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ORIGINAL RESEARCH

Factors Associated with Liver Fibrosis in Chinese Patients with Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease

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Purpose: Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are frequently co-occurring diseases. Liver fibrosis (LF), with increasing incidence, has a prognostic value for NAFLD mortality. Our study aimed to investigate the relevant factors for FL in T2DM individuals with NAFLD.

Patients and Methods: A total of 565 T2DM patients with NAFLD from Hebei General Hospital participated in the study. Patients underwent an abdominal ultrasound, a questionnaire and laboratory tests. The fibrosis-4 index (FIB-4) was used to evaluate LF, with FIB ≥1.3 indicating LF and FIB ≥2.67 indicating F3-4 fibrosis.

Results: Compared with NLF group, LF group had higher levels of systolic blood pressure (SBP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (GGT). The glomerular filtration rate (GFR), low-density lipoprotein cholesterol (LDL), glycated hemoglobin (HbA1c), and platelets (PLT) in LF patients were lower than those without LF. Patients with LF were older than those without LF. ALT, AST, and GGT in patients with severe LF were higher than those with mild LF, while platelet was lower. Age, SBP, duration of diabetes, ALT, AST, and GGT were positively correlated with FIB-4, while eGFR, TC, LDL, and HbA1c were negatively correlated with FIB-4. Logistic regression showed that age, SBP, ALT, GGT, LDL, and PLT were independently associated with LF.

Conclusion: For T2DM patients combined with NAFLD, older age, higher SBP, higher ALT, higher GGT, lower LDL, and lower PLT were relevant factors for LF.

Keywords: type 2 diabetes mellitus, non-alcoholic fatty liver disease, fibrosis-4 index, liver fibrosis

Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic disease, with an estimated global prevalence of between 6% and 9%.[1] Its pathogenesis involves insulin resistance (IR) and relatively insufficient insulin secretion, with hyperglycemia as its feature. Some epidemiological studies have reported a high comorbidity rate between T2DM and non-alcoholic fatty liver disease (NAFLD). NAFLD is regarded as a manifestation of metabolic syndrome (MS) in the liver. With a prevalence of about 25%, it has been the primary cause of chronic liver disease.[2,3] It refers to a group of diseases that range from simple steatohepatitis to non-alcoholic steatohepatitis (NASH). In some cases, it can further progress to liver fibrosis (LF), cirrhosis, and hepatocellular carcinoma. In addition, NAFLD is associated with an increased risk of extra-hepatic cancers, including colorectal and breast cancers.[3]

LF serves as a crucial mortality predictor for those with NAFLD. The all-cause and liver-related mortality in NAFLD patients increases dramatically with the severity of fibrosis.[4] According to a meta-analysis of 49,419 participants, the prevalence of NAFLD in T2DM patients was approximately 55.5%, and the proportion of severe LF was as high as

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17.7%.[5] LF is associated with diabetic nephropathy, diabetic peripheral neuropathy, cardiovascular disease, and osteoporosis.[6–9] Early LF could still be reversed with early intervention.[10] Therefore, it is meaningful to screen LF in T2DM patients with NAFLD so that early intervention can be provided.

Some studies have looked into the causes of LF in those who have both T2DM and NAFLD. Most studies diagnosed LF by transient elastography (TE) and FibroScan. Obesity, which is manifested as a higher body mass index (BMI) and waist circumference, has proven to be one of the outstanding risk factors for LF.[11–13] Higher levels of liver enzymes are independently associated with LF.[14–16] Other risk factors include age,[17,18] dyslipidemia,[19] hypertension[20] and race.[11,21] To date, there are few studies to explore the relevant factors of LF in Chinese diabetes patients combined with NAFLD.

TE, FibroScan, and serological diagnostic panels are recommended noninvasive methods for screening LF. The fibrosis-4 index (FIB-4), AST-to-platelet (PLT) ratio index (APRI) and NAFLD fibrosis score (NFS) are common serological diagnostic panels. Serological diagnostic panels are cheaper and more suitable for primary screening LF in community hospitals than TE and FibroScan. FIB-4 was proposed by Sterling and initially used to assess LF in patients with viral hepatitis.[22] A meta-analysis that compared different noninvasive methods of diagnosing LF showed that FIB-4 had a negative predictive value of 95% and a positive predictive value of 70% for LF with a 1.30 cut-off.[23] In addition, FIB ≥2.67 was found to identify F3-4 fibrosis.[24] This study is the first to use FIB-4 to assess LF in Chinese patients with T2DM combined with NAFLD and to explore its associated factors.

Patients and Methods

Participants

All participants were selected from individuals with T2DM and NAFLD, who were hospitalized in the Department of Endocrinology, Hebei General Hospital from January 2019 to January 2020. Inclusion criteria were as follows: (1) T2DM was diagnosed by the diagnostic criteria for diabetes issued by the World Health Organization in 1999 or according to the self-reported history of T2DM; (2) Abdominal ultrasound indicated fatty liver; (3) Participants were at least 18 years old and at most 80 years old; (4) No history of alcohol consumption or alcohol consumption <70 gram every week for women and <140 gram every week for men. Exclusion criteria were as follows: (1) autoimmune hepatitis, drug-related liver injury, viral hepatitis, hepatomegaly, and other liver diseases; (2) type 1 diabetes, specific types of diabetes, gestational diabetes mellitus, and T2DM with acute complications; (3) malignant tumors and hematological diseases or recent received chemotherapy or immunotherapy; (4) taking drugs that may cause fatty liver; (5) pregnant or lactating women; (6) others: hypothyroidism, acute cardiovascular and cerebrovascular diseases, mental diseases and severe renal dysfunction, defined as glomerular filtration rate (GFR) <30 mL/min. The study eventually included 565 participants. Our study conformed to the Declaration of Helsinki and was approved by the Hebei General Hospital Ethics Committee. All subjects signed written informed consent. We promised that all patients' information was confidential.

Methods

Basic information such as age, gender, duration of diabetes and history of underlying diseases and current medicine were collected through a questionnaire survey. Height and weight were measured while wearing light clothing and without shoes. Systolic/diastolic blood pressure (SBP/DBP) was measured after the patient rested quietly for at least 10 minutes. All patients had venous blood samples drawn after fasting for at least 8 hours to perform laboratory examinations, including total protein (TP), albumin (ALB), globulin (GLB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), serum creatinine (Scr), serum uric acid (SUA), glomerular filtration rate (GFR), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), fasting plasma glucose (FPG), fasting insulin (FINS), glycosylated hemoglobin (HbAlc), hemoglobin (HGB), and platelet (PLT). In addition, all subjects underwent abdominal ultrasonography operated by experienced technicians on an empty stomach.

SBP ≥140 mmHg and/or DBP ≥90 mmHg was defined as hypertension, as well as a history of antihypertensive medication use. Hyperlipidemia was defined as total cholesterol ≥5.7 mmol/L and/or triglycerides ≥1.7 mmol/L and a history of lipid-lowering drug use. Body mass index (BMI) was calculated by dividing weight (kg) by height (m)

squared. A BMI of 25 kg/m^2 or more was considered obese. Homeostasis assessment of insulin resistance (HOMA-IR) was equal to the product of FPG and FINS divided by 22.5. $FIB4 = \text{age} \times \text{AST}/\text{PLT} \times \sqrt{\text{ALT}}$. $NFS = -1.675 + 0.037 \times age + 0.094 \times \text{BMI} + 1.13 + 0.99 \times AST/ALT - 0.013 \times PLT - 0.66 \times ALB$. $APRI = AST/AST_{ULN} \times 100/PLT$.

The data was analyzed by SPSS 26.0. The Kolmogorov–Smirnov test was used to determine whether continuous variables had a normal distribution. The Normally distributed variables were expressed as mean ± standard deviation, and the ANOVA test was used to compare group differences. The non-normal distributed variables were expressed as quartile, and differences between groups were compared using Nonparametric test. The enumeration data was expressed in the form of percentile and the Chi-square test was applied to test differences between groups. Spearman correlation analysis and binary logistic regression analysis were carried out to determine the relevant factors for LF. And $P < 0.05$ was deemed statistically significant.

Results

A total of 565 participants were included in the study (median age: 57 years and BMI: 27.31 kg/m^2), and 334 (59.12%) of them were male. The number of patients in the NLF group (FIB-4 <1.3) was 336 while 229 patients were in the LF group (FIB-4 ≥1.3). Of the patients with LF, 44 had F3-4 fibrosis (FIB-4 ≥2.67).

Clinical Characters of T2DM Patients with and without LF

There was no significant difference between the two groups in terms of gender, DBP, BMI, duration of diabetes, TP, ALB, GLB, ALP, FBG, BUN, Scr, UA, TC, TG, HDL, HGB, and HOMA-IR according to the data in Table 1. Patients with LF had lower GFR, LDL, HbAlc, and PLT than those without LF. Meanwhile, the age was older, and the levels of

Table 1 Comparison of Clinical Parameters Between Patients with and without Liver Fibrosis

Variable	All Patients	Non-Liver Fibrosis Group (FIB-4 <1.30)	Liver Fibrosis Group (FIB-4 ≥1.30)
N	565	336	229
Age (year)	57.00(48.00, 66.00)	55.00(45.25, 61.00)	62.00(53.50, 69.00)**
Male (%)	59.12	61.31	56.77
SBP (mmHg)	134.00(123.00, 148.50)	133.00(123.00, 144.00)	137.00(124.00, 154.00)*
DBP (mmHg)	83.00(76.00, 91.00)	83.00(76.00, 91.00)	83.00(75.00, 91.50)
BMI (kg/m^2)	27.31(25.22, 29.41)	27.13(24.81, 29.37)	27.43(25.53, 29.52)
Duration (year)	8.00(3.00, 13.00)	8.00(3.00, 12.00)	8.00(3.00, 15.00)
TP (g/L)	68.52±5.93	68.63±5.93	68.37±5.94
ALB (g/L)	42.20(40.00.44.45)	42.38(40.20, 44.48)	41.90(40.00, 44.45)
GLB (g/L)	25.90(23.10, 29.30)	26.20(23.40, 29.39)	25.55(22.87, 29.15)
ALT (U/L)	19.90(14.90, 29.95)	17.35(13.65, 22.90)	25.80(17.45, 41.65)**
AST (U/L)	19.70(16.30, 24.55)	17.60(15.10, 20.96)	24.20(19.60, 35.45)**
GGT (U/L)	27.00(19.25, 39.65)	25.75(18.75, 36.55)	30.40(20.15, 47.55)**
ALP (U/L)	80.80(66.35, 96.55)	79.20(66.00, 95.68)	82.80(66.70, 97.15)
BUN (mmol/L)	5.25(4.40, 6.40)	5.29(4.40, 6.58)	5.23(4.42, 6.00)
Scr (μmol/L)	66.50(57.30, 77.10)	66.50(57.83, 76.15)	66.20(56.00, 78.25)
SUA (μmol/L)	316.80(261.75, 377.41)	314.75(262.10, 373.88)	323.75(260.90, 383.60)
GFR (mL/min)	97.80(88.05, 107.33)	100.66(90.94, 108.95)	94.46(86.07, 103.40)**
TC (mmol/L)	4.88(4.02, 5.66)	4.98(4.13, 5.70)	4.69(3.95, 5.65)
TG (mmol/L)	1.62(1.18, 2.44)	1.58(1.14, 2.39)	1.66(1.22, 2.53)
HDL (mmol/L)	1.04(0.90, 1.22)	1.03(0.90, 1.22)	1.04(0.89, 1.22)
LDL (mmol/L)	3.14(2.56, 3.74)	3.21(2.65, 3.75)	3.00(2.47, 3.66)*
FPG (mmol/L)	8.20(6.74, 10.44)	8.35(6.76, 10.74)	8.01(6.66, 10.08)
HbA1c (%)	8.60(7.50, 10.20)	8.75(7.50, 10.48)	8.40(7.40, 9.90)*
HOMA-IR	3.46(2.02, 6.03)	3.42(2.02, 6.21)	3.65(2.02, 5.47)

(*Continued*)

Table 1 (Continued).

Variable	All Patients	Non-Liver Fibrosis Group (FIB-4 <1.30)	Liver Fibrosis Group (FIB-4 ≥1.30)
HGB (g/L)	144.00(132.50, 156.00)	145.00(133.00, 156.00)	143.00(132.00, 154.40)
PLT ($\times 10^9$/L)	226.00(192.00, 265.00)	245.50(211.00, 279.00)	201.00(173.50, 238.00)**
APRI	0.25(0.20, 0.35)	0.21(0.17, 0.25)	0.36(0.27, 0.49)**
NFS	−0.68(−1.34, 0.04)	−0.95(−1.78,-2.28)	−0.14(−0.89, 0.46)**

Notes: Date was presented as mean ± SD, median (P25, P75) or percentage. *P < 0.05; **P < 0.01.
Abbreviations: FIB-4, fibrosis-4 index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TP, total protein; ALB, albumin; GLB, globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; GFR, glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis assessment of insulin resistance; HGB, hemoglobin; PLT, platelets; APRI, aspartate aminotransferase-to-platelets ratio index; NFS, nonalcoholic fatty liver disease fibrosis score.

SBP, ALT, AST, GGT were higher in patients with LF compared to those without LF. Compared to the NLF group, the other two LF scores, APRI and NFS in the LF group were higher. Figure 1 showed that no difference was found in the prevalence of obesity and hyperlipidemia between the LF and NLF groups, while the proportion of hypertensive patients was higher in the LF group than that in the NLF group.

Comparison of Clinical Parameters in Patients with Different Degrees of LF

Patients were further divided into F1-2 (1.3≤ FIB <2.67) and F3-4 (FIB-4 ≥2.67) fibrosis groups. As shown in Table 2, ALT, AST, and GGT in patients with F3-4 fibrosis were higher than those with F1-2 fibrosis, while platelet was lower. There were no group differences in terms of other clinical parameters.

Spearman Correlation Analysis of the FIB-4 and Other Factors

Table 3 showed that FIB-4 was positively correlated with age, SBP, duration of diabetes, ALT, AST, GGT, APRI, and NFS, while negatively correlated with GFR, TC, LDL, and HbA1c. DBP, BMI, TP, GLB, ALP, BUN, Scr, UA, TG, HDL, FPG, HOMA-IR, and HGB were not correlated with FIB-4.

Logistic Regression Analysis of LF in T2DM Patients Combined with NAFLD

LF was used as the dependent variable, with age, SBP, ALT, AST, GGT, GFR, LDL, PLT, and HbAlc as the independent variables. Age, SBP, ALT, GGT, LDL, and PLT were all independently associated with LF in T2DM patients with

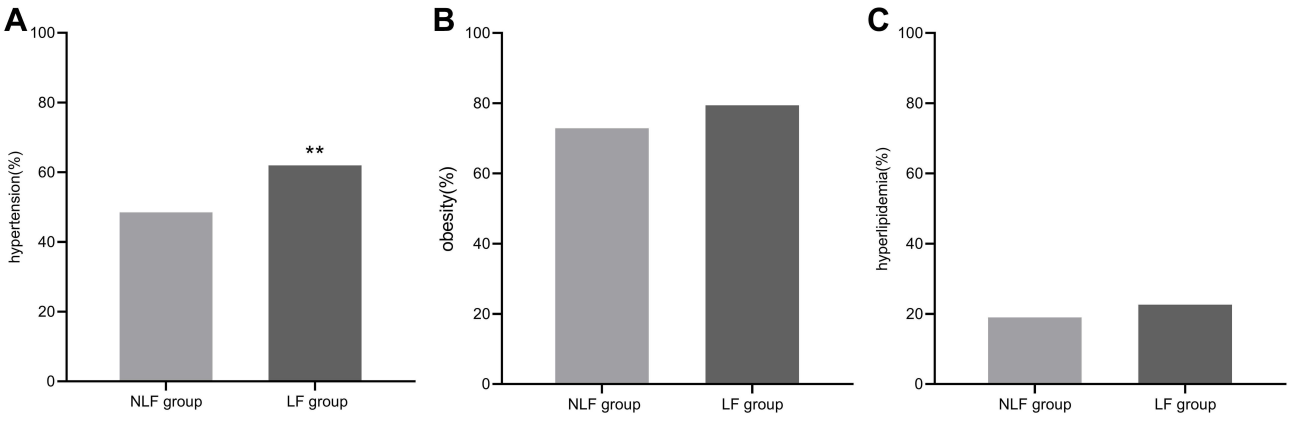

Figure 1 Comparison of prevalence of hypertension, hyperlipidemia, and obesity between NLF group and LF group. (**A**) Comparison of prevalence of hypertension, between NLF group and LF group; (**B**) Comparison of prevalence of hyperlipidemia between NLF group and LF group; (**C**) Comparison of prevalence of obesity between NLF group and LF group. **P < 0.01.

Table 2 Comparison of Clinical Parameters in Patients with Different Degrees of Liver Fibrosis

Variable	F1-2 (1.3 ≤ FIB-4 <2.67)	F3-4 (FIB-4 ≥2.67)
N	185	44
Age (year)	62.00(53.00, 69.00)	62.50(54.00, 70.75)
Male (%)	104	24
SBP (mmHg)	136.00(124.50, 154.00)	141.00(121.25, 154.75)
DBP (mmHg)	83.00(74.50, 92.00)	83.50(75.50, 90.75)
BMI (kg/m^2)	27.64(25.53, 29.60)	27.23(25.35, 29.32)
Duration (year)	9.00(3.00, 14.50)	6.00(2.00, 15.75)
TP (g/L)	68.13±5.76	69.38±6.63
ALB (g/L)	41.86(39.95, 44.16)	42.70(40.05, 45.18)
GLB (g/L)	25.5(22.79, 29.15)	26.80(23.43, 29.32)
ALT (U/L)	23.90(16.25, 34.05)	41.60(29.75, 69.25)**
AST (U/L)	23.10(19.10, 31.60)	39.40(28.48, 51.68)**
GGT (U/L)	28.30(19.65, 42.00)	36.95(23.80, 74.35)*
ALP (U/L)	83.60(67.15, 97.80)	79.40(61.08, 94.40)
BUN (mmol/L)	5.30(4.50, 6.05)	5.10(4.33, 5.75)
Scr (μmol/L)	66.60(55.90, 79.95)	64.69(56.05, 73.78)
SUA (μmol/L)	323.75(258.35, 381.83)	323.95(278.33, 384.08)
GFR (mL/min)	94.56(86.16, 102.97)	93.61(85.01, 105.21)
TC (mmol/L)	4.68(3.95, 5.56)	4.83(3.97, 6.39)
TG (mmol/L)	1.64(1.20, 2.51)	1.75(1.30, 2.58)
HDL (mmol/L)	1.03(0.88, 1.20)	1.11(0.94, 1.32)
LDL (mmol/L)	3.00(2.47, 3.61)	3.02(2.47, 4.21)
FPG (mmol/L)	8.31(6.69, 10.08)	7.61(6.54, 10.14)
HbA1c (%)	8.40(7.50, 9.90)	8.35(7.25, 9.95)
HOMA-IR	3.54(2.15, 5.67)	4.13(1.62, 5.44)
HGB (g/L)	143.00(133.50, 154.50)	142.50(130.25, 154.25)
PLT (×10^9/L)	211.00(179.00, 250.00)	183.50(164.25, 204.25)**

Notes: Date was presented as mean ± SD, median (P25, P75) or percentage. *P < 0.05; **P < 0.01.
Abbreviations: FIB-4, fibrosis-4 index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TP, total protein; ALB, albumin; GLB, globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; GFR, glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis assessment of insulin resistance; HGB, hemoglobin; PLT, platelets.

NAFLD according to the binary logistic regression analysis. However, this association was not found between LF and AST, GFR, and HbA1c. The results were shown in Table 4.

Discussion

To our knowledge, FIB-4 is the first to be used as the diagnostic indicator for LF in Chinese T2DM patients with NAFLD to investigate the relevant factors. FIB-4 was found to be positively correlated with age, SBP, duration of diabetes, ALT, AST, GGT, APRI, and NFS, while negatively correlated with GFR, TC, LDL, and HbA1c. After adjustment for confounding factors, logistic regression showed that age, SBP, ALT, GGT, LDL, and PLT were independently correlated with LF.

In our study, the LF group showed higher ALT, AST and GGT than the NLF group. Further analysis showed that ALT, AST and GGT were positively correlated with FIB-4. However, after adjusting for confounding factors, only ALT and GGT were associated with LF. Previous studies have found that subjects with LF had higher ALT, AST and GGT levels compared with those without LF.[25–28] Liver enzymes reflect liver function and hepatocellular injury and have been

Table 3 Correlation Between FIB-4 and Other Indicators

Variable	*r*	Variable	*r*
Age (year)	0.338**	SUA (μmol/L)	0.069
SBP (mmHg)	0.125**	GFR (mL/min)	−0.231**
DBP (mmHg)	−0.044	TC (mmol/L)	−0.091*
BMI (kg/m^2)	0.056	TG (mmol/L)	−0.010
Duration (year)	0.111**	HDL (mmol/L)	0.005
TP (g/L)	−0.026	LDL (mmol/L)	−0.096*
ALB (g/L)	−0.036	FPG (mmol/L)	−0.076
GLB (g/L)	−0.026	HbA1c (%)	−0.102*
ALT (U/L)	0.409**	HOMA-IR	0.027
AST (U/L)	0.582**	HGB (g/L)	−0.022
GGT (U/L)	0.116**	PLT (×10^9/L)	−0.464**
ALP (U/L)	0.050	APRI	0.754**
BUN (mmol/L)	−0.032	NFS	0.454**
Scr (μmol/L)	0.026		

Notes: Spearman correlation analysis was applied in this part. *P < 0.05; **P < 0.01.

Abbreviations: FIB-4, fibrosis-4 index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TP, total protein; ALB, albumin; GLB, globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; GFR, glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis assessment of insulin resistance; HGB, hemoglobin; PLT, platelets; APRI, aspartate aminotransferase-to-platelets ratio index; NFS, non-alcoholic fatty liver disease fibrosis score.

Table 4 Logistic Regression Analysis of Liver Fibrosis in Type 2 Diabetes Mellitus Patients Combined with Non-Alcoholic Fatty Liver Disease

Variable		OR	95% CI
Age (year)	< 50		
	≥50	4.315**	2.252–8.266
SBP (mmHg)		1.012*	1.001–1.024
ALT (U/L)	< 40		
	≥40	11.686**	2.881–47.400
AST (U/L)	< 50		
	≥50	1.296	0.1880–8.916
GGT (U/L)		1.010*	1.002–1.018
GFR (mL/min)		0.990	0.976–1.004
LDL (mmol/L)		0.761*	0.599–0.967
HbA1c (%)		0.954	0.852–1.068
PLT (×10^9/L)	< 260		
	≥260	0.252**	0.165–0.384

Notes: Liver fibrosis was used as the dependent variable, and age, SBP, ALT, AST, GGT, eGFR, LDL, HbAlc, and PLT were used as independent variables. *P < 0.05; **P < 0.01.

Abbreviations: SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; GFR, glomerular filtration rate; LDL, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; PLT, platelets.

suggested to predict NAFLD.[29] AST is mainly found in mitochondria and elevated AST is often associated with severe hepatocellular injury.[14] Our study found that AST was not an independent predictor of FL, perhaps because our patients had less severe liver lesions.

Our findings demonstrated that age was a risk factor for LF. Individuals aged ≥50 years were 4.315 times more likely to develop LF than patients aged <50 years. It agrees with the findings of several studies.[30,31] The prevalence of NAFLD is high in the elderly.[32] It may be related to the fact that elderly patients are prone to hypertension, obesity and dyslipidemia, which are all risk factors for NAFLD. On the other hand, liver function deteriorates with ageing and chronic liver disease is more likely to worsen in older patients.[20,33]

We found that SBP but not DBP was correlated with LF after correction for confounding factors. Hypertension and NAFLD are both considered to be manifestations of MS, showing a potential mutual causality.[34–37] Hypertension is often accompanied by RAS activation, and studies have shown that Angiotensin II (Ang II) is associated with LF. Ang II can activate hepatic stellate cells (HSCs) and cause LF.[38] Meanwhile, Ang II can aggravate IR though activating insulin signaling pathways.[39] Yuan et al[40] found that mice with hypertension showed more severe LF than those without hypertension, and that cytokine activation and inflammation played an important role. RAS activation, IR, and inflammation are important pathophysiological mechanisms underlying the co-morbidity of hypertension and NAFLD.[41,42]

In our study, lower levels of LDL in the LF group were observed compared to the NLF group. Meanwhile, LDL was negatively associated with LF. There are some studies supporting our results. Jaafar et al[43] found that LDL in patients with T2DM combined with NAFLD was lower compared to the patients with NAFLD alone. Another study assessing LF with FIB-4 also showed a negative correlation between LDL and LF.[44] Low LDL levels may reflect decreased liver function. As liver function worsens, so does the hepatic ability to synthesize LDL. In addition, genetic mutations may be involved. PNPLA-3 is a genetic variant closely related to NAFLD, and people carrying the PNPLA3rs738409 GG allele show lower TC and LDL.[45] The exact mechanism is unclear.

As the results illustrated, the LF group showed lower HbAlc and FBG levels compared with the NLF group. As we know, the liver is the hub of glucose metabolism. In some liver diseases, including LF, cirrhosis, and liver cancer, blood glucose levels decrease as the ability of the liver to store glycogen and gluconeogenesis decreases.[46] This is also associated with large fluctuations in blood glucose, mainly manifested as decreased FBG and increased postprandial blood glucose.[47] Some patients with NAFLD already have subclinical hypersplenism at the time of initial diagnosis.[48] Our study also showed the FL group had lower levels of PLT and HGB than the NFL group, although PLT and HGB in both groups were in the normal range. Due to shortened erythrocyte lifespan as a result of hypersplenism, they have lower HbAlc levels.[49] However, some studies have found that HbA1c is positively correlated with NAFLD, regardless of whether diabetes is present.[50–53] A study showed that each 1% increase in HbA1c increased the probability of LF progress by 15%.[54] Subclinical hypersplenism was not excluded in our study population, so HBA1C did not truly reflect blood glucose. Continuous glucose monitoring system and time in range may be more suitable for blood glucose monitoring in patients with T2DM complicated with chronic liver disease.

Moreover, our results showed that HOMA-IR in both LF and NLF groups was ≥3, indicating IR existed in both groups, although HOMA-IR was not statistically different between groups. Our study revealed that IR may not be connected to the development of LF. Mikolasevic et al[26] found that HOMA-IR was independently associated with hepatic steatosis, but not with moderate and advanced LF in T2DM patients with NAFLD. Mantovani et al[55] conducted a cross-sectional study on T2DM patients who were not treated with insulin. The diagnosis of NAFLD is based on abdominal color ultrasound and liver hardness measurement. Their results showed that HOMA-IR was not independently associated with LF. However, some studies found that IR was closely related to LF in NAFLD patients whether or not diabetes is present.[56–58] The reasons for this discrepancy are not fully elucidated, but race and experimental methods may be underlying factors.

Our research had some limitations. Firstly, as a cross-sectional study, it cannot provide evidence for further exploration of the causal relationship between relevant factors and LF. Secondly, FIB-4 was used to diagnose LF and grade the lesion degree, which may be different from the actual clinical situation. Third, this was a single-center study, and it was not possible to generalize the findings to the other population.

Conclusion

In conclusion, LF is independently associated with age, SBP, ALT, GGT, LDL, and PLT in patients with T2DM and NAFLD. For T2DM patients with NAFLD, intensive comprehensive care of blood glucose, blood pressure, and blood lipid is required. When conditions are suitable, further liver biopsy is advised to identify the severity of NAFLD.

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Disclosure

The authors report no conflicts of interest in this work.

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