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ORIGINAL RESEARCH

Association of Fasting C-Peptide to High Density Lipoprotein Cholesterol Ratio with Non-Alcoholic Fatty Liver Disease in Chinese Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study

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Objective: To investigate fasting C-peptide to high-density lipoprotein cholesterol ratio (FHR) as a predictor for non-alcoholic fatty liver disease (NAFLD) in Chinese adults with type 2 diabetes mellitus (T2DM).

Methods: This study enrolled 718 participants with T2DM from Shenzhen People's Hospital, China. Participants were stratified by FCP/HDL-C ratio (FHR) quartiles. Multiple linear regression assessed the association between FHR and NAFLD. A generalized additive model (GAM) tested for nonlinearity. Subgroup analyses evaluated result robustness. The area under the curve (AUC) evaluated the performance of the FHR model for NAFLD occurrence.

Results: After adjusting for relevant variables, FHR was positively correlated with NAFLD (OR = 1.30, 95% CI (1.15, 1.48)). FHR demonstrated a nonlinear association with NAFLD, characterized by a threshold value of 1.23. The effect sizes and confidence intervals on the left and right sides of the inflection point were 3.07 (1.51, 6.24) and 1.20 (1.05, 1.37), respectively. Subgroup analysis showed a stronger correlation could be detected in patients with systolic blood pressure (SBP) <140 mmHg, alanine transaminase (ALT) > 40U/L, fasting blood glucose (FBG) ⩽7 mmol/L, urinary albumin to creatinine ratio (UACR) ⩽30mg/g, triglyceride (TG) ⩽1.7 mmol/L and the patients with drinking history. The FHR ratio model exhibited better discriminative ability in NAFLD (AUC = 0.697) compared to individual FCP (AUC = 0.649) or HDL-C (AUC = 0.635) alone.

Conclusion: The association between FHR and NAFLD was nonlinear, with a positive relationship observed when FHR exceeded the threshold of 1.23.

Keywords: fasting C-peptide to high-density lipoprotein cholesterol ratio, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, insulin resistance, overweight, obesity, diabetes mellitus

Introduction

NAFLD is one of the most common chronic liver disorder characterized by excessive lipid accumulation in hepatocytes, excluding alcohol and other established liver injury factors. The disease spectrum includes non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), with potential progression to advanced liver disease (fibrosis, cirrhosis) or hepatocellular carcinoma.[1] It is important to note that the international nomenclature for NAFLD has recently evolved, with the term metabolic dysfunction-associated fatty liver disease (MAFLD) introduced in 2020,[2] later

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updated to metabolic dysfunction-associated steatotic liver disease (MASLD) in 2023.[3] As the data for our study were collected during 2018–2019 under the NAFLD framework, we retain this original term to ensure diagnostic accuracy and historical consistency with the original data. The global prevalence of NAFLD is estimated at 32.4%.[4] In China, the pooled prevalence among adults over the past two decades stands at 29.6%,[5] demonstrating a consistent annual increase, with males exhibiting a higher incidence than females.[4,5] Notably, the global prevalence of NAFLD in individuals with T2DM reaches 65%,[6] whereas the corresponding rate in Chinese T2DM patients is 51.8%.[7] Geographically, China demonstrates the highest NAFLD incidence and the most rapid increase in prevalence globally.[4,8] The poor prognosis of NAFLD is primarily associated with cardiovascular diseases and non-liver malignancies.[9,10] Notably, T2DM exerts a more pronounced adverse effect on clinical outcomes in NAFLD patients compared to obesity.[11,12] Furthermore, NAFLD patients demonstrate significantly higher incidence rates of diabetes mellitus, coronary artery disease, chronic kidney disease and cerebrovascular events relative to healthy individuals.[13,14] NAFLD arises from hepatic lipid accumulation, driven by insulin resistance, dysregulated lipid metabolism, and mitochondrial dysfunction, which induce lipotoxicity, oxidative stress, and pro-inflammatory cytokine activation, ultimately promoting steatohepatitis and fibrosis progression.[15] β-cells secrete C-peptide and insulin at equimolar levels, with C-peptide serving as a reliable marker for evaluating endogenous insulin secretion. However, circulating C-peptide and insulin levels typically diverge due to differential clearance mechanisms and half-lives.[16] Elevated C-peptide levels signify both exacerbated insulin resistance and compensatory β-cell hypersecretion, as peripheral insulin resistance drives increased insulin and C-peptide production to sustain glucose homeostasis.[17] Previous studies have reported inconsistent conclusions regarding the impact of C-peptide on NAFLD and hepatic fibrosis. Related studies have demonstrated that C-peptide is an independent risk factor for NAFLD, with elevated C-peptide levels increasing the risk of NAFLD development and hepatic fibrosis.[18,19] However, other studies have shown that C-peptide positively correlates with inflammatory progression in hepatic steatosis but negatively associates with fibrosis progression.[20]

Dyslipidemia, characterized by elevated triglycerides (TG), increased low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C), is strongly linked to NAFLD.[21,22] HDL-C, the cholesterol component of high-density lipoprotein particles, serves as a critical mediator in cholesterol metabolism by transporting excess cholesterol from peripheral tissues to the liver for processing. Through the reverse cholesterol transport pathway, HDL-C facilitates dietary cholesterol efflux and exhibits additional anti-inflammatory and antioxidant properties.[23] Therefore, decreased HDL-C may contribute to the development of NAFLD.[24] Numerous studies have indicated that HDL-C is inversely associated with NAFLD, and elevated levels of HDL-C may effectively reduce the risk of developing NAFLD.[25,26] However, scientific debate persists regarding the causality, functionality and therapeutic targeting of HDL-C in NAFLD. The development of NAFLD is associated with insulin resistance and dyslipidemia. Previous studies have demonstrated significant associations of both C-peptide and HDL-C with NAFLD. Whether the FCP/HDL-C ratio (FHR) is a superior predictor of NAFLD development remains unclear due to the lack of studies investigating this relationship. This study investigated the association between FHR and NAFLD in T2DM patients.

Materials and Methods

Study Population and Design

This cross-sectional study consecutively enrolled 982 adults with T2DM from the Endocrinology Department of Shenzhen People's Hospital, Shenzhen, China between April 2018 and July 2019. Non-selective recruitment minimized selection and observation biases. Anonymized participant data were securely stored in the hospital's electronic medical record system to protect privacy. The study protocol was approved by the Medical Research Ethics Committee of Shenzhen People's Hospital. Participants were included if they met all the following criteria: 1) Diagnosis of T2DM based on the 1999 World Health Organization (WHO) criteria; 2) Age≥18 years at the time of T2DM diagnosis; 3) Availability of complete FCP and HDL-C measurements; 4) Liver ultrasound data; 5) No history of hemodialysis or peritoneal dialysis. Exclusion criteria were applied to rule out participants with: 1) Viral hepatitis (hepatitis B/C); 2) Alcoholic fatty liver disease (alcohol intake >20 g/day for women or >30 g/day for men); 3) Severe comorbidities

(uremia, malignancies, stroke, or cardiovascular disease); 4) Liver or kidney transplantation history; 5) Pregnancy or lactation. After rigorous screening, 718 participants fulfilled the eligibility criteria and were included in the final analysis.

General Clinical Features

Patient medical histories were reviewed to record: gender, age, diabetes duration, family history of diabetes, hypertension history, alcohol drinking history, weight, height, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Following ≥ 20 minutes of rest, SBP and DBP were measured at the right brachial artery using a mercury sphygmomanometer. Height and weight were measured using standardized protocols, with body mass index (BMI) calculated as weight (kg)/height (m^2).

Laboratory Measurements and Clinical Assessments

Venous blood samples collected after ≥ 8-hour overnight fasting underwent biochemical analysis at Shenzhen People's Hospital's central laboratory. Quantified parameters included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), γ-glutamyltransferase (GGTP), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), fasting C-peptide (FCP), serum creatinine (SCr), serum uric acid (SUA), urinary albumin to creatinine ratio (UACR), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C). Enzymatic colorimetric assays (Roche Cobas 8000 analyzer) were employed to measure ALT, AST, TP, ALB, GGTP, FBG, SCr, SUA, TC, TG, HDL-C, LDL-C. HbA1c levels were measured using high-performance liquid chromatography (Bio-Rad D-10 system), while FCP concentrations were determined using chemiluminescent immunoassays (Siemens ADVIA Centaur XP). Estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation: eGFR (mL/min/1.73 m^2) = $186\times(SCr/88.4)^{-1.154}\times age^{-0.203}\times$gender factor (male: 1.0; female: 0.742). First-morning urine specimens were collected on two consecutive days for urinary albumin-to-creatinine ratio (UACR) measurement using immunoturbidimetry (Mindray BS-800M analyzer), with the mean value utilized for statistical analysis.

Vascular and Neurological Evaluations

Ankle-brachial index (ABI) was measured with an automatic waveform analyzer (ParryMed F5001, Sweden), while vibration perception threshold (VPT) was evaluated with a standardized digital biothesiometer (Sensiometer A200, Beijing Dimeidel). VPT severity was categorized as follows: Normal: <10V; Mild impairment: 10–14.9V; Moderate impairment: 15–24.9V; Severe impairment: ≥25V. All ABI and VPT measurements were performed by a trained nurse in the Department of Endocrinology to minimize interobserver variability. The fundus assessment is performed by a professional ophthalmologist.

Liver Ultrasonography Evaluation

The diagnosis of NAFLD was confirmed through abdominal ultrasound imaging performed by certified radiologists. To maintain objectivity, the evaluating radiologists were deliberately kept unaware of participants' laboratory data during image interpretation. Participants with a history of excessive alcohol consumption (>20 g/day for women or >30 g/day for men) were excluded from the NAFLD cohort. The diagnostic criteria required fulfillment of at least two out of four characteristic sonographic findings: evidence of hepatic steatosis, hepatorenal echo contrast with liver echogenicity exceeding renal echogenicity, impaired visualization of intrahepatic vascular structures, and posterior attenuation of the ultrasound beam.[27]

FCP/HDL-C Ratio (FHR)

The unit of FCP is ng/mL, and the unit of HDL-C is mmol/L. By dividing FCP by HDL-C, we calculated it as the key analytical variable.

Covariates

The initial selection of covariates was based on clinical experience and existing literature.[28–30] Variables that altered the effect estimates by≥10% were further retained in the final model.[31] Based on the above principles, the following variables

were treated as covariates: (1) continuous variables: age, BMI, DBP, ALT, ALB, FBG, SUA, UACR, TG; (2) categorical variables: gender, alcohol drinking history.

Statistical Analysis

Missing values were addressed through distinct strategies based on variable type: Continuous variables were imputed using mean or median values, while categorical variables incorporated missing data as a separate category (designated as "NA").[32]

Participants were stratified into quartiles according to their FCP/HDL-C ratio (FHR). Continuous variables were summarized as mean ± standard deviation (normally distributed) or median (interquartile range, non-normal distribution). Categorical variables were presented as frequencies (percentages). Intergroup differences were assessed using one-way ANOVA (normal distributions), Kruskal–Wallis tests (non-normal distributions), or chi-square tests (categorical variables), as appropriate. Multivariable logistic regression models were employed to evaluate associations between FHR and NAFLD risk, with results expressed as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Three adjustment levels were implemented: unadjusted, partially adjusted (demographic variables), and fully adjusted (demographic and clinical covariates). Sensitivity analyses assessed model robustness. Potential nonlinear relationships were examined using generalized additive models (GAM). When nonlinearity was detected ($P < 0.05$ via log-likelihood ratio tests), piecewise linear regression identified threshold effects. The inflection point was determined through iterative maximum likelihood estimation. E-values were calculated to evaluate the potential influence of unmeasured confounders on the relationship between FHR and NAFLD.[33] Stratified analyses evaluated effect modification by demographic and clinical variables (gender, age, BMI, etc)., with interaction terms tested via likelihood ratio tests. Receiver operating characteristic curves (ROC) compared the discriminative ability of FCP, HDL-C, and their ratio for NAFLD diagnosis. The STROBE criteria were followed while writing up all of the results.[34] Analyses were conducted using R (version 4.3.1; R Foundation) and EmpowerStats (version 4.1). Two-tailed P-values <0.05 indicated statistical significance.

Results

Selected Participants

A total of 718 participants aged 18–90 years with T2DM were recruited from the Endocrinology Department, Shenzhen People's Hospital, between April 2018 and July 2019, based on predefined eligibility criteria (Figure 1).

Baseline Characteristics

The study population consisted of 58.24 ± 11.72 years old participants, with a male-to-female ratio of 63.4% to 36.6%. The mean FHR value was 2.06, and NAFLD prevalence was 45%. Data omission was observed in the following parameters: ALT (n=13), AST (n=12), UACR (n=12), TP (n=14), ALB (n=14), GGTP (n=27), HbA1C (n=5), SUA (n=18), VPT (n=28), and ABI (n=35). Participants were stratified into four subgroups based on quartiles of the FCP/HDL-C ratio (FHR): ≤ 0.97, 0.98–1.69, 1.70–2.63, and≥2.64. The baseline characteristics of the 718 participants stratified by quartiles of FHR levels are displayed in Table 1. Those in the highest FHR quartile exhibited significantly higher levels of BMI, DBP, ALT, TP, ALB, FBG, SUA, TG, and ABI (right), as well as higher NAFLD prevalence, and were associated with lower eGFR and HbA1c levels. No Statistical significances were observed across FHR quartiles in gender, age, diabetes duration, SBP, AST, GGTP, UACR, TC, LDL-C, ABI(left), family history of diabetes, smoking history, alcohol drinking history and VPT.

Univariate Analysis

Univariate analysis results are detailed in Table 2. We found BMI, DBP, ALT, ALB, FBG, SUA, TG and FHR levels were positively correlated with the incidence of NAFLD, while age and UACR were negatively correlated with NAFLD. Additionally, we have found that patients with a history of alcohol consumption are more prone to developing NAFLD.

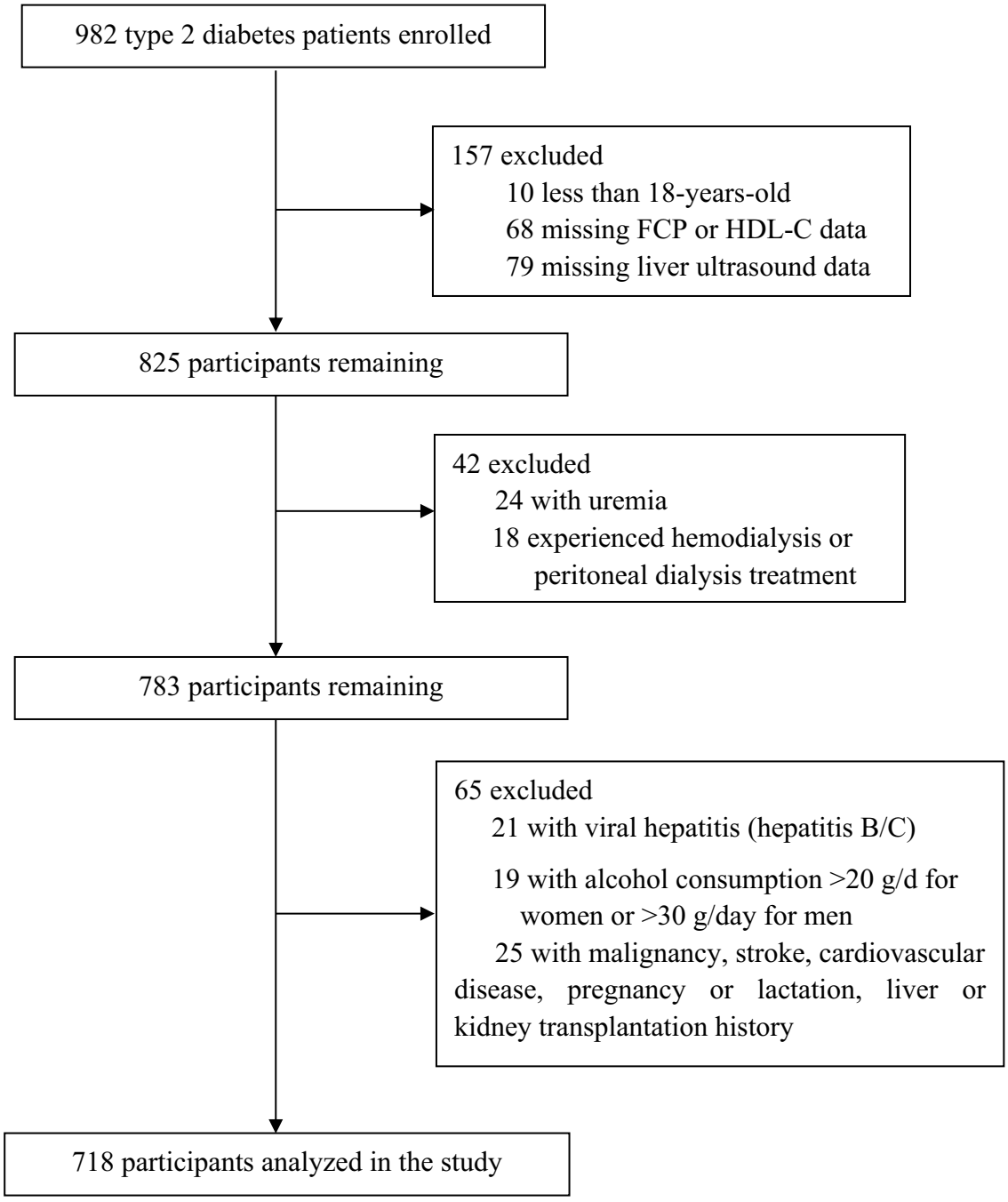

Figure 1 Flowchart of research participant selection.

The Relationship Between FHR and NAFLD

A multiple linear regression analysis was conducted to assess the association between FHR and NAFLD, including both unadjusted and adjusted models, as presented in Table 3. FHR exhibited a positive correlation with NAFLD (OR= 1.46, 95% confidence interval (CI): 1.31 to 1.64, P<0.0001). In model II, fully adjusted for all variables (gender, age, BMI, DBP, ALT, ALB, FBG, SUA, UACR, TG, alcohol drinking history), we still found the same correlation (OR= 1.30, 95% CI: (1.15 to 1.48, P<0.0001). In other words, a 1-unit increase in FHR was associated with a 0.3 (30%) increase in the incidence of NAFLD. For sensitivity analysis, FHR was analyzed as a categorical variable (quartiles). In Model II, compared with Q1 (reference group), the risk of NAFLD occurrence increased in Q2, Q3, and Q4 by 1.29 (129%), 1.40

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Table 1 The Baseline Characteristics of Participants According to FCP/HDL-C Ratio (FHR) Quartiles

FCP/HDL-C Ratio (FHR) Quartile	Q1 (≤0.97)	Q2 (0.98–1.69)	Q3 (1.70–2.63)	Q4 (≥2.64)	P-value
Participants, n	180	179	179	180	
Age, year	58.91 ± 11.03	59.25 ± 11.52	57.89 ± 11.83	56.91 ± 12.41	0.221
BMI, kg/m^2	22.93 ± 4.52	24.41 ± 2.91	25.54 ± 3.18	26.11 ± 3.77	<0.001
Diabetes duration, year	13.15 ± 7.52	10.68 ± 7.59	12.43 ± 23.75	9.94 ± 6.88	0.086
SBP, mmHg	128.26 ± 30.17	127.62 ± 21.55	127.89 ± 19.72	127.81 ± 15.97	0.995
DBP, mmHg	76.68 ± 10.85	79.22 ± 10.71	79.31 ± 11.23	80.16 ± 10.10	0.015
ALT, U/L	19.45 ± 15.21	21.15 ± 12.88	26.45 ± 31.88	26.49 ± 20.55	0.002
AST, U/L	19.12 ± 9.61	18.85 ± 8.13	21.36 ± 23.03	21.42 ± 12.75	0.187
TP, g/L	68.30 ± 5.35	68.89 ± 6.19	69.69 ± 5.89	70.46 ± 5.97	0.004
ALB, g/L	39.42 ± 3.98	40.43 ± 4.12	40.65 ± 4.52	40.45 ± 4.27	0.028
GGTP, U/L	43.29 ± 141.94	32.64 ± 31.29	35.14 ± 41.16	36.28 ± 25.24	0.608
FBG, mmol/L	7.47 ± 3.70	7.87 ± 2.75	8.44 ± 2.77	8.81 ± 5.90	0.008
HbA1C, %	9.59 ± 2.33	8.92 ± 2.29	8.40 ± 2.09	8.21 ± 1.98	<0.001
eGFR, mL/min/1.73m^2	127.62 ± 519.26	156.47 ± 914.07	88.27 ± 22.60	78.64 ± 29.03	<0.001
SUA, mmol/L	327.63 ± 185.62	340.97 ± 88.05	344.97 ± 90.03	386.89 ± 98.99	<0.001
UACR, mg/g	247.42 ± 985.68	136.73 ± 518.63	193.55 ± 806.08	400.44 ± 1099.17	0.124
TG, mmol/L	1.22 ± 0.84	1.89 ± 2.77	2.01 ± 1.42	2.98 ± 2.81	<0.001
TC, mmol/L	4.62 ± 1.35	4.79 ± 1.39	4.56 ± 1.29	7.33 ± 39.65	0.486
LDL-C, mmol/L	2.84 ± 1.06	2.95 ± 1.20	5.69 ± 27.87	2.46 ± 0.94	0.108
ABI (left)	1.08 ± 0.16	1.10 ± 0.14	1.11 ± 0.14	1.10 ± 0.16	0.229
ABI (right)	1.08 ± 0.17	1.11 ± 0.14	1.13 ± 0.15	1.10 ± 0.16	0.023
Gender (n, %)					0.064
Male	104 (57.78%)	111 (62.01%)	112 (62.57%)	128 (71.11%)	
Female	76 (42.22%)	68 (37.99%)	67 (37.43%)	52 (28.89%)	
Family history of Diabetes (n, %)					0.072
No	94 (52.22%)	85 (47.49%)	107 (59.78%)	105 (58.33%)	
Yes	86 (47.78%)	94 (52.51%)	72 (40.22%)	75 (41.67%)	
Smoking history (n, %)					0.464
No	122 (67.78%)	115 (64.25%)	126 (70.39%)	114 (63.33%)	
Yes	58 (32.22%)	64 (35.75%)	53 (29.61%)	66 (36.67%)	
Alcohol drinking history (n, %)					0.476
No	136 (75.56%)	146 (81.56%)	144 (80.45%)	139 (77.22%)	
Yes	44 (24.44%)	33 (18.44%)	35 (19.55%)	41 (22.78%)	

(*Continued*)

Table 1 (Continued).

FCP/HDL-C Ratio (FHR) Quartile	Q1 (≤0.97)	Q2 (0.98–1.69)	Q3 (1.70–2.63)	Q4 (≥2.64)	P-value
NAFLD (n, %)					<0.001
No	141 (78.33%)	103 (57.54%)	85 (47.49%)	66 (36.67%)	
Yes	39 (21.67%)	76 (42.46%)	94 (52.51%)	114 (63.33%)	
VPT (n, %)					0.973
Fine	90 (50.00%)	79 (44.13%)	84 (46.93%)	91 (50.56%)	
Mild	47 (26.11%)	46 (25.70%)	50 (27.93%)	40 (22.22%)	
Moderate	31 (17.22%)	33 (18.43%)	27 (15.08%)	33 (18.33%)	
Severe	10 (5.56%)	10 (5.59%)	9 (5.03%)	10 (5.56%)	
NA	2 (1.11%)	11 (6.15%)	9 (5.03%)	6 (3.33%)	

Notes: Continuous data are shown as mean ± SD (normal distribution) or median (quartile) (skewed distribution). Categorical data are shown as n (%).
Abbreviations: FCP/HDL Ratio, fasting c-peptide to high density lipoprotein cholesterol ratio; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, serum albumin; GGTP, gamma glutamyl transpeptidase; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; UACR, urine albumin creatinine ratio; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; ABI, ankle brachial index; VPT, Vibration perception threshold; NA, not available.

Table 2 The Results of Univariate Analysis of NAFLD

	Statistics	OR (95% CI)	P-value
Age, year	58.24 ± 11.72	0.98 (0.96, 0.99)	0.0005
BMI, kg/m^2	24.75 ± 3.84	1.24 (1.18, 1.31)	<0.0001
Diabetes duration, year	11.55 ± 13.49	1.00 (0.99, 1.01)	0.6472
SBP, mmHg	127.90 ± 22.42	0.99 (0.99, 1.00)	0.0812
DBP, mmHg	78.84 ± 10.79	1.02 (1.00, 1.03)	0.0170
ALT, U/L	23.38 ± 21.63	1.02 (1.01, 1.02)	0.0015
AST, U/L	20.19 ± 14.62	1.01 (1.00, 1.02)	0.2336
TP, g/L	69.33 ± 5.90	1.02 (0.99, 1.04)	0.1974
ALB, g/L	40.23 ± 4.24	1.08 (1.04, 1.12)	<0.0001
GGTP, U/L	36.85 ± 76.57	1.00 (1.00, 1.00)	0.4877
FBG, mmol/L	8.14 ± 4.01	1.08 (1.04, 1.14)	0.0007
HbA1C, %	8.78 ± 2.24	1.04 (0.98, 1.11)	0.2266
eGFR, mL/min/1.73m^2	112.72 ± 525.40	1.00 (1.00, 1.00)	0.5424
SUA, mmol/L	350.31 ± 124.70	1.00 (1.00, 1.00)	0.0001
UACR, mg/g	244.54 ± 883.99	0.99 (0.99, 1.00)	0.0436
TG, mmol/L	2.02 ± 2.22	1.15 (1.05, 1.26)	0.0024
TC, mmol/L	5.33 ± 19.88	0.99 (0.97, 1.01)	0.5623

(*Continued*)

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Table 2 (Continued).

	Statistics	OR (95% CI)	P-value
LDL-C, mmol/L	3.48 ± 13.98	0.98 (0.92, 1.04)	0.5524
ABI (left)	1.10 ± 0.15	1.71 (0.61, 4.76)	0.3075
ABI (right)	1.10 ± 0.16	1.33 (0.50, 3.51)	0.5682
FCP/HDL ratio (FHR)	2.06 ± 1.66	1.46 (1.31, 1.64)	<0.0001
Gender (n, %)			
Male	455 (63.37%)	Ref	
Female	263 (36.63%)	0.82 (0.60, 1.11)	0.1958
Family history of Diabetes (n, %)			
No	391 (54.46%)	Ref	
Yes	327 (45.54%)	1.00 (0.74, 1.34)	0.9874
Smoking history (n, %)			
No	477 (66.43%)	Ref	
Yes	241 (33.57%)	1.01 (0.74, 1.39)	0.9261
Alcohol drinking history (n, %)			
No	565 (78.69%)	Ref	
Yes	153 (21.31%)	1.61 (1.12, 2.30)	0.0098
VPT (n, %)			
Fine	344 (49.86%)	Ref	
Mild	183 (26.52%)	0.79 (0.55, 1.13)	0.1900
Moderate	124 (17.97%)	0.66 (0.44, 1.00)	0.0519
Severe	39 (5.65%)	0.70 (0.36, 1.38)	0.3057

Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, serum albumin; GGTP, gamma glutamyl transpeptidase; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; UACR, urine albumin creatinine ratio; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; ABI, ankle brachial index; FCP/HDL ratio, fasting c-peptide to high density lipoprotein cholesterol ratio; VPT, Vibration perception threshold; Ref, Reference; CI, Confidence interval.

(140%), and 2.81 (281%), respectively. A significant trend was observed across quartiles (P for trend ≤ 0.001). However, these results were inconsistent with those obtained when FHR was treated as a continuous variable, suggesting a possible nonlinear relationship between FHR and NAFLD.

Non-Linear Relationship Between FHR and NAFLD

In this study, since FHR is a continuous variable, we used the generalized additive model (GAM) to assess whether a non-linear relationship exists between FHR and NAFLD. The GAM analysis revealed a non-linear relationship between FHR and NAFLD after adjusting for gender, age, BMI, DBP, ALT, ALB, FBG, SUA, UACR, TG, and alcohol drinking history (Figure 2). To analyze the relationship between FHR and NAFLD, we compared the linear regression model with a two-stage linear regression model. The log-likelihood ratio test yielded a P-value of 0.013 (P<0.05) (Table 4). A two-stage linear

Table 3 Relationship Between FCP/HDL-C Ratio (FHR) and NAFLD in Different Models of Multivariate Analysis

Variable	Crude Model (OR, 95% CI, P)	Model I (OR, 95% CI, P)	Model II (OR, 95% CI, P)
FCP/HDL-C ratio (FHR)	1.46 (1.31, 1.64) <0.0001	1.32 (1.18, 1.48) <0.0001	1.30 (1.15, 1.48) <0.0001
FHR (quartiles)			
Q1 (≤0.97)	Ref	Ref	Ref
Q2 (0.98–1.69)	2.67 (1.68, 4.23) <0.001	2.23 (1.38, 3.60) 0.001	2.29 (1.38, 3.80) 0.001
Q3 (1.70–2.63)	4.00 (2.52, 6.33) <0.001	2.78 (1.71, 4.53) <0.001	2.40 (1.43, 4.05) 0.001
Q4 (≥2.64)	6.24 (3.92, 9.96) <0.001	4.16 (2.53, 6.83) <0.001	3.81 (2.20, 6.58) <0.001
P for trend	<0.001	≤0.001	≤0.001

Notes: Crude model: No variables are adjusted. Model I: Adjusted gender, age, BMI. Model II: Adjusted gender, age, BMI, DBP, ALT, ALB, FBG, SUA, UACR, TG, alcohol drinking history. Non-adjusted model adjust for: None.

Abbreviations: FCP, fasting C-peptide; HDL-C, high-density lipoprotein cholesterol; FHR, fasting C-peptide to high-density lipoprotein cholesterol ratio; NAFLD, non-alcoholic fatty liver disease; CI, Confidence interval; Ref, Reference.

regression identified an FHR inflection point at 1.23. Below this threshold, NAFLD odds increased significantly (OR = 3.07, 95% CI: 1.51–6.24, P = 0.0019), while above it, the association attenuated (OR = 1.20, 95% CI: 1.05–1.37, P = 0.0081). Additionally, we calculated an E-value to evaluate the potential impact of unmeasured confounding. The E-value of 1.54 indicated that any unmeasured or unknown confounding factors would have little influence on the observed association between FHR and incident NAFLD, as it was greater than the relative risk of unmeasured confounders and FHR.

Subgroup and Interaction Analysis

We conducted subgroup analyses to investigate potential factors that could influence the relationship between FHR and NAFLD. Stratified variables included gender, age, BMI, SBP, DBP, ALT, FBG, SUA, UACR, TG, and alcohol drinking history to assess the trend of effect sizes across these variables (Figure 3). We found interactions for SBP, ALT, FBG, UACR,

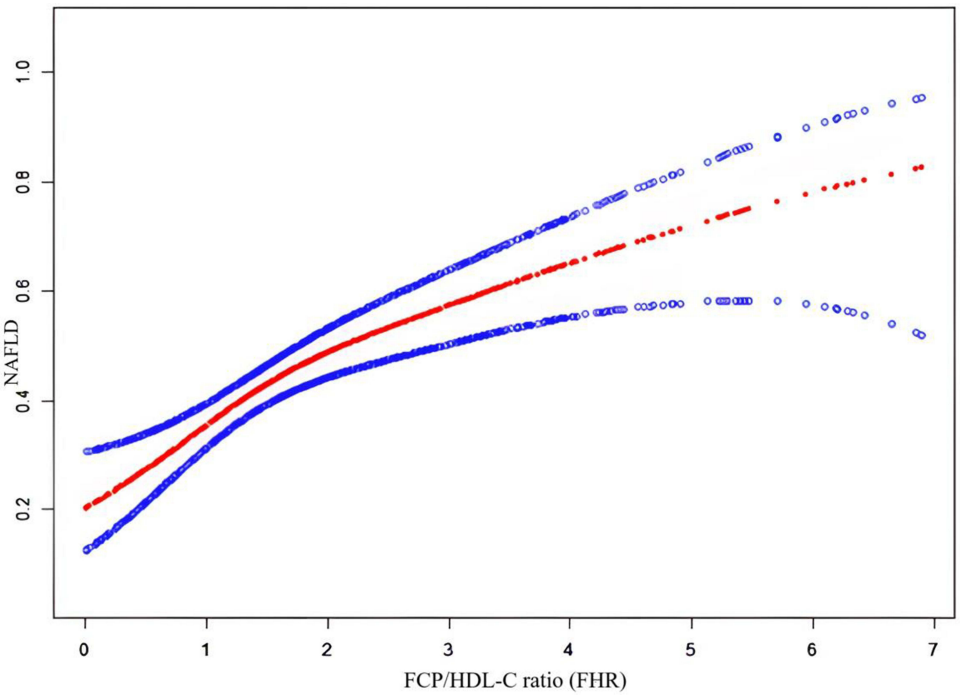

Figure 2 The non-linear relationship between FHR and NAFLD.

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Table 4 Two-Piecewise Linear Regression Model to Evaluate Relationship Between FCP/HDL-C Ratio (FHR) and NAFLD

	NAFLD (OR 95% CI)	P-value
Fitting model by standard linear regression	1.30 (1.15, 1.48)	<0.0001
Fitting model by two-piecewise linear regression inflection point of NAFLD		
≤1.23	3.07 (1.51, 6.24)	0.0019
>1.23	1.20 (1.05, 1.37)	0.0081
P for log likelihood ratio test		0.013

Note: We adjusted gender, age, BMI, DBP; ALT, ALB, FBG, SUA, UACR, TG, alcohol drinking history.
Abbreviations: FCP, fasting C-peptide; HDL-C, high-density lipoprotein cholesterol; FHR, fasting C-peptide to high-density lipoprotein cholesterol ratio; NAFLD, non-alcoholic fatty liver disease; CI, Confidence interval.

TG, alcohol drinking history (all P values for interaction < 0.05). Stronger associations were present in patients with SBP <140 mmHg, ALT > 40U/L, FBG ⩽7 mmol/L, UACR ⩽30mg/g, TG ⩽1.7 mmol/L and the patients with alcohol drinking history between FHR and NAFLD. In comparison, weaker associations were apparent in patients with SBP ≥140 mmHg, ALT ⩽ 40U/L, FBG >7 mmol/L, UACR >30mg/g, TG >1.7 mmol/L and the patients without alcohol drinking history.

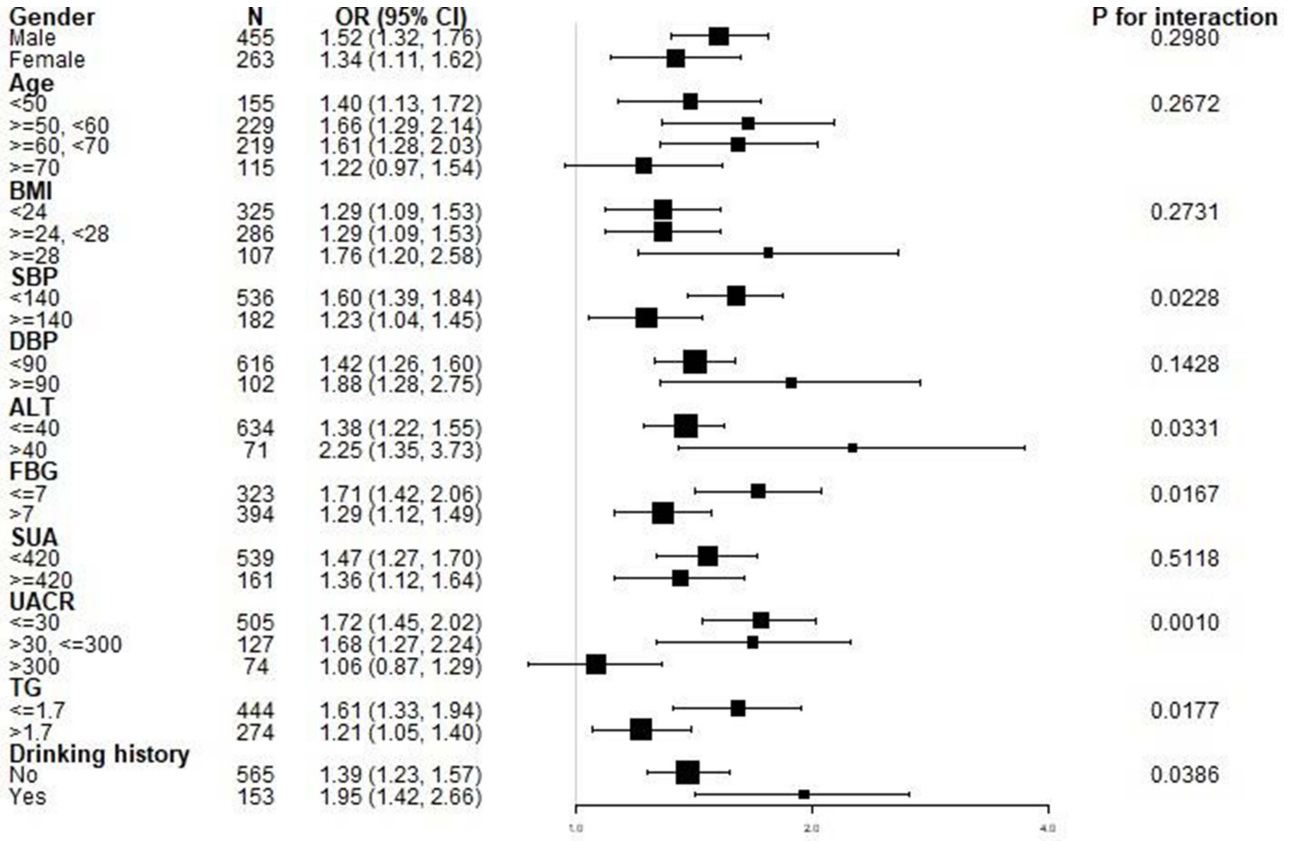

Figure 3 Forest plot for subgroup analysis and interaction analysis of FHR on NAFLD.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine transaminase; FBG, fasting blood glucose; SUA, serum uric acid; UACR, urinary albumin to creatinine ratio; TG, triglyceride; FHR, fasting C-peptide to high-density lipoprotein cholesterol ratio; NAFLD, non-alcoholic fatty liver disease; CI, Confidence interval.

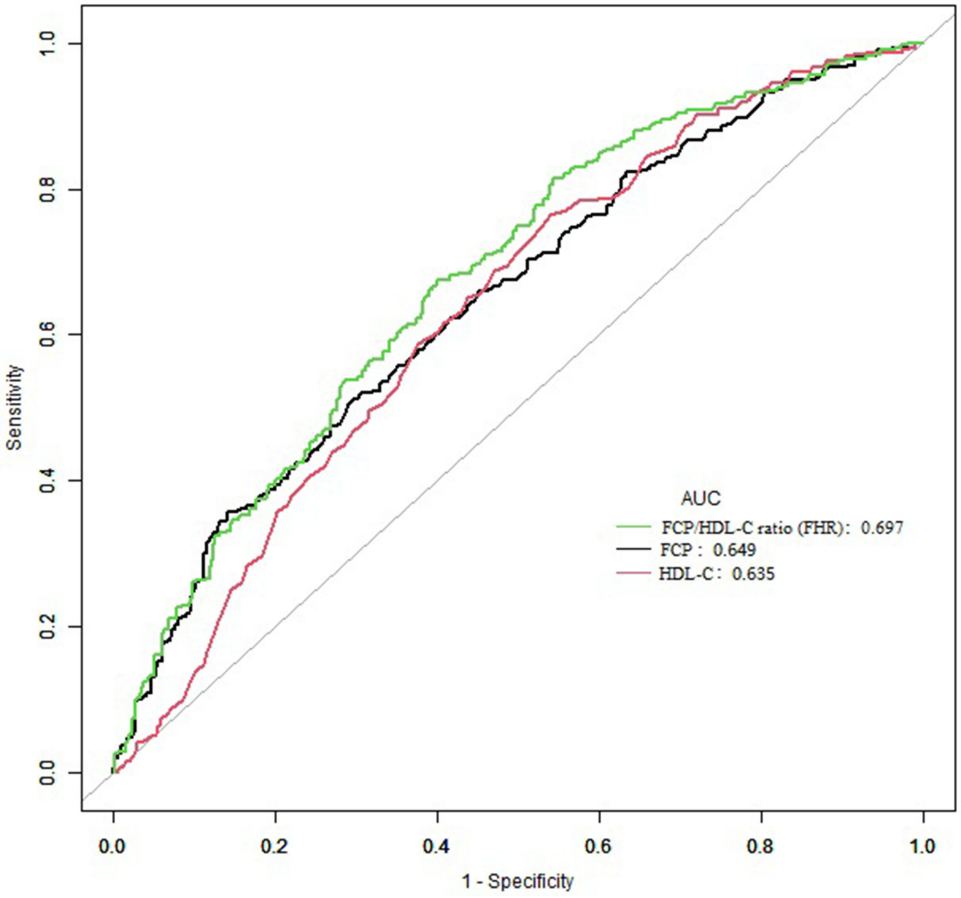

Figure 4 The FCP/HDL-C ratio (FHR) in NAFLD by ROC analyses.
Abbreviations: FCP, fasting C-peptide; HDL-C, high-density lipoprotein cholesterol; FHR, fasting C-peptide to high-density lipoprotein cholesterol ratio; AUC, area under the curve; NAFLD, non-alcoholic fatty liver disease; ROC, receiver operating characteristic curves.

ROC Curve Analysis of the FHR and NAFLD Association

The associations of FCP, HDL-C, and FHR with NAFLD were examined via a Receiver Operating Characteristic (ROC) curve (Figure 4). Areas under the curves are listed for each variable were as follow: FCP: 0.649; HDL-C: 0.635; FHR: 0.697. The best cut-of value was 2.125, 1.175, and 1.608, respectively, based on the Youden index of the FCP, HDL-C, and FHR were 0.215, 0.226, and 0.355 (Table 5). FHR demonstrated a stronger association with NAFLD status, as indicated by its highest Youden index and AUC in Table 5 compared to other variables.

Table 5 Areas Under the Receiver Operating Characteristic Curves (AUROC) for Each Evaluated Parameter in Identifying NAFLD

Parameter	AUROC	95% CI	Best Threshold	Specificity	Sensitivity	Youden Index
FCP	0.649	0.609–0.689	2.125	0.704	0.511	0.215
HDL-C	0.635	0.594–0.675	1.175	0.461	0.765	0.226
FHR	0.697	0.658–0.736	1.608	0.680	0.675	0.355

Abbreviations: FCP, fasting C-peptide; HDL-C, high-density lipoprotein cholesterol; FHR, fasting C-peptide to high-density lipoprotein cholesterol ratio; NAFLD, non-alcoholic fatty liver disease; CI, Confidence interval.

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Discussion

This cross-sectional study demonstrated a significant positive association between FHR and incident NAFLD in T2DM patients through adjusted linear regression analysis. Each 1-unit increase in FHR corresponded to a 30% elevated risk of NAFLD development. Sensitivity analysis using GAM revealed a non-linear relationship, with divergent effect magnitudes across the threshold [left (OR= 3.07, 95% CI: 1.51 to 6.24, P = 0.0019); right (OR= 1.20, 95% CI: 1.05 to 1.37, P=0.0081)], suggesting a saturation effect beyond an inflection point of FHR is 1.23. Below this threshold, each unit increase in FHR was linked to a 207% surge in NAFLD risk, whereas above 1.23, the risk increment attenuated to 20% per unit. Subgroup analyses further delineated heterogeneous associations across populations. Enhanced correlations were observed in individuals with SBP <140 mmHg, ALT > 40 U/L, FBG ≤7 mmol/L, UACR≤30 mg/g, TG≤1.7 mmol/L, and those with a drinking history. Conversely, weaker associations emerged in subgroups with SBP ≥140 mmHg, ALT ≤40 U/L, FBG >7 mmol/L, UACR >300 mg/g, TG >1.7 mmol/L, and non-drinkers.

Liver biopsy is the gold standard for diagnosing NAFLD, but due to its invasive nature, high cost, procedural risks, and other limitations, it remains challenging to widely implement in clinical practice. Abdominal ultrasound remains the most widely used clinical method for assessing hepatic steatosis. However, its diagnostic accuracy is limited by operator-dependent subjectivity and low sensitivity for mild cases.[35] While computed tomography (CT) and magnetic resonance imaging (MRI) demonstrate no significant superiority over ultrasound for hepatic fat evaluation. Controlled attenuation parameter (CAP), a quantitative technique based on transient elastography, provides objective assessment of liver fat content in NAFLD but is substantially confounded by abdominal subcutaneous adipose thickness in obese individuals. Therefore, utilizing existing serum biomarkers for identifying and understanding NAFLD is of critical importance.

A recent cohort study involving 4120 Chinese patients with T2DM showed that C-peptide was positively correlated with NAFLD (OR: 1.78, 95% CI: 1.56–2.04, P < 0.001), however, it was also positively correlated with the inflammatory progression of hepatic steatosis but negatively correlated with the fibrotic progression.[20] Another study using the National Health and Nutrition Examination Survey (NHANES) database, which included 3235 patients, also reached the conclusion that C-peptide levels were positively correlated with NAFLD.[18] A multivariable Mendelian randomization analysis demonstrated that elevated HDL-C levels independently reduced the risk of NAFLD development.[36] Alkassabany et al found that low HDL-C in schoolchildren is associated with NAFLD,[37] and DeFilippis et al discovered that low serum HDL-C levels are correlated with NAFLD in the population with normal body weight.[38] Casimiro et al revealed at the genetic level that reduced HDL-C exacerbates hepatocyte lipid metabolism disorders, thereby promoting the development of NAFLD.[39] A recent study has shown that in the absence of diabetes, the insulin to high-density lipoprotein cholesterol (HDL-C) ratio can serve as a novel independent predictor for esophageal varices in patients with hepatitis C virus-related cirrhosis, and this indicator might be more sensitive than the traditional homeostatic model assessment of insulin resistance (HOMA-IR) score.[40] C-peptide, a stable by-product of proinsulin cleavage, is unaffected by exogenous insulin administration, making it a valuable tool in clinical evaluations of islet β-cell function.[41] Can the insulin to HDL-C ratio be considered analogous to FCP to HDL-C ratio? Through a comprehensive literature search, there is a lack of data regarding the relationship between the FCP/HDL-C ratio (FHR) and the probability of developing NAFLD currently. However, a rise in this ratio implies either a surge in FCP or a decline in HDL-C. As a result, our data back up the previously mentioned results suggesting that FHR levels have a significant correlation with NAFLD.

Additionally, sensitivity analyses demonstrated that the association remained consistent in populations with systolic blood pressure (SBP) <140 mmHg, alanine aminotransferase (ALT) > 40 U/L, fasting blood glucose (FBG) ≤7 mmol/L, urinary albumin-to-creatinine ratio (UACR) ≤30 mg/g, triglycerides (TG) ≤1.7 mmol/L, and alcohol consumption history. These findings confirm the robust association between the FCP/HDL-C ratio (FHR) and NAFLD risk, lending support to the rationale for investigating the link between mitigating NAFLD incidence through FHR reduction. We further evaluated thecapacity of FCP/HDL-C ratio (FHR), FCP, and HDL-C for NAFLD using ROC curve. The FHR exhibited superior discriminative performance compared to FCP or HDL-C alone. Elevated FHR levels were significantly associated with increased NAFLD prevalence. Longitudinal increases in FHR during follow-up further indicated heightened NAFLD susceptibility, underscoring the importance of lifestyle modifications to reduce disease incidence. This evidence highlights FHR as a clinically relevant indicator that is significantly associated with NAFLD. NAFLD represents a spectrum of metabolic dysregulation, encompassing insulin resistance, lipotoxicity, and fibrogenesis driven

by complex interactions between systemic factors and hepatic microenvironmental responses.[42] Emerging evidence highlights the dual role of C-peptide as both a mediator of pathogenesis and an indicator of hyperinsulinemia-associated hepatic injury, while HDL-C serves as a critical protective axis through anti-inflammatory and anti-fibrotic mechanisms.[43–47] Here, we explore the clinical and mechanistic relevance of elevated FCP/HDL-C ratio in NAFLD progression, bridging biochemical markers to pathophysiological pathways.

C-peptide, a byproduct of insulin processing, has been mechanistically implicated in exacerbating NAFLD through multi-pronged pathways. Its direct activation of extracellular signal-regulated kinases (ERK) and downstream NF-κB and JNK signaling triggers inflammatory cascades, increasing monocyte chemoattractant protein-1 (MCP-1) expression and promoting monocyte recruitment to the liver.[43,44] Concurrently, C-peptide stimulates ceramide synthesis, a lipotoxic messenger that dysregulates mitochondrial function and exacerbates hepatocyte apoptosis.[45] Furthermore, elevated C-peptide reflects failure of pancreatic β-cells to respond to early-phase insulin demand, leading to compensatory hyperinsulinemia - a hallmark of insulin resistance that perpetuates hepatic steatosis via enhanced gluconeogenesis and lipid accumulation.[46] Importantly, this dual mechanism positions C-peptide not only as a direct hepatotoxin but also as an indirect marker for the systemic insulin derangement underpinning fibrogenesis. In contrast, HDL-C has been proven to possess a variety of biological activities, including reverse cholesterol transport, antioxidant, anti-inflammatory, anti-apoptotic, antithrombotic, and anti-atherosclerotic effects.[48,49] HDL-C exerts salutary effects through its antioxidant properties, mediating reverse cholesterol transport, and activating hepatic AMP-activated protein kinase (AMPK) α2 subunit.[50,51] AMPK activation suppresses gluconeogenesis in the liver and concurrently enhances thermogenesis in brown adipose tissue, thereby counteracting systemic insulin resistance and hepatic lipid oversupply.[52] Deficit in AMPK signaling or reduced HDL-C levels disrupt this axis, aggravating steatosis and inflammation. The elevation of fasting C-peptide/HDL-C ratio encapsulates the metabolic imbalance central to NAFLD pathogenesis. Elevated C-peptide amplifies pro-fibrotic and pro-inflammatory signals, while low HDL-C impairs anti-inflammatory and anti-lipotoxic countermeasures. This imbalance creates a “metabolic amplification loop” wherein increased C-peptide drives insulin resistance, further stimulating β-cell hypersecretion (C-peptide elevation), while diminished HDL-C worsens hepatic oxidative stress and fibrogenesis. The dual elevation of C-peptide and suppression of HDL-C’s protective role thus synergistically accelerate NAFLD progression.

It has significant clinical implications due to the curvilinear correlation between FHR and NAFLD. In T2DM patients, having an FHR below 1.23 was associated with a lower NAFLD prevalence, with a sharper negative correlation observed when FHR was under this threshold. This research helps clinicians improve understanding of factors associated with NAFLD. The FHR is a novel indicator associated with NAFLD, better than single indices. Elevated C - peptide alone may miss β-cell dysfunction without considering HDL - C deficiency. This ratio can enhance understanding of past studies on traditional markers. Therapeutically, targeting C - peptide bioactivity and enhancing HDL-C functionality is a dual approach. AMPK activators can improve insulin sensitivity and counter hepatocyte injury, and HDL mimetics or lipase inhibitors can restore HDL’s anti - inflammatory roles. But C-peptide’s dual functions need careful analysis. Despite support from cellular and observational studies, the key questions still remain. Longitudinal studies are required to check if the ratio predicts NASH progression and treatment response. The molecular links between C - peptide and AMPK, and the interaction between gut microbiota and HDL - related anti - inflammatory pathways need further study. Stratifying patients by this ratio can help to find high risk subgroups better. In summary, the FHR is a promising way to understand NAFLD.

The following are some of our research’s advantages: 1) This is the first study to explore the correlation between the FHR and NAFLD. 2) The study emphasizes the nonlinear relationship between FHR and NAFLD, better illustrating the relationship between dose and response. 3) To address potential confounders, rigorous statistical methods were employed to control for covariates, and E-values were calculated to assess the impact of any unmeasured confounding, thereby strengthening the reliability of our results. 4) Dual analytical approaches (continuous and categorical) were implemented for FHR assessment, mitigating random fluctuations in data interpretation while strengthening methodological rigor. 5) Stratified exploration with interaction testing optimized data utilization through multidimensional examination, ensuring more reliable inferences across population subsets. Of course, our study also has several limitations. First, the cross-sectional design cannot clarify the causal relationship between FHR and NAFLD. Second, being a single-center

investigation, findings may lack generalizability to China's broader population. Third, single measurements of FCP and HDL-C reduce data stability and specificity. Fourth, despite adjustments for variables, residual confounding from unmeasured factors such as medications, lifestyle, and comorbidities may persist. However, an E-value was calculated to assess the robustness of the findings to unmeasured confounders, and such confounding was considered unlikely to explain the results. Fifthly, while we demonstrate a significant association between the FCP/HDL-C ratio and NAFLD, we did not compare its performance to other established indices. This important validation represents a key objective for future research. Finally, ultrasound diagnosis of NAFLD has inherent sensitivity limitations compared to gold-standard methods. It should be noted, however, that it has been widely used in epidemiological studies.[11,53] Future research could enhance NAFLD identification using superior techniques, such as liver biopsy. Furthermore, validating these findings necessitates a larger, more diverse sample. To enhance the reliability of the findings, future research could consider conducting long-term follow-ups or case-control studies.

Conclusion

Based on the cumulative evidence, this study identified a nonlinear association between FHR levels and the risk of NAFLD among Chinese individuals with T2DM. These findings suggest the potential associative value of FHR as a novel indicator for integration into NAFLD risk assessment. While FHR measurement may provide a potential tool for identifying individuals with a higher statistical likelihood of NAFLD, its clinical utility remains to be established. Further prospective validation through larger, multi-center cohort studies is required to confirm these findings and assess their generalizability across diverse populations.

Data Sharing Statement

All data generated or analyzed in this study are stored in the Department of Endocrinology, Shenzhen People's Hospital, Shenzhen, Guangdong Province, China, and can be obtained from the corresponding author upon reasonable request.

Ethical Statement and Consent to Participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2008 revision). Ethics Committee approval (LL-KY-2025062-02) was obtained from Shenzhen People's Hospital. Prior to study participation, informed consent was obtained from all participants.

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Author Contributions

Qian Liang: conceptualization, methodology, formal analysis, writing -original draft. Haofei Hu: formal analysis, software, investigation, writing - review & editing. Xuan Chen: methodology, investigation, validation, writing - review & editing. Shufen Yang: data curation, visualization, writing - review & editing. Ying Zhang: investigation, validation, writing - review & editing. Yan Wu: resources, writing - review & editing. Xinyu Wang: supervision, project administration, funding acquisition, writing - review & editing. Hong Chen: supervision, project administration, funding acquisition, writing - review & editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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