0.002	4.02 (1.64, 9.82)	0.002
Men						
Continuous DII	1.04 (0.86, 1.26)	0.670	1.04 (0.82, 1.33)	0.726	1.04 (0.82, 1.33)	0.724
Categorical DII						
T1 group	1.00 (reference)		1.00 (reference)		1.00 (reference)	
T2 group	1.97 (0.88, 4.44)	0.100	2.48 (1.03, 5.96)	0.042	2.87 (1.11, 7.41)	0.030
T3 group	1.58 (0.67, 3.73)	0.301	1.38 (0.42, 4.49)	0.596	1.41 (0.43, 4.60)	0.564

Model 1: Unadjusted variables.
Model 2: Adjusted for age, race, BMI.
Model 3: adjusted for age, race, BMI, Alcohol intake, smoking, significant fibrosis, diabetes, TC, TG, HDL-C and HbA1c.

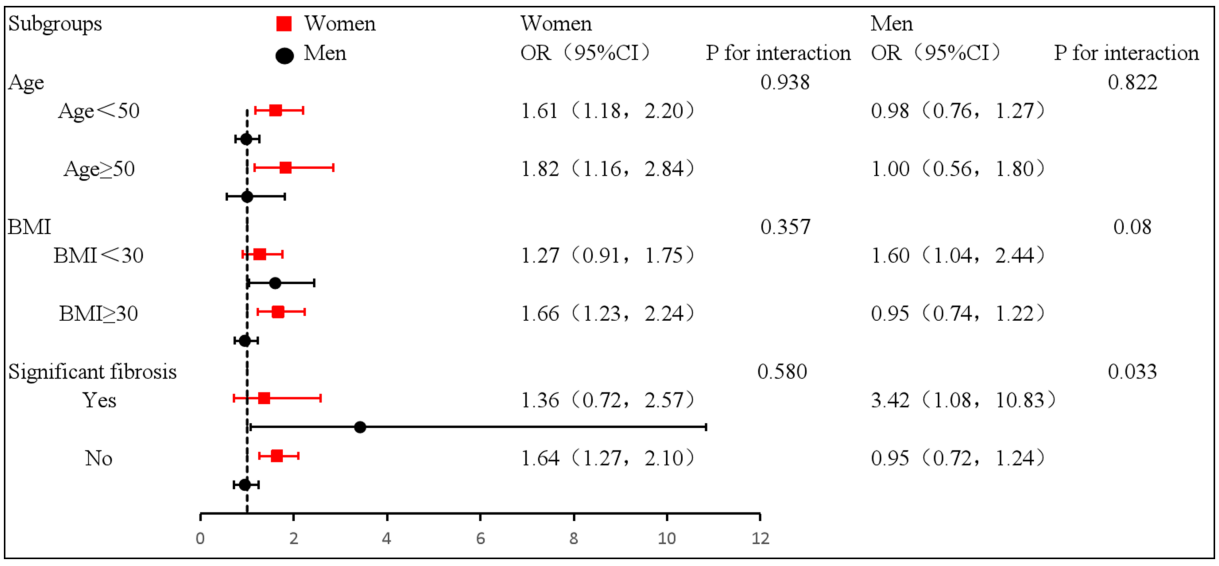

FIGURE 2
Forest plot of stratified analysis of the correlation between DII and the risk of sarcopenia in patients with MAFLD.

be an essential means of preventing sarcopenia. Increasing the intake of anti-inflammatory components (dietary fiber, vitamins, certain unsaturated fatty acids, etc.) and decreasing the intake of pro-inflammatory components (certain saturated fats, cholesterol, etc.) may be effective in preventing the development of sarcopenia in patients with MAFLD. However, the DII score is related to each nutrient component, and excessive control of the pro-inflammatory diet, which results in low intake of energy, protein, etc., may lead to

TABLE 4 Multivariate linear regression model between DII and ALMBMI (weighted).

ALM_{BMI}	Model 1		Model 2	
	β (95%CI)	*p*-value	β (95%CI)	*p*-value
Women	−0.008 (−0.014, −0.003)	0.004	−0.007 (−0.012, −0.002)	0.010
Men	−0.007 (−0.013, −0.001)	0.042	−0.005 (−0.013, 0.001)	0.049

Model 1: Adjusted for age, race, BMI.
Model 2: adjusted for all remaining variables based on model 1.

malnutrition and thus loss of skeletal muscle, increasing the risk of sarcopenia (37). Adequate protein intake plays a vital role in ensuring muscle mass (38), and higher protein intake associated with lower prevalence of sarcopenia (39). Therefore, attention should be paid to energy and protein intake while controlling pro-inflammatory diets in patients with MAFLD. Data for this study were obtained from the National Health and Nutrition Examination Survey database, weighted according to officially recommended weights, and participants were representative of the entire U.S. population. Our study provides some valuable information on the dietary aspects of preventing sarcopenia in patients with MAFLD. It gives some reference for the prevention and control of MAFLD combined with sarcopenia. An anti-inflammatory diet may become one of the effective measures for the prevention of sarcopenia; therefore, we recommend that patients with MAFLD reduce the intake of pro-inflammatory dietary components and increase the intake of anti-inflammatory dietary components appropriately. However, the management of MAFLD combined with sarcopenia needs to place greater emphasis on a personalized approach and the acceptance of multiple possible diet solutions.

5 Limitations

The present study has some limitations; first, the dietary components used to calculate DII were obtained from a 24-h dietary recall interview, and recall bias is inevitable. Secondly, this study is a cross-sectional study, which can only conclude the correlation between DII and the occurrence of sarcopenia in the MAFLD population but cannot establish a causal relationship. In retrospective studies, dietary habits and environmental factors, etc., may not be able to match well with this population, so a large number of prospective studies are still needed in the future to confirm this conclusion.

6 Conclusion

The pro-inflammatory diet represented by higher DII scores was significantly associated with the risk of sarcopenia in female patients with MAFLD, with higher DII scores related to a higher risk of sarcopenia. Higher DII scores related to a higher risk of sarcopenia in men with significant fibrosis. DII was negatively correlated with body mass index-adjusted skeletal muscle mass in the extremities. A high DII score is a risk factor for sarcopenia in female patients with MAFLD.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XW: Writing – original draft, Writing – review & editing, Investigation, Methodology, Software, Validation, Visualization. RS: Project administration, Supervision, Writing – review & editing. YZ: Data curation, Investigation, Writing – review & editing. JL: Investigation, Methodology, Writing – review & editing.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1486898/full#supplementary-material

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Non-linear relationship between the first meal time of the day and gallstone incidence in American adults: a population-based cross-sectional study

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Background: Irregular meal time is associated with gallstones. The time–dose effect between meal time and gallstone formation remains unknown.

Objective: This study aimed to investigate the association between the first meal time (FMT) of the day and the prevalence of gallstones.

Methods: Based on data from the National Health and Nutrition Examination Survey from 2017 to March 2020, the associations between the FMT of the day and the prevalence of gallstones were analyzed via multivariable logistic regression, restricted cubic spline curves, subgroup analysis, and interaction tests.

Results: A total of 6,547 participants were included. The fully adjusted model indicated a positive correlation between the FMT of the day and the prevalence of gallstones (odds ratio [OR] = 1.05, 95% confidence interval [CI] = 1.02 ~ 1.08); this association was consistent across subgroups. The risk of developing gallstones was the greatest when the FMT was between 09:00 and 14:00 (OR [95% CI] = 1.49 [1.24 ~ 1.77]). There was a non-linear relationship between the FMT and gallstone incidence (*P* for non-linearity = 0.042), with an inflection point at 13.4 h. After the 13.4-h mark, the risk of developing gallstones did not increase further.

Conclusion: The FMT of the day is positively correlated with the prevalence of gallstones, and there is a non-linear relationship and threshold effect between the two. Skipping breakfast is associated with a greater risk of developing gallstones. This study provides new evidence for the dietary prevention of gallstones.

KEYWORDS

first meal time, gallstone, American adults, NHANES, non-linear relationship, threshold effect, dietary

1 Introduction

Gallstones are a common digestive system disease, and there are significant differences in prevalence across different regions and populations. The prevalence is higher in developed countries (1). In the United States, more than 20 million people have gallstones, making it the second most common gastrointestinal, liver, and pancreatic disease diagnosed, accounting for approximately 20% of all related diseases (2–4). The prevalence in Europe is slightly higher, especially in Scandinavian countries, where it can exceed 20% (2). Among American Indians, the prevalence of gallstones is as high as 70%, whereas it is 10–15% among adult Caucasians (2). In contrast, the prevalence among Asian populations is relatively low (5). Most people with gallstones are asymptomatic, but 3–8% of patients may develop complications such as cholecystitis, cholangitis, and pancreatitis, which require surgical treatment (6). In the United States, the medical costs associated with gallstones amount to billions of dollars annually, imposing a significant economic burden on public health (2).

Gallstones can be classified into cholesterol stones, pigment stones, and mixed stones. In developed countries, cholesterol stones account for approximately 80–85% of all cases (2). Risk factors for gallstones include age > 40 years, female sex, obesity, pregnancy, short-acting contraceptive use, diabetes and metabolic syndrome (7–10). Additionally, diet is an important factor influencing gallstone formation. A diet high in fat, high in cholesterol, and low in fiber increases the risk of developing gallstones (11, 12). Irregular meal times can lead to irregular gallbladder emptying, which may increase the retention time of bile in the gallbladder, which can lead to increased bile concentrations and thus an increased risk of stone formation. A study has shown that those who regularly work at night, participate in nighttime entertainment and food consumption, or work long shifts are at a greater risk of developing gallstone disease (13).

The overall association between the overnight fasting period and gallstones has been elucidated (14–16). However, the specific time–dose effect between meal time and gallstones still requires further investigation. This study aimed to explore the association between the first meal time (FMT) of the day and the prevalence of gallstones to provide new evidence for the prevention of gallstones.

2 Materials and methods

2.1 Study design and population

The National Health and Nutrition Examination Survey (NHANES) is a stratified, multistage design, randomized sample study combining interviews, physical examinations, and laboratory tests. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. The study protocol was approved by the National Center for Health Statistics Research Ethics Review Board. Informed consent was obtained from each participant prior to data collection. This study collected data from 2017 to March 2020 and included a total of 15,560 participants, excluding 6,328 participants younger than 20 years old, 1,537 participants with missing data on meal times, 13 participants with missing gallstone data, and 1,225 participants with other missing covariates. Finally, 6,457 participants were included, of whom 695 reported the presence of gallstones (Figure 1).

2.2 FMT and gallstones

The exposure variable for this study was the FMT of the day, which was defined as the time of the first oral intake of solid or liquid food on that day, obtained through the first 24-h dietary review, i.e., individual foods. After determining the FMT of the day, the corresponding food code was identified and then compared with the United States Department of Agriculture food code file (Supplementary USDA Food Code) in the NHANES database to determine the food type. If the food type was water, tea, wine, coffee, juice, soda, a sports drink, or an energy drink, it was not considered a meal. Although some of these foods contain sugar, electrolytes, and/or vitamins, they lack comprehensive nutrients such as proteins, fats, and dietary fibers; they are rapidly absorbed and excreted in the digestive system, failing to provide sustained energy and satiety (17–19). Therefore, the consumption of these foods is not considered a meal. Gallstones are the outcome variable in this study and the diagnosis of gallstones is based on self-reported data from a questionnaire, which asks, "Has a doctor or other health professional ever told {you/SP} that {you/s/he} had gallstones?".

2.3 Covariates

The covariates in this study refer to previous studies (6, 15, 20–22) and include sex, age, race, education level, marital status, the ratio of family income to poverty (PIR), BMI, physical activity level, alcohol use, smoking status, diabetes status, hypertension status, energy level, protein intake, carbohydrate intake, dietary fiber intake, total fat intake, total saturated fatty acid intake, and cholesterol intake. Physical activity is a binary variable, with "yes" indicating engaging in any moderate-intensity exercise, fitness, or recreational activities that cause a slight increase in breathing or heart rate within a week. Alcohol use is a binary variable, with "yes" indicating having consumed at least one drink of any kind of alcohol in one's lifetime. Smoking status is a binary variable, with "yes" indicating having smoked at least 100 cigarettes in one's lifetime. Diabetes is defined as a self-reported diagnosis or the current use of diabetes medication. Hypertension is defined similarly to diabetes. Energy and nutrient covariates were obtained through the first 24-h dietary review-total nutrient intake assessment.

2.4 Statistical analysis

Categorical variables are presented as frequencies (percentages) and were analyzed via the chi-square test. Continuous variables are reported as medians (1st quartile, 3rd quartile) and were analyzed via the Mann–Whitney *U* test. Multivariate logistic regression was used to analyze the association between the FMT and the prevalence of gallstones. Model 1 did not adjust for covariates. Model 2 was adjusted for sex, age, and race. Model 3 was adjusted for all covariates. The FMT was also converted into categorical variables, which were divided into 00:00–09:00 (breakfast period), 09:00–14:00 (lunch period), 14:00–20:00 (dinner period), and 20:00–24:00 (late-night snack period), for further analysis of its

Abbreviations: FMT, first meal time; PIR, ratio of family income to poverty; RCS, restricted cubic spline.

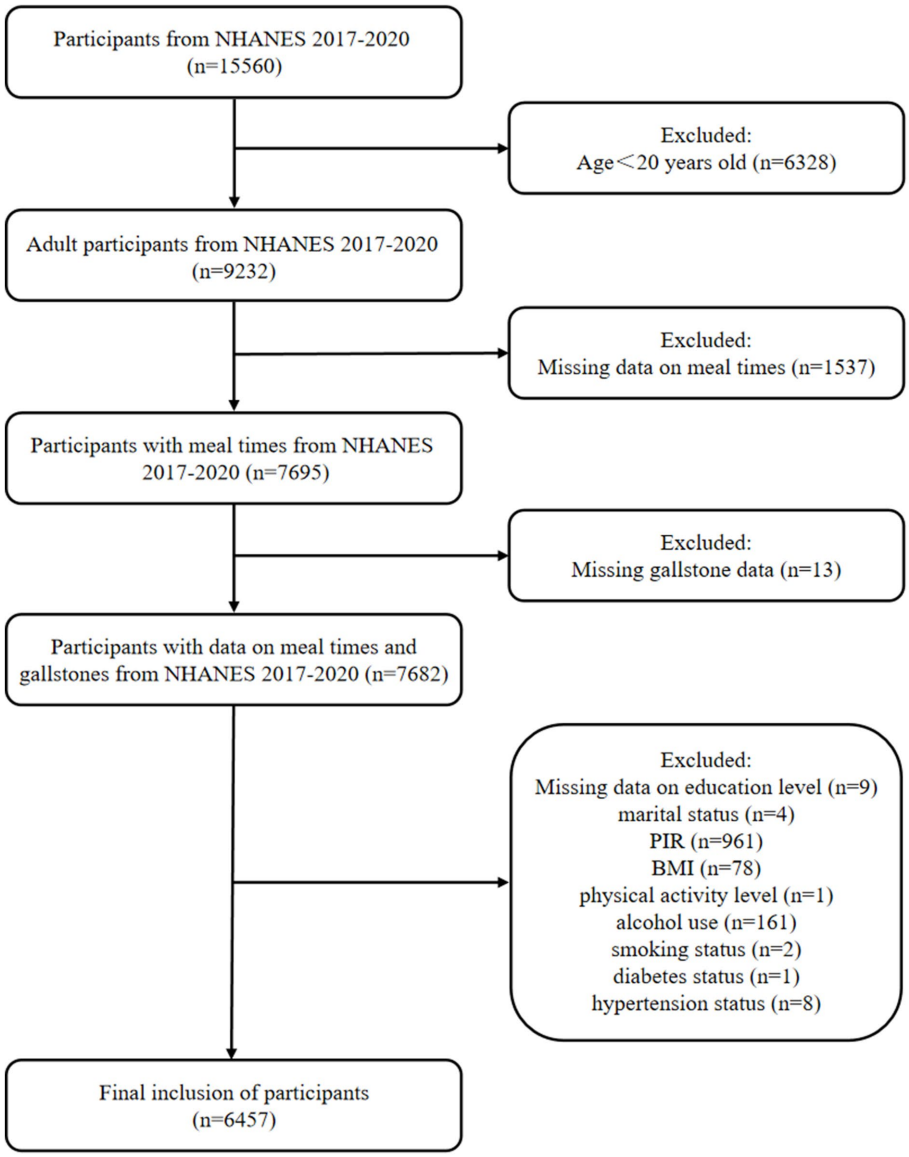

FIGURE 1
Flow chart of participant selection. PIR, ratio of family income to poverty.

association with gallstones. Restricted cubic spline (RCS) curves were used to analyze the non-linear trends and threshold effects between the FMT and gallstones. Non-linearity was tested using the likelihood ratio test. Subgroup analysis and interaction tests were conducted to explore the robustness of the association between the FMT and gallstones in different subgroups. All tests were two-sided, with a $p < 0.05$ considered statistically significant. Statistical analyses were conducted via EmpowerStats (version 4.1) and R Software (version 4.3.0).

3 Results

3.1 Baseline characteristics

Table 1 presents the baseline characteristics of the participants. Among the 6,457 adult participants, 3,318 (51.39%) were female, 2,443 (37.83%) were Non-Hispanic White, and 695 (10.76%) had gallstones. The median age was 52.00 (36.00, 64.00) years, and the median first mealtime was 9:00 (7:50, 11:00) hours. There were statistically significant differences ($p < 0.05$) between the two groups in terms of age, BMI, FMT, energy level, protein intake, carbohydrate intake, dietary fiber intake, total fat intake, total saturated fatty acid intake, cholesterol intake, sex, race, marital status, physical activity level, smoking status, diabetes status, and hypertension status.

3.2 Association between the FMT and the prevalence of gallstones

Table 2 shows the relationship between the FMT and the presence of gallstones. The unadjusted model (OR [95% CI] = 1.03

TABLE 1 Baseline characteristics of participants.

Variables	Total (n = 6,457)	Non-gallstone (n = 5,762)	Gallstone (n = 695)	P
Age (years)	52.00 (36.00, 64.00)	50.00 (35.00, 63.00)	60.00 (46.00, 70.00)	<0.001
Sex, n(%)				<0.001
Female	3,318 (51.39)	2,818 (48.91)	500 (71.94)	
Male	3,139 (48.61)	2,944 (51.09)	195 (28.06)	
Race, n(%)				<0.001
Mexican American	727 (11.26)	645 (11.19)	82 (11.80)	
Other Hispanic	616 (9.54)	537 (9.32)	79 (11.37)	
Non-Hispanic White	2,443 (37.83)	2,126 (36.90)	317 (45.61)	
Non-Hispanic Black	1,669 (25.85)	1,537 (26.67)	132 (18.99)	
Other Race	1,002 (15.52)	917 (15.91)	85 (12.23)	
Education level, n(%)				0.423
Below high school	1,053 (16.31)	936 (16.24)	117 (16.83)	
High school	1,553 (24.05)	1,374 (23.85)	179 (25.76)	
Above high school	3,851 (59.64)	3,452 (59.91)	399 (57.41)	
Marital status, n(%)				<0.001
Cohabitation	3,778 (58.51)	3,364 (58.38)	414 (59.57)	
Living alone	1,452 (22.49)	1,253 (21.75)	199 (28.63)	
Never married	1,227 (19.00)	1,145 (19.87)	82 (11.80)	
PIR	2.40 (1.26, 4.56)	2.41 (1.25, 4.57)	2.25 (1.33, 4.25)	0.573
BMI (Kg/m^2)	28.90 (25.00, 34.10)	28.60 (24.70, 33.60)	32.00 (27.80, 38.05)	<0.001
Physical activity level, n(%)				<0.001
No	3,825 (59.24)	3,373 (58.54)	452 (65.04)	
Yes	2,632 (40.76)	2,389 (41.46)	243 (34.96)	
Alcohol use, n(%)				0.899
No	540 (8.36)	481 (8.35)	59 (8.49)	
Yes	5,917 (91.64)	5,281 (91.65)	636 (91.51)	
Smoking status, n(%)				0.001
No	3,694 (57.21)	3,336 (57.90)	358 (51.51)	
Yes	2,763 (42.79)	2,426 (42.10)	337 (48.49)	
Diabetes status, n(%)				<0.001
No	5,292 (81.96)	4,802 (83.34)	490 (70.50)	
Borderline	181 (2.80)	160 (2.78)	21 (3.02)	
Yes	984 (15.24)	800 (13.88)	184 (26.47)	
Hypertension status, n(%)				<0.001
No	3,983 (61.68)	3,664 (63.59)	319 (45.90)	
Yes	2,474 (38.32)	2098 (36.41)	376 (54.10)	
FMT (hours)	9.00 (7.50, 11.00)	9.00 (7.50, 11.00)	9.00 (8.00, 11.00)	0.003
Energy level (kcal)	1976.00 (1443.00, 2642.00)	2000.50 (1463.25, 2668.75)	1773.00 (1337.50, 2340.00)	<0.001
Protein intake (g)	72.08 (51.60, 100.48)	73.23 (52.25, 102.20)	62.93 (46.13, 89.20)	<0.001
Carbohydrate intake (g)	226.55 (161.94, 312.04)	228.24 (163.60, 314.54)	211.06 (147.59, 291.34)	<0.001
Dietary fiber intake (g)	14.20 (9.00, 21.40)	14.40 (9.10, 21.60)	12.80 (8.20, 19.00)	<0.001
Total fat intake (g)	79.69 (53.88, 113.08)	80.65 (54.34, 114.58)	72.77 (50.77, 100.79)	<0.001
Total saturated fatty acids intake (g)	24.72 (15.86, 36.85)	25.07 (15.89, 37.11)	22.11 (15.49, 33.48)	<0.001
Cholesterol intake (mg)	247.00 (135.00, 432.00)	251.00 (138.00, 435.00)	214.00 (115.00, 403.00)	<0.001

Variables are presented as frequencies (percentages) or medians (1st quartile, 3rd quartile). The baseline characteristics of participants were analyzed via the chi-square test and the Mann–Whitney U test. Sex and race are self-reported. FMT, first meal time; PIR, ratio of family income to poverty.

TABLE 2 Association between the first meal time and the prevalence of gallstones.

Variables	Model 1[1]			Model 2[2]			Model 3[3]		
	OR (95% CI)	*P*	*P* for trend	OR (95% CI)	*P*	*P* for trend	OR (95% CI)	*P*	*P* for trend
FMT (continuous)	1.03 (1.00 ~ 1.05)	0.033		1.06 (1.03 ~ 1.09)	<0.001		1.05 (1.02 ~ 1.08)	0.001	
FMT (categorical)									
00:00–09:00	1.00 (Reference)			1.00 (Reference)		<0.001	1.00 (Reference)		
09:00–14:00	1.33 (1.13 ~ 1.57)	<0.001	0.382	1.55 (1.31 ~ 1.85)	<0.001		1.49 (1.20 ~ 1.77)	<0.001	0.008
14:00–20:00	1.06 (0.78 ~ 1.45)	0.701		1.54 (1.11 ~ 2.14)	0.009		1.35 (0.96 ~ 1.91)	0.082	
20:00–24:00	0.75 (0.27 ~ 2.08)	0.577		1.43 (0.50 ~ 4.06)	0.507		1.33 (0.46 ~ 3.84)	0.597	

Multivariate logistic regression and trend test were used to analyze the association between the FMT and the prevalence of gallstones. [1]No covariates were adjusted. [2]Sex, age, race were adjusted. [3]Sex, age, race, education level, marital status, PIR, BMI, physical activity level, alcohol use, smoking status, diabetes status, hypertension status, energy level, protein intake, carbohydrate intake, dietary fiber intake, total fat intake, total saturated fatty acid intake, and cholesterol intake were adjusted. FMT, first meal time; PIR, ratio of family income to poverty.

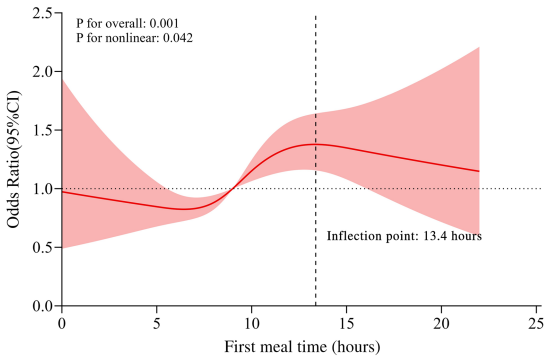

FIGURE 2
The time–dose effect between the first meal and the prevalence of gallstones. The RCS curve based on the fully adjusted model was plotted to further explore the non-linear trend and threshold effect between the FMT and the presence of gallstones. Sex, age, race, education level, marital status, PIR, BMI, physical activity level, alcohol use, smoking status, diabetes status, hypertension status, energy level, protein intake, carbohydrate intake, dietary fiber intake, total fat intake, total saturated fatty acid intake, and cholesterol intake were adjusted. The red solid line represents the estimated values, and the shaded area represents the 95% CI. The intersection of the vertical black dashed line and the red solid line represents the inflection point. FMT, first meal time; PIR, ratio of family income to poverty; RCS, restricted cubic spline.

[1.00 ~ 1.05]), the partially adjusted model (OR [95% CI] = 1.06 [1.03 ~ 1.09]), and the fully adjusted model (OR [95% CI] = 1.05 [1.02 ~ 1.08]) all indicated a positive correlation between the FMT and gallstones. The fully adjusted model shows that for every one-hour delay in the FMT, the risk of developing gallstones increases by 5%. When the FMT was converted into categorical variables for further analysis, the fully adjusted model revealed that, compared with the FMT between 00:00 and 09:00 (breakfast period), the risk of gallstones increased by 49% (OR [95% CI] = 1.49 [1.24 ~ 1.77]) for the FMT between 09:00 and 14:00 (lunch period), by 35% (OR [95% CI] = 1.35 [0.96 ~ 1.91]) for the FMT between 14:00 and 20:00 (dinner period), and by 33% (OR [95% CI] = 1.33 [0.46 ~ 3.84]) for the FMT between 20:00 and 24:00 (late-night snack period). The risk of gallstones tended to decrease with increasing FMT, and the trend test indicated that this decreasing trend was statistically significant (*P* for trend = 0.008).

TABLE 3 Threshold effect analysis between the first meal time and the prevalence of gallstones.

Two-piecewise logistic regression model[1]	OR (95% CI)	*P*	*P* for non-linearity
FMT ≤ 13.4 h	1.07 (1.03 ~ 1.12)	0.002	0.042
FMT > 13.4 h	1.04 (0.90 ~ 1.19)	0.617	

The two-piecewise logistic regression analysis identified threshold effect between the FMT and the presence of gallstones. [1]Sex, age, race, education level, marital status, PIR, BMI, physical activity level, alcohol use, smoking status, diabetes status, hypertension status, energy level, protein intake, carbohydrate intake, dietary fiber intake, total fat intake, total saturated fatty acid intake, and cholesterol intake were adjusted. FMT, first meal time; PIR, ratio of family income to poverty.

3.3 Non-linear trend and threshold effect analysis

An RCS curve based on the fully adjusted model was plotted to further explore the non-linear trend and threshold effect between the FMT and the presence of gallstones. The results revealed a non-linear relationship between the FMT and the prevalence of gallstones (*P* for non-linearity = 0.042) (Figure 2). A two-piecewise logistic regression analysis identified an inflection point at 13.4 h. When the FMT duration was less than 13.4 h, each additional hour was associated with a 7% increase in the risk of gallstones (OR [95% CI] = 1.07 [1.03 ~ 1.12]). When the FMT duration was 13.4 h or more, the positive correlation between the FMT and gallstones was no longer significant (OR [95% CI] = 1.04 [0.90 ~ 1.19]) (Table 3).

3.4 Subgroup analysis

The participants were stratified according to sex, race, age, BMI, education level, marital status, physical activity level, alcohol use, smoking status, diabetes status, and hypertension status for subgroup analysis and interaction tests. The results revealed a significant positive correlation between the FMT and gallstones among women, married individuals, those with no exercise habits, alcohol drinkers, smokers, individuals with diabetes, those without hypertension, and those aged 60 years or older. However, the interactions between the FMT and these subgroups were not significant. Overall, the positive correlation between the FMT and gallstones was consistent across different subgroups (Figure 3).

Subgroups	n (%)	OR (95% CI)	P	P for interaction
All patients	6457 (100.00)	1.04 (1.01 ~ 1.07)	0.015	
Sex				0.304
Female	3318 (51.39)	1.04 (1.00 ~ 1.08)	0.034	
Male	3139 (48.61)	1.03 (0.98 ~ 1.08)	0.292	
Race				0.943
Mexican American	727 (11.26)	1.09 (0.98 ~ 1.20)	0.104	
Other Hispanic	616 (9.54)	1.03 (0.94 ~ 1.14)	0.486	
Non-Hispanic White	2443 (37.83)	1.04 (0.99 ~ 1.08)	0.104	
Non-Hispanic Black	1669 (25.85)	1.01 (0.96 ~ 1.07)	0.612	
Other Race	1002 (15.52)	1.03 (0.94 ~ 1.12)	0.545	
Education level				0.475
Below high school	1053 (16.31)	1.06 (1.00 ~ 1.14)	0.069	
High school	1553 (24.05)	1.03 (0.98 ~ 1.09)	0.268	
Above high school	3851 (59.64)	1.02 (0.99 ~ 1.06)	0.215	
Marital status				0.584
Cohabitation	3778 (58.51)	1.05 (1.01 ~ 1.09)	0.015	
Living alone	1452 (22.49)	1.03 (0.98 ~ 1.09)	0.232	
Never married	1227 (19.00)	1.01 (0.94 ~ 1.08)	0.794	
Physical activity level				0.554
No	3825 (59.24)	1.04 (1.00 ~ 1.08)	0.025	
Yes	2632 (40.76)	1.02 (0.97 ~ 1.08)	0.358	
Alcohol use				0.537
No	540 (8.36)	1.10 (0.99 ~ 1.23)	0.077	
Yes	5917 (91.64)	1.03 (1.00 ~ 1.06)	0.039	
Smoking status				0.303
No	3694 (57.21)	1.03 (0.98 ~ 1.07)	0.247	
Yes	2763 (42.79)	1.04 (1.00 ~ 1.08)	0.038	
Diabetes status				0.323
No	5292 (81.96)	1.02 (0.99 ~ 1.06)	0.215	
Borderline	181 (2.80)	1.08 (0.82 ~ 1.43)	0.589	
Yes	984 (15.24)	1.08 (1.02 ~ 1.15)	0.009	
Hypertension status				0.251
No	3983 (61.68)	1.04 (1.00 ~ 1.09)	0.045	
Yes	2474 (38.32)	1.03 (0.99 ~ 1.07)	0.169	
Age (years)				0.740
<60	4136 (64.05)	1.02 (0.99 ~ 1.06)	0.232	
⩾60	2321 (35.95)	1.06 (1.01 ~ 1.11)	0.013	
BMI (Kg/m²)				0.832
<24.9	1569 (24.30)	1.06 (0.98 ~ 1.15)	0.116	
25–29.9	1995 (30.90)	1.05 (0.99 ~ 1.11)	0.086	
⩾30	2893 (44.80)	1.02 (0.99 ~ 1.06)	0.186	

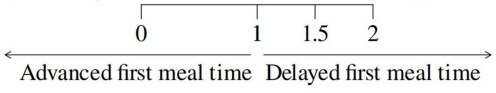

FIGURE 3
Subgroup analysis of the association between the first meal time and the prevalence of gallstones. Subgroup analysis and interaction tests were conducted to explore the robustness of the association between the FMT and gallstones in different subgroups. Sex, age, race, education level, marital status, PIR, BMI, physical activity level, alcohol use, smoking status, diabetes status, hypertension status, energy level, protein intake, carbohydrate intake, dietary fiber intake, total fat intake, total saturated fatty acid intake, and cholesterol intake were adjusted. FMT, first meal time; PIR, ratio of family income to poverty.

4 Discussion

This study examined the time–dose effect between the FMT of the day and the presence of gallstones in a large population sample. The study revealed that the FMT was positively correlated with the prevalence of gallstones and remained consistent across various subgroups. Compared with that when the FMT was between 0:00 and 09:00, the risk of gallstones was greater when the FMT was between 09:00 and 14:00, indicating that skipping breakfast was more correlated with the development of gallstones. Additionally, we found a non-linear relationship between the FMT and gallstones. When the FMT exceeded 13.4 h, the risk of

developing gallstones no longer increased with further delays in the FMT.

Previous studies have shown that a prolonged overnight fasting period may increase the risk of developing gallstones. Capron et al. (14) reported in a short report that short-term prolonged fasting in French women aged 20–35 years may increase the risk of gallstone formation. Sichieri et al. (15) reported in a prospective study that the risk of hospitalization due to gallstones in American women increased with prolonged overnight fasting, with the highest risk observed for fasting periods of 14 h or more. In a cross-sectional study of an Italian population, Attili et al. (16) reported that the prevalence of gallstones was greater in individuals who fasted for more than 12 h at night than in those who fasted for less than 12 h. The results of this study revealed that the prevalence of gallstones gradually increased with the delay in the first meal of the day, which is consistent with the findings of the aforementioned studies. Prolonged fasting can cause bile to remain in the gallbladder for an extended period, during which its water content is gradually absorbed, leading to an increased bile concentration. The increased saturation of cholesterol makes it more likely to aggregate and crystallize within the gallbladder, forming stones (23, 24). Williams et al. (25) reported that among women without gallstones, 4.5% had cholesterol-saturated bile after 9 h of fasting, and this percentage increased to 54.5% after 16 h of fasting. Additionally, during fasting, bile acids are partially stored in the unemptied gallbladder, temporarily interrupting the enterohepatic circulation of bile acids. This leads to a decreased secretion rate of bile acids and an increased proportion of cholesterol in the bile, thereby increasing the risk of cholesterol precipitation and gallstone formation (26).

Further examination of the time–dose effect between the FMT and the prevalence of gallstones revealed a non-linear relationship. Compared with the FMT from 0:00–09:00, the risk of gallstones was relatively greater from 09:00–14:00, and the risk of gallstones from 14:00–20:00 and 20:00–24:00 showed a downward trend. A similar non-linear relationship was reported by Bloch et al. (26), with results that showed the average cholesterol saturation index in 9 healthy women was significantly greater after 15 h of fasting than after 10 h of fasting, with a significant decrease after 20 h of fasting. A possible explanation is that reduced hepatic cholesterol synthesis leads to unsaturated hepatic bile. In the livers of rats, the activity of the rate-limiting enzyme (hydroxymethyl-glutaryl coenzyme-A reductase) in cholesterol synthesis begins to decrease within 6–8 h of fasting, reaching its lowest level 14 h after the last meal (27–29). Gälman et al. (30) reported a possible peak in bile acid synthesis at 13:00, which alters the ratio of bile acid to cholesterol in bile and increases cholesterol solubility, possibly explaining why the risk of gallstones did not increase further after the FMT reached the inflection point of 13.4 h.

In Table 1, we observed that the median BMI of the gallstone group was higher than that of the non-gallstone group. However, participants in the gallstone group reported lower total energy, saturated fatty acids, and cholesterol intake compared to the non-gallstone group, which contrasts with findings from prior studies. One possible explanation is that participants diagnosed with gallstones may have altered their diets following medical advice, reducing their intake of calories, saturated fatty acids, and cholesterol to manage symptoms and slow the progression of gallstone. Moreover, obese participants in the gallstone group may prioritize dietary management more actively. They could adopt low-calorie, low-fat diets as a strategy to manage their weight or improve their overall health. Furthermore, when reporting their dietary intake, they might underreport their actual caloric and fat consumption, whether consciously or unconsciously. Inconsistencies in findings regarding the relationship between dietary factors and gallstone risk have also been reported in previous studies. For example, both the studies by Attili et al. (16) and Smith and Gee (31) found a negative correlation between low caloric intake and the risk of developing gallstones. Festi et al. (32) noted that very low-calorie diets in obese individuals might increase the risk of gallstone formation. Similarly, studies investigating the relationship between total fat intake and cholesterol gallstones have yielded mixed results, ranging from positive to non-significant associations (24). These discrepancies likely stem from the complexity of human dietary patterns, as well as variations in sample characteristics and overall health status.

This study has several strengths. The first is the use of a representative sample of the U.S. population from the NHANES database, with participants strictly adhering to the study protocol and being supervised by comprehensive quality control and assurance measures, thereby ensuring the reliability and accuracy of the study results. The second strength is the further exploration of the non-linear relationship and threshold effect between the first meal time of the day and the prevalence of gallbladder stones. The study's limitations include the cross-sectional study design, which cannot establish a causal relationship between the first meal time and the prevalence of gallbladder stones. Additionally, too many variables related to gallbladder stones are included in the model to control for confounding bias. Finally, due to the inability to differentiate between gallstone compositions, our study may not fully capture the association between the FMT of the day and different types of gallstones. This limitation could restrict a complete understanding of the pathogenesis of gallstones, particularly in relation to dietary habits and lifestyle factors. We recommend that future research utilize datasets containing more comprehensive information on gallstone composition to enable a deeper investigation of these associations.

This study revealed that the FMT of the day is positively correlated with the prevalence of gallstones among U.S. adults and remains consistent across various subgroups. The risk of developing gallstones is relatively high when the FMT is between 09:00 and 14:00. There was a non-linear relationship between the FMT and gallstones, with an inflection point at 13.4 h. This research supplements previous findings, but large-scale prospective cohort studies are still needed to further validate these results.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The studies involving humans were approved by National Center for Health Statistics Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

TS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. LZ: Data curation, Investigation, Project administration, Supervision, Writing – review & editing. YL: Data curation, Investigation, Project administration, Supervision, Writing – review & editing. XZ: Data curation, Formal analysis, Investigation, Writing – review & editing. JC: Data curation, Investigation, Writing – review & editing. TY: Data curation, Investigation, Writing – review & editing. DZ: Data curation, Investigation, Writing – review & editing. BZ: Data curation, Formal analysis, Investigation, Visualization, Writing – review & editing. SZ: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing – review & editing.

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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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

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The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio as a predictive indicator of CKD risk in NAFLD patients: NHANES 2017–2020

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Background: Non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are both closely related to dyslipidemia. However, the relationship between dyslipidemia in patients with NAFLD and CKD is not yet clear. The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) is an innovative and comprehensive lipid index. The purpose of this study was to investigate the correlation between NHHR and CKD risk in NAFLD patients with or without fibrosis.

Methods: This study used data from the National Health and Nutrition Examination Survey (NHANES) from 2017 to 2020 for analysis, including a total of 4,041 subjects diagnosed with NAFLD. Among the NAFLD subjects, 3,315 individuals without liver fibrosis and 726 individuals with fibrosis. Weighted multivariate linear regression, weighted logistic regression, restricted cubic spline (RCS) curves, and subgroup analysis were used to evaluate the correlation between NHHR and CKD in patients with NAFLD.

Results: Our findings indicate that in NAFLD subjects without liver fibrosis, the highest tertile of NHHR, as compared to the lowest tertile, was inversely related to glomerular filtration rate (eGFR) (β: −2.14, 95% CI: −3.97, −0.32, $p < 0.05$) and positively related to CKD (OR: 1.67, 95% CI: 1.12, 2.49, $p < 0.05$). No significant associations were observed between NHHR and eGFR, urinary albumin to creatinine ratio (ACR) in NAFLD subjects with liver fibrosis. The RCS revealed a linear relationship between NHHR and ACR, CKD in NAFLD subjects without liver fibrosis, while a U-shaped relationship was observed between NHHR and ACR, CKD in NAFLD subjects with liver fibrosis.

Conclusion: In patients with non-fibrotic NAFLD, a significantly elevated NHHR is closely associated with an increased risk of CKD and shows a linear relationship with CKD. In patients with fibrotic NAFLD, NHHR shows a U-shaped relationship with CKD. LD, Our findings underscore the practical utility of NHHR as a biomarker for early risk stratification of CKD in patients with NAFLD.

KEYWORDS

NAFLD, fibrosis, CKD, NHHR, lipid metabolism, NHANES

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease, affecting approximately 25% of the global adult population, according to statistics (1, 2). The spectrum of NAFLD encompasses nonalcoholic fatty liver, nonalcoholic steatohepatitis, progressing to liver fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (3). NAFLD is closely linked to insulin resistance, chronic inflammation, and metabolic disorder (4). In this context, NAFLD, as a multisystem disease, not only impairs the normal function of the liver but also affects the kidneys, cardiovascular system, pancreas, and other organs (4, 5).

Chronic kidney disease (CKD) denotes abnormalities in kidney structure or function, with its diagnosis relying on the detection of markers for kidney damage and the duration of such damage (6). Research indicates that patients with NAFLD have a CKD incidence rate ranging from 20 to 55%, significantly higher than the 5 to 35% observed in non-NAFLD patients (7). Moreover, the incidence of CKD differs among patients with NAFLD at varying stages, the progress of NAFLD was positively associated with incidence of CKD (8). The aforementioned studies suggest that NAFLD is a significant contributor to the development of CKD. However, the initial symptoms of patients with NAFLD are often subtle, and some patients are already in the fibrosis stage when they seek medical care. By then, their risk of developing CKD will increase significantly. Therefore, early and timely identification of high-risk populations among NAFLD patients is a critical step in preventing the occurrence of CKD in NAFLD patients.

Numerous researches have identified the intricate link between dyslipidemia and CKD. Dyslipidemia has been identified as a potentially driving factors of CKD (9, 10). The dyslipidemia of CKD patients primarily consists of elevated levels of triglycerides and triglyceride-rich lipoprotein particles, along with reduced levels of high-density lipoprotein cholesterol (HDL-C) (9). In the cardiovascular system, HDL can exert a protective effect through the reverse cholesterol transport (6). However, the protective effect of HDL on CKD is still controversial. In certain research, excessively high levels of HDL can also damage kidney function (11–13). Additionally, a prospective cohort study found that multiple lipids or lipoproteins, including triglycerides, high-density lipoprotein, and low-density lipoprotein, cannot be used as independent predictors of CKD (14). Based on the above research results, a single lipid or lipoprotein is not suitable as a biomarker for determining the severity and progression of CKD.

Non-HDL-C primarily comprises LDL-C, very low-density lipoprotein (VLDL), intermediate -density lipoprotein, and the cholesterol within lipoprotein (a) (15). The Non-HDL-C to HDL-C ratio (NHHR) serves as a new comprehensive index that includes multiple lipid particles related to atherosclerosis (16). Research has shown that compared to traditional lipid markers, NHHR exhibits higher diagnostic performance in predicting insulin resistance and metabolic syndrome (17). However, it is still unclear whether NHHR can be used to predict the risk of developing CKD in NAFLD patients. Therefore, utilizing data from the National Health and Nutrition Examination Survey (NHANES), this study aimed to uncover the relationship between the NHHR and the risk of developing CKD in NAFLD patients. This study hypothesized that there would be a strong association between the NHHR and the risk of developing CKD in NAFLD patients.

2 Methods

2.1 Study design

This study employed clinical data collected from NHANES database (2017–2020). Participants were interviewed in their homes, followed by physical examinations and laboratory tests at the Mobile Examination Center (MEC). NHANES was conducted with the approval of the Institutional Review Board of the National Center for Health Statistics in the United States and secured informed written consent from all participants (18).

2.2 Participants

To evaluate the correlation between NHHR and CKD in NAFLD subjects with or without liver fibrosis, this study included subjects diagnosed with NAFLD and liver fibrosis. Consequently, a total of 24,814 participants were examined across four interview periods spanning from 2017 to 2020. The following participants were excluded from this study: (1) age < 18 years (N = 9,265); (2) missing covariate data (N = 5,835); (3) missing ACR data (N = 18); (4) missing CAP data (N = 328); and (5) participants without steatosis (N = 5,327). Ultimately, 4,041 participants were included in this study. In the NAFLD population, there were 3,315 individuals without liver fibrosis and 726 individuals with fibrosis (Figure 1).

This study evaluated liver steatosis and fibrosis using controllable attenuation parameters (CAP) and liver stiffness measurement (LSM) determined by vibration control transient elastography. CAP ≥ 274 dB/m is defined as NAFLD (19). LSM above 8kpa is defined as liver fibrosis, and below 8kpa is defined as no fibrosis (20).

2.3 Exposure variables

The exposure variable is NHHR, derived from the ratio of Non-HDL-C (mmol/L) to HDL-C (mmol/L). Non-HDL-C is calculated as the difference between total cholesterol (TC) and HDL-c in the blood (21). Subjects were categorized into three groups based on the third quartiles of NHHR: Q1 group (0.28, 2.49), Q2 group (2.49, 3.54), and Q3 group (3.54, 24.5). Outcome variables included eGFR, ACR, and CKD. In this study, CKD was defined as meeting any of the following criteria, as per guidelines: (1) glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2, as calculated using the Chronic Kidney Disease Epidemiology Collaboration equation and (2) albuminuria ≥ 30 mg/g (22, 23).

2.4 Covariates

The covariates included in this study include age (years), sex (male or female), eth (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, and other races), BMI (kg/m^2), smoke (former, never or now), alcohol (heavy, moderate, mild or never), Alt (mg/dL), Ast (mg/dL), HbA1c (%), TC (mmol/L), HDL-C (mmol/L), Non-HDL-C (mmol/L), ACR, DM (DM, IFG or no), Hypertension (yes or no), CKD (yes or no).

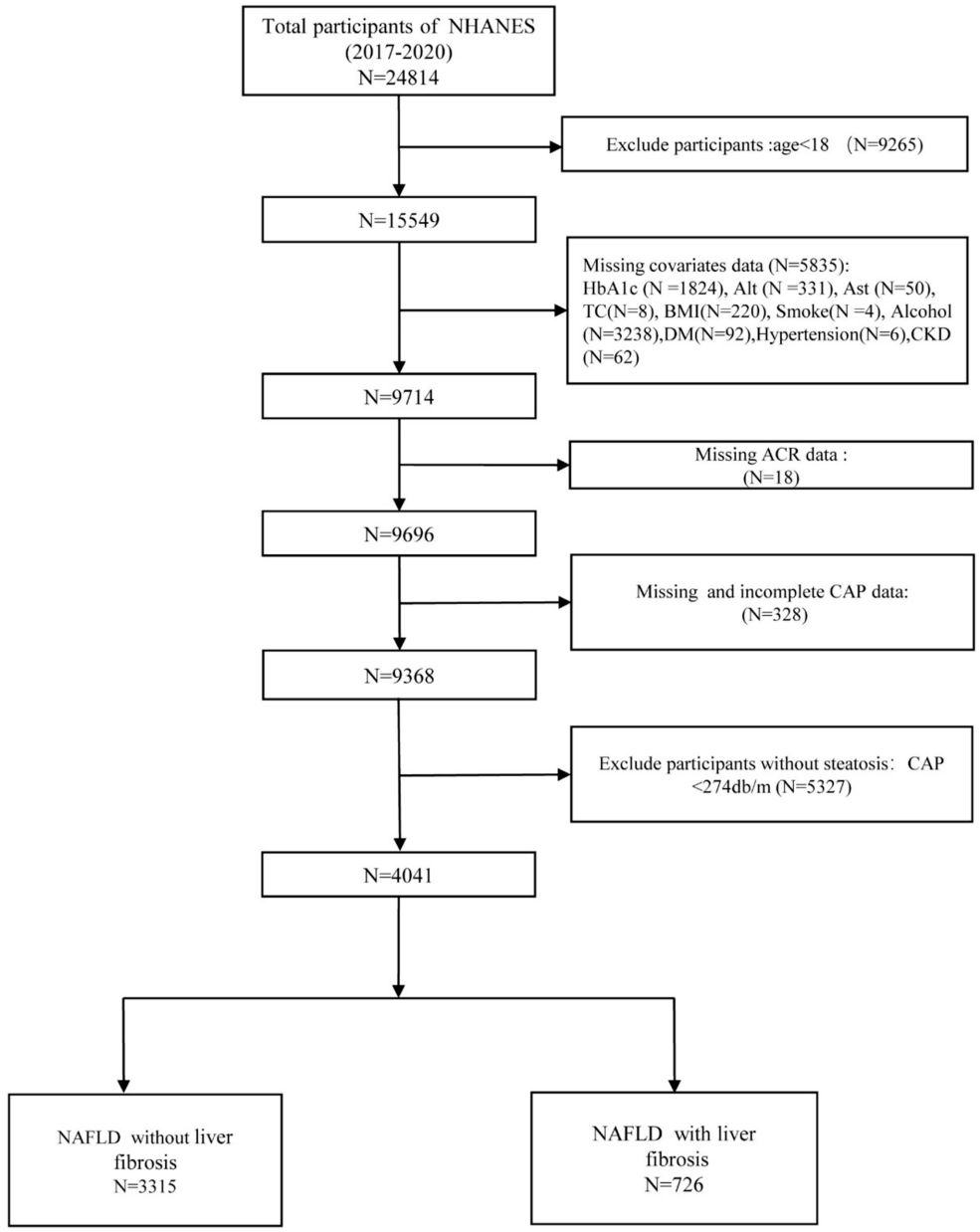

FIGURE 1
Flowchart of participant enrollment and exclusion in this study.

2.5 Statistical analysis

Considering the complex sampling design of the NHANES database, this study employed weighted approaches throughout the data analysis to ensure the generation of representative estimates reflective of the US national population. Continuous variables were expressed as means and standard errors, utilizing weighted *t*-tests. Categorical variables are expressed using *N* and weighted percentages (%), with differences compared using weighted chi-square tests.

Multiple linear regression and logistic regression were utilized to analyze the association between the third quartile of NHHR and eGFR, ACR, CKD, respectively. This study utilized unadjusted, minimally adjusted, and fully adjusted models for evaluation. Crude model: Single-factor linear and logistic regression models; Model 1: Adjusted for age and sex; Model 2: Further adjusted for eth, BMI, smoking, alcohol, TC, Alt, Ast, HbA1c, and hypertension.

RCS curve model was used to analyze the nonlinear relationship between NHHR and eGFR, ACR, CKD. Subsequently, subgroup analyses were performed to assess the stability of the association between NHHR and CKD across various stratifications, with the results visualized as forest plots. Subgroups were stratified by sex, eth, BMI, smoking, alcohol, DM, and hypertension. If the P for interaction across different stratifications is >0.05, it suggests the results are reliable across different subgroups; otherwise, it may indicate the presence of special populations (24, 25).

3 Results

3.1 Basic characteristics of participants

Table 1 presents the demographic characteristics of 4,041 NAFLD participants, with an average age of 49.26 years, 56.99% being male, and 43.01% being female. The majority of the subjects were Non-Hispanic White (62.84%). Compared to participants in the lowest tertile of NHHR, those in the higher tertile were typically younger, predominantly male, former or current smokers, heavy drinkers, with lower levels of HDL-C, higher levels of BMI, TC, Non-HDL-C, HbA1c, ALT, AST, ACR, and an increased prevalence of CKD ($p < 0.05$).

TABLE 1 Clinical characteristics based on the third quartile of NHHR.

Variable	Total	Q1	Q2	Q3	*p*
Age	49.26 (0.62)	52.47 (1.03)	49.18 (0.78)	46.30 (0.63)	<0.0001
Sex					<0.0001
Female	1798 (43.01)	743 (54.74)	636 (46.05)	419 (28.90)	
Male	2,243 (56.99)	605 (45.26)	709 (53.95)	929 (71.10)	
Eth					0.003
Mexican American	737 (12.58)	209 (10.51)	252 (12.55)	276 (14.56)	
Non-Hispanic Black	786 (8.31)	350 (11.26)	250 (7.72)	186 (6.11)	
Non-Hispanic White	1,446 (62.84)	480 (64.31)	495 (63.47)	471 (60.81)	
Other Hispanic	410 (6.67)	119 (5.87)	135 (6.39)	156 (7.71)	
Other Race	662 (9.60)	190 (8.05)	213 (9.87)	259 (10.81)	
BMI (kg/m^2)	33.65 (0.24)	32.46 (0.35)	33.87 (0.32)	34.56 (0.26)	<0.0001
Smoke					<0.001
Former	1,014 (27.38)	363 (28.48)	321 (22.49)	330 (31.18)	
Never	2,360 (57.69)	822 (60.64)	792 (61.44)	746 (51.18)	
Now	667 (14.93)	163 (10.88)	232 (16.07)	272 (17.64)	
Alcohol					<0.001
Heavy	955 (25.34)	298 (23.08)	291 (24.18)	366 (28.65)	
Moderate	747 (19.29)	300 (21.71)	239 (20.04)	208 (16.25)	
Mild	1854 (46.46)	615 (49.33)	613 (43.28)	626 (46.89)	
Never	485 (8.91)	135 (5.88)	202 (12.50)	148 (8.22)	
TC (mmol/L)	4.98 (0.04)	4.38 (0.05)	4.91 (0.04)	5.62 (0.05)	<0.0001
HDL-C (mmol/L)	1.26 (0.01)	1.55 (0.02)	1.23 (0.01)	1.01 (0.01)	<0.0001
Non-HDL-C (mmol/L)	3.73 (0.04)	2.83 (0.04)	3.68 (0.03)	4.61 (0.04)	<0.0001
HbA1c (%)	5.90 (0.03)	5.85 (0.03)	5.82 (0.05)	6.02 (0.04)	0.003
Alt (mg/dL)	28.21 (0.46)	25.30 (0.63)	25.76 (0.50)	33.40 (0.95)	<0.0001
Ast (mg/dL)	23.54 (0.34)	23.45 (0.58)	21.89 (0.33)	25.24 (0.63)	<0.0001
ACR	33.27 (3.60)	23.15 (3.17)	20.12 (2.02)	55.85 (10.54)	0.003
eGFR	94.68 (0.78)	92.62 (1.49)	95.10 (0.98)	96.21 (0.83)	0.06
Hypertension					0.15
No	2047 (52.95)	664 (55.82)	674 (52.23)	709 (50.95)	
Yes	1994 (47.05)	684 (44.18)	671 (47.77)	639 (49.05)	
DM					0.15
DM	1,118 (23.72)	400 (24.77)	344 (22.01)	374 (24.43)	
IFG	404 (10.96)	136 (11.60)	135 (8.99)	133 (12.31)	
No	2,519 (65.31)	812 (63.63)	866 (69.00)	841 (63.26)	
CKD					0.04
No	3,301 (84.07)	1,102 (86.84)	1,100 (84.38)	1,099 (81.14)	
Yes	740 (15.93)	246 (13.16)	245 (15.62)	249 (18.86)	

All the variables are presented as the mean (SE) or *n* (%). BMI, body mass index; HbA1c, glycated haemoglobin; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; Alt, alanine aminotransferase; Ast, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ACR, urinary albumin to creatinine ratio.

3.2 Association between NHHR and CKD in NAFLD without liver fibrosis

We observed that NHHR was significantly associated with eGFR and CKD risk in individuals with NAFLD without fibrosis (Table 2). When NHHR is considered as a continuous variable, it shows significant correlation with both eGFR and CKD. In the unadjusted model (Crudel Model), NHHR was positively correlated with eGFR ($\beta = 0.95$, 95%CI: 0.10, 1.80, $p < 0.05$). In Model 1, NHHR was negatively correlated with eGFR ($\beta = -0.56$, 95%CI: −0.96, −0.16, $p < 0.05$). It is noteworthy that a significant negative correlation still exists in the fully adjusted model (Model 2) ($\beta = -0.93$, 95%CI: −1.26, −0.60, $p < 0.0001$). In addition, NHHR was positively correlated with increased risk of CKD, and this positive correlation was statistically significant in both Model 1 ($\beta = 1.16$, 95%CI: 1.04, 1.30) and Model 2 ($\beta = 1.11$, 95%CI: 1.01, 1.22). However, in the fully adjusted model, we did not observe a significant correlation between NHHR and ACR ($p > 0.05$). Similar results were also shown when NHHR was analyzed as a categorical variable (tertile). Compared with the lowest tertile of NHHR, a negative correlation was still observed between the highest tertile of NHHR and eGFR ($\beta = -2.14$, 95%CI: −3.97, −0.32, $p < 0.05$). In the adjusted multivariate model, NHHR was positively correlated with CKD (Model 1: 1.16, 95% CI: 1.04, 1.30, $p < 0.05$; Model 2: OR: 1.11, 95% CI: 1.01, 1.22, $p < 0.05$).

3.3 The correlation between NHHR and CKD NAFLD with liver fibrosis

As shown in Table 3, when NHHR was considered as a continuous variable, NHHR was significantly positively correlated with CKD risk in both the unadjusted model and Model 1 [Crude Model: β(95CI%) 1.18 (1.02, 1.38); Model 1: β(95CI%) 1.24 (1.08, 1.41), $p < 0.05$]. However, in the fully adjusted model, this significance disappeared ($p > 0.05$). We did not find a significant relationship between NHHR and eGFR, ACR. When NHHR is treated as a categorical variable, the results are consistent with those previously observed.

3.4 Nonlinear relationships

The RCS curve model was used to further explore the possible nonlinear relationship between NHHR and eGFR, ACR, and CKD (Figure 2). After adjusting all confounding variables in Model 2, the results showed that there was a linear relationship between NHHR and ACR, CKD in NAFLD without liver fibrosis (P overall >0.05, P nonlinear >0.05). A U-shaped nonlinear relationship between NHHR and ACR, CKD was observed in NAFLD with liver fibrosis (thresholds were 3.20 and 3.45, respectively).

TABLE 2 The correlation between NHHR and CKD in NAFLD without fibrosis.

	Crude model		Model 1		Model 2	
	OR/β (95%CI)	*p*	OR/β (95%CI)	*p*	OR/β (95%CI)	*p*
eGFR						
NHHR (continuous)	0.95 (0.10, 1.80)	0.03	−0.56 (−0.96, −0.16)	0.01	−0.93 (−1.26, −0.60)	<0.0001
NHHR (quartile)						
Q1	Ref		Ref		Ref	
Q2	2.83 (−0.70, 6.36)	0.11	−0.06 (−2.22, 2.10)	0.96	0.04 (−1.97, 2.06)	0.96
Q3	4.34 (1.07, 7.61)	0.01	−1.11 (−2.95, 0.73)	0.23	−2.14 (−3.97, −0.32)	0.02
P for trend		0.01		0.23		0.02
ACR						
NHHR (continuous)	7.37 (0.00, 14.74)	0.05	8.18 (1.01, 15.34)	0.03	4.48 (−0.79, 9.75)	0.09
NHHR (quartile)						
Q1	Ref		Ref		Ref	
Q2	−2.86 (−11.71, 5.99)	0.52	−1.29 (−9.83, 7.26)	0.76	−2.53 (−11.88, 6.82)	0.58
Q3	29.84 (−0.33, 60.01)	0.05	33.38 (4.41, 62.35)	0.03	24.36 (2.35, 51.07)	0.07
P for trend		0.05		0.02		0.07
CKD						
NHHR (continuous)	1.07 (0.97, 1.18)	0.18	1.16 (1.04, 1.30)	0.01	1.11 (1.01, 1.22)	0.03
NHHR (quartile)						
Q1	Ref		Ref		Ref	
Q2	1.22 (0.81, 1.82)	0.34	1.46 (0.94, 2.25)	0.09	1.33 (0.78, 2.28)	0.28
Q3	1.42 (0.98, 2.05)	0.06	2.06 (1.40, 3.04)	<0.001	1.67 (1.12, 2.49)	0.02
P for trend		0.06		<0.001		0.01

Data are expressed as β or OR and 95% confidence interval (CI). Crude model: unadjusted model; Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, eth, BMI, smoking, alcohol, Alt, Ast, HbA1c, hypertension, and DM.

TABLE 3 Correlation between NHHR and CKD in NAFLD with fibrosis.

	Crude model		Model 1		Model 2	
	95%CI	*p*	95%CI	*p*	95%CI	*p*
eGFR						
NHHR (continuous)	0.95 (−0.32, 2.22)	0.14	0.51 (−0.20, 1.23)	0.15	0.57 (−0.04, 1.18)	0.07
NHHR (quartile)						
Q1	Ref		Ref		Ref	
Q2	−2.06 (−7.55, 3.42)	0.45	−3.24 (−8.06, 1.59)	0.18	−1.57 (−5.88, 2.75)	0.46
Q3	1.94 (−4.26, 8.14)	0.53	−1.09 (−4.95, 2.77)	0.57	0.72 (−2.92, 4.36)	0.68
p for trend		0.44		0.72		0.59
ACR						
NHHR (continuous)	47.2 (−4.91, 99.32)	0.07	49.38 (−3.72, 102.49)	0.07	48.51 (−4.82, 101.84)	0.07
NHHR (quartile)						
Q1	Ref		Ref		Ref	
Q2	−10.35 (−32.67, 11.98)	0.35	−10.74 (−32.98, 11.50)	0.33	21.32 (−53.92, 11.28)	0.19
Q3	38.37 (−22.94, 99.68)	0.21	39.44 (−22.02, 100.90)	0.20	34.29 (−29.56, 98.15)	0.28
P for trend		0.18		0.18		0.24
CKD						
NHHR (continuous)	1.18 (1.02, 1.38)	0.03	1.24 (1.08, 1.41)	0.003	1.14 (0.98, 1.31)	0.09
NHHR (quartile)						
Q1	Ref		Ref		Ref	
Q2	0.96 (0.47, 1.98)	0.91	1.04 (0.45, 2.39)	0.92	0.85 (0.40, 1.78)	0.65
Q3	1.30 (0.71, 2.39)	0.39	1.56 (0.83, 2.92)	0.16	1.05 (0.53, 2.12)	0.88
P for trend		0.37		0.14		0.81

Data are expressed as β or OR and 95% confidence interval (CI). Crude model: unadjusted model; Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, eth, BMI, smoking, alcohol, Alt, Ast, HbA1c, hypertension, and DM.

3.5 Subgroup analysis

To further assess the impact of NHHR on outcome measures, we analyzed NHHR as a continuous variable in subgroups defined by sex, eth, BMI, smoke, alcohol, DM, and hypertension (Figure 3). The results showed that in NAFLD individuals without fibrosis, a positive correlation between NHHR and CKD was observed in female, BMI <25, previous smokers, moderate alcohol, DM, and IFG patients (P for interaction <0.05), while there was no significant interaction in the subgroups of eth and hypertension. In addition, in NAFLD individuals with fibrosis, NHHR was significantly associated with CKD in those who were mildly or never alcohol, non-DM, and IFG (P for interaction <0.05), while no significant interaction was observed in any other subgroups.

4 Discussion

Our study from this large cross-sectional study reveals the association between NHHR and the risk of developing CKD in patients with NAFLD. Our study indicates a U-shaped relationship between NHHR and CKD in NAFLD patients with liver fibrosis as well as a linear relationship with CKD in NAFLD patients without liver fibrosis. Our findings underscore the practical utility of NHHR as a biomarker for early risk stratification of CKD in patients with NAFLD.

Due to the global prevalence of obesity, type 2 diabetes, and hypertension, the incidence rate of NAFLD and CKD has rapidly increased in recent decades. Four similarities imply a substantial link between NAFLD and CKD: both are common in chronic disease populations, both are closely related to metabolic disorders, both are linked with an increased risk of cardiovascular events, and there are gender differences in incidence rates (4, 26, 27). Although, the overlap in pathogenesis and risk factors between NAFLD and CKD makes it difficult to distinguish the causal relationship between the two diseases. However, many studies still clearly indicate that the presence of NAFLD increases the likelihood of CKD, and the increase in the incidence rate of CKD is directly proportional to the severity of NAFLD (8, 28–30). Therefore, NAFLD is an independent risk factor for the development of CKD.

Patients with NAFLD frequently exhibit dysregulated lipid metabolism, with their lipid profiles typically displaying elevated levels of non-HDL cholesterol and reduced levels of HDL cholesterol. Insulin resistance reduces the sensitivity of organs like the liver and adipose tissue to insulin, resulting in heightened fatty acid synthesis within the liver (31, 32). To maintain the lipid metabolism homeostasis, the liver increases the synthesis and secretion of VLDL triglyceride (VLDL-TG) (33–35). After VLDL-TG enters the blood circulation, the triglyceride in VLDL

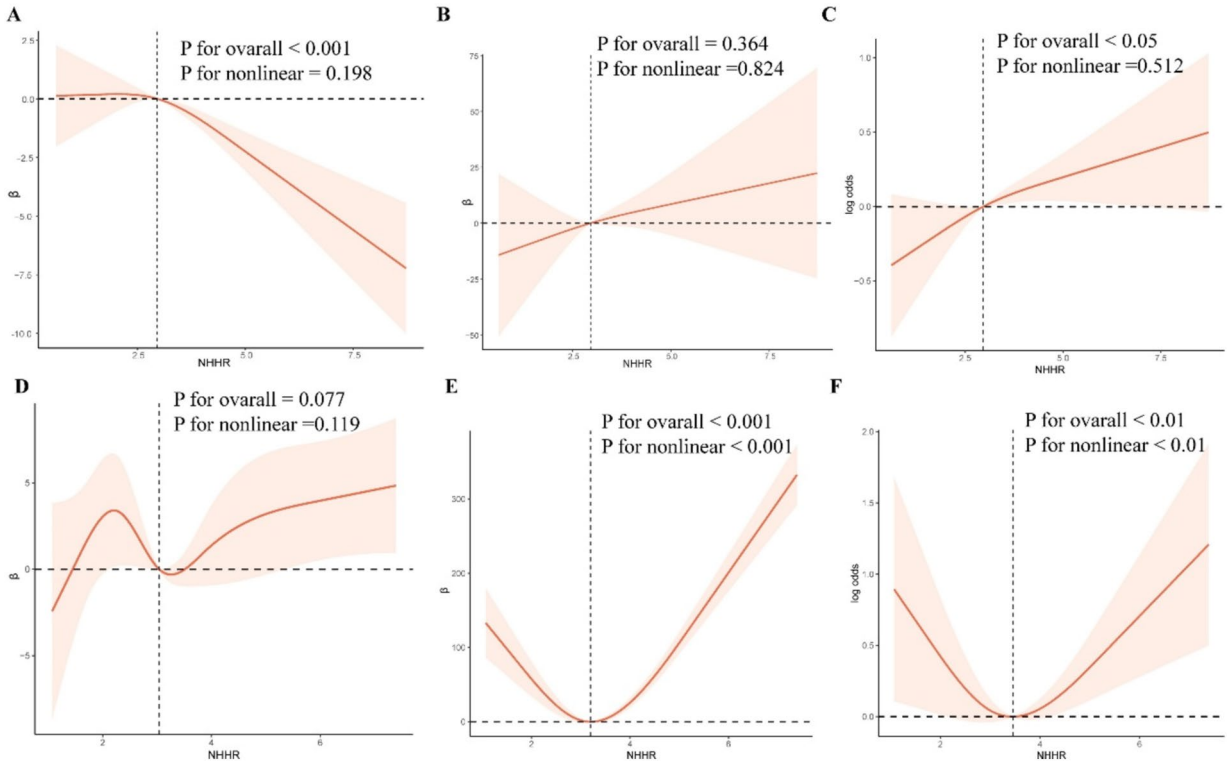

FIGURE 2
RCS curve model. After adjusting for confounding variables, RCS was used to analyze the nonlinear relationship between NHHR and eGFR, ACR, and CKD.

Character	NAFLD without fibrosis OR(95% CI)	*P*	*P* for interaction	NAFLD with fibrosis OR(95% CI)	*p*	*P* for interaction
Sex			0.01			0.8
Female	1.29(1.06,1.56)	0.01		1.22(0.92,1.61)	0.16	
Male	1.00(0.91,1.11)	0.96		1.17(0.97,1.41)	0.09	
Eth			0.19			0.73
Non-Hispanic Black	1.15(0.92,1.43)	0.22		1.21(0.82,1.79)	0.32	
Mexican American	1.11(0.90,1.37)	0.33		0.89(0.56,1.42)	0.6	
Non-Hispanic White	1.15(0.97,1.35)	0.11		1.19(0.96,1.46)	0.1	
Other Hispanic	0.99(0.91,1.09)	0.85		1.22(0.86,1.71)	0.24	
Other Race	0.85(0.67,1.09)	0.21		1.08(0.56,2.08)	0.79	
BMI			0.02			0.05
25-30	0.93(0.78,1.11)	0.44		1.25(1.08,1.46)	0.004	
<25	1.37(1.03,1.81)	0.03		0.80(0.50,1.30)	0.35	
>=30	1.12(0.98,1.28)	0.09		0.85(0.22,3.30)	0.69	
Smoke			< 0.001			0.16
former	1.32(1.11,1.58)	0.003		1.25(0.95,1.65)	0.11	
never	0.94(0.81,1.08)	0.36		0.83(0.59,1.16)	0.26	
now	1.11(0.95,1.30)	0.18		1.23(1.01,1.50)	0.04	
Alcohol			0.02			0.004
mild	1.02(0.89,1.18)	0.76		1.33(1.08,1.62)	0.01	
moderate	1.54(1.17,2.02)	0.003		1.26(0.76,2.10)	0.34	
heavy	1.12(0.98,1.28)	0.09		1.26(0.92,1.74)	0.15	
never	0.88(0.67,1.14)	0.32		0.49(0.32,0.76)	0.002	
DM			< 0.001			0.002
DM	1.26(1.06,1.49)	0.01		1.04(0.83,1.31)	0.71	
no	1.06(0.96,1.17)	0.26		1.22(1.06,1.41)	0.01	
IFG	0.54(0.35,0.84)	0.01		0.24(0.09,0.63)	0.01	
Hypertension			0.79			0.57
yes	1.07(0.93,1.24)	0.32		1.12(0.91,1.39)	0.27	
no	1.10(0.98,1.23)	0.11		1.21(1.01,1.46)	0.04	

FIGURE 3
Subgroup analysis.

are hydrolyzed under the action of lipoprotein lipase (36). At the same time, VLDL receives cholesterol esters (CE) from HDL. As the exchange continues, the TG content in VLDL decreases, while the CE content increases. VLDL eventually becomes IDL and LDL, which have higher density and smaller diameter (37). Additionally, multiple studies found that HDL lever in NAFLD patients are often lower than normal (38, 39). The exchange of triglycerides and cholesterol esters between HDL and non-HDL is regulated by cholesteryl ester transfer protein (CETP). In patients with NAFLD, the increased activity of CETP promotes the production and degradation of TG-rich HDL, resulting in a decrease in HDL-C levels (37, 40). The increase in Non-HDL-C levels, along with the decrease in HDL-C levels, jointly contribute to the elevation of NHHR indicators in patients with NAFLD. The increase of NHHR can be used as a characteristic marker of dyslipidemia and insulin resistance in patients with NAFLD.

In terms of the risk of CKD, multiple studies have indicated that the presence of insulin resistance greatly increases the risk of CKD in patients with NAFLD (5, 41, 42). As mentioned above, an increase in NHHR can be considered a sign of insulin resistance (17, 43). Therefore, insulin resistance may be one of the key mechanisms explaining NHHR as an assessment of the risk of developing CKD in NAFLD patients. In addition, HDL is well-known for its antioxidant, anti-inflammatory, and maintaining endothelial function properties. The deficiency of HDL promotes the infiltration of inflammatory cells and the dysfunction of endothelial cells, which contributes to the progression of kidney diseases (44). Meanwhile, In patients with non-alcoholic fatty liver disease (NAFLD), the imbalance between increased secretion and clearance of VLDL-TG leads to hypertriglyceridemia, which in turn leads to an increase in the number of small dense LDL (sd-LDL) particles (45, 46). The sd-LDL particles are easily oxidized by free radicals, and the oxidized low density lipoprotein (ox-LDL) has strong lipotoxicity (47). Ox-LDL can induce the onset of CKD by enhancing the activity of the fibrotic signaling pathway, fostering the infiltration of inflammatory cells, and encouraging epithelial-mesenchymal transition in renal tubular epithelial cells (48–51). Increased Non-HDL-C levels and decreased HDL-C levels are two important risk factors for CKD. In summary, the dysregulation of lipid metabolism caused by NAFLD is involved in the development of CKD. Compared with other markers, NHHR, as a comprehensive lipid metabolism marker, integrates key lipid information related to dyslipidemia and can better reflect the overall lipid status of patients. Our research results further found that NHHR can be used to predict the risk of developing CKD in patients with NAFLD.

Within this research, the stratification groups of the subjects were divided into three tertiles based on the NHHR. Our study reveals that in NAFLD patients without liver fibrosis, eGFR is negatively correlated with NHHR and the risk of developing CKD is higher in the group with the highest NHHR compared to the group with the lowest. The RCS curve model results indicate that the risk of developing CKD in NAFLD patients with without liver fibrosis escalates with NHHR values rise. However, for NAFLD patients with liver fibrosis, the impact of NHHR on the risk of developing CKD has changed. In the NAFLD with liver fibrosis group, although the correlation analysis results were negative, new findings were discovered in the RCS curve model results. The RCS curve model results showed a U-shaped relationship between NHHR and CKD in NAFLD patients with liver fibrosis. These findings indicate that although an elevated NHHR is a risk factor for CKD in NAFLD patients, an excessively low NHHR is not beneficial. For patients with NAFLD, maintaining NHHR within an appropriate range can significantly reduce the risk of developing CKD. It also indicates that there are population-based differences in NHHR among patients with NAFLD, and NHHR has different impacts on different groups of patients with NAFLD.

In NAFLD patients without liver fibrosis, subgroup analysis results show that NHHR is more significantly associated with a higher risk of CKD in female patients, a phenomenon that may be closely related to endocrine factors. Multiple studies have pointed out that normal estrogen secretion before menopause is a key mechanism for women to resist the development of NAFLD. One of the core mechanisms of NAFLD is the excessive accumulation of lipids in the liver and the death of liver cells caused by excessive fat accumulation. The presence of estrogen helps to increase tissue sensitivity to insulin and further promotes the oxidation of free fatty acids in the liver, the secretion of VLDL, and the deposition of fat in subcutaneous tissue, inhibiting the deposition of lipids in the liver and achieving the purpose of preventing the occurrence of NAFLD (27, 52). At the same time, studies have shown that estrogen can slow down the progression of kidney disease by dilating renal blood vessels and inhibiting renal interstitial fibrosis (53–55). The average age of the population included in this study is 49 years old, and some female patients may have entered menopause. The sharp decline in estrogen levels during menopause can lead to the loss of estrogen's protective effects on the liver and kidneys. In addition, a considerable number of NAFLD patients also suffer from diabetes. In women, the occurrence of diabetes is often related to the increase in male hormone levels and the decrease in estrogen levels (56–58). Studies have shown that testosterone can cause kidney function damage by activating the C-jun or fibrotic signaling pathways (59, 60). Therefore, diabetes may be another reason for the higher risk of CKD in female patients. Thirdly, in terms of sex hormone disorders, we cannot ignore the impact of polycystic ovary syndrome on female patients' hormone levels. One of the specific manifestations of polycystic ovary syndrome is excessive secretion of androgens (61). Studies have shown that polycystic ovary syndrome is associated with the occurrence of CKD, and common comorbidities of polycystic ovary syndrome include diabetes, obesity, and other metabolic-related diseases (62). Therefore, age, diabetes, and sex hormone disorders caused by polycystic ovary syndrome may be the reasons for the correlation between NHHR and a higher risk of CKD in female NAFLD without fibrosis patients.

Additionally, in the subgroup analysis of NAFLD with fibrosis, it was found that NHHR is more significantly associated with a higher risk of CKD in non-diabetic patients. However, in the subgroup analysis of NAFLD without fibrosis, NHHR is more significantly associated with a higher risk of CKD in diabetic patients. The etiology of CKD is multifactorial, involving both unchangeable factors such as age and genetic susceptibility, as well as modifiable factors such as diabetes, hypertension, and obesity. The overlap of risk factors between CKD and NAFLD has been mentioned above. Furthermore, Chang et al. found that in non-hypertensive and non-diabetic NAFLD patients, NAFLD remains an independent risk factor for increased

CKD risk (28). Ryu et al. discovered that the biomarkers gamma-glutamyltransferase, which can be used for the diagnosis of NAFLD, can also serve as independent predictors for assessing the risk of CKD in non-hypertensive and non-diabetic patients (63–65). From the above studies, it can be seen that the impact of NAFLD on CKD is independent of metabolic disorders such as diabetes. However, the mediating role of metabolic factors such as insulin resistance and lipid metabolism disorders in the promotion of CKD by NAFLD cannot be overlooked (66, 67). Therefore, both glucose metabolism disorders and NAFLD are involved in the occurrence of CKD, which is a reasonable explanation for the different impacts of diabetes on different NAFLD patient groups. Moreover, the effects of glucose metabolism disorders and NAFLD on CKD are both interconnected and independent.

Our study possesses several limitations. Firstly, this study is a cross-sectional analysis, focusing on an adult population in the United States, which may have population-specific constraints, especially in countries with different epidemiological characteristics of dyslipidemia, NAFLD, and CKD. Secondly, the assessment of liver fibrosis in this study was not based on precise liver biopsies. Thirdly, although the association between NHHR and CKD has been clearly emphasized in this study, it is not possible to determine whether an increase in NHHR directly leads to deterioration of renal function. Longitudinal studies are needed to confirm this causal relationship and further elucidate the biological mechanisms underlying the observed association. Additionally, missing self-reported data or variables in NHANES, which may introduce potential biases. Lastly, this study did not categorize CKD stages, thus it cannot provide a detailed understanding of the impact of NHHR on different stages of CKD in NAFLD patients. Future research is needed to further explore the relationship between NHHR and different stages of CKD.

5 Conclusion

In conclusion, our study found a U-shaped relationship between NHHR and CKD in NAFLD patients with liver fibrosis as well as a linear relationship with CKD in NAFLD patients without liver fibrosis. Our findings underscore the practical utility of NHHR as a biomarker for early risk stratification of CKD in patients with NAFLD. Monitoring NHHR may assist in assessing the risk of CKD in patients with NAFLD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by NCHS Ethics Review Board (ERB) Approval. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Y-qF: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. HW: Formal analysis, Software, Writing – review & editing. P-pW: Formal analysis, Software, Writing – review & editing. Z-yS: Conceptualization, Investigation, Validation, Visualization, Writing – review & editing. YW: Conceptualization, Investigation, Validation, Visualization, Writing – review & editing. JX: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing.

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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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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Associations between Life's Essential 8 and liver function: a cross-sectional study

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Background: Life's Essential 8 (LE8) score, developed by the American Heart Association, assesses cardiovascular health using eight components: diet, physical activity, nicotine exposure, sleep health, body mass index, lipids, blood glucose, and blood pressure. Liver function is a critical indicator of overall health, with impairments linked to numerous chronic diseases. While the LE8 score has been extensively studied in relation to cardiovascular outcomes, its association with liver function remains underexplored. Understanding this relationship is crucial for integrating cardiovascular and hepatic health management, particularly given the shared metabolic pathways underlying these systems. This study aims to examine the relationship between LE8 scores and liver function indicators in a large cohort, addressing a critical gap in understanding the interplay between cardiovascular and liver health.

Methods: Data from the 2007–2018 National Health and Nutrition Examination Survey (NHANES) were used in this cross-sectional study. The study included 21,873 participants, stratified into low (0–49), moderate (50–79), and high (80–100) LE8 score categories. The relationship between LE8 scores and liver function markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and ALT/AST ratio, was evaluated using multivariable linear regression, smoothed curve fitting, threshold effect analysis, and weighted quantile sum (WQS) regression. Subgroup analyses were performed based on sex and age to assess potential interactions.

Results: Higher LE8 scores were significantly associated with improved liver function, particularly highlighted by two major findings. First, nonlinear associations were observed between LE8 scores and liver function parameters, including ALT and ALT/AST ratio, with stronger effects beyond specific thresholds (ALT: 50.625, ALT/AST: 61.875). Second, subgroup analyses revealed that these associations were more pronounced in younger participants (<60 years), suggesting age-specific differences in the relationship. These age-related differences might be attributed to variations in metabolic function or differences in the severity of cardiovascular and liver-related risk factors between younger and older individuals. WQS regression identified body mass index, blood pressure, blood glucose, and nicotine exposure as the strongest contributors to liver function markers. These findings underscore the potential of LE8 scores as a comprehensive indicator for liver health, particularly in younger populations.

Conclusion: This study suggests that LE8 scores is associated with improved liver function. Clinicians and public health practitioners could consider integrating LE8 scores into routine assessments to help identify individuals at risk for liver dysfunction, particularly among younger populations. Further research should

explore whether interventions targeting cardiovascular health could also improve liver function outcomes.

KEYWORDS

Life's Essential 8, NHANES, liver function, cardiovascular health, cross-sectional study

1 Introduction

The liver, a vital organ responsible for metabolism, detoxification, and biochemical synthesis, is essential for maintaining overall health (1). Approximately 2 million deaths occur each year due to liver diseases (2). Liver function can be impaired by various factors such as viral infections, excessive alcohol consumption, drug-induced hepatotoxicity, and metabolic disorders (3). Liver function parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), the ALT/AST ratio, gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) are essential indicators for assessing liver health. Moreover, they are involved in metabolic processes that link liver health to other bodily systems. For example, within the Framingham Heart Study cohort, higher GGT levels were associated with increased plasma triglycerides, body mass index (BMI), and blood pressure (4). Given these connections, the relationship between liver function and cardiovascular health (CVH) has attracted increasing attention.

In 2010, the American Heart Association (AHA) introduced Life's Simple 7 (LS7), a set of metrics for assessing CVH (5). However, the LS7 did not account for individual variations and changes over time, prompting the AHA to develop Life's Essential 8 (LE8) in 2022 (6). The LE8 score includes eight key measures: diet, physical activity, nicotine exposure, sleep health, BMI, lipids, blood glucose, and blood pressure. The LE8 score has shown promise in predicting a range of health outcomes beyond CVD. Higher LE8 scores are inversely associated with several non-communicable diseases, including biological aging (7), testosterone deficiency (8), and depression (9), and is associated with increased longevity (10). Emerging evidence also suggests a connection between CVH, as measured by LE8, and liver diseases (11, 12). It is worth noting that the components of LE8 are not only important for CVH, but also have potential effects on liver function. For instance, poor sleep health has been associated with metabolic dysregulation, which can lead to liver fat accumulation and increased liver enzymes. Nicotine exposure has been linked to oxidative stress, which may contribute to liver injury and inflammation. Elevated blood glucose levels are a known risk factor for non-alcoholic fatty liver disease (NAFLD), which in turn can elevate liver enzymes such as ALT and AST. Similarly, high BMI and poor lipid profiles are associated with liver fat deposition and hepatocyte damage, potentially increasing liver enzyme levels. Given these associations, the LE8 score may be an effective tool for assessing overall liver function. While some studies have shown associations between poor CVH and adverse liver outcomes (13–15), few have explored the role of comprehensive CVH measures like LE8 in relation to specific liver function parameters. In addition, most studies assume a linear relationship between CVH and liver outcomes without considering potential non-linear associations.

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative dataset. NHANES includes detailed demographic, lifestyle, and clinical data, making it ideal for examining the association between LE8 scores and liver function. The purpose of this study is to examine the association between LE8 scores and liver function parameters in a representative sample of US adults. Additionally, through nonlinear curve fitting and subgroup analysis, we aim to reveal complex, age-dependent associations between CVH and liver function, providing novel insights into how improving CVH might protect liver function.

2 Materials and methods

2.1 Study population

This study utilized data from the NHANES spanning the years 2007 to 2018. NHANES was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and all the participants provided written informed consent. The research was conducted in accordance with the STROBE reporting criteria for cross-sectional studies.

Initially, 59,842 participants were included in the dataset. Participants were excluded for the following reasons: 34,598 for missing LE8 data, 114 for missing liver function data, 118 for being hepatitis B surface antigen positive, 289 for being hepatitis C RNA positive, 591 for being younger than 20 years, 261 for being pregnant, and 1,998 for missing covariate data (17 for education level, 1,981 for family poverty income ratio). Ultimately, the study included 21,873 participants. A detailed participant flow diagram is provided in Figure 1 to visually represent the exclusion process.

2.2 LE8 scoring

The LE8 score includes eight CVH indicators: four health factors (BMI, blood pressure, blood glucose, non-high-density lipoprotein cholesterol (HDL)) and four health behaviors (diet, nicotine exposure, physical activity, sleep health). Diet metric was assessed using the Healthy Eating Index-2015 (HEI-2015), which is based on two 24-h dietary recall interviews. The HEI-2015 score is a measure of adherence to dietary guidelines and overall diet quality. Physical activity was measured by self-reported questionnaires on the frequency and duration of vigorous or moderate-intensity physical activity per week. Secondhand smoke exposure and self-reported smoking status were used to determine nicotine exposure. The assessment of sleep health was done through self-reported average sleep duration each night. BMI was calculated from measured weight and height (kg/m^2). To determine blood pressure, three consecutive readings were averaged during the physical exam. The measurement of blood glucose was done using fasting blood glucose or glycated hemoglobin (HbA1c) from blood samples. HDL cholesterol was calculated from blood lipid profiles. Each indicator is scored on a scale from 0 to 100, and the overall LE8 score is calculated as the mean of these eight scores

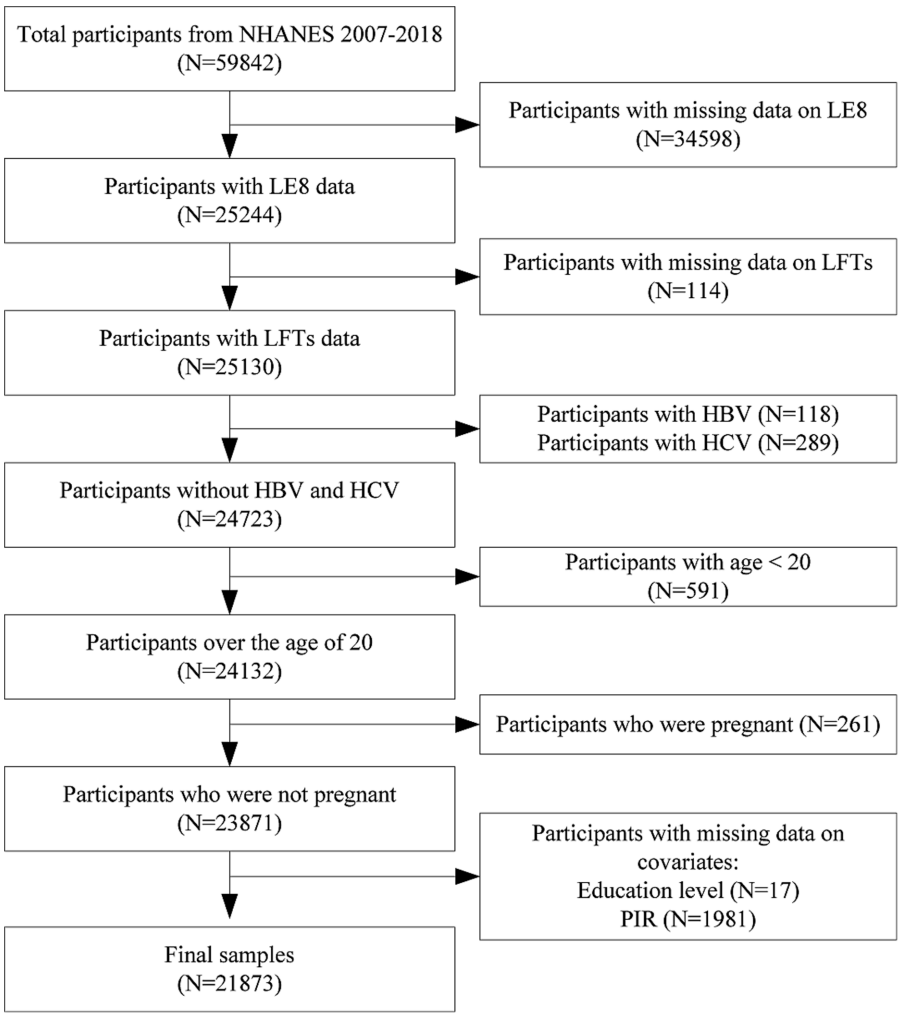

FIGURE 1
Flowchart of participants selection. NHANES, national health and nutrition examination survey; LE8, life's Essential 8; LFTs, liver function tests; HBV, hepatitis B virus; HCV, hepatitis C virus.

(Supplementary Table S1). A score of 80–100 denotes high CVH, 50–79 indicates moderate CVH, and 0–49 reflects low CVH.

2.3 Liver function assessment

Fasting blood samples were collected at NHANES mobile examination centers and analyzed centrally using the Beckman Coulter DxC800 Synchron clinical system. Liver function parameters include ALT, AST, GGT, ALP, and the ALT/AST ratio. These parameters help measure liver function and detect liver damage. ALT is an enzyme found primarily in the liver that is critical for amino acid metabolism. Elevated ALT levels indicate liver cell damage and can be an early marker of liver disease. AST is found in the liver, muscles, heart, and other tissues. Although not as specific to the liver as ALT, increased AST levels also suggest liver injury or damage. The ALT/ AST ratio helps to differentiate between various liver diseases. For example, a ratio greater than 1 typically indicates alcoholic liver disease, while a ratio less than 1 indicates non-alcoholic fatty liver disease or chronic hepatitis. ALP is related to the bile ducts. Elevated ALP levels may indicate bile duct obstruction, cholestasis, or other liver disease. GGT is involved in the metabolism of glutathione and is an indicator of liver disease, particularly those involving cholestasis or bile duct obstruction.

2.4 Measurement of covariates

Given the large number of variables in the LE8 score, this study adjusted for a limited number of covariates to avoid overfitting the model. The covariates included in this study were age, gender, race, education level, and poverty income ratio (PIR).

2.5 Statistical analysis

To account for the complex sampling design of the NHANES data, weighted analyses were conducted according to NCHS guidelines. Weights, strata, and primary sampling units were considered in this study. Continuous variables were expressed as weighted means and compared using weighted linear regression. Categorical variables were

presented as counts (weighted percentages) and compared using weighted chi-square tests. The association between LE8 scores and liver function biomarkers was evaluated using weighted univariate and multivariate linear regression models. Model 1 evaluated the raw relationship between LE8 score and liver function without covariate adjustment. Model 2 adjusted for gender, age, and race. Model 3 further adjusted for education level and PIR based on Model 2. Dose–response relationships were examined using smoothed curve fitting, and weighted quantile sum (WQS) regression models were used to analyze the relationships between mixed exposures of LE8 indicators and liver function, as well as the relative contributions of each indicator. A *p*-value of less than 0.05 (two-sided) was defined as statistically significant. Statistical analyses were performed using EmpowerStats (version 4.2) and R software (version 4.3.0).

3 Results

3.1 Baseline characteristics

Baseline characteristics of the study population, stratified by LE8 score category, are detailed in Table 1. A total of 21,873 participants were included, divided into low ($N = 4,149$), moderate ($N = 15,177$), and high ($N = 2,547$) LE8 score groups. The mean age showed a decreasing trend across the LE8 score groups, with the highest age observed in the low LE8 score group (53.22 years, 95% CI: 52.52–53.93), followed by the moderate (48.05 years, 95% CI: 47.45–48.65), and the lowest in the high score group (39.77 years, 95% CI, 38.78–40.76), with significant differences between groups ($p < 0.001$). Gender distribution also varied across LE8 score groups, with a higher proportion of females in the high LE8 score group (59.45%) compared to the low (51.53%) and moderate (50.03%) groups ($p < 0.001$). Racial composition differed significantly across the LE8 score categories, with non-Hispanic white participants more prevalent in the high LE8 score group (73.85%) compared to the low (62.52%) and moderate (68.65%) groups, while non-Hispanic black participants were more concentrated in the low score group (17.14%) ($p < 0.001$). Educational attainment showed a clear gradient with increasing LE8 score. A higher proportion of participants with education above high school was observed in the high LE8 score group (80.44%) compared to the low (46.54%) and moderate (63.51%) groups ($p < 0.001$). Similarly, PIR demonstrated significant differences, with the high LE8 score group showing a larger percentage of participants in the highest income category (PIR >3: 59.26%) compared to the low (34.95%) and

TABLE 1 Baseline characteristics of participants according to LE8 score.

Characteristics	LE8 score			*P*-value
	Low ($N = 4,149$)	Moderate ($N = 15,177$)	High ($N = 2,547$)	
Age, years	53.22 (52.52–53.93)	48.05 (47.45–48.65)	39.77 (38.78–40.76)	<0.001
Gender				<0.001
Male	2003 (48.47%)	7,527 (49.97%)	1,020 (40.55%)	
Female	2,146 (51.53%)	7,650 (50.03%)	1,527 (59.45%)	
Race				<0.001
Mexican American	594 (8.62%)	2,195 (8.61%)	358 (7.45%)	
Other Hispanic	389 (5.5%)	1,510 (5.48%)	254 (5.45%)	
Non-Hispanic White	1705 (62.52%)	6,938 (68.65%)	1,258 (73.85%)	
Non-Hispanic Black	1,214 (17.14%)	2,877 (9.6%)	258 (5.01%)	
Other Race-Including Multi-Racial	247 (6.21%)	1,657 (7.66%)	419 (8.25%)	
Education level				<0.001
Less than high school	1,317 (24.4%)	3,116 (13.21%)	286 (6.49%)	
Completed high school	1,093 (29.06%)	3,495 (23.27%)	381 (13.06%)	
Above high school	1739 (46.54%)	8,566 (63.51%)	1880 (80.44%)	
PIR				<0.001
≤1.3	1737 (33.12%)	4,362 (19.82%)	583 (15.89%)	
1.3–3	1,366 (31.93%)	4,847 (28.25%)	720 (24.84%)	
>3	1,046 (34.95%)	5,968 (51.94%)	1,244 (59.26%)	
ALT, U/L	28.10 (27.20–29.00)	24.95 (24.59–25.30)	20.90 (20.20–21.61)	<0.001
AST, U/L	26.27 (25.43–27.11)	24.74 (24.45–25.03)	24.29 (23.37–25.21)	0.001
ALT/AST	1.05 (1.04–1.07)	0.99 (0.98–1.00)	0.87 (0.85–0.88)	<0.001
ALP, U/L	76.22 (75.06–77.38)	67.70 (67.10–68.29)	60.10 (58.92–61.27)	<0.001
GGT, U/L	38.04 (35.72–40.36)	26.68 (25.82–27.53)	18.66 (16.52–20.80)	<0.001

For continuous variables: survey-weighted mean (95% CI), *p*-value was by survey-weighted linear regression. For categorical variables: survey-weighted N (percentage), *p*-value was by survey-weighted Chi-square test. LE8, Life's Essential 8; PIR, family income-to-poverty ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

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TABLE 2 Association between LE8 and liver function parameters.

	Model 1	Model 2	Model 3
	β (95%CI) *p* value	β (95%CI) *p* value	β (95%CI) *p* value
ALT			
Life's Essential 8 (per 1 points)	−0.164 (−0.187, −0.141) <0.001	−0.196 (−0.219, −0.172) <0.001	−0.214 (−0.239, −0.189) <0.001
LE8 classification			
Low (0–49)	Ref	Ref	Ref
Moderate (50–79)	−3.151 (−4.051, −2.251) <0.001	−4.054 (−4.921, −3.188) <0.001	−4.432 (−5.321, −3.544) <0.001
High (80–100)	−7.195 (−8.410, −5.979) <0.001	−8.204 (−9.413, −6.995) <0.001	−8.723 (−9.940, −7.506) <0.001
AST			
Life's Essential 8 (per 1 points)	−0.054 (−0.076, −0.032) <0.001	−0.051 (−0.073, −0.028) <0.001	−0.057 (−0.082, −0.031) <0.001
LE8 classification			
Low (0–49)	Ref	Ref	Ref
Moderate (50–79)	−1.530 (−2.382, −0.677) <0.001	−1.619 (−2.491, −0.747) <0.001	−1.734 (−2.645, −0.822) <0.001
High (80–100)	−1.980 (−3.193, −0.768) 0.002	−1.654 (−2.882, −0.425) <0.001	−1.805 (−3.124, −0.485) 0.009
ALT/AST			
Life's Essential 8 (per 1 points)	−0.004 (−0.004, −0.004) <0.001	−0.005 (−0.006, −0.005) <0.001	−0.006 (−0.006, −0.005) <0.001
LE8 classification			
Low (0–49)	Ref	Ref	Ref
Moderate (50–79)	−0.061 (−0.076, −0.046) <0.001	−0.088 (−0.103, −0.073) <0.001	−0.099 (−0.114, −0.083) <0.001
High (80–100)	−0.186 (−0.208, −0.163) <0.001	−0.228 (−0.250, −0.206) <0.001	−0.242 (−0.265, −0.220) <0.001
ALP			
Life's Essential 8 (per 1 points)	−0.369 (−0.396, −0.341) <0.001	−0.320 (−0.351, −0.290) <0.001	−0.271 (−0.300, −0.241) <0.001
LE8 classification			
Low (0–49)	Ref	Ref	Ref
Moderate (50–79)	−8.522 (−9.746, −7.298) <0.001	−7.504 (−8.760, −6.247) <0.001	−6.288 (−7.503, −5.072) <0.001
High (80–100)	−16.123 (−17.605, −14.641) <0.001	−13.545 (−15.033, −12.057) <0.001	−11.150 (−12.603, −9.697) <0.001
GGT			
Life's Essential 8 (per 1 points)	−0.472 (−0.527, −0.416) <0.001	−0.458 (−0.521, −0.396) <0.001	−0.463 (−0.530, −0.396) <0.001
LE8 classification			
Low (0–49)	Ref	Ref	Ref
Moderate (50–79)	−11.362 (−13.870, −8.853) <0.001	−11.154 (−13.858, −8.450) <0.001	−11.044 (−13.688, −8.400) <0.001
High (80–100)	−19.382 (−22.598, −16.167) <0.001	−17.930 (−21.292, −14.567) <0.001	−17.539 (−21.002, −14.075) <0.001

Model 1: Adjusted for no covariates. Model 2: Adjusted for age, gender, and race. Model 2: Adjusted for age, gender, race, education and RIP (ratio of family income to poverty). LE8, Life's Essential 8; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

moderate (51.94%) groups ($p < 0.001$). Liver function parameters, including ALT, AST, ALT/AST ratio, ALP, and GGT levels, displayed significant and consistent decreases across the increasing LE8 score categories (all $p < 0.001$), with the lowest levels seen in the high LE8 score group.

3.2 Relationship LE8 score and liver function parameters

Analysis revealed significant negative associations between LE8 scores and liver function indicators in all models (Table 2). For ALT, each one-point increase in the LE8 score was associated with a corresponding decrease in ALT levels, with β-values of −0.164 (95% CI: −0.187, −0.141) in Model 1, −0.196 (95% CI: −0.219, −0.172) in Model 2, and − 0.214 (95% CI: −0.239, −0.189) in Model 3 (all $p < 0.001$). Similarly, participants in the moderate (50–79) and high (80–100) LE8 categories had significantly lower ALT levels compared to the low (0–49) LE8 group. Similar trends were observed for AST, where each one-point increase in LE8 score corresponded to decreases in AST levels, with β-values of −0.054 (95% CI: −0.076, −0.032) in Model 1, −0.051 (95% CI: −0.073, −0.028) in Model 2, and − 0.057 (95% CI: −0.082, −0.031) in Model 3 (all $p < 0.001$). The ALT/AST ratio, ALP and GGT also showed consistent negative associations with LE8 scores, suggesting that higher LE8 scores are associated with better liver function. Specifically, for each one-point increase in LE8 score, ALP levels declined by 0.369 U/L in Model 1, 0.320 U/L in Model 2, and 0.271 U/L in Model 3 (all $p < 0.001$). GGT levels also

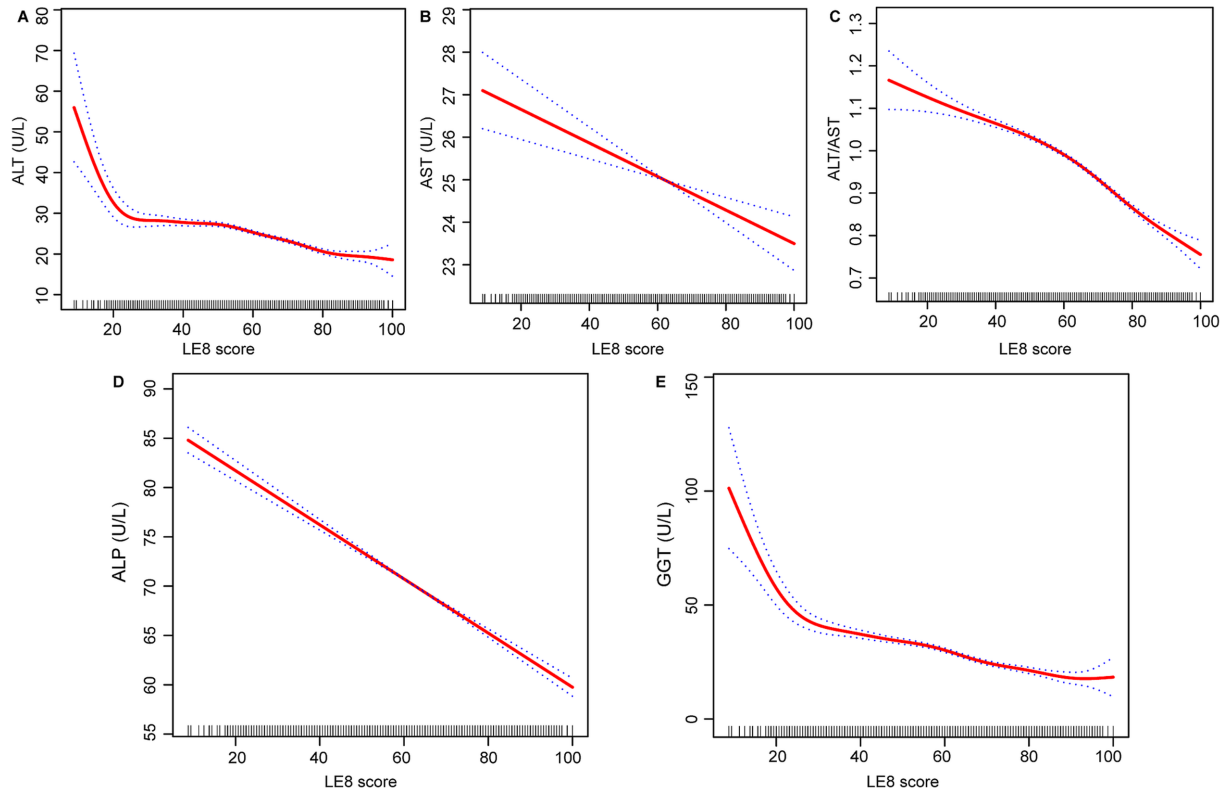

FIGURE 2
Relationship between LE8 score, **(A)** ALT, **(B)** AST, **(C)** ALT/AST, **(D)** ALP, and **(E)** GGT. LE8, life's Essential 8; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

decreased significantly with each one-point increase in LE8 score, with β-values of −0.472 in Model 1, −0.458 in Model 2, and −0.463 in Model 3 (all $p < 0.001$). These results consistently suggest that better CVH, as measured by LE8 scores, is associated with lower levels of liver enzymes.

3.3 Smoothed curve and threshold effect analysis

The effect relationship between LE8 score and liver function parameters was shown by smooth curve fitting (Figures 2A–E). The dose–response relationship was further assessed by threshold effect analysis (Table 3), which revealed significant nonlinear associations (p-value <0.001 for log-likelihood ratio test) between LE8 score and two liver function parameters (ALT and ALT/AST ratio), while the nonlinear effects for the other three liver function parameters (AST, ALP, and GGT) were not significant (p-values for log-likelihood ratio test of 0.378, 0.190, 0.059, respectively). For ALT, we identified an inflection point at 50.625. To the left of this inflection point, the estimated effect for ALT was −0.079 (95% CI: −0.137, −0.021, $p = 0.008$), whereas to the right, the effect increased significantly to −0.211 (95% CI: −0.236, −0.187, $p < 0.001$). This difference in effect between the two segments was significant (−0.132, 95% CI: −0.204, −0.061, $p < 0.001$). This suggests that the negative correlation between ALT and LE8 scores is stronger when LE8 scores are greater than 50.625, with ALT levels decreasing by 0.211 U/L for each 1-point increase in LE8 scores. The inflection point for the association of LE8 scores with ALT/AST ratio was 61.875, with an estimated effect of −0.004 on the left side of the inflection point, increasing to −0.007 on the right side of the inflection point. Similarly, AST, ALP, and GGT showed some variation in effects before and after their respective inflection points. However, the difference in AST and ALP did not reach statistical significance ($p = 0.378$ for AST, $p = 0.190$ for ALP), while GGT showed borderline significance ($p = 0.059$).

3.4 WQS regression

The eight components that make up the LE8 score were evaluated for their impact on these liver function parameters (Figures 3A–E). Specifically, WQS regression analyses were performed to assess the relative contribution of different components to different liver function parameters. For ALT, BMI and blood lipids were identified as the most influential factors with weights of 24.95 and 21.38%, respectively. Similarly, blood pressure and sleep health emerged as the most significant contributors to AST, accounting for 29.83 and 23.67%, respectively. For the ALT/AST ratio, BMI and physical activity were important determinants with weights of 33.09 and 22.13%, respectively. Blood glucose had the greatest contribution to ALP with a weight of 23.12%, while nicotine exposure had the greatest influence on GGT with a weight of 26.13%.

TABLE 3 Threshold effect analysis of LE8 on liver function parameters.

LE8 scores	Model: threshold effect analysis [β (95% CI) p value]				
	ALT	AST	ALP	GGT	ALT/AST
Inflection point (K)	50.625	50.625	84.375	38.75	61.875
<K, effect 1	−0.079 (−0.137, −0.021) 0.008	−0.017 (−0.070, 0.036) 0.529	−0.281 (−0.307, −0.255) <0.001	−0.714 (−1.021, −0.408) <0.001	−0.004 (−0.004, −0.003) <0.001
>K, effect 2	−0.211 (−0.236, −0.187) <0.001	−0.046 (−0.068, −0.024) <0.001	−0.118 (−0.353, 0.118) 0.328	−0.403 (−0.448, −0.358) <0.001	−0.007 (−0.007, −0.006) <0.001
Difference between the effects of 2 and 1	−0.132 (−0.204, −0.061) <0.001	−0.029 (−0.094, 0.036) 0.378	0.163 (−0.081, 0.407) 0.190	0.311 (−0.012, 0.634) 0.059	−0.003 (−0.004, −0.002) <0.001
Log-likelihood ratio	<0.001	0.378	0.190	0.059	<0.001

Age, gender, race, education and RIP (ratio of family income to poverty) were adjusted. LE8, Life's Essential 8; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

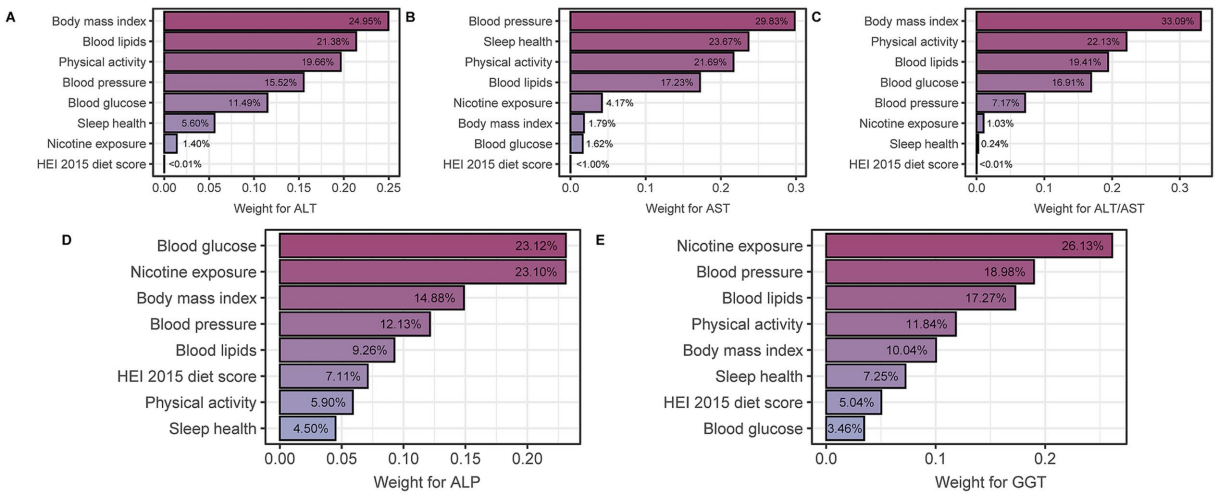

FIGURE 3
WQS model regression index weights for **(A)** ALT, **(B)** AST, **(C)** ALT/AST, **(D)** ALP, and **(E)** GGT, adjusted for age, gender, race, education and RIP (ratio of family income to poverty). LE8, life's Essential 8; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

3.5 Subgroup analysis

In subgroup analyses stratified by sex, results showed consistent negative correlations between outcome variables (ALT, AST, ALT/AST, ALP, and GGT) and LE8 scores in both the male and female groups (Figure 4A). Specifically, the effect estimates for ALT were − 0.181 (95% CI: −0.206, −0.155) in males and − 0.182 (95% CI: −0.206, −0.157) in females, with no significant interaction between sex and ALT levels (P for interaction = 0.953). Similar patterns were observed for AST, ALT/AST ratio, ALP, and GGT, with no significant interaction effects except for ALP (P for interaction <0.001), where the effect was significantly stronger in females. Age-stratified analysis revealed notable differences in the associations (Figure 4B). For ALT, the effect estimate was stronger in participants aged 60 years or younger (−0.202, 95% CI: −0.223, −0.181) compared to those older than 60 years (−0.051, 95% CI: −0.086, −0.017), with a significant interaction between age and ALT levels (P for interaction <0.001). This interaction was also significant for AST, ALT/AST ratio, ALP, and GGT, indicating that the associations were modified by age. The effects were consistently more pronounced in the younger age group for most biomarkers, particularly for GGT.

4 Discussion

In this large cross-sectional study, we observed significant inverse associations between the LE8 score and liver function parameters, including ALT, AST, ALP, GGT, and the ALT/AST ratio. The relationship between LE8 scores and ALT and ALT/AST ratio showed nonlinear patterns, with significant decreases occurring at LE8 scores above 50.625 and 61.875, respectively. These findings underline the potential utility of the LE8 score in liver health monitoring, particularly for early identification of individuals at higher risk of liver dysfunction.

One of the key findings of this study was that the LE8 score was significantly associated with liver function parameters. A cross-sectional study by Labayen et al. recruiting 637 adolescents in 9 European countries found a positive association between ideal CVH and lower GGT and ALT (13). In a separate cross-sectional study of 1,084 European adolescents, they found that a lower AST/ALT ratio was also associated with higher cardiometabolic risk factors (16). A landmark study in 1995 first identified a significant association between GGT levels and mortality from coronary heart disease (17). Recent systematic reviews and meta-analyses have confirmed this association,

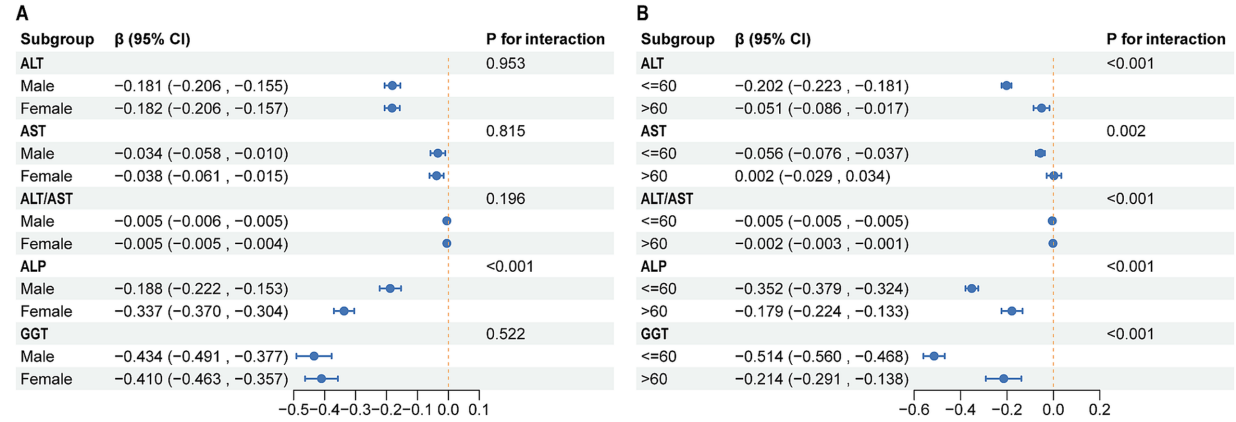

FIGURE 4
Subgroup analysis of the association between LE8 and liver function parameters. **(A)** Subgroup analyses stratified by sex. **(B)** Subgroup analyses stratified by sex. LE8, life's Essential 8; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

showing a 60% increased relative risk of all-cause mortality in the highest tertile of GGT levels and a 7% increased risk per 5 U/L increase in GGT levels (18). In a cohort study of Austrian adults, high GGT was found to be significantly associated with CVD mortality in a dose–response relationship (19). In men and women, the hazard ratios for GGT were 1.66 and 1.64, respectively, with a stronger association in younger participants. In addition, the Rotterdam Study found that individuals in the top 5% of GGT levels had a 55% higher risk of all-cause mortality (20). Another meta-analysis showed a 56% increase in all-cause mortality for the highest versus lowest GGT quartile (21). Our study shows a negative association between LE8 scores and GGT levels, suggesting that better CVH, as reflected by higher LE8 scores, is associated with lower GGT levels. This finding is consistent with previous research and supports the role of GGT as a potential biomarker of CVH and mortality risk. The relationship between serum aminotransferases, particularly ALT and AST, with CVD risk has been extensively studied, though with varying degrees of association. However, when considering the LE8 score, which is designed to assess CVH, the interaction between these liver enzymes and LE8 components requires careful interpretation. Existing evidence suggests that the association between ALT and CVD risk is not as strong or consistent as that observed for GGT. For example, while the Framingham Offspring Heart Study found that elevated ALT levels were initially associated with a higher risk of CVD events, this association was attenuated after adjustment for multiple variables, suggesting that ALT may not independently predict CVD risk (22). However, an independent association between ALT levels and increased CVD mortality was found in a cohort study of 37,085 Korean participants (23). This nuanced relationship may extend to its association with LE8 scores, where ALT might correlate with some LE8 components, such as BMI and blood lipids, but not necessarily with overall cardiovascular risk. Similar trends are observed with AST, where its association with CVD events remains inconclusive. A meta-analysis of prospective cohort studies found no significant link between AST levels and increased risk of CVD mortality (24). Our results suggest a weak relationship between AST and LE8 score, which may reflect the limited role of CVH as an independent marker of AST. In contrast, ALP has shown a more consistent association with CVD risk. Higher levels of ALP have been associated with an increased risk of CHD and all-cause mortality, even after adjusting for traditional risk factors and excluding individuals with chronic kidney disease (25). This consistent association suggests that ALP may have a more direct relationship with CVH and, by extension, LE8 scores. The LE8 score, which includes several CVH factors, may interact with ALP levels in a way that reflects the enzyme's role in vascular calcification and other cardiovascular processes.

The inverse relationship between the LE8 score and liver enzyme levels, particularly GGT, may be explained by several potential mechanisms. A healthier lifestyle, as reflected by a higher LE8 score, may reduce inflammatory stress, improve insulin sensitivity, and prevent excess adiposity (14). These factors contribute to a more favorable cardiovascular risk profile and may also reduce pathways leading to liver enzyme elevation. For example, adherence to dietary patterns such as the Mediterranean or DASH diets, which are characterized by a high intake of monounsaturated fatty acids, phytochemicals, fiber, and antioxidants, has been demonstrated to reduce inflammation and improve insulin resistance (26, 27). Participants who performed physical activity improved insulin sensitivity by decreasing immune cell activation and increasing glucose transporter type 4 translocation (28, 29). In addition, recent evidence indicates physical activity can directly affect lipogenesis and/or hepatic oxidation, thereby affecting hepatic lipid content (30). Avoiding obesity plays a critical role in preventing the release of inflammatory cytokines and free fatty acids from dysfunctional adipose tissue, which are known to contribute to lipotoxicity and hepatic steatosis (13, 31). Moreover, GGT has been implicated in promoting the oxidation of low-density lipoprotein (LDL) through redox reactions within atherosclerotic plaques, contributing to plaque development and progression (32). These mechanistic insights suggest that GGT is more strongly associated with LE8 scores than other liver enzymes, such as ALT, AST, and ALP, which may be due to its multifaceted role in oxidative stress and inflammation.

A key takeaway from this study is that the LE8 score can serve as an integrated measure for monitoring liver health and guiding CVH promotion. Given that CVD and liver dysfunction are often interconnected and share common risk factors, the LE8 score could serve as a dual marker to assess the overall health status of patients. Integrating LE8 scoring into routine clinical practice could be particularly

beneficial in identifying individuals at high risk for both cardiovascular and liver diseases. By providing a holistic assessment of lifestyle factors, LE8 scores can help clinicians screen for early signs of liver dysfunction, such as elevated liver enzymes, while simultaneously monitoring cardiovascular risk. Furthermore, the use of the LE8 score in clinical practice could enhance personalized treatment strategies. For example, clinicians could tailor interventions to improve both cardiovascular and liver health based on a patient's LE8 score. Interventions could include lifestyle modifications such as improved diet, increased physical activity, and smoking cessation. In this way, the LE8 score could contribute to a more integrated approach to managing patients' overall health, potentially reducing the burden of both CVD and liver disorders. However, the feasibility of incorporating LE8 scoring into routine clinical practice would depend on the availability of relevant data in electronic health records and the development of standardized assessment tools for LE8 scoring. Training healthcare providers to interpret LE8 scores and use them to guide clinical decisions would also be necessary. Therefore, we call for future guidelines to consider incorporating the LE8 scores as part of routine health assessments to better understand its impact on patient outcomes and healthcare efficiency.

The strengths of our study are noteworthy. A key strength is the innovative use of the LE8 score, a comprehensive metric that integrates multiple lifestyle factors to provide a holistic assessment of CVH. This comprehensive approach may provide valuable insights into identifying individuals at higher risk for liver function abnormalities who may benefit from targeted interventions. In addition, our study used the WQS regression model, a novel methodological approach that allowed us to identify the most influential components of the LE8 score on liver enzyme levels. The use of data from the NHANES, a large-scale, nationally representative cross-sectional survey, further strengthens the generalizability of our findings to the broader U.S. population. The multistage probability sampling design of NHANES ensures that our results are applicable to different demographic groups. Furthermore, our study included detailed subgroup and interaction analyses, which provided a deeper understanding of how different population characteristics may influence the relationship between the LE8 score and liver enzyme levels. This approach highlights the necessity of adapting interventions to particular subgroups, thereby increasing the likelihood of developing more personalized and effective prevention strategies.

This study has several limitations. First, the cross-sectional design of the study limits the ability to infer causality. Although we observed correlations between LE8 scores and liver function, causal relationships cannot be established. Second, despite adjustment for numerous potential confounders, it is not possible to completely eliminate all sources of bias. For example, dietary recall data based on 24-h recall methods may be susceptible to recall or reporting bias, potentially affecting the accuracy of dietary intake data. Finally, because the NHANES database does not provide exact dates for dietary recall interviews and blood sample collection, we are unable to directly analyze the temporal relationship between these variables, which limits the assessment of time-dependent effects of dietary intake and blood biomarkers on liver function parameters.

5 Conclusion

The present study reveals a significant inverse relationship between the LE8 scores and liver enzyme levels. This finding indicates that higher LE8 scores, which reflect better CVH, are associated with improved liver function. Nonlinear analyses identified key inflection points for ALT and the ALT/AST ratio, indicating that the advantages of elevated LE8 scores on liver function may be more pronounced above specific thresholds. Given the potential of the LE8 score to guide early identification of individuals at risk for liver diseases, future guidelines could incorporate the LE8 score as part of routine screening and preventive measures. However, given the limitations of the current study, future prospective studies are needed to confirm these associations and explore the underlying mechanisms further.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics (NCHS) Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

QL: Conceptualization, Writing – original draft. MZ: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. ZP: Conceptualization, Investigation, Supervision, Writing – review & editing.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1515883/full#supplementary-material

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Wernicke encephalopathy in a patient with drug-induced liver failure: a case report

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Introduction: Wernicke encephalopathy is a metabolic disease mainly associated with vitamin B1 deficiency, which is common in chronic alcoholism. Non-alcoholic Wernicke encephalopathy is difficult for early diagnosis.

Case presentation: One case involved a 62-year-old man who was admitted to hospital with drug-induced liver failure. He presented lower extremity weakness and progressive worsening of consciousness disturbance post-admission and was eventually identified as Wernicke encephalopathy by magnetic resonance imaging scan and deficiency in vitamin B1. The classic symmetric hyperintense signals on T2-weighted and diffusion-weighted images were reversible after intravenous vitamin B1 supplementation.

Conclusion: A high index of clinical suspicion is required for early diagnosis and appropriate preventive and therapeutic strategies by adequate and immediate vitamin B1 supplements in the reversible stage of Wernicke encephalopathy.

KEYWORDS

Wernicke encephalopathy, non-alcoholic, drug-induced liver injury, liver failure, vitamin B1

Introduction

Wernicke encephalopathy is a metabolic disease mainly associated with vitamin B1 deficiency which leads to permanent brain injury and life-threatening complications (1). Wernicke encephalopathy is common in chronic alcoholism, but non-alcoholic Wernicke encephalopathy is difficult for early diagnosis due to the various presentations. In this study, we reported a non-alcoholic patient with drug-induced liver failure who developed Wernicke encephalopathy.

Case report

A 62-year-old man was admitted to our department for jaundice and new onset ascites for 2 days. He had a history of administrating herbal medicine for 6 months due to the diagnosis of lung nodules in a routine physical examination. He was noted to have progressive fatigue and poor appetite 2 weeks before the admission. Laboratory evaluation yielded the following: white blood cell count, 7.19 $\times$ 10^9/L; neutrophil ratio, 70.4%; red blood cell count, 5.18 $\times$ 10^{12}/L; hemoglobin, 158 g/L; platelet count, 178 $\times$ 10^9/L; total bilirubin, 344.1 μmol/L; alanine aminotransferase, 830 U/L; aspartate aminotransferase, 966 U/L; alkaline phosphatase, 123 U/L, gamma-glutamyl transferase, 135 U/L; albumin,

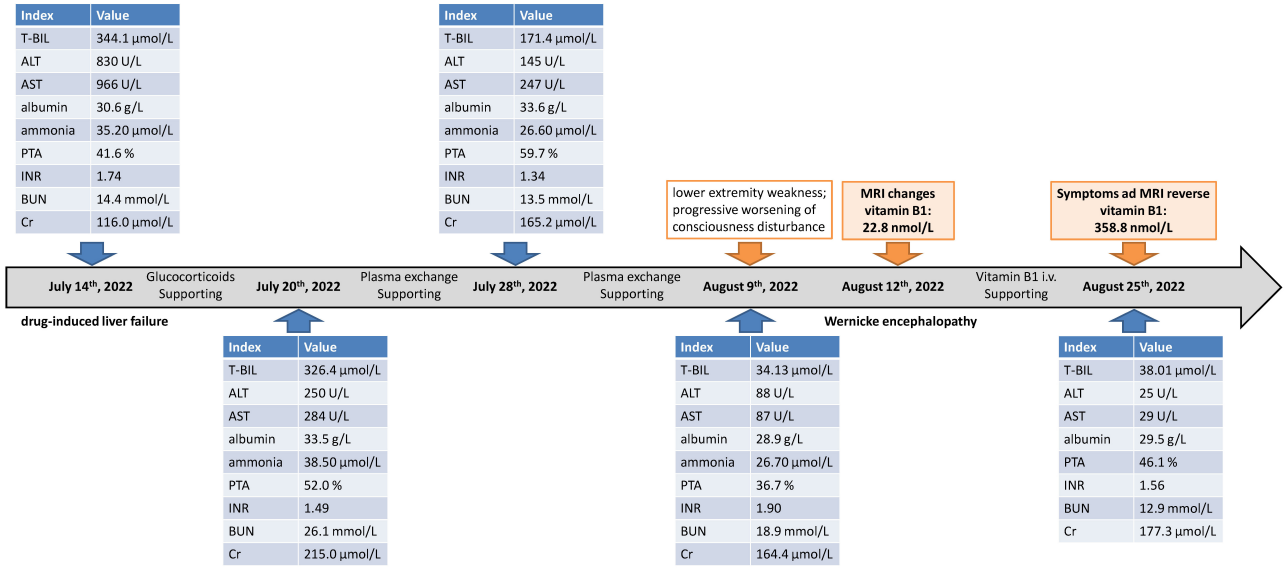

FIGURE 1
Showcase of timeline with the changes in liver function, coagulation function, renal function, and vitamin B1. T-Bil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PTA, prothrombin activity; INR, international normalized ratio; BUN, blood urea nitrogen; Cr, creatinine; MRI, magnetic resonance imaging; i.v., intravenous.

30.6 g/L; blood ammonia, 35.20 μmol/L; blood urea nitrogen, 14.4 mmol/L; creatinine, 116.0 μmol/L; prothrombin activity, 41.6 %; international normalized ratio, 1.74; and alpha-fetoprotein, 21.80 ng/mL. The results were negative for hepatitis viruses, human immunodeficiency virus-1, cytomegalovirus, Epstein–Barr virus, parvovirus B19, and autoimmune diseases. Abdominal ultrasonography showed diffuse changes in the liver and ascites. He was diagnosed with drug-induced liver failure based on the medical history and the symptoms of acute hepatic insult.

He was treated with supportive measurements (including liver protective treatments, glucocorticoids, prophylactic antibiotics, diuresis, and lactulose) and plasma exchange. The laboratory parameters for liver and renal function were progressively improved (Figure 1). However, the patient had very poor appetite, and always nausea and vomiting after meals. Three weeks post-admission, he presented lower extremity weakness and progressive worsening of consciousness disturbance, manifesting as dysphoria, ecmnesia, and delirium to light coma. A neurological evaluation was then conducted. Thyroid function parameters, adrenal hormones, blood ammonia, blood sugar, and electrolyte levels were within normal limits. The result of the electrocardiographic examination was normal. The symptoms were not reserved with anti-hepatic encephalopathy therapies. Cerebral magnetic resonance imaging (MRI) showed symmetric hyperintense signals on T2-weighted images in the bilateral inferior cerebellar peduncle, dorsal pons, and medial thalami as well as increased signal intensities on diffusion-weighted images within bilateral thalami and hypothalamus (Figure 2A). He was vitamin B1-deficient at a level of 22.8 nmol/L (normal range: 70–180 nmol/L). He was diagnosed with Wernicke encephalopathy and immediately received intravenous vitamin B1 supplementation (200 mg per 8 h). His neurological symptoms improved, serum vitamin B1 level returned to 358.8 nmol/L (Figure 1), and the lesions in MRI were reversible 12 days post-vitamin B1 replacement therapy (Figure 2B). The vitamin B1 administration was changed to oral supplementation (200 mg/day) for 2 weeks. He was regularly followed up for 18 months after discharge, and no abnormalities were found during the follow-up period.

Discussion

Wernicke encephalopathy was first reported in chronic alcoholism (2) and has occasionally been described as malnutrition due to a variety of causes, such as gastrointestinal surgery (3), organ transplantation (4), and upper gastrointestinal obstruction (5). Wernicke encephalopathy has also been reported in hepatitis B liver failure (6, 7). In this case, the patient did not have a history of chronic liver diseases or alcoholism but had a history of herbal medicine and was diagnosed with drug-induced liver failure. Poor appetite, insufficient dietary intake, and vomiting caused by impaired liver and renal function mainly contribute to the development of Wernicke encephalopathy. However, for patients with liver failure, the differential diagnosis of hepatic encephalopathy and Wernicke encephalopathy might be a tough problem in an emergency condition. In this case, the patient had normal blood ammonia and did not respond to anti-hepatic encephalopathy treatments. The symmetry variability in MRI revealed the metabolic encephalopathy, and vitamin B1 deficiency further confirmed the diagnosis of Wernicke encephalopathy.

Vitamin B1 can only be taken in from food and can neither be synthesized nor stored in the human body. Thiamine pyrophosphate is the biologically active form of vitamin B1 and plays a vital role in the tricarboxylic acid cycle. Vitamin B1

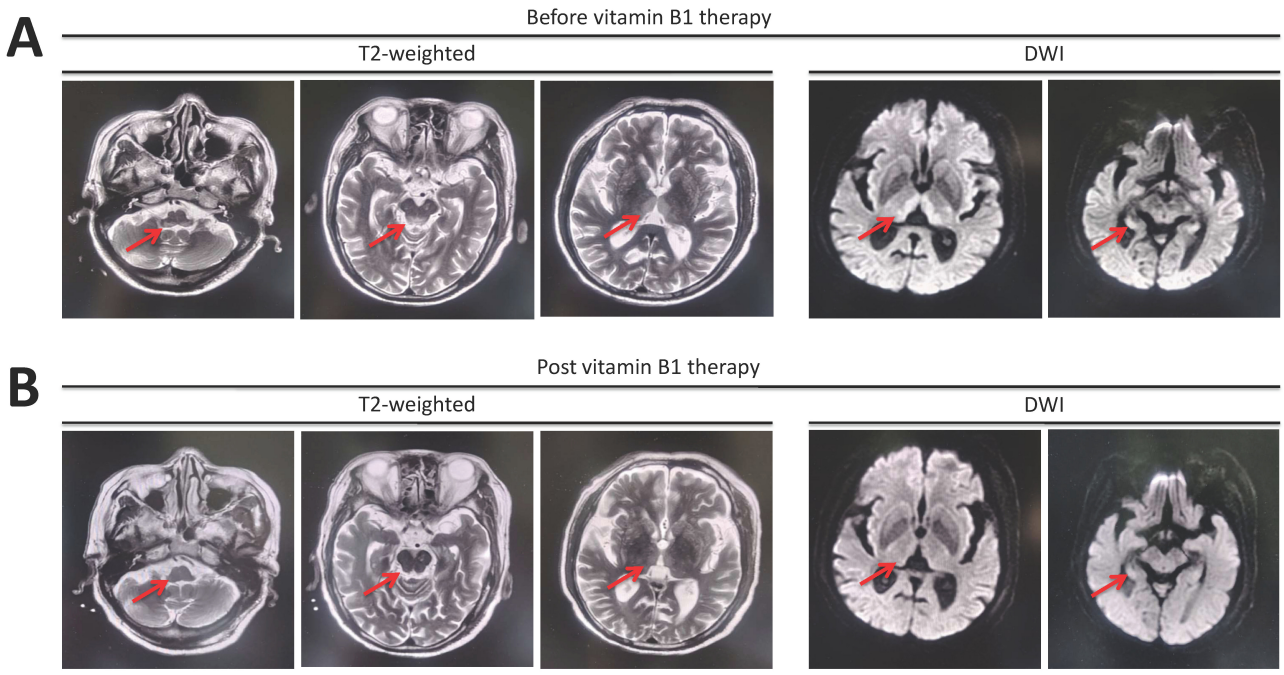

FIGURE 2
Magnetic resonance imaging manifestation reveals **(A)** symmetric hyperintense signals on T2-weighted images in the bilateral inferior cerebellar peduncle, dorsal pons, and medial thalami as well as increased signal intensities on diffusion-weighted images (DWI) in bilateral thalami and hypothalamus. **(B)** The lesions were reversible after 12 days of intravenous vitamin B1 supplementation.

deficiency results in lactic acid accumulation and acidosis, thereby interfering with neurotransmitter production, release, and re-uptake, and finally leads to Wernicke encephalopathy (1). The degree of brain congestion and edema will be further aggravated in Wernicke encephalopathy due to the failure of prompt vitamin B1 supplementation (4). In this case, the usage of glucocorticoids might increase the consumption of vitamin B1, leading to the aggravation of Wernicke encephalopathy.

Three clinical components of Wernicke encephalopathy are impaired consciousness, ophthalmoplegia, and gait ataxia. However, the classical triad is only fully recognized in 10–38% of patients (8). The clinical diagnosis of Wernicke encephalopathy in alcoholics requires two of the following four signs, including (i) dietary deficiencies, (ii) eye signs, (iii) cerebellar dysfunction, and (iv) either an altered mental state or mild memory impairment based on the diagnostic criteria proposed by 2010 European Union of Neuroscience Association (8). Although the patient in this case was not an alcoholic, he still confirmed three of four elements. Furthermore, cerebral MRI is the most sensitive examination for the early diagnosis of Wernicke encephalopathy. The sensitivity and specificity of cerebral MRI for the diagnosis of Wernicke encephalopathy are 53% and 93%, respectively (9). Basal ganglia and thalamic region are mostly involved because these regions seem to be particularly vulnerable to oxygen deprivation (5) and presented symmetric high T1, T2, and T2 flair signal intensities (10). His cerebral MRI supported Wernicke encephalopathy, the laboratory test confirmed vitamin B1 deficiency, and he rapidly recovered after vitamin B1 supplementation without any sequelae. We definitively diagnosed Wernicke encephalopathy during drug-induced liver failure.

Once diagnosed or even suspected as Wernicke encephalopathy, the patient should immediately receive vitamin B1 administration, preferably intravenously with 200 mg thrice daily before any carbohydrate (8). The overall safety of vitamin B1 is good since vitamin B1 is water-soluble and can easily be excreted through the kidney (8). In this case, the patient received intravenous vitamin B1 immediately upon consideration of Wernicke encephalopathy. His clinical symptoms improved, and the lesions in the MRI were reversed 12 days later. He received oral supplementation of vitamin B1 for another 2 weeks. Vitamin B1 therapy was safe and effective.

In summary, we reported Wernicke encephalopathy developing in a patient with drug-induced liver failure. Patients with liver failure should be on the alert for starvation-induced Wernicke encephalopathy. A high index of clinical suspicion is required for early diagnosis and appropriate preventive and therapeutic strategies by adequate and immediate vitamin B1 supplements in the reversible stage of Wernicke encephalopathy. Furthermore, it is important for vitamin testing and supplements in patients with liver injury, especially for those who have insufficient dietary intake.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Tangdu Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

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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.

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The impact of dietary fiber on colorectal cancer patients based on machine learning

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Objective: This study aimed to evaluate the impact of enteral nutrition with dietary fiber on patients undergoing laparoscopic colorectal cancer (CRC) surgery.

Methods: Between January 2023 and August 2024, 164 CRC patients were randomly assigned to two groups at our hospital. The control group received standard nutritional intervention, while the observation group received enteral nutritional support containing dietary fiber. Both groups were subjected to intervention and continuously observed until the 14th postoperative day. An observational analysis assessed the impact of dietary fiber intake on postoperative nutritional status in CRC patients. The study compared infection stress index, inflammatory factors, nutritional status, intestinal function recovery, and complication incidence between groups. Additionally, four machine learning models—Logistic Regression (LR), Random Forest (RF), Neural Network (NN), and Support Vector Machine (SVM)—were developed based on nutritional and clinical indicators.

Results: In the observation group, levels of procalcitonin (PCT), beta-endorphin (β-EP), C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) were significantly lower compared to the control group ($p < 0.01$). Conversely, levels of albumin (ALB), hemoglobin (HB), transferrin (TRF), and prealbumin (PAB) in the observation group were significantly higher than those in the control group ($p < 0.01$). Furthermore, LR, RF, NN, and SVM models can effectively predict the effects of dietary fiber on the immune function and inflammatory response of postoperative CRC patients, with the NN model performing the best. Through the screening of machine learning models, four key predictors for CRC patients were identified: PCT, PAB, ALB, and IL-1.

Conclusion: Postoperative dietary fiber administration in colorectal cancer enhances immune function, reduces disease-related inflammation, and inhibits tumor proliferation. Machine learning-based CRC prediction models hold clinical value.

KEYWORDS

colorectal cancer, dietary fiber, enteral nutrition support, nutritional status, machine learning

1 Introduction

Colorectal cancer (CRC) ranks as the third most prevalent malignancy worldwide, and its incidence rate is on the rise (1). In 2018, there were 18.1 million new cancer cases globally, with CRC ranking fourth among them. Given this prevalence, understanding the pathogenesis of CRC and developing practical treatment approaches is crucial (2, 3). The development of CRC is complex, involving genetic and environmental factors that work together to promote abnormal growth in colorectal tissue, leading to tumor formation. Environmental factors, particularly dietary habits, exposure to radiation, and environmental toxins, significantly influence CRC development. High-calorie, high-fat diets, coupled with disruptions in intestinal microbiota and local inflammation, are critical factors in initiating CRC (4).

The impact of dietary factors on CRC is significant (5). Prolonged consumption of high-calorie, high-fat diets can disrupt the balance of intestinal bacteria and lead to local inflammation, creating an environment conducive to CRC development. Chronic inflammation resulting from prolonged synthesis of pro-inflammatory cytokines is a crucial contributor to autoimmune diseases and cancer (6). Addressing this inflammation and restoring immune balance is critical in preventing complications. In conclusion, given the global burden of CRC and its multifaceted etiology involving genetic and environmental factors, particularly dietary habits and inflammation, there is an urgent need to explore dietary interventions that can mitigate inflammation, prevent associated complications, and restore immune balance effectively (7).

In the context of postoperative care for CRC patients, the role of dietary fiber is pivotal due to its impact on intestinal health (8). Dietary fiber plays a crucial role in safeguarding the intestinal barrier, regulating immune function, and mitigating postoperative inflammatory reactions (9). Despite these benefits, limited research exists on the early integration of dietary fiber into CRC patient management post-surgery. Malnutrition not only hampers recovery but also heightens the risk of complications and mortality rates. Moreover, immune suppression could potentially enhance the chances of tumor metastasis and recurrence. Consequently, providing early nutritional support after CRC surgery is paramount. In recent years, the advancement of machine learning has led to the widespread application of algorithms such as Random Forest (RF), Logistic Regression (LR), Support Vector Machine (SVM), and Neural Network (NN) in clinical research (10). These algorithms facilitate the development of disease diagnosis and prediction models, thereby enhancing decision-making processes (11). This study aimed to investigate the effects of dietary fiber on postoperative immune function and inflammatory responses in CRC patients, identify critical factors influencing CRC, and offer valuable insights for the prevention and management of CRC.

2 Methodology

2.1 Materials and methods

We conducted a prospective randomized controlled trial on CRC patients undergoing surgical treatment, focusing on the effects of dietary fiber intervention on the patients. The study received written approval from our hospital's review committee (Ethical Review No. 2023027), and all participating CRC patients provided informed consent. The trial procedures complied with clinical practice guidelines as well as the principles outlined in the Helsinki Declaration.

2.2 Patient selection

From January 2023 to August 2024, we selected 164 CRC patients admitted to our Department of Gastroenterology and randomly assigned them to control group and observation group, each consisting of 82 patients (Table 1). The observation group consisted of 46 males and 36 females, with a mean age of 54.9 ± 11.1 years. The control group included 44 males and 38 females, with a mean age of 56.2 ± 13.9 years. Comparison of general data between the two patient groups indicated that there were no statistically significant differences

TABLE 1 Characteristics of cases.

Variable	Observation group (*n* = 82)	Control group (*n* = 82)	*p*
Sex (%)			
Male	46 (56.1)	44 (53.7)	0.61
Female	36 (43.9)	38 (36.7)	0.57
Age mean (SD) year	54.9 ± 11.1	56.2 ± 13.9	0.66
Alcohol status (%)			
Drinkers	30 (36.6)	34 (41.5)	0.72
Nondrinkers	52 (63.4)	48 (58.5)	0.79
Smoke status (%)			
Smokers	34 (41.5)	36 (43.9)	0.67
No smokers	48 (58.5)	46 (56.1)	0.71
TNM stage (%)			
I and II	42 (51.2)	36 (43.9)	0.81
III	40 (48.8)	46 (56.1)	0.86

Observation group: using enteral nutrition support containing dietary fiber; Control group: using routine nutritional interventions.

($p > 0.01$). Notably, this study received approval from the Ethics Committee of the China Railway Center Hospital of China National Pharmaceutical Corporation, and informed consent was obtained from both patients and their families. All surgeries were conducted in accordance with the guiding principles established by the Helsinki Declaration.

Inclusion criteria: The diagnosis was confirmed by clinical symptoms and signs, endoscopic imaging, and laboratory tests in our hospital, according to the criteria of "Consensus opinion on diagnosis and treatment of inflammatory bowel disease diseases." Truelove-witts score was used as a reference for the diagnosis of severity, and the diagnosis was confirmed by pathological examination.

Exclusion criteria: complicated with other types of organ dysfunction; complicated with intestinal fungal or viral infection; complicated with colon polyp; pregnant or lactating women; For various reasons caused by the lack of clinical data.

Observational indicators: In this study, we aim to compare various indicators between two groups of patients following CRC surgery. Specifically, we will analyze infection stress markers, inflammatory response factors, nutritional status, recovery of intestinal function, and the occurrence of complications in both groups.

Before and after the intervention, 5 mL of venous blood will be collected from each patient to assessed infection stress markers such as procalcitonin (PCT), β-endorphin (β-EP), and C-reactive protein (CRP). Additionally, we used the same method to measure inflammatory response factors in both groups, including interleukin-1 (IL-1), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α). Before and after the intervention, 3 mL of fasting venous blood samples was drawn from each patient to evaluate parameters like hemoglobin (HB), albumin (ALB), transferrin (TRF), and prealbumin (PAB) to track changes in their health status. We assessed immune function through markers like cluster of differentiation 4 positive (CD4+), cluster of differentiation 3 positive (CD3+), cluster of differentiation 8 positive (CD8+), immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) levels. Lastly, we recorded crucial postoperative indicators such as bowel sound recovery, the first appearance of anal gas passage, and the timing of the first defecation to track the progress of each patient's recovery journey.

2.3 Methods

None of the patients had a gastrointestinal decompression tube inserted before surgery. The observation group and the control group were given continuous nutritional intervention for 14 days post-surgery. For the observation group, the nutritional intervention during postoperative days 1–7 included an intravenous drip of 500 mL of Rui Gao (Fresenius Kabi Huarui Pharmaceuticals Co., Ltd.), oral administration of 25 g of dietary fiber (Tiantian Yikang Biotechnology Co., Ltd., composed primarily of polyglucose, oligofructose, glycerol, citric acid, and potassium sorbate), and 4 g of Golden Bifidobacterium (Shuangqi Pharmaceutical Co., Ltd.). From postoperative days 8 to 14, the intravenous drip of Rui Gao was increased to 1,000 mL daily, while the oral doses of dietary fiber (25 g) and Golden Bifidobacterium (4 g) remained consistent. The infusion rate during days 1 to 7 post-surgery was set at 30 to 50 mL/h, which was then increased to 60 to 70 mL/h from days 8 to 14, adjusted according to each patient's physiological tolerance. For the control group, nutritional interventions from postoperative days 1 to 7 included an intravenous drip of 500 mL of Rui Gao and oral administration of 4 g of Golden Bifidobacterium. From postoperative days 8 to 14, the intravenous drip of Rui Gao was increased to 1,000 mL daily, while the oral dose of Golden Bifidobacterium (4 g) remained the same. However, the method and infusion rate remained identical to those in the observation group. Both groups were continuously monitored and assessed over the 14 days following surgery.

2.4 Statistical analysis

Statistical analysis was carried out using SPSS 22.0 software in this observational study. Pairwise comparisons within the group were performed utilizing paired t-tests for continuous variables, which were depicted as mean ± standard deviation ($\overline{x} \pm s$). Descriptive statistics were employed for continuous data, whereas paired t-tests were utilized for analysis. Categorical variables were characterized by their frequencies and percentages, and the analysis was conducted using the chi-square test. All cases were randomly divided into a training set (80%) and a testing set (20%). The NN model in this study includes input layer, hidden layer, and output layer. Among them, the input layer has 9 neurons, the hidden layer has 30 neurons, and the output layer has 1 neuron. The activation function was ReLU, and the output layer used the Sigmoid activation function. The machine learning models LR, RF, NN, and SVM in this study were developed using Python 3.10. The performance of all models was assessed using the area under the curve (AUC), accuracy, sensitivity, specificity, and F1 score metrics. A significance level of $p < 0.01$ denoted statistical significance throughout the analysis.

3 Results

3.1 Comparison of infection stress indexes

The infection stress indicators (PCT, β-EP, and CRP) of each group in POD-7 and POD-14 were significantly reduced compared to POP levels. Although no significant differences were found in the levels of PCT, β-EP, and CRP between the groups at different time points ($p > 0.01$), it is important to note that, at two specific time points, PCT, β-EP, and CRP levels in the observation group were significantly lower than those in the control group ($p < 0.01$), as shown in Table 2.

3.2 Comparison of inflammatory response factors

The levels of IL-1, IL-8, and TNF-α in both groups gradually decreased at POD-7 and POD-14, and the differences in the levels of inflammatory response factors within the groups at each time point were not statistically significant ($p > 0.01$). The levels of IL-1, IL-8, and TNF-α in the observation group at POD-14 were significantly lower than those in the control group ($p < 0.01$), as shown in Table 3.

TABLE 2 Comparison of infection stress indexes between the two groups.

Variable	POP	POD-7	POD-14
PCT (μg/L)			
Control group	6.62 ± 1.33	2.21 ± 0.31	1.55 ± 0.23
Observation group	6.79 ± 1.26	2.01 ± 0.21*	1.39 ± 0.19*
Mean difference	6.71 ± 1.29	2.11 ± 0.26	1.47 ± 0.21
t	0.117	1.883	3.780
p	0.611	<0.01	<0.01
β-EP (ng/L)			
Control group	71.55 ± 5.33	52.31 ± 4.69	46.37 ± 4.44
Observation group	71.32 ± 5.16	50.12 ± 4.71*	39.77 ± 4.16*
Mean difference	71.44 ± 5.25	51.22 ± 4.70	43.07 ± 4.30
t	0.073	7.61	9.19
p	0.761	<0.01	<0.01
CRP (ng/L)			
Control group	6.62 ± 1.33	2.21 ± 0.31	1.55 ± 0.23
Observation group	6.79 ± 1.26	2.01 ± 0.21*	1.39 ± 0.19*
Mean difference	6.71 ± 1.29	2.11 ± 0.26	1.47 ± 0.21
t	0.065	11.66	13.11
p	0.854	<0.01	<0.01

POP, pre-operation; POD, postoperative day; PCT, procalcitonin; β-EP, β-endorphin; CRP, C-reactive protein; t, *t*-test compared to the observation group; *$p < 0.01$, compared with the observation group.

TABLE 3 Comparison of inflammatory response factors between the two groups.

Variable	POP	POD-7	POD-14
IL-1			
Control group	59.96 ± 5.06	51.63 ± 4.11	46.11 ± 3.33
Observation group	60.31 ± 5.13	45.39 ± 3.96*	30.97 ± 3.67*
Mean difference	60.12 ± 5.10	48.51 ± 4.04	38.54 ± 3.50
t	0.029	9.33	20.181
p	0.773	<0.01	<0.01
IL-8			
Control group	61.16 ± 4.96	44.16 ± 4.41	38.93 ± 4.11
Observation group	61.11 ± 5.01	29.16 ± 4.33	20.87 ± 3.91*
Mean difference	61.14 ± 4.99	36.66 ± 4.37	29.90 ± 4.01
t	0.049	17.36	19.117
p	0.962	0.09	<0.01
TNF-α			
Control group	37.88 ± 3.24	27.03 ± 3.11	17.15 ± 2.76
Observation group	37.85 ± 3.21	19.61 ± 2.73*	13.54 ± 2.21*
Mean difference	37.87 ± 3.23	23.32 ± 2.92	15.35 ± 2.49
t	0.071	5.73	7.331
p	0.964	<0.01	<0.01

POP, pre-operation; POD, postoperative day; IL-1, interleukin-1; IL-8, interleukin-8; TNF-α, tumor necrosis factor-alpha; t, *t*-test compared to the observation group; *$p < 0.01$, compared with the observation group.

3.3 Comparison of nutritional status

As shown in Table 4, the levels of nutritional factors: HB, ALB, PAB, and TRF increased significantly between the two groups at POD-7 and POD-14 at each time points, but the differences in the levels of each nutritional indicator within the groups were not statistically significant ($p > 0.01$). As shown in Figure 1, the nutritional parameters HB, ALB, PAB, and TRF were significantly elevated in the POD-14 observation groups compared to the control group ($p < 0.01$).

TABLE 4 Comparison of nutritional status between the two groups.

Variable	POP	POD-7	POD-14
HB (g/L)			
Control group	124.26 ± 10.17	131.46 ± 10.77	136.23 ± 15.73
Observation group	125.37 ± 10.22	146.31 ± 11.63*	159.16 ± 16.12*
Mean difference	124.82 ± 10.20	138.89 ± 11.20	147.70 ± 15.93
t	0.547	3.23	6.71
p	0.581	<0.01	<0.01
ALB (g/L)			
Control group	33.81 ± 4.13	35.23 ± 3.11	36.65 ± 4.31
Observation group	33.89 ± 4.27	38.81 ± 3.75*	43.19 ± 4.63*
Mean difference	33.85 ± 4.20	37.02 ± 3.43	39.92 ± 4.47
t	0.178	5.103	6.871
p	0.769	<0.01	<0.01
TRF (g/L)			
Control group	1.67 ± 0.21	1.71 ± 0.26	1.75 ± 0.29
Observation group	1.69 ± 0.23	1.83 ± 0.28	1.87 ± 0.30*
Mean difference	1.68 ± 0.22	1.77 ± 0.27	1.81 ± 0.30
t	0.046	0.863	1.712
p	0.901	0.06	<0.01
PAB (mg/L)			
Control group	205.37 ± 17.43	233.08 ± 18.67	246.13 ± 20.11
Observation group	206.41 ± 18.31	259.89 ± 22.77*	271.33 ± 24.32*
Mean difference	205.89 ± 17.87	246.49 ± 20.72	258.73 ± 22.22
t	0.438	3.111	5.901
p	0.836	<0.01	<0.01

POP, pre-operation; POD, postoperative day; HB, Hemoglobin; ALB, albumin; PAB, pre-albumin; TRF, transferring; t, *t*-test compared to the observation group; *$p < 0.01$, compared with the observation group.

3.4 Comparison of intestinal function recovery

As shown in Table 5, compared with before intervention, the recovery of intestinal function in the observation group on the 7th and 14th days after intervention was better than the control group ($p < 0.01$).

3.5 Comparison of immune function

The levels of CD3+, CD4+, CD4+ / CD8+, IgA, IgM, and IgG in both groups of patients significantly decreased on POD-7 and gradually increased on POD-14. However, the differences in immune indicator levels between the two groups at each time point were not statistically significant ($p > 0.01$). As depicted in Table 6, after 7 days of dietary fiber support post-surgery, the levels of immune indicators in the observation group were significantly elevated compared to those in the control group ($p < 0.01$).

3.6 Model training process

To develop and evaluate classification models, we employed four commonly used machine learning algorithms: NN, SVM, LR, and RF. Additionally, we combined these classification models using ensemble and cascaded methods to assess the performance of the integrated classifier.

3.7 Assessment outcomes of various machine learning algorithms

This study assessed the performance of four machine learning algorithms by employing five essential evaluation metrics: AUC, F1, specificity, accuracy, and sensitivity score, as shown in Table 7. We plotted ROC curves for models built with the training and testing sets (Figure 2). The NN model distinguished itself as the best performer among the models. In the training set, the NN model achieved an AUC of 0.851, and in the testing set, it reached an AUC of 0.861. In comparison, the AUC values for the LR, RF, and SVM models were significantly lower. Given the superior performance demonstrated by the NN model, we ultimately chose it as the final model for this investigation.

3.8 Predictors of model

We utilized the top-performing NN model to visualize the importance of nine variables based on their respective weights. The

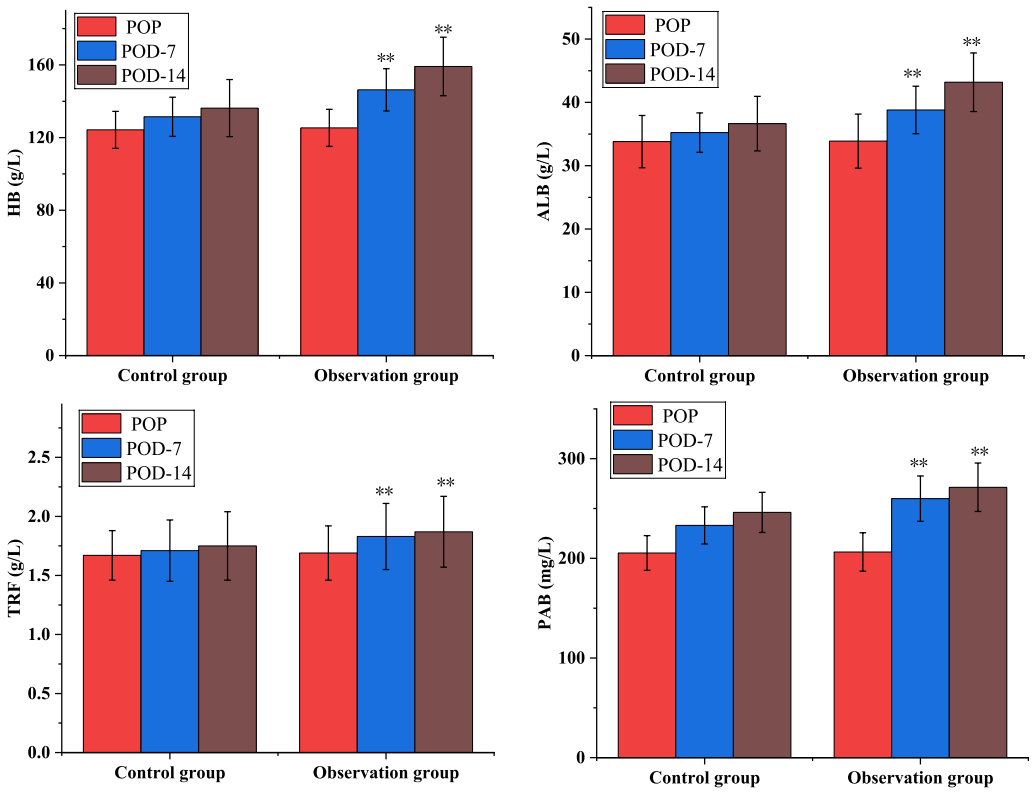

FIGURE 1
Comparison of nutritional status of patients.

TABLE 5 Comparative analysis of intestinal function between the two groups.

Variable	Recovery of intestinal sounds (h)	First anal exhaust (h)	First bowel movement (h)
Control group	34.26 ± 3.57	59.89 ± 5.11	91.23 ± 11.03
Observation group	25.31 ± 3.36*	47.74 ± 5.23*	71.22 ± 8.62*
t	11.101	9.76	10.37
p	<0.01	<0.01	<0.01

t, *t*-test compared to the observation group; *$p < 0.01$, compared with the observation group.

length of each bar in the chart is proportional to the significance of each variable. The variables refined by the NN model were then incorporated into a Logistic regression model, employing a stepwise regression method, ultimately retaining four critical influencing factors: PCT, PAB, ALB, and IL-1, as shown in Table 8 (Figure 3).

4 Discussion

This study analyzed the impact of dietary fiber intake on the postoperative nutritional status of CRC patients. The levels of PCT, β-EP, CRP, IL-1, IL-8, and TNF-α in the observation group were significantly lower compared to those in the control group ($p < 0.01$). Furthermore, we developed LR, RF, NN, and SVM models, which demonstrated excellent performance in predicting and diagnosing CRC. The NN model outperformed the others, achieving an AUC of 0.851 in training and 0.861 in testing. PCT, PAB, ALB, and IL-1 are key factors for predicting CRC patients.

CRC is a common malignant disease that impacts the digestive system and is frequently managed through laparoscopic surgery to improve patient health and prolong survival (12). Although malnutrition is common among CRC patients, originating from the disease and surgical procedures, as well as the possibility of exacerbation by anesthetic drugs and stress responses during surgery, addressing these concerns is vital (13, 14). Due to the substantial malnutrition rates in CRC patients stemming from the disease and surgical impacts, compounded by possible exacerbation by anesthesia and surgical stress responses, addressing these issues directly is paramount. Changes in the gut microbiota, influenced by factors like surgical anesthesia and surgical stress responses, may result in dysbiosis and worsen malnutrition, increasing the risk of postoperative infections and inflammation, which can hinder patient recovery and long-term outlook (15).

Implementing scientifically proven nutritional support strategies is crucial to improve postoperative nutritional wellbeing in patients (16). These interventions include preoperative nutritional assessments,

TABLE 6 Comparative analysis of immune function between the two groups.

Variable	POP	POD-7	POD-14
CD3+ (%)			
Control group	53.47 ± 5.17	49.77 ± 6.33	51.88 ± 6.93
Observation group	54.03 ± 6.52	51.21 ± 7.03*	56.11 ± 7.43*
Mean difference	53.75 ± 5.85	50.49 ± 6.68	53.99 ± 7.18
t	0.147	4.697	6.382
p	0.761	<0.01	<0.01
CD4+/CD8+			
Control group	0.91 ± 0.37	0.89 ± 0.39	1.07 ± 0.57
Observation group	0.84 ± 0.41	1.01 ± 0.43*	1.31 ± 0.61*
Mean difference	0.88 ± 0.39	0.95 ± 0.41	1.19 ± 0.59
t	0.009	3.94	4.23
p	0.823	<0.01	<0.01
CD4+ (%)			
Control group	32.49 ± 4.32	34.23 ± 5.11	35.15 ± 6.21
Observation group	32.10 ± 4.13	34.91 ± 5.77*	39.21 ± 6.67*
Mean difference	32.29 ± 4.23	34.57 ± 5.44	37.18 ± 6.44
t	0.113	4.891	6.151
p	0.969	<0.01	<0.01
IgM (g/L)			
Control group	1.71 ± 0.37	1.51 ± 0.31	1.95 ± 0.76
Observation group	1.74 ± 0.31	2.27 ± 0.47*	2.51 ± 0.55*
Mean difference	1.73 ± 0.34	1.89 ± 0.39	2.23 ± 0.66
t	0.055	13.45	13.78
p	0.901	<0.01	<0.01
IgA (g/L)			
Control group	1.63 ± 0.41	1.81 ± 0.62	2.53 ± 0.60
Observation group	1.66 ± 0.37	2.27 ± 0.57*	3.19 ± 0.69*
Mean difference	1.65 ± 0.39	2.04 ± 0.59	2.86 ± 0.65
t	0.038	3.31	5.99
p	0.76	<0.01	<0.01
IgG (g/L)			
Control group	10.11 ± 3.27	7.21 ± 2.56	9.03 ± 7.78
Observation group	9.43 ± 2.73	8.39 ± 2.27*	10.93 ± 3.53*
Mean difference	9.77 ± 3.0	7.8 ± 2.41	9.98 ± 5.66
t	0.072	2.34	2.97
p	0.501	<0.01	<0.01

POP, pre-operation; POD, postoperative day; CD3+, cluster of differentiation 3 positive; CD4+, cluster of differentiation 4 positive; CD8+, cluster of differentiation 8 positive; IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin G; t, *t*-test compared to the observation group; *$p < 0.01$, compared with the observation group.

perioperative nutritional support, and the utilization of appropriate diets and intestinal nutritional supplements. Tailored nutritional plans should be created according to the individual conditions and dietary requirements of each patient. Nutritional improvements can be achieved through dietary modifications, oral supplements, and other appropriate approaches before surgery. Enteral or parenteral nutritional support can be administered during and after surgery to fulfill the patient's energy, protein, and other dietary needs. Vigilant monitoring of patients' nutritional statuses and relevant indicators is essential to adjust intervention plans as needed in a timely.

Early intestinal nutritional support is crucial for accelerating gastrointestinal function recovery during postoperative care of CRC patients (17). Research has shown that promptly initiating soluble dietary fiber for enteral nutrition offers advantages, including improved nutritional markers, gradual weight loss, and a lower incidence of gastrointestinal complications. These interventions have significantly

TABLE 7 The efficacy of various machine learning algorithm models.

	AUC	Accuracy	Sensitivity	Specificity	F1
LR					
Train	0.811	0.801	0.723	0.841	0.737
Test	0.723	0.711	0.663	0.857	0.681
NN					
Train	0.851	0.811	0.689	0.831	0.724
Test	0.861	0.828	0.716	0.837	0.767
RF					
Train	0.741	0.788	0.632	0.743	0.661
Test	0.807	0.796	0.593	0.821	0.613
SVM					
Train	0.756	0.721	0.754	0.756	0.673
Test	0.656	0.746	0.704	0.803	0.676

LR, Logistic regression; NN, Neural network; RF, Random forest; SVM, Support vector machine.

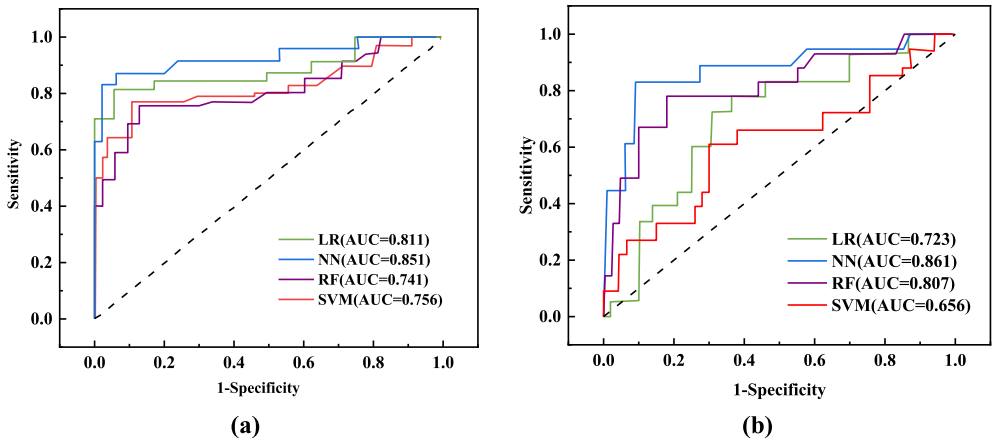

FIGURE 2
ROC curve analysis of different models. **(A)** ROC curves of 4 machine learning models in the training set; **(B)** ROC curves of 4 machine learning models in the test set.

TABLE 8 Factors influencing the screening characteristics of logistic regression analysis.

Variable	*β*	*OR*	95%*CI*	*p*	*SE*	*Wald* χ^2
PCT	0.019	1.011	1.001–1.016	0.001	0.002	8.116
PAB	0.146	1.122	1.046–1.197	0.003	0.037	7.343
ALB	−1.103	0.287	0.071–0.501	0.000	0.111	65.167
IL-1	0.216	1.206	1.097–1.311	0.001	0.061	10.89
Intercept	−6.597	0.003	0.000–7.161	0.102	4.151	2.316

PCT, procalcitonin; PAB, prealbumin; ALB, albumin; IL-1, interleukin-1.

improved nutritional wellbeing after surgery, leading to a reduction in complications. Dietary fibers are more than inert plant materials in the human digestive system; they interact actively with nutrients, generating beneficial metabolites, regulating nutrient absorption, and stimulating the growth of small intestine villi (18). This interactive process leads to increased nutrient absorption and an overall enhancement in nutritional status. Categorized as soluble or insoluble, these fibers exhibit specific traits - soluble fibers undergo fermentation easily, unlike insoluble fibers. Recent studies have highlighted the significance of colon dietary fiber fermentation, resulting in the synthesis of short-chain fatty acids (19). These fatty acids, after transportation to the liver through the portal venous system, can be transformed into glutamine, a vital nutrient that directly nourishes the small intestine through the bloodstream, enhancing nutritional absorption and overall wellbeing (20).

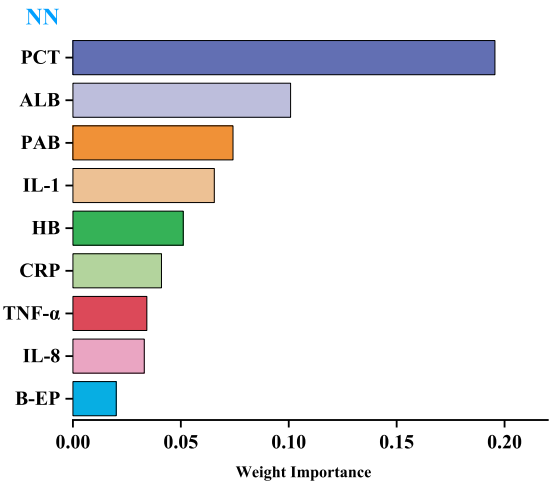

FIGURE 3
Importance of predictors for NN model.

Enteral nutrition support containing dietary fiber can prevent the occurrence of intestinal flora disorder, effectively inhibit the reproduction of intestinal pathogenic bacteria, and promote the growth of probiotics (21, 22). The findings of this study indicated that following the intervention, the levels of PCT, β-EP, CRP, IL-1, IL-8, and TNF-α were lower in the observation group compared to the control group. Contrastingly, there was an increase in the levels of Hb, ALB, PA and TRF, particularly notable post-14 days ($p < 0.01$). This indicates that enteral nutrition support with dietary fiber can reduce the infection stress response and inflammatory factor levels of patients after laparoscopic CRC surgery, promote the improvement of the nutritional status of patients, accelerate the recovery of intestinal function (23, 24).

In response to appropriate dietary fiber intake, gastrointestinal hormones are boosted, aiding in the restoration of intestinal motility following CRC surgery (25). Studies suggest that such fiber intake heightens small intestine activity significantly. Our observations reveal shortened intervals for gas passage post-surgery in the dietary fiber group compared to controls (47.74 ± 5.23 h vs. 59.89 ± 5.11 h, $p < 0.01$). Similarly, the dietary fiber group displayed quicker recovery of intestinal sounds (25.31 ± 3.36 h vs. 34.26 ± 3.57 h, $p < 0.01$), indicative of enhanced intestinal peristalsis recovery. Inflammation signifies the body's acute reaction to tissue injury induced by microbial infections and other harmful triggers (26). This study aims to explore dietary fiber's impact on postoperative immune function and inflammatory responses in CRC patients. Our findings depict a notable decline in immune parameters for both patient groups by the seventh postoperative day, reflecting a potential compromise in immune functionality. However, by the 14th day, these indices showcased gradual improvement. Notably, on the 14th-day post-surgery, the observation group exhibited significantly elevated levels of CD4+, IgA, and IgG in comparison to the control group (39.21 ± 6.67 vs. 35.15 ± 6.21, 3.19 ± 0.69 vs. 2.53 ± 0.60 g/L, and 10.93 ± 3.53 vs. 9.03 ± 7.78 g/L, respectively, $p < 0.01$). This underscores the role of dietary fiber in enhancing immune responses and bolstering humoral and cellular immunity postoperatively (27, 28). Moreover, dietary fiber improves postoperative gastrointestinal motility, reducing the chances of abdominal distension and diarrhea (29). This nutritional intervention method ensures patient safety throughout the perioperative phase and promotes swift recovery.

Recently, artificial intelligence has made significant advancements in medicine (30–33). Machine learning utilizes clinical data attributes and algorithms to predict outcomes and develop models (34). Comparing different algorithms can enhance the accuracy of clinical predictions. This technology analyzes diverse data modules to identify outcome-related variables, discover risk factors, and explore patterns, facilitating the iterative refinement of mathematical models. This research seeks to develop a cost-effective and highly accurate diagnostic system for colorectal cancer CRC, with the intention of aiding clinicians in making timely and informed decisions (35). We utilized clinical outcomes from CRC patients to construct four machine learning models—LR, RF, NN, and SVM—to predict the impact of dietary fiber on postoperative immune function and inflammation. The NN model outperformed the others, achieving an AUC of 0.851 in training and 0.861 in testing. Consequently, the NN model was selected as the final model due to its superior performance.

Recently, many experts have used predictive models to assess the impact of variables on outcome indicators, achieved through variable importance scoring (36, 37). The higher the importance score of a variable, the more significant its impact on the model's prediction results. This study visualized weights using NN model, with the level of variable importance being positively correlated with the length of the bar in the bar chart. The results revealed that the top four variables were PCT, PAB, ALB, and IL-1, indicating that these variables have a significant impact on the prediction of CRC.

5 Conclusion

Early postoperative intake of dietary fiber is feasible for improving the condition of CRC patients. The LR, RF, NN, and SVM models developed in this study reliably diagnosed CRC, with the NN model showing the highest accuracy. Machine learning models offer considerable clinical value in diagnosing and predicting CRC and are anticipated to serve as supplementary treatment options for patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans and animals were approved by the Clinical Ethics Committee of Yantaishan Hospital, Shandong, China (Ethical review no. 2023027), and informed consent was obtained from each patient's guardian. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XJ: Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing – review & editing. LW: Methodology, Project administration, Resources, Software, Writing – original draft. PL: Investigation, Methodology, Project administration, Resources, Writing – original draft. JL: Data curation, Funding acquisition, Software, Validation, Writing – review & editing. WC: Formal analysis, Funding acquisition, Software, Supervision, Writing – review & editing.

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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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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Exploring the association between pro-inflammatory diets and chronic liver diseases: evidence from the UK Biobank

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Background: Chronic liver diseases (CLD) continue to pose a significant global burden, potentially exacerbated by pro-inflammatory diets. This study explores the relationship between the Dietary Inflammatory Index (DII), a measure of dietary inflammatory potential, and CLD risk.

Methods: Utilizing data from the UK Biobank cohort, we assessed the dietary information and calculated the DII for each participant. Cox proportional hazards models and Fine-Gray competing risk models were employed to evaluate the association between DII and CLD incidence, adjusting for potential confounders.

Results: Our analysis included 121,329 participants with a median follow-up of 604.43 weeks, during which 4,018 developed CLD. A higher DII, indicating a more inflammatory diet, was associated with a 16% increased risk of CLD [hazard ratio (HR) = 1.162, $P = 0.001$], with each unit increase in DII elevating the risk by 3.3% (HR: 1.033, $P < 0.001$). A significant linear association between DII and CLD was observed. Competing risk analyses, which accounted for cirrhosis, liver cancer, and death, supported these findings. Subgroup analyses confirmed the robustness of the DII's association across various demographic and lifestyle factors. Moreover, a higher DII was positively associated with the progression of CLD to cirrhosis. Sensitivity analyses, including energy-adjusted DII and typical dietary DII, reinforced our results. Additionally, adherence to anti-inflammatory dietary patterns, as indicated by higher Healthy Eating Index 2020 and Mediterranean Diet Score values, was inversely associated with CLD risk.

Conclusion: Our study highlights the potential benefits of adopting anti-inflammatory diets as a strategy for the prevention and management of CLD. Comprehensive dietary interventions may play a pivotal role in mitigating the global burden of CLD.

KEYWORDS

dietary inflammatory index, pro-inflammatory diet, dietary pattern, chronic liver diseases (CLD), UK Biobank

1 Introduction

Chronic liver diseases (CLD) remain a significant global health burden, responsible for ~2 million deaths annually, ranking as the 11th leading cause of death and the 15th leading cause of disability-associated life-years worldwide (1). Although recent progress in viral hepatitis prevention and treatment, such as hepatitis B and hepatitis C, the challenge remains substantial, particularly in developing countries (2). This issue is further compounded by the increasing prevalence of non-alcoholic fatty liver disease (NAFLD), now termed metabolic dysfunction-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD), driven by rising metabolic risk factors such as obesity and diabetes. These conditions are projected to more than double the incidence of advanced liver diseases by 2030, exacerbated by worrying trends in obesity among children and adolescents, which significantly heighten the likelihood of liver disease in later life (3). The economic impact is similarly profound, with liver disease incurring a cost of $32.5 billion in the United States in 2016 alone (1). These significant health and economic challenges necessitate coordinated global efforts to manage the burden of CLD and mitigate its growing impact worldwide.

CLD is intricately linked to the liver's role as the largest internal organ, pivotal in metabolic processes. Responsible for the metabolism of carbohydrates, fats, and proteins, as well as detoxification and hormone production, the liver's function is profoundly affected by diet (4). Diets high in free sugars, saturated fats, and excess calories can exacerbate fat accumulation in the liver, contributing to NAFLD. Intrahepatic triglyceride (IHTG) synthesis primarily relies on fatty acids in the liver, but it can also arise from non-lipid dietary sources, such as excessive free sugar intake. These substrates are converted into saturated fatty acids (SFAs) via hepatic *de novo* lipogenesis (5). A larger cohort study involving Chinese adults ($n = 4{,}365$) revealed that patients with NAFLD (diagnosed by ultrasonography) consumed a diet richer in carbohydrates and free sugars than participants without NAFLD (6). The consumption of free sugars, particularly fructose, has been linked to liver cancer development in another cohort study (7). Fructose has been implicated in the development of liver cancer, with high fructose intake shown to promote hepatocellular carcinoma (HCC) through the enhancement of O-GlcNAcylation mediated by microbiota-derived acetate in an HCC mouse model (8). Additionally, in a diethylnitrosamine (DEN)-induced liver tumor model, dietary fructose enhanced the proliferation, invasion, and tumorigenicity of hepatic progenitor cells, providing further mechanistic support for fructose's role in liver tumorigenesis (9). However, it is noted that some studies have yielded inconsistent results (10, 11). This inconsistency may be due to the diverse and complex dietary habits influenced by geographic, ethnic, and cultural differences.

Investigating overall dietary patterns, rather than individual foods, may provide deeper insights into the relationship between nutrition and the risk of CLD. The prevalent "Western dietary pattern" in modern society, characterized by desserts and processed meats, is a contributing factor to the rising incidence of CLD in recent years (1, 12). Pro-inflammatory diets, measured using the Dietary Inflammatory Index (DII) (13), have been linked to several chronic diseases (14–16). While several studies have assessed the association between DII and CLD risk, most have been limited by a focus on specific diseases, small sample sizes or cross-sectional designs (17–21). A recent study using data from the UK Biobank indicated that diets with high energy-adjusted DII (eDII) increased the risk of severe NAFLD [hazard ratio (HR): 1.19; 95% CI: 1.03–1.38] (22). On the other hand, CLD includes diverse conditions such as alcoholic liver disease, drug-induced liver injury (DILI), autoimmune liver disease, cirrhosis, and liver cancer. Given that inflammation is a shared pathological feature in CLD, the DII score may influence a broader range of liver conditions. However, the link between DII and the full spectrum of CLD remains unclear, highlighting the need for more comprehensive research to address this gap.

Therefore, we aim to investigate the relationship between the DII and the incidence of all types of CLD in a large, prospective, long-term follow-up cohort of UK Biobank, seeking to provide a more comprehensive understanding of how pro-inflammatory diets may influence overall liver health.

2 Methods

2.1 Study design and participants

This prospective cohort study used data from the UK Biobank, a large population-based study of ~500,000 individuals aged 37–73 years, recruited between 2006 and 2010 from 22 assessment centers across England, Scotland, and Wales (23). Participants provided informed consent, and ethical approval was granted by the North West Multi-Center Research Ethics Committee. At baseline, all participants visited an assessment center, where they provided information about their medical history and lifestyle, underwent a physical examination, and submitted urine and blood samples. Further details regarding the UK Biobank protocol are available online at http://www.ukbiobank.ac.uk.

2.2 DII calculation

Dietary intake was assessed using the Oxford WebQ, an online 24-h dietary recall questionnaire, which was administered to participants at different time points between February 2011 and April 2012. The Oxford WebQ captures information on the consumption of over 200 common food items and beverages, automatically generating estimates of energy and nutrient intake (24). The average nutrient intake across different time points was used in this study to calculate participants' DII. The validity of this questionnaire for nutritional assessment has been demonstrated in multiple prior clinical studies (19, 25). The DII is a scoring system developed to assess the inflammatory potential of an individual's diet based on a variety of food and nutrient components. In this study, the DII was calculated using 29 dietary parameters available from the UK Biobank dataset (Supplementary Table S1). Each component was weighted based on its known pro-inflammatory or anti-inflammatory effects, with reference to a global mean and

standard deviation (SD) obtained from the literature. For each dietary component, a *Z*-score was calculated by comparing an individual's intake to the global mean. Specifically, the global mean intake was subtracted from the individual's average intake, and the difference was divided by the global SD. This *Z*-score reflects how much the individual's intake deviates from the global average, standardized by the variation within the global population. The *Z*-scores were then converted to percentiles, ranging from −1 to 1, to ensure comparability with the global reference data. Next, each percentile score was multiplied by the component's inflammatory weight (based on its overall inflammatory effect) to calculate the score for each component. Finally, the DII for each individual was computed as the sum of the component-specific DII scores. Additionally, the eDII was calculated by normalizing nutrient intake using the density method (nutrient intake per 1,000 kcal of total energy). The remaining calculation steps followed the same process as the DII calculation (25).

2.3 Inclusion and exclusion criteria

In this research, an average of five 24-h dietary recalls was utilized, with data collected between April 2009 (the 1st instance) and June 2012 (the 4th instance), as detailed on the UK Biobank website (UKB category 100090). Participants from the UK Biobank who completed at least one online 24-h dietary recall questionnaire were included, with the start date determined by the completion date of the first questionnaire. The exclusion criteria were as follows: (1) participants who were missing vital nutrient component data, characteristic data, or personal lifestyle data; (2) participants with a history of CLD or malignant tumors, defined by self-reported medical conditions (UKB field IDs 20001 and 20002), and those diagnosed with CLD or a malignant tumor prior to the baseline; and (3) given the chronic nature of CLD, a 1-year landmark analysis was used to exclude participants who experienced relevant events within the first year of the study.

2.4 Outcome determination

The primary outcome of this study was the incidence of CLD, which includes conditions such as fatty liver disease, hepatitis, cirrhosis, liver fibrosis, and HCC. CLD cases were identified through linked hospital records (UKB category 2002) and cancer registries (UKB category 100092) data, using International Classification of Diseases (ICD-10) codes listed in the Supplementary Table S2. Incident cases were defined as those with a first diagnosis of CLD (UKB category 1712) during follow-up, and deaths of participants were captured through national death registries (UKB category 100093).

2.5 Baseline covariates and reclassification

Baseline covariates were collected via self-reported questionnaires and physical measurements from the UK Biobank database. These included age, sex, ethnicity, education, smoking and alcohol consumption status, physical activity levels, body mass index (BMI), blood pressure, and diabetes status. Socioeconomic status was measured using the Townsend deprivation index (TDI), which is derived from participants' residential postal codes and reflects local unemployment, home ownership, and overcrowding rates. Age was classified into younger or older group by the median age (58 years old); TDI was also divided into high or low by the median level (−2.3); Participants' educational qualifications (UKB field ID 6138) were reclassified into three broader categories: High, Median, and Low. The High Education category included participants who reported having a College or University degree (original code: 1). The Median Education category included those with intermediate qualifications such as Advanced Level/Advanced Subsidiary Level or equivalent (code 2), National Vocational Qualification, Higher National Diploma, or Higher National Certificate or equivalent (code 5), and Other professional qualifications such as nursing or teaching (code 6). The Low Education category comprised participants with Ordinary Level/General Certificate of Secondary Education or equivalent (code 3), Certificate of Secondary Education or equivalent (code 4), and those reporting None of the above (code 7), as well as individuals who selected Prefer not to answer (code 3); participants' blood pressure levels were reclassified into 4 categories based on systolic pressure (SP) and diastolic pressure (DP), following standard clinical guidelines. The categories were: Normal, Elevated, Stage 1 Hypertension, and Stage 2 Hypertension. Participants with an SP of <120 mmHg and a DP of <80 mmHg were classified as "Normal". Those with an SP between 120 and 129 mmHg and a DP of <80 mmHg were classified as "Elevated". Individuals were classified as "Stage 1 Hypertension" if they had an SP between 130 and 139 mmHg or a DP between 80 and 89 mmHg. Finally, those with an SP of 140 mmHg or higher, or a DP of 90 mmHg or higher, were classified as "Stage 2 Hypertension".

2.6 Statistical analyses

In the baseline characteristic comparison, categorical variables were presented as frequencies and proportions, while continuous variables were depicted as means with SDs or medians with interquartile ranges (IQR). The analysis of categorical variables employed the Pearson chi-square test, whereas continuous variables were compared using the Analysis of Variance (ANOVA) for normally distributed variables or the Kruskal-Wallis test for non-normally distributed data. Cox proportional hazards (PH) regression models were used to examine the association between DII and the risk of developing CLD. HRs and 95% confidence intervals (CIs) were calculated to estimate the risk of CLD across quartiles of DII. The models were adjusted for potential confounders, including age, sex, ethnicity, education, physical activity, BMI, smoking status, alcohol consumption, diabetes, and socioeconomic status. To evaluate a linear trend, the median of each quartile of the DII was treated as a continuous variable in each model. Additionally, restricted cubic splines were applied to assess potential non-linear associations between DII and CLD risk. The proportional hazards assumption was tested using Schoenfeld residuals. The PH assumption test was used to access the Cox

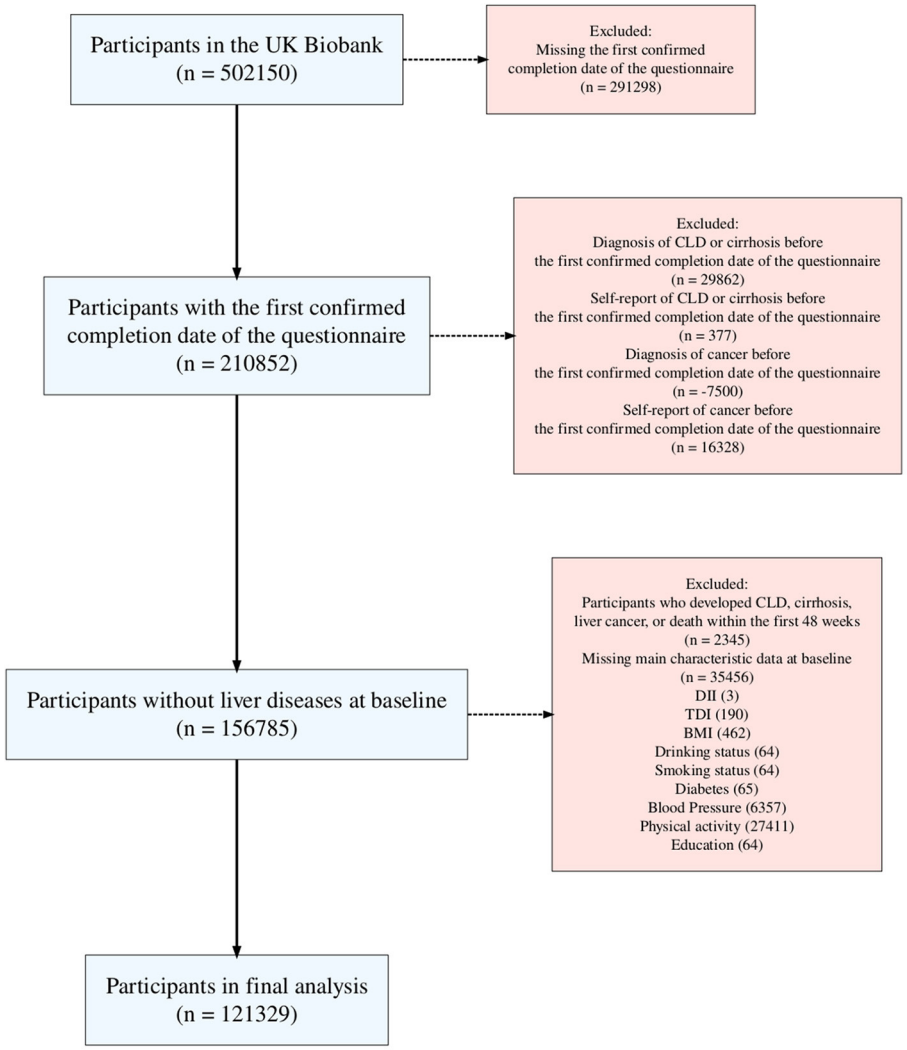

FIGURE 1
The flowchart of participant selection.

PH models confirming that HRs of each covariate should remain constant over time. For those models failed to pass the PH assumption test, the alternative accelerated failure time (AFT) models, which do not rely on the PH assumption test (26), were applied. Considering that the occurrences of cirrhosis, liver cancer and death were the competing events for CLD, the Fine-Gray models were used to calculate subdistribution HR (sHR) for further depicting the relationship between DII and CLD risk. To explore disease progression, participants who developed CLD were analyzed for cirrhosis or liver cancer risk, with the follow-up period defined as the time from CLD diagnosis to cirrhosis or liver cancer occurrence.

To validate the relationship between DII and CLD risk, subgroup analyses were performed for each category of covariables. Sensitivity analyses were also conducted, including the similar analysis with eDII, the association of DII and inflammation indexes, and the participant with typical dietary pattern (UKB field ID 100020) to reduce the potential changes in dietary patterns over time. Furthermore, two dietary pattern scoring system, including the healthy eating index 2020 (HEI-2020) (27) and the Mediterranean diet score (MEDS) (28), were calculated to investigate the link between pro-inflammation dietary and CLD (Supplementary Tables S3, S4). For all the above analyses, a *P*-value of <0.05 was considered statistically significant. All analyses in this study, including data management, statistical analysis, model construction, and graph plotting, were conducted using R statistical software (version 4.3.1; R Foundation Inc.; http://cran.r-project.org/).

3 Results

3.1 Characteristics of participants

A total of 121,329 participants were included in this study (Figure 1), with a median follow-up time of 604.43 (IQR 569.14–646) weeks. During the follow-up period, 4,018 participants developed CLD, including 1,168 (29.07%) with NAFLD, 131 with biliary liver disease, 172 with alcoholic disease, 73 with viral liver disease, 60 with autoimmune liver disease, and 19 with

DILI. Liver disease types with small case numbers, rare or less common liver diseases, and those that could not be classified under specific etiologies were grouped into the "Others" category. Table 1 presents the baseline characteristics of the participants in this study according to the quartiles of DII. Participants in the high DII group were more likely to be younger, female, and from areas with higher deprivation. They tended to have higher BMI, lower education levels, and were more likely to be current drinkers and smokers and less physically active. While differences in diabetes prevalence and blood pressure categories were statistically significant, the absolute differences were small.

3.2 DII and CLD risk

The analysis of the association between DII and CLD incidence (Table 2) revealed a significant correlation. Individuals with higher DII levels (Q4 vs. Q1) exhibited an increased risk of developing CLD (HR: 1.162; 95%CI: 1.065–1.268; $P = 0.001$) based on the Cox PH model (Model 3), after adjusting for various confounding factors such as age, sex, race, educational level, TDI, alcohol use, smoking, BMI, physical activity, blood pressure, and diabetes. When DII was treated as a continuous variable, the HR for CLD risk was 1.033 (95% CI: 1.017–1.050; $P < 0.001$), adjusted for the same factors. Furthermore, trend analysis indicated a significant positive linear association between DII and CLD risk (P for trend <0.001). Conversely, no statistically significant non-linear relationship was detected ($P = 0.148$), suggesting that the association between DII and CLD is predominantly linear (Figure 2A). To further explore this association, competing risk analyses were applied, considering cirrhosis, liver cancer and death as competing events. After adjustment for the aforementioned covariates (Model 3), the results were consistent with the Cox PH model: participants in the highest DII quartile exhibited an 14.5% higher risk of CLD compared to those in the lowest quartile (sHR = 1.145, 95% CI: 1.049–1.249, $P = 0.002$). Additionally, each unit increase in DII was associated with a 3.0% rise in CLD risk (sHR = 1.030, 95% CI: 1.013–1.047, $P = 0.001$).

In the subgroup analyses (Figure 3), the association between the DII score and the risk of CLD generally remained consistent across various categories, including sex (P for interaction = 0.334), physical activity (P for interaction = 0.349), smoking status (P for interaction = 0.456), drinking status (P for interaction = 0.402), ethnicity (P for interaction = 0.615), education level (P for interaction = 0.373), TDI (P for interaction = 0.126), age (P for interaction = 0.562), and diabetes status (P for interaction = 0.368), indicating no significant differences in the DII and CLD association within these subgroups. However, a significant interaction was observed with blood pressure (P for interaction = 0.034), where higher HR among those with Stage 1 and Stage 2 blood pressure suggest that the risk of CLD associated with higher DII scores may be more pronounced in individuals with elevated blood pressure levels, indicating a potential moderating effect of hypertension on this relationship.

To examine the influence of the DII on the progression of CLD to cirrhosis or liver cancer, a separate analysis was conducted on those 4,018 CLD patients. The analysis indicated that the DII score, assessed both as quartiles and a continuous variable, significantly correlate with the risk of cirrhosis development (highest vs. lowest quartile: HR = 1.583, 95% CI: 1.139–2.199, $P = 0.006$; continuous DII: HR = 1.110, 95% CI: 1.045–1.178, $P < 0.001$). For liver cancer, no significant association was found between DII and progression (Table 3; Figure 2B). These findings suggest that while DII may contribute to CLD and cirrhosis development, it does not appear to significantly influence progression to liver cancer in this cohort.

To further validate the association between the DII and CLD risk, several sensitivity analyses were conducted. The eDII showed similar associations with increased CLD risk (highest vs. lowest quartile: HR = 1.138, 95% CI: 1.042–1.244, $P = 0.004$; continuous eDII: HR = 1.036, 95% CI: 1.017–1.054, $P < 0.001$), supporting the robustness of primary findings (Supplementary Table S5, Model 3; Figure 2C). Additionally, analysis of a subset of participants reporting typical dietary intake revealed consistent results, demonstrating higher DII scores associated with increased CLD risk (Supplementary Table S5, Model 3; Figure 2E). Both eDII and DII from typical dietary presented a significant positive relationship with cirrhosis progression, but not with liver cancer in CLD (Table 3; Figures 2D, F). Significant yet weak positive correlations were observed between the DII and inflammatory biomarkers, including white blood cells (WBC: $r = 0.062$), neutrophils (NE: $r = 0.054$), and C-reactive protein (CRP: $r = 0.053$), with all P-values <0.05, suggesting that the DII effectively measures dietary inflammation. These sensitivity analyses collectively reinforce the link between higher dietary inflammatory potential and an increased CLD risk across different analytical approaches and subgroups.

3.3 Dietary pattern and CLD risk

After adjusting for multiple covariates, including age, sex, ethnicity, education, TDI, alcohol consumption, smoking history, BMI, physical activity, diabetes status, and blood pressure, both the HEI-2020 and the MEDS remained significantly associated with CLD risk. Specifically, individuals in the highest quartile of HEI-2020 had a significantly reduced risk of CLD compared to those in the lowest quartile (HR = 0.923, 95% CI: 0.860–0.992, $P = 0.016$), and each unit increase in the continuous HEI-2020 score was associated with a modest yet significant decrease in CLD risk (HR = 0.995, 95% CI: 0.992–0.998, $P = 0.002$) (Supplementary Table S6; Supplementary Figure 1A). Similarly, higher adherence to the Mediterranean diet, as measured by the MEDS, was linked to an reduced risk of CLD (HR = 0.961. 95% CI: 0.992–0.998, $P < 0.001$) (Supplementary Table S7; Supplementary Figure 1C). These results are consistent with the findings from the DII, highlighting the importance of overall dietary patterns in influencing CLD risk. Notably, only MEDS showed a significant negative link to cirrhosis development (Supplementary Figures 1B, D). Neither the HEI-2020 nor MEDS were significantly related to liver cancer (Table 3).

TABLE 1 Characteristics of Participants according to the quartiles of DII.

	Total (*n* = 121,329)	Q1 (*n* = 30,333)	Q2 (*n* = 30,332)	Q3 (*n* = 30,332)	Q4 (*n* = 30,332)	*P*
CLD						
Cases/participants	4,018/117,311	962/29,371	920/29,412	986/29,346	1,150/29,182	
Cirrhosis						
Cases/participants	296/121,033	62/30,271	55/30,277	82/30,250	97/30,235	
Liver cancer						
Cases/participants	185/121,144	54/30,279	35/30,297	43/30,289	53/30,279	
Follow-up (weeks)	604.43 (569.14, 646)	604.14 (568.29, 646.29)	604.29 (569.71, 645)	604.43 (569.86, 645)	604.57 (569.29, 647.57)	0.005
Age, *n* (%)						<0.001
Older	57,821 (48)	16,227 (53)	15,019 (50)	14,112 (47)	12,463 (41)	
Younger	63,508 (52)	14,106 (47)	15,313 (50)	16,220 (53)	17,869 (59)	
Sex, *n* (%)						<0.001
Female	63,575 (52)	14,828 (49)	15,463 (51)	16,066 (53)	17,218 (57)	
Male	57,754 (48)	15,505 (51)	14,869 (49)	14,266 (47)	13,114 (43)	
TDI, *n* (%)						<0.001
High	60,380 (50)	14,722 (49)	14,569 (48)	14,919 (49)	16,170 (53)	
Low	60,949 (50)	15,611 (51)	15,763 (52)	15,413 (51)	14,162 (47)	
Ethnicity, *n* (%)						<0.001
White	115,596 (95)	29,026 (96)	29,276 (97)	29,065 (96)	28,229 (93)	
Others	5,733 (5)	1,307 (4)	1,056 (3)	1,267 (4)	2,103 (7)	
BMI	26.3 (23.81, 29.34)	26.03 (23.59, 28.98)	26.1 (23.7, 29.03)	26.35 (23.9, 29.34)	26.76 (24.1, 29.97)	<0.001
Alcohol, *n* (%)						<0.001
Rare	3,797 (3)	858 (3)	774 (3)	873 (3)	1,292 (4)	
Previous	3,591 (3)	827 (3)	754 (2)	852 (3)	1,158 (4)	
Current	113,941 (94)	28,648 (94)	28,804 (95)	28,607 (94)	27,882 (92)	
Smoking, *n* (%)						<0.001
Rare	68,079 (56)	17,091 (56)	17,339 (57)	17,025 (56)	16,624 (55)	
Previous	43,751 (36)	11,395 (38)	11,019 (36)	10,955 (36)	10,382 (34)	
Current	9,499 (8)	1,847 (6)	1,974 (7)	2,352 (8)	3,326 (11)	
PA, *n* (%)						<0.001
No reach	21,702 (18)	4,088 (13)	5,072 (17)	5,911 (19)	6,631 (22)	
Reach	99,627 (82)	26,245 (87)	25,260 (83)	24,421 (81)	23,701 (78)	
Education, *n* (%)						<0.001
Low	27,360 (23)	6,214 (20)	6,018 (20)	6,797 (22)	8,331 (27)	
Median	40,983 (34)	9,975 (33)	9,958 (33)	10,413 (34)	10,637 (35)	
High	52,986 (44)	14,144 (47)	14,356 (47)	13,122 (43)	11,364 (37)	
BP, *n* (%)						<0.001
Normal	17,908 (15)	4,132 (14)	4,306 (14)	4,481 (15)	4,989 (16)	
Elevated	22,497 (19)	5,302 (17)	5,655 (19)	5,682 (19)	5,858 (19)	
Stage 1	45,474 (37)	11,714 (39)	11,534 (38)	11,274 (37)	10,952 (36)	
Stage 2	35,450 (29)	9,185 (30)	8,837 (29)	8,895 (29)	8,533 (28)	

(Continued)

TABLE 1 (Continued)

	Total (*n* = 121,329)	Q1 (*n* = 30,333)	Q2 (*n* = 30,332)	Q3 (*n* = 30,332)	Q4 (*n* = 30,332)	*P*
Diabetes, *n* (%)						<0.001
No	116,189 (96)	29,038 (96)	29,121 (96)	29,107 (96)	28,923 (95)	
Yes	5,140 (4)	1,295 (4)	1,211 (4)	1,225 (4)	1,409 (5)	

TDI, townsend deprivation index; PA, physical activity.

TABLE 2 Associations of DII and CLD risk.

Models	Q1	Q2	Q3	Q4	Continous	*P* for trend
Cox regression						
Model 1	1 (reference)	0.98 (0.895–1.073) 0.66	1.062 (0.971–1.161) 0.186	1.26 (1.156–1.374) < 0.001	1.051 (1.034–1.068) < 0.001	<0.001
Model 2	1 (reference)	0.97 (0.886–1.062) 0.511	1.025 (0.938–1.121) 0.58	1.16 (1.064–1.266) 0.001	1.033 (1.016–1.050) < 0.001	<0.001
Model 3	1 (reference)	0.971 (0.887–1.062) 0.517	1.027 (0.94–1.123) 0.554	1.162 (1.065–1.268) 0.001	1.033 (1.017–1.050) < 0.001	<0.001
Fine-gray						
Model 1	1 (reference)	0.976 (0.892–1.069) 0.6	1.049 (0.96–1.147) 0.29	1.229 (1.127–1.34) < 0.001	1.045 (1.028–1.063) < 0.001	/
Model 2	1 (reference)	0.968 (0.885–1.06) 0.49	1.017 (0.93–1.112) 0.71	1.139 (1.044–1.242) 0.004	1.028 (1.012–1.046) 0.001	/
Model 3	1 (reference)	0.97 (0.886–1.062) 0.51	1.02 (0.933–1.115) 0.66	1.145 (1.049–1.249) 0.002	1.030 (1.013–1.047) 0.001	/

Model 1, Adjusted for age, sex, ethnicity, education, and the Townsend Deprivation Index; Model 2, Further adjusted for drinking status, smoking status, body mass index, and physical activity in addition to the variables in Model 1; Model 3, Includes adjustments for all variables in Model 2, with additional consideration for diabetes and blood pressure status; Cox regression Model: the hazard ratios (HR) are reported; Fine-Gray Models: Adjustments are made for cirrhosis, liver cancer, and death, with subdistribution hazard ratios (sHR) reported; Data are presented as HR or sHR with 95% confidence intervals and the corresponding p-values.

4 Discussion

This study investigated the association between the DII and the risk of CLD in a large prospective cohort of 121,329 participants, followed for over 12 years. The primary findings demonstrated a significant positive correlation between higher DII scores and an elevated risk of CLD, with individuals in the highest DII quartile exhibiting a 16.2% greater risk compared to those in the lowest quartile. This relationship persisted across sociodemographic, lifestyle, and health-related subgroups. Competing risk analyses, which accounted for outcomes such as cirrhosis, liver cancer, and death, produced consistent results, reinforcing the sustained positive correlation between higher dietary inflammatory potential (as indicated by elevated DII scores) and increased CLD risk. Moreover, DII was positively associated with the progression of CLD to cirrhosis, but not to liver cancer. Sensitivity analyses, including models adjusted for total energy intake and typical dietary, further validated these findings. Overall, the study suggests that a more pro-inflammatory diet is associated with an increased risk of developing CLD, underscoring the potential role of dietary inflammation in liver health.

There is a close connection between the gut and the liver. The enterohepatic tissues are organized into multiple layers of physical, chemical, microbial, and immunological barriers that play a crucial role in maintaining intestinal homeostasis. These barriers serve to regulate the movement of intestinal antigens, microbial components, and microorganisms, thereby preventing their translocation and limiting their spread to other organs, particularly the liver. The concept of a Gut–Liver axis was put forward to emphasize the clinically relevant link between gut and liver diseases, initially to describe antibodies directed against intestinal microorganisms and food antigens in the circulation of patients with CLD (4, 29, 30). Once materials (including microorganisms and food antigens) cross the gut epithelium, various immune cells, including innate lymphoid cells, invariant T cells, and T cell subsets, interact with gut luminal contents and microbiota, helping regulate gut homeostasis and protective immune responses. Mononuclear phagocytes (e.g., macrophages and dendritic cells) play a crucial role in directly handling foreign material and producing antibodies, notably IgA, that affect gut antigen uptake and response (31, 32). In addition to the immune control conducted by phagocytes and antibodies, materials that evade direct immune regulation must still traverse the vascular endothelium before entering the circulatory system. The gut-vascular barrier (GVB) is crucial for preventing bacterial translocation from the intestine to the liver (33, 34). Disruption of this barrier has been linked to the pathogenesis of NAFLD (35), and liver metastasis in colorectal cancer (36). Certain gut luminal

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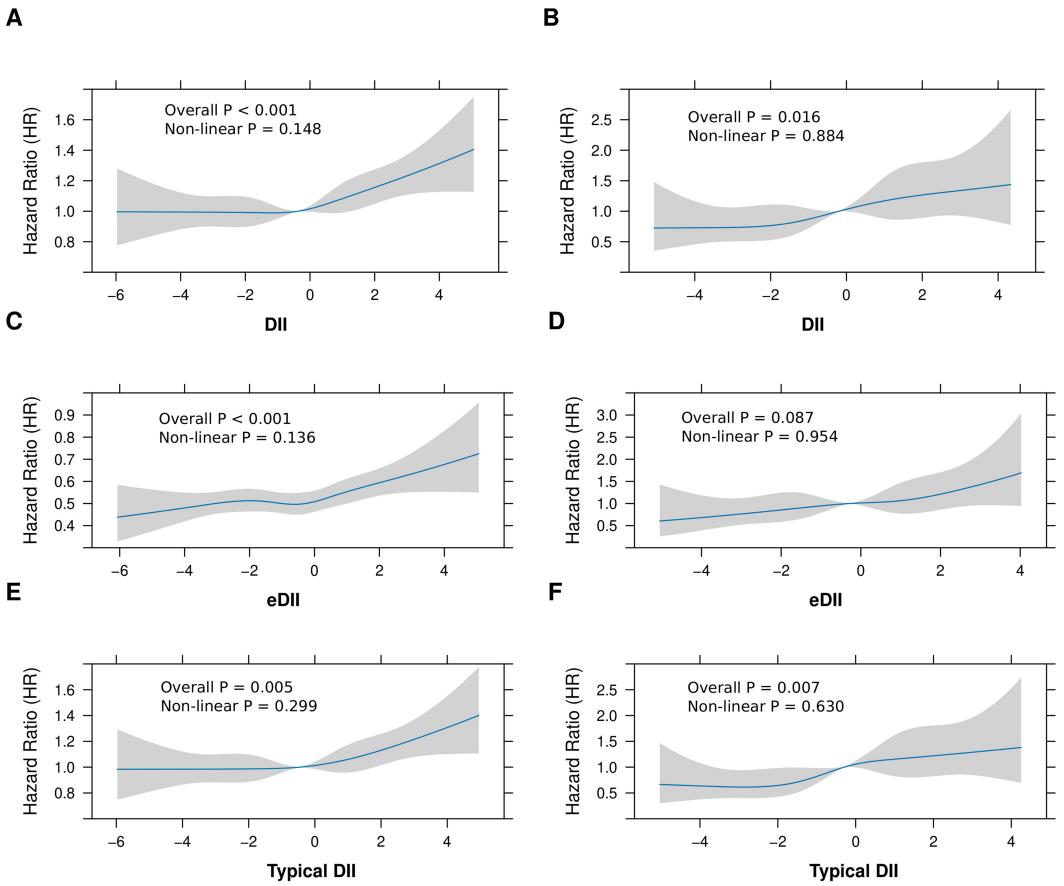

FIGURE 2
Non-linear associations between dietary inflammatory indices and risk of CLD and Cirrhosis. This figure illustrates the associations between dietary inflammatory indices (DII, eDII, and DII from typical dietary) and hazard ratios (HR) for CLD and cirrhosis. **(A, B)** Depict the relationships between DII and the risk of CLD **(A)** and cirrhosis **(B)**. Similarly, **(C, D)** present the associations for eDII with CLD and cirrhosis, respectively, while **(E, F)** show the effects of DII from typical dietary on the risks of CLD **(E)** and cirrhosis **(F)**. The *blue lines* represent the estimated HRs, with shaded regions denoting 95% confidence intervals. Statistical significance and deviations from linearity are evaluated using both overall and non-linear *P*-values.

contents, such as live commensal and pathogenic microorganisms, as well as hormones, cytokines, bacterial Pathogen-associated molecular patterns (PAMPs), and metabolites, can cross the gut barrier and enter the bloodstream, where they are transported to the liver via portal blood (37). The hepatic immune system, including Kupffer cells and dendritic cells, works similarly to its gut counterpart by trapping and processing antigens, thus preventing their spread throughout the body (38). Impairment of intestinal barrier could lead to progression of CLD by increasing hepatic inflammation, fibrosis, and portal hypertension, meanwhile further weakens intestinal barrier integrity and exacerbates the gut-liver axis dysregulation. In advanced stages of CLD, the rise in portal pressure and gut-derived systemic inflammation increases the risk of multiple organ failure, worsening complications and mortality (39).

The stability of the gut microbiota is critical to maintaining intestinal barrier function and preventing liver disease progression, including HCC, DILI, and viral hepatitis. In hepatocarcinogenesis, disrupted gut microbiota and translocated lipopolysaccharides (LPS) promote cancer development through the Toll-like receptor (TLR4)-dependent pathways (40). Genetically driven dysbiosis, such as a deficiency in NACHT, LRR, and PYD domains protein 6 (NLRP6), exacerbates steatohepatitis (41), while obesity-induced dysbiosis promotes HCC formation through the cytotoxic effects of secondary bile acids (42, 43). Gut-derived bile acids influence hepatic immune surveillance by recruiting natural killer T cells (44, 45). In NAFLD-related HCC, dysbiosis is linked to systemic inflammation, with fecal microbiota from these patients suppressing T cell responses, and microbial DNA in cirrhotic livers correlating with immune exhaustion (42). In DILI, interventions targeting gut dysbiosis, such as LPS-binding peptides or probiotics, have shown efficacy in ameliorating conditions like acetaminophen-induced injury (46). Long-term use of antibiotics or proton pump inhibitors, indicative of gut dysbiosis, is associated with a higher risk of acute liver failure (47). In the context of viral hepatitis, the gut microbiota plays a critical role in facilitating hepatitis B virus clearance via TLR4 signaling pathways (48). Additionally, in hepatitis C virus-related cirrhosis, disruption in gut fatty acid metabolism was observed (49). Generally, dietary patterns could influence gut microbial

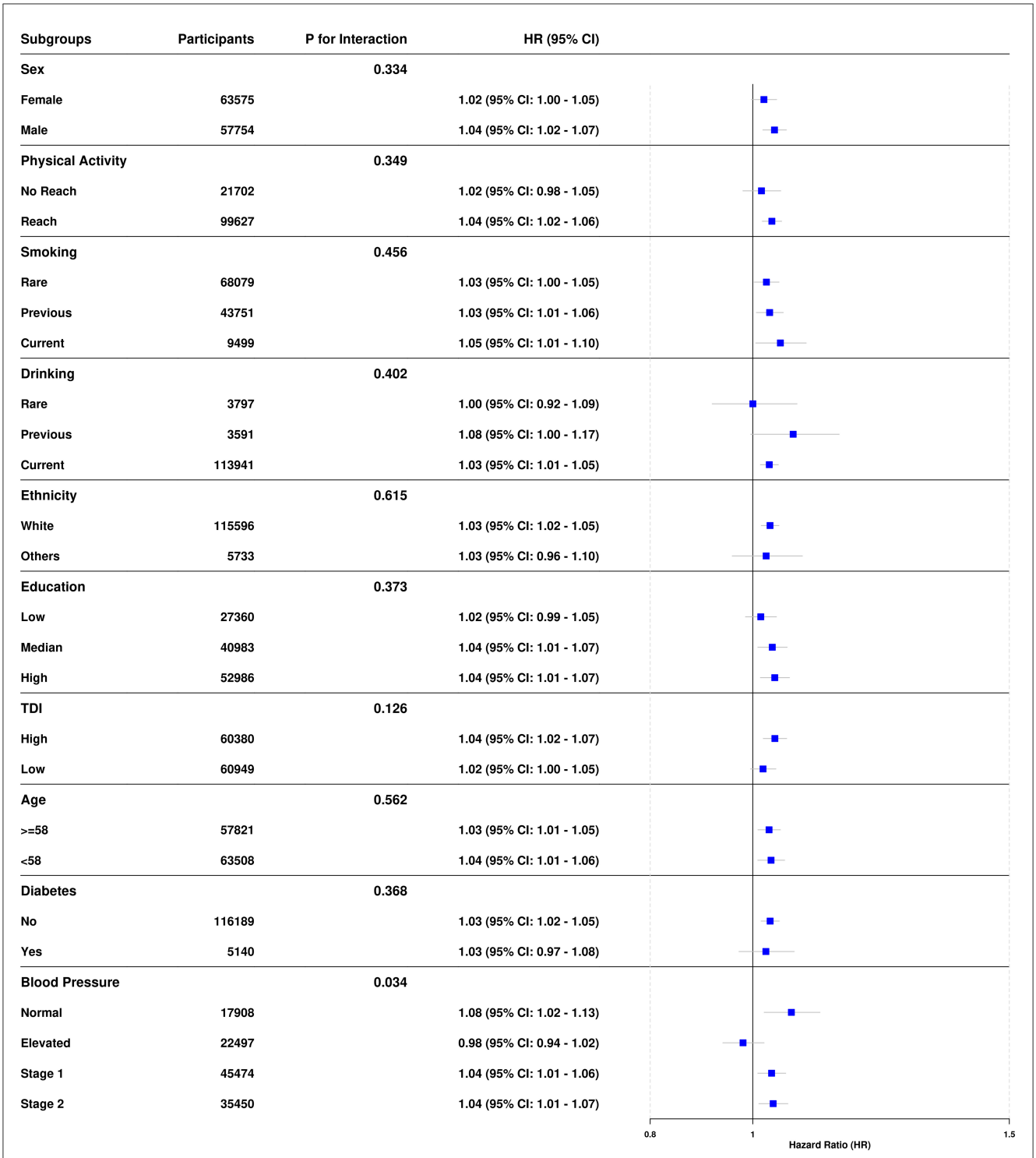

FIGURE 3
Associations between DII and CLD risk across subgroups. Hazard ratios (HR) and 95% confidence intervals for various subgroups, adjusted for potential confounders including age, sex, ethnicity, education level, Townsend deprivation index, smoking, drinking, physical activity, diabetes status, and blood pressure categories. Interaction *P*-values assess heterogeneity across subgroups. A reference HR of 1.0 indicates no effect, with deviations suggesting increased or decreased risk within each subgroup. Subgroup comparisons are visualized using forest plots for clarity.

stability, highlighting the importance of nutrition in managing liver diseases.

Common dietary pattern assessments include the DII, HEI-2020, and MEDS (50). The DII specifically measures the inflammatory potential of the diet, which evaluates how food components and nutrients either promote or alleviate inflammation. In our study, a higher DII, reflecting a more pro-inflammatory diet, was linked with significantly increased

10.3389/fnut.2025.1537855

TABLE 3 Associations between dietary inflammatory indices and dietary patterns with risk of cirrhosis and liver cancer.

Models	Q1	Q2	Q3	Q4	Continous	*P* for trend
DII						
Cirrhosis	1 (reference)	1.074 (0.743–1.552) 0.705	1.374 (0.980–1.927) 0.065	1.583 (1.139–2.199) 0.006	1.110 (1.045–1.178) < 0.001	0.001
*Liver cancer	1 (reference)	0.551 (0.267–1.137) 0.069	0.714 (0.387–1.318) 0.275	0.905 (0.497–1.648) 0.735	0.997 (0.885–1.123) 0.954	0.513
eDII						
Cirrhosis	1 (reference)	1.190 (0.825–1.716) 0.352	1.176 (0.828–1.671) 0.365	1.486 (1.062–2.079) 0.021	1.010 (1.028–1.176) 0.006	0.017
*Liver cancer	1 (reference)	1.123 (0.599–2.107) 0.716	1.167 (0.633–2.153) 0.624	0.878 (0.448–1.721) 0.690	0.974 (0.860–1.102) 0.682	0.402
DII (typical dietary)						
Cirrhosis	1 (reference)	1.178 (0.753–1.841) 0.474	1.846 (1.248–2.730) 0.002	1.902 (1.291–2.801) 0.001	1.134 (1.059–1.214) < 0.001	0.001
*Liver cancer	1 (reference)	0.600 (0.370–0.973) 0.038	0.870 (0.568–1.334) 0.524	0.840 (0.545–1.294) 0.430	1.003 (0.924–1.090) 0.936	0.78
HEI2020						
Cirrhosis	1 (reference)	0.749 (0.544–1.032) 0.077	0.939 (0.689–1.280) 0.689	0.874 (0.631–1.211) 0.419	0.994 (0.982–1.006) 0.317	0.524
*Liver cancer	1 (reference)	0.647 (0.429–0.978) 0.039	0.970 (0.662–1.421) 0.875	0.720 (0.471–1.103) 0.131	0.993 (0.977–1.008) 0.346	0.3
MEDS						
Cirrhosis	/	/	/	/	0.896 (0.827–0.971) 0.007	/
*Liver cancer	/	/	/	/	1.007 (0.856–1.153) 0.931	/

*Accelerated Failure Time model; DII, dietary inflammatort index; eDII; energy-adjuested DII; HEI2020, Healthy Eating Index 2020; MEDS, Mediterranean Diet Score; All models were adjusted for age, sex, ethnicity, education, the Townsend Deprivation Index, drinking status, smoking status, body mass index, physical activity, diabetes and blood pressure status; The Cox regression model reports hazard ratios (HRs), indicating effects on hazard; The AFT models provide adjusted time ratios from model coefficients, reflecting time scaling; Data include 95% confidence intervals and *P*-values.

CLD risk. This aligns with the growing evidence around chronic inflammation being a key driver in liver disease progression, including NAFLD and cirrhosis (51, 52). Diets rich in pro-inflammatory components, such as processed foods, refined carbohydrates, and unhealthy fats, may exacerbate liver damage over time through inflammatory pathways (5). In contrast, the HEI-2020 was developed to capture adherence to overall dietary quality as recommended by the Dietary Guidelines for Americans. A higher HEI-2020 score reflects a diet rich in fruits, vegetables, whole grains, lean proteins, and low in added sugars, sodium, and saturated fats (27). Importantly, our results showed that participants in the highest quartile of HEI-2020 scores had significantly lower risks of CLD compared to those in the lowest quartile, and each unit increase in HEI-2020 as a continuous variable was similarly associated with a lower risk of CLD. These findings suggest that overall diet quality, characterized by nutrient-dense and anti-inflammatory foods, offers protection against the development of liver diseases. The MEDS, which measures adherence to the Mediterranean diet, a diet high in plant foods, healthy fats like olive oil, moderate to low in animal products, and low in saturated fats, was also significantly associated with a lower CLD risk. Our results showed that each unit increase in the MEDS corresponded to a reduction in CLD risk. The Mediterranean diet is known for its anti-inflammatory and antioxidant-rich properties, which may delay or prevent liver damage. Our results align with the previous studies in steatotic liver disease and cirrhosis (53, 54). In addition, Guo et al. utilized food frequency questionnaire (FFQ) data from UKB and applied principal component analysis (PCA) to study the effect of dietary patterns on NAFLD, cirrhosis, and liver cancer, showing that the participants with high tertile of Western dietary pattern score had and higher risk of NAFLD, cirrhosis and liver cancer compared with those with low tertile, with increased risk 18%, 21%, and 24%, respectively (12). However, DII is widely validated by researchers, which is considered a relatively reliable and universal tool to assess dietary patterns. A recent meta-analysis, including 10 studies with 242,006 participants from the U.S., UK, Portugal, and Iran, indicated that individuals with higher DII had a significantly increased risk of fatty liver disease (OR 1.63; 95% CI 1.08–2.45) and liver fibrosis (OR 1.15; 95% CI 1.09–1.21) compared to those with lower DII (51). The current study, however, used dietary data from the Oxford WebQ to calculate DII and evaluate its association with CLD risk. Unlike FFQ data, which is designed to capture habitual dietary intake over a long-term

period (55), the Oxford WebQ assesses dietary intake over the previous 24 h, allowing for a more accurate estimation of daily food consumption.

Our findings suggest that a pro-inflammatory dietary pattern is associated with a higher risk of CLD, providing further insight into diet's role in liver disease prevention. However, our study did not identify a significant association between the DII and liver cancer, which diverges from the results of a previous prospective multi-center study conducted in the United States, involving 582 participants over a 4-year follow-up period (56). This discrepancy may be attributed to the heterogeneity in tumor development mechanisms, including environmental and genetic factors. Furthermore, variations in participant numbers and follow-up duration could also account for the differences observed between the previous study and our research. Previous study investigating the relationship between diet and liver cancer has also reported similarly null association (10). However, several limitations of this study should be noted: (1) CLD diagnoses were primarily based on participants' hospitalization records, potentially underrepresenting mild or asymptomatic cases that did not seek medical care. (2) The relatively small number of CLD cases may limit the statistical power of the survival models, warranting a cautious interpretation of the results. (3) Baseline exclusion of CLD was partially based on self-reported data, possibly introducing selection bias, although this was mitigated by employing a 1-year landmark analysis. (4) DILI is one of the most common forms of CLD. Due to the wide variety of hepatotoxic substances or drugs linked to DILI, as well as significant inter-individual variability in susceptibility, this study did not include hepatotoxic agents or medications as covariates in the analysis of DII. This could influence the reliability of the results. (5) DII calculations were based on 29 food/nutrient components available in the UK Biobank database, fewer than the 45 components recommended for the original DII assessment, but previous studies have demonstrated that 29–30 components are sufficient to assess dietary inflammatory potential. (6) The UK Biobank participants are predominantly British European and in middle age, possibly limiting the generalizability of the findings to more diverse populations. Therefore, prospective multi-centers studies should be conducted in different countries and ethnic groups in the future.

5 Conclusion

In conclusion, our study utilizing data from a large prospective cohort demonstrated that participants following a pro-inflammatory dietary pattern had a significantly higher risk of CLD and an elevated risk of cirrhosis progression among those with CLD. These findings suggest the potential benefits of adhering to an anti-inflammatory diet, which may play a crucial role in both the prevention and management of CLD.

Data availability statement

The data used in this study were obtained from the UK Biobank and are subject to licensing restrictions, making them unavailable for public access. These data were utilized under license specifically for this study. However, they can be provided by the authors upon reasonable request and with the approval of the UK Biobank. Similarly, the R code employed in this study is available from the corresponding authors upon reasonable request.

Ethics statement

The studies involving humans were approved by the North West Multi-Center Research Ethics Committee (16/NW/0274). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LP: Data curation, Formal analysis, Funding acquisition, Investigation, Software, Writing – original draft. ZX: Data curation, Formal analysis, Investigation, Software, Writing – review & editing. YL: Investigation, Writing – review & editing. GC: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. HG: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing. SL: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

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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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2025.1537855/full#supplementary-material

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Correlation between liver fibrosis in non-alcoholic fatty liver disease and insulin resistance indicators: a cross-sectional study from NHANES 2017–2020

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide, with liver fibrosis (LF) being a crucial pathological feature in the progression of NAFLD. Insulin resistance (IR) is believed to play an important role in the pathogenesis of NAFLD and the development of LF. This study aims to explore the relationship between various IR indicators and LF in patients with NAFLD.

Methods: This study utilized data from the National Health and Nutrition Examination Survey 2017-2020 cycles. Liver steatosis and fibrosis were assessed using liver ultrasound transient elastography. To assess the association between multiple IR indicators and LF, the study methodology included univariate and multivariate logistic regression, as well as restricted cubic spline (RCS) analysis. Subsequently, we used multivariate logistic regression to develop and validate a predictive model for LF, and evaluated the model's performance using the area under the curve (AUC) and calibration curve.

Results: A total of 904 patients were included in the final analysis. Among these NAFLD patients, 153 (16.92%) had LF. Compared to non-LF patients, LF patients had significantly higher body mass index (BMI), waist circumference (WC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), HbA1c, and fasting blood glucose (FBG) levels (all $p < 0.05$). Analysis of IR indicators showed that LF patients had significantly higher levels of TyG, TyG-WHtR, TyG-BMI, TyG-WC, TyG-GGT, METS-IR, and HOMA-IR (all $p < 0.05$). After adjusting for covariates, TyG-WHtR remained an independent risk factor (OR=2.69; 95% CI: 2.08-3.47), indicating a strong correlation with LF. The developed nomogram, incorporating AST, TyG, TyG-BMI, and diabetes, showed an AUC of 0.809 (95% CI: 0.771-0.847), indicating good predictive performance for LF in NAFLD patients.

Conclusions: This study confirms that a significant association between various IR and LF in NAFLD patients, and the developed nomogram provides a practical tool for early risk assessment. These findings underscore the clinical value of incorporating IR indices into routine practice to identify high-risk patients, enabling timely interventions to prevent fibrosis progression and improve outcomes.

KEYWORDS

non-alcoholic fatty liver disease, liver fibrosis, insulin resistance, logistic regression, TyG-WHtR

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the excessive accumulation of fat in the liver in the absence of significant alcohol consumption. It is often regarded as the hepatic manifestation of metabolic syndrome and is commonly associated with metabolic disorders such as obesity, type 2 diabetes, and hyperlipidemia (1). In recent years, the incidence of NAFLD has increased, surpassing that of viral hepatitis to become the predominant chronic liver disease globally (2). The pathogenesis of NAFLD is complex and ranges from simple fatty liver, characterized by excess fat in the liver without significant inflammation or fibrosis, to non-alcoholic steatohepatitis (NASH), which not only involves fat accumulation but also accompanies liver cell inflammation and damage, ultimately leading to liver fibrosis (LF) (3). LF is a key pathological feature in the progression of NAFLD and a major risk factor for the development of cirrhosis and hepatocellular carcinoma. In recent years, an increasing number of studies have focused on the epidemiology of LF caused by NAFLD, with results indicating that the prevalence of LF significantly increases with the severity of NAFLD (4, 5). Therefore, it is crucial to promptly identify the risk factors for LF in patients with NAFLD.

Insulin resistance (IR) is a well-recognized factor in the pathogenesis of NAFLD and plays a critical role in its progression. IR leads to an imbalance in lipid metabolism, promoting hepatic fat accumulation and contributing to liver inflammation and fibrosis (6). Given the close relationship between IR and NAFLD, indicators of IR, such as fasting blood glucose (FBG), fasting insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR), have been widely used as biomarkers to assess metabolic dysfunction in patients with NAFLD (7, 8). In addition to traditional markers of IR, the triglyceride-glucose index (TyG) has drawn increasing attention in recent years. The TyG index is a calculated measure based on fasting triglycerides and FBG. Due to its simplicity, ease of availability, and strong correlation with IR, it has been widely utilized for assessing IR and cardiovascular disease risk (9, 10). Moreover, the indicators combining TyG with body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR) further enhance the assessment of an individual's metabolic status and have been shown to be closely associated with the presence and severity of NAFLD (11). Although the association between NAFLD and IR is well-established, the exact relationship between various IR indicators (including the TyG index) and the degree of LF in NAFLD remains unclear. Most previous studies have primarily focused on the presence of NAFLD and its progression to NASH, with comparatively less attention given to the specific correlation between these IR indicators and the degree of hepatic fibrosis in NAFLD patients (12, 13). A deeper exploration of the association between the TyG index and HOMA-IR with LF in NAFLD patients will enhance our understanding of the metabolic mechanisms underlying the disease and provide new insights for early risk assessment.

Histopathological examination of liver biopsy specimens has long been considered the gold standard for diagnosing NAFLD and LF. Nonetheless, this method presents several limitations, including its invasive nature, low acceptability, and high cost (14). In recent years, liver ultrasound transient elastography (LUTE) has emerged as an accurate and non-invasive technique for assessing the degree of steatosis and fibrosis in patients with NAFLD (15). A meta-analysis found that LUTE exhibits good sensitivity and specificity for LF, with sensitivity and specificity values of 0.79 and 0.78, respectively (16). Previous research has focused on developing non-invasive diagnostic methods for LF. Several studies have developed serological models based on biochemical markers and clinical information to predict LF, including the fibrosis-4 index, aspartate aminotransferase (AST) to platelet ratio, AST to alanine aminotransferase (ALT) ratio, Forns index, and BARD score (17–19). However, when these scoring systems are used to predict LF in NAFLD patients, they do not include metabolic indicators such as the TyG index. The lack of these key metabolic markers may reduce the accuracy of the models, failing to fully reflect the fibrosis risk caused by NAFLD.

In our study, we aim to utilize data from the National Health and Nutrition Examination Survey (NHANES) database to assess NAFLD and LF using LUTE. We will then explore the correlation between LF and various IR indicators in NAFLD patients.

Additionally, we will attempt to develop a predictive model for NAFLD-related LF based on these metabolic indicators. This study will provide valuable insights into the potential role of IR in the progression of LF and help identify key markers for early risk stratification and management, thereby enabling a more accurate prediction of fibrosis risk in NAFLD patients.

2 Materials and methods

2.1 Study design and participants

The NHANES is a complex, multistage, cross-sectional survey conducted every two years to assess the health and nutritional status of adults in the United States. This study utilized NHANES data from the 2017 to March 2020 cycles, with a total sample size of 15,560 individuals. The following participants were excluded: individuals under 18 years of age (n=5,867), those with excessive alcohol consumption (more than 3 drinks per day for men or more than 2 drinks per day for women, n=2,877), individuals with viral hepatitis (including those positive for hepatitis B surface antigen or hepatitis virus RNA, n=560), individuals with a history of autoimmune hepatitis or other liver diseases (n=24), individuals lacking LUTE data (n=1,206), and individuals missing covariate data (including BMI, FBG, WC, high-density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), ALT, AST, diabetes, and hypertension, n=2,967). Additionally, patients with non-NAFLD (n=1,155) were excluded. In the final analysis, 904 participants with NAFLD were included. A detailed flowchart is shown in Figure 1. The specific original data can be found in the Supplementary Materials. The NHANES study protocol received approval from the National Center for Health Statistics Research Ethics Review Board, and all participants were fully informed and provided written consent in compliance with the ethical guidelines.

2.2 Definition of NAFLD and LF

The definition of NAFLD and LF was primarily determined using LUTE, which provided liver stiffness measurements (LSM), and simultaneously measured the ultrasound attenuation associated with liver steatosis, recorded as the controlled attenuation parameter (CAP). Specifically, CAP≥274 dB/m was used to define NAFLD, and participants with LSM ≥ 8.2 kPa were defined as having LF (20).

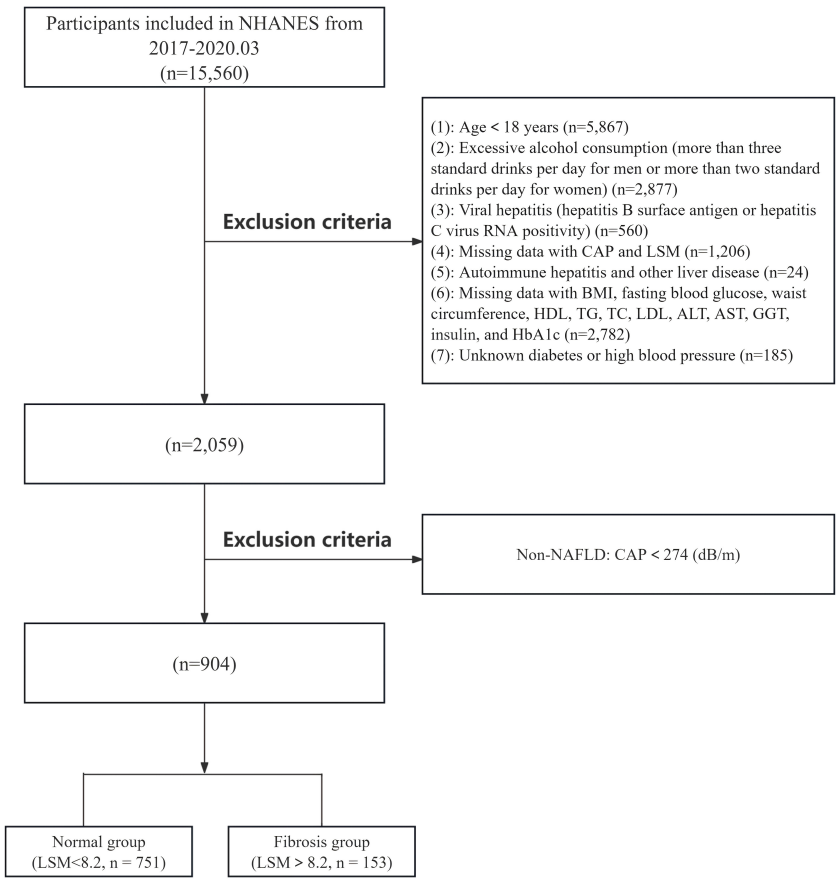

FIGURE 1
Flowchart of inclusion and exclusion criteria for NAFLD patients in the NHANES database. NAFLD, non-alcoholic fatty liver disease.

2.3 Definitions of IR index

The different IR indices were calculated by the following equations (21–25):

$$\text{WHtR} = \text{WC (cm)} / \text{height (cm)}$$

$$\text{TyG} = \ln[(\text{TG (mg/dL)} \times \text{FPG (mg/dL)})/2]$$

$$\text{TyG} - \text{WC} = \text{TyG} \times \text{WC}$$

$$\text{TyG} - \text{BMI} = \text{TyG} \times \text{BMI}$$

$$\text{TyG} - \text{WHtR} = \text{TyG} \times \text{WHtR}$$

$$\text{TyG} - \text{GGT} = \text{TyG} \times \text{GGT}$$

$$\text{METS} - \text{IR} = \ln[(2 \times \text{FPG (mg/dL)}) + \text{TG (mg/dL)}] \times \text{BMI} / \ln(\text{HDL (mg/dL)})$$

$$\text{HOMA} - \text{IR} = (\text{FPG (mg/dL)} \times \text{fasting insulin } (\mu\text{U/mL})) / 22.5$$

2.4 Covariates

In our study, we identified several potential factors associated with LF in NAFLD patients, known as covariates, including variables such as ALT, AST, BMI, and WC, which have been previously reported to be related to the occurrence of LF (26, 27). To control for the influence of these confounding factors on our study results, we implemented covariate adjustments in our statistical models to minimize potential bias. Specifically, our analytical approach included adjustments for the following covariates: demographic characteristics (age, gender, BMI, WC), laboratory indicators (ALT, AST, TC, TG, HDL, LDL, and FBG), and underlying diseases (self-reported physician-diagnosed hypertension or diabetes, and current use of antihypertensive or antidiabetic medications as indicators of hypertension or diabetes). These standardized interviews and questionnaires were administered by trained healthcare professionals.

2.5 Statistical analysis

The baseline characteristics of all included patients were stratified based on the occurrence of LF. Non-normally distributed variables were presented as interquartile ranges and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as percentages and compared using the chi-square test. To investigate the relationship between various factors and LF in patients with NAFLD, we initially conducted a univariate logistic regression analysis and visualized the results using a forest plot, which presented the odds ratio (OR) along with their corresponding 95% confidence interval (CI) for each factor. Subsequently, we constructed four multivariate logistic regression models to further assess the independent associations between each IR indicator and LF. The OR and their 95% CI for all models were calculated by exponentiating the regression coefficients, with adjustments for potential confounding factors incorporated in the multivariate models (28). Additionally, the study group used restricted cubic spline (RCS) plots to visualize the linear relationship between IR indicators and LF in NAFLD patients more intuitively (29, 30). The value of IR indicators for diagnosing disease prognosis was assessed using receiver operating characteristic (ROC) curves (31). Based on the multivariate logistic regression models, a nomogram was constructed using statistically significant indicators to diagnose the disease (32). To evaluate the validity of the nomogram, the area under the ROC curve (AUC) and calibration curves were calculated. All statistical analyses were performed using R software (version 4.3.0) and STATA 17.0 (64-bit), with a two-sided P-value <0.05 considered statistically significant.

3 Results

3.1 Demographic and clinical characteristics of participants

The study cohort included a total of 904 NAFLD patients based on inclusion and exclusion criteria, comprising 751 non-LF patients (83.08%) and 153 LF patients (16.92%). Table 1 compares the baseline clinical characteristics between patients with LF and those without. Analysis revealed that compared to non-LF patients, LF patients had significantly higher BMI (median: 31.10 [27.90, 35.45] vs. 37.30 [32.50, 43.80], $p < 0.001$) and WC (median: 106.70 [98.00, 116.50] vs. 122.20 [112.50, 131.70], $p < 0.001$). Analysis of laboratory markers indicated that LF patients had significantly higher levels of ALT, AST, GGT, HbA1c, and FBG, while TC, HDL, and LDL were significantly lower compared to non-LF patients (all $p < 0.05$). Analysis of various IR indicators showed that LF patients had significantly higher TyG, TyG-WHtR, TyG-BMI, TyG-WC, TyG-GGT, METS-IR, and HOMA-IR compared to non-LF patients (all $p < 0.05$). Among patients with comorbidities, those with diabetes or hypertension were significantly more likely to develop LF than those without (all $p < 0.05$). For other variables, no significant differences were found in sex or age between the two groups (all $p > 0.05$).

3.2 Analysis of factors contributing to LF in NAFLD patients

To identify the factors associated with the progression of NAFLD to LF, we performed a univariate logistic regression analysis, as shown in the forest plot in Figure 2. The analysis revealed that IR indicators, including TyG, TyG-WHtR, TyG-BMI, TyG-WC, TyG-GGT, METS-IR, and HOMA-IR, were significantly associated with the development of LF in NAFLD patients (all $p < 0.05$). Among these, TyG (OR=1.44; 95% CI: 1.10-1.88, $p < 0.01$)

10.3389/fendo.2025.1514093

TABLE 1 Baseline demographic and clinical characteristics of participating patients.

Characteristics	Total No. (%)	Non-Fibrosis No. (%)	Fibrosis No. (%)	*p*-value
Total	904	751 (83.08)	153 (16.92)	
Gender, n(%)				0.322
Male	493 (54.5%)	404 (53.8%)	89 (58.2%)	
Female	411 (45.5%)	347 (46.2%)	64 (41.8%)	
Age (years)	57.00(43.00, 67.00)	57.00(42.00, 67.00)	59.00(47.00, 68.00)	0.220
BMI	32.00(28.30, 37.20)	31.10(27.90, 35.45)	37.30(32.50, 43.80)	<0.001
WC	108.85(99.70, 119.82)	106.70(98.00, 116.50)	122.20(112.50, 131.70)	<0.001
ALT (U/L)	21.00(15.00, 30.00)	20.00(15.00, 28.00)	25.00(16.00, 40.00)	<0.001
AST (U/L)	19.00(16.00, 24.00)	19.00(16.00, 24.00)	21.00(17.00, 29.00)	<0.001
GGT (U/L)	24.00(18.00, 35.00)	24.00(17.00, 33.00)	29.00(21.00, 54.00)	<0.001
TC (mmol/L)	4.63(4.01, 5.38)	4.65(4.09, 5.48)	4.42(3.83, 5.04)	<0.001
TG (mmol/L)	1.29(0.90, 1.79)	1.28(0.89, 1.79)	1.32(0.95, 1.77)	0.592
HDL (mmol/L)	1.16(1.01, 1.40)	1.19(1.01, 1.42)	1.14(0.98, 1.32)	0.044
LDL (mmol/L)	2.74(2.20, 3.14)	2.82(2.25, 3.46)	2.46(1.99, 3.13)	<0.001
HbA1c (%)	5.80(5.50, 6.50)	5.80(5.40, 6.25)	6.20(5.70, 7.60)	<0.001
FBG (mmol/L)	6.11(5.61, 7.11)	6.05(5.55, 6.94)	6.72(5.94, 8.55)	<0.001
TyG	8.77(8.39, 9.23)	8.72(8.37, 9.21)	8.93(8.51, 9.26)	0.005
TyG-WHtR	5.78(5.15, 6.46)	5.60(5.07, 6.23)	6.51(5.90, 7.20)	<0.001
TyG-BMI	282.69(246.32, 333.08)	274.72(241.95, 316.41)	336.98(292.24, 385.13)	<0.001
TyG-WC	961.78(857.68, 1074.51)	939.90(846.10, 1046.47)	1091.97(997.30, 1199.98)	<0.001
TyG-GGT	215.80(154.08, 309.09)	208.09(147.84, 293.14)	266.58(183.50, 502.69)	<0.001
METS-IR	49.57(42.89, 58.82)	48.00(41.88, 56.52)	59.07(51.54, 68.38)	<0.001
HOMA-IR	4.41(2.75, 7.22)	4.05(2.59, 6.15)	7.48(4.29, 11.05)	<0.001
Diabetes, n(%)				<0.001
YES	254 (28.1%)	176 (23.4%)	78 (51.0%)	
NO	650 (71.9%)	575 (76.6%)	75 (49.0%)	
Hypertension, n(%)				<0.001
YES	445 (49.2%)	349 (46.5%)	96 (62.7%)	
NO	459 (50.8%)	402 (53.5%)	57 (37.3%)	

BMI, Body Mass Index; WC, Waist Circumference; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; TC, Total Cholesterol; TG, Triglycerides; HDL, High-Density Lipoprotein Cholesterol; LDL, Low-Density Lipoprotein Cholesterol; FBG, Fasting Blood Glucose; TyG, Triglyceride-Glucose Index; TyG-WHtR, Triglyceride-Glucose Index to Waist-to-Height Ratio; TyG-BMI, Triglyceride-Glucose Index to Body Mass Index; TyG-WC, Triglyceride-Glucose Index to Waist Circumference; TyG-GGT, Triglyceride-Glucose Index to Gamma-Glutamyl Transferase; METS-IR, Metabolic Score for Insulin Resistance; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

and TyG-WHtR (OR=2.75; 95% CI: 2.23-3.40, $p < 0.01$) showed the most notable associations. Additionally, we found that a higher BMI increased the likelihood of LF in NAFLD patients (OR=1.13; 95% CI: 1.10-1.16, $p < 0.01$). Similarly, higher values of WC, ALT, AST, GGT, TC, LDL, HbA1c, and FBG were associated with an increased risk of LF, with LDL (OR=1.46; 95% CI: 1.19-1.72, $p < 0.01$) and HbA1c (OR=1.36; 95% CI: 1.22-1.52, $p < 0.01$) being particularly relevant. Analysis of comorbidities showed that patients with hypertension (OR=3.40; 95% CI: 2.37-4.87, $p < 0.01$) and diabetes (OR=1.94; 95% CI: 1.36-2.77, $p < 0.01$) were more likely to develop LF.

Based on the results of the logistic regression analysis, an RCS plot was constructed to visualize the relationship between different IR indicators and the risk of LF in NAFLD patients (Figure 3). It was found that TyG, TyG-WHtR, TyG-BMI, TyG-WC, TyG-GGT, METS-IR, and HOMA-IR were positively correlated with the development of LF in NAFLD patients, further validating the above findings.

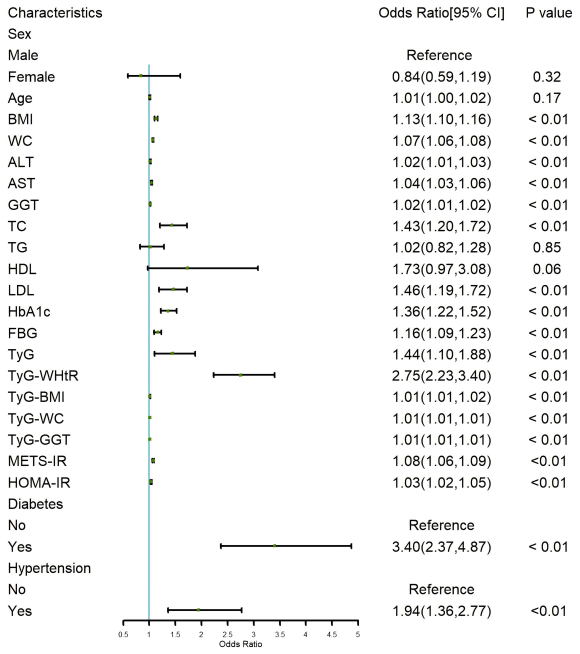

FIGURE 2
Forest plot of univariate logistic regression for risk factors of LF in NAFLD Patients. LF, liver fibrosis; NAFLD, non-alcoholic fatty liver disease.

3.3 Analysis of independent risk factors for LF in NAFLD patients

We constructed four multivariate logistic regression models to further determine whether IR is an independent risk factor for LF in NAFLD patients (Table 2). In Model 1, which was unadjusted for any variables, the analysis showed that TyG (OR=1.44; 95% CI: 1.10-1.88, $p < 0.01$) and TyG-WHtR (OR=2.75; 95% CI: 2.23-3.40, $p < 0.01$) were most significantly associated with LF, consistent with the univariate logistic regression results, while the other IR indicators were also statistically significant but had weaker associations. After adjusting for age and sex in Model 2, the analysis revealed that the association for TyG-WHtR became more pronounced (OR=3.01; 95% CI: 2.40-3.76, $p < 0.01$), while the other indicators showed no significant changes compared to Model 1. In Model 3, we further adjusted for comorbidities such as diabetes and hypertension based on Model 2. It was found that the association of TyG-WHtR (OR=2.66; 95% CI: 2.10-3.37, $p < 0.01$) weakened significantly, and TyG lost statistical significance after adjustment, while the other indicators remained largely unchanged and were all statistically significant (all $p < 0.05$). Subsequently, in Model 4, additional adjustments for BMI, WC, ALT, AST, GGT, TC, LDL, HbA1c, and FBG were made based on Model 3. It was found that TyG-GGT and METS-IR were no longer statistically significant, while the other indicators remained significantly associated, with TyG (OR=1.23; 95% CI: 1.09-1.45, $p = 0.04$) and TyG-WHtR (OR=2.69; 95% CI: 2.08-3.47, $p < 0.01$) being the most notable. Through the construction of these different models, we found that TyG, TyG-WHtR, TyG-BMI, TyG-WC, and HOMA-IR were independent risk factors for the development of LF in NAFLD patients, with strong associations.

3.4 Predictive value of multiple IR indicators for diagnosing LF in NAFLD patients

To further explore the clinical diagnostic predictive value of various IR indicators for LF in NAFLD patients, an ROC curve diagnostic analysis model was established (Figure 4). The analysis revealed that TyG and TyG-GGT did not show good predictive value for disease diagnosis, with AUCs of 0.572 and 0.647, respectively, both below 0.7. The remaining indicators—TyG-WHtR, TyG-BMI, TyG-WC, METS-IR, and HOMA-IR—all had AUCs greater than 0.7, with TyG-WC having the highest AUC of 0.764, indicating relatively high predictive value for diagnosis.

3.5 Construction of predictive model for LF in NAFLD patients and evaluation of its effectiveness

We performed a multivariate logistic regression analysis on all indicators to construct the diagnostic model. From 24 variables, we identified four variables as risk factors for predicting LF: AST, TyG, TyG-BMI, and diabetes. The risk scores for each factor included in the nomogram are shown in Figure 5, with higher scores indicating a higher risk of LF. To evaluate the performance of the constructed nomogram, we plotted the ROC curve and the calibration curve in Figure 6. The ROC curve shows an AUC of 0.809 (95% CI:0.771 –0.847), and the calibration curve closely approximates the diagonal, indicating considerable consistency and high calibration quality. These results suggest that the nomogram has good predictive performance.

4 Discussion

This study systematically investigated the relationship between various IR indices and LF among patients with NAFLD. Our results demonstrated that indices such as TyG-WHtR, TyG-BMI, and HOMA-IR were significantly associated with the occurrence of LF in NAFLD patients, with TyG-WHtR emerging as the most prominent predictor. Even after adjusting for a range of covariates, TyG-WHtR maintained a strong correlation, suggesting its potential utility as an independent predictor of LF in this patient population. Additionally, we developed a predictive model for LF in NAFLD patients, which highlights the potential of these indices to be incorporated into routine clinical practice for risk assessment and early intervention.

The findings of this study have significant implications for clinical practice, particularly in the early identification and management of LF in patients with NAFLD. The strong association between TyG-WHtR and LF underscores its potential as a simple, non-invasive tool for risk stratification in routine

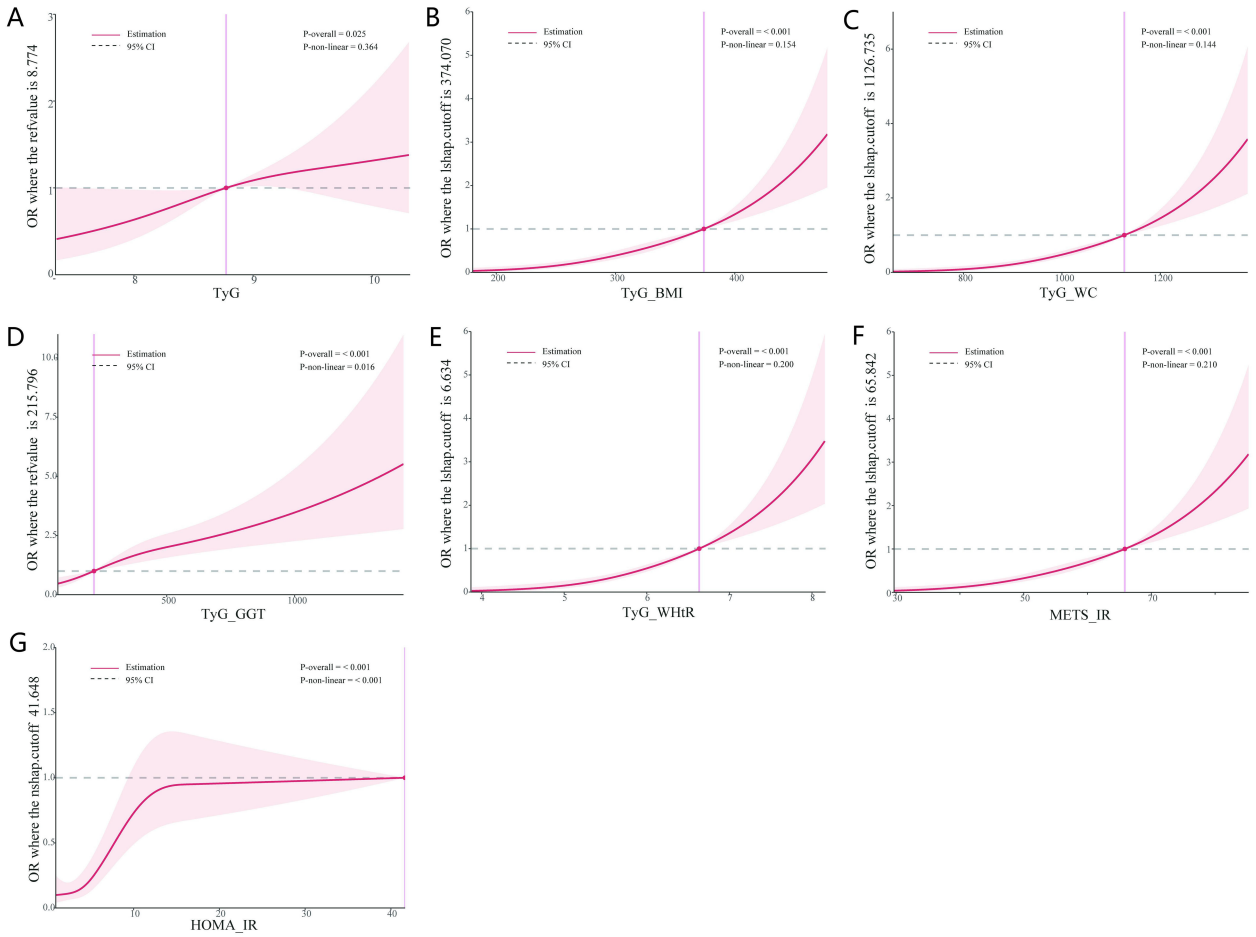

FIGURE 3
Dose-response between IR indices and the risk of LF. **(A)** Dose-response between TyG and the risk of LF. **(B)** Dose-response between TyG-BMI and the risk of LF. **(C)** Dose-response between TyG-WC and the risk of LF. **(D)** Dose-response between TyG-GGT and the risk of LF. **(E)** Dose-response between TyG-WHtR and the risk of LF. **(F)** Dose-response between METS-IR and the risk of LF. **(G)** Dose-response between HOMA-IR and the risk of LF. IR, insulin resistance; LF, liver fibrosis.

clinical settings. The TyG-WHtR is a non-invasive, simple, low-cost index that only tests TG, FPG, WC, and height to produce results. Compared to liver puncture biopsy, CT, and MRI, TyG-WHtR offers a superior cost-benefit ratio. By incorporating TyG-WHtR and other IR indices into standard metabolic assessments, clinicians can more effectively identify high-risk patients who may benefit from closer monitoring or early intervention. The predictive nomogram developed in this study, which integrates AST, TyG, TyG-BMI, and diabetes, provides a practical and accessible tool for individualized risk assessment. This approach is particularly valuable in resource-limited settings where advanced diagnostic tools may not be readily available. Clinicians can use this nomogram to estimate fibrosis risk using readily available clinical data, enabling targeted therapies such as lifestyle modifications, weight management, and insulin-sensitizing treatments to slow or prevent fibrosis progression (33, 34). These findings advocate for the integration of IR indices into routine clinical practice to enhance early detection, risk assessment, and personalized management of NAFLD-related fibrosis.

Our findings emphasize that obesity, as reflected by higher BMI and WC, and other metabolic factors, such as increased ALT, AST, GGT, and HbA1c levels, were more prevalent in NAFLD patients with LF compared to those without. The liver, an essential organ for metabolic processes, regulates the metabolism of both lipids and glucose. Chiang et al. reported that increased obesity and IR significantly contribute to the progression from NASH to fibrosis through the development of a profibrotic environment in the liver (35). Additionally, Koppe et al. reported that IR leads to widespread metabolic disturbances, resulting in a net effect of TG accumulation in the liver. Some patients may develop hepatocellular injury and LF, which can progress to cirrhosis (36). In comparison to previous research, Khamseh et al. identified TyG-WC, TyG-BMI, and TyG-WHtR as the best predictors of metabolic-associated fatty liver disease (37). Although their study did not establish a clear relationship between these indicators and LF, our research further confirms this link. We found that several IR markers, particularly TyG-WHtR, TyG-BMI, and HOMA-IR, were significantly elevated in LF patients, indicating that metabolic dysfunction plays a central role in the pathogenesis of the disease.

TABLE 2 Multivariate logistic regression models assessing IR as an independent risk factor for LF in NAFLD patients.

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI), *p*-value	OR (95% CI), *p*-value	OR (95% CI), *p*-value	OR (95% CI), *p*-value
TyG	1.44(1.10,1.88)< 0.01	1.44(1.09–1.91)< 0.01	1.02(0.75–1.37) 0.91	1.23(1.09–1.45) 0.04
TyG-WHtR	2.75(2.23,3.40)< 0.01	3.01(2.40–3.76)< 0.01	2.66(2.10–3.37)< 0.01	2.69(2.08–3.47)< 0.01
TyG-BMI	1.01(1.01,1.02)< 0.01	1.02(1.01–1.02)< 0.01	1.01(1.01,1.01)< 0.01	1.01(1.01,1.01) 0.02
TyG-WC	1.01(1.01,1.01)< 0.01	1.01(1.01,1.01)< 0.01	1.01(1.01,1.00)< 0.01	1.01(1.01,1.01) 0.02
TyG-GGT	1.01(1.01,1.01)< 0.01	1.01(1.01,1.02)< 0.01	1.01(1.01,1.02)< 0.01	0.99(0.98,1.01) 0.82
METS-IR	1.08(1.06,1.09)< 0.01	1.08(1.06,1.10)< 0.01	1.07(1.06,1.09)< 0.01	0.95(0.90,1.01) 0.06
HOMA-IR	1.03(1.02,1.05)< 0.01	1.03(1.01,1.05)< 0.01	1.02(1.01,1.04)< 0.01	1.01(1.01,1.02)< 0.01

Model 1 was a non-adjusted model.
Model 2 was adjusted for age (years), gender and race.
Model 3 was adjusted for the same parameters as Model 2 with additional adjustments for hypertension (No or Yes) and diabetes (No or Yes).
Model 4 was adjusted for the same parameters as Model 3 with additional adjustments for BMI、WC、ALT、AST、GGT、TC、LDL、HbA1c、FBG.
OR, odds ratio; 95% CI, 95% confidence interval.
IR, insulin resistance; LF, liver fibrosis; NAFLD, non-alcoholic fatty liver disease.

IR indices are not only widely applied in metabolic diseases such as type 2 diabetes and obesity but are also used in other conditions, including cardiovascular diseases, chronic kidney disease, and polycystic ovary syndrome, where they have also been shown to predict adverse outcomes (38–41). Several studies have demonstrated that IR triggers lipotoxic pathways in the liver, leading to an accumulation of toxic lipid species such as ceramides and diacylglycerol, which further exacerbate liver injury and fibrogenesis (42–44). TyG-WHtR showed a significant correlation with LF in this study. High levels of TyG-WHtR indicate severe visceral fat accumulation, which is a key factor in the progression of LF (45). This relationship is particularly significant in the context of NAFLD, where visceral fat plays a crucial role in metabolic dysfunction. The accumulation of visceral fat is linked to various metabolic complications, including increased liver fat content, which can exacerbate liver inflammation and fibrosis (46). Therefore, TyG-WHtR can serve as an independent predictor of LF risk in NAFLD patients, with potential clinical utility.

In recent years, the TyG index has been increasingly applied in liver diseases, especially in predicting the progression of NAFLD, showing a significant association with NAFLD and LF (37, 47). To better evaluate the combined effects of IR and obesity, TyG-BMI

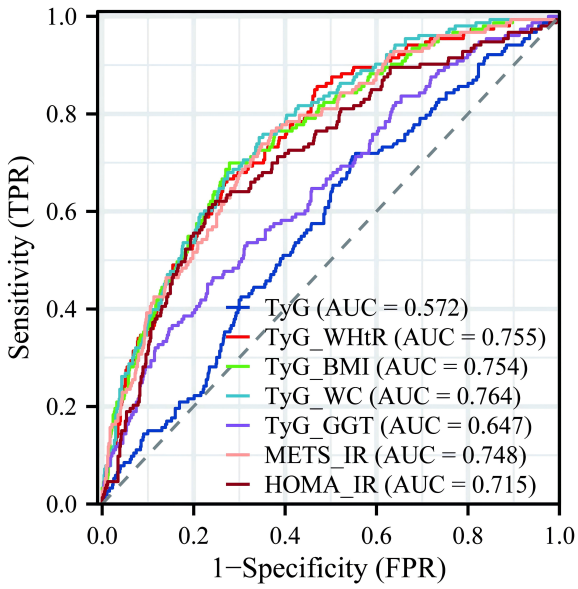

FIGURE 4
Predictive value of multiple IR indicators for diagnosing LF. IR, insulin resistance; LF, liver fibrosis.

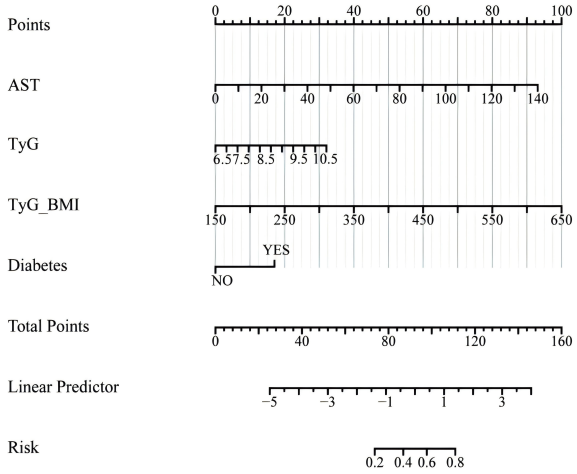

FIGURE 5
Nomogram for predicting the risk of LF. LF, liver fibrosis.

integrates BMI, which reflects overall body weight status, making it more advantageous in assessing metabolic risk (22, 48). Our study found that TyG-BMI levels were significantly elevated in LF patients, highlighting the core role of the synergy between obesity and IR in LF progression. Compared to single IR indicators, TyG-BMI provides a more comprehensive assessment of metabolic risk, offering important insights for early identification and intervention of LF. Additionally, in our study, we found that TyG-GGT is not an independent risk factor for LF in NAFLD patients. In contrast, Lei Jin et al. suggested that TyG-GGT has strong predictive accuracy for advanced LF in overweight or obese patients (25). However, their study was limited by a small sample size, a retrospective design that did not fully control for confounding factors, and a lack of strong statistical significance. Additionally, both METS-IR and HOMA-IR are strongly associated with LF, reflecting the relationship between IR and metabolic syndrome. Consistent with previous studies, our findings show that these indicators have strong predictive power for LF in NAFLD patients (49–51). Additionally, HOMA-IR is considered an independent predictor of advanced LF in non-diabetic NAFLD patients (50). It accelerates fibrosis progression by promoting liver fat accumulation, inflammatory responses, and hepatic stellate cell activation (52). Therefore, METS-IR and HOMA-IR can serve as effective tools in clinical practice for assessing the risk of fibrosis in NAFLD patients. In addition to our findings, several studies from China have also reported a strong association between IR and the progression of NAFLD, as well as its correlation with fibrosis staging (47, 53). By integrating these findings, our study contributes to a growing body of evidence that underscores the clinical utility of IR indices in predicting LF risk in NAFLD patients.

This study has several notable strengths. First, it focuses on a specific population of NAFLD patients with LF, making the results more targeted and clinically relevant, thereby providing important insights for the management of this high-risk group. Second, we systematically employed various analytical methods, including

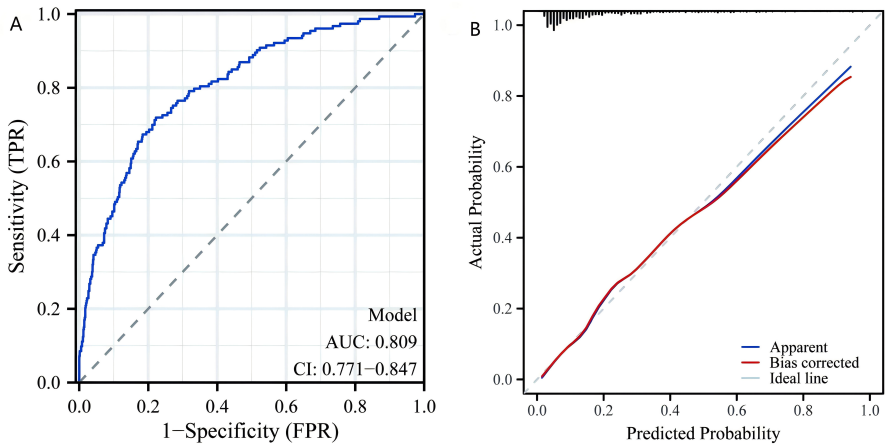

FIGURE 6
Nomogram model validation. **(A)** Receiver operating characteristic curve for evaluating the discriminative ability of the predictive model. **(B)** Calibration plot for assessing the agreement between predicted probabilities and actual outcomes of LF. LF, liver fibrosis.

logistic regression and RCS, to comprehensively evaluate the relationship between multiple IR indices and LF, clarifying the predictive value of these indices. Finally, we developed a LF prediction model based on multivariable logistic regression and constructed a nomogram, providing a scientific and effective tool for early risk identification and individualized intervention in clinical practice, with high practical value.

Despite providing further evidence of the close relationship between IR and LF in NAFLD patients, our study has several limitations that warrant discussion. First, as this study is based on cross-sectional data, we cannot establish a causal relationship between IR and LF. Longitudinal studies are therefore needed to verify the causal role of IR in the progression of NAFLD. Second, the relatively small sample size and the fact that our cohort was limited to the U.S. population may limit the external validity of the findings, particularly across different ethnicities and regions. Future research should include larger cohorts from diverse populations to validate the applicability and predictive value of these IR indices in a broader context. Additionally, our study mainly focused on epidemiological associations and lacked an in-depth exploration of the underlying molecular mechanisms. Thus, future basic research should aim to elucidate how IR promotes LF through specific cellular signaling pathways, providing theoretical support for targeted interventions.

5 Conclusion

In summary, this study identifies TyG-WHtR, TyG-BMI, and other IR indices as independent predictors of LF in NAFLD patients, highlighting their clinical utility in early risk stratification. These findings underscore the importance of integrating metabolic indicators into routine clinical practice to enhance early detection and intervention. The predictive nomogram developed in this study offers a practical, non-invasive tool for clinicians to identify high-risk patients. By focusing on metabolic risk factors, clinicians can implement targeted therapies —such as lifestyle modifications and insulin-sensitizing treatments —to slow or prevent fibrosis progression, ultimately improving long-term patient outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

BY: Conceptualization, Data curation, Methodology, Writing – original draft. MG: Methodology, Software, Writing – original draft. XZ: Data curation, Resources, Validation, Writing – original draft. YL: Methodology, Writing – original draft. RL: Conceptualization, Writing – original draft. HM: Resources, Supervision, Validation, Writing – review & editing. YW: Supervision, Writing – review & editing.

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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.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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The effect of replacing grains with quinoa on cardiometabolic risk factors and liver function in patients with non-alcoholic fatty liver: a randomized-controlled clinical trial

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Purpose: Quinoa is a food containing dietary fiber and various phytochemicals with high nutritional value, which has a structure similar to whole grains. This randomized controlled trial aimed to assess the effect of substituting grains with quinoa on cardiovascular risk factors and liver function in individuals with Non-alcoholic fatty liver disease (NAFLD).

Methods: Forty-six participants were randomly assigned to either a control group, which maintained their regular grain-based diet, or an intervention group, where grains were replaced with quinoa for 12 weeks. Participants in the quinoa group were instructed to substitute grains with quinoa during lunch for 12 weeks. The primary outcome was to assess the changes in the Controlled Attenuation Parameter (CAP) score between the intervention and control groups. Secondary outcomes included the difference in cardiometabolic risk factors and liver function between the two groups.

Results: Following 12 weeks of intervention with quinoa, a significant reduction in weight, and waist circumferences (WC) were observed compared to the control group (p value < 0.05). Furthermore, even after adjustment for weight change, there was a significant reduction in CAP score, serum levels of low-density lipoprotein cholesterol (LDL-C), and an improvement in homeostatic model assessment for insulin resistance (HOMA-IR) in the quinoa group compared to the control group after the 12 weeks (p value < 0.05). However, no significant changes were observed in other measured parameters, including liver enzymes, fibroscan, fasting plasma glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and inflammatory factors.

Conclusion: This study demonstrated that replacing grains with quinoa led to a significant improvement in the CAP score, HOMA-IR, and LDL-C in individuals with NAFLD, regardless of any weight changes. Thus, incorporating quinoa—a plentiful and low-cost source of bioactive compounds—into the diets of NAFLS patients as a staple food could improve several cardiometabolic risk factors in these individuals.

Clinical Trial Registration: IRCT20100524004010N37.

KEYWORDS

quinoa, NAFLD, liver function, lipid profile, randomized controlled trial, cardiovascular disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent liver diseases in the world. NAFLD includes a wide range of pathological conditions, from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH). Simple hepatic steatosis is characterized by a high accumulation of triglycerides (TG) in more than 5% of liver weight/volume, while NASH involves liver cell inflammation and destruction that can progress to cirrhosis and hepatocellular carcinoma (1). The worldwide prevalence of NAFLD is estimated at 25%, with this number steadily rising due to the obesity epidemic (2). NAFLD often co-occurs with metabolic syndrome manifestations in the liver, such as dyslipidemia, insulin resistance, obesity, and hypertension (3). Pathological factors like insulin resistance, lipid metabolism dysfunction, oxidative stress, inflammation, apoptosis, and fibrosis are closely associated with NAFLD (4). This condition is recognized as a leading cause of mortality from liver diseases (5).

The main risk factors associated with this condition involve a diet rich in fat, excessive consumption of simple sugar, and consuming large meals close to bedtime (2). Treatment strategies for managing NAFLD include a combination of pharmacological and non-pharmacological approaches. Lifestyle modifications, maintaining healthy dietary habits, weight reduction for overweight individuals, and consistent physical activity are among the most successful interventions for NAFLD (6, 7). Studies have indicated that a diet high in antioxidants can be an effective treatment for NAFLD (8).

Quinoa, scientifically known as *Chenopodium quinoa*, has gained significant popularity in European, African, and North American countries in recent times (9). It is recognized as a valuable source of phytochemicals with antioxidant properties, including flavonoids, phenolic acids, and fat-soluble vitamins (10). Quinoa boasts a higher quantity and quality of protein compared to other grains and is gluten-free, easily digestible, and rich in protein content (11). Additionally, it has a low glycemic index, an optimal omega-6 to omega-3 ratio, 10% dietary fiber, and is abundant in vitamins such as riboflavin, folic acid, and thiamine, surpassing rice in these nutrients (11, 12). Its nutritional and biological characteristics have led to its designation as "one of the grains of the 21st century," with documented beneficial effects on obesity, cancer, diabetes, immune regulation, and cholesterol reduction (13). Research suggests that the favorable properties of quinoa may influence various metabolic factors, potentially benefiting individuals with conditions like obesity and type 2 diabetes (14). Additionally, another study involving quinoa in a high-fat diet in rats showed improvement in hepatic steatosis, oxidative stress, and inflammatory responses, along with reduced levels of non-esterified fatty acids in the liver and adipose tissue (15). Therefore, it seems that all these beneficial factors in quinoa may have positive health effects on many metabolic factors. Some evidence and human studies on obese individuals and those with type 2 diabetes indicate the potentially beneficial effects of quinoa on metabolic factors involved in the pathogenesis of NAFLD disease (16–18). Animal studies have indicated that quinoa consumption can lower total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), liver TG, liver enzymes aspartate transaminase (AST) and alanine transaminase (ALT), and malondialdehyde levels, as well as mitigate liver damage (19, 20).

While human studies investigating the effects of quinoa on NAFLD patients are lacking, existing research on other populations has yielded conflicting results. This study aims to investigate the effects of quinoa consumption on cardiovascular risk factors and liver function in individuals with NAFLD.

Materials and methods

Participants and study design

This is a randomized controlled trial (RCT). This RCT was registered in the Iranian Registry of Clinical Trials (IRCT) (code: IRCT20100524004010N37).[1] The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study. At the commencement of the trial, written informed consent was obtained from all subjects.

Of the participants who attended the clinic Gastroenterology and Hepatology at hospitals affiliated with Shahid Beheshti University of Medical Sciences, Tehran, from July 23, 2023, to October 25, 2023. A total of 115 NAFLD subjects were screened. Diagnosis of NAFLD was performed according to the criteria of the American Gastroenterology Association (21), including evidence of liver steatosis based on liver elastography (grade 1 to 3 fatty liver) and a Controlled Attenuation Parameter (CAP) score of more than 263. Eligible participants had a clinical diagnosis of NAFLD, were aged 18–50 years, and had a body mass index (BMI) of more than 25 kg/m^2. Exclusion criteria included dietary changes due to a specific disease, weight loss of more than 5% in the last 6 months, kidney and/or liver disease (such as Wilson disease, autoimmune liver disease, hemochromatosis, viral infections, or alcoholic fatty liver), cardiovascular disease, diabetes, malignancy, thyroid disorder, autoimmune disease, and the use of hepatotoxic drugs (such as methotrexate, amiodarone, tamoxifen, nifedipine, corticosteroids, valproate, and antiviral drugs), history of smoking, drug abuse, using dietary supplements, and history of quinoa allergy.

Randomization and allocation concealment

Permuted block randomization sequences (six participants per block) were created by the randomization website.[2] Participants were assigned randomly (1:1 ratio) to either the quinoa group or the control group. The recruitment of participants is shown in Figure 1.

1 https://en.irct.ir/trial/37196

2 http://www.randomization.com

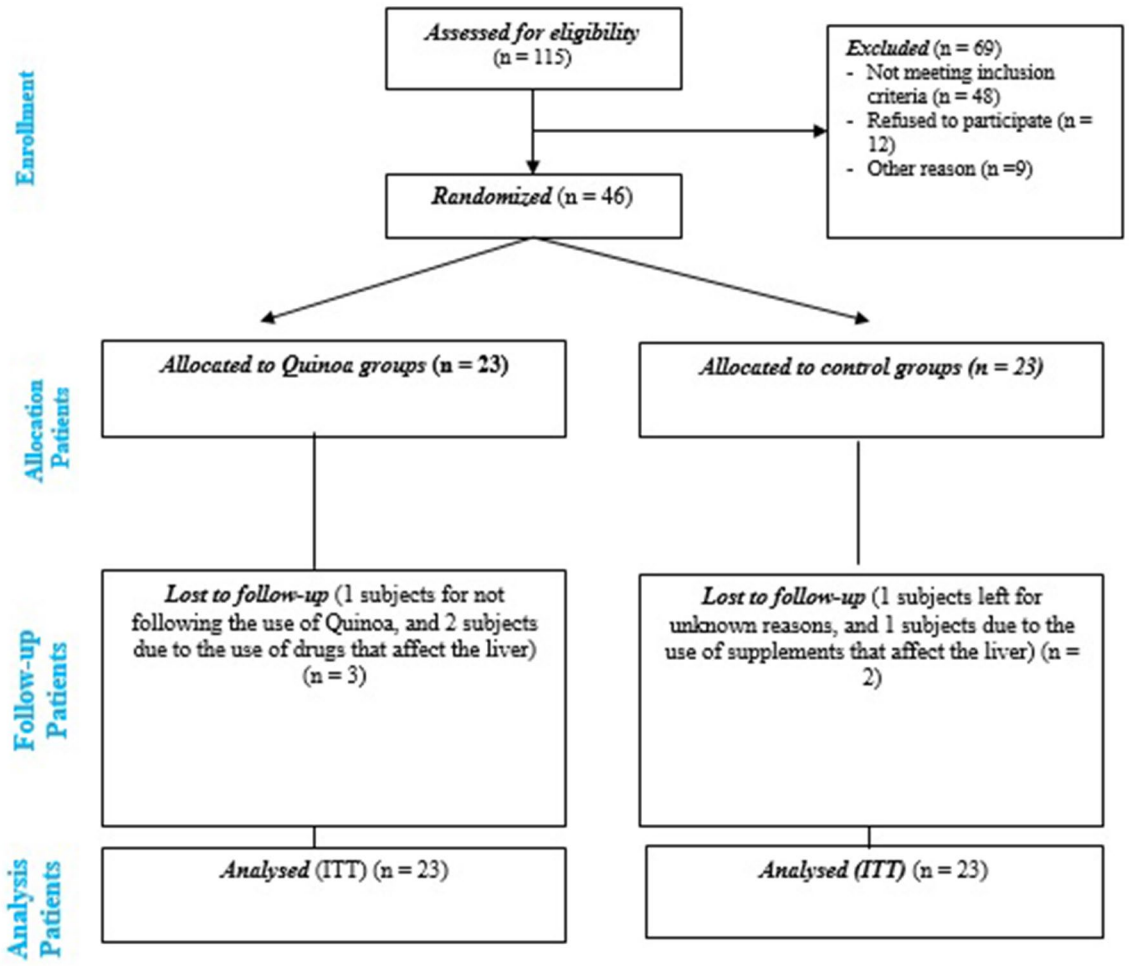

FIGURE 1
Consort flow diagram for the trial.

An independent staff member randomly assigned the participants to one of the two interventions. The treatment allocation was concealed from all researchers using sequentially numbered sealed opaque envelopes. These envelopes were opened sequentially in the presence of participants during their initial visit.

Blinding

In the current study, regarding the type of interventions, blinding of participants to their group allocation was not achievable. Nevertheless, before enrollment, participants were unaware of their group assignments. The researcher and laboratory technicians evaluating the outcome were kept blind to the intervention sequences.

Dietary interventions

At the beginning of the study, the objectives were explained to the participants and general recommendations regarding healthy food intake were provided for 2 weeks (run-in period). Eligible participants were randomly allocated to the quinoa group or control group over 12 weeks. Participants in the quinoa group were instructed to substitute grains with quinoa during lunch for 12 weeks. Due to the participants being overweight and obese, the dietary interventions were structured to provide 500 kcal/d less than their energy requirement. The amount of macronutrients was calculated as 55% from carbohydrates, 15% from protein, and 30% from fat. The amount of quinoa consumed at lunch by each person was determined according to the calories and carbohydrates calculated based on weight, height, and gender, averaging 49.56 ± 8.77 grams in the studied population (intervention group).

The quinoa used in this study was purchased from Kara Quinoa Company, (Hamedan, Iran). The macronutrient, micronutrient, and vitamin contents of cooked quinoa are shown, respectively, in Table 1 and Supplementary Table S1. The researcher provided instructions on how to cook quinoa in the intervention group. Furthermore, participants in the control group were instructed to avoid consuming products containing quinoa throughout the study.

The researcher contacted the participants weekly to monitor the consumption of quinoa and grains in the intervention and control groups, respectively. To assess the adherence to interventions, the researcher compared the intake of quinoa and grains by the participants with the dietary instructions and reinforced their dietary

10.3389/fnut.2025.1505183

TABLE 1 Macro-nutrient contents of quinoa and selected foods, per 100 grams cooked weight.

	Quinoa	Bean	Maize	Rice	Wheat
Energy (Kcal/100 g)	399	367	408	372	392
Protein (g/100 g)	16.5	28.0	10.2	7.6	14.3
Fat (g/100 g)	6.3	1.1	4.7	2.2	2.3
Total carbohydrate (g/100 g)	69.0	61.2	81.1	80.4	78.4

adherence. Non-adherence was defined as consuming less than 80% of the recommended amount of Quinoa. Additionally, dietary information was gathered using 24-h dietary recall throughout the study. The intake of macro- and micronutrients was determined using NUTRITIONIST IV version 7.0 (N-Squared Computing, Salem, OR, United States), designed for Iranian foods. Participants were instructed to maintain their level of physical activity and not alter their medications during the 12-week interventions unless advised by their healthcare providers.

Primary and secondary outcomes

The primary outcome was the difference in the change of CAP score between the two groups from baseline until the 12-week follow-up. The secondary outcomes included changes in ALT, AST, Gamma-glutamyltransferase (GGT), Fibroscan, weight, WC, fasting blood sugar (FBS), insulin, homeostatic model assessment for insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), High-sensitivity C-reactive protein (hs-CRP), and lipid profiles.

Measurements

Demographic and dietary intake assessment

The International Physical Activity Questionnaire (IPAQ) (22) was utilized to regulate and evaluate the participants' degree of physical activity, serving as a confounding factor in assessing physical activity levels. The participants' physical activity, as measured by this questionnaire, was assessed at the beginning and end of the study.

Anthropometric assessment

Weight was assessed using a Seca portable digital scale manufactured in Germany, which has a precision of 100 g. The measurement was taken with minimum clothing and without wearing shoes. The height was determined using a stadiometer, which has a precision of 0.5 cm, and the measurement was taken without wearing shoes. BMI was computed using the formula: weight (in kilograms) divided by height squared (in meters). The waist circumference (WC) were measured using a Seca waist measuring instrument, namely in the central area between the iliac crest and the final rib.

At the baseline and the 12-week follow-up, following a fasting period of 10–12 h, the laboratory technician collected 10 mL of venous blood from the participants. Following coagulation in the surroundings, the serum was promptly separated using centrifugation and stored at a temperature of −70°C until it was dispatched to the laboratory for analysis. The liver enzymes ALT, AST, and GGT, as well as high-density lipoprotein cholesterol (HDL-C), TG, and FBS content were assessed using a Pars Azmon Company kit (Pars Azmon, Tehran, Iran) and an enzymatic colorimetric approach. The Pars test kit utilized enzyme photometry to quantify the levels of TC (Pars Azmon, Tehran, Iran). LDL-C concentration was also calculated using Friedewald formula (23): LDL-C (mg/dL) = TC (mg/dL) − HDL-C (mg/dL) − TG (mg/dL)/5. Serum insulin concentration was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (DiaSorin ELISA kit, Italy, REF 310360).

HOMA-IR (insulin resistance index) and QUICKI (insulin sensitivity index) indices were calculated using the following formulas.

$$\text{HOMA} - \text{IR} = \left[\text{FBS}\left(\text{mg} / \text{dl}\right) \times \text{Fasting Insulin}\left(\mu U / \text{ml}\right)\right] / 405$$

(24).

$$\text{QUICKI} = 1 / \left[\log \text{Fasting Insulin}\left(\mu U / \text{ml}\right) + \log \text{FBS}\left(\text{mg} / \text{dl}\right)\right]$$

(24).

The manufacturer's instructions were followed to measure serum levels of hs-CRP using a colorimetric enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).

Changes in liver function and liver fibrosis were also performed using fibroscan under the supervision of a gastroenterology and liver specialist.

Statistical analysis methods

All analyses were conducted using Stata software version 14.0 (StataCorp LLC, TX, United States). In the current study, 42 participants were required to detect (α error = 0.05, β error = 0.20) differences in a 25 IU/L reduction in ALT between quinoa and control groups (25). Accounting for an attrition rate of 10%, finally 23 participants were included in each group.

All participants who were randomly assigned to the dietary interventions underwent analyses following the intention-to-treat (ITT) principle. The Multiple imputation, Chained Equations (MICD) procedure was used to impute missing data for both primary and secondary outcomes for the 5 participants who withdrew from the study. The predictors in the multiple imputation process encompassed all variables listed in Table 2.

The demographic variables and dietary variables are reported as mean ± standard deviation (SD), and dichotomous variables as count (percentage) in the baseline characteristics. The histograms and the Shapiro–Wilk test were used to evaluate the normal distribution of primary and secondary outcomes. Analysis of covariance (ANCOVA), with adjustment for baseline values (model 1) and weight change (model 2), was employed to compare the effects of quinoa versus the control group on changes in the primary and secondary outcomes. All statistical tests were considered statistically significant when the p value was <0.05.

Results

Characteristics of the participants

This RCT was conducted from July 23, 2023, to October 25, 2023. A total of 46 eligible participants with NAFLD were randomly

10.3389/fnut.2025.1505183

TABLE 2 Baseline characteristics of participants according to group of intervention.

	Quinoa group (n = 23)	Control group (n = 23)	p value
Age, y	39.6 ± 5.1	39.9 ± 5.5	0.884
Male, n (%)	19 (51.4)	18 (48.6)	0.500
Weight, Kg	92.3 ± 12.0	92.5 ± 11.1	0.976
BMI, kg/m^2	29.9 ± 5.1	31.7 ± 5.1	0.248
Waist circumference, Cm	111.3 ± 7.7	109.5 ± 7.8	0.421
Physical activity, Met. h/wk	30.5 ± 4.3	30.6 ± 4.7	0.874
CAP score	315 ± 35	315 ± 36	0.949
FPS, mg/dl	94.3 ± 10.2	98.8 ± 10.7	0.158
HOMA-IR	3.7 ± 1.9	3.5 ± 1.8	0.724
QUICKI	0.32 ± 0.021	0.32 ± 0.023	0.685
Insulin	15.8 ± 7.4	14.4 ± 6.9	0.508
ALT, IU/L	35.6 ± 13.1	33.1 ± 11.4	0.495
AST, IU/L	30.6 ± 8.8	30.6 ± 9.7	0.892
GGT, IU/L	33.3 ± 17.7	34.2 ± 14.2	0.872
TC, mg/dl	186 ± 29	190 ± 29	0.624
TG, mg/dl	177 ± 48	176 ± 57	0.964
HDL-C, mg/dl	39.1 ± 3.7	39.4 ± 6.5	0.824
LDL-C, mg/dl	116 ± 26.2	119 ± 25.6	0.696
FibroScan	5.9 ± 2.1	6.2 ± 2.1	0.663
hs-CRP, mg/L	4.2 ± 3.3	4.1 ± 2.9	0.942

Data are mean ± SD unless otherwise indicated.
FPS, fasting plasma glucose; BMI: Body mass index; WC: waist circumference; CAP; Controlled Attenuation Parameter; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; QUICKI, Quantitative insulin sensitivity check index; ALT, Alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TC, total cholesterol; TG, triglycerides, HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, High sensitivity C-reactive protein.

assigned to either quinoa (n = 23) or control (n = 23) groups. Five participants withdrew from the study. Finally, all patients (23 in the quinoa and 23 in the control groups) entered the analysis with intention-to-treat (ITT) analysis (Figure 1).

Table 2 presents the baseline characteristics of participants. There were no significant differences observed between the quinoa and control groups in terms of basic characteristics including sex, age, physical activity level, anthropometric characteristics, liver enzymes, liver function, glycaemic status, and lipid profile. The mean age and BMI of the participants were 39.6 ± 5.1 years and 32.2 ± 4.4 kg/m^2 in the quinoa group and 39.9 ± 8.5 years and 31.7 ± 5.1 kg/m^2 in the control group, respectively.

The dietary intake of macronutrients and micronutrients for participants in both the quinoa and control groups is presented in Table 3. At the end of the follow-up period, both the Quina and control groups showed a decrease in energy and carbohydrate intake, along with an increase in Vitamin E intake. In the quinoa group, fat and omega-6 consumption decreased, while omega-3 intake increased at the end of intervention. There were no significant differences found in the intake of protein, saturated fatty acid (SFA), cholesterol, fiber, magnesium, and vitamins at the end of the study in both groups.

Primary outcomes

A reduction in CAP score was observed at week 12 in the quinoa group after adjustment for baseline value. The mean difference ± SD in change was −32.3 ± 6.2 in the quinoa group compared to −13.8 ± 6.2 in the control group, with a p value of 0.044. The difference in change of CAP score between the groups remained significant, after adjusting for weight change (−29.0 ± 6.4 in the quinoa group vs. 12.2 ± 6.3 in the control group; p value = 0.039) (Table 4).

Secondary outcomes

Based on the results presented in Table 4, at week 12, the quinoa group exhibited decreases in ALT (−7.32 ± 2.2 in the quinoa group vs. −3.59 ± 2.2 in the control group; p value = 0.251), AST (−7.42 ± 3.1 in the quinoa group vs. 0.30 ± 3.1 in the control group; p value = 0.101), and fibroScan (−0.56 ± 0.2 in the quinoa group vs. −0.17 ± 0.2 in the control group; p value = 0.146); however, the difference between the two groups was not significant.

Additionally, within the quinoa group, significant decreases were observed in HOMA-IR (−0.97 ± 0.23 in the quinoa group vs. -0.03 ± 0.23 in the control group; p value = 0.009) and insulin concentration (−3.65 ± 0.9 in the quinoa group vs. −0.50 ± 0.9 in the control group; p value = 0.021). However, after adjustment for baseline value and weight change, only HOMA-IR displayed a reduction after 12 weeks of quinoa intervention, when compared to the control group (−0.85 ± 0.24 in the quinoa group vs. −0.15 ± 0.24 in the control group; p value = 0.050).

Furthermore, significant reductions in TG (−17.2 ± 6.1 in the quinoa group vs. 3.1 ± 6.1 in the control group; p value = 0.024) and LDL-C (−13.83 ± 0.3.7 in the quinoa group vs. 2.19 ± 3.7 in the control group; p value = 0.005) levels were noted in the quinoa group, compared to the control group. However, after adjustment for baseline value and weight change, only LDL-C displayed a reduction after 12 weeks of quinoa intervention, when compared to the control group (−12.81 ± 3.9 in the quinoa group vs. 1.18 ± 3.9 in the control group; p value = 0.018).

Both weight (−3.1 ± 0.7 in the quinoa group vs. -0.5 ± 0.7 in the control group; p value = 0.017) and WC (−2.3 ± 0.6 in the quinoa group vs. −0.5 ± 0.6 in the control group; p value = 0.035) decreased following quinoa consumption, and the difference between the two dietary interventions was significant. Lastly, no significant difference in hs-CRP concentration was reported at week 12 in either quinoa or control groups (Table 4).

Discussion

To our knowledge, this study is the first randomized control trial that has assessed the effects of substituting lunch grains with quinoa on obesity indicators, lipid profile, glycemic status, and liver function in patients with NAFLD. This study revealed that the substitution of grains with quinoa significantly improved the CAP score, HOMA-IR, and LDL-C in NAFLD subjects, independent of weight change.

The findings of our study showed a significant decrease in CAP score after 12 -weeks of intervention with quinoa compared to the control group. However, we did not observe beneficial or significant

10.3389/fnut.2025.1505183

TABLE 3 Dietary intake of the participants according to quinoa and control groups.

	Quinoa			Control			*p* value[b]
	Baseline	After 12	*p* value[a]	Baseline	After	*p* value[a]	
Energy (Kcal/d)	**2,359 ± 473**	**2089.3 ± 360.4**	**<0.001**	**2,526 ± 740.8**	**2,240 ± 791**	**0.003**	0.420
Carbohydrate (g/d)	**298 ± 77.5**	**259.12 ± 55.4**	**0.001**	**338 ± 127**	**265 ± 112**	**<0.001**	0.822
Protein (g/d)	94.2 ± 21.6	92.8 ± 21.8	0.739	97.2 ± 35.1	95.1 ± 25.8	0.304	0.762
Fat (g/d)	**92.7 ± 17.3**	**79.8 ± 15.9**	**0.002**	95.4 ± 30.9	84.8 ± 50.5	0.116	0.662
SFA (g/d)	23.6 ± 5.0	21.8 ± 5.0	0.098	30.3 ± 27.3	27.5 ± 21.0	0.353	0.221
MUFA (g/d)	41.8 ± 40.2	30.1 ± 7.7	0.188	29.4 ± 6.9	26.9 ± 19.3	0.640	0.475
Cholesterol (mg/d)	254 ± 85.7	246 ± 83.6	0.731	263 ± 163.5	228 ± 142.4	0.163	0.602
Fiber (g/d)	27.1 ± 7.3	25.5 ± 6.5	0.325	26.3 ± 11.9	26.8 ± 14.1	0.601	0.692
Omega 3 (mg/d)	**1.2 ± 0.6**	**3.5 ± 11.2**	**<0.001**	1.41 ± 1.0	1.26 ± 1.2	0.676	0.401
Omega 6 (mg/d)	**7.8 ± 2.4**	**6.2 ± 2.3**	**<0.001**	15.9 ± 28.1	14.2 ± 23.1	0.125	0.110
Magnesium (mg/d)	278 ± 139	270 ± 137	0.317	245.7 ± 112.6	239.4 ± 102.6	0.700	0.229
Vitamin A (RE)	945 ± 157	1,022 ± 162	0.312	894 ± 490	963 ± 318	0.447	0.593
Vitamin E (mg/d)	**8.3 ± 6.1**	**10.4 ± 4.9**	**0.036**	**9.8 ± 7.4**	**11.4 ± 5**	**0.042**	0.810
Vitamin C (mg/d)	90.8 ± 43	90.1 ± 54	0.701	86.1 ± 35.3	97.6 ± 33.3	0.670	0.502
Vitamin D (mcg/d)	8.7 ± 6	9.1 ± 3.6	0.481	8.8 ± 5.3	9.6 ± 5.7	0.268	0.471

Data are expressed as Mean ± SD.
PUFA, Polyunsaturated fatty acid; SFA, Saturated fatty acid; MUFA, Monounsaturated fatty acid.
[a]*p*-values for comparison of within-group differences.
[b]*p*-values for comparison of mean values between two groups.
Bold values are significant.

effects on liver enzymes and fibroscan. Despite the potential benefits of quinoa on liver tissue function, it does not seem to reduce inflammatory processes caused by elevated liver enzyme levels. Our findings are clinically significant as a CAP score above 280 or 290 dB/m indicates severe steatosis with a 22% prevalence of increased liver stiffness in subjects with metabolic risk factors, while a CAP score between 248 and 290 dB/m is associated with only a 5% prevalence of increased liver stiffness (26). To our knowledge, no human studies have been conducted to investigate these aspects of liver function, with current studies limited to animal studies. For instance, a study by Song et al. in 2021 investigated the effect of feeding varying amounts of quinoa (300 grams per day) for 12 weeks in male rats with fatty liver (19). The results showed reduced TG and TC levels in the liver, decreased liver damage, increased antioxidant activities, and overall prevention of NAFLD by controlling body weight, reducing oxidative stress, and regulating lipid metabolism and immune response gene expression (19). The relatively low levels of liver enzymes may explain the modest effect of this intervention. Additionally, the small average intake of quinoa (about 49 grams) compared to the animal study may also contribute to these findings.

Furthermore, significant and decreasing changes were shown in all anthropometric factors, including weight, and WC, in the quinoa group compared to the control group. As weight loss interventions are considered crucial in the treatment of certain conditions, these findings may contribute to improving various pathogenic processes associated with the disease (21). Evidence suggests that a weight loss of at least 5% of body weight is necessary to enhance histological and functional liver symptoms. The observed weight loss of approximately 3% following quinoa intervention could explain some of our results, such as the lack of significant effects on liver enzymes (21). Therefore, combining quinoa intervention with weight loss regimes may enhance treatment outcomes and improve patients' adherence to weight loss protocols. A meta-analysis conducted in 2021 on five RCT studies with a total of 206 participants, revealed that supplementation with quinoa seeds led to a significant reduction in weight, WC, and fat mass (27). However, no significant effect on BMI reduction was reported, possibly due to the limited number of studies and also some trials involving individuals with normal weight. Laboratory studies suggest that phytoectosteroids, particularly 20-hydroxyecdysone, play a key role in the weight loss mechanism induced by quinoa consumption. These compounds are believed to reduce the size and storage capacity of fat cells, downregulate genes involved in fat accumulation such as lipoprotein lipase, and modulate related to inflammatory adipokines (28, 29). Several mechanisms are proposed to be involved in this weight loss process, including favorable alterations in hormone level that influence appetite regulation, such as leptin and ghrelin (30). Additionally, quinoa's high content of soluble and insoluble fiber may increase satiety and correct intestinal dysbiosis (31, 32). Furthermore, the presence of quinoa saponins is thought to reduce systematic inflammation (33). These combined mechanisms highlight the potential of quinoa as a beneficial dietary component for weight management and overall health.

The current study's findings indicate that, except for HOMA-IR, there were no significant differences in glycemic indices after 12 weeks of substituting lunch grains with quinoa compared to the control group. Similar results were also reported in other studies. For instance, a prospective and double-blind study involving 35 overweight women found no significant effect on FBS when comparing the group consuming 25 grams of quinoa flakes to those having corn flakes after 4 weeks of intervention (34). Another study

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TABLE 4 The 12-week change in anthropometric characteristics, liver enzymes, liver function, glycaemic indices, and lipid profile after the quinoa and control groups.

	Quinoa group (n = 23)	Control group (n = 23)	p value
Primary outcome			
CAP score			
Model 1	**−32.3 ± 6.2**	**−13.8 ± 6.2**	**0.044**
Model 2	**−29.0 ± 6.4**	**−12.2 ± 6.3**	**0.039**
Secondary outcomes			
Weight, Kg			
Model 1	**−3.1 ± 0.7**	−0.5 ± **0.7**	**0.017**
WC, Cm			
Model 1	**−2.3 ± 0.6**	−0.5 ± 0.6	**0.035**
Liver enzyme and liver function			
ALT, IU/L			
Model 1	**−8.22** ± 2.1	−2.69 ± 2.1	0.081
Model 2	**−7.32** ± 2.2	−3.59 ± 2.2	0.251
AST, IU/L			
Model 1	−6.96 ± 3.0	−0.16 ± 3.0	0.121
Model 2	−7.42 ± 3.1	0.30 ± 3.1	0.101
FibroScan			
Model 1	**−0.60 ± 0.2**	−0.12 ± **0.2**	0.061
Model 2	−0.56 ± 0.2	−0.17 ± 0.2	0.146
GGT, IU/L			
Model 1	−0.28 ± 2.8	1.52 ± 2.8	0.655
Model 2	0.72 ± 2.8	0.51 ± 2.8	0.961
Glycaemic indices			
FPG, mg/dL			
Model 1	−1.6 ± 2.0	1.9 ± 2.1	0.230
Model 2	−1.7 ± 2.1	2.1 ± 2.1	0.226
HOMA-IR			
Model 1	**−0.97 ± 0.23**	**−0.03 ± 0.23**	**0.009**
Model 2	**−0.85 ± 0.24**	**−0.15 ± 0.24**	**0.050**
QUICKI			
Model 1	0.011 ± 0.01	0.006 ± 0.01	0.530
Model 2	0.012 ± 0.01	0.005 ± 0.01	0.409
Insulin			
Model 1	**−3.65 ± 0.9**	−0.50 ± **0.9**	**0.021**
Model 2	**−3.14 ± 0.9**	−1.00 ± **0.9**	0.106
Lipid profile			
TC, mg/dL			
Model 1	−8.46 ± 4.2	−1.06 ± 4.2	0.222
Model 2	−7.83 ± 4.3	−1.69 ± 4.3	0.343
LDL-C, mg/dL			
Model 1	**−13.83 ± 3.7**	**2.19 ± 3.7**	**0.005**
Model 2	**−12.81 ± 3.9**	**1.18 ± 3.9**	**0.018**

(Continued)

TABLE 4 (Continued)

	Quinoa group (n = 23)	Control group (n = 23)	p value
TG, mg/dL			
Model 1	**−17.2 ± 6.1**	3.1 ± **6.1**	**0.024**
Model 2	**−15.9 ± 6.3**	1.6 ± **6.3**	0.063
HDL-C, mg/dL			
Model 1	−0.39 ± 0.4	−0.19 ± 0.4	0.753
Model 2	−0.25 ± 0.4	−0.33 ± 0.4	0.898
Inflammatory marker			
hs-CRP, mg/L			
Model 1	0.32 ± 0.4	0.62 ± 0.4	0.565
Model 2	0.32 ± 0.4	0.62 ± 0.4	0.594

Data are expressed as Mean ± SEM.
Significant data is bolded.
FPS, fasting plasma glucose; BMI, Body mass index; WC, waist circumference; CAP, Controlled Attenuation Parameter; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; QUICKI, Quantitative insulin sensitivity check index; ALT, Alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TC, total cholesterol; TG, triglycerides, HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, High sensitivity C-reactive protein.
Model 1 adjusted for baseline values.
Model 2 adjusted for baseline values and weight change.

in Brazil involving students aged 18–45 years did not show significant effects on glycemic index after a 30-day intervention with quinoa (35). Furthermore, a RCT with a parallel design investigating the effects of 25 and 50 grams of quinoa per day on 50 overweight and obese participants over 12 weeks did not report significant effects on FBS and insulin levels (18). Overall, evidence suggests that the major effect of quinoa on glycemic status is related to postprandial glucose response and enhanced insulin sensitivity (17). Compounds like 20-hydroxyecdysone and polyphenols, particularly flavonoids present in quinoa, may increase insulin sensitivity and improve hepatic gluconeogenesis by affecting PI3K-dependent insulin signaling pathways (29, 36). In addition, the high fiber content and low glycemic index of quinoa compared to other grains may also contribute to these beneficial effects (34).

After 12 weeks of intervention with quinoa compared to the control group, there was a significant decrease in serum TG and LDL-C levels. The effect of quinoa on TG concentration disappeared after adjustment for weight change. Consistent with our findings, various studies have reported similar results showing a significant reduction in TG and no significant impact on serum HDL-C following quinoa intervention (16, 18, 27, 34). However, conflicting results have been reported regarding TC and LDL-C levels. For instance, a comprehensive study demonstrated a decrease in both factors after quinoa consumption (27), while a study involving obese and overweight individuals did not show significant effects after a 12-week intervention (18). These contradictory results can be caused by the variety in the type of quinoa-containing products, the dosage administered to participants, and notably, the variation in baseline levels of these factors across studies. The beneficial effects of quinoa on lipid profile levels may be attributed to its high fiber content, and the presence of compounds such as 20-hydroxyecdysone, polyphenols, and phytosterols, which are key factors in reducing blood lipid levels (27). Additionally, the protein isolated from quinoa could play a role in lowering cholesterol by reducing the expression of hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and increasing bile acid excretion from the intestine (37).

According to comprehensive review (38), there is no evidence that quinoa has a different effect on cardiovascular risk factors between men and women. Therefore, gender is not a relevant variable in this study and we did not perform analyses based on gender.

One of the most important strengths of this study was the interpretation of the findings based on the ITT principles, a low dropout rate, and a RCT design that allowed for controlling the confounders. Additionally, this study was the first human investigation into the potential benefits of substituting lunch grains with quinoa for patients with NAFLD. However, several limitations warrant consideration. The assessment of adherence to dietary interventions relied on self-report diet records, and due to limited funding, we were unable to measure the effective amount of bioactive substances in quinoa to assess adherence accurately. To address this, a dietitian contacted participants weekly to reinforce adherence to dietary recommendations. Another limitation was the lack of blinding participants to the study objectives, potentially influencing their behaviors. Furthermore, not conducting liver biopsies, the gold standard for NAFLD treatment assessment, was another constraint in the current study.

Conclusion

The findings of our study indicate that substituting quinoa for traditional lunch grains may have a beneficial effect on weight management, insulin resistance, and LDL-C levels. Thus, incorporating quinoa—a plentiful and low-cost source of bioactive compounds—into the diets of NAFLS patients as a staple food could improve several cardiometabolic risk factors in these individuals. However, additional high-quality studies with larger sample sizes, as well as investigation into the bioactive components of quinoa, are necessary to validate and strengthen our results.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Shahid Beheshti University of Medical Sciences. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AG: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Software, Validation, Writing – original draft, Writing – review & editing. SH-N: Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. PM: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. AH: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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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.

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Supplementary material

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Association of ultra-processed foods consumption with increased liver steatosis in U.S. adults

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Background: Recent studies demonstrated a strong association between dietary habits and liver health, particularly in the development of steatosis and fibrosis. This study aimed to examine the impact of ultra-processed foods (UPFs) on liver health, focusing specifically on their influence on the risks of liver steatosis and fibrosis.

Methods: A cross-sectional analysis was conducted on 4,992 participants aged 18 years and older from the 2017–2020 National Health and Nutrition Examination Survey (NHANES). Dietary intake was assessed using one or two 24-h dietary recalls, and foods were categorized by their processing level using the NOVA classification system. UPFs consumption was measured in grams and divided into quartiles. Liver health was assessed using controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) via elastography, to evaluate steatosis and fibrosis, respectively. Linear regression models were applied to assess the relationship between UPFs consumption and liver outcomes, adjusting for sociodemographic (age, sex, ethnicity), lifestyle (alcohol consumption, physical activity), and biomedical factors (liver enzyme levels).

Results: Higher UPF intake was significantly associated with increased CAP values, indicating a higher risk of liver steatosis. While liver fibrosis, measured by LSM, was also associated with UPF consumption, this relationship did not reach statistical significance. Multivariate analysis showed that increased UPF consumption did not significantly affect LSM ($p = 0.110$) but was strongly associated with elevated CAP values ($p = 0.009$). In participants with fatty liver (CAP $>$ 248 dB/m), the association between UPF intake and CAP remained significant ($p = 0.020$). Participants in the highest quartile of UPFs consumption (Q4) exhibited higher CAP values compared to those in the lowest quartile (Q1) ($\beta = 1.22$; 95% CI: 1.02, 1.47). Stratified analysis revealed that the association between UPF intake and CAP was more pronounced in obese individuals (HR = 1.08, 95% CI: 1.03–1.15, $p = 0.022$) and those with high waist circumference (HR = 1.06, 95% CI: 1.01–1.10, $p = 0.032$).

Conclusion: These results underscore the adverse impact of UPFs on liver health, particularly by increasing steatosis, while the connection with fibrosis remains less straightforward.

KEYWORDS

ultra-processed food, liver health, fatty liver disease, liver fibrosis, NHANES

1 Background

Metabolic dysfunction-associated steatotic liver disease (MASLD) is rapidly emerging as a major global health concern, currently affecting ~32% of the adult population worldwide (1). Accounting for 59% of all chronic liver diseases (2), MASLD can progress to non-alcoholic steatohepatitis (NASH), significantly increasing the risks of cirrhosis, hepatocellular carcinoma (HCC), and mortality. The hallmark of MASLD is hepatic steatosis, characterized by excessive fat accumulation in the liver, which can lead to varying degrees of inflammation and fibrosis. This condition adversely affects metabolic, immune, and cardiovascular health, and is associated with an increased risk of hyperlipidemia and type 2 diabetes (3). A direct correlation was observed between the severity of hepatic steatosis and fibrosis progression (4), along with an increase in liver-related mortality (5). Dietary habits, particularly the consumption of soft drinks, red meat, and processed meats, are linked to an increased risk of MASLD, while diets low in free sugars—such as the Mediterranean diet—and those rich in dietary antioxidants may help reduce hepatic fat accumulation (6).

Ultra-processed foods (UPFs), characterized by their high content of refined ingredients and various additives, are typically lacking in whole food components. These products are often high in sugars, trans fats, sodium, and refined starches, yet deficient in essential nutrients such as fiber, protein, vitamins, and minerals (7). Numerous studies demonstrated a strong association between regular UPFs consumption and an increased risk of obesity in both children and adults (8, 9), as well as a higher prevalence of metabolic disorders, cardiovascular diseases (9–11), and certain cancers. From 2001 to 2018, UPFs consumption among American adults increased significantly, while intake of minimally processed foods declined (12). This dietary shift aligns with rising trends in obesity and metabolic syndrome in the United States, suggesting a potential connection between UPFs consumption and these growing health concerns. However, the specific relationship between UPFs intake and conditions such as fatty liver or liver fibrosis, particularly among adults, remains underexplored.

This study aims to investigate the association between UPF consumption and the prevalence of fatty liver and liver fibrosis in adults using data from the National Health and Nutrition Examination Survey (NHANES). By analyzing dietary patterns in a large, nationally representative adult sample, we seek to elucidate the potential role of UPFs in liver health and contribute to the growing body of research on the relationship between diet and liver disease.

2 Methods

2.1 Study participant

This investigation utilized NHANES dataset, a comprehensive series of cross-sectional surveys administered by National Center for Health Statistics (NCHS) under the auspices of the centers for disease control and prevention (CDC) (13). The NHANES protocol received approval from the NCHS Institutional Review Board, ensuring all participants provided written informed consent (14). Since its inception in 1999, NHANES has consistently enrolled around 6,000 individuals each year and continues to do so, with findings being disseminated biennially (15). Our analysis specifically targeted the 2017–2020 NHANES cohort, a period which included the acquisition of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) through vibration-controlled transient elastography (VCTE).

The study focused on adults aged 18 and above, who had complete LSM data and provided dual 24-h dietary recall information. These participants were selected via a sophisticated multistage probability sampling methodology. Initial data collection commenced with in-home interviews where participants completed a screener questionnaire. This was followed by structured interviews at mobile examination center (MEC) to assess eligibility based on detailed sociodemographic and health history. The MEC visits also included comprehensive physical examinations, laboratory testing, and dietary assessments. A follow-up dietary interview, conducted via telephone 3–10 days post-MEC visit, enabled the collection of in-depth dietary information from selected individuals. This rigorous process facilitated a detailed estimation of the type and quantity of food and beverage intake, encompassing their energy and nutrient profiles, as elaborated in the NHANES Dietary Interviewers Procedures Manual (16).

From the NHANES 2017−2020 data set, an initial pool of 15,560 individuals was considered. After excluding minors (n = 5,867), 9,693 adults were identified as potential participants. This number was further narrowed down by removing individuals with incomplete VCTE (n = 1,376) and dietary data (n = 820), leaving 7,497 subjects. In addition, participants with incomplete alcohol consumption data and those with excessive alcohol intake [5 or more alcoholic drinks (male), or 4 or more drinks (female), on the same occasion on at least 1 day in the past 30 days (17), n = 2,343] were excluded. Furthermore, individuals diagnosed with chronic liver diseases, including autoimmune liver disease, hepatitis B, hepatitis C, and liver cancer, were also excluded, resulting in a final analytical sample of 4,992 participants. This rigorous selection process ensured a robust sample representative of the adult population, facilitating an in-depth analysis of the relationship between UPFs consumption and health outcomes (Figure 1).

2.2 Dietary assessment

In this study, dietary intake data obtained from recalls were classified according to the NOVA system, which categorized foods based on their processing level (18). The NOVA system divides foods into four categories: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and UPFs (8).

Processed foods, like canned fish, vegetables, artisanal bread, and cheese, result from adding culinary ingredients to unprocessed foods. UPFs, on the other hand, are characterized by their industrial formulation and typically consist of five or more ingredients (19).

To assign foods or beverages to one of the four new categories, we employed the food codes provided by NHANES. For homemade recipes, NOVA was applied to the basic ingredients

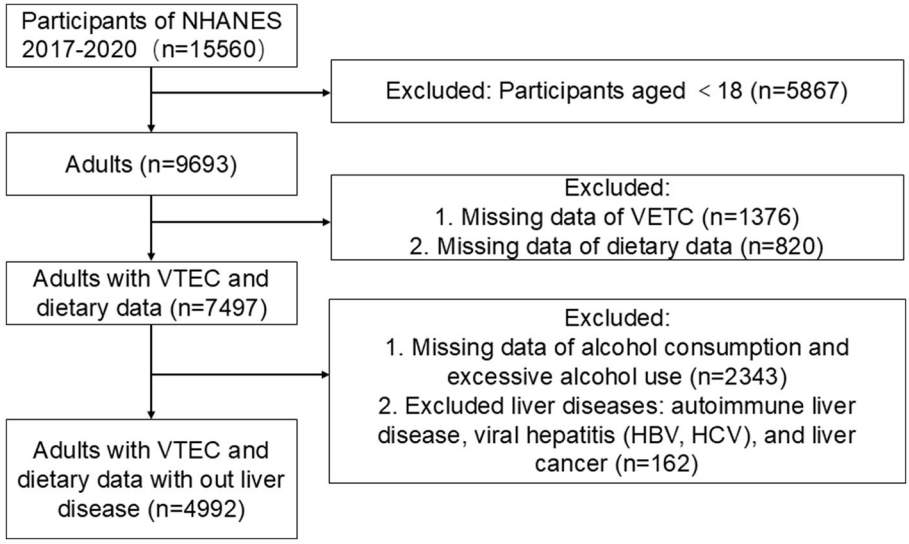

FIGURE 1
Flowchart of the study.

(standard reference codes). The USDA's Food and Nutrient Database for Dietary Studies for the specific period was used, with the USDA's National Nutrient Database serving as the standard reference (20). The food descriptions and ingredient lists for each NHANES food code were assessed against these databases.

2.3 VCTE evaluation of hepatic steatosis and fibrosis

Hepatic steatosis and fibrosis were assessed using VCTE via FibroScan. Measurements followed NHANES protocols for accuracy and reliability.

For evaluating liver fibrosis and steatosis, an LSM value exceeding 7 kPa was indicative of a high fibrosis risk (21). Steatosis was determined using a CAP threshold of over 248 dB/m (22).

2.4 Assessment of other variables

Demographic and lifestyle data were systematically gathered using computer-assisted personal interviewing (CAPI) system (23). Demographic information encompassed age, delineated into three categories (18–44, 45–59, and 60+ years) (24), and gender. Ethnic backgrounds were categorized into Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and Other/Multi-Racial (25). Educational attainment was classified as high school completion or higher. Marital status was segmented into married/living with partner and other classifications. Economic status was gauged through the poverty income ratio (PIR), separating individuals into low and non-low income groups.

Lifestyle variables assessed comprised smoking status, identified as current, former, or never smoker, and alcohol consumption, categorized into less than once a week, once a week or more, and abstinent in the past year. Physical activity was quantified based on self-reported instances of moderate and vigorous exercise. Body mass index (BMI) calculations were performed using height and weight measurements, conducted by trained professionals, with BMI computed as the individual's weight in kilograms divided by the square of their height in meters, rounded to one decimal point. BMI was categorized using a cutoff of 25 kg/m^2, classifying individuals as lean or obese (13). Waist circumference was stratified based on sex-specific thresholds, with high waist circumference defined as $\geq$102 cm for men and $\geq$88 cm for women (26).

Biological markers pertinent to liver health were selectively included based on their presence in NHANES data and relevance in scientific literature. These markers included alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT), providing a comprehensive overview of potential liver function abnormalities.

2.5 Statistical analysis

Categorical and continuous variables were characterized using frequencies (*n*), percentages (%), and quartiles, respectively. Due to the skewed nature of the data, the $\chi\wedge2$ test was employed for categorical variables, and the Kruskal-Wallis test was applied to continuous variables for comparative analyses. Multivariate logistic regression models were utilized to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for liver steatosis (defined as CAP $>$ 248 dB/m) and significant fibrosis (LSM $>$ 7 kPa) across the quartiles of UPFs consumption (Q1 through Q4).

The analysis included covariates that could potentially affect liver fibrosis and steatosis, such as age, ethnicity, education level, marital status, annual household income, BMI, waist

circumference, alcohol and smoking status, physical activity, and liver enzyme levels. To evaluate potential differences in the association between UPF consumption and hepatic steatosis across subgroups, we conducted stratified analyses. Stratification was performed based on age, sex, BMI, and waist circumference to explore potential effect modification.

To ensure that the study findings were representative of the U.S. population, survey sample parameters, including clustering, strata, and weights, were meticulously integrated into the statistical analysis. All analyses were performed using R version 4.3.3 (R Core Team, Vienna, Austria), with statistical significance set at a p-value of <0.05 (two-tailed).

3 Results

3.1 Clinical characteristics of the study participants

Referencing Table 1 from the NHANES 2017–2020 dataset, which included 4,992 adults, demographic analysis revealed statistically significant disparities in gender and ethnic distributions across UPFs consumption quartiles. Notably, a higher proportion of males, non-Hispanic White participants was observed in Q4. With an increase in UPFs consumption, BMI and waist circumference increased, while physical activity declined. These observations underscored a significant link between UPFs consumption and liver health metrics, where elevated CAP values ($p < 0.001$) in the highest quartile hinted at an increased risk for steatosis. This pattern indicates a tangible correlation between dietary habits and health outcomes, particularly in the context of liver fibrosis and steatosis.

3.2 Multivariate analysis of factors influencing factors on MASLD and hepatic fibrosis relative to UFP quartiles

Table 2 examines the correlation between UPFs consumption and liver health parameters within the NHANES 2017–2020 adult cohort, specifically analyzing LSM and CAP across UPFs consumption quartiles. In the unadjusted model, higher UPF intake was significantly associated with increased LSM values, showing a positive trend (p for trend < 0.001). After adjusting for demographic factors (Model 1), the association remained significant, particularly in the highest UPF quartile (Q4: $\beta = 1.15$; 95% CI: 1.08–1.22). However, when further adjusting for lifestyle factors such as alcohol consumption, smoking status, and waist circumference (Model 2), the association attenuated and became non-significant (p *for* trend $= 0.140$). In the fully adjusted model (Model 3), which included biochemical markers (ALT, AST, and GGT), the association between UPF consumption and LSM remained statistically insignificant (p for trend $= 0.110$), suggesting that UPF intake may have a limited impact on liver fibrosis.

Table 2 highlights that increased UPF intake is significantly associated with higher CAP values, suggesting a greater likelihood of hepatic steatosis. Higher UPF intake was strongly associated with increased CAP values, indicating a higher risk of liver steatosis. The unadjusted model showed a significant association (p for trend < 0.001), with CAP values increasing across UPF quartiles. This association remained robust in Model 1 after adjusting for demographic factors (Q4: $\beta = 1.10$; 95% CI: 1.05–1.15). Even after further adjustments for lifestyle factors in Model 2 and biochemical markers in Model 3, the association persisted (Model 3: Q4: $\beta = 1.04$; 95% CI: 1.00–1.08; p for trend $= 0.009$).

Table 3 in the results segment presents the link between UPFs intake and liver health indicators. It provides beta coefficients and 95% CIs across UPFs consumption quartiles for LSM (>7 kPa) and CAP (>248 dB/m), which serve as fatty liver and fibrosis, respectively. The unadjusted model showed a significant association ($p < 0.001$) between increased UPFs consumption and elevated LSM and CAP values. After adjusting for demographic, lifestyle, and metabolic factors, this association remained significant, particularly in the highest UPF quartile. However, in Models 2 and 3, the p-trend for LSM was no longer statistically significant, while the association with CAP remained robust. These findings suggested that excessive UPF consumption was independently associated with an increased risk of hepatic steatosis, underscoring the potential impact of dietary patterns on liver health.

3.3 Dose-response analysis of UPFS with CAP and LSM values

Figure 2 illustrates a graphical insight into the relationship between UPFs consumption and liver health metrics derived from VCTE in healthy adults. Panel A depicts the correlation between UPFs intake and the CAP, expressed on a log-transformed scale ($\log(\text{UPF} + 1)$), indicative of fatty liver deposition. The scatter plot in this panel shows an upward trend, with smooth curve fitting indicating that increased UPFs consumption is associated with higher CAP values, signaling enhanced liver fat accumulation. The 95% confidence interval, represented by the shaded area, underscores the statistical reliability of this trend. Panel B presents the relationship between UPFs consumption, expressed on a log-transformed scale ($\log(\text{UPF} + 1)$), and LSM, a biomarker for liver fibrosis. The graphical representation here shows a relatively constant LSM value across different levels of UPFs intake, as denoted by the nearly flat line. These visual analyses highlight that UPFs exerted a more pronounced effect on liver fat accumulation than on liver stiffness across the analyzed UPFs consumption spectrum. The graphical representation facilitates the comprehension of the potential dietary influences on liver health metrics, with a statistically significant impact observed in CAP trends ($p < 0.05$), contrasting with the non-significant trends in LSM. Additionally, a quantitative analysis revealed that an increase of 500 g/day in UPF consumption corresponded to an estimated 18.93 dB/m increase in CAP but had a more modest effect on LSM (1.06 kPa increase).

3.4 Subgroup analyses

Figure 3 presents a stratified analysis of the association between UPF consumption and CAP, further elucidating its impact across different subgroups. The results indicate that the

TABLE 1 Characteristics by categories of UPFs among adults NHANES 2017–2020.

Characteristic	Overall, N =4,922 (100%)[a]	Q1, N = 1,511 (25%)[a]	Q2, N = 1,292 (25%)[a]	Q3, N = 1,177 (25%)[a]	Q4, N = 1,012 (25%)[a]	P-Value[b]
Gender						**<0.001**
Female	2,592 (52%)	961 (66%)	742 (60%)	570 (51%)	319 (32%)	
Male	2,400 (48%)	550 (34%)	550 (40%)	607 (49%)	693 (68%)	
Age (year)						0.130
18–44	2,164 (46%)	649 (48%)	561 (47%)	517 (45%)	437 (43%)	
45–59	1,227 (26%)	349 (24%)	305 (23%)	290 (26%)	283 (31%)	
≥60	1,601 (28%)	513 (29%)	426 (30%)	370 (28%)	292 (27%)	
Race						**<0.001**
Hispanic	1,011 (15%)	349 (19%)	285 (17%)	226 (14%)	151 (9.3%)	
Non-Hispanic Asian	608 (6.3%)	360 (16%)	129 (5.1%)	85 (3.3%)	34 (1.3%)	
Non-Hispanic Black	1,353 (12%)	395 (13%)	394 (14%)	340 (12%)	224 (7.6%)	
Non-Hispanic White	1,776 (63%)	343 (49%)	427 (61%)	471 (67%)	535 (77%)	
Other/multi-racial	244 (3.9%)	64 (3.8%)	57 (3.7%)	55 (3.7%)	68 (4.5%)	
Education						**0.010**
High education	4,061 (93%)	1,152 (91%)	1,052 (92%)	1,011 (95%)	846 (92%)	
Low education	648 (7.5%)	240 (9.5%)	156 (7.8%)	115 (5.1%)	137 (7.5%)	
Marital						**0.013**
Married/living with partner	2,798 (61%)	810 (57%)	686 (57%)	695 (64%)	607 (66%)	
Other	2,194 (39%)	701 (43%)	606 (43%)	482 (36%)	405 (34%)	
PIR						0.300
Low income	725 (11%)	233 (12%)	180 (11%)	169 (9.1%)	143 (11%)	
Not low income	3,655 (89%)	1,072 (88%)	945 (89%)	880 (91%)	758 (89%)	
Alcohol						**<0.001**
No drinking in the past year	683 (9.8%)	377 (19%)	157 (11%)	95 (5.5%)	54 (3.7%)	
Less than once a week	2,801 (54%)	812 (54%)	788 (59%)	669 (56%)	532 (48%)	
Once a week or more	1,506 (36%)	321 (27%)	347 (30%)	413 (39%)	425 (48%)	
Missing	2 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)	1 (<0.1%)	
Smoking						**<0.001**
Current smoker	711 (13%)	115 (8.2%)	143 (10%)	194 (14%)	259 (22%)	
Former smoker	1,069 (23%)	238 (16%)	271 (22%)	302 (30%)	258 (25%)	
Never smoker	3,211 (63%)	1,157 (76%)	878 (68%)	681 (57%)	495 (53%)	
BMI (kg/m^2)	28 (24, 33)	27 (23, 31)	28 (24, 33)	29 (25, 33)	29 (26, 34)	**<0.001**
Waist circumference (cm)	98 (87, 110)	93 (83, 104)	97 (86, 108)	99 (89, 112)	102 (91, 113)	**<0.001**
Vigorous activity						**0.002**
Yes	1,458 (33%)	457 (39%)	407 (37%)	343 (31%)	251 (26%)	
No	3,534 (67%)	1,054 (61%)	885 (63%)	834 (69%)	761 (74%)	
Moderate activity						0.200
Yes	2,235 (51%)	726 (55%)	590 (53%)	498 (48%)	421 (47%)	

(Continued)

TABLE 1 (Continued)

Characteristic	Overall, N =4,922 (100%)[a]	Q1, N = 1,511 (25%)[a]	Q2, N = 1,292 (25%)[a]	Q3, N = 1,177 (25%)[a]	Q4, N = 1,012 (25%)[a]	P-Value[b]
No	2,755 (49%)	785 (45%)	701 (47%)	678 (52%)	591 (53%)	
ALT (U/L)	18 (13, 27)	17 (13, 24)	18 (14, 27)	17 (13, 26)	20 (15, 30)	**<0.001**
AST (U/L)	19 (16, 23)	19 (16, 23)	20 (16, 24)	19 (16, 23)	19 (16, 24)	0.140
GGT (U/L)	19 (13, 30)	17 (12, 27)	19 (13, 30)	19 (14, 28)	22 (15, 36)	**<0.001**
LSM (kPa)	4.80 (4.00, 6.00)	4.70 (3.80, 5.70)	4.80 (4.00, 5.90)	4.90 (4.00, 6.20)	5.00 (4.20, 6.20)	**0.003**
CAP (dB/m)	256 (215, 304)	240 (208, 291)	249 (211, 295)	256 (212, 306)	275 (231, 319)	**<0.001**

[a]Median (IQR) for continuous; *n* (%) for categorical.
[b]Chi-squared test with Rao & Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples.
The values in bold indicate $P < 0.05$.

TABLE 2 Relationship between UPFs and VCTE in adults in NHANES.

	Non-adjusted model		Model 1		Model 2		Model 3	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
LSM (kPa)(continues)								
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	1.34	1.00, 1.78	1.07	1.00, 1.14	1.03	0.96, 1.10	1.02	0.94, 1.09
Q3	2.04	1.40, 2.97	1.13	1.05, 1.22	1.07	0.99, 1.15	1.07	0.97, 1.17
Q4	2.52	1.71, 3.73	1.15	1.08, 1.22	1.05	0.99, 1.12	1.06	0.99, 1.14
P for trend	**<0.001**		**<0.001**		0.140		0.110	
CAP (dB/m) (continues)								
Q1			Ref.		Ref.		Ref.	
Q2	1.03	1.00, 1.07	1.05	1.00, 1.09	1.02	0.99, 1.05	1.02	0.98, 1.05
Q3	1.06	1.03, 1.10	1.05	1.01, 1.09	1.01	0.91, 1.04	1.02	0.98, 1.05
Q4	1.12	1.09, 1.15	1.10	1.05, 1.15	1.04	1.01,1.07	1.04	1.00 1.08
P for trend	**<0.001**		**<0.001**		**0.003**		**0.009**	

Model 1: Adjusted for demographic factors (gender, age, race, education level, marital status).
Model 2: Further adjusted for lifestyle factors (alcohol intake, smoking status, waist circumference).
Model 3: Further adjusted for biochemical markers (ALT, AST, GGT).
The values in bold indicate $P < 0.05$.

association between UPF intake and CAP remains consistent across multiple demographic and metabolic subgroups, with higher UPF consumption corresponding to increased CAP values. Notably, the effect of UPFs on CAP was more pronounced among individuals with obesity and those with high waist circumference, suggesting a potential interaction between excess adiposity and dietary patterns in hepatic fat accumulation. These findings reinforced the independent association between UPF intake and liver fat deposition while highlighting the modifying effects of metabolic risk factors.

4 Discussion

In this cross-sectional analysis of 4,992 American adults, we found that increased UPFs consumption is linked to a higher risk of developing fatty liver and liver fibrosis, as evidenced by the accelerated accumulation of liver fat.

Socio-demographic factors played a significant role in UPFs consumption patterns, with higher intake predominantly seen in males, non-Hispanic White, and regular alcohol consumers. This indicates varied dietary habits across different demographic groups. Historical NHANES data from 1999 to 2010 indicated that the dietary quality of non-Hispanic White adults was generally lower than that of Mexican American adults (25). Additionally, a rise in UPFs consumption correlated with an increase in BMI, highlighting the substantial influence of UPFs on the prevalence of overweight and obesity. In line with prior research, our analysis also demonstrated a positive relationship between UPFs consumption and body fat accumulation (25).

Our study establishes a definitive link between UPFs consumption and increased liver fat content, leading to a higher risk of fatty liver disease. Individuals with greater UPFs intake showed significant increases in liver fat. Utilizing CAP with a cutoff of > 248 dB/m for fatty liver definition, these individuals had a considerably elevated risk. In a detailed analysis of a subgroup of

TABLE 3 Association of UPFs with fatty liver and liver fibrosis in adults in NHANES.

	Non-adjusted model		Model 1		Model 2		Model 3	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
LSM >7 kPa								
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	1.00	0.98, 1.03	1.21	0.74, 1.97	1.03	0.63, 1.69	1.05	0.60, 1.84
Q3	1.04	1.01, 1.08	1.69	1.03, 2.78	1.26	0.76, 2.10	1.21	0.67, 2.17
Q4	1.05	1.02, 1.08	1.75	1.10, 2.80	1.19	0.71, 2.00	1.27	0.68, 2.36
P for trend	**0.002**		**0.031**		0.6		0.7	
CAP > 248 dB/m								
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	1.11	0.95, 1.30	1.17	0.97, 1.40	1.06	0.88, 1.29	1.06	0.85, 1.33
Q3	1.29	1.09, 1.52	1.24	1.02, 1.52	1.06	0.91, 1.25	1.09	0.89, 1.33
Q4	1.56	1.35, 1.81	1.48	1.21, 1.81	1.21	1.04,1.41	1.22	1.02, 1.47
P for trend	**<0.001**		**<0.001**		**0.022**		**0.020**	

Model 1: Adjusted for demographic factors (gender, age, race, education level, marital status).
Model 2: Further adjusted for lifestyle factors (alcohol intake, smoking status, waist circumference).
Model 3: Further adjusted for biochemical markers (ALT, AST, GGT).
The values in bold indicate $P < 0.05$.

adults with obesity and metabolic syndrome, a higher consumption of UPFs was consistently linked to increased visceral fat, an elevated fat ratio, and greater total body fat accumulation (27). The consumption of saturated fats is known to quickly increase liver lipid storage, alter energy metabolism and insulin resistance, and affect liver gene expression and signaling pathways, potentially accelerating the onset of fatty liver disease (28). Studies showed that diets low in carbohydrates and fats, combined with aerobic and resistance exercises, led to reductions in body weight, total and visceral fat, and hepatic lipid content (29), ultimately decreasing liver fat (30).

Our examination of the connection between UPFs consumption and liver fat buildup considered multiple factors. UPFs often have a poor nutritional profile, enriched with high levels of saturated and trans fatty acids to enhance flavor and stability (7), factors closely linked to increased liver fat in humans. Additionally, UPFs typically lack dietary fiber (31), a deficiency tied to the development of MASLD. Large-scale studies demonstrate an inverse relationship between dietary fiber intake and MASLD prevalence (32). Dietary fiber is vital for maintaining gut microbiome balance and increasing satiety, which indirectly reduces the intake of high-fat and high-sugar foods, thereby lowering the risk of liver fat accumulation. UPFs are also rich in refined carbohydrates, leading to postprandial hyperglycemia (33), closely associated with disturbances in glucose, insulin, and lipid metabolism, crucial factors in liver fat increase (34, 35). Furthermore, experimental studies show that certain additives in UPFs, like nanoparticles, can induce gastotoxicity and hepatotoxicity, and disrupt the gut microbiome (36), highlighting the complex risks of UPFs consumption and its potential impact on liver health.

The normal liver parenchyma, supported by thin connective tissue capsules and the extracellular matrix (ECM), maintains flexibility, allowing increased blood flow without significant intrahepatic pressure rise. However, an increase in ECM components, especially collagen, and subsequent changes in liver parenchyma vascular architecture lead to increased tissue stiffness. Fibrosis involves a significant rise in fibrous tissue or collagen, directly associated with increased tissue stiffness (37). Liver fibrosis is a dynamic condition where excessive ECM buildup, prompted by injury and inflammation, is balanced by its degradation and remodeling (38). When fibrogenesis surpasses degradation, it alters vascular structures, leading to cirrhosis. This fibrosis progression is often slow initially, potentially accelerating in later stages or under immunocompromised conditions. LSM aligns with liver fibrosis stages, showing gradual increases in early disease phases (stages 0–2) and sharp rises in advanced stages (stages 3–4) (39). Our study used LSM to examine the effect of UPFs consumption on liver fibrosis and found that although LSM values increased with higher UPFs intake, the rise wasn't consistent, preventing a definitive claim that increased UPFs consumption directly heightens liver fibrosis risk. This variability may be due to the slow progression of fibrogenesis in early fibrosis, affected by factors like inflammation, edema, venous congestion, and biliary obstruction, which all increase liver parenchyma stiffness. Moreover, the specific nutritional content of different UPFs categories could differently influence fibrogenesis, making it challenging to establish a direct causal link between UPFs consumption and fibrosis risk.

Our study boasts significant strengths, such as its large, nationally representative American sample, lending external validity to our findings. Using LSM and CAP as biomarkers provides accurate, objective liver health assessments. Nevertheless, the study's cross-sectional nature limits our ability to deduce temporal causality. Confirming our results requires longitudinal studies. Additionally, daily food consumption variability and potential dietary recall bias, possibly leading to UPFs intake underreporting, need careful consideration. The varied impact of

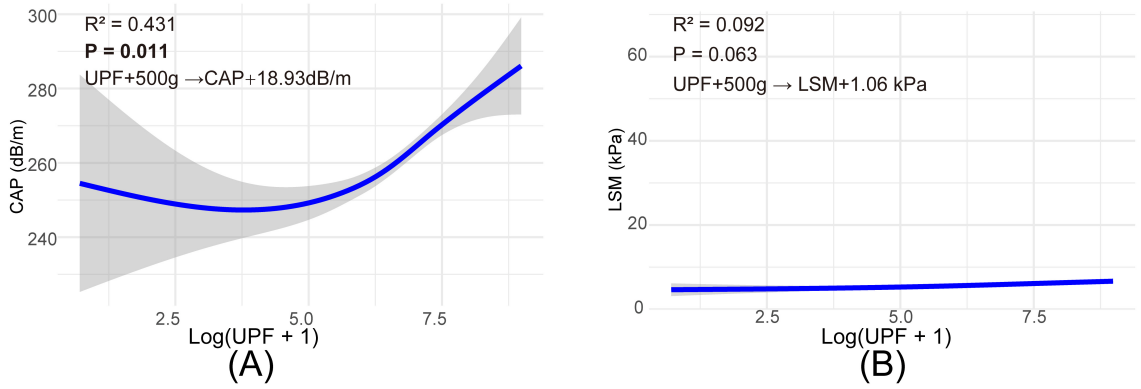

FIGURE 2
Smooth curve fitting to describe the linear relationship between log(UPF + 1) consumption and VTEC. **(A)** Association between log(UPF +1) consumption and CAP values, **(B)** association between log(UPF +1) consumption and LSM values.

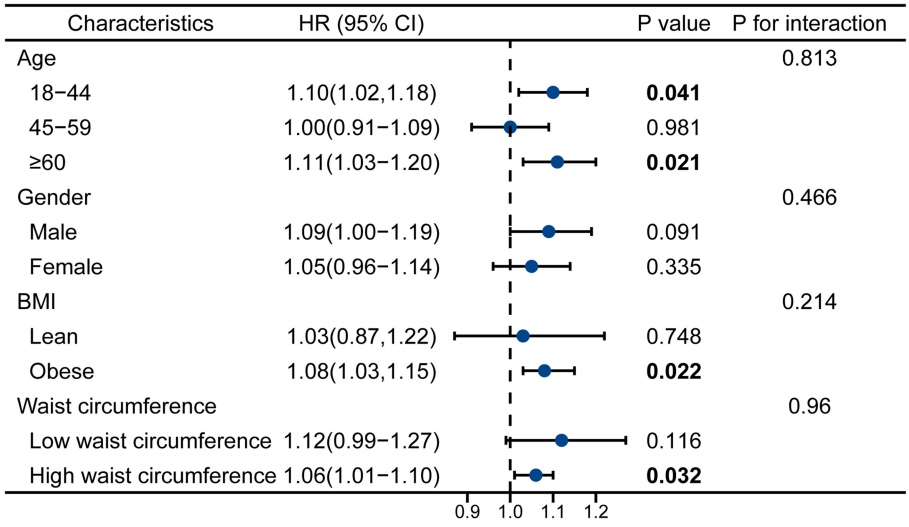

FIGURE 3
Stratified analysis of UPF consumption and CAP across different subgroups.

different UPFs categories on liver health also requires further detailed study. Prospective research is crucial to validate our findings. If confirmed, reducing UPFs consumption could become a key strategy for preserving liver health in adults.

5 Conclusions

In conclusion, our research emphasizes a strong correlation between UPFs consumption and the risk of fatty liver disease in American adults, with a higher intake of UPFs associated with increased liver fat. The association between UPFs consumption and liver fibrosis, however, is less clear, necessitating further study to clarify the mechanisms and potential causal links. Prospective studies are needed to confirm these findings and assess the long-term effects of UPFs on liver health. Limiting UPFs intake may be a strategic preventive measure against fatty liver disease and fibrosis, thus improving liver health outcomes in the adult population.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by NCHS Research Ethics Review Board (ERB), National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), and U.S. Department of Health and Human Services (HHS). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication

of any potentially identifiable images or data included in this article.

Author contributions

JS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. SC: Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. KQ: Methodology, Software, Validation, Writing – original draft, Writing – review & editing. WY: Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing.

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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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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Serum manganese and its association with non-alcoholic fatty liver disease: findings from NHANES

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Objective: This study examines the link between serum manganese (Mn) levels and non-alcoholic fatty liver disease (NAFLD), with a focus on gender differences.

Methods: Utilizing data from the NHANES 2017–2018, we included participants aged 18 and older, excluding those without ultrasonic liver assessment, serum Mn data, or with hepatitis or significant alcohol use. The final analysis comprised 4,294 individuals, with 2,708 in the NAFLD group and 1,586 in the non-NAFLD group. Serum Mn was quantified via inductively coupled plasma mass spectrometry. We compared demographic and health-related variables between groups using appropriate statistical tests and categorized participants into quartiles based on Mn levels. Multivariate logistic regression and spline regression analyses were conducted to evaluate the association between serum Mn and NAFLD risk by gender.

Results: Serum Mn was significantly elevated in the NAFLD group compared to non-NAFLD individuals (9.06 vs. 9.33 μg/L, $Z = 2.815$, $p = 0.005$). After adjustments, males in the third Mn quartile showed a higher NAFLD risk (OR = 1.575; 95% CI: 1.193–2.087), while females in the fourth quartile also had increased risk (OR = 1.725; 95% CI: 1.313–2.269), both compared to the first quartile ($p < 0.01$). A positive dose–response relationship was found for both genders (P for trend <0.01), with nonlinear associations in males (P for nonlinearity <0.01) and linear associations in females (P for nonlinearity = 0.818). Significant interactions with ethnicity in males and hypertension in females were also noted.

Conclusion: Higher serum Mn levels are significantly associated with increased NAFLD risk in both genders, highlighting the need for gender-specific considerations in future studies and clinical practices.

KEYWORDS

serum manganese, non-alcoholic fatty liver disease, transient elastography of liver, body mass index, hypertension, ethnicity, gender

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinical-pathological syndrome characterized by diffuse macrovesicular fatty degeneration and lipid accumulation in hepatocytes, primarily affecting the liver lobule. Unlike other liver diseases, NAFLD is not attributable to alcohol consumption or other clearly hepatotoxic factors (1). Epidemiological

surveys have highlighted the growing prevalence of NAFLD, which stands at 25.24% globally, making it the most common chronic liver condition worldwide (2). The increasing incidence of NAFLD is closely linked to rising obesity rates, influenced by improved living standards, dietary changes, sedentary lifestyles, and environmental contaminants, which have established etiologic roles with strong sex-dimorphism (3, 4). Projections suggest that by 2030, the number of NAFLD cases will escalate by 21%, reaching 100.9 million from 83.1 million in 2015 (5). If left unmanaged, NAFLD can progress to more severe liver conditions, such as fibrosis, cirrhosis, and hepatocellular carcinoma (6).

Manganese (Mn) is a trace element with toxic potential, which enters the body mainly through the gastrointestinal tract from sources such as dietary intake, including the consumption of vegetables and fruits contaminated with fungicides such as maneb and mancozeb, as well as other environmental exposures (7). Mn is crucial for the clearance of reactive oxygen species (ROS) from mitochondrial oxidative stress, primarily through its role in the enzyme manganese superoxide dismutase (Mn-SOD). The C47T polymorphism in the SOD2 gene, which affects Mn-SOD's mitochondrial targeting and activity, has been identified as an independent risk factor for advanced fibrosis in NAFLD (8). Although the exact pathogenesis of NAFLD remains elusive, the involvement of ROS, oxidative stress, inflammation, and fatty acid metabolism imbalances are key contributing factors (9). Elevated serum Mn levels can exacerbate NAFLD progression by influencing fat accumulation, lipogenesis, insulin resistance, oxidative stress, and inflammation (10).

With the modernization of agriculture and industry, metal pollution has intensified, leading to a growing concern about the impact of various metals on health. Studies have demonstrated significant associations between NAFLD and exposures to metals such as cadmium (11) and arsenic (12), among others (13). Despite the lack of safe and effective treatments for NAFLD, research on the correlation between trace metal Mn and NAFLD is still limited. Notably, serum Mn levels exhibit significant gender differences, with females showing higher levels than males (14).

However, it is important to note that serum Mn levels may not be fully predictive of internal contamination. Studies suggest that matrices like hair could provide a more accurate assessment of Mn exposure due to its longer retention time and less fluctuation compared to serum levels (14). This limitation should be considered when interpreting the results of this study.

This study aims to analyze these gender differences separately, exploring the correlation between serum Mn levels and the risk of NAFLD progression in both males and females. By doing so, the study seeks to enhance the understanding of NAFLD pathogenesis from different perspectives and identify potential biomarkers for its development. This could ultimately aid in formulating effective prevention strategies at both the individual and population levels.

Participants and methods

Participants

The National Health and Nutrition Examination Survey (NHANES) is a comprehensive cross-sectional study aimed at evaluating the health and nutritional status of the U.S. population (15). Conducted every 2 years, NHANES gathers extensive data encompassing demographic, lifestyle, health, and nutritional information from participants. The NHANES public database can be accessed at NHANES CDC.[1] For this investigation, we utilized data from the 2017–2018 NHANES cycle. Our inclusion criteria focused on registered participants aged 18 years and older, yielding an initial cohort of 5,856 individuals. We applied several exclusion criteria: (1) absence of liver ultrasound transient elastography results ($n = 253$); (2) diagnosis of hepatitis B or C ($n = 85$); (3) significant alcohol intake (men >30 g/day, women >20 g/day) ($n = 478$); (4) missing critical laboratory data such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ($n = 489$); and (5) unavailability of serum manganese (Mn) levels ($n = 257$). Ultimately, a total of 4,294 participants were retained for analysis.

Assessment of NAFLD

Liver ultrasound transient elastography serves as a non-invasive, objective method for diagnosing non-alcoholic fatty liver disease (NAFLD), noted for its robust sensitivity and specificity in population studies (16). The Controlled Attenuation Parameter (CAP) is a key indicator for NAFLD detection, with performance comparable to that of liver biopsy, which is considered the gold standard. A diagnosis of NAFLD is established with a CAP value of 223 dB/m or above, while excluding individuals with hepatitis B, hepatitis C, autoimmune liver disorders, and significant alcohol use (men >30 g/day, women >20 g/day) (17).

Serum Mn levels

Serum manganese levels were measured at the Environmental Health Sciences Laboratory of the National Center for Environmental Health using inductively coupled plasma dynamic reaction cell mass spectrometry. This process adheres to rigorous quality control standards (18). Normal serum Mn concentrations typically range from 4 to 15 μg/L. (19) In this study, the detection threshold for serum Mn was set at 0.990 μg/L, with any values below this limit substituted with the detection limit divided by the square root of 2.

Statistical methods

We conducted statistical analyses using R version 4.2.2. For data that exhibited skewed distributions, results are presented as medians (M) with interquartile ranges (P25, P75), and comparisons were performed using the Wilcoxon rank-sum test. Categorical variables were represented as counts and percentages, with differences assessed via the chi-square (χ^2) test. To explore the association between serum Mn levels and NAFLD, we employed multivariate adjusted logistic regression models. Serum Mn levels were analyzed both as continuous and categorical variables, stratified into quartiles with the first quartile serving as the reference group. Odds ratios (OR) and 95% confidence intervals (CI)

1 https://www.cdc.gov/nchs/nhanes/

were computed across three modeling approaches: Model 1, which included no adjustments; Model 2, which adjusted for demographic factors such as age, ethnicity, education, marital status, Family-to-Poverty Ratio (FMPIR), and Body Mass Index (BMI); and Model 3, which further adjusted for health-related factors including smoking, alcohol consumption, diabetes, hypertension, and hyperlipidemia.

We also utilized restricted cubic spline regression to examine non-linear relationships between serum Mn levels and NAFLD, visualizing the dose–response association. Additionally, subgroup analyses were performed, categorizing participants by age, ethnicity, education, marital status, FMPIR, smoking status, alcohol consumption, and history of diabetes, hypertension, and hyperlipidemia. Interaction terms were incorporated into our models, and likelihood ratio tests were conducted to assess the presence of interactions, thereby uncovering potential variations in the relationship between serum Mn levels and NAFLD. A p-value of less than 0.05 was deemed statistically significant.

Results

Demographic characteristics of study participants

The study comprised 4,294 participants, divided into 2,708 individuals with NAFLD and 1,586 without NAFLD. Notable differences in demographic and clinical features were evident between these groups. Participants with NAFLD were significantly older and included a higher proportion of males, Mexican Americans, individuals with high school education or less, and those with a history of smoking more than 100 cigarettes in their lifetime. Additionally, the NAFLD group had more married individuals or those living with a partner, and a larger proportion fell within the FMPIR range of 1.30 to 3.50 and had a BMI of 30 or higher.

Clinically, the NAFLD group exhibited elevated levels of systolic and diastolic blood pressure, HOMA-IR, waist circumference, triglycerides, ALT, AST, GGT, fasting glucose, CRP, HbA1c, and CAP, along with reduced levels of HDL-C. The prevalence of diabetes, hypertension, and hyperlipidemia was also significantly higher in the NAFLD group ($p < 0.01$). Furthermore, serum manganese (Mn) levels were higher in the NAFLD group compared to the non-NAFLD group. Detailed demographic and clinical data are presented in Table 1.

Logistic analysis of serum Mn and NAFLD by gender

To determine the association between serum Mn levels and NAFLD, multivariate logistic regression models were employed, stratified by gender. Serum Mn was assessed both as a continuous variable and across quartiles.

For males, each quartile increase in serum Mn was associated with a 25.20% (OR = 1.252, 95% CI: 1.097–1.429), 17.70% (OR = 1.177, 95% CI: 1.020–1.358), and 18.90% (OR = 1.189, 95% CI: 1.028–1.375) higher risk of NAFLD in models 1, 2, and 3, respectively. When analyzed by quartiles, in model 3, the risk of NAFLD increased by 40.70% (OR = 1.407, 95% CI: 1.097–1.807) and 57.50% (OR = 1.575, 95% CI: 1.193–2.087) in the Q2 and Q3 groups compared to the lowest Mn group (Q1).

For females, similar trends were observed. The risk of NAFLD increased by 12.90% (OR = 1.129, 95% CI: 1.018–1.252), 26.60% (OR = 1.266, 95% CI: 1.128–1.421), and 32.40% (OR = 1.324, 95% CI: 1.176–1.491) per quartile increase in serum Mn in models 1, 2, and 3, respectively. When comparing quartiles in model 3, the risk of NAFLD was higher by 30.60% (OR = 1.306, 95% CI: 1.006–1.696), 44.40% (OR = 1.444, 95% CI: 1.109–1.882), and 72.50% (OR = 1.725, 95% CI: 1.313–2.269) in the Q2, Q3, and Q4 groups, respectively, relative to the lowest Mn group (Q1).

These findings highlight a significant association between elevated serum Mn levels and increased risk of NAFLD, with varying degrees of risk observed across different quartiles of Mn concentration. Detailed logistic regression results are provided in Tables 2, 3.

Dose–response relationship between serum manganese (Mn) and NAFLD by gender

After adjusting for variables such as age, ethnicity, education, marital status, FMPIR, BMI, smoking, alcohol consumption, diabetes, hypertension, and hyperlipidemia, we employed restricted cubic spline regression analysis to examine the relationship between serum manganese (Mn) levels and the risk of non-alcoholic fatty liver disease (NAFLD) by gender.

In males, a positive dose–response relationship was observed between serum Mn levels and the risk of NAFLD ($p < 0.01$), with a significant non-linear component (P for nonlinearity <0.01). Specifically, serum Mn levels below 8.747 μg/L were protective against NAFLD, with the protective effect diminishing as Mn levels increased. Between 8.747 μg/L and 10.909 μg/L, serum Mn levels were associated with an increased risk of NAFLD, and this risk continued to rise with higher levels. Beyond 10.909 μg/L, no significant association with NAFLD risk was detected.

In females, the positive dose–response relationship between serum Mn levels and NAFLD risk was also significant ($p < 0.01$), but the relationship was linear (P for nonlinearity = 0.818). Serum Mn levels below 9.850 μg/L were protective, with the protective effect declining as levels increased. When serum Mn levels exceeded 9.850 μg/L, the risk of NAFLD increased significantly.

Figures 1, 2 provide a detailed illustration of these relationships.

Subgroup analysis of serum Mn and NAFLD by gender

In males, significant interactions were found between serum Mn levels and both ethnicity ($p = 0.011$) and education ($p = 0.020$). For non-Hispanic Black males, each quartile increase in serum Mn was associated with a 52.90% increase in the risk of NAFLD (OR = 1.529; 95% CI: 1.164–2.008). Additionally, males with education below high school experienced a 70.30% increase in NAFLD risk (OR = 1.703; 95% CI: 1.233–2.351), with these differences being statistically significant ($p < 0.01$).

In females, a significant interaction was observed between serum Mn levels and hypertension status ($p = 0.006$). Hypertensive females experienced a 65.80% increase in NAFLD risk (OR = 1.658; 95% CI: 1.153–2.386) with each quartile increase in serum Mn. Conversely, non-hypertensive females had a 31.40% increase in NAFLD risk

TABLE 1 Basic characteristics of research subjects.

Characteristics	Non-NAFLD Group (n = 1,586)	NAFLD Group (n = 2,708)	z/χ^2 value	p value
Age (Years)[a]	41 (27, 61)	55 (40, 66)	13.899	<0.001
Age Group[b]				
18–39 Years	755 (47.60)	643 (23.74)		
40-59 Years	370 (23.33)	917 (33.86)	159.321	<0.001
≥ 60 Years	461 (29.07)	1,148 (42.39)		
Gender[b]				
Female	924 (58.26)	1,336 (49.34)		
Male	662 (41.74)	1,372 (50.66)	31.954	<0.001
Ethnicity[b]				
Mexican American	154 (9.71)	447 (16.51)		
Non-Hispanic Black	428 (26.99)	540 (19.94)	55.251	<0.001
Non-Hispanic White	548 (34.55)	954 (35.23)		
Other	456 (28.75)	767 (28.32)		
Education[b]				
College or Above	939 (59.21)	1,511 (55.80)		
High School	378 (23.83)	654 (24.15)	7.131	0.028
Below High School	269 (16.96)	543 (20.05)		
Lifetime Smoking Number[b]				
< 100 Cigarettes	995 (62.74)	1,577 (58.24)		
≥ 100 Cigarettes	591 (37.26)	1,131 (41.76)	8.438	0.004
Marital Status[b]				
Married/Living with Partner	807 (50.88)	1,656 (61.15)		
Never Married	453 (28.56)	428 (15.80)	100.530	<0.001
Widowed/Divorced/Separated	326 (20.56)	624 (23.04)		
Alcohol Consumption[a]	1.392 (87.77)	2,409 (88.96)	1.395	0.258
FMPIR[a]	2.03 (1.10, 3.98)	2.19 (1.22, 4.17)	2.404	0.016
FMPIR Grouping[b]				
<1.30	504 (31.78)	741 (27.36)		
≥3.50	475 (29.95)	846 (31.24)	9.690	0.008
1.30 ≤ FMPIR < 3.50	607 (38.27)	1,121 (41.40)		
BMI (kg/m^2)[a]	24.7 (21.7,28.0)	30.4 (26.8, 35.2)	12.879	<0.001
BMIGrouping[b]				
< 25 kg/m^2	823 (51.89)	376 (13.88)		
≥ 30 kg/m^2	275 (17.34)	1,429 (52.77)	835.881	<0.001
25 ~ <30 kg/m^2	488 (30.77)	903 (33.35)		
Systolic Blood Pressure (mmHg)[a]	117 (107,130)	125 (115,136)	13.976	<0.001
Diastolic Blood Pressure (mmHg)[a]	70 (63, 77)	73 (66, 81)	9.425	<0.001
HOMA-IR[a]	1.73 (1.11, 2.68)	3.14 (2.03, 4.98)	26.577	<0.001
WC(cm)[a]	87.20 (78.70, 96.80)	104.20 (95.10,115.70)	33.555	<0.001
TG (mmol/L)[a]	1.00 (0.73, 1.42)	1.47 (1.05, 2.03)	22.057	<0.001
ALT (μ/L)[a]	14 (11, 19)	18 (14, 25)	16.639	<0.001
AST (μ/L)[a]	18 (15, 21)	19 (16, 23)	4.680	<0.001
GGT (IU/L)[a]	16 (12, 22)	21 (16, 29)	17.662	<0.001
HDL-C (mmol/L)[a]	1.45 (1.24, 1.71)	1.24 (1.06, 1.50)	17.203	<0.001

(Continued)

TABLE 1 (Continued)

Characteristics	Non-NAFLD Group (n = 1,586)	NAFLD Group (n = 2,708)	z/χ^2 value	p value
GLU (mmol/L)[a]	5.50 (5.16, 5.88)	5.94 (5.50, 6.66)	20.859	<0.001
CRP (mg/L)[a]	1.14 (0.60, 2.78)	2.31 (1.08, 4.72)	16.532	<0.001
HbA1c (%)[a]	5.40 (5.20, 5.70)	5.70 (5.40, 6.10)	18.207	<0.001
CAP (db/m)[a]	205 (182, 221)	292 (265, 327)	54.772	<0.001
Hypertension[b]	173 (10.91)	489 (18.06)	39.209	<0.001
Hyperlipidemia[a]	60 (3.78)	370 (13.66)	108.331	<0.001
Diabetes[b]	95 (5.99)	526 (19.42)	145.919	<0.001
Serum Mn (μg/L)[a]	9.06 (7.25, 11.38)	9.33 (7.54, 11.52)	2.815	0.005

[a]Data are presented as M (P25, P75).
[b]Data are presented as cases (%).

TABLE 2 Logistic analysis of serum Mn and NAFLD in male.

Group	Model 1		Model 2		Model 3	
	OR(95%CI)	p value	OR(95%CI)	p value	OR(95%CI)	p value
Mn	1.252 (1.097,1.429)	0.001	1.177 (1.020,1.358)	0.026	1.189 (1.028–1.375)	0.020
Q1 Group	1.000	-	1.000	-	1.000	-
Q2 Group	1.468 (1.164, 1.854)	0.001	1.374 (1.074, 1.759)	0.012	1.407 (1.097–1.807)	0.007
Q3 Group	1.714 (1.325, 2.227)	<0.001	1.573 (1.196, 2.076)	0.002	1.575 (1.193–2.087)	0.001
Q4 Group	1.325 (0.995, 1.772)	0.056	1.159 (0.851, 1.585)	0.352	1.180 (0.861–1.624)	0.306

TABLE 3 Logistic analysis of serum Mn and NAFLD in female.

Group	Model 1		Model 2		Model 3	
	OR(95%CI)	p value	OR(95%CI)	p value	OR(95%CI)	p value
Mn	1.129 (1.018, 1.252)	0.022	1.266 (1.128, 1.421)	<0.001	1.324 (1.176–1.491)	<0.001
Q1 Group	1.000	—	1.000	—	1.000	—
Q2 Group	1.147 (0.903, 1.458)	0.261	1.243 (0.964, 1.603)	0.094	1.306 (1.006–1.696)	0.045
Q3 Group	1.172 (0.922, 1.490)	0.195	1.367 (1.057, 1.769)	0.017	1.444 (1.109–1.882)	0.006
Q4 Group	1.254 (0.986, 1.595)	0.065	1.563 (1.198, 2.040)	0.001	1.725 (1.313–2.269)	<0.001

Model 1: No confounders adjusted. Model 2: Adjusted for sociodemographic variables including age, ethnicity, education, marital status, FMPIR, and BMI. Model 3: Further adjusted for health-related variables including smoking, alcohol consumption, diabetes, hypertension, and hyperlipidemia on the basis of Model 2. —: No value available.

(OR = 1.314; 95% CI: 1.143–1.511), with both interactions showing statistically significant differences ($p < 0.01$).

Tables 4, 5 provide detailed results of these subgroup analyses.

Discussion

Based on the NHANES 2017–2018 survey data, this study found that serum Mn levels in the NAFLD group were significantly higher than those in the control group ($p = 0.005$). After constructing multivariate logistic regression models and adjusting for confounders, serum Mn levels were positively associated with NAFLD in both males and females (male Q3 vs. Q1: OR = 1.575, 95% CI: 1.193–2.087; female Q4 vs. Q1: OR = 1.725, 95% CI: 1.313–2.267).

The restricted cubic spline regression revealed a nonlinear dose–response relationship in males, where Mn acted protectively at lower concentrations (≤8.747 μg/L) but transitioned to a risk factor at intermediate levels (8.747–10.909 μg/L). In contrast, females exhibited a linear relationship, with Mn becoming a risk factor above 9.850 μg/L. These gender-specific patterns may stem from differences in Mn metabolism, hormonal influences, or genetic factors. For instance, estrogen has been shown to modulate Mn homeostasis by affecting transporters like SLC30A10, which regulates Mn excretion (20). Additionally, males may experience higher oxidative stress due to lower baseline antioxidant enzyme activity (e.g., Mn-SOD), amplifying Mn's toxic effects at intermediate levels (21).

The gender disparity in dose–response relationships could also arise from differences in body composition (e.g., higher lean mass in males altering Mn distribution) or sex-specific expression of Mn-binding proteins (22).

Mechanistically, Mn's dual role—as a nutrient and toxin—may explain the observed thresholds. At physiological levels, Mn supports mitochondrial function and antioxidant defense via Mn-SOD (23). However, beyond optimal levels, Mn's toxicity may outweigh its beneficial effects, contributing to the pathogenesis of NAFLD through mechanisms such as increased oxidative stress and inflammation (24, 25).

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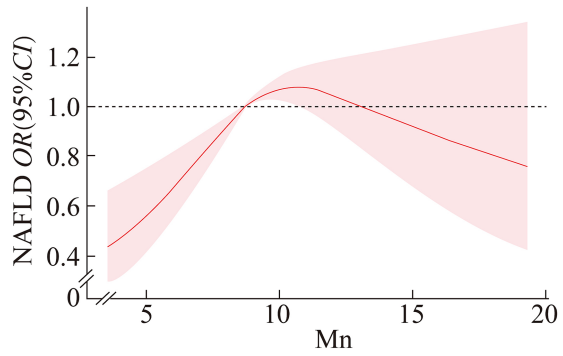

FIGURE 1
Dose–response relationship between serum Mn and NAFLD in male.

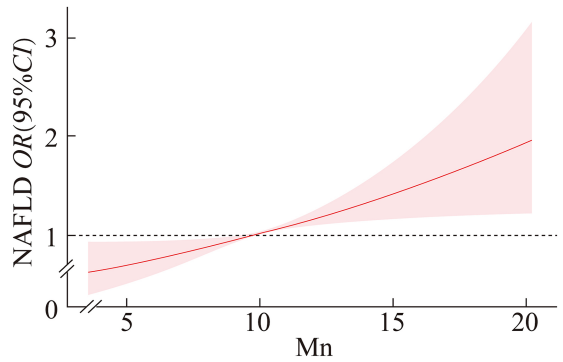

FIGURE 2
Dose–response relationship between serum Mn and NAFLD in female.

Notably, conflicting findings from prior studies warrant discussion. While animal models report lower hepatic Mn levels in NAFLD (26), this discrepancy may reflect species-specific Mn metabolism or compensatory mechanisms in chronic disease. Serum Mn levels may not fully correlate with tissue accumulation in advanced NAFLD, as hepatic damage could impair Mn storage or increase systemic release (23). Furthermore, human studies using serum Mn (27) versus tissue-specific measurements (26) may yield divergent results. For example, serum Mn elevation in NAFLD could indicate dysregulated excretion (e.g., via bile) rather than tissue overload (28), a hypothesis requiring validation through paired serum and liver biopsy studies.

Subgroup analyses highlighted interactions between Mn and sociodemographic/clinical factors. In males, ethnicity and education modified Mn-NAFLD associations, possibly due to environmental or occupational Mn exposure disparities (e.g., non-Hispanic Black individuals facing higher industrial pollution). Hypertensive females exhibited stronger Mn-NAFLD links, suggesting shared pathways between Mn toxicity, oxidative stress, and endothelial dysfunction.

Limitations of this cross-sectional study preclude causal inferences. While serum Mn levels are a practical biomarker, they may not fully reflect hepatic Mn accumulation or long-term exposure. Prospective cohort studies with repeated Mn measurements and tissue-level data (e.g., liver biopsies) are needed to clarify causality. Additionally, confounding by unmeasured factors (e.g., dietary Mn intake, genetic polymorphisms in Mn transporters) and recall bias in self-reported covariates (e.g., alcohol use) may influence results.

In conclusion, this study underscores serum Mn as a potential risk factor for NAFLD, with gender-specific thresholds and mechanisms. Future research should prioritize elucidating Mn's tissue-specific

TABLE 4 Subgroup analysis of serum Mn and NAFLD in male.

Characteristics	OR(95%CI)	*p* value
Ethnicity		
Mexican American	1.450 (0.950–2.215)	0.085
Other	0.916 (0.730–1.151)	0.453
Non-Hispanic White	1.119 (0.903–1.387)	0.303
Non-Hispanic Black	1.529 (1.164–2.008)	0.002
Education		
Below High School	1.703 (1.233–2.351)	0.001
High School	1.122 (0.876–1.439)	0.362
College or Above	1.052 (0.879–1.261)	0.579
Marital Status		
Married/Living with Partner	1.158 (0.971–1.381)	0.102
Never Married	1.107 (0.858–1.429)	0.435
Widowed/Divorced/ Separated	1.295 (0.917–1.828)	0.142
Age		
18–39 Years	1.087 (0.878–1.345)	0.444
40–60 Years	1.193 (0.901–1.579)	0.218
> 60 Years	1.219 (0.977–1.520)	0.079
FMPIR		
< 1.30	1.308 (1.025–1.670)	0.031
1.30 ≤ FMPIR <3.50	1.114 (0.897–1.383)	0.328
≥ 3.50	1.149 (0.909–1.453)	0.245
BMI		
< 25 kg/m^2	1.146 (0.986–1.332)	0.076
≥ 30 kg/m^2	1.136 (0.987–1.308)	0.075
25 -< 30 kg/m^2	1.143 (0.986–1.324)	0.076
Lifetime Smoking Number		
< 100 Cigarettes	1.144 (0.957–1.367)	0.140
≥ 100 Cigarettes	1.173 (0.972–1.416)	0.096
Alcohol Consumption		
Yes	1.181 (1.032–1.351)	0.016
No	0.850 (0.510–1.416)	0.533
Diabetes		
Yes	1.238 (0.810–1.891)	0.323
No	1.151 (1.002–1.322)	0.046
Hypertension		
Yes	1.197 (0.785–1.824)	0.404
No	1.167 (1.015–1.342)	0.030
Hyperlipidemia		
Yes	0.776 (0.498–1.211)	0.264
No	1.211 (1.054–1.391)	0.007

TABLE 5 Subgroup analysis of serum MN and NAFLD in female.

Characteristics	OR (95%CI)	*p* value
Ethnicity		
Mexican American	1.232 (0.856–1.774)	0.261
Other	1.657 (1.285–2.138)	<0.001
Non-Hispanic White	1.198 (0.989–1.451)	0.065
Non-Hispanic Black	1.239 (0.999–1.537)	0.052
Education		
Below High School	1.565 (1.121–2.184)	0.009
High School	1.330 (1.129–1.566)	0.052
College or Above	1.330 (1.129–1.566)	0.001
Marital Status		
Married/Living with Partner	1.465 (1.225–1.753)	<0.001
Never Married	1.519 (1.140–2.023)	0.004
Widowed/Divorced/ Separated	1.056 (0.843–1.323)	0.633
Age		
18–39 Years	1.810 (1.444–2.268)	<0.001
40–60 Years	1.093 (0.874–1.368)	0.436
60+ Years	1.174 (0.950–1.451)	0.137
FMPIR		
< 1.30	1.399 (1.119–1.748)	0.003
1.30 ≤ FMPIR <3.50	1.368 (1.113–1.682)	0.003
≥ 3.50	1.271 (1.000–1.615)	0.050
BMI		
< 25 kg/m^2	1.306 (0.999–1.539)	0.052
≥ 30 kg/m^2	1.266 (1.106–1.449)	0.001
25 -< 30 kg/m^2	1.278 (1.110–1.471)	0.001
Smoking		
Lifetime Smoking ≥ 100 Cigarettes	1.164 (0.94–1.441)	0.163
Lifetime Smoking < 100 Cigarettes	1.438 (1.231–1.68)	<0.001
Alcohol Consumption		
Yes	1.282 (1.120–1.467)	<0.001
No	1.719 (1.207–2.449)	0.003
Diabetes		
Yes	1.016 (0.658–1.567)	0.944
No	1.385 (1.212–1.583)	<0.001
Hypertension		
Yes	1.658 (1.153–2.386)	0.006
No	1.314 (1.143–1.511)	<0.001
Hyperlipidemia		
Yes	1.177 (0.615–2.252)	0.622
No	1.356 (1.191–1.544)	<0.001

dynamics, longitudinal associations, and molecular pathways in NAFLD pathogenesis. Clinically, monitoring serum Mn in high-risk populations (e.g., industrial workers) and addressing gender-specific risk profiles could enhance NAFLD prevention strategies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Beijing Chao-Yang Hospital. All Patients and their families participated voluntarily and signed informed consent forms, and the study was performed in accordance with the Helsinki II declaration. Informed consent was obtained from all the study subjects before enrollment. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZH: Conceptualization, Investigation, Writing – original draft. YZ: Methodology, Supervision, Writing – original draft. HT: Conceptualization, Formal analysis, Methodology, Writing – review & editing.

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Association between hypoglycemia and poor clinical outcomes in hospitalized non-diabetic patients with liver cirrhosis:– a narrative review

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Hypoglycemia is rarely highlighted as a complication that requires close monitoring in patients with chronic liver disease, despite substantial evidence of its occurrence in cirrhotic patients. This narrative review aims to evaluate whether hypoglycemia in liver cirrhosis patients, irrespective of diabetes status, exacerbates complications and warrants targeted management strategies. Our analysis reveals that hypoglycemia is prevalent in cirrhotic patients and is associated with increased mortality and complications compared to normoglycemic patients. Although literature in this topic is limited, our review suggests that early identification of high-risk liver disease patients and the implementation of novel, clinically relevant strategies to minimize hypoglycemia may improve clinical outcomes and health-related quality of life as well as reduce morbidity and mortality. Further research will be required to validate thesel strategies.

KEYWORDS

hypoglycemia, chronic liver disease, cirrhosis, complications, clinical guidelines

Introduction

Hypoglycemia is commonly discussed in relation to diabetic patients, particularly those using oral hypoglycemic agents or insulin therapy. However, its occurrence in patients with liver disease is also notable. This can be attributed to various factors, including the liver's critical role in glucose metabolism. Despite this, the significance of hypoglycemia in chronic liver disease is rarely addressed, and international clinical guidelines for cirrhosis often overlook its management. This narrative review aims to bridge this gap by critically reviewing the current literature to elucidate the relationship between hypoglycemia and liver cirrhosis. We aim to assess whether protocol implementation to identify and prevent hypoglycemia could improve patient outcomes, irrespective of diabetes status. By focusing on this unexplored aspect of liver disease management, we seek to highlight gaps in the existing literature and contribute to better clinical practice and improved care for patients with liver cirrhosis.

Methods

The authors conducted an extensive literature review in Ovid Medline, Ovid Embase, CINHL, Web of Science, and PsychINFO (OVID), employing the following Medical Subject Headings (MeSH) terms: hypoglycemia, chronic liver disease, cirrhosis, acute on chronic liver disease and decompensated cirrhosis. The review identified 222 studies related to the association between hypoglycemia and chronic liver disease. After scanning the titles and abstracts to remove duplicates, case reports, and editorial comments, 12 publications were selected for full-text screening to explore the significance of hypoglycemia in hospitalized patients with chronic liver disease. The Oxford Equator PRISMA checklist was applied to ensure that the review adhered to evidence-based standards for narrative reviews. This checklist, an internationally recognized guideline, ensures transparency, integrity, and validity in reporting systematic and narrative reviews.

Overview

Hypoglycemia is defined by serum glucose levels typically below 3.9 mmol/L (1). It is a well-known and feared complication in the management of diabetic patients (2). Severe hypoglycemia refers to any hypoglycemic event that requires external assistance for recovery (3). It is associated with falls, neurological disease, cardiovascular events, cognitive impairment, and increased mortality (4).

Cirrhosis is a chronic progressive, end-stage liver disease characterized by the replacement of normal liver tissue with fibrous scar tissue, which disrupts the liver's normal structure and function (5). This includes alterations in key hepatic metabolic processes, such as gluconeogenesis and glycogenolysis, both of which normally contribute to maintaining higher serum glucose levels (6).

During a 2–6 h fast, hepatocytes initiate glycogenolysis, breaking down stored glycogen to release glucose for energy (2). In a state of prolonged fasting, hepatocytes utilize substrates like lactic acid, amino acids, and glycerol to synthesize glucose through gluconeogenesis (2). However, abnormal liver metabolism or cellular damage impairs the liver's ability to regulate blood glucose. Approximately 5%–7% of cirrhotic patients progress to decompensated cirrhosis each year (7). Decompensated cirrhosis is an advanced stage of the disease, marked by severe complications such as hepatic encephalopathy, ascites, and/or variceal bleeding (7).

Is hypoglycemia prevalent among cirrhotic patients without diabetes

Hypoglycemia is frequently observed in cirrhotic patients. Singh et al. (8) reported hypoglycemia in 67% of cirrhotic patients without diabetes, while Noul et al. (9) found it in 50% of individuals hospitalized for septicemia (8, 9), none of whom were on hypoglycemic agents (9). Majeed et al. (10), through a cross-sectional study, also found hypoglycemia in 51.2% of liver cirrhosis patients after excluding those with diabetes, although significant grammatical errors in the study affected its reliability. While less pronounced, Gladys-Oryhon et al. (11) still observed hypoglycemic events in 34.7% of non-diabetic cirrhotic inpatients .

Several factors contribute to the high prevalence of hypoglycemia in cirrhotic patients, including (i) persistent cachexia, especially in decompensated cirrhosis, (ii) reduced hepatocyte mass, leading to decreased gluconeogenic capacity, (iii) sarcopenia, which limits the availability of amino acids necessary for hepatic gluconeogenesis, and (iv) comorbid conditions such as congestive heart failure, chronic pancreatitis with glucagon deficiency, chronic kidney disease, and hepatorenal syndrome. As the liver function deteriorates, the incidence of fasting hypoglycemia rises significantly, indicating the liver's inability to regulate insulin glucose homeostasis in chronic disease (12).

What do current guidelines suggest regarding hypoglycemia in cirrhotic patients?

Whilst continual glucose monitoring is strongly emphasized in hospitalized diabetic patients, regardless of cirrhosis, the European Association for the Study of the Liver (EASL) clinical practice guidelines do not mention tight glucose control for patients admitted with decompensated cirrhosis (13). Similarly, guidelines for compensated liver cirrhosis, such as those by Yoshiji et al. (14) and the British Society of Gastroenterology, do not address hypoglycemia management in non-diabetic cirrhotic patients (15). Whether hypoglycemia should be a concern in cirrhotic patients admitted for reasons other than decompensation, warrants further review.

Another important question is whether avoiding hypoglycemic episodes in hospitalized cirrhotic patients, decompensated or otherwise, could improve outcomes. The only guideline we found that explicitly addresses this is from the American Society of Critical Care Medicine, which states that preventing hypoglycemia in ICU patients with acute-on-chronic liver disease can improve outcomes (16). However, this recommendation is limited to ICU patients, and no clear guidance exists for managing hypoglycemia in non-ICU cirrhotic inpatients, whether admitted with decompensation, acute-on-chronic disease, or other conditions.

Although hypoglycemia management is not specifically included in liver disease guidelines, the American Society of Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism recommended that patients with severe liver dysfunction consume extra nighttime meals to prevent hypoglycemia during temporary fasting.

However, these guidelines do not elaborate on whether this practice should be generalized to all cirrhotic patients (17, 18).

The current literature clearly indicates that hypoglycemia is common amongst cirrhotic patients, irrespective of their diabetes status. To address the significance of identifying hypoglycemia, we reviewed the available evidence. Our goal was to determine whether hypoglycemia is linked to poor outcomes and whether preventing these hypoglycemic events could lead to improved patient outcomes.

Increased adverse outcomes in hypoglycemic patients with cirrhosis admitted to hospital

Obeidat et al. (19) conducted a retrospective study involving 1,778,829 in-patients with cirrhosis, excluding those with diabetes.

The study revealed that in-patient mortality was significantly higher than in the hypoglycemia group compared to the non-hypoglycemia group of cirrhotic patients (OR 6.8; CI 95% 6.4–7.24, *P*-value < 0.001) (19). Additionally, patients in the hypoglycemic group had a longer and more complicated hospital stay, with increased likelihood of vasopressor use, mechanical ventilation, cardiac arrest, and ICU admission (19).

Similarly, Hung et al. (20) reported a 30 days mortality rate of 30.2% in the hypoglycemic group, compared to 7.4% in the non-hypoglycemic group ($P < 0.001$) among hospitalized cirrhotic patients without diabetes. This study further found that the 30 days mortality was even higher in patients with hypoglycemia and hepatocellular carcinoma (HCC), with a hazard ratio of 6.11 (95% CI 4.40–8.49, $P < 0.001$) compared to 4.96 (95% CI 4.05–6.08, $P < 0.001$) for patients without either condition (20).

Although many studies have demonstrated poor outcomes in cirrhotic patients with hypoglycemia, the benefit of preventing hypoglycemia remains unclear. Additionally, there are no current consensus guidelines for monitoring glucose levels in cirrhotic patients. It is also unclear whether hypoglycemia prevention should be applied universally to all cirrhotic patients or targeted specifically to higher-risk groups. Future studies are needed to address these questions and potentially improve the clinical outcome of cirrhotic patients.

Increased adverse outcomes in hypoglycemic patients with cirrhosis admitted in hospital with decompensated cirrhosis

The study by Pfortmueller et al. (21) explored the relationship between hypoglycemia on admission in patients presenting to the emergency department with acutely decompensated cirrhosis. The study found that patients with hypoglycemia were significantly more likely to be admitted to the ICU compared to normoglycemic patients (20.4% vs 10.3%, $P < 0.011$). Additionally, the hypoglycemic group had a higher mortality rate rather than the normoglycemic group (28.6% vs 10.3%, $P < 0.049$), with an estimated survival of 36 days compared to 54 days for the normoglycemic group ($P < 0.007$) (21).

The study also showed a significant association between hypoglycemia and hepatorenal syndrome in decompensated cirrhosis, which may contribute to the increased mortality in the hypoglycemic group (21, 22). Olson et al. (22) highlighted that there are currently no recommendations to treat hypoglycemia in these patients on admission, despite clear evidence of worse prognosis and clinical outcomes. Therefore, the author suggests evaluating whether prophylactic glucose administration could improve clinical outcomes in hypoglycemic patients (22). Future studies should investigate the potential benefit of preventing hypoglycemia in cirrhotic patients through strategies such as prophylactic glucose and nighttime carbohydrate consumption (18, 22).

Increased adverse outcomes in hypoglycemic patients who were admitted to hospital with acute on chronic liver failure

Acute-on-chronic liver failure is a syndrome characterized by the acute deterioration of liver function in patients with pre-existing chronic liver disease, often triggered by factors such as infection, gastrointestinal bleeding, or alcohol consumption (23). A study by Yang et al. (24) involving 218 patients with acute-on-chronic liver failure found hypoglycemia in 45.41% of cases. Hypoglycemia was associated with significantly higher 90 days mortality compared to non-hypoglycemic patients (72.73% vs 48.74%, $P < 0.001$).

The increased mortality was further reflected in additional findings, with hypoglycemic patients showing higher levels of AST (264 vs 216), total bilirubin (379 vs 308), and MELD score (31 vs 25), consistent with the findings of Olsen et al. (22). The analysis of risk factors for hypoglycemia in these patients revealed that liver cirrhosis (OR 5.16) and higher MELD score (OR 1.29) were significant risk factors for hypoglycemia (24). Conversely, higher fibrinogen levels appeared to reduce the risk of hypoglycemia (OR 0.17) (24).

These findings suggest that hypoglycemia may serve as an early indicator of acute-on-chronic liver failure, as evidenced by elevated AST, INR, creatinine, and bilirubin level in hypoglycemia patients, which were not observed in normoglycemic individuals (22).

These findings not only reinforce the evidence of increased adverse outcomes in hypoglycemic cirrhotic patients but also suggest a potential pathway for stratifying and identifying the most at-risk cohorts. This stratification could be based on various criteria, including AST, bilirubin, INR, creatinine, MELD scores and fibrinogen levels (22, 24). Further exploration may provide insights into how stratification can be applied to ensure that high-risk patients are promptly identified and closely monitored.

Hypoglycemia among cirrhosis patients as a predictor of bacteremia and septicemia?

In addition to the increased mortality seen in cirrhotic patients experiencing hypoglycemia, a study by Yedidya et al. (25) demonstrated that hypoglycemia is predictive of bacteremia. Among 1,274 cirrhosis admissions, glucose levels below 5.6 mmol/L increased the likelihood of subsequent bacteremia, even in normothermic patients (25). This study suggests that hypoglycemia could be used as a clinical predictor for bacteremia, raising the question of whether prophylactic antibiotic therapy may be warranted in cirrhotic patients with hypoglycemic events. There is some supporting evidence that prophylactic antibiotics might reduce acute exacerbations of chronic liver diseases (25).

Another study by Nouel et al. (9) found that 50% of cirrhotic patients with septicemia had asymptomatic hypoglycemia. The study also noted that hypoglycemia is commonly seen in cirrhotic patients with septic shock, potentially secondary to endotoxemia. Tanveer et al. (26) further established that hypoglycemia in decompensated cirrhotic patients was consistently associated with septicemia.

Ultimately, future studies are needed to determine whether early identification of hypoglycemia could serve as a predictor for septicemia and justify the use of prophylactic antibiotics or further investigations, such as blood cultures, to improve patient outcomes.

Is there a clear protocol or recommendation for managing hypoglycemia among cirrhosis patients to improve clinical outcomes?

On the balance of the current literature review, a few recommendations can be clearly summarized as follows:

TABLE 1 Characteristics, main results, possible bias of included studies.

References	Study design	Study population	Purpose of study	Main results	Possible bias
Singh et al. (8)	Cross sectional study	100 patients with liver cirrhosis > 12 years of age at Liaquat University Hospital in Hyderabad, Pakistan.	To identify hypoglycemia among cirrhotic patients without diabetes.	Hypoglycemia was observed in 67% of patients with liver cirrhosis.	Selection bias – patients recruited from a single hospital. Sampling bias – $n = 100$, limits generalizability. Measurement bias – glucose levels measured using glucometers, which may be less accurate that laboratory testing. A single-time-point assessment may miss intermittent or nocturnal hypoglycemia. Lack of confounding variable control – nutritional status, infection status, comorbid conditions, are not controlled for in this study, despite potentially influencing glucose levels. Grammar – grammatical errors throughout article may reduce clarity.
Nouel et al. (9)	Observational prospective cohort study	30 patients with cirrhosis and septicemia in Hopital Beaujon, France.	To identify relationship between hypoglycemia, septicemia and mortality among cirrhotic patients.	50% of cirrhosis patients with septicemia had hypoglycemia. 100% of patients with hypoglycemia developed circulatory failure (septic shock), compared to 0% of normoglycemic patients. 11/15 of hypoglycemia patients died within 24–48 h due to septic shock; 3/15 died later due to liver failure; only 1/15 survived. (Mortality rate: 93%). Among normoglycemic patients, 10/15 died, none due to septic shock (mortality rate: 67%).	Sampling bias – $n = 30$, reduces statistical power. Measurement bias – glucose measured only once daily, which may potentially omit intermittent or nocturnal hypoglycemia. Confounding – severity of underlying liver disease, could be responsible for hypoglycemia and development of septic shock. The study doesn't stratify according to degree of liver cirrhosis. Degree of sepsis is also not commented on, as patients with more prominent infections may be at risk of both shock, mortality and hypoglycemia. Lack of control group – no comparison to cirrhotic patients without sepsis or septic patients without cirrhosis, limiting causal conclusions.
Majeed et al. (10)	Cross sectional study.	84 patients in Mayo Hospital, Lahore, Pakistan, who were aged 16–75 with liver cirrhosis and non-diabetic.	To identify hypoglycemia among cirrhotic patients without diabetes.	Hypoglycemia was observed in 51.2% with liver cirrhosis and who didn't have diabetes. There was no correlation between severity of cirrhosis (as per Child Pugh score) and hypoglycemia.	Selection bias – single hospital. Sampling bias – $n = 84$, which limits statistical power. Measurement bias – use of glucometer less accurate than laboratory measurement. Single time-point may miss fluctuations in glucose levels. Confounding variables such as nutritional status, medications, comorbidities were not controlled.
Gladys-Oryhon et al. (11)	Retrospective chart review.	101 non-diabetic cirrhotic patients from a tertiary care hospital. Mean age 62 years.	To identify hypoglycemia among cirrhotic patients without diabetes.	22.8% of patients with cirrhosis and no diabetes, experienced hypoglycemia. Only 35% (35/101) had routine point of care (POC) glucose monitoring.	Selection bias – single center study. Information bias – retrospective design depends on accuracy of medical records. Confounding – no adjustment for severity of liver disease, nutritional status, infections, or medications. Detection bias – limited POC monitoring likely led to underestimation of hypoglycemia.

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TABLE 1 (Continued)

References	Study design	Study population	Purpose of study	Main results	Possible bias
Honda et al. (12)	Cross sectional study.	105 patients with chronic liver disease with type 2 diabetes mellitus.	Aimed to identify hypoglycemia in cirrhotic patients with type 2 diabetes.	CGM was useful for detecting asymptomatic nocturnal hypoglycemia and undetected postprandial hypoglycemia. 22% of patients had nocturnal hypoglycemia.	Lack of control group of healthy individuals or chronic liver disease patients without diabetes, making it hard to generalize the results. Selection bias – $n = 105$, relatively small. Study was limited to T2DM patients, hence did not explore glycemic variability in non-diabetic patients.
Obeidat et al. (19)	Retrospective cohort study.	31,615 cirrhotic patients aged 18 or over, without diabetes were identified from the National Inpatient Sample database in the United States, from 2016 to 2019.	Aimed to analyze the impact that hypoglycemia had on patients with liver cirrhosis and without diabetes.	In-hospital mortality was significantly higher in the cirrhosis patient group with hypoglycemia (adjusted OR: 6.8). Other complications like mechanical ventilation (aOR: 5), vasopressor use (aOR: 4.33), cardiac arrest (aOR: 4.97) and ICU admissions (aOR: 5.09) were more frequent in the hypoglycemia patient group. Hypoglycemia was associated with longer length of stay (7.79 days vs 6.2 days in non-hypoglycemic group).	Use of ICD-10 codes for classification of cirrhosis and hypoglycemia may not be accurate or specific, leading to misclassification of patient's conditions. Confounding bias – the study did control variables such as age, gender, race, comorbidities but did not factor in nutritional status, liver disease etiology or medications. Due to retrospective design, a definitive causality between cirrhosis, hypoglycemia and in-hospital complications cannot be established.
Hung et al. (20)	Retrospective cohort study.	636 cirrhotic patients without diabetes mellitus who presented with hypoglycemia from the Taiwan National Health Insurance Database (2010–2013).	To assess the effect of hypoglycemia at admission on 30 days mortality.	30 days mortality: 30.2% in hypoglycemia group vs 7.4% in non-hypoglycemia group. Adjusted hazard ratio: 4.96 for hypoglycemia; 6.11 when combined with HCC.	Use of ICD-9 codes for classification of cirrhosis and hypoglycemia may lead to diagnostic inaccuracies. Selection bias – may exclude patients with undetected hypoglycemia on admission. Confounding bias – the study did control variables of age, sex and comorbidities, however, other factors such as degree of liver function, medications, nutritional status were not controlled. The study claims that mortality is higher in hypoglycemia group with HCC, but there is no clarification on stage of HCC, as this can be a confounder affecting mortality independent of hypoglycemic state. Measurement bias – study did not clarify the definition of hypoglycemia. There may also be underreporting of hypoglycemia, especially if blood glucose levels not measured routinely in cirrhosis patients presenting to hospital. The patient demographics may not be generalizable to populations outside of Taiwan.
Pfortmueller et al. (21)	Retrospective cohort study.	312 patients aged 16 years and over, admitted into the Emergency Department of Inselspital, Bern University Hospital, Switzerland, between 1 Jan 2002 and 31 Dec 2012, with a primary diagnosis of acute decompensated liver cirrhosis. Patients identified using medical database software (Qualicare Office).	Study aimed to identify rate of glucose disturbance and outcomes associated including ICU admission and mortality in patients presenting with acute decompensated liver cirrhosis.	28.5% of patients experiences glucose disturbances; 15.7% hypoglycemia, 12.8% hyperglycemia. In-hospital mortality; 28.6% in hypoglycemic group vs 7.5% in hyperglycemic group vs 10.3% in normoglycemic group. Survival analysis indicated hypoglycemic group had lower survival (36 days) compared to normoglycemic (54 days) or hyperglycaemic (45 days) groups. ICU admissions were more likely in the hypoglycemia group. 20.4% of hypoglycemic patient's vs 10.8% hyperglycemic patients vs 10.3% normoglycemic patients, were admitted to ICU.	Use of a database inherently has limitations and there may reporting bias present as a result. Detection bias – since serial glucose measurements were not performed, the true detection of hypoglycemia may be underestimated. Confounding – although the study accounted for age, sex, liver disease extent (using Child Pugh classification), and etiology of cirrhosis, it didn't factor in medications, nutritional status and infection state.

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TABLE 1 (Continued)

References	Study design	Study population	Purpose of study	Main results	Possible bias
Yang et al. (24)	Retrospective cohort study	218 patients diagnosed with acute on chronic liver failure. Study was conducted at First Affiliated Hospital of Xi'an Jiaotong University, China, between Jan 2019 and Aug 2021.	Aimed to identify risk factors for hypoglycemia and the impact of hypoglycemia on 90 days mortality.	Risk factors for hypoglycemia were liver cirrhosis (OR 5.16), a higher MELD score (OR 1.29), higher Fibrinogen (FIB) levels (OR 0.17). 45.41% of patients with acute on chronic liver failure had hypoglycemia. 90 days mortality was 72.73% in hypoglycemia group vs 48.74% in non-hypoglycemia group. After adjustment for hepatic encephalopathy, MELD score, and cirrhosis, hypoglycemia remained an independent risk factor for 90 days mortality (OR = 8.72).	Retrospective design – using historical data has its inherent bias, and potentially incomplete or missing records may result in errors. Generalizability may be limited as the population is from a single hospital only. Confounding – although the study adjusted for hepatic encephalopathy, cirrhosis, MELD scores, there may still be confounding variables such as medications, nutritional status, which may influence hypoglycemia and mortality. The study identified hypoglycemia as a risk factor for mortality, however, it does not investigate whether treatment of hypoglycemia may reduce mortality.
Yedidya et al. (25)	Retrospective case-control	1,274 patients aged 18 and over admitted with cirrhosis who had blood culture results. University of Pennsylvania Health System.	Aimed to identify relationship between hypoglycemia in cirrhotic patients and bacteremia.	52.7% of blood cultures were positive for bacteremia. 10.1% of patients with positive blood cultures had hypoglycemia 24–72 h prior, compared to 6.1% in those with negative blood cultures. Minimum glucose 24–72 h prior to blood culture result was a significant predictor for blood culture positivity. Glucose level < 100 mg/dL increased probability of positive blood culture (OR 1.89 for 50 mg/dL vs 100 mg/dL).	Use of ICD-9 codes for classification may not be accurate or specific, potentially leading to misclassification of patient's conditions. Selection bias – single healthcare system used, may not be fully representative of generalized population. Information bias due to inherently being a retrospective study, and hence inaccuracies or missing data in the records could be present, including exact time of glucose measurement and culture results.
Tanveer et al. (26)	Cross sectional study	84 patients diagnosed with liver cirrhosis without diabetes. Study conducted in Department of Medicine, Mayo Hospital, Lahore, Pakistan.	Aimed to identify hypoglycemic patients.	51.2% had hypoglycemia.	Selection bias – single hospital. Findings may not generalize to greater population. Study only included outpatients and excluded hospitalized patients with cirrhosis. Information bias – using glucometer may have inaccuracies. Confounding bias – multiple factors such as medications, comorbidities, lifestyle factors do not seem to be adjusted in this study.
Krahenbuhl et al. (27)	Cross sectional study	Patients undergoing liver surgery. 17 cirrhotic patients (nine alcoholic cirrhosis and eight biliary cirrhosis), 14 control patients underdoing liver surgery but without cirrhosis.	Aimed to identify glycogen content and mRNA expression of glycogen metabolism related enzymes in control vs cirrhosis patients.	Cirrhotic patients had significantly lower hepatic glycogen content compared to control. Hepatic mRNA expression of glycogen metabolism-related enzymes was approximately 50% lower in cirrhosis patients compared to control.	Selection bias – sample size small with total 31 patients. Control group may not be representative of general population without liver disease. Measurement bias – the methods used for glycogen quantification may have errors from technical factors. Confounding – alcoholic and biliary cirrhosis may have different pathophysiology that dictates glycogen storage independent to liver cirrhosis. There is limited reporting on clinical outcomes, which creates a query regarding the significance that reduced glycogen stores may have in cirrhotic patients.

10.3389/fmed.2025.1541471

1. Preventing hypoglycemia in ICU patients with acute-on-chronic liver disease and decompensated liver cirrhosis.
2. Preventing hypoglycemia in cirrhotic patients with severe liver dysfunction.
3. Preventing hypoglycemia in cirrhotic patients with acute-on-chronic liver failure.
4. Preventing hypoglycemia in cirrhotic patients with hepatorenal syndrome.
5. Hypoglycemia can be used as a clinical predictor for bacteremia and septicemia, and prophylactic antibiotics can be used in cirrhotic patients to reduce acute exacerbations of chronic liver diseases.

These recommendations are targeted specifically to higher-risk groups without an overarching statement to declare that hypoglycemia prevention can be applied universally to all cirrhotic patients due to the study's small sample size and methodological limitations. Future studies with large sample sizes and improved methodological design are needed to address these questions and limitations as well as the related study biases for the potential improvement of clinical outcomes with cirrhotic patients.

Conclusion

Although current chronic liver disease management guidelines rarely address hypoglycemia in non-diabetic patients, this review highlights its significance in hospitalized patients with liver disease. There is limited but compelling evidence linking hypoglycemia to poor clinical outcomes in liver disease patients, whether admitted with another condition, decompensated cirrhosis, or acute-on-chronic liver disease, independent of diabetes (9, 18–26).

Given the scarcity of studies on hypoglycemia in cirrhotic patients, there is significant potential for multi-center trials to explore these uncertainties and inform updates to existing management guidelines. This includes developing tools that utilize clinical parameters such as MELD score, AST, bilirubin, and others to (1) identify and stratify patients at high risk for hypoglycemia and (2) prevent hypoglycemic events, thereby reducing associated poor outcomes such as mortality, ICU admissions, and complications like septicemia (22–24).

While hypoglycemia is clearly associated with poor clinical outcomes, it remains unclear whether prevention strategies-such as prophylactic glucose administration, nighttime carbohydrate intake, and early identification -will improve patient outcomes (18, 22).

Moreover, the interaction between septicemia, cirrhosis, and hypoglycemia raises important questions about the potential benefits of (1) administering prophylactic antibiotics and (2) conducting prompt blood cultures when hypoglycemia is detected, or when a cirrhotic patient is identified as being at high risk for hypoglycemic events (25, 26).

Furthermore, the mechanism of hypoglycemia in cirrhotic patients has been shown to be related to reduced hepatic glycogen stores in patients with liver cirrhosis (27). The conclusion of this study is that patients with alcoholic or biliary cirrhosis have decreased hepatic glycogen stores per volume of hepatocytes and per liver, and decreased glucokinase activity may be the important underlying mechanism (27). Identification of the mechanism of hypoglycemia with cirrhotic patients will be one of the priorities for future research.

Table 1 has a detailed summary of the characteristics, main results and possible bias of the included studies for discussion and analysis in this mini review to raise our research questions for overcoming the above-mentioned limitations. Addressing these questions through future research could significantly improve the management and clinical outcomes of hospitalized patients with liver cirrhosis, which may translate into improved quality of life, reduced morbidity, or even mortality.

Author contributions

RG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Writing – original draft, Writing – review and editing. JC: Data curation, Investigation, Methodology, Software, Validation, Writing – review and editing. KZ: Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review and editing. WH: Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review and editing. DX: Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. MK: Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review and editing.

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Association between Life's Crucial 9 and metabolic dysfunction-associated steatotic liver disease: the mediating role of neutrophil-percentage-to-albumin ratio

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Background: The development of metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with cardiovascular health (CVH) status and chronic inflammation. Life's Crucial 9 (LC9) is the most recent index to assess CVH; its association with MASLD and liver fibrosis is unclear. This study aimed to investigate the association of LC9 with MASLD and hepatic fibrosis and to reveal for the first time the mediating role of a novel inflammatory marker, neutrophil percentage-to-albumin ratio (NPAR), in the association between LC9 and MASLD.

Methods: This study was a cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2018. The United States Fatty Liver Index (US-FLI) ≥ 30 was used to diagnose MASLD, and liver stiffness measurement (LSM) > 8.2 is defined as liver fibrosis. Weighted multifactorial regression, restricted cubic spline analysis (RCS), and subgroup analyses were used to assess the association between LC9 and MASLD and liver fibrosis. Mediation analysis was used to explore the possible mediating role of NPAR in the association of LC9 with MASLD.

Results: A total of 9,623 participants were included in this study. After adjusting for all confounders, LC9 was significantly and negatively associated with both MASLD (OR = 0.59, 95% CI: 0.54–0.64) and hepatic fibrosis (OR = 0.66, 95% CI: 0.45–0.97), with each 10-point increase in the LC9 score decreasing the prevalence by 41% and 34%, respectively. In subgroup analyses, interaction tests showed that age, education, deprivation, obesity, smoking, hypertension, diabetes, and hyperlipidemia significantly affected the association between LC9 and MASLD (P for interaction < 0.05). In addition, NPAR was positively associated with the prevalence of MASLD, with a 5% increase in the prevalence of MASLD for each unit increase in NPAR (OR = 1.05, 95% CI: 1.01–1.09). The positive association between NPAR and MASLD was stronger in younger age groups (<60 years), non-drinkers, and participants without diabetes or hyperlipidemia. Mediation analysis showed that NPAR mediated 2.84% of the association between LC9 and MASLD ($p < 0.001$).

Conclusion: Good CVH status (high LC9 score) was associated with lower prevalence of MASLD and liver fibrosis, and NPAR partially mediated the association between LC9 and MASLD. This study provides new epidemiological evidence for preventing MASLD by improving CVH and inflammatory modulation.

KEYWORDS
Life's Crucial 9, MASLD, liver fibrosis, NPAR, NHANES, mediation analysis

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disease worldwide, affecting approximately 30% of the world's population. The disease burden of MASLD is increasing with the rising prevalence of obesity, type 2 diabetes, and metabolic syndrome. The pathological process of MASLD progresses from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma, posing a serious threat to the health of patients (1, 2). As a hepatic manifestation of metabolic syndrome, MASLD shares several common risk factors with cardiovascular disease (CVD), such as obesity, insulin resistance, hypertension, and dyslipidemia (3). Clinical studies have demonstrated that patients with MASLD have a significantly increased risk of CVD (4–6). Meanwhile, hepatic fibrosis accompanying the progression of MASLD, as a key pathological link in the development of the disease toward the end stage, not only directly affects liver function but also interacts with systemic metabolic disorders and inflammatory responses, further exacerbating the disease deterioration (7). Therefore, a comprehensive assessment of the risk factors associated with the onset and progression of MASLD is essential for early intervention and management of the disease.

In 2022, the American Heart Association (AHA) proposed Life's Essential 8 (LE8) as a metric for assessing cardiovascular health (CVH), which consists of four health behaviors (healthy diet, physical activity, avoid nicotine exposure, and healthy sleep) and four health factors (weight management, cholesterol control, stable blood glucose levels, and stable blood pressure levels) (8). This assessment model is proposed to provide a quantitative basis for cardiovascular disease risk prediction. In recent years, with the deepening of medical research, the impact of mental health on overall health has gradually become the focus of the academic community. Clinical evidence suggests that psychological disorders such as depression are closely related to pathological processes such as metabolic disorders and inflammatory responses and are independent risk factors for cardiovascular disease (9). The Life's Crucial 9 (LC9), an emerging comprehensive scoring system, builds on the LE8 by innovatively incorporating mental health dimensions into the assessment, providing a more thorough assessment tool for predicting and preventing cardiovascular disease (10). Several studies have shown that higher LE8 scores are associated with a lower prevalence of MASLD (11–13); Liang et al. showed that LE8 was negatively related to MASLD and advanced liver fibrosis (14). However, the relationship between LC9 and MASLD and liver fibrosis is unclear.

Chronic inflammation plays a central role in the pathological process of MASLD, in which local inflammatory responses in the liver interact with systemic metabolic disturbances to drive the progression of steatosis to steatohepatitis and hepatic fibrosis through the activation of pro-inflammatory signalling pathways and the induction of oxidative stress (15). The neutrophil percentage-to-albumin ratio (NPAR), a novel inflammatory indicator, is significantly associated with NPAR and risk of NAFLD and advanced liver fibrosis (16). Dong et al. found that NPAR levels were positively associated with all-cause mortality and CVD mortality in patients with MASLD (17). In addition, a national representative study in the United States showed that higher levels of NPAR were associated with an increased risk of depression (18), which suggests that NPAR plays a vital role in metabolic diseases and mental health.

Therefore, we hypothesized that LC9 is negatively associated with the risk of developing MASLD and hepatic fibrosis and that NPAR may mediate in the LC9–MASLD association. In this study, we utilized data from the National Health and Nutrition Examination Surveys (NHANES) to verify the above hypotheses and provide a new theoretical basis and research direction for early risk assessment and intervention of MASLD and liver fibrosis.

Methods

Study participants

NHANES is an ongoing, nationally representative, cross-sectional survey designed to systematically assess the health and nutritional status of the US population (19). It is administered by the National Center for Health Statistics (NCHS), the NCHS Ethics Review Board approved the study protocol, and all participants provided written informed consent. The NHANES data were made available to the public anonymously, and researchers were not required to apply for ethical review when using the data. The study strictly adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (20) to ensure the standardization, scientificity, and transparency of the reporting of the study results.

This study analyzed data from seven NHANES cycles from 2005 to 2018, which included 70,190 participants. After excluding individuals under the age of 20 and pregnant participants, 39,038 participants remained. Subsequently, further exclusions were then applied to those who met any of the following criteria: (1) hepatitis B ($n = 203$); (2) hepatitis C ($n = 473$); (3) HIV-positive ($n = 101$); (4) iron overload ($n = 216$); (5) excessive alcohol consumption ($n = 6,384$) (defined as ≥4 drinks per day for men, ≥3 drinks per day for women or ≥5 drinking days per month); and (6) participants with incomplete NPAR data and US-FLI data ($n = 10,475$). The specific flow is shown in Figure 1. In total, 9,623 adult participants were included in this study.

Definition of MASLD and liver fibrosis

In this study, we used the United States Fatty Liver Index (USFLI) to define hepatic steatosis. The FLI index is a non-invasive assessment tool developed by CE Ruhl et al. and has been validated in several studies with good sensitivity and specificity (21–23). The calculation

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; LC9, Life's Crucial 9; NPAR, neutrophil percentage-to-albumin ratio; CVD, cardiovascular disease; CVH, cardiovascular health; AHA, American Heart Association; PIR, poverty income ratio; NHANES, National Health and Nutrition Examination Survey; NCHS, National Center for Health Statistics; STROBE, Strengthening the reporting of Observational Studies in Epidemiology; BMI, body mass index; HEI, Healthy Eating Index; OR, odds ratio; CI, confidence interval.

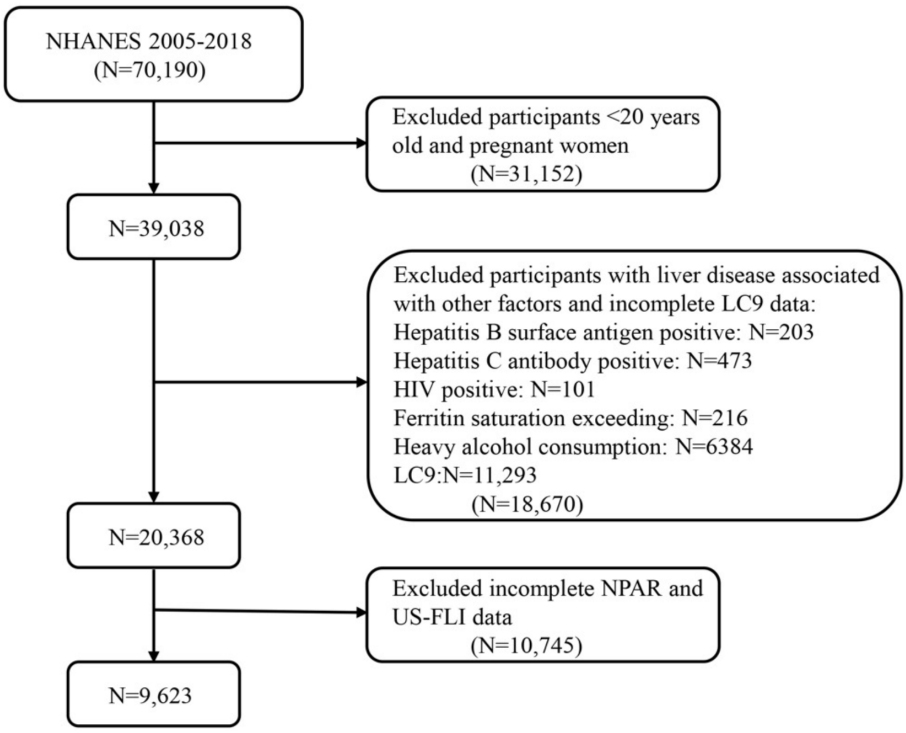

FIGURE 1
Flow diagram of eligible participant selection in the National Health and Nutrition Examination Survey. MASLD, metabolic dysfunction-associated steatotic liver disease; LC9, Life's Crucial 9; NPAR, neutrophil percentage-to-albumin ratio.

of the FLI index requires only basic clinical and laboratory data, including body mass index (BMI), waist circumference, triglycerides (TG), and γ-glutamyl transferase. Compared with liver biopsy and other non-invasive methods, FLI is safer, simpler, and less expensive, making it suitable for large-scale population screening and epidemiological studies. In this study, US-FLI $\geq$ 30 was used as a criterion for diagnosing MASLD after excluding the other liver diseases mentioned above (24). In contrast, liver fibrosis was diagnosed when the LSM value was $\geq$8.2 kPa (25).

Measurement of LC9

The LC9 incorporates a depression score based on the LE8, consisting of the following nine components: diet, physical activity, nicotine exposure, sleep health, BMI, lipids, blood glucose, blood pressure, and mental health. Each cardiovascular health (CVH) factor has a standardized score between 0 and 100. The composite LC9 score is calculated as the average of these standardized scores for the nine indicators and reflects an individual's overall health (10). Dietary indicators are assessed by the Healthy Eating Index (HEI-2015) (26). Physical activity, smoking status, and sleep health were obtained through standardized questionnaires. Trained professionals measured BMI, lipids, blood glucose, and blood pressure. Mental health assessment was obtained from the Patient Health Questionnaire 9 (PHQ-9) (27). Specific calculations for each indicator refer to previous studies, and detailed definitions and scoring methods for the LC9 are provided in the Supplementary Tables S1, S2.

Assessment of NPAR

In the NHANES database, professional researchers use automated hematological analysis equipment to measure and record the number of neutrophils in blood samples and the serum albumin concentration using the bromocresol purple method. Based on previous studies, NPAR was defined as the neutrophil percentage-to-albumin ratio, and NPAR was calculated according to the following formula: neutrophil percentage (%) $\times$ 100/Albumin (g/dL) (18).

Covariates

Based on previous studies, covariates in this study included age, sex, race, education, marital status, poverty income ratio (PIR), hypertension, diabetes mellitus, and hyperlipidemia. For more information on these covariates, please see Supplementary Table S3.

Standardized questionnaires were used to collect data on age, gender, ethnicity (Mexican American, Non-Hispanic Black, Non-Hispanic White, Other Race), education level (Below high school, High School or above), marital status (Married/Living with partner or not), and the ratio of family income to poverty (Poor: <1.3; Not Poor: $\geq$1.3). Body measurements, including height and weight, were collected during visits to a mobile examination center (MEC), and body mass index (BMI) was calculated using the formula: weight (kg) / height^2 (m^2). Drinking status was categorized into moderate drinking, mild drinking, and never drinking. Smoking status was classified as never smoker (defined as <100 cigarettes in a lifetime), current smoker (defined as $\geq$100 cigarettes in a lifetime), and former

smoker (defined as ≥100 cigarettes and had quit smoking). Hypertension, diabetes, and hyperlipidemia were diagnosed through measurement indicators, prior medication use, and self-reported questionnaire data.

Statistical analysis

To ensure the accuracy and national representativeness of the analyses, this study considered the NHANES complex sampling design, including sample weights, clustering, and stratification in all statistical analyses. Weights were recalculated for 2005–2018 using "WTMEC2YR" as the weighting variable (new weight = 1/7 × WTMEC2YR). Continuous variables are expressed as mean ± standard deviation; categorical variables are presented as the weighted sample size (percentages). Comparisons of differences between non-MASLD and MASLD groups were analyzed using a weighted Student *t*-test for continuous variables and weighted chi-squared tests for categorical variables.

Weighted multivariate logistic regression was used to explore the association between LC9 and MASLD and liver fibrosis, and weighted linear regression was used to assess the relationship between LC9 and NPAR. To control for confounders as much as possible, the regression model was divided into three levels: Model 1 was not adjusted for any confounders; model 2 adjusted for age, gender, education level, marital status, PIR, and race; and model 3 further adjusted for obesity, smoking status, drinking status, hypertension, diabetes mellitus, and hyperlipidemia based on model 2. The results are presented as odds ratios (OR) or β coefficients with 95% confidence intervals (95% CI). Restricted cubic spline regression (RCS) was used to assess the dose–response relationships between LC9 and MASLD, LC9 and liver fibrosis, and NPAR and MASLD.

This study performed subgroup analyses based on the covariates in model 3 to investigate the differences in the relationship between LC9 and MASLD and NPAR and MASLD in different populations. In addition, mediation analyses were performed to assess whether NPAR mediated the effect of LC9 on MASLD occurrence.

All statistical analyses were implemented using the R software (version 4.4.0). The main R packages used were the "survey" package, the "tableone" package, the "rms" package, the "mediation" package, and the "ggplot2" package. Statistical significance was defined as a *p*-value of less than 0.05 on both sides.

Results

Baseline characteristics

A total of 9,623 participants were enrolled in this study, and the baseline characteristics of the study population are summarized by the MASLD status categories in Table 1. Study participants were 54% female, predominantly non-Hispanic White (72%), and 33% had MASLD. Compared with non-MASLD participants, those with MASLD were older and had a higher proportion of males, lower educational attainment, higher rates of poverty, higher rates of obesity, and higher rates of metabolism-related disorders (e.g., hypertension, diabetes, and hyperlipidemia). People with MASLD also had lower LC9 scores, HEI-2015 diet scores, and PHQ-9 scores and significantly higher NPAR values.

Association of LC9 with MASLD and liver fibrosis

The association between LC9 and MASLD and liver fibrosis was analyzed using weighted logistic regression, and the results in Table 2 show a significant negative association between LC9 and MASLD prevalence. After adjusting for all confounding variables, an increase of 10 points per LC9 was associated with a 41% reduction in the prevalence of MASLD (OR = 0.59, 95% CI (0.54, 0.64), $p < 0.001$). Compared with the lowest LC9 tertile, the second tertile adjusted OR was 0.65 (95% CI (0.54, 0.79), $p < 0.001$), and the third tertile adjusted OR was 0.25 (95% CI (0.19, 0.34), $p < 0.001$). Higher LC9 scores were significantly associated with reduced MASLD prevalence (P for trend<0.001). Figure 2A shows the results of the RCS, revealing a significant negative association between the LC9 score and MASLD risk. Subgroup analysis in Figure 3A showed that the LC9 score was negatively associated with MASLD prevalence in all subgroups. Interaction tests showed that age, education, PIR, obesity, smoking, hypertension, diabetes, and hyperlipidemia significantly affected the correlation between LC9 score and MASLD (P for interaction <0.05).

For liver fibrosis, the results in Supplementary Table S4 showed a significant negative association between LC9 and liver fibrosis, with a 34% reduction in the likelihood of developing liver fibrosis for every 10-point increase in LC9 after adjusting for all confounding variables (OR = 0.66, 95% CI (0.45, 0.97), $p = 0.030$). Compared with the lowest tertile of LC9 scores, the adjusted OR for the second tertile was 0.52 (95% CI (0.26, 1.06), $p = 0.070$), and for the third tertile was 0.17 (95% CI (0.04, 0.68), $p = 0.020$). Higher LC9 scores were associated with a lower prevalence of MASLD (trend $p = 0.010$). As shown in Supplementary Figure S1, the RCS results revealed a significant negative correlation between the LC9 score and the risk of liver fibrosis.

The association between NPAR and MASLD

Table 2 illustrates the association between NPAR and MASLD. After adjusting the model for all confounding variables, a significant positive association between NPAR and the prevalence of MASLD was found. Each unit increase in NPAR was associated with a 5% increase in MASLD prevalence (OR = 1.05, 95% CI (1.01, 1.09), $p = 0.02$). Compared with the lowest NPAR tertile, the second tertile adjusted OR increased from 1.19 (95% CI (0.99, 1.43), $p = 0.070$) to 1.48 (95% CI (1.18, 1.86), $p = 0.070$) in the third tertile, with a 48% increase in MASLD prevalence. Higher NPAR was significantly associated with increased MASLD prevalence (P for trend<0.001).

Figure 2B shows a significant positive association between NPAR and MASLD. Figure 3 shows the results of the subgroup analyses; the positive correlation between NPAR and the risk of MASLD was stronger in participants who were younger than 60 years of age, who had never consumed alcohol, who consumed small amounts of alcohol, and who did not have diabetes mellitus or hyperlipidemia.

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TABLE 1 Baseline characteristics of all participants were stratified by MASLD, weighted.

Characteristic	Overall, *N* = 43,115,591 (100%)	Non-MASLD, *N* = 28,803,022 (67%)	MASLD, *N* = 14,312,569 (33%)	*p*-value
No. of participants in the sample	9,623	6,367	3,256	–
Age (%)				**<0.001**
20–40	12,601,391 (29%)	9,877,653 (34%)	2,723,737 (19%)	
41–60	16,486,021 (38%)	10,705,082 (37%)	5,780,939 (40%)	
>60	14,028,179 (33%)	8,220,287 (29%)	5,807,893 (41%)	
Sex (%)				**<0.001**
Female	23,120,488 (54%)	16,451,140 (57%)	6,669,348 (47%)	
Male	19,995,103 (46%)	12,351,882 (43%)	7,643,221 (53%)	
Race (%)				**<0.001**
Non-Hispanic White	31,079,023 (72%)	20,396,903 (71%)	10,682,120 (75%)	
Non-Hispanic Black	4,271,829 (9.9%)	3,438,119 (12%)	833,710 (5.8%)	
Other	5,062,740 (12%)	3,578,146 (12%)	1,484,594 (10%)	
Mexican American	2,701,999 (6.3%)	1,389,854 (4.8%)	1,312,144 (9.2%)	
Married/live with partner (%)				**0.114**
No	14,220,002 (33%)	9,738,752 (34%)	4,481,249 (31%)	
Yes	28,886,054 (67%)	19,064,270 (66%)	9,821,785 (69%)	
Education level (%)				**<0.001**
Below high school	5,921,388 (14%)	3,338,243 (12%)	2,583,145 (18%)	
High school or above	37,183,981 (86%)	25,455,890 (88%)	11,728,091 (82%)	
PIR (%)				**<0.001**
Poor	7,199,888 (18%)	4,536,278 (17%)	2,663,610 (20%)	
Not poor	33,357,918 (82%)	22,534,332 (83%)	10,823,586 (80%)	
Obesity (%)				**<0.001**
No	27,217,107 (63%)	23,186,896 (81%)	4,030,211 (28%)	
Yes	15,898,484 (37%)	5,616,126 (19%)	10,282,359 (72%)	
Smoking (%)				**<0.001**
Never	25,062,227 (58%)	17,550,126 (61%)	7,512,101 (52%)	
Former	12,047,802 (28%)	7,150,466 (25%)	4,897,336 (34%)	
Current	6,005,562 (14%)	4,102,430 (14%)	1,903,133 (13%)	
Drinking (%)				**<0.001**
Never	5,385,756 (13%)	3,578,953 (13%)	1,806,803 (13%)	
Former	7,165,716 (17%)	4,102,767 (15%)	3,062,949 (22%)	
Mild	20,274,501 (49%)	13,893,516 (49%)	6,380,985 (47%)	
Moderate	8,938,342 (21%)	6,498,398 (23%)	2,439,944 (18%)	
Hypertension (%)				**<0.001**
No	25,256,342 (59%)	19,618,226 (68%)	5,638,116 (39%)	
Yes	17,859,249 (41%)	9,184,796 (32%)	8,674,453 (61%)	
Diabetes (%)				**<0.001**
No	35,984,078 (83%)	26,311,528 (91%)	9,672,550 (68%)	
Yes	7,131,513 (17%)	2,491,494 (8.7%)	4,640,020 (32%)	
Hyperlipidemia (%)				**<0.001**
No	11,173,700 (26%)	9,566,627 (33%)	1,607,073 (11%)	
Yes	31,941,891 (74%)	19,236,395 (67%)	12,705,496 (89%)	

(Continued)

TABLE 1 (Continued)

Characteristic	Overall, *N* = 43,115,591 (100%)	Non-MASLD, *N* = 28,803,022 (67%)	MASLD, *N* = 14,312,569 (33%)	*p*-value
Mean LC9 score (mean (SD))	71.22 (13.64)	75.41 (12.45)	62.79 (11.92)	**<0.001**
LC9, Tertile (%)				**<0.001**
T1	14,407,462 (33%)	6,354,684 (22%)	8,052,778 (56%)	
T2	14,362,207 (33%)	9,300,651 (32%)	5,061,556 (35%)	
T3	14,345,922 (33%)	13,147,687 (46%)	1,198,235 (8.4%)	
Mean psychological health score (mean (SD))	90.50 (21.79)	91.86 (20.02)	87.77 (24.76)	**<0.001**
Mean HEI-2015 diet score (mean (SD))	40.83 (31.74)	43.54 (32.05)	35.39 (30.39)	**<0.001**
Mean physical activity score (mean (SD))	70.62 (41.55)	73.78 (39.82)	64.28 (44.15)	**<0.001**
Mean tobacco exposure score (mean (SD))	76.14 (35.08)	76.60 (35.60)	75.22 (34.01)	**<0.001**
Mean sleep health score (mean (SD))	84.08 (23.93)	85.15 (23.18)	81.93 (25.23)	**<0.001**
Mean body mass index score (mean (SD))	60.80 (33.64)	74.08 (28.00)	34.07 (27.58)	**<0.001**
Mean blood lipid score (mean (SD))	64.21 (29.89)	67.91 (29.58)	56.77 (29.13)	**<0.001**
Mean blood glucose score (mean (SD))	85.43 (24.78)	91.62 (19.32)	72.96 (29.43)	**<0.001**
Mean blood pressure score (mean (SD))	68.40 (31.47)	74.19 (30.28)	56.73 (30.56)	**<0.001**
NPAR (mean (SD))	13.74 (2.52)	13.46 (2.50)	14.31 (2.48)	**<0.001**
NPAR, Tertile (%)				**<0.001**
T1	14,385,766 (33%)	10,916,831 (38%)	3,468,934 (24%)	
T2	14,341,828 (33%)	9,645,147 (33%)	4,696,681 (33%)	
T3	14,387,997 (33%)	8,241,043 (29%)	6,146,954 (43%)	

Mean (SD) for continuous variables: the *p*-value was calculated by the weighted Student *t*-test. Weighted sample size (percentages) for categorical variables: the *p*-value was calculated by the weighted chi-squared test. MASLD, metabolic dysfunction-associated steatotic liver disease; LC9, Life's Crucial 9; NPAR, neutrophil percentage-to-albumin ratio; PIR, poverty income ratio. Bold values indicate $p < 0.05$.

The association between LC9 and NPAR

Table 3 shows the association between LC9 and NPAR, which was statistically significant after adjusting for all covariates ($\beta = -0.38$, 95% CI (−0.44, −0.31), $p < 0.001$).

Mediating role of NPAR in the association of LC9 and MASLD

Our study fulfilled the prerequisites for conducting mediation analyses based on the above analyses. As shown in Figure 4, after adjusting for all covariates, we observed a mediating effect of NPAR. The indirect impact of NPAR = $-2.42^{*}10^{-4}$, $p < 0.001$ and direct effect = $-8.16^{*}10^{-3}$, $p = 0.036$ mediates 2.84% of the correlation between the LC9 score and MASLD.

Discussion

In this nationally representative study of US adults, we demonstrated for the first time that the most recent CVH indicator, the LC9, was significantly and negatively associated with both MASLD and hepatic fibrosis; a 10-point increase in LC9 score was associated with a 41% reduction in the prevalence of MASLD and a 34% reduction in the prevalence of hepatic fibrosis. Subgroup analyses showed that age, education, PIR, obesity, smoking, hypertension, diabetes, and hyperlipidemia significantly moderated the strength of the association between LC9 score and MASLD (interaction test $p < 0.05$). In addition, NPAR, a novel marker of inflammatory response, was significantly and positively associated with MASLD, and this association was more prominent in younger age groups (<60 years), non-drinkers, and individuals without diabetes or hyperlipidemia. Notably, NPAR played an important mediating role between LC9 and MASLD, suggesting that elevated LC9 scores may indirectly reduce the risk of MASLD development by modulating the inflammatory state.

Our findings showed a significant negative association between the latest CVH metric, LC9, and the prevalence of MASLD and liver fibrosis, consistent with several previous studies' findings. A cross-sectional study of the U.S. population found that adults with higher CVH indicators assessed by the LE8 score had a lower risk of developing MAFLD and advanced liver fibrosis (14). An extensive cohort study in China demonstrated that an ideal cardiovascular health baseline and cumulative exposure levels were significantly associated with a reduced risk of NAFLD development and an increased likelihood of regression (28). A prospective analysis in the UK Biobank found that a good lifestyle and better CVH assessed by LE8 were significantly associated with a lower risk of new-onset severe NAFLD (29). The Life's LC9 cardiovascular health scoring system based on a comprehensive mental health dimension was significantly and negatively associated with MASLD and its progression to liver fibrosis.

TABLE 2 Association between LC9, NPAR, and MASLD.

Characteristics	Model 1 [OR (95% CI)]	*p*-value	Model 2 [OR (95% CI)]	*p*-value	Model 3 [OR (95% CI)]	*p*-value
LC9–MASLD						
Continuous (per 10 scores)	0.45 (0.43, 0.48)	<0.001	0.42 (0.39, 0.45)	<0.001	0.59 (0.54, 0.64)	<0.001
Tertile						
T1	1 (ref.)		1 (ref.)		1 (ref.)	
T2	0.43 (0.37, 0.50)	<0.001	0.39 (0.33, 0.46)	<0.001	0.65 (0.54, 0.79)	<0.001
T3	0.07 (0.06, 0.09)	<0.001	0.07 (0.05, 0.08)	<0.001	0.25 (0.19, 0.34)	<0.001
P for trend	<0.001		<0.001		<0.001	
NPAR–MASLD						
Continuous	1.15 (1.12, 1.18)	<0.001	1.13 (1.10, 1.17)	<0.001	1.05 (1.01, 1.09)	0.020
Tertile						
T1	1 (ref.)		1 (ref.)		1 (ref.)	
T2	1.53 (1.31, 1.80)	<0.001	1.48 (1.25, 1.75)	<0.001	1.19 (0.99, 1.43)	0.070
T3	2.35 (1.99, 2.77)	<0.001	2.23 (1.87, 2.67)	<0.001	1.48 (1.18, 1.86)	<0.001
P for trend	<0.001		<0.001		<0.001	

Model 1: no covariates were adjusted.
Model 2: age, sex, education level, marital status, PIR, and race were adjusted.
Model 3: age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia were adjusted.
MASLD, metabolic dysfunction-associated steatotic liver disease; NPAR, neutrophil percentage-to-albumin ratio; PIR, ratio of family income to poverty; OR, odds ratio; CI, confidence interval.

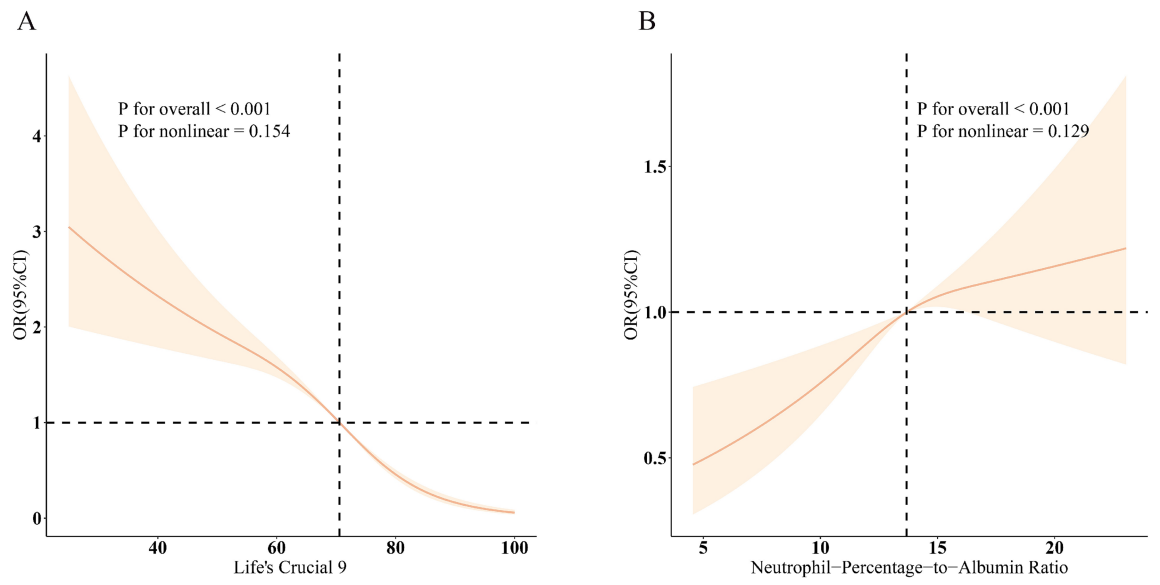

FIGURE 2
Dose–response relationships between LC9, NPAR, and MASLD. **(A)** LC9–MASLD; **(B)** NPAR–MASLD. OR (solid lines) and 95% confidence levels (shaded areas) were adjusted for age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia.

Neutrophil percentage-to-albumin ratio (NPAR) is a novel inflammatory marker integrating neutrophil percentage and peripheral blood albumin levels. Elevated neutrophil percentage implies activation of the innate immune system, which plays a vital role in mediating the inflammatory response, while albumin exerts anti-inflammatory and antioxidant effects (30). Therefore, NPAR is a more comprehensive assessment of inflammation than a single marker. A national study in the United States found that a per-unit increase in NPAR was significantly associated with an increased risk of developing NAFLD (16). In addition, a recent study showed that NPAR has good predictive efficacy for all-cause mortality and CVD mortality in patients with MASLD (17). In our research, NPAR was also significantly positively correlated with the prevalence of MASLD, further validating the previous findings. The present study innovatively revealed that NPAR

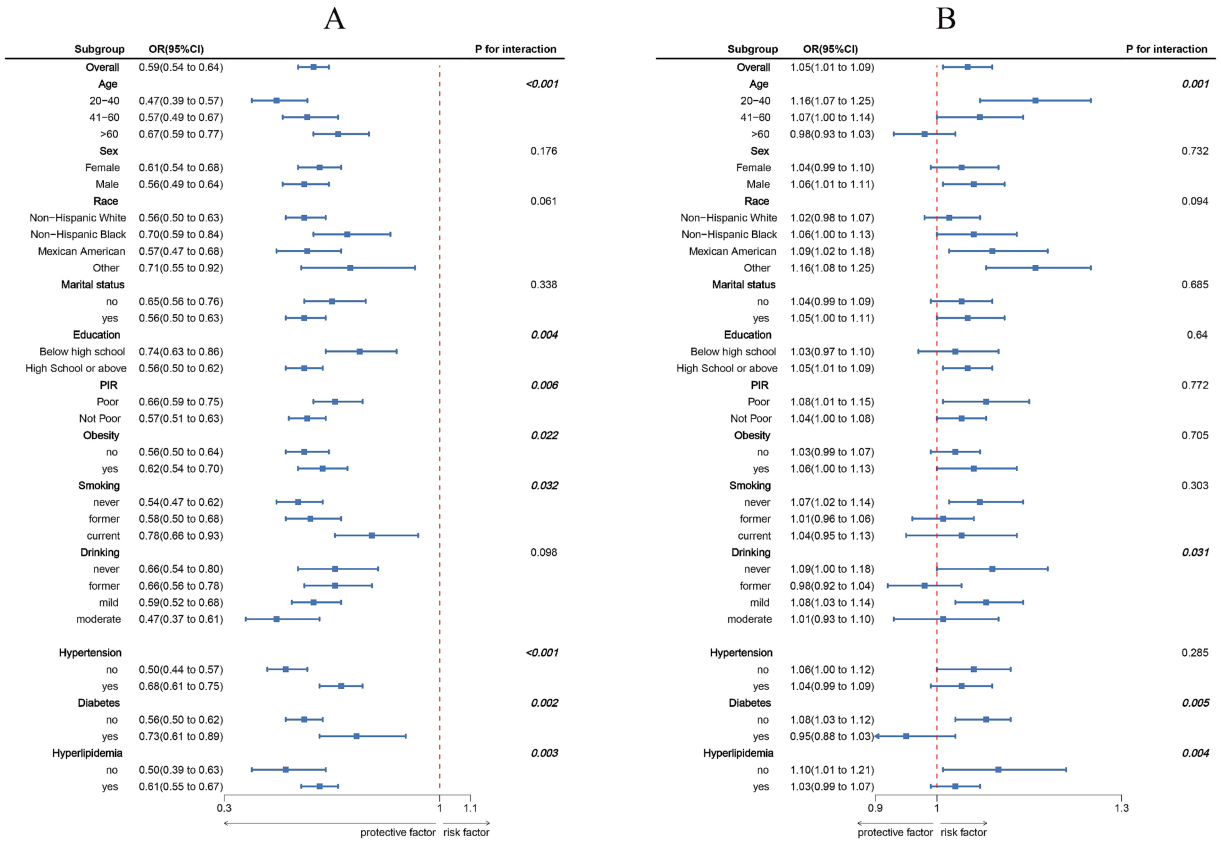

FIGURE 3
Subgroup analysis between LC9, NPAR, and MASLD. **(A)** LC9–MASLD; **(B)** NPAR–MASLD. ORs were calculated per 10-unit increase in LC9, and each standard deviation increased in NPAR. Analyses were adjusted for age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia.

TABLE 3 Association between LC9 and NPAR.

Characteristic	β	95%CI	*p*-value
LC9–NPAR	−0.38	(−0.44, −0.31)	<0.001

Adjusted for age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia.

may be a key mediator in regulating the negative association between LC9 and MASLD. This finding not only expands the existing knowledge but also suggests that chronic inflammation plays an important role in the progression of MASLD and its interaction with CVD, which provides a new perspective for understanding the pathological mechanisms of metabolic liver disease.

The pathogenesis of MASLD is complex and involves multifactorial interactions such as obesity, insulin resistance, chronic inflammation, oxidative stress, and lipid metabolism disorders (28). The health behaviors and factors included in LC9 scores may influence the onset and progression of MASLD by improving systemic levels of inflammation, enhancing insulin sensitivity, and reducing fat accumulation. Healthy dietary patterns, such as the Mediterranean diet, are prized for its richness in whole grains, fruits, vegetables, legumes, and healthy fats, and whose anti-inflammatory and antioxidant properties are effective in reducing liver fat deposits and improving insulin sensitivity (31). A very-low-calorie ketogenic diet (VLCKD) also improves hepatic steatosis and hepatic fibrosis by reducing systemic and hepatic hypo-inflammation, thereby reducing hepatic steatosis and hepatic fibrosis (32). Studies have shown that aerobic exercise reduces intrahepatic fat by increasing fat oxidation and improving insulin sensitivity. Resistance exercise increases muscle mass, improves muscle uptake and utilization of glucose, and reduces liver burden (33). Avoiding smoking reduces oxidative stress and inflammatory responses (34). Good sleep helps maintain normal metabolic function and improves insulin sensitivity, which is essential for maintaining a healthy weight and stabilizing metabolic status (35). Obesity is one of the significant risk factors for MASLD. Inflammatory cytokines secreted by adipose tissue under obesity trigger systemic inflammation, leading to insulin resistance, which further contributes to hepatic fat deposition and exacerbates the condition of MASLD (36). Vilar-Gomez et al. showed that a target weight loss of 7–10% effectively reduced lipid accumulation, increased metabolic flexibility, and improved insulin resistance (37). Appropriate non-HDL cholesterol levels, blood pressure, and blood glucose levels may reduce oxidative stress and inflammatory responses, improve insulin resistance, and reduce the risk of MASLD. Depression may lead to immune-mediated destruction of pancreatic β-cells, resulting in insulin resistance and diabetes (38). In addition, it has been shown that the prevalence of liver fibrosis and steatosis is significantly higher in the population of patients with type 2 diabetes mellitus (39). Based on the above pathomechanism, it is scientifically plausible that there is a significant correlation between the LC9 score and the prevalence of MASLD and advanced hepatic fibrosis.

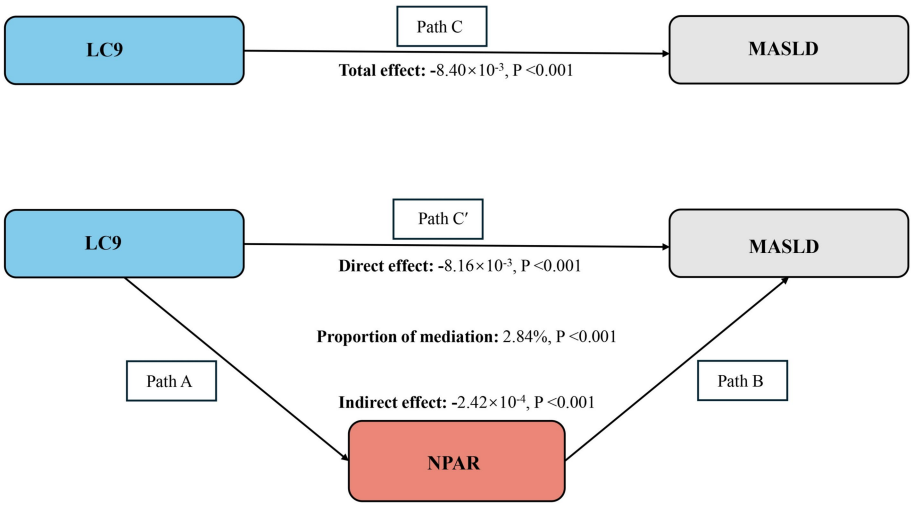

FIGURE 4
Schematic diagram of the mediation effect analysis. Path C indicates the total effect; path C′ indicates the direct effect. The indirect effect is estimated as the multiplication of paths A and B (path A*B). The mediated proportion is calculated as indirect effect/(indirect effect + direct effect) × 100%. MASLD, metabolic dysfunction-associated steatotic liver disease; LC9, Life's Crucial 9; NPAR, neutrophil percentage-to-albumin ratio. Analyses were adjusted for age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia.

Notably, subgroup analyses showed that age, education, PIR, obesity, smoking, and hypertension, diabetes, and hyperlipidemia significantly moderated the strength of the association between LC9 score and MASLD (P for interaction < 0.05). This difference may be due to the differences in health behaviors, medical resources, and disease susceptibility: Young people are more sensitive to health interventions, and highly educated people are more aware of health management, whereas poor people have limited living and medical conditions, which weaken the protective effect of the LC9; obesity, smoking, and metabolic disease patients have reduced preventive efficacy of the LC9 score due to inflammation and metabolic disorders (40). The positive association between NPAR and MASLD was more pronounced in individuals <60 years of age, non-alcohol drinkers, and non-diabetic/hyperlipidemic individuals. The positive association between NPAR and MASLD is more pronounced in individuals <60, non-drinkers, and non-diabetic/hyperlipidemic individuals. The predictive value of NPAR is more prominent in the younger age group, which is metabolically active (41), where the effect of inflammation on hepatic lipid metabolism is likely to be more direct. The association may be masked by complex metabolic disorders in people with comorbid metabolic diseases.

The major strength of this study is the use of a nationally representative sample of US adults to explore for the first time the association of LC9 with the prevalence of MASLD and liver fibrosis. In addition, through mediation analysis, this study revealed the mediating effect of NPAR between LC9 and MASLD, which further enriches our understanding of the mechanisms of MASLD. LC9 is a comprehensive indicator of CVH and provides a new tool for universal health management. NPAR, as an inflammatory marker, can effectively complement the traditional metabolic risk assessment system. These findings provide a solid theoretical basis for developing MASLD prevention strategies.

There are some limitations to this study. First, the non-invasive USFLI score used in this study as a diagnostic tool for hepatic steatosis is not as accurate as liver biopsy, which may lead to misclassification of disease prevalence and, consequently, underestimation or overestimation of the actual risk level of MASLD. Second, the CVH behavioral indicator assessment relied on self-report questionnaires, which may be subject to some measurement error that may affect the accuracy of the study results. Third, although we have adjusted for a variety of potential confounders, there may still be some unmeasured or uncontrolled variables that may have some impact on the study results, thus affecting the generalizability of the findings. Finally, the limitations of the cross-sectional design of this study prevented us from making causal inferences, and further longitudinal studies are needed in the future to investigate the relationship between LC9 scores, NPAR, and MASLD.

Conclusion

In conclusion, this study shows a significant negative association between LC9 and the prevalence of MASLD and liver fibrosis. NPAR mediates this LC9–MASLD association. This suggests that improving cardiovascular health effectively reduces the risk of MASLD by modulating chronic inflammation and that a comprehensive strategy combining enhanced cardiovascular health with anti-inflammation is an essential public health measure for the prevention and management of MASLD.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Ethics statement

The NHANES study was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and all participants signed a written informed consent form.

Author contributions

NZ: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Methodology. YaL: Data curation, Investigation, Writing – review & editing. YiL: Data curation, Investigation, Writing – review & editing. XC: Data curation, Investigation, Writing – review & editing. XL: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2025.1549089/full#supplementary-material

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Insulin resistance as a mediator of the association between obesity, high-intensity binge drinking, and liver enzyme abnormalities in young and middle-aged adults: a cross-sectional study

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Background: Binge drinking (BD) and obesity are well-established risk factors for liver enzyme abnormalities, but how varying intensities of BD interact with obesity to affect liver function remains unclear. This study aims to examine whether insulin resistance (IR) mediates the associations between different levels of BD, obesity, their interaction, and liver enzyme abnormalities.

Methods: This cross-sectional study included 137,878 young and middle-aged adults who underwent physical examinations in southern China between August 2017 and March 2024. BD was self-reported, and IR was assessed using the triglyceride–glucose (TyG) index. Causal mediation analysis within the counterfactual framework was used to quantify the mediating role of the TyG index in the associations involving BD intensity, obesity, their interaction, and liver enzyme abnormalities.

Results: The interaction between obesity and high-intensity binge drinking (HIBD) was significantly associated with liver enzyme abnormalities (OR, 1.591; 95% CI, 1.401–1.806). IR, measured by the TyG index, statistically accounted for 36.6% (OR, 1.034; 95% CI, 1.029–1.039) of this association, exceeding the proportion explained in the HIBD alone (25.9%) or obesity alone (16.7%) pathways. No significant mediating effect of IR was observed for non-BD or low-intensity BD, regardless of obesity status.

Conclusion: The TyG index serves as a critical mediator in the synergistic effects of HIBD and obesity on liver enzyme abnormalities. Targeting IR and reducing the intensity of alcohol consumption may help mitigate liver injury in young and middle-aged adults with obesity.

KEYWORDS

insulin resistance, obesity, binge drinking, liver enzymes, metabolic dysfunction, young and middle-aged

1 Introduction

Abnormal liver enzymes are key indicators of hepatic injury (1) and are closely associated with chronic liver and metabolic diseases (2). In recent years, the prevalence of liver enzyme abnormalities has increased among young and middle-aged populations (3), largely driven by increasing rates of obesity (4) and binge drinking (BD) (5). Liver health in this demographic not only affects the individual quality of life but also has broader socioeconomic implications. Therefore, understanding the underlying mechanisms of liver enzyme abnormalities in this population holds significant clinical and public health importance.

Young and middle-aged adults exhibit the highest prevalence of BD, with an increasing trend observed in even younger age groups (6, 7). BD is a major behavioral risk factor for liver damage, and its intensity has a substantial impact on metabolic health (8). High-intensity binge drinking (HIBD) causes hepatocellular injury through toxic metabolites such as acetaldehyde and reactive oxygen species (ROS) (9), including ROS generated via neutrophil cytosolic factor 1-dependent pathways (10) and gastrin-releasing peptide receptor-mediated activation of NADPH oxidase 2 (11). These ROS suppress AMP-activated protein kinase and the anti-inflammatory microRNA-223 (10, 11), promote hepatic lipid accumulation and inflammation, disrupt mitochondrial function, and trigger oxidative stress-induced hepatocyte death (12–14), ultimately elevating the risk of liver enzyme abnormalities. Obesity, another global public health concern (15, 16), contributes to liver injury through chronic low-grade inflammation and oxidative stress driven by excess adipose tissue accumulation (17–19). Moreover, obesity increases hepatic susceptibility to alcohol-induced damage, suggesting a synergistic interaction that aggravates liver injury beyond the independent effects of either condition (20–22). However, the biological mechanisms underlying these interactions, particularly the synergistic effects of obesity and BD on liver injury, remain insufficiently understood and warrant further investigation (23, 24).

Insulin resistance (IR), a hallmark of metabolic disorders, may serve as a shared mediating mechanism and a central contributor to the synergistic effects of BD and obesity on liver injury in young and middle-aged populations. Obesity-induced chronic inflammation and lipid accumulation impair insulin signaling pathways by promoting the secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-12 (IL-12), as well as by increasing the release of free fatty acids (FFAs) from visceral adipose tissue (VAT), thereby reducing insulin sensitivity and aggravating intrahepatic lipid deposition and oxidative stress (25, 26). Simultaneously, BD impairs insulin signaling via acetaldehyde and ROS, which inhibit the phosphorylation of insulin receptor substrate-1 (IRS-1) and reduce glucose transport efficiency (27, 28). Experimental studies further indicate that HIBD exacerbates IR in individuals with obesity, intensifying metabolic dysfunction (28). IR contributes to liver injury through multiple interrelated mechanisms, including increased hepatic *de novo* lipogenesis, inadequate suppression of gluconeogenesis, elevated FFA influx from adipose tissue, and intracellular accumulation of lipotoxic intermediates such as diacylglycerol and ceramides (29, 30). These metabolic disturbances promote mitochondrial dysfunction, oxidative stress, and activation of inflammatory pathways, ultimately leading to hepatic steatosis, inflammation, and fibrosis (29–32). Within this context, IR may not only magnify the independent effects of obesity and BD on liver dysfunction but also serve as a key mediator of their synergistic impact on liver enzyme abnormalities (31, 32).

Given these considerations, this study hypothesizes that IR mediates the associations between BD, obesity, and their interaction with liver enzyme abnormalities. The magnitude of this mediating effect is expected to vary by BD intensity and to be the strongest in the interaction between HIBD and obesity. Utilizing data from a large cross-sectional health survey in China, this study aims to examine these mediation effects across different levels of BD in young and middle-aged adults and to quantify the extent of the mediating effects.

2 Methods

2.1 Participants

Participants in this cross-sectional study were recruited through convenience sampling from the Health Management Center of a comprehensive hospital in China. The inclusion criteria were as follows: (1) age between 18 and 59 years; (2) willingness to participate free of charge; and (3) sufficient reading comprehension to complete a self-reported health questionnaire in Chinese. The exclusion criteria included (1) diagnosis of a severe mental disorder and (2) diagnosis of some chronic conditions such as hypertension, stroke, coronary heart disease, chronic kidney disease, chronic gastritis or peptic ulcer, chronic obstructive pulmonary disease, chronic pancreatitis, chronic hepatitis or liver cirrhosis, hyperuricemia, or malignancy, as well as the current use of medications for these conditions.

2.2 Study design and procedures

This single-center cross-sectional study was conducted from August 2017 to March 2024. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist to ensure comprehensive and transparent reporting. Based on the hypothesized framework, the primary exposures included five levels of BD intensity, obesity, and their interaction. The proposed mediator was IR, assessed using the triglyceride–glucose (TyG) index, and the primary outcome was liver enzyme abnormality, defined by serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Before undergoing the health examination, all participants received a text message with a link to an electronic health self-assessment questionnaire, which they completed online. After the examination, laboratory test results were extracted from the hospital's electronic medical record system by the research team. Written informed consent was obtained from all participants. Participation was entirely voluntary, and no financial compensation was provided. This study protocol was approved by the Ethics Committee of the Third Xiangya Hospital, Central South University (NO. quick-24556). A total of 137,878 participants were included in the final analyses, providing

sufficient statistical power to detect both main and interaction effects, as well as the mediation pathways.

2.3 Data collection

General information was collected from participants via a health self-assessment questionnaire designed by researchers, including sex, age, alcohol consumption, smoking status, and exercise. Venous blood samples were collected from participants after an 8–12-h fasting period, and trained medical technicians measured serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and fasting blood glucose (FBG) using standardized laboratory methods. Variables with a p-value of < 0.05 in univariate analyses and those identified as potential confounders based on prior literature were included in the multivariable model. Detailed measurement methods for covariates are provided in the Supplementary materials.

2.3.1 Obesity assessment

The height and weight of participants were measured by trained medical staff using a calibrated electronic stadiometer, with height recorded to the nearest 0.1 cm and weight recorded to the nearest 0.1 kg. Body mass index (BMI) was calculated as the ratio of weight (kg) to height squared (m^2). According to the World Health Organization criteria for Asian adults, BMI was categorized as follows: underweight (< 18.50 kg/m^2), normal weight (18.50–22.90 kg/m^2), overweight (23.00–24.90 kg/m^2), and obesity (≥ 25.00 kg/m^2) (33). In this study, the underweight group was merged with the normal-weight category due to the small number of participants in the underweight group.

2.3.2 Insulin resistance assessment

IR in this study was assessed using the TyG index, which has been validated as a reliable surrogate marker for IR. Compared to the hyperinsulinemic-euglycemic clamp technique, the TyG index is more practical and suitable for large-scale epidemiological studies (21, 34). The TyG index was calculated as ln[fasting TG (mg/dl) * FBG (mg/dl)/2]. Serum TG levels were measured using the triglyceride lipase method, and FBG was assessed using the glucose oxidase method. Both tests were conducted using an automated biochemical analyzer.

2.3.3 Definition of liver enzyme abnormalities

In this study, liver enzyme abnormalities were defined based on the ALT and AST levels, which are commonly used markers of hepatocellular injury. Participants were considered to have abnormal liver enzymes if they met any of the following sex-specific criteria: ALT > 50 U/L for men, ALT > 35 U/L for women, or AST > 34 U/L. (16, 35). The ALT and AST levels were measured using the enzymatic rate method on an automated biochemical analyzer.

2.3.4 Evaluation of binge drinking

Information on alcohol consumption was collected through the health self-assessment questionnaire, including drinking frequency per week, volume per drinking occasion, and type of alcoholic beverage. The questionnaire was developed based on previously published surveys assessing drinking patterns in epidemiological studies (36, 37). To enhance cultural relevance and comprehension, the instrument was adapted linguistically (e.g., using the traditional Chinese unit "liang" instead of milliliters). The questionnaire demonstrated high response completeness, with a low missing data rate of 0.72% for BD variables. Based on alcohol concentrations—53% for Chinese liquor, 12% for wine, and 4% for beer—and an alcohol density of 0.79 g/mL (38), the standard alcohol content per milliliter was calculated as follows: Chinese liquor, 0.53 * 0.79 = 0.42 g/mL; wine, 0.12 * 0.79 = 0.09 g/mL; beer, 0.04 * 0.79 = 0.03 g/mL. The total amount of alcohol consumed per occasion was calculated by multiplying the standard alcohol content by the volume consumed. In this study, BD behavior was categorized based on the amount of alcohol consumed per drinking occasion. Non-BD was classified as an alcohol intake of ≤ 60 g per occasion for men and ≤ 40 g for women. Level I BD was defined as intake > 60 g but ≤ 120 g for men and > 40 g but ≤ 80 g for women. Level II BD corresponded to > 120 g but ≤ 180 g for men and > 80 g but ≤ 120 g for women. Level III BD was categorized as intake > 180 g for men and > 120 g for women (22, 39). Based on these thresholds, participants were classified into five drinking behavior groups: never drank, past drinker, non-BD, BD-I, and HIBD.

2.4 Statistical analysis

All statistical analyses were performed using Stata version 18.0. A two-sided p-value of < 0.05 was considered statistically significant. Continuous variables following a normal distribution were described as the mean ± standard deviation, and categorical variables were summarized as frequencies with percentages. Linear regression was used to assess the association between BD behavior or obesity and the TyG index. Logistic regression was applied to assess the associations between BD, the TyG index, and obesity and abnormal liver enzyme outcomes.

To visualize the overlap and co-occurrence of obesity, HIBD, and IR (as measured by the TyG index) in relation to liver enzyme abnormalities, a three-set Venn diagram was constructed. Participants were categorized based on the presence or absence of each risk factor. Given the lack of a universally accepted cutoff value for the TyG index, participants were stratified into tertiles (low, medium, and high) based on its distribution, with the highest tertile defined as the "high TyG" group for risk classification (40, 41). For each of the eight possible exposure combinations (no exposure, single, dual, or triple exposure), corresponding sample sizes and liver enzyme abnormality rates were calculated and graphically displayed.

The hypothesized relationships among variables are illustrated in Figure 1. To investigate the mediating role of the TyG index in the associations between different BD intensities, obesity, their interaction, and liver enzyme abnormalities, causal mediation analysis was performed within a counterfactual framework (42–44). This approach decomposes the total effect (TE) of an exposure into two distinct components: the natural indirect effect (NIE), representing the portion of the effect mediated by the TyG index (i.e., the expected change in liver enzyme abnormalities

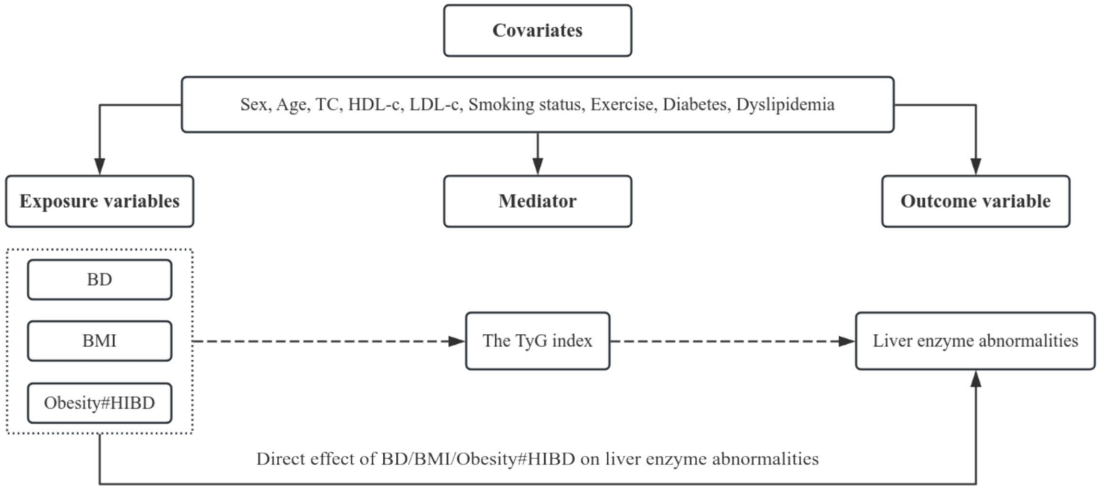

FIGURE 1
Hypothetical variable relationships diagram. BD, Binge drinking; BMI, Body mass index; HIBD, High-intensity binge drinking; Obesity#HIBD, Interaction term for obesity (BMI ≥ 25.00 kg/m^2) and high-intensity binge drinking; TyG, Triglyceride–glucose; TC, Total cholesterol; HDL-c, High-density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol. The diagram underlying this study illustrated the potential mechanisms through which the associations between BD levels, BMI, or the interaction term for obesity (BMI ≥ 25.00 kg/m^2) and HIBD and liver enzyme abnormalities were mediated by the TyG index. All statistical models in this study were based on this structure and adjusted for sex, age, TC, HDL-c, LDL-c, smoking status, exercise, history of diabetes, and dyslipidemia. Dashed arrows represent indirect pathways mediated through the TyG index.

when the TyG index changes due to the exposure), while holding the exposure constant, and the natural direct effect (NDE), representing the portion of the effect independent of the TyG index (44, 45) (i.e., the expected change in liver enzyme abnormalities if the exposure changed, while the TyG index is fixed at the level it would naturally take under the unexposed condition). For instance, a significant NIE implies that IR, represented by the TyG index, partially mediates the relationship between BD, obesity, or their interaction and liver enzyme abnormalities. A significant NDE indicates a direct effect of the exposure, independent of IR. To further evaluate the interaction between obesity (BMI ≥ 25.00 kg/m^2) and HIBD, an interaction term was included in the mediation model, using the non-obese and non-binge-drinking group as the reference category. This approach allowed for the assessment of the extent to which IR mediates the joint impact of obesity and HIBD on liver enzyme abnormalities.

To ensure the robustness of the mediation effects, multiple sensitivity analyses were conducted. First, participants with baseline FBG levels ≥ 7 mmol/L were excluded (n = 5,324 in the full sample; n = 3,300 in the obese subgroup). Second, we excluded participants in the top 10% (full sample, n = 13,701) or 5% (obese subgroup, n = 4,500) of BMI values to address the influence of extreme body weight on outcomes. Third, underweight participants (BMI < 18.50 kg/m^2, n = 2,938) were excluded to evaluate the impact of merging underweight and normal-weight individuals in the main analysis. Fourth, the potential impact of unmeasured confounding was examined. Finally, propensity score matching (PSM) was employed to balance baseline characteristics between groups, and mediation analyses were repeated in the matched sample. Additionally, subgroup analyses were conducted to explore whether the mediation effect of the TyG index varied by obesity status. Participants were stratified by BMI into non-obese (BMI < 25.00 kg/m^2) and obese (BMI ≥ 25.00 kg/m^2) groups.

3 Results

3.1 Basic characteristics of young and middle-aged participants

A total of 185,900 individuals were initially recruited for this study. After applying inclusion and exclusion criteria and removing cases with missing key variables, 48,022 participants were excluded. The final analytical sample included 137,878 participants, consisting of 71,453 men (51.8%) and 66,425 women (48.2%). The study flow is shown in Figure 2. The mean age of the participants was 40.98 ± 9.89 years. The overall prevalence of abnormal liver enzymes was 12.08%. Approximately one-third of the participants (45,852) were classified as obese. The prevalence of BD was 9.1%, with 1.5% of participants engaging in HIBD. The mean TyG index was 7.06. Participants with abnormal liver enzyme levels were younger and had lower HDL-c levels compared to those without abnormalities. In contrast, TC, TG, LDL-c, FBG, TyG index, obesity prevalence, and BD rates were all significantly higher in the abnormal liver enzymes group (p < 0.001; Table 1).

3.2 Visualization of overlapping risk profiles and liver enzyme abnormalities

Figure 3 presents a Venn diagram illustrating the overlapping distribution of participants with HIBD, obesity, and IR, along with the corresponding liver enzyme abnormality rates in each exposure category. Detailed data are provided in Table 2. The highest abnormality rate (33.2%) was observed in participants exposed to all

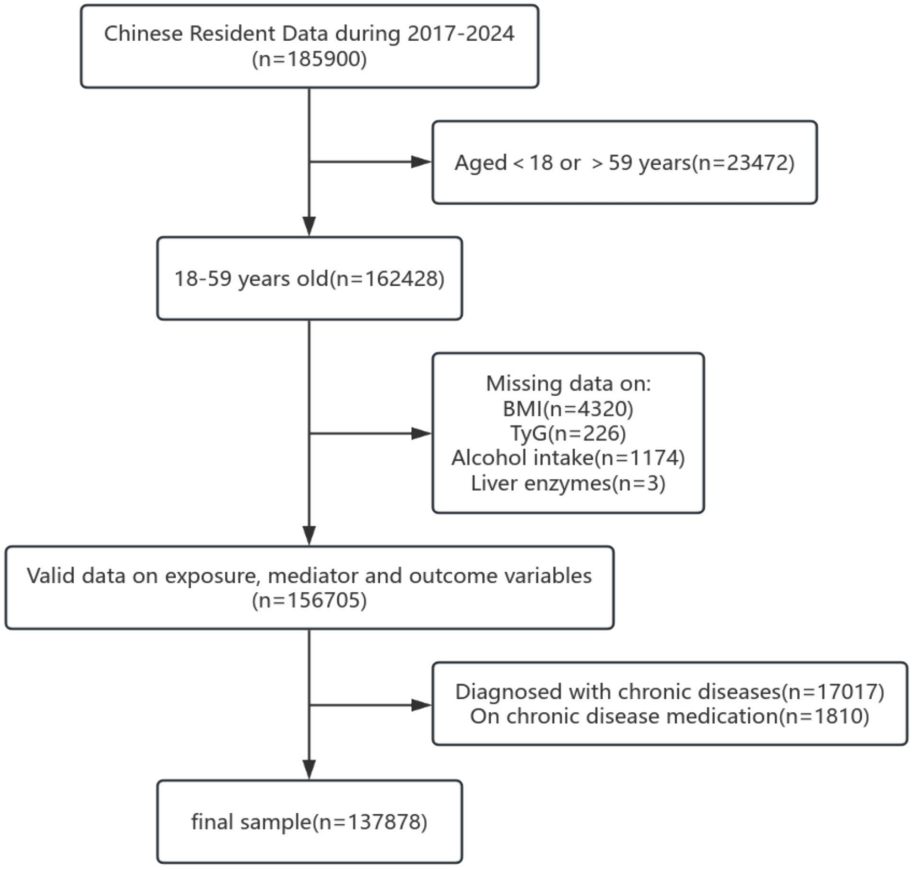

FIGURE 2
The flow chart of participant recruitment and selection process.

three risk factors (n = 996). In contrast, single-risk groups had lower rates. Participants without any of the three exposures showed the lowest abnormality rate (5.6%). These findings suggest a cumulative and potentially synergistic effect of the three factors on liver function.

3.3 Multivariable analysis

Multivariable analysis revealed that HIBD, obesity, and the TyG index were each independently associated with an increased risk of liver enzyme abnormalities. Participants with both obesity and HIBD had a 59.1% higher likelihood of liver enzyme abnormalities than those with neither risk factor (OR, 1.591; 95% CI, 1.401–1.806; Supplementary Table 1).

3.4 Mediation analysis

The decomposition of TE into NDE and NIE, mediated by the TyG index, is presented in Table 3 and visualized in Figure 4. Among individuals with obesity, the TyG index statistically explained 16.7% of the observed association with liver enzyme abnormalities (OR, 1.015; 95% CI, 1.075–1.083). For BD, a statistically significant indirect effect was observed only among participants in the HIBD group, where the TyG index accounted for 25.9% of the association (OR, 1.014; 95% CI, 1.012–1.016). The interaction between obesity and HIBD demonstrated the strongest indirect contribution, with the TyG index explaining 36.6% of the observed association (OR, 1.034; 95% CI, 1.029–1.039).

3.5 Subgroup analysis

Subgroup analysis stratified by BMI (non-obese group: BMI < 25 kg/m^2; obese group: BMI ≥ 25 kg/m^2) revealed distinct mediation effects of the TyG index in the association between HIBD and liver enzyme abnormalities (Table 4). In the obese group, the TyG index statistically accounted for 31.8% of the observed association between HIBD and liver enzyme abnormalities (OR, 1.014; 95% CI, 1.011–1.017), demonstrating a stronger indirect association compared to the non-obese group (16.9%; Figure 4).

3.6 Sensitivity analysis

Sensitivity analysis confirmed the robustness of the mediating role of the TyG index across all examined pathways, including HIBD, obesity, their interaction, and HIBD among individuals with obesity. Excluding participants with FBG ≥ 7 mmol/L slightly reduced the proportion of the association statistically explained by the TyG index for HIBD (from 25.9 to 24.5%) and

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TABLE 1 Baseline characteristics and univariate analysis of all participants (n = 137,878).

Characteristic	Total (n = 137,878)	No abnormal liver enzymes (n = 121,227, 87.92%)	Abnormal liver enzymes (n = 16,651, 12.08%)	χ^2/t^1
Age (years)	40.98 ± 9.89	41.03 ± 9.92	40.62 ± 9.62	5.06***
Sex				2925.23***
Male	71,453 (51.80%)	59,554 (49.10%)	11,899 (71.50%)	
Female	66,425 (48.20%)	61,673 (50.90%)	4,752 (28.50%)	
TC (mmol/L)	5.00 ± 0.96	4.99 ± 0.95	5.09 ± 0.99	−12.69***
TG (mmol/L)	1.73 ± 1.75	1.69 ± 1.72	1.96 ± 1.89	−18.40***
HDL-c (mmol/L)	1.34 ± 0.30	1.34 ± 0.30	1.30 ± 0.30	18.67***
LDL-c (mmol/L)	2.89 ± 0.80	2.88 ± 0.79	2.92 ± 0.82	−4.82***
FBG (mmol/L)	5.40 ± 1.16	5.38 ± 1.13	5.53 ± 1.0.35	−16.11***
TyG index	7.06 ± 0.70	7.00 ± 0.67	7.49 ± 0.77	−86.64***
BMI categories				6057.19***
<23.00 kg/m^2	59,719 (43.30%)	56,366 (46.50%)	3,353 (20.10%)	
23.00–24.99 kg/m^2	32,307 (23.40%)	28,773 (23.70%)	3,534 (21.20%)	
≥25.00 kg/m^2	45,852 (33.30%)	36,088 (29.80%)	9,764 (58.60%)	
BD intensity				1083.88***
Never	97,735 (70.90%)	87,553 (72.20%)	10,182 (61.10%)	
Stop	1,471 (1.10%)	1,237 (1.00%)	234 (1.40%)	
Non-BD	26,077 (18.90%)	22,224 (18.3%)	3,853 (23.1%)	
BD-I	10,471 (7.60%)	8,611 (7.10%)	1,860 (11.20%)	
HIBD	2,124 (1.50%)	1,602 (1.40%)	522 (3.1%)	
Diabetes Mellitus				2583.24***
No	119,640 (86.80%)	107,275 (88.50%)	12,365 (74.30%)	
Yes	18,238 (13.20%)	13,952 (11.50%)	4,286 (25.70%)	
Dyslipidemia				3593.39***
No	100,305 (72.70%)	91,421 (75.40%)	8,884 (53.40%)	
Yes	37,573 (27.30%)	29,806 (24.60%)	7,767 (46.60%)	
Smoking				978.49***
Never	98,291 (71.30%)	88,101 (72.70%)	10,190 (61.20%)	
Current	29,320 (21.30%)	24,377 (20.10%)	4,943 (29.70%)	
Past	3,884 (2.80%)	3,272 (2.70%)	612 (3.70%)	
Smoking				978.49***
Passive	6,383 (4.60%)	5,477 (4.50%)	906 (5.40%)	
Exercise				171.15***
No	53,789 (39.00%)	46,521 (38.40%)	7,268 (43.60%)	
Yes	84,089 (61.00%)	74,706 (61.60%)	9,383 (56.40%)	

*p < 0.05, **p < 0.01, ***p < 0.001. TC, Total cholesterol; TG, Triglycerides; HDL-c, High-density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; FBG, Fasting blood glucose; TyG, Triglyceride-glucose; BMI, Body mass index; BD, Binge drinking; BD-I, Level I binge drinking; HIBD, High-intensity binge drinking; [1]p-values were calculated using the χ2 test for categorical variables and the t test for continuous variables.

for the interaction pathways (from 36.6 to 35.9%). Similar marginal decreases were observed when individuals in the top 10% of BMI were excluded. We also conducted a sensitivity analysis excluding underweight individuals, which yielded results consistent with the main analysis, supporting the methodological decision to merge underweight and normal-weight participants. Although unmeasured confounders led to moderate reductions in the proportions explained, these changes remained within an acceptable range. Following PSM, the proportion explained for HIBD decreased to 21.1%, while the effects observed in other pathways remained stable. Overall, these findings support the consistency and reliability of the observed indirect contributions of the TyG index across all sensitivity analyses (Supplementary Table 2).

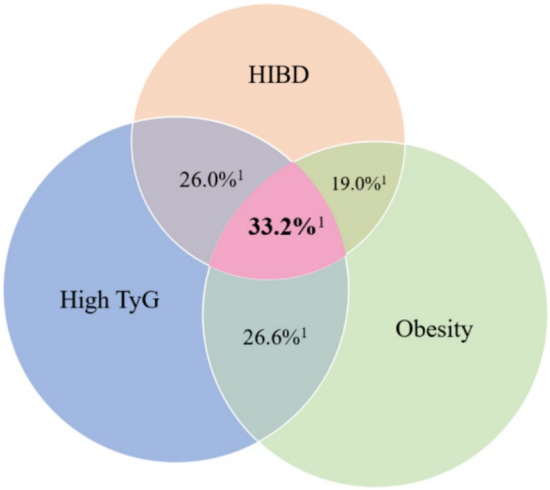

FIGURE 3
Venn diagram of high-intensity binge drinking, obesity, and insulin resistance showing corresponding liver enzyme abnormality rates. HIBD, High-intensity binge drinking; TyG, Triglyceride–glucose. [1]Liver enzyme abnormality rates.

TABLE 2 Liver enzyme abnormality rates by combinations of high-intensity binge drinking, obesity, and high TyG index.

Exposure combinations[1]	*N* (Participants)[2]	Liver enzyme abnormalities, *n* (%)
No risk factors	71,959	4,062 (5.6%)
Only HIBD	487	50 (10.3%)
Only Obesity	19,115	2,614 (13.7%)
Only High TyG	19,236	2,687 (14.0%)
HIBD + Obesity	332	63 (19.0%)
HIBD + High TyG	339	88 (26.0%)
Obesity + High TyG	25,420	6,764 (26.6%)
HIBD + Obesity + High TyG	996	321 (33.2%)

HIBD, High-intensity binge drinking; TyG, Triglyceride-glucose.
[1]Exposure combinations are defined by the presence or absence of HIBD, obesity, and insulin resistance, defined as the highest tertile of the TyG index.
[2]Total number of participants within each exposure combination.

4 Discussion

To the best of our knowledge, this is the first large-scale study in a young and middle-aged Chinese population to examine how IR, measured by the TyG index, statistically accounts for the associations between BD of varying intensities, obesity, their interaction, and liver enzyme abnormalities. While the overall prevalence of BD was 9.1%, it increased to 16.0% among individuals with obesity, highlighting a high-risk subgroup that warrants targeted investigation. Our findings show that IR statistically explained a meaningful proportion of the observed associations between HIBD, obesity, and liver enzyme abnormalities, with the greatest proportion observed for the interaction between HIBD and obesity. In contrast, no significant indirect contribution via IR was found for non-BD or low-intensity BD, suggesting an intensity-dependent metabolic mechanism. Sensitivity analysis validated the robustness of these results, and subgroup analysis revealed that the indirect role of IR was more pronounced in individuals with obesity. These results underscore the synergistic impact of obesity and HIBD on liver dysfunction through the pathway of IR. Although the effect sizes were modest, they were statistically significant and biologically meaningful, especially in high-risk populations such as individuals with obesity who engage in HIBD. These insights advance our understanding of the metabolic pathways linking lifestyle factors to liver injury and highlight the clinical relevance of targeting IR in prevention efforts.

Obesity and HIBD are two major risk factors for liver enzyme abnormalities, each contributing to liver injury through distinct but converging mechanisms. Obesity is characterized by a chronic low-grade inflammatory state, largely driven by VAT (46, 47). This state promotes the release of FFAs, which impair mitochondrial β-oxidation and increase the production of ROS, leading to oxidative stress and hepatocellular injury. FFAs also activate pro-inflammatory signaling pathways within hepatocytes, further aggravating liver damage (18). Similarly, HIBD exacerbates liver damage by increasing circulating lipopolysaccharides and pro-inflammatory cytokines, impairing mitochondrial function, and triggering oxidative stress and inflammatory responses, ultimately leading to hepatocyte apoptosis (12, 14). Additionally, HIBD worsens obesity-related metabolic disturbances. For instance, it accelerates the progression from simple steatosis to steatohepatitis and intensifies systemic and hepatic inflammation (13). When HIBD coexists with obesity, the combined metabolic burden leads to upregulation of hepatic cytochrome P450 2E1 (CYP2E1) activity and excessive ROS generation, exacerbating oxidative damage and liver dysfunction (9, 20). These findings suggest that obesity and HIBD not only have independent effects on liver injury but also interact synergistically through shared oxidative and inflammatory mechanisms, thereby increasing the likelihood and severity of liver enzyme abnormalities.

IR serves as a critical pathway linking HIBD and obesity with liver enzyme abnormalities, amplifying their synergistic effects. In obesity, elevated FFAs interfere with insulin signaling by impairing the tyrosine phosphorylation of IRS-1, which contributes to the development of IR, hepatic lipid accumulation, and oxidative stress (48). HIBD further contributes to hepatic inflammation and mitochondrial dysfunction, exacerbating IR through similar mechanisms (49). This convergence of metabolic disturbances exacerbates IR, which promotes hepatic lipid accumulation, increases CYP2E1 expression, and weakens antioxidant defenses, creating a feedback loop of oxidative stress and liver damage (27, 31, 32). Observational studies have linked excessive alcohol consumption (≥122 g/week) to an increased risk of type 2 diabetes (50), and liver enzymes such as ALT have been validated as a biomarker for IR (51). Together, these findings suggest that IR not only mediates the individual effects of obesity and HIBD but also serves as a shared mechanistic bridge through which these exposures jointly accelerate liver damage. Targeting IR may therefore represent a strategic intervention point for preventing or attenuating metabolically driven liver dysfunction.

Interestingly, no significant indirect contribution of IR was observed in individuals with non-BD or low-intensity BD, regardless of obesity status. Two explanations may account for this finding. First, the effects of BD on liver enzymes vary significantly

TABLE 3 Direct and TyG index-mediated associations of BMI categories, binge drinking levels, and the interaction between obesity (BMI ≥ 25.00 kg/m²) and high-intensity binge drinking with abnormal liver enzymes.

Exposure	TE OR(95% CI)	NDE OR(95% CI)	NIE OR(95% CI)	Proportion Mediated, %
BMI categories[1,2,4,5]				
<23.00 kg/m²	Reference	Reference	Reference	
23.00–24.99 kg/m²	0.985***(0.981,0.989)	0.984***(0.980,0.988)	1.001***(1.000,1.001)	−6.667
≥25.00 kg/m²	1.094***(1.090,1.100)	1.078***(1.075,1.083)	1.015***(1.075,1.083)	16.667
BD[1,2,4,5]				
Never	Reference	Reference	Reference	
Stop	1.003(0.988,1.018)	1.009(0.993,1.025)	0.994***(0.993,0.996)	--
Non-BD	0.998(0.994,1.003)	0.993**(0.989,0.997)	1.006***(1.005,1.006)	--
BD-I	1.006(1.000,1.012)	0.998(0.992,1.004)	1.008***(1.007,1.009)	--
HIBD	1.055***(1.040,1.071)	1.040***(1.027,1.055)	1.014***(1.012,1.016)	25.926
Obesity#HIBD[1,3,4,5]	1.097***(1.075,1.120)	1.061***(1.042,1.081)	1.034***(1.029,1.039)	36.559

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. BMI, Body mass index; BD, Binge drinking; BD-I, Level I binge drinking; HIBD, High-intensity binge drinking; Obesity#HIBD, Interaction term for obesity (BMI ≥ 25.00 kg/m²) and high-intensity binge drinking; Coef, Coefficient; CI, Confidence interval; OR, Odds ratio; TE, Total effect; NDE, Natural direct effect; NIE, Natural indirect effect; Reference, Reference category.

[1]All models were adjusted for sex, age, TC, HDL-c, LDL-c, smoking status, exercise, history of diabetes, and dyslipidemia.

[2]When examining the mediating role of the TyG index between BMI categories and abnormal liver enzymes, binge drinking was included as a control variable. When examining the mediating role of the TyG index between binge drinking level and abnormal liver enzymes, BMI categories were included as a control variable.

[3]The model used non-obese and non-high-intensity drinkers as the reference.

[4]In the BMI categories model, the treatment-mediator interaction term was included, whereas in the binge drinking levels model and the obesity-high-intensity binge drinking interaction model, it was not included.

[5]Causal mediation analysis was applied to decompose the total effect into natural indirect effect and natural direct effect; The mediate command in Stata 18.0 was used for analysis.

by intensity (8). While HIBD increases the metabolic burden on the liver, moderate drinking may exert protective effects against hepatic steatosis (52, 53). In this study, moderate alcohol consumption appeared to act as a protective factor against liver enzyme abnormalities, and no significant association was found between low-intensity drinking and liver enzyme abnormalities. Second, low-intensity or moderate alcohol consumption is generally not linked to IR and may even improve insulin sensitivity (53). For example, consuming 1–2 glasses of wine per occasion has been shown to reduce oxidative stress, increase HDL-c, and elevate adiponectin levels (8). These effects may help mitigate metabolic dysfunction. Systematic reviews and observational studies have reported that moderate alcohol consumption enhances insulin sensitivity and reduces the risk of type 2 diabetes (54, 55). Potential mechanisms include increased levels of adiponectin and hepatic glutathione, both recognized as insulin sensitizers, as well as the modulation of inflammatory mediators and oxidative stress by ethanol and polyphenols in red wine (8, 54).

Building on the primary findings, subgroup analysis revealed that the indirect contribution of IR between HIBD and liver enzyme abnormalities was nearly twice as strong in individuals with obesity compared to those without. This finding suggests that the greater metabolic burden in individuals with obesity amplifies the adverse effects of HIBD on liver function via IR. These findings align with the primary results of this study, emphasizing IR as a key statistical mediator in the relationship between the interaction of obesity, HIBD, and liver enzyme abnormalities. Importantly, they underscore the synergistic nature of this interaction and highlight IR as a potential therapeutic target. Addressing IR in individuals with obesity may offer a focused strategy to mitigate alcohol-related liver damage more effectively than targeting either risk factor alone.

From a public health standpoint, our findings emphasize the need for targeted interventions in individuals with obesity who engage in HIBD, a group at particular high risk for liver dysfunction. Interventions that improve insulin sensitivity, such as structured lifestyle modifications (e.g., diet and exercise) or pharmacologic therapies, combined with efforts to reduce alcohol intake, may be especially effective in mitigating liver enzyme abnormalities in this population. Notably, this dual-targeted strategy may be more feasible and sustainable than interventions focused solely on weight reduction, which often face challenges in adherence and delayed therapeutic effects (56, 57). Given the central role of IR in statistically linking both obesity and HIBD to liver-related outcomes, IR represents a promising and actionable intervention target for reducing the burden of metabolically driven liver injury at the population level.

Several limitations were present in this study. First, its single-center cross-sectional design precludes causal inference. However, the use of causal mediation analysis was justified by strong theoretical and biological plausibility, supported by prior experimental evidence linking obesity and BD to IR and IR to liver injury. The counterfactual framework allows the decomposition of effects under assumed causal direction and minimal unmeasured confounding. While our findings offer insight into potential mediation pathways, they reflect statistical rather than causal mediation and should be interpreted accordingly. Second, liver function was assessed using only ALT and AST, omitting markers like gamma-glutamyl transferase and alkaline phosphatase, which may underestimate the true extent of liver injury. Third, IR was measured solely by the TyG index. The absence of homeostatic model assessment of IR and glycated hemoglobin A1c limited a more comprehensive metabolic assessment. Fourth, unmeasured factors such as genetic background and diet may confound the results, though sensitivity analyses suggest limited impact. Additionally, self-reported

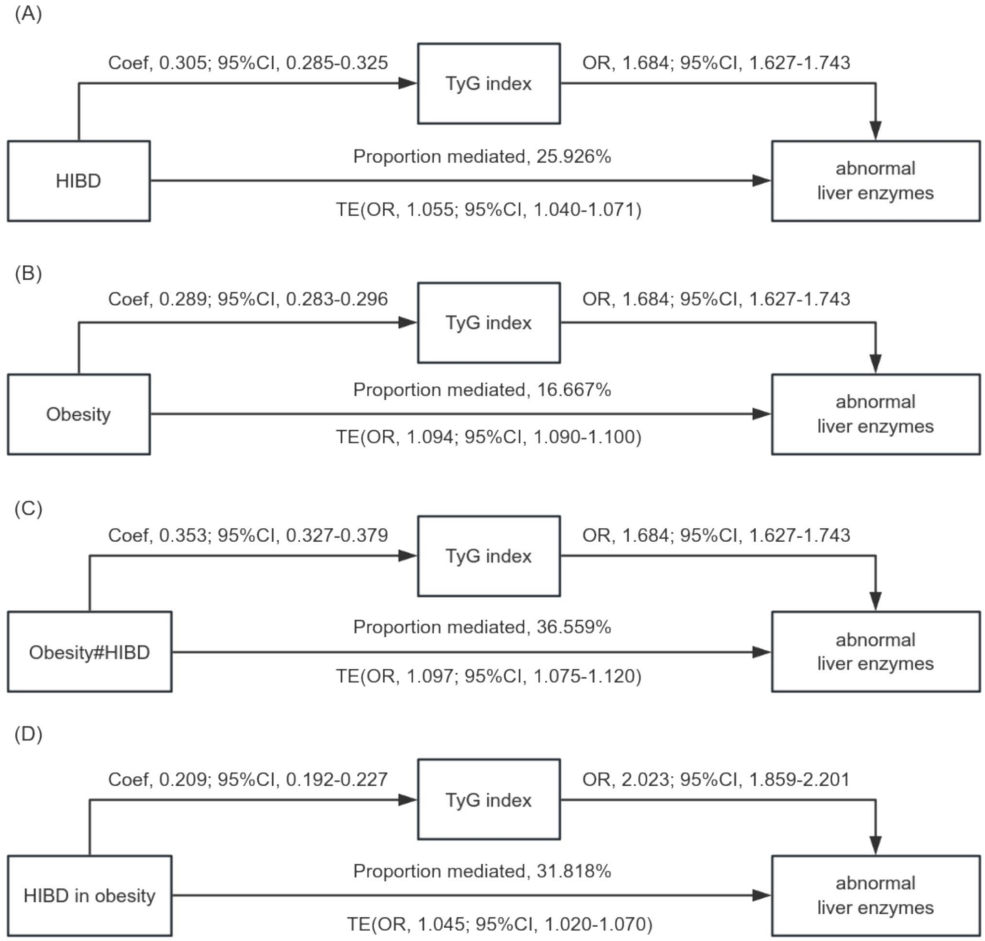

FIGURE 4
(A) Mediation role of TyG index in the relationship between high-intensity binge drinking and liver enzyme abnormalities. **(B)** Mediation role of TyG index in the relationship between obesity and liver enzyme abnormalities. **(C)** Mediation role of TyG index in the relationship between interaction term for obesity (BMI ≥ 25.00 kg/m^2) and high-intensity binge drinking and liver enzyme abnormalities. **(D)** Mediation role of TyG index in the relationship between high-intensity binge drinking in obesity and liver enzyme abnormalities.

TABLE 4 Subgroup analysis of the TyG Index mediation in the relationship between binge drinking levels and liver enzyme abnormalities, stratified by BMI.

Characteristic	BD Intensity	TE OR (95% CI)	NDE OR (95% CI)	NIE OR (95% CI)	Proportion Mediated, %
Non-obese (n = 92,026)[1,2]	Never (n = 71,776)	Reference	Reference	Reference	
	Stop (n = 817)	1.004(0.987,1.021)	1.008(0.990,1.026)	0.996***(0.994,0.998)	--
	Non-BD (n = 14,193)	0.997(0.993,1.002)	0.994*(0.989,0.999)	1.003***(1.003,1.004)	--
	BD-I (n = 4,414)	1.012**(1.004,1.020)	1.007(0.999,1.014)	1.005***(1.004,1.006)	--
	HIBD (n = 826)	1.065***(1.044,1.089)	1.055***(1.034,1.079)	1.011***(1.008,1.014)	16.923
Obese (n = 45,852)[1,2]	Never (n = 25,959)	Reference	Reference	Reference	
	Stop (654)	1.009(0.976,1.042)	1.015(0.982,1.049)	0.994***(0.990,0.997)	--
	Non-BD (n = 11,884)	1.009(1.000,1.019)	0.998(0.989,1.007)	1.011***(1.010,1.012)	--
	BD-I (n = 6,057)	1.017**(1.005,1.029)	1.004(0.992,1.016)	1.013***(1.012,1.015)	--
	HIBD (n = 1,298)	1.045***(1.020,1.070)	1.031*(1.007,1.055)	1.014***(1.011,1.017)	31.818

*p < 0.05, **p < 0.01, ***p < 0.001. BD, Binge drinking; BD-I, Level I binge drinking; HIBD, Heavy-intensity binge drinking; Coef, Coefficient; CI, Confidence interval; OR, Odds ratio; TE, Total effect; NDE, Natural direct effect; NIE, Natural indirect effect; Reference, Reference category.
[1]All models were adjusted for sex, age, TC, HDL-c, LDL-c, smoking status, exercise, history of diabetes, and dyslipidemia.
[2]Causal mediation analysis was applied to decompose the total effect into natural indirect effect and natural direct effect; The mediate command in Stata 18.0 was used for analyses.

alcohol consumption may be influenced by cultural patterns specific to China. In certain regions, individuals frequently consume unrecorded, homemade alcoholic beverages with potentially high ethanol concentrations, which are often underreported (58). Moreover, alcohol use is commonly embedded in social occasions rather than solitary behavior (58), which may contribute to recall or social desirability bias. These factors could lead to an underestimation of BD intensity, particularly at higher levels.

In conclusion, this study identified IR as a critical mediator of the synergistic effect of obesity and HIBD on liver enzyme abnormalities. The pathways of liver injury differ by BD intensity, with minimal indirect contributions of IR observed in low-intensity drinking. These findings highlight the need for dual-target public health strategies, improving IR through lifestyle modification and implementing stepwise alcohol reduction plans. For high-risk individuals, such as individuals with obesity engaging in HIBD, early screening using the TyG index and targeted metabolic interventions may help prevent liver enzyme abnormalities and reduce the long-term burden of liver disease. Future research should adopt longitudinal designs, include diverse populations, and explore targeted interventions to enhance the understanding and management of these complex associations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

The studies involving humans were approved by the third xiangya hospital's ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JZ: Writing – original draft, Conceptualization, Data curation, Formal analysis. YD: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. YiL: Conceptualization, Data curation, Investigation, Project administration, Writing – review & editing. YZ: Conceptualization, Investigation, Visualization, Writing – review & editing. ZL: Conceptualization, Data curation, Visualization, Writing – review & editing. NC: Investigation, Visualization, Writing – review & editing. JL: Investigation, Visualization, Writing – review & editing. XW: Investigation, Visualization, Writing – review & editing. XD: Data curation, Investigation, Visualization, Writing – review & editing. AC: Conceptualization, Visualization, Writing – review & editing. YuL: Conceptualization, Project administration, Resources, Supervision, Writing – review & editing.

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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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2025.1554392/full#supplementary-material

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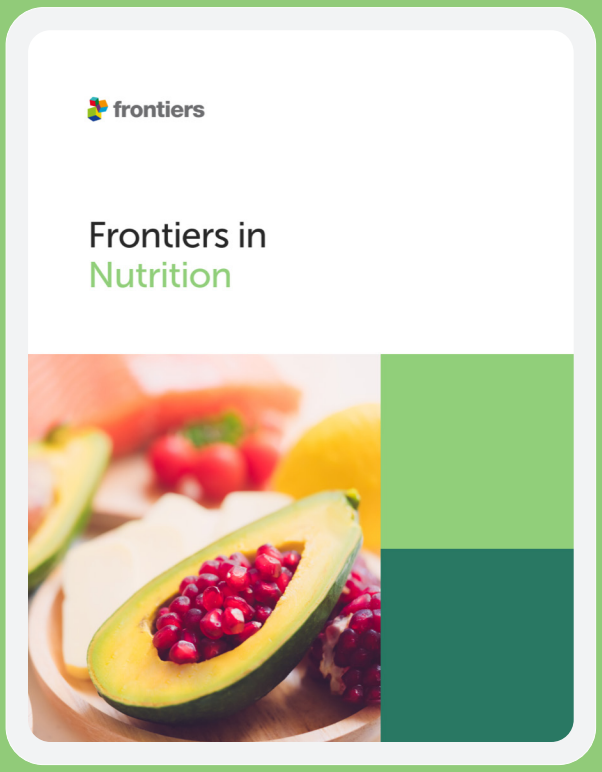

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