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The HbA1c/HDL-C ratio as a screening indicator of NAFLD in U.S. adults: a cross-sectional NHANES analysis (2017–2020)

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Abstract

Background Non-alcoholic fatty liver disease (NAFLD), a metabolic liver disorder closely associated with obesity and diabetes, urgently requires early screening. This population-based study is the first to explore the relationship between glycemic control and a novel dyslipidemia composite index—the glycated hemoglobin/high-density lipoprotein cholesterol (HbA1c/HDL-C) ratio in individuals with NAFLD and liver fibrosis.

Methods Data from 5,891 adults in the 2017–2020 National Health and Nutrition Examination Survey (NHANES) were analyzed. Binary logistic regression and restricted cubic spline (RCS) analyses were used to evaluate the association between HbA1c/HDL-C ratio and the risk of NAFLD and liver fibrosis. The reliability of the results was confirmed using subgroup, interaction, and sensitivity analyses. Screening performance was assessed using receiver operating characteristic (ROC) curves, and differences between various indicators were compared using the DeLong test.

Results After adjusting for confounding factors, each 1% increase in the HbA1c/HDL-C ratio was associated with a 20% higher risk of NAFLD (odds ratio [OR] = 1.20, 95% confidence interval [CI]: 1.14–1.27, $P < 0.001$). Sensitivity analyses confirmed the robustness of these findings ($P < 0.001$). However, the associations with liver fibrosis ($P = 0.064$) and moderate-to-severe liver fibrosis ($P = 0.130$) were not statistically significant. Participants in the highest HbA1c/HDL-C quartile had significantly higher odds of NAFLD than those in the lowest quartile (OR = 2.21, 95% CI: 1.74–2.79). RCS analysis revealed a non-linear positive correlation between the HbA1c/HDL-C and NAFLD risk (P for non-linear = 0.003). Subgroup and interaction analyses showed that this association was more pronounced in the non-diabetic population. The ROC curve yielded an AUC of 0.713 for NAFLD screening.

Conclusion In U.S. adults, the HbA1c/HDL-C appears to be an effective tool for NAFLD screening. As a novel composite index, it also holds considerable reference value for identifying NAFLD risk in the non-diabetic population.

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Keywords Plasma glycosylated hemoglobin to high-density lipoprotein cholesterol ratio (HbA1c/HDL-C), Non-alcoholic fatty liver disease (NAFLD), Practical indicator, National health and nutrition examination survey (NHANES)

Background

Nonalcoholic fatty liver disease (NAFLD) has emerged as a leading cause of chronic liver disease (CLD) globally, affecting approximately one-third of the population [1]. Its natural progression ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), which may be accompanied by varying degrees of liver fibrosis [2]. As a global health issue, NAFLD contributes not only to liver-related complications, such as cirrhosis, hepatocellular carcinoma, and liver failure, but is also closely linked to cardiovascular disease. This presents significant challenges and substantial burdens on public health systems and economic development [3]. In the United States alone, approximately 80 million individuals are affected by NAFLD [1]. However, more than 80% of patients with NAFLD lack obvious clinical symptoms in the early stages and are often diagnosed only after the disease has progressed and complications have developed. Therefore, early NAFLD screening remains a significant challenge in clinical practice [4]. There is an urgent need to identify effective and reliable noninvasive methods for early screening and assessment of NAFLD and liver fibrosis to promote early disease detection, risk stratification, and management [5].

NAFLD is strongly associated with hepatic glucose and lipid metabolism dysfunction [6]. Elevated plasma glycosylated hemoglobin (HbA1c), an important biomarker reflecting long-term blood glucose levels, indicates abnormal glucose metabolism [7]. High-density lipoprotein cholesterol (HDL-C), a unique component of the lipid family, plays various physiological roles including reverse cholesterol transport and anti-inflammatory functions [8]. These metabolic disturbances are central to the development and progression of NAFLD, highlighting the need for effective biomarkers to assess and monitor this disease. Therefore, evaluating both glucose and lipid dysregulation may provide a more reliable indicator of NAFLD risk than glucose or lipid markers alone. The ratio of plasma glycosylated hemoglobin to high-density lipoprotein cholesterol (HbA1c/HDL-C) is a novel composite marker used to assess glucose homeostasis and lipid abnormalities. Previous studies confirmed its strong association with the risk of carotid atherosclerosis and stroke [9, 10]. However, evidence regarding its relationship with NAFLD and liver fibrosis remains limited. Further research is required to explore the potential of this ratio as a predictive tool for these conditions.

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

This cross-sectional study used data from the 2017–2020 NHANES to examine the association between the HbA1c/HDL-C ratio and NAFLD, as well as liver fibrosis in U.S. adults. Additionally, we assessed the potential value of HbA1c/HDL-C ratio as a screening tool for NAFLD.

Methods

Study population

The study cohort consisted of 15,560 participants from the 2017 to March 2020 NHANES survey. Liver steatosis and fibrosis were assessed using vibration-controlled transient elastography (VCTE), a non-invasive technique that has been part of NHANES since 2017. The study protocol was approved by the National Center for Health Statistics Research Ethics Review Board and all participants provided written informed consent. Further details are available on the website: https://www.cdc.gov/nchs/nhanes/index.htm.

Participants were excluded based on the following criteria (Fig. 1) (1) Age < 20 (2) Based on the question "On the days when you drank alcoholic beverages in the past 12 months, how many drinks did you typically have?" Men who consumed more than 3 drinks per day and women who consumed more than 2 drinks per day were classified as excessive drinkers (3). Individuals with hepatitis B virus (positive for hepatitis B surface antigen) or hepatitis C virus (positive for hepatitis C antibody or HCV virus RNA) [11] (4). Participants with elevated transferrin saturation levels (men > 60%; women > 50%) [12] (5). Participants with missing HbA1c or HDL-C data, which prevented calculation of the HbA1c/HDL-C

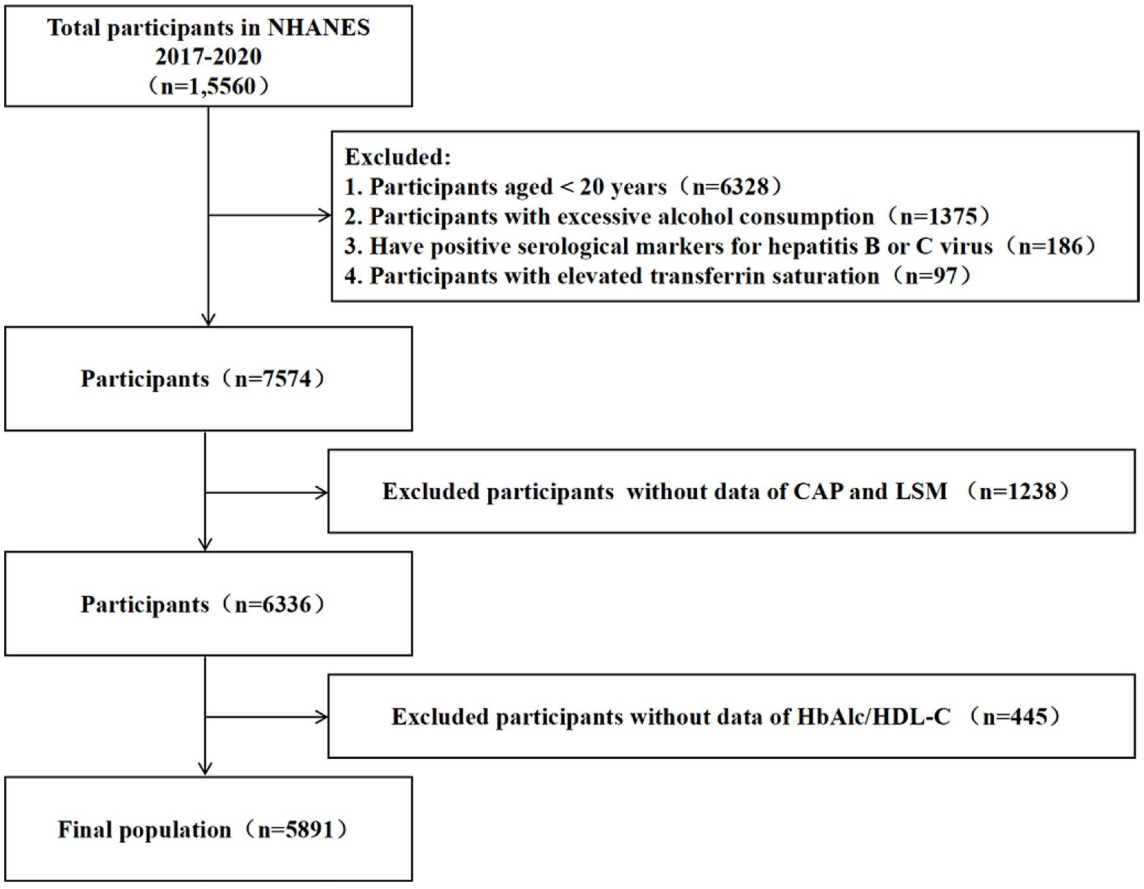

Fig. 1 Participant Inclusion and Exclusion Flowchart for NHANES 2017–2020

ratio. Finally, 5,891 participants were included in the analysis.

Calculation of the HbA1c/HDL-C ratio

The HbA1c/HDL-C ratio was calculated as follows: HbA1c (%) / HDL-C (mmol/L).

NAFLD and liver fibrosis evaluation

During the NHANES survey from 2017 to March 2020, all participants aged ≥ 12 years underwent transient elastography. The examination used an ultrasound system equipped with a handheld transducer (Liver Elastography System® model 502 V2 Touch; Echosens, Waltham, USA) to perform Controlled Attenuation Parameter (CAP) measurements. This was done to assess the participants' Liver Stiffness Measurement (LSM) and CAP values. If the median CAP is ≥ 274 dB/m, the diagnosis is NAFLD. If the median LSM is ≥ 7.0 kPa and the LSM value is ≥ 8.2 kPa, it indicates the presence of liver fibrosis, with a higher likelihood of moderate to advanced liver fibrosis [13].

According to the AASLD NAFLD Clinical Practice Guidelines, NAFLD is characterized by the presence of macrovesicular steatosis in ≥ 5% of hepatocytes in the absence of significant confounders(such as drugs, fasting, monogenic diseases.), and minimal alcohol consumption (< 20 g/day for women and < 30 g/day for men) [14].

Assessment of covariates

To evaluate the independent association between the HbA1c/HDL-C ratio and the risk of NAFLD and liver fibrosis, this study adjusted for potential confounding factors in the statistical analysis. The adjusted variables included socio-demographic and health-related factors.

Sociodemographic variables included age, sex (female and male), race/ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other races), education (categorized as less than high school, high school, and more than high school), and family income-to-poverty ratio (PIR), categorized as: <1.3, 1.3–3.5, and > 3.5.

Health-related variables included body mass index (BMI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides (TG), total cholesterol (TC), history of diabetes, hypertension, coronary heart disease, and smoking status. BMI was directly measured by the examination center and calculated as weight divided by the square of height (kg/m^2). After processing,

serum samples were sent to the University of Minnesota laboratory to analyze TG, TC, HDL-C, ALT, and AST levels following the procedures outlined in the NHANES laboratory manual. The smoking status was classified as nonsmoker, former smoker, or current smoker based on the following criteria: individuals with a smoking history of fewer than 100 cigarettes were classified as nonsmokers; those with a smoking history of more than 100 cigarettes but who no longer smoked were classified as former smokers; and individuals with a smoking history of more than 100 cigarettes and who currently smoked were classified as current smokers. The diagnostic criteria for a history of diabetes were as follows: if the participants answered positively to at least one of the five related questions, they were diagnosed with diabetes. The related questions included: whether they were currently using insulin, whether a doctor had informed them they had diabetes, whether they were using anti-diabetic medications, or if their HbA1c was ≥ 6.5%, or their fasting blood glucose was ≥ 126 mg/dL. The diagnostic criteria for a history of hypertension were: if the participant was informed of having hypertension in two or more different visits, was prescribed medication for hypertension, or if the average systolic blood pressure from three consecutive measurements was ≥ 140 mmHg, or the average diastolic blood pressure from three consecutive measurements was ≥ 90 mmHg. History of coronary heart disease was defined based on whether the individual had been diagnosed with myocardial infarction, angina, coronary heart disease, congestive heart failure, or stroke.

Statistical analysis

Statistical analysis was conducted using R version 4.2.2 and Empower (R) version 2.0. The final analysis sample consisted of 5,891 participants. During data processing, demographic data and questionnaire responses marked as 'refused' or 'don't know' were treated as missing values. Variables with a missing data proportion of ≥ 20% were excluded from the analysis. We applied Little's MCAR test to determine whether the missing data for variables with less than 20% missingness were missing completely at random (MCAR). If the missing data were confirmed to be missing at random (or not at random), we handled the missing values using multiple imputation, generating five imputed datasets. Regression models were constructed using the imputed datasets. The imputation method employed random sampling, with five imputations generating the final dataset for analysis. A *P*-value of < 0.05 was considered statistically significant in all analyses. The baseline characteristics of the study population were described statistically using the CAP and LSM subgroups. Normally distributed data are expressed as mean ± standard deviation, while skewed data are expressed as median (interquartile range). Comparisons between normally distributed data were performed using t-tests, skewed data were compared using the rank-sum test, and categorical data were compared using the chi-square test.

We calculated the variance inflation factor (VIF) values for all covariates and adjusted for non-collinear variables with a VIF < 5 in the subsequent models (Supplementary Table 1). The adjusted covariates included gender, age, race, education level, PIR, BMI, smoking status, history of diabetes, history of hypertension, history of coronary heart disease, as well as ALT, AST, TG, and TC. A binary logistic regression model was used to analyze the association between HbA1c/HDL-C and NAFLD, as well as liver fibrosis, calculating the odds ratio (OR) and its 95% confidence interval (CI). HbA1c/HDL-C was divided into four quartiles, with the lowest quartile serving as the reference group. To enhance the reliability of the results and minimize the impact of confounding factors, we constructed three models and progressively adjusted for covariates. Model 1 adjusted for age, gender, race, PIR, and education level. Model 2 further adjusted for BMI, hypertension, diabetes, coronary heart disease, and smoking status. Model 3 additionally adjusted for ALT, AST, TG, and TC. Simultaneously, similar statistical analyses were conducted for different subgroups, and interaction tests were performed to examine the relationships between the subgroups. Additionally, restricted cubic splines (RCS) were used to explore the potential nonlinear relationship between HbA1c/HDL-C and NAFLD, further identifying any potential inflection points. To further validate the stability and reliability of the association between HbA1c/HDL-C and NAFLD, propensity score matching (PSM) was performed for sensitivity analysis. The propensity scores were calculated based on five key demographic variables: gender, age, race, education level, and PIR. A 1:1 matching was conducted between the NAFLD and non-NAFLD groups, with a caliper value set at 0.01. The comparison of demographic data between the adjusted groups is shown in Supplementary Table 4. After matching, the data were analyzed using multivariable logistic regression to assess whether the association between HbA1c/HDL-C and NAFLD remained significant [15]. Finally, receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to evaluate the discriminatory value of HbA1c/HDL-C, HbA1c, and HDL-C for the preliminary screening of NAFLD. These results were then compared with existing indicators (such as FLI [16], HIS [17], TyG [18], NHHR [19], NHR [20], etc.) to further explore the potential value of HbA1c/HDL-C in NAFLD screening.

Results

Baseline characteristics of participants

A total of 5,891 participants met the inclusion criteria. The baseline demographic and clinical characteristics of the cohort are presented according to the presence of NAFLD, liver fibrosis, and moderate-to-severe liver fibrosis. Among these participants, the average age was 52.50 ± 17.23 years, with 47.9% males and 52.1% females. Of these, 2,641 were diagnosed with NAFLD, 979 with liver fibrosis, and 617 with moderate-to-severe liver fibrosis, representing 44.83%, 16.62%, and 10.47% of the study population, respectively.

The results indicated that compared with participants without NAFLD, those with NAFLD were more likely to be aged ≥ 60 years, male, non-Hispanic White, and to have higher rates of diabetes, hypertension, and coronary heart disease. Patients with NAFLD also had higher BMI, ALT, AST, TG, TC, HbA1c, and HbA1c/HDL-C ratios, while their HDL-C levels were lower. The detailed characteristics are shown in Table 1. Similar trends were observed in patients with liver fibrosis and moderate-to-severe liver fibrosis (Supplementary Tables 2 and 3).

Association of HbA1c/HDL-C ratio with NAFLD and liver fibrosis

The results of the multivariate logistic regression analysis showed a significant positive correlation between HbA1c/HDL-C and NAFLD, which was consistently confirmed across all models [OR: Model 1, 1.64(1.57,1.71); Model 2, 1.32(1.25,1.38); Model 3, 1.20(1.14,1.27); all $P < 0.001$]. In the fully adjusted model, for every 1-unit increase in HbA1c/HDL-C ratio, the risk of developing NAFLD increased by 20%. Grouping HbA1c/HDL-C ratios by quartile revealed that the NAFLD risk in the fourth quartile was 121% higher than that in the first quartile (Table 2). However, this correlation was not significant for liver fibrosis (Table 3) or moderate to severe liver fibrosis (Table 4). To verify the reliability of the results further, we conducted a sensitivity analysis. The results still indicated a positive correlation between HbA1c/HDL-C and the prevalence of NAFLD (Model 3: OR = 1.21, 95% CI: 1.14–1.28), with specific data presented in Table 5.

Dose–response relationship between the HbA1c/HDL-C and risk of NAFLD

The relationship between HbA1c/HDL-C and NAFLD was analyzed using the RCS (Fig. 2A), adjusting for variables such as sex, age, race, education level, PIR, BMI, smoking status, diabetes, hypertension, coronary heart disease, and ALT, AST, TG, and TC levels. A two-stage linear regression model (Table 6) revealed a nonlinear association between HbA1c/HDL-C ratio and NAFLD, showing an increasing trend with an inflection point at 5.743. The predicted value at the inflection point, along with its 95%CI is 0.646(0.543,0.750). The risk of NAFLD increased as the ratio was < 5.743. However, when the ratio exceeded 5.743, the association between HbA1c/HDL-C ratio and NAFLD was no longer significant. These findings suggest a non-linear association, with the predictive effect of HbA1c/HDL-C plateauing beyond a threshold of 5.743.

Subgroup analysis and interactions

The results of the subgroup analysis are shown in Fig. 3. Based on sex, age, race, education level, diabetes, hypertension, and coronary heart disease status, the association between HbA1c/HDL-C and the risk of NAFLD was statistically significant in five subgroups: sex, education, diabetes, hypertension, and coronary heart disease ($P < 0.05$). Significant interactions were observed between age, education level, hypertension, and HbA1c/HDL-C (P for interaction < 0.05), indicating that these variables significantly affected the association between HbA1c/HDL-C and NAFLD risk in the different subgroups.

Subgroup and interaction analysis results showed that, compared to diabetic patients, the risk of NAFLD was higher in the non-diabetic population. Further exploration of the relationship between HbA1c/HDL-C ratio and NAFLD risk in the non-diabetic population revealed a significant positive correlation. Logistic regression analysis indicated that in the non-diabetic population, HbA1c/HDL-C was significantly positively correlated with NAFLD (Supplementary Table 5). This relationship was confirmed in all models [OR: Model 1, 1.81(1.70,1.92); Model 2, 1.40(1.31,1.50); and Model 3, 1.25(1.15,1.35); all $P < 0.001$]. The RCS further confirmed this result (Fig. 2B).

Evaluate the accuracy of indicators in identifying NAFLD

Figure 4A shows the AUC values of the three indicators, HbA1c/HDL-C, HbA1c, and HDL-C, in NAFLD screening. The results indicated that the AUC value for HbA1c/HDL-C in the overall population was higher than that for HbA1c and HDL-C, with AUC values of 0.713, 0.664, and 0.676, respectively. Figure 4B shows the AUC values in the non-diabetic population, where HbA1c/HDL-C still outperformed HbA1c and HDL-C with AUC values of 0.686, 0.608, and 0.668, respectively. Figure 4C compares the AUC values of the six indicators (FLI, TyG, HbA1c/HDL-C, HSI, NHHR, and NHR) for NAFLD screening. The results showed that FLI had the highest AUC value, whereas HbA1c/HDL-C performed better than HSI, NHHR, and NHR in the overall population, with AUC values of 0.713, 0.696, 0.665, and 0.654, respectively. Additionally, the Delong test results indicated no statistically significant differences between the AUC values of the TyG index and HbA1c/HDL-C ratio (Table 7).

Table 1 Baseline characteristics of the participants based on the presence of NAFLD

Variables	Total (*n* = 5891)	NAFLD (*n* = 2641)	Non-NAFLD (*n* = 3250)	Test of significance
Age, [M (P25, P 75)]	54.00 (38.00–66.00)	56.00 (43.00–67.00)	51.00 (34.00–66.00)	< 0.001#
< 40	1574 (26.7)	511 (19.3)	1063 (32.7)	< 0.001
40–59	1970 (33.4)	973 (36.8)	997 (30.7)	
≥ 60	2348 (39.9)	1157 (43.8)	1190 (36.6)	
Gender(%)				< 0.001
Male	2821 (47.9)	1406 (53.2)	1415 (43.5)	
Female	3070 (52.1)	1235 (46.8)	1835 (56.5)	
Education level (%)				0.168
Less than high school	1056 (17.9)	501 (19.0)	555 (17.1)	
High school	1356 (23.0)	598 (22.6)	758 (23.3)	
More than high school	3479 (59.0)	1542 (58.4)	1937 (59.6)	
Race/ethnicity (%)				< 0.001
Mexican American	639 (10.8)	371 (14.0)	268 (8.2)	
Other Hispanic	600 (10.2)	271 (10.3)	329 (10.1)	
Non-Hispanic White	2057 (34.9)	969 (36.7)	1088 (33.5)	
Non-Hispanic Black	1541 (26.2)	582 (22.0)	959 (29.5)	
Other Race	1054 (17.9)	448 (17.0)	606 (18.6)	
PIR (%)				0.318
< 1.3	1544 (26.2)	667 (25.3)	877 (27.0)	
≥ 1.3,<3.5	2292 (38.9)	1044 (39.5)	1248 (38.4)	
≥ 3.5	2055 (34.9)	930 (35.2)	1125 (34.6)	
BMI, [M (P25, P 75)]	28.70 (25.00-33.60)	33.48 (7.49)	27.16 (5.86)	< 0.001#
Smoking status (%)				< 0.001
Never	3670 (62.3)	1611 (61.0)	2059 (63.4)	
Former	1428 (24.2)	720 (27.3)	708 (21.8)	
Current smoker	793 (13.5)	310 (11.7)	483 (14.9)	
Comorbidities				
Diabetes (%)				< 0.001
Yes	1286 (21.8)	871 (33.0)	415 (12.8)	
No	4605 (78.2)	1770 (67.0)	2835 (87.2)	
Hypertension (%)				< 0.001
Yes	2825 (48.0)	1511 (57.2)	1314 (40.4)	
No	3066 (52.0)	1130 (42.8)	1936 (59.6)	
Coronary heart disease (%)				< 0.001
Yes	697 (11.8)	364 (13.8)	333 (10.2)	
No	5194 (88.2)	2277 (86.2)	2917 (89.8)	
Laboratory findings				
ALT, [M (P25, P 75)]	17.00 (13.00–25.00)	20.00 (15.00–29.00)	15.00 (12.00–21.00)	< 0.001#
AST, [M (P25, P 75)]	19.00 (16.00–23.00)	20.00 (16.00–25.00)	18.00 (16.00–22.00)	< 0.001#
TG, [M (P25, P 75)]	1.28 (0.89–1.86)	1.56 (1.12–2.25)	1.07 (0.79–1.56)	< 0.001#
TC, [M (P25, P 75)]	4.73 (4.09–5.46)	4.78 (4.11–5.51)	4.71 (4.06–5.40)	0.007#
HbA1c, [M (P25, P 75)]	5.60 (5.30-6.00)	5.80 (5.50–6.40)	5.50 (5.30–5.80)	< 0.001#
HDL, [M (P25, P 75)]	1.32 (1.09–1.58)	1.19 (1.01–1.42)	1.42 (1.19–1.71)	< 0.001#
HbA1c/HDL, [M (P25, P 75)]	4.34 (3.49–5.41)	5.00 (4.06–6.12)	3.88 (3.22–4.77)	< 0.001#

Values are n (%) or mean (standard deviation). Abbreviations: NAFLD, nonalcoholic fatty liver disease; PIR, poverty to income ratio. BMI, body mass index; ALT, alanine aminotransferase. AST, Aspartate Aminotransferase; TC, total cholesterol; TG, triglyceride; HbA1c, Glycated Hemoglobin; HDL, High-Density Lipoprotein. HbA1c/HDL-C ratio: hemoglobin A1c to high-density lipoprotein cholesterol ratio. "#" indicates that the rank-sum test was used

Table 2 Association between HbA1c/HDL-C and NAFLD

	Model 1		Model 2		Model 3	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
HbA1c/HDL-C	1.64 (1.57, 1.71)	< 0.001	1.32 (1.25, 1.38)	< 0.001	1.20 (1.14, 1.27)	**< 0.001**
HbA1c/HDL-C quartile						
Q1	reference		reference		reference	
Q2	1.98 (1.67, 2.33)	< 0.001	1.30 (1.09, 1.57)	0.0046	1.24 (1.03, 1.50)	0.0249
Q3	3.64 (3.08, 4.29)	< 0.001	1.81 (1.50, 2.18)	< 0.001	1.57 (1.28, 1.92)	< 0.001
Q4	8.01 (6.72, 9.55)	< 0.001	3.06 (2.49, 3.76)	< 0.001	2.21 (1.74, 2.79)	< 0.001

Abbreviations: HbA1c/HDL-C ratio: hemoglobin A1c to high-density lipoprotein cholesterol ratio; NAFLD: nonalcoholic fatty liver disease; OR: Odds ratios; CI: confidence interval

Model1 is adjusted for gender, age, race, PIR, education level. Model2 is further adjusted for BMI, smoking, diabetes, Coronary heart disease and hypertension based on Model1. Model3 is additionally adjusted for TG, TC, AST and ALT based on Model2

Table 3 Association between HbA1c/HDL-C and liver fibrosis

	Model 1		Model 2		Model 3	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
HbA1c/HDL-C	1.28 (1.23, 1.33)	< 0.001	1.09 (1.04, 1.14)	< 0.001	1.05 (1.00, 1.11)	**0.064**
HbA1c/HDL-C quartile						
Q1	reference		reference		reference	
Q2	1.49 (1.17, 1.90)	0.001	1.01 (0.78, 1.30)	0.940	1.02 (0.79, 1.33)	0.861
Q3	2.30 (1.83, 2.90)	< 0.001	1.13 (0.88, 1.46)	0.325	1.10 (0.85, 1.43)	0.462
Q4	3.70 (2.95, 4.63)	< 0.001	1.30 (1.00, 1.69)	0.049	1.14 (0.86, 1.52)	0.376

Abbreviations: HbA1c/HDL-C ratio: hemoglobin A1c to high-density lipoprotein cholesterol ratio; OR: Odds ratios; CI: confidence interval

Model1 is adjusted for gender, age, race, PIR, education level. Model2 is further adjusted for BMI, smoking, diabetes, Coronary heart disease and hypertension based on Model1. Model3 is additionally adjusted for TG, TC, AST and ALT based on Model2

Table 4 Association between HbA1c/HDL-C and Moderate-to-advanced fibrosis

	Model 1		Model 2		Model 3	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
HbA1c/HDL-C	1.28 (1.23, 1.34)	< 0.001	1.08 (1.02, 1.14)	0.005	1.05 (0.99, 1.11)	**0.130**
HbA1c/HDL-C quartile						
Q1	reference		reference		reference	
Q2	1.40 (1.02, 1.92)	0.036	0.87 (0.63, 1.22)	0.428	0.90 (0.64, 1.28)	0.569
Q3	2.51 (1.87, 3.36)	< 0.001	1.08 (0.78, 1.48)	0.655	1.08 (0.77, 1.51)	0.653
Q4	3.99 (3.00, 5.30)	< 0.001	1.13 (0.81, 1.58)	0.463	1.02 (0.71, 1.46)	0.907

Abbreviations: HbA1c/HDL-C ratio: hemoglobin A1c to high-density lipoprotein cholesterol ratio; OR: Odds ratios; CI: confidence interval

Model1 is adjusted for gender, age, race, PIR, education level. Model2 is further adjusted for BMI, smoking, diabetes, Coronary heart disease and hypertension based on Model1. Model3 is additionally adjusted for TG, TC, AST and ALT based on Model2

Table 5 Association of HbA1c/HDL-C with NAFLD after PSM

	Model 1		Model 2		Model 3	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
HbA1c/HDL-C	1.63 (1.55, 1.70)	< 0.001	1.32 (1.25, 1.39)	< 0.001	1.21 (1.14, 1.28)	**< 0.001**
HbA1c/HDL-C quartile						
Q1	reference		reference		reference	
Q2	2.05 (1.73, 2.43)	0.001	1.36 (1.13, 1.64)	0.001	1.29 (1.06, 1.57)	0.010
Q3	3.74 (3.15, 4.45)	< 0.001	1.88 (1.55, 2.29)	< 0.001	1.61 (1.31, 1.98)	< 0.001
Q4	7.61 (6.33, 9.15)	< 0.001	3.04 (2.44, 3.78)	< 0.001	1.61 (1.31, 1.98)	< 0.001

Abbreviations: HbA1c/HDL-C ratio: hemoglobin A1c to high-density lipoprotein cholesterol ratio; NAFLD: nonalcoholic fatty liver disease; PSM: Propensity score matching; OR: Odds ratios; CI: confidence interval

Model1 is adjusted for gender, age, race, PIR, education level. Model2 is further adjusted for BMI, smoking, diabetes, Coronary heart disease and hypertension based on Model1. Model3 is additionally adjusted for TG, TC, AST and ALT based on Model2

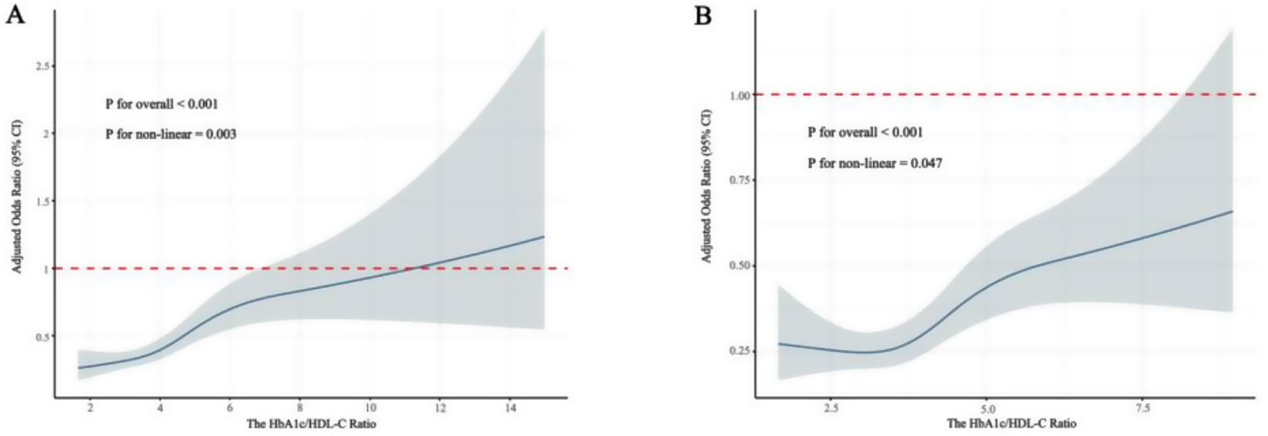

Fig. 2 The relationship between HbA1c/HDL-C and NAFLD in the entire study population (**A**) and the non-diabetic population (**B**). Adjusted for age, gender, race, BMI, tobacco use, education, hypertension, family income-poverty ratio, and other covariates. The solid line and blue area represent the estimated values and their corresponding 95% CIs, respectively

Table 6 Threshold effect analysis of HbA1c/HDL-C on NAFLD using a linear regression model

Non-Alcoholic Fatty Liver Disease	Adjusted OR (95% CI), *P* - value
Fitting by the standard linear model	1.203(1.137,1.272) < 0.001
Fitting by the two-piecewise linear model	
Inflection point	5.743
HbA1c/HDL-C < 5.743	1.323(1.218,1.436) < 0.001
HbA1c/HDL-C > 5.743	1.080(0.992,1.174) 0.075
The predicted values of the equation at the inflection point.	0.646(0.543,0.750)
Log likelihood ratio	0.002

Abbreviations: HbA1c/HDL-C ratio: hemoglobin A1c to high-density lipoprotein cholesterol ratio; OR: Odds ratios; CI: confidence interval

Further analysis of the AUC values in the non-diabetic population (Fig. 4D) revealed results similar to those observed in the overall population.

Discussion

This study utilized data from 2017 to 2020 NHANES database, involving 5,891 American adults, in a cross-sectional analysis to evaluate the potential association between the HbA1c/HDL-C ratio and NAFLD as well as liver fibrosis severity. Our results showed that the HbA1c/HDL-C ratio, a composite indicator of blood glucose homeostasis and dyslipidemia, was significantly and positively correlated with NAFLD, even after adjusting for covariates such as age, sex, and race. Sensitivity analysis further validated the robustness of this relationship. However, no significant associations were observed between these ratios and liver fibrosis. RCS analysis revealed a nonlinear relationship between HbA1c/HDL-C ratio and NAFLD, with an inflection point at 5.743. The results of the subgroup analysis indicate that, compared to diabetic patients, the association between HbA1c/HDL-C levels and the risk of NAFLD is more pronounced in the non-diabetic population. Further ROC curve analysis suggested that the HbA1c/HDL-C ratio has a good screening performance for NAFLD.

Liver biopsy is considered the gold standard for evaluating fatty liver disease. However, owing to its invasive nature, variability in sampling sites, and limitations in large-scale screening, there is a pressing need to identify more convenient and noninvasive serum biomarkers for early screening and diagnosis [5]. Other relevant studies have provided valuable references to advance our understanding and develop alternative diagnostic approaches. Wang et al. [21] analyzed NHANES data from 2017 to 2020 and found that the TG/HDL-C ratio had a nonlinear positive correlation with the prevalence of NAFLD, although this correlation was not observed for liver fibrosis. Similarly, Zhang et al. [22] included 393 patients diagnosed with NAFLD through liver biopsy and found that TyG-BMI and its multivariable models could serve as valuable non-invasive indicators for NAFLD diagnosis, risk stratification, and disease progression monitoring. Additionally, Santo Colosimo et al. [23] conducted a study on 857 patients with NAFLD who underwent liver biopsy and staging, revealing that HbA1c level provided important information for predicting the severity of NAFLD, and its role was more significant than that of BMI. In contrast to Wang et al. and other studies, our research integrated indicators of glucose and lipid metabolism, focusing on the impact of both glucose and lipid metabolism on the disease. For the first time, we explored the relationship between the new indicator HbA1c/HDL-C ratio and NAFLD and liver fibrosis, extending the existing research further.

Based on these findings, it is particularly important to further explore the potential physiological mechanisms underlying HbA1c/HDL-C ratio and its association with NAFLD. NAFLD is a chronic condition closely associated

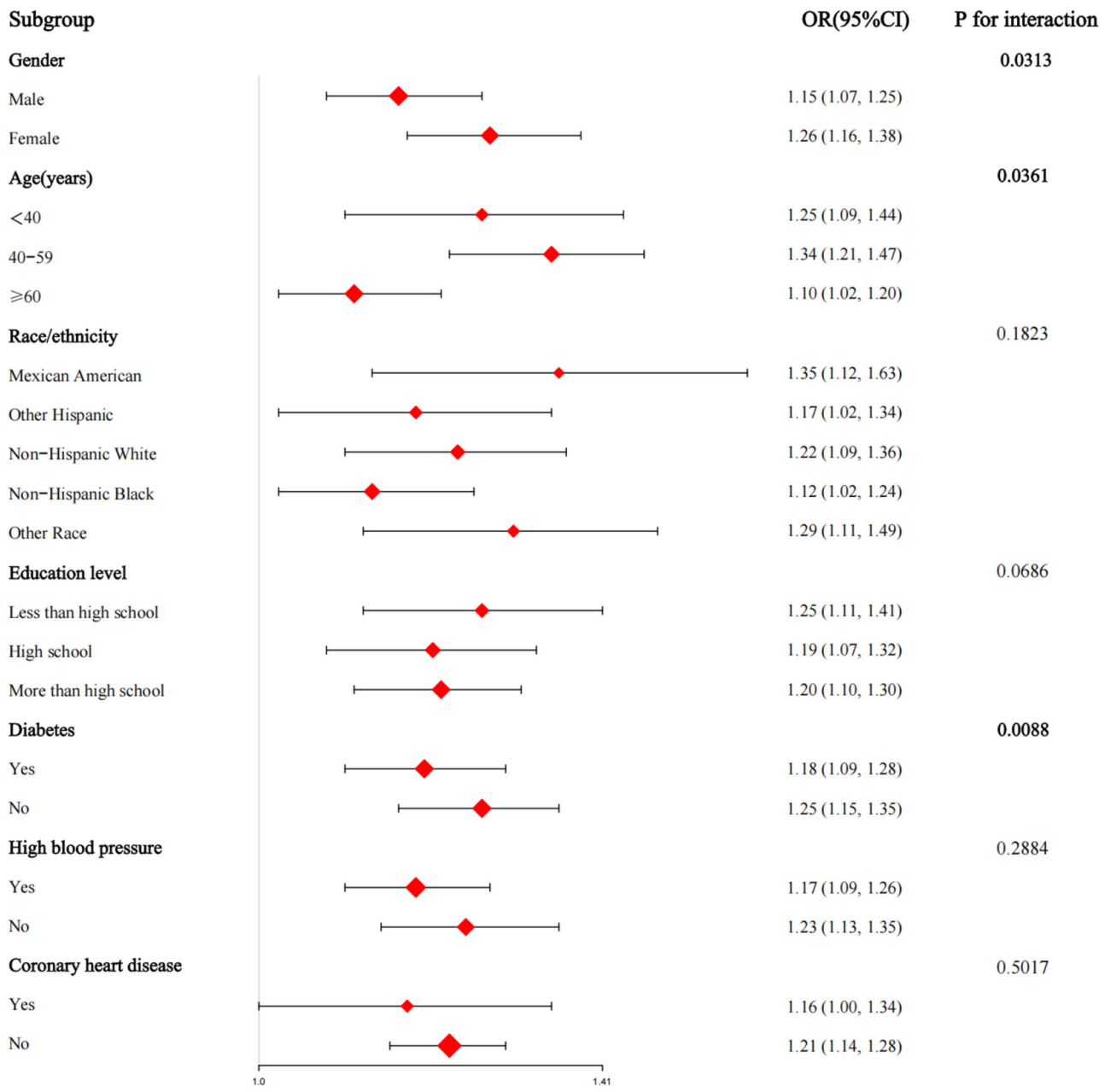

Fig. 3 Forest plots of the relationship between HbA1c/HDL-C and NAFLD with subgroups. Abbreviations: OR, Odds Ratio; CI, Confidence Interval

with metabolic syndrome, characterized primarily by hepatic fat accumulation, and is often accompanied by metabolic disorders such as abnormal blood glucose, lipid profiles, and hypertension [24, 25]. An increase in intrahepatic triglycerides (IHTG) is a hallmark feature of NAFLD, and de novo lipogenesis (DNL) in the liver plays a crucial role in regulating IHTG content [26]. Insulin resistance (IR) reduces the body's sensitivity to insulin, leading to elevated blood glucose and insulin levels, which activate transcription factors, such as carbohydrate response element-binding protein (ChREBP). This activation enhanced hepatic DNL levels and promoted IHTG accumulation [27, 28]. Elevated blood glucose is not only a manifestation of insulin resistance, but also directly affects lipid metabolism [26], creating a vicious cycle that exacerbates the development of NAFLD. Animal studies have shown that poor blood glucose control is a key driver of NAFLD [29]. Additionally, a large-scale cross-sectional study showed that, from a clinical perspective, there is an independent association between blood glucose control and hepatic fat accumulation [30]. Blood glucose control can be effectively reflected by HbA1c levels, which are closely related to the onset and progression of NAFLD.

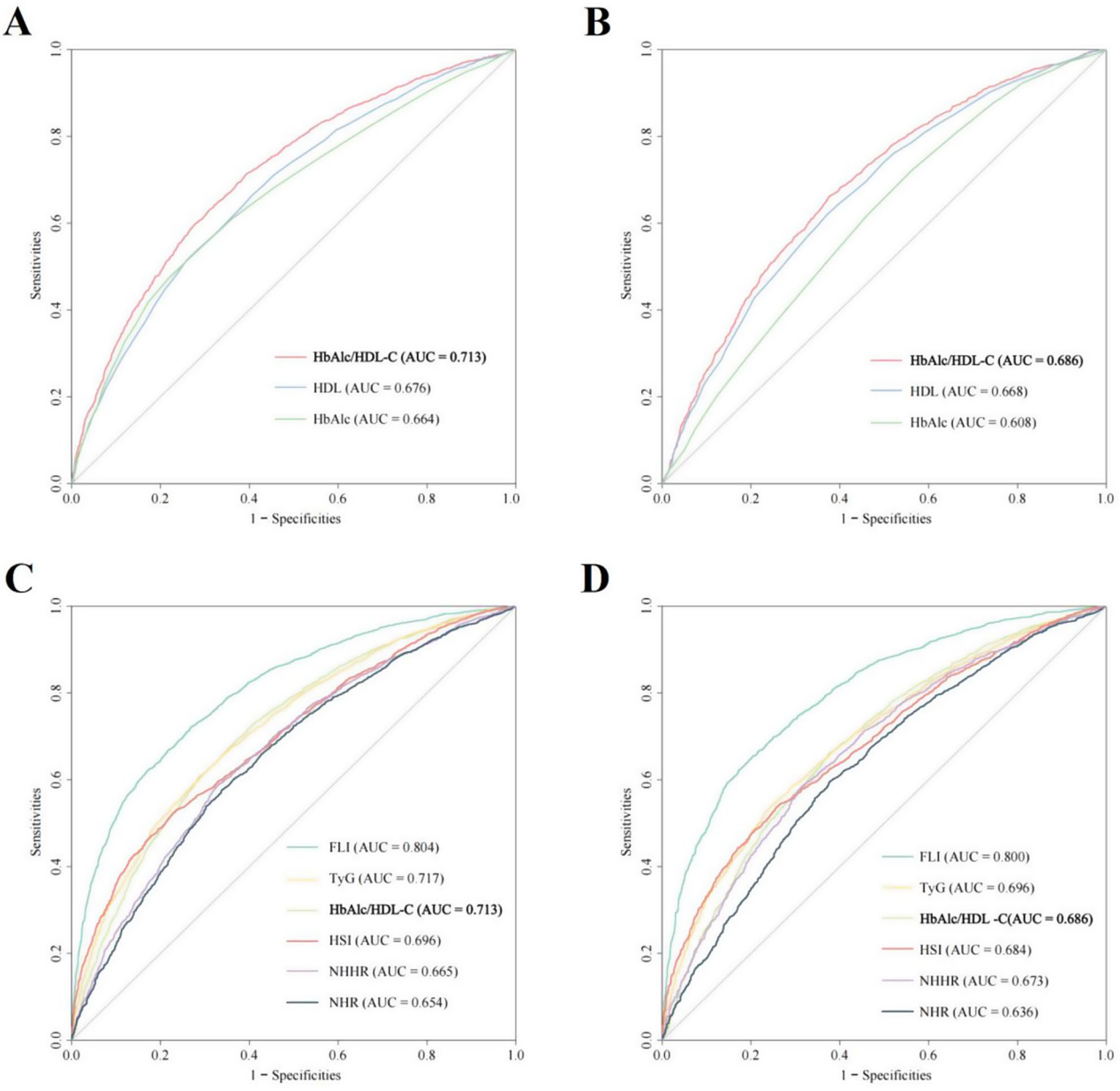

Fig. 4 Area under the receiver operating characteristic curve (AUC) for HbA1c/HDL-C ratio, HDL-C and HbA1c for identifying NAFLD in the overall population (**A**) and in the non-diabetic population (**B**). Area under the receiver operating characteristic curve (AUC) for FLI, TyG, HbA1c/HDL-C ratio, HSI, NHHR, and NHR for identifying NAFLD in the overall population (**C**) and in the non-diabetic population (**D**)

Disruption of hepatic and extrahepatic lipid metabolism is another major driving factor in the development of NAFLD. In this pathological process, HDL-C plays a key role in removing cholesterol from macrophages within arterial plaques and transporting it to the liver for metabolism, thus facilitating reverse cholesterol transport and reducing the burden on the liver [31]. Mocciaro et al. [32] found that the HDL lipidome in patients with NAFLD underwent significant changes, particularly in the composition of polyunsaturated fatty acids (PUFAs). These changes are closely associated with insulin resistance (IR), suggesting that the HDL lipidome plays a crucial role in the metabolic abnormalities of NAFLD. Additionally, this study revealed that certain lipid components of HDL, such as phosphatidylglycerol (PG) and sphingomyelin (SM), were negatively correlated with hepatocellular ballooning, liver inflammation, and liver fibrosis. This further supports the notion that HDL is not only a cholesterol transport carrier but also that changes in its lipid composition and function play a key role in the development of NAFLD, insulin resistance, liver damage, and inflammation. Multiple studies have indicated that

Table 7 ROC analysis of identifying NAFLD

	AUC	95%CI	Specificity	Sensitivity	Delong *P*-value
HbA1c/HDL-C	0.713	(0.700-0.726)	0.627	0.693	
HDL-C	0.676	(0.662–0.690)	0.594	0.664	<0.01[a]
HbA1c	0.664	(0.650–0.678)	0.783	0.471	<0.01[b]
FLI	0.804	(0.793–0.815)	0.731	0.723	<0.01[c]
TyG	0.717	(0.704–0.730)	0.693	0.626	0.52[d]
HSI	0.696	(0.683–0.709)	0.772	0.523	0.05[e]
NHHR	0.665	(0.652–0.679)	0.672	0.587	<0.01[f]
NHR	0.654	(0.640–0.668)	0.661	0.578	<0.01[g]

Abbreviations: AUC: area under the receiver operating characteristic curve; CI: Confidence interval

[a] compare with HDL-C (Delong test); [b] compare with HbA1c (Delong test); [c] compare with FLI (Delong test); [d] compare with TyG (Delong test); [e] compare with HSI (Delong test); [f] compare with NHHR (Delong test); [g] compare with NHR (Delong test)

HDL-C levels negatively correlate with the risk of developing NAFLD [33], suggesting that higher HDL-C levels may reduce the incidence of NAFLD.

Previous studies have demonstrated an interaction between dyslipidemia and glucose homeostasis [34, 35]. HDL-C helps lower blood glucose by increasing plasma insulin levels and activating the AMPK pathway in skeletal muscle, which promotes glucose clearance [36]. Conversely, changes in blood glucose levels directly affect the hepatic lipid metabolism [26]. Inflammation plays a key role in the progression of NAFLD, primarily by promoting hepatic inflammation and steatosis through the TNF signaling pathway, thereby exacerbating the worsening of NAFLD [37, 38]. HDL-C alleviates the early stages of hepatic inflammation by inhibiting the recruitment and activation of neutrophils and macrophages, thereby alleviating hepatocyte damage and hepatic steatosis [39]. In contrast, hyperglycemia promotes the production of mitochondrial reactive oxygen species (ROS) [40]. Excessive ROS can attack intracellular biomolecules inside the cell, particularly polyunsaturated fatty acids (PUFAs), thereby exacerbating cellular damage [41]. Accumulation of ROS can lead to mitochondrial dysfunction. Mitochondria are a major source of ROS, and excessive ROS can damage the mitochondrial membrane, impair electron transport chain function, and reduce cellular energy production, which in turn exacerbates hepatic fat accumulation [42, 43]. Excess ROS can also stimulate the production of inflammatory factors, leading to chronic liver inflammation and further driving NAFLD progression [40]. Thus, the combined effect of hyperglycemia and low HDL-C may synergistically promote hepatic steatosis, which is consistent with the positive correlation observed in the present study.

This study found a nonlinear relationship between HbA1c/HDL-C ratio and NAFLD, with a turning point value of 5.743. An HbA1c level of < 5.7% represents the upper limit of the normal range [44], suggesting that blood glucose is under control and that this ratio may be closely related to blood glucose regulation. When the HbA1c/HDL-C ratio was < 5.743, the risk of NAFLD increased significantly as the ratio rises, which may be related to the protective role of higher HDL-C levels. However, when the ratio exceeded 5.743, the effect of the HbA1c/HDL-C ratio on the NAFLD risk became more gradual or weakened. Therefore, we propose that, in cases of normal or slightly elevated blood glucose levels, the HbA1c/HDL-C ratio could serve as a potential indicator for assessing the risk of NAFLD.

Our study found that the HbA1c/HDL-C ratio was associated with the risk of NAFLD in both diabetic and non-diabetic individuals. Further analysis revealed that in the nondiabetic population, the HbA1c/HDL-C ratio was positively correlated with the risk of NAFLD, and this result was confirmed by RCS analysis. This indicates that the HbA1c/HDL-C ratio is clinically significant not only for diabetic patients but also holds an important reference value for non-diabetic individuals. Based on these findings, personalized thresholds can be set according to the characteristics of different populations, offering guidance for early screening and prevention. Specifically, individuals without diabetes should pay particular attention to blood glucose and lipid management with regular monitoring to effectively reduce the risk of NAFLD.

ROC curve analysis showed that the FLI performed significantly better than the other indicators in NAFLD screening. Despite its high value in the screening and diagnosis of NAFLD, the calculation of the FLI is relatively complex and relies on multiple clinical laboratory parameters (such as GGT), which are not routinely measured in clinical practice. This adds to the difficulty of applying the FLI in everyday clinical settings. In contrast, the proposed indicator has a simpler calculation and is more easily accessible in clinical practice. Although it showed an AUC value similar to that of the TyG index, it demonstrated a higher stability. However, the TyG index, relies on blood glucose levels, which require fasting for accurate assessment, and its stability in previous analyses is poor, as it has not been standardized. Blood glucose concentrations are also susceptible to acute fluctuations caused by various factors, and the measurement results can vary depending on the sample type (e.g., plasma or whole blood) and source (e.g., capillary, venous, or interstitial fluid) [45]. Our proposed indicator combines HbA1c and HDL-C levels, both of which offer distinct

advantages. HbA1c has low inter-individual variability and its testing method is well standardized, allowing for testing at any time without the need for fasting. Unlike blood glucose levels [45, 46], HDL-C levels are not influenced by short-term fluctuations. The HbA1c/HDL-C ratio exhibited higher stability than other indicators that rely on blood glucose measurements, making it a more reliable and consistent metric for screening NAFLD risk.

Although our study found a significant positive correlation between HbA1c/HDL-C ratio and NAFLD, no clear association was observed with liver fibrosis. This may be related to the limitations of VCTE in assessing liver fibrosis, particularly in the context of moderate-to-advanced stages of fibrosis. VCTE may have reduced the sensitivity or accuracy of detecting and quantifying fibrosis in these later stages, potentially explaining the lack of a strong correlation between HbA1c/HDL-C ratio and liver fibrosis in our study. In a systematic review and meta-analysis, Selvaraj et al. [47] noted that elastography-based indicators demonstrated high accuracy in diagnosing advanced fibrosis and cirrhosis. However, the full clinical potential of these indicators has not yet been comprehensively assessed owing to the lack of clear diagnostic target analysis and pre-set threshold validation. Oeda et al. [48] further suggested that both LSM and CAP are not only influenced by the degree of liver fibrosis and steatosis but are also affected by various other factors. LSM measurements may be influenced by factors such as inflammation, venous pressure, cholestasis, amyloidosis, and food intake. Additionally, CAP measurements can be affected by changes in BMI. We believe that the HbA1c/HDL-C ratio may be related only to steatosis rather than to the progression of liver fibrosis, which could be one of the reasons for the lack of correlation with fibrosis. Current studies do not clearly determine whether an elevated HbA1c/HDL-C ratio reflects disease severity in patients with NAFLD or whether it is associated with other potential factors. Therefore, the underlying mechanisms need to be further explored. In the future, it will be important to explore more clinically meaningful markers or adopt more precise diagnostic tools to clarify the relationship between this ratio and the degree of liver fibrosis.

Advantages and Limitations of the Research Results:

The main strength of this study lies in the use of a large nationally representative sample that included diverse racial groups of adults from North America (the United States). Additionally, this study is the first to systematically explore the relationship between the HbA1c/HDL-C ratio and liver fibrosis, as well as moderate-to-severe liver fibrosis. To enhance the reliability and generalizability of the results, the study was adjusted for multiple potential confounding variables during analysis, thereby increasing the scientific rigor and broad applicability of the conclusions.

The limitations of this study are as follows: [1] The NHANES is an observational study that may be subject to selection and information bias, and it is limited to the U.S. population, which restricts its external applicability [2]. Due of its cross-sectional design, causal relationships could not be established. Therefore, prospective cohort studies or randomized trials are needed to better understand causality. In addition, NAFLD may further affect glucose and lipid metabolism, making it impossible to rule out reverse causality [3]. The study lacked dynamic data on HbA1c and HDL-C levels and did not analyze the long-term patient outcomes. Therefore, further longitudinal studies are required to address this gap [4]. There are still missing data in the NHANES 2017–2020 database, which may result in the omission of other unrecorded confounding factors, thereby affecting the accuracy of the results [5]. The reliance on self-reported data may lead to misclassification of alcohol consumption or diabetes status [6]. While VCTE provides valuable information for assessing liver steatosis and fibrosis, it is not the gold standard for diagnosis, and there are limitations to its ability to diagnose liver fibrosis. Therefore, a liver biopsy is a necessary diagnostic tool.

Conclusion

In U.S. adults, a higher HbA1c/HDL-C ratio is significantly associated with NAFLD. The HbA1c/HDL-C ratio is independently associated with NAFLD and may serve as a practical screening biomarker, especially in non-diabetic populations.

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
NHANES	National Health and Nutrition Examination Survey
PIR	Ratio of family income to poverty
BMI	Body mass index
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
TG	Triglycerides
TC	Total cholesterol
PSM	Propensity score matching
ROC	Receiver operating characteristic
AUC	Area under the curve

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03974-0.

Supplementary Material 1

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Author contributions

JW, WY, LH, SH was responsible for data extraction, statistical analysis, and writing the initial draft. YH, ZH, ZD participated in data cleaning and revised

the manuscript. JY, ZN was responsible for the final revisions and review. All authors have read and approved the final manuscript.

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Data availability
This study analyzed publicly available datasets. The data can be found at the following link: https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
This study involving human participants, human materials, or human data was conducted in accordance with the Declaration of Helsinki and approved by the NCHS Ethics Review Committee. Patients/participants provided written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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