BMC Endocrine Disorders

RESEARCH

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Increased risk of vascular complications in patients with type 2 diabetes and fatty liver disease

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Abstract

Background The prevalence of steatotic liver disease (SLD) in patients with type 2 diabetes (T2DM) exceeds 50%. This study aimed to investigate the clinical characteristics of SLD and liver fibrosis in Chinese patients with T2DM.

Methods Inpatients from 2021 to 2023 were included in the study. Fatty liver index (FLI) and fibrosis-4 (FIB-4) were calculated to assess hepatic steatosis and fibrosis respectively. Statistical analysis was completed by SPSS v25 and GraphPad Prism v8.0.1.

Results Of the 1466 participants, about one-third of the patients in T2DM-SLD group were diagnosed with liver fibrosis (LF), and the percentage of patients over 50 years old was 85.9%. Patients with SLD had higher levels of BMI, blood pressure, liver enzymes, fasting blood glucose (FBG), HbA1c, C-peptide, total cholesterol (TC) and triglyceride (TG) ($P<0.05$ for all). Patients with liver fibrosis had lower TC, TG, hemoglobin (Hb), erythrocyte count (RBC), leukocyte count (WBC) and platelet (PLT) levels ($P<0.05$ for all). Compared with simple T2DM and SLD-NLF (non-liver fibrosis) groups, for patients over 50 years old, the prevalence of coronary heart disease, stroke, tumor, and diabetic nephropathy was higher in patients with liver fibrosis. Liver fibrosis might be the risk factor of arterial stiffness, stroke, coronary heart disease and numbness based on multivariable logistic regression analysis.

Conclusion Hepatic steatosis and fibrosis were common in patients with T2DM. Liver fibrosis was relevant to many macrovascular and microvascular diabetic complications.

Keywords Liver steatosis, Liver fibrosis, Type 2 diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disease manifested as hyperglycemia and insulin resistance. Currently, diabetes affects over 500 million individuals worldwide, and more than 1.3 billion people are projected to have diabetes by 2050 [1]. Steatotic liver disease (SLD) is one of the most common liver disease worldwide, the prevalence of which was up to 38% [2]. T2DM and SLD are closely linked with each other, with shared mechanisms such as insulin resistance, inflammation, and altered lipid metabolism [3]. It was estimated that nearly 70% T2DM patients had SLD [4]. One third of T2DM patients with SLD could develop to steatohepatitis, liver fibrosis (LF) and cirrhosis [5].

Liver fibrosis was associated with all-cause, cardiovascular, and liver-related mortality [6]. Owing to the possibility of early-phase liver fibrosis reversal by intervention, early identification and management of liver fibrosis is of great importance. There are more and more studies on liver fibrosis. Circulating fatty acids were reported to have association with advanced liver fibrosis and hepatic carcinoma (HCC) [7, 8]. Some studies reported that patients with SLD had a higher risk of cardiovascular disease (CVD) and the severity of liver fibrosis is a risk factor of subclinical atherosclerosis [9]. Microvascular diseases were recommended to be taken into account in the personalized risk assessment for patients with SLD [10]. However, the correlation between metabolism parameters, macrovascular complications, microvascular complications and chronic liver disease still remains unclear in patients with T2DM.

Liver biopsy is the gold standard for diagnosis of SLD and liver fibrosis. Due to high cost and invasion, it cannot be widely applied especially in primary medical care. Ultrasound, a technique with low sensitivity, cannot detect SLD until it is obvious [11], leading to the delay in diagnosis of liver fibrosis [12]. Other imaging examinations including magnetic resonance and transient elastography are not available in many clinics. So, many low-cost, easy and non-invasive scoring systems based on routine laboratory parameters were proposed for screening of fatty liver and hepatic fibrosis. Among these, fatty liver index (FLI) developed initially by *Bedogni* showed well-validated accuracy for hepatic steatosis in general population at the recommended cutoff of 60 [13]. The fibrosis-4 index (FIB-4) had a comparable diagnostic accuracy with a cutoff of 1.3 for diagnosing LF in adults with SLD [14]. It was also relevant to many intrahepatic and extrahepatic comorbidities in individuals with or without T2DM [6, 15].

The present study was designed to assess the clinical features of SLD and LF defined by noninvasive scores among Chinese individuals with T2DM. Additionally, we endeavored to explore the correlation between diabetic complications and the presence of liver fibrosis in T2DM patients.

Materials and methods

Participants

Given the absence of prospectively collected data, our study employed a retrospective design to leverage existing data sources. T2DM inpatients from January of 2021 to March of 2023 were enrolled in the study. Individuals with excessive alcohol consumption (30 g/day for males and 20 g/day for females) or any other liver disease were excluded.

The research was in accordance to the Declaration of Helsinki and approved by Zhongda Hospital Affiliated to Southeast University Ethics Committee. The requirement to obtain informed written consent was waived. All personal identifiers have been removed from the dataset, and any potentially identifiable information has been replaced with pseudonyms.

Data collections

Clinical information such as gender, age, diastolic blood pressure (DBP), systolic blood pressure (SBP), body mass index (BMI), waist-to-hip ratio (WHR), and the ratio of visceral to subcutaneous (VSR) were collected. Blood samples were collected after fasting for at least 8 h. Laboratory examinations included fasting blood glucose (FBG), two-hour postprandial blood glucose (2hPG), glycated hemoglobin (HbA1c), C-peptide, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), hemoglobin (Hb), erythrocyte count (RBC), leukocyte count (WBC), platelet (PLT), high-sensitivity C reaction protein (hsCRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), albumin (ALB), blood urea nitrogen (BUN), blood and serum creatinine (Cr), albumin to creatinine ratio (ACR), uric acid (UA).

Diabetic complications were assessed in this research. Diabetic nephropathy was defined by ACR ≥ 30 mg/g and arterial stiffness was defined as brachial-ankle pulse wave velocity (baPWV) ≥ 1400 cm/s. BaPWV was a non-invasive method used to assess the stiffness of the arteries. It measured the speed at which the pulse wave travelled from the brachial artery to the ankle artery, indicating the elasticity of blood vessels. Diagnosis of numbness, diabetic foot, CVD, stroke and tumor was according to self-reported or recorded disease history of subjects.

T2DM patients were divided into simple T2DM group (T2DM group) and T2DM patients with steatotic liver disease (T2DM-SLD group) based on fat liver index (FLI). Individuals with FLI scores of ≥ 60 were classified as having hepatic steatosis and FLI scores of <30 were classified as non-steatosis [16]. In recent research, Brian et al.

reported that FLI identified fatty liver and held potential for risk stratification of cardiometabolic, malignant disease outcomes as well as all-cause mortality [17]. Then patients in T2DM-SLD group were further divided into two groups based on fibrosis 4 score (FIB-4). We defined the presence of significant liver fibrosis using a FIB-4 index cutoff of ≥1.3. This threshold was supported by many clinical guidelines and literature, which suggested that a FIB-4 score above this value is associated with a higher risk of advanced liver fibrosis and related complications in patients with chronic liver diseases [18].

Statistical analysis

The statistical analysis was completed using SPSS v25 and GraphPad Prism v8.0.1. To assess the association between fatty liver and diabetes complications, we conducted a sample size calculation to ensure the statistical rigor of our findings. We set a significance level of 0.05 to control for type I error and aimed for a power of 0.8. For clinical data with a normalized distribution, it was represented as mean±SD, and significance was calculated using Levene's test between the two groups (T2DM vs. T2DM-SLD; SLD-LF vs. SLD-NLF). For clinical data with a non-normalized distribution, it was represented as median (interquartile range), and significance was assessed using the nonparametric Mann-Whitney U test. For clinical data with categorical variables, it was represented as absolute numbers and percentage (%). Chi-square test was selected to analyze the difference in the prevalence of adverse events including numbness, diabetic nephropathy, diabetic foot, arterial stiffness, coronary heart disease, stroke and history of tumor between the groups (T2DM vs. SLD-NLF; T2DM-SLD vs. SLD-LF; SLD-LF vs. SLD-NLF). A multivariable logistic regression was then used to analyze the association between liver fibrosis and vascular complications. P value<0.05 was considered statistically significant.

Results

The epidemiology of SLD and FL in patients with T2DM

In this retrospective analysis, we enrolled a total of 1,466 diabetic patients, consisting of 917 males and 549 females. Of the patients, 72.2% were individuals over 50 years old. Among 1,466 patients with T2DM, 686 patients were assessed as hepatic steatosis (T2DM-SLD group) based on FLI score (≥60). Moreover, patients with SLD were divided into simple steatosis group (n=459, SLD-NLF group) and fibrosis group (n=227, SLD-LF group) according to FIB-4 score (≥1.3).

In this study, we found that more than a half of the patients with SLD was younger than 50 years old (56.4%), though those over 50 accounted for most of the enrolled patients. In addition, about one-third of the patients in T2DM-SLD group were diagnosed with liver fibrosis, and in the fibrosis group the percentage of patients over 50 years old was up to 85.9%.

Clinical parameters of T2DM-SLD and SLD-LF

Compared to T2DM group, the patients with SLD had higher levels of weight, BMI, WHR, VSR, DBP, and SBP (Table 1). Liver enzymes (ALT, AST, γ-GT), ALB, Hb, RBC, PLT and WBC also elevated in T2DM-SLD group. Moreover, the indices associated with glucose and lipid metabolism increased in T2DM-SLD group, including FBG, HbA1C, C-peptide, TC, and TG. Levels of BUN, Cr and ACR were also higher in patients with hepatic steatosis. Interestingly, the value of baPWV was lower in T2DM-SLD group. Patients with SLD might not have arterial stiffness because hepatic steatosis was considered initially benign, though it can progress to liver fibrosis, cirrhosis and cancer.

Liver fibrosis could lead to many intrahepatic and extrahepatic complications. Therefore, it was essential to screen and analysis the clinical-pathological features of people with liver fibrosis. The patients in SLD-LF group were elder compared to SLD-NLF group (62y vs. 47y). Levels of liver enzymes especially AST were higher in patients with liver fibrosis. There was no significant difference on glucose metabolism parameters (HbA1c, blood glucose, C-peptide) between SLD-NLF and SLD-LF group. Patients with liver fibrosis had lower TC, TG, Hb, RBC, PLT and WBC. Levels of Cr and BUN in SLD-LF group were higher although ACR had no significant difference. A significant increase in baPWV was observed in the SLD-LF group. These results suggested that not all variables synchronized with liver function deterioration (Table 2).

Liver fibrosis not liver steatosis increases the risk of adverse events for T2DM patients

We assessed the prevalence of vascular complications among different groups (T2DM vs. SLD-NLF vs. SLD-LF) (Fig. 1). Compared to T2DM group, a higher prevalence of diabetic foot and numbness were observed in SLD-NLF group (under or over 50 years old). With the progression of liver injury, for the patients under the age of 50, a higher rate of tumor history was observed in the SLD-LF group than other groups (T2DM and SLD-NLF). For the patients over 50 years old, individuals with coronary heart disease were more in SLD-LF group than other groups. These results suggested that patients with liver fibrosis might be more susceptible to vascular complications. Aging might play an important role in vascular dysfunction.

The associations between SLD-LF and diabetic complications were then analyzed by multivariable logistic regression (Fig. 2). It was shown that liver fibrosis mighe be a risk factor for arterial stiffness (OR=1.98, 95% CI

Table 1 Clinical parameters in patients with and without steatotic liver diseases

Variable		T2DM (*n* = 780)	T2DM-SLD (*n* = 686)	*P* value
Age, years		60 (54,66)	52 (42,62)	< 0.001
Height, cm		165.5 (159.5,171)	169.5 (162.5,175.5)	< 0.001
Body weight, kg		61.8 (55.85,67.35)	80.3 (72.7,89.6)	< 0.001
BMI, kg/m^2		22.6 (21.1,24)	28.2 (26.1,30.9)	< 0.001
WHR		0.91 (0.88,0.95)	0.98 (0.95,1.02)	< 0.001
Head circumference, cm		55 (54,57)	57 (56,59)	< 0.001
Neck circumference, cm		37 (34,39)	41 (38.5,44)	< 0.001
VSR		0.38 (0.29,0.47)	0.48 (0.40,0.55)	0.001
Heart rate		79 (72,87)	82 (75,90)	< 0.001
DBP, mmHg		70 (63,78)	77 (70,84)	< 0.001
SBP, mmHg		126 (114,142)	132 (119,144)	< 0.001
Blood glucose, mmol/L	0 min	7.58 (5.94,10.90)	8.48 (6.75,11.65)	< 0.001
	120 min	17.81 (14.17,20.95)	16.94 (13.55,19.7)	< 0.001
HbA1C, %		8.46 (6.97,10.48)	9.1 (7.59,10.57)	< 0.001
C-peptide, nmol/L	0 min	0.40 (0.25,0.56)	0.73 (0.50,0.99)	< 0.001
	120 min	1.41 (0.845,2.18)	2.15 (1.50,2.99)	< 0.001
TC, mmol/L		4.29 (3.55,5.04)	4.79 (3.95,5,54)	< 0.001
TG, mmol/L		0.97 (0.74,1.31)	2.36 (1.66,3.65)	< 0.001
HDL-c, mmol/L		1.22 (1.03,1.42)	0.96 (0.8,1.14)	< 0.001
LDL-c, mmol/L		2.46 (1.91,3.08)	2.53 (1.86,3.1)	0.667
UA, μmol/L		279 (227,334)	345.5 (285,418.25)	< 0.001
ALT, U/L		15 (11,20)	29 (18,47)	< 0.001
AST, U/L		16 (14,20)	22 (16,33)	< 0.001
ALP, U/L		72 (60,88)	81 (67,96)	< 0.001
γ-GT, U/L		17 (13,22)	44 (30,72)	< 0.001
ALB, g/L		40.7 (38.3,43.2)	41.8 (39.4,44.4)	< 0.001
Hb, g/L		138 (126,148)	147 (136,157)	< 0.001
RBC, ×10^9/L		4.6 (4.22,4.94)	4.89 (4.52,5.25)	< 0.001
WBC, ×10^9/L		6.07 (5.11,7.23)	6.78 (5.67,8.17)	< 0.001
PLT, ×10^9/L		208 (175,248)	217 (175,262.75)	0.02
hsCRP, mg/L		1.59 (0.81,5.15)	2.7 (1.05,6.73)	< 0.001
BUN, mmol/L		6.1 (5,7.4)	5.6 (4.5,6.9)	< 0.001
Urine Cr, μmol/L		94.46 (60.21,137.30)	122.55 (79.66,180.73)	< 0.001
Blood Cr, μmol/L		62 (52,75)	65 (53,79.5)	0.003
ACR, mg/g		17.93 (9.37,44.35)	22.07 (10.64,65.77)	0.004
FT3, pmol/L		4.37 (3.94,4.74)	4.62 (4.14,5.14)	< 0.001
FT4, pmol/L		16.9 (15.3,18.7)	16.7 (14.9,18.4)	0.042
TSH, mIU/ml		1.76 (1.17,2.69)	1.77 (1.15,2.62)	0.795
FLI		16.27 (9.82,22.50)	78.81 (69.40,89.97)	< 0.001
BaPWV, cm/s		1653 (1445.75,1884.5)	1564 (1381,1811)	< 0.001

Data was characteristic as non-normal distribution through *Kolmogorov-Smirnov normality* test. Then they were all represented as median (IQR, p25-p75). And the significance was calculated by *Mann-Whitney U* test

Abbreviations BMI, body mass index; WHR, waist to hip ratio; VSR, the ratio of visceral to subcutaneous; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein; LDL-c, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase; ALB, albumin; Hb, hemoglobin; RBC, Erythrocyte count; WBC, Leukocyte count; PLT, platelet; hsCRP, high-sensitivity C reaction protein; BUN, blood urea nitrogen; FT3, free T3; FT4, free T4; TSH, thyrotropin; UA, urine acid; ACR, albumin to creatinine ratio; baPWV, brachial ankle pulse wave velocity

1.25–3.12), stoke (OR = 1.57, 95% CI 1.12–2.26), coronary heart disease (OR = 2.10, 95% CI 1.24–3.42) and numbness (OR = 1.77, 95% CI 1.18–3.10) after adjusting for drinking, smoking, sex, BMI, diabetes duration, HbA1c and TG. Overall, liver fibrosis might increase the risk of vascular complications especially in patients over 50 years old.

Discussion

Few studies investigated the prevalence and the risks of vascular adverse events in T2DM patients with SLD and liver fibrosis. In this research, about one-third of the patients in T2DM-SLD group had liver fibrosis, and 85.9% of them were over 50 years old. We found not all parameters were in parallel with the progression of liver

Table 2 Clinical parameters in patients with and without liver fibrosis

Variables		SLD-NLF (*n* = 459)	SLD-LF (*n* = 227)	*P* value
Age, years		47 (38.5,57)	62 (525,67.5)	< 0.001
Height, cm		171 (164,176)	167 (160,172)	< 0.001
Weight, kg		82.4 (74.45,91.7)	77.6 (69.75,85.95)	< 0.001
BMI, kg/m^2		28.4 (26.3,31.1)	27.8 (26,30.1)	0.068
WHR		0.99 (0.95,1.02)	0.98 (0.95,1.01)	0.529
Head circumference, cm		57 (56,59)	57 (55,58.5)	0.005
Neck circumference, cm		41 (39,44)	40.5 (38,43)	0.006
VSR		0.48 ± 0.11	0.48 ± 0.12	0.93
Heart rate		83 (76,91.5)	81 (71,87)	< 0.001
DBP, mmHg		78 (70.5,85)	75 (67.5,82)	0.001
SBP, mmHg		130 (119,143.5)	133 (119,146)	0.227
Blood glucose, mmol/L	0 min	8.7 (6.81,11.37)	8.25 (6.72,12.51)	0.843
	120 min	16.87 (13.31,19.60)	17.23 (13.94,19.98)	0.138
HbA1C, %		9.12 (7.68,10.59)	9.03 (7.44,10.52)	0.533
C-peptide, nmol/L	0 min	0.71 (0.50,0.95)	0.78 (0.54,1.00)	0.158
	120 min	2.13 (1.44,3.00)	2.26 (1.53,2.96)	0.385
TC, mmo/L		4.8 (4.09,5.64)	4.73 (3.80,5.36)	0.037
TG, mmol/L		2.52 (1.77,3.91)	2.14 (1.58,3.19)	0.001
HDL-c, mmol/L		0.96 (0.8,1.13)	0.98 (0.80,1.18)	0.174
LDL-c, mmol/L		2.55 ± 0.92	2.43 ± 0.98	0.105
UA, μmol/L		347 (290,419)	341.5 (275.25,414.25)	0.293
Hb, g/L		149 (138,159)	143 (132,153)	< 0.001
RBC, ×10^9/L		4.97 ± 0.56	4.67 ± 0.52	< 0.001
WBC, ×10^9/L		6.9 (5.79,8.49)	6.43 (5.45,7.63)	< 0.001
PLT, ×10^9/L		245 (205.5,284))	171 (153,206.5)	< 0.001
hsCRP, mg/L		2.46 (0.98,7.43)	3.13 (1.23,6.20)	0.817
ALT, U/L		29 (18,45)	30 (18,51.5)	0.257
AST, U/L		20 (16,30)	28 (19,43)	< 0.001
ALP, U/L		80 (67,95.5)	82.5 (68,97)	0.5
γ-GT, U/L		43 (29,69)	46 (30,79)	0.235
ALB, g/L		42 (39.65,44.8)	41.5 (38.9,43.7)	0.028
BUN, mmol/L		5.4 (4.4,6.7)	6.1 (5,7.4)	< 0.001
Serum Cr, μmol/L		63 (52,76)	69 (56,85)	0.001
Urine Cr, μmol/L		138.42 (86.27,194.68)	99.32 (72.79,138.58)	< 0.001
ACR, mg/g		20.51 (10.28,64.01)	27.28 (13.36,79.05)	0.074
FT3, pmol/L		4.7 (4.21,5.24)	4.46 (4.04,4.87)	< 0.001
FT4, pmol/L		16.8 (15.1,18.5)	16.1 (14.6,18.1)	< 0.001
TSH, mIU/ml		1.72 (1.11,2.49)	1.97 (1.31,2.96)	0.009
BaPWV, cm/s		1522 (1353,1737.5)	1700 (1480.5,1959.5)	< 0.001
FLI		80.50 (69.75,90.48)	77.80 (69.25,87.31)	0.073
FIB-4		0.73 (0.53,0.90)	1.75 (1.48,2.20)	< 0.001

The data of Bfp, LDL-c, and RBC was characteristic as normal distribution through *Kolmogorov-Smirnov normality* test, and they were represented as mean ± SD, the significance was calculated by *Levene's* test. Other parameters were characteristic as non-normal distribution through *Kolmogorov-Smirnov normality* test, they were represented as median (IQR, p25-75). Then the significance was analyzed by *Mann-Whitney U* test

disease in T2DM patients. Levels of serum lipid including LDL-c, TC, TG were lower in SLD-LF group. Interestingly, liver fibrosis but not SLD might increase the risks of arterial stiffness, diabetic nephropathy, CVD, and stroke, especially in patients over 50 years old.

Elder patients were more susceptible to T2DM and its liver comorbidities. Recently, it was found the patients over 50 years old were 2.6 times more likely to develop T2DM and multiple comorbidities than patients under 50 years old [19]. Our study revealed that advanced fibrosis was more common in elder individuals, which was consistent with previous findings [19]. More and more studies showed that aging could act as one of the determinants for the development of metabolic disorders including T2DM and chronic liver diseases [20, 21]. Aging might act on liver disease progression by oxidative stress, increased inflammation, and liver injury [22].

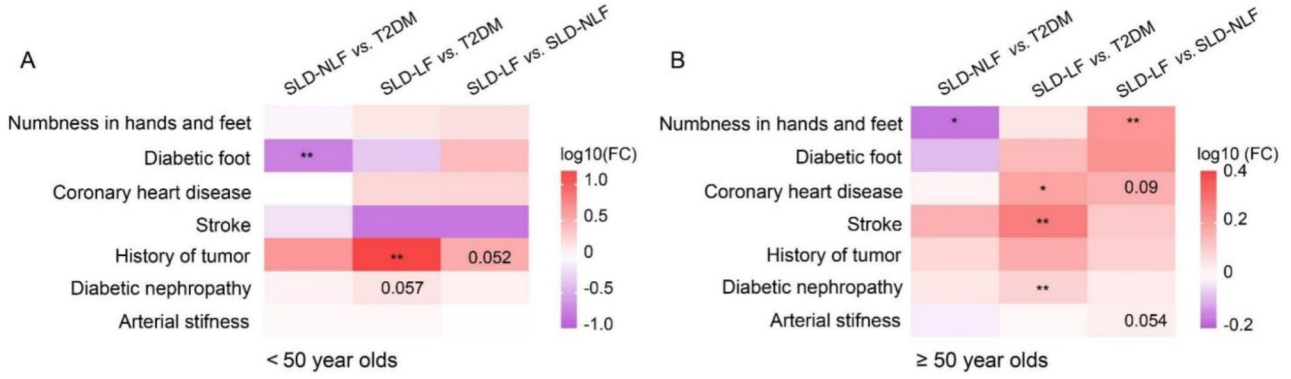

Fig. 1 Comparisons of adverse events between groups at different level of liver diseases. (**A**) Comparisons in patients less than 50 years old. (**B**) Comparisons in patients more than 50 years old. For graph (**A**, **B**), data represented the pairwise comparison adverse events between groups, such as numbness, diabetic foot, coronary heart disease, stroke, history of tumor, diabetic nephropathy, and arterial stiffness. The color of each block represented the fold change of prevalence in the former group compared to the latter group (purple indicated decreased, red indicated increased). The significance was calculated by *Chi*-square test. *, $p < 0.05$; **, $p < 0.01$

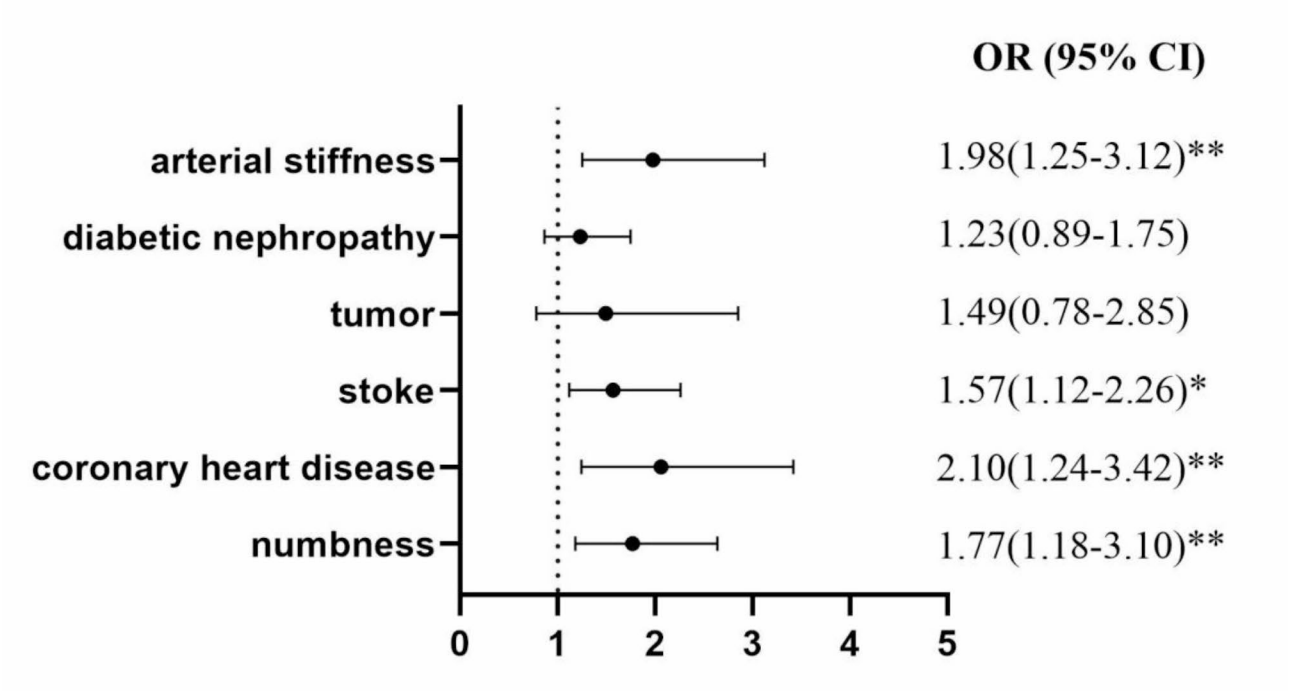

Fig. 2 Multivariable logistic regression analysis between liver fibrosis and major adverse events in patients with T2DM. Model was control for drinking, smoking, sex, BMI, diabetes duration, HbA1c and TG. *$p < 0.05$, **$p < 0.01$

T2DM patients with SLD had higher levels of WHR, VSR and BMI compared to those without SLD, which were consistent with previous findings [23]. Meanwhile, serum lipid and glucose parameters including blood glucose, HbA1C, C-peptide, TC, TG, LDL-c, and UA were higher in T2DM patients with hepatic steatosis. To our knowledge, T2DM and hepatic steatosis might share common pathophysiologic mechanism. Insulin resistance was the basis of T2DM and closely related to the pathogenesis of hepatic steatosis [24]. Insulin resistance led to reduction of hepatic glycogen synthesis and an increase of lipogenesis, then promoting hyperglycemia, the deposition of visceral adipocytes and further impaired metabolism [24, 25].

Based on the key role of liver on lipid metabolism, the relationship between liver diseases and lipid profile was investigated in this study. Higher level of HDL-c and lower levels of TC, TG, and LDL-c were observed in SLD-LF group compared with SLD-NLF group. Dyslipidemia was linked to SLD. Several genes （PNPLA3, TM6SF2,

MBOAT7) and transcription factors (SREBP-2, FXR, and LXR9) of lipid metabolism were found involved in susceptibility to hepatic steatosis [26]. Similar results were reported by *Liu et al.* in schistosomiasis japonica patients with liver fibrosis [27]. A negative correlation between LDL-c and LF was also observed in LF patients assessed by FIB-4 [24]. Decreased LDL-c might result from the reduction of synthesis of apolipoprotein B (ApoB) in the liver [29]. Further research is needed to elucidate the mechanisms underlying the relationship between liver fibrosis and lipid levels, as well as the potential implications for the management of patients with liver fibrosis.

In this study, we observed a slight increase in prevalence of nephropathy in T2DM-SLD patients compared to those without SLD. To the best of our knowledge, hepatic steatosis is not only a manifestation of intrahepatic diseases, but also a multi-system disease that is closely associated with multiple extrahepatic diseases such as chronic kidney disease (CKD) and CVD [30, 31]. Moreover, LF significantly increased the prevalence of diabetic nephropathy, which was consistent with the previous findings. The risk of prevalent CKD elevated over 3 times in patients with liver fibrosis [32]. We speculated that stimulated CKD might result from the up-regulated pro-fibrogenic cytokines and low-grade inflammations by steatosis and its progression toward fibrosis.

The prevalence of arterial stiffness and coronary heart disease was higher in SLD-LF group than SLD-NLF group, especially in elder patients (over 50 years old). It was reported that the stage of fibrosis was considered to be the most important determinant of CVD in patients with SLD [33]. Pathologically, LF shared multiple common risk factors with CVD, such as genetic factors, cytokines, inflammation, insulin resistance, angiogenesis, the gut-liver-axis, and endothelia dysfunction [34], and aging was one of the major risk factors that contributed to cardiovascular events [35]. Liver sinusoidal endothelial cell (LSEC) dysfunction played a critical role in the progression of SLD via numerous mechanisms, including the regulation of the inflammatory process, hepatic stellate activation, augmented vascular resistance, and the distortion of microcirculation [36]. It was reported that CVD risk was in parallel with the level of fibrosis. In patients with T2DM and SLD, insulin resistance, production of atherogenic lipids, multiple proinflammatory, prothrombogenic, and vasoactive mediators might result in the development and progression of arterial stiffness, CVD and stroke [37].

Several limitations were included in this study. First, due to an observational and cross-sectional design, although the risk factors for liver fibrosis have been analyzed, we cannot infer a causal relationship between vascular complications and liver fibrosis. Longitudinal data is critical to identify this subset of patients for appropriate follow up and prevention. Second, in addition to the risk factors mentioned, other factors such as lifestyle, medical treatment and genetic predispositions also have an impact on the progression of liver fibrosis and vascular complications. More confounding factors should be taken into account in the future studies. Third, liver biopsy is still the gold standard for diagnosis of SLD and LF. In this study, non-invasive scores were applied to monitor metabolic liver disease. The results should be validated with liver biopsy or imaging techniques in future work in a larger scale of population. Despite these, our study showed decreased lipids levels and increased prevalence of microvascular and macrovascular adverse events in LF patients. So, more emphasis should be put on prevention and management of liver fibrosis and vascular complications in T2DM patients.

Conclusions

In this retrospective study, changes in clinical parameters along with liver disease progression were analyzed in T2DM patients. Hepatic steatosis and fibrosis were common in patients with T2DM and about one-third of the patients had liver fibrosis. In addition, in the presence of steatotic liver disease, patients with liver fibrosis might have a higher risk of vascular complications such as arterial stiffness, stoke and coronary heart disease, especially in patients over 50 years old. So, effective screening strategy and intervention for early detection and prevention of liver fibrosis were essential for T2DM patients. We will track the health status of participants, including the progression of T2DM and liver fibrosis, and how they affect vascular complications in future.

Acknowledgements

We would like to thank all participants in this study.

Author contributions

All authors read and approved the final version of the manuscript. Sun WX, Wang LY, Li L: Conceptualization, Methodology, Writing - Review & Editing. Liu DC, Yang T: Resources, Writing - Original Draft. Zhou ZW, Li D, Zhao ZX, Zhang X: Formal analysis, Investigation.

Funding

This work was supported by National Natural Science Foundation Major International (Regional) Joint Research Program (82320108003), National Natural Science Foundation (82170845, 82000740), the Key Research & Development Program (No.BE2022853) and Medical Key Discipline (ZDXK202203) of Jiangsu Province. This work was funded by the Open Project of Key Laboratory of Environmental Medicine Engineering of Ministry of Education (2024EME001).

Data availability

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The research was in accordance to the Declaration of Helsinki and approved by Zhongda Hospital Affiliated to Southeast University Ethics Committee. The

requirement to obtain informed written consent was waived. Clinical data of patients were protected and anonymous.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 9 July 2024 / Accepted: 23 October 2024
Published online: 05 November 2024

References

1. Global regional, national burden of diabetes. From 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of Disease Study 2021. Lancet. 2023;402(10397):203–34.
2. Miao L, Targher G, Byrne CD, Cao YY, Zheng MH. Current status and future trends of the global burden of MASLD. Trends Endocrinol Metab. 2024;35(8):697–707.
3. Lee CH, Lui DT, Lam KS. Non-alcoholic fatty liver disease and type 2 diabetes: an update. J Diabetes Investig. 2022;13(6):930–40.
4. Forlano R, Stanic T, Jayawardana S, et al. A prospective study on the prevalence of MASLD in people with type-2 diabetes in the community. Cost effectiveness of screening strategies. Liver Int. 2024;44(1):61–71.
5. En Li Cho E, Ang CZ, Quek J, et al. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. Gut. 2023;72(11):2138–48.
6. Seo YG, Polyzos SA, Park KH, Mantzoros CS. Fibrosis-4 Index predicts long-term All-Cause, Cardiovascular and Liver-related mortality in the adult Korean Population. Clin Gastroenterol Hepatol. 2023;21(13):3322–35.
7. Liu Z, Huang H, Xie J, Xu Y, Xu C. Circulating fatty acids and risk of hepatocellular carcinoma and chronic liver disease mortality in the UK Biobank. Nat Commun. 2024;15(1):3707.
8. Croce AC, Ferrigno A, Palladini G, Mannucci B, Vairetti M, Di Pasqua LG. Fatty acids and bilirubin as intrinsic autofluorescence serum biomarkers of drug action in a rat model of liver ischemia and reperfusion. Molecules 2023; 28(9).
9. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. Gut. 2024;73(4):691–702.
10. Ebert T, Widman L, Stenvinkel P, Hagström H. Increased risk for microvascular outcomes in NAFLD-A nationwide, population-based cohort study. J Intern Med. 2023;294(2):216–27.
11. Bril F, Ortiz-Lopez C, Lomonaco R, et al. Clinical value of liver ultrasound for the diagnosis of nonalcoholic fatty liver disease in overweight and obese patients. Liver Int. 2015;35(9):2139–46.
12. Portillo-Sanchez P, Bril F, Maximos M, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes Mellitus and normal plasma aminotransferase levels. J Clin Endocrinol Metab. 2015;100(6):2231–8.
13. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33.
14. Mózes FE, Lee JA, Vali Y, et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(8):704–13.
15. Anstee QM, Berentzen TL, Nitze LM, et al. Prognostic utility of Fibrosis-4 index for risk of subsequent liver and cardiovascular events, and all-cause mortality in individuals with obesity and/or type 2 diabetes: a longitudinal cohort study. Lancet Reg Health Eur. 2024;36:100780.
16. Koehler EM, Schouten JN, Hansen BE, Hofman A, Stricker BH, Janssen HL. External validation of the fatty liver index for identifying nonalcoholic fatty liver disease in a population-based study. Clin Gastroenterol Hepatol. 2013;11(9):1201–4.
17. Ho B, Thompson A, Jorgensen AL, Pirmohamed M. Role of fatty liver index in risk-stratifying comorbid disease outcomes in non-alcoholic fatty liver disease. JHEP Rep. 2023;5(12):100896.
18. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77(5):1797–835.
19. Bellary S, Kyrou I, Brown JE, Bailey CJ. Type 2 diabetes mellitus in older adults: clinical considerations and management. Nat Rev Endocrinol. 2021;17(9):534–48.
20. Agyapong G, Dashti F, Banini BA. Nonalcoholic liver disease: Epidemiology, risk factors, natural history, and management strategies. Ann N Y Acad Sci. 2023;1526(1):16–29.
21. Li Y, Adeniji NT, Fan W, Kunimoto K, Török NJ. Non-alcoholic fatty liver disease and liver fibrosis during aging. Aging Dis. 2022;13(4):1239–51.
22. Wan Y, Li X, Slevin E, et al. Endothelial dysfunction in pathological processes of chronic liver disease during aging. Faseb j. 2022;36(1):e22125.
23. Mittal N, Siddiqi H, Madamba E, et al. A prospective study on the prevalence of at-risk MASH in patients with type 2 diabetes mellitus in the United States. Aliment Pharmacol Ther. 2024;59(12):1571–8.
24. Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. Nat Rev Endocrinol. 2018;14(2):99–114.
25. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol. 2022;10(4):284–96.
26. Foster C, Gagnon CA, Ashraf AP. Altered lipid metabolism and the development of metabolic-associated fatty liver disease. Curr Opin Lipidol. 2024;35(4):200–7.
27. Liu Y, Zhang P, Li J, et al. Association between serum lipid profile and liver fibrosis in patients infected with Schistosoma Japonicum. Parasit Vectors. 2022;15(1):268.
28. Fujihara Y, Hamanoue N, Yano H, et al. High sex hormone-binding globulin concentration is a risk factor for high fibrosis-4 index in middle-aged Japanese men. Endocr J. 2019;66(7):637–45.
29. Jaafar RF, Hajj Ali AM, Zaghal AM, et al. Fibroscan and low-density lipoprotein as determinants of severe liver fibrosis in diabetic patients with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol. 2019;31(12):1540–4.
30. Bilson J, Mantovani A, Byrne CD, Targher G. Steatotic liver disease, MASLD and risk of chronic kidney disease. Diabetes Metab. 2024;50(1):101506.
31. Lee HH, Lee HA, Kim EJ, et al. Metabolic dysfunction-associated steatotic liver disease and risk of cardiovascular disease. Gut. 2024;73(3):533–40.
32. Mantovani A, Turino T, Lando MG, et al. Screening for non-alcoholic fatty liver disease using liver stiffness measurement and its association with chronic kidney disease and cardiovascular complications in patients with type 2 diabetes. Diabetes Metab. 2020;46(4):296–303.
33. Tamaki N, Kurosaki M, Takahashi Y, et al. Liver fibrosis and fatty liver as independent risk factors for cardiovascular disease. J Gastroenterol Hepatol. 2021;36(10):2960–6.
34. Ismaiel A, Dumitraşcu DL. Cardiovascular risk in fatty liver disease: the Liver-Heart Axis-Literature Review. Front Med (Lausanne). 2019;6:202.
35. Wagner JUG, Tombor LS, Malacarne PF, et al. Aging impairs the neurovascular interface in the heart. Science. 2023;381(6660):897–906.
36. Velliou RI, Legaki AI, Nikolakopoulou P, Vlachogiannis NI, Chatzigeorgiou A. Liver endothelial cells in NAFLD and transition to NASH and HCC. Cell Mol Life Sci. 2023;80(11):314.
37. Ma CX, Ma XN, Guan CH, Li YD, Mauricio D, Fu SB. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. Cardiovasc Diabetol. 2022;21(1):74.

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