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Type 2 Diabetes Subtypes and Their Role in Metabolic Liver Disease and Fibrosis Progression

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Background: The relationship between different subgroups of type 2 diabetes (T2D) and the progression of metabolic dysfunction-associated steatotic liver disease (MASLD) and liver fibrosis has not been thoroughly studied. This study aims to determine the association between T2D subgroups and the risk of developing advanced liver fibrosis using the Fibrosis-4 (FIB-4) index, a non-invasive marker for assessing liver fibrosis risk.

Material/Methods: A total of 1205 patients with T2D were categorized into 4 distinct subgroups: severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD), and mild age-related diabetes (MARD). The FIB-4 index was calculated for each patient to estimate the degree of liver fibrosis, with the following cutoff points: <1.3 indicating no or mild fibrosis, 1.3-2.67 suggesting moderate fibrosis, and >2.67 indicating advanced fibrosis (F3-F4). Logistic regression was used to compare the odds of advanced fibrosis across these subgroups.

Results: The SIRD subgroup exhibited significantly higher odds of advanced liver fibrosis (F3-F4), compared with the other subgroups, as indicated by elevated FIB-4 scores ($P<0.05$). In contrast, the SIDD and MOD subgroups had lower odds of advanced fibrosis, while the MARD subgroup showed an intermediate association.

Conclusions: The findings suggest that the FIB-4 index, as a noninvasive assessment tool, effectively stratifies liver fibrosis risk among different T2D subgroups. This stratification can inform more personalized management strategies for patients with MASLD, underscoring the importance of accounting for the heterogeneity within T2D in clinical assessments of liver fibrosis risk.

Keywords: Diabetes Mellitus, Type 2 • Insulin Resistance • Liver Diseases

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Introduction

Type 2 diabetes represents a significant public health problem in Mexico and worldwide [1,2]. Approximately 536 million people globally have type 2 diabetes, and the number is expected to increase in the coming decades [2]. Although the main complications of type 2 diabetes are cardiovascular events and chronic kidney disease, liver damage due to metabolic dysfunction, that is, chronic glycemic control issues, has become more involved in recent years [3,4].

Historically, diabetes has been classified into type 1 (autoimmune origin), type 2 (chronic insulin resistance), and some subtypes, such as latent autoimmune diabetes in adults [3]. Nonetheless, a novel subgroup classification for type 2 diabetes has been proposed and validated in the Mexican population [3,5,6]. Based on the hypothesis that certain subgroups of patients potentially respond better to specific treatments, patients with type 2 diabetes have been subclassified into 4 subgroups: severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD), and mild age-related diabetes (MARD) [5]. The Encuesta Nacional de Salud y Nutrición 2020 data report a high prevalence of SIDD (41.25%), followed by MOD (33.60%), MARD (14.72%), and SIRD (10.43%) [5]. Generally, using these classification models, patients with SIRD have a higher frequency of diabetic kidney disease, while patients with SIDD have a higher frequency of diabetic retinopathy. Unfortunately, there is no reported data on the frequency of hepatic steatosis or chronic liver failure associated with these new subgroups of type 2 diabetes [3,5].

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as the leading cause of chronic liver disease globally, reflecting its growing prevalence and significant impact on public health [1,4]. MASLD is characterized by the accumulation of fat in the liver that is not related to alcohol consumption. It represents a broad spectrum of liver conditions, beginning with simple hepatic steatosis, in which fat accumulates in the liver cells without significant inflammation or fibrosis [7]. However, MASLD can progress to more severe forms, including non-alcoholic steatohepatitis, which is marked by inflammation and liver cell damage in addition to fat accumulation [7,8]. If left untreated, non-alcoholic steatohepatitis can advance to liver fibrosis, cirrhosis, and even hepatocellular carcinoma, representing a significant escalation in disease severity and risk of mortality [8].

The pathophysiology of MASLD is closely linked with metabolic dysfunctions, primarily insulin resistance, a hallmark of type 2 diabetes [1]. Insulin resistance increases free fatty acids in the bloodstream, promoting fat accumulation in the liver. Additionally, hyperglycemia and hyperinsulinemia in diabetes exacerbate liver inflammation and fibrosis, making MASLD a common comorbidity in patients with diabetes [7,8]. Nearly 30% of patients with type 2 diabetes are estimated to have MASLD, and this dual diagnosis significantly increases the risk of developing more advanced liver diseases, such as cirrhosis and liver cancer [1,7,8].

The clinical burden of MASLD is considerable, not only because of its potential to progress to severe liver disease but also due to its association with other complications of diabetes, including cardiovascular disease and chronic kidney disease. Despite the well-known microvascular and macrovascular complications of diabetes, liver-related complications, particularly liver fibrosis, remain under-recognized, contributing to a growing but often overlooked global healthcare burden [9-11]. Identifying and managing MASLD in patients with diabetes is crucial, given the silent progression of liver fibrosis and the limited treatment options available at advanced stages [9,12].

Nonetheless, during the progression of type 2 diabetes, MASLD can remain silent and asymptomatic until clinical signs of advanced liver fibrosis emerge [9]. Given the variability in how MASLD develops and progresses among different type 2 diabetes subgroups, this study aims to evaluate the prevalence and clinical characteristics liver fibrosis. Specifically, we seek to determine how the distinct clusters of adult-onset diabetes – SIRD, SIDD, MOD, and MARD – affect MASLD development and the progression of liver fibrosis. Understanding these differences could provide insights into the tailored management of MASLD in patients with diabetes.

Material and Methods

Ethics Statement

The present study was approved by the Hospital General Dr. Manuel Gea González (HGDMGG) Research Committee and Research Ethics Committee (ref. 14-68-2023). Patient anonymity was guaranteed, following the 1975 Declaration of Helsinki. All patients or their guardians provided written informed consent for using their medical information for teaching, research, and publication purposes.

Study Design and Patient Selection

This retrospective observational study, which used medical records from the Outpatient Clinic of Internal Medicine from January 2018 to December 2023, was conducted at the HGDMGG and followed the STROBE guidelines for observational studies.

Inclusion and Exclusion Criteria

The inclusion criteria were patients with type 2 diabetes diagnosed at or referred to our outpatient clinic. The exclusion

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criteria were determined using detailed medical files and the ICD-10 coding system, ensuring the exclusion of patients with an average daily alcohol consumption of more than 30 g/day (ICD-10 code Z72.1), history of alcoholic hepatitis (ICD-10 code K70.1), history of hepatitis B (ICD-10 code B18.1) or C (ICD-10 code B18.2), current antiretroviral therapy (ICD-10 code Z79.899) or treatment for tuberculosis (ICD-10 codes A15-A19), history of systemic lupus erythematosus (ICD-10 code M32) or rheumatoid arthritis (ICD-10 code M06), history of autoimmune-related liver diseases (ICD-10 code K75.4), and any non-diabetic glomerulopathy (ICD-10 codes N00-N08).

Diagnosis and Categorization of Patients

MASLD was evaluated using the fatty liver index (FLI), a non-invasive marker calculated using the formula:
FLI=ey/(1+ey)×100, where y=0.953×Ln (triglycerides, mg/dL)+0.139×body mass index (BMI; kg/m^2)+0.718×Ln (GGT, U/L)+0.053×waist circumference, cm-15.745.
A FLI score of >60 indicated the presence of MASLD [13].

Liver fibrosis was assessed using the FIB-4 index, which was calculated using the following formula: Age×AST (aspartate aminotransferase; IU/L)/platelet count (×10^9/L)×√ALT (alanine aminotransferase; IU/L) [14]. The following cutoff points were considered for liver fibrosis: <1.299 indicated F0, 1.3 to 2.66 indicated F1-F2, and >2.67 indicated F3-F4 [13,14].

The 4-diabetes subgroup estimation classified the patients as SIDD, SIRD, MOD, and MARD using an electronic-based application previously developed by Bello-Chavolla et al, available at https://uiem.shinyapps.io/diabetes_clusters_app/ [5]. This application uses clinical and biochemical data to categorize patients into specific diabetes subgroups. The variables used for clustering included:

- **BMI:** Calculated as weight in kilograms divided by height in meters squared (kg/m^2).
- **Height:** Measured in centimeters (cm).
- **Age at diabetes onset:** Recorded as the patient's age in years when diagnosed with type 2 diabetes.
- **Hemoglobin A1c (HbA1c):** Expressed as a percentage (%), indicating average blood glucose levels over the past 3 months.
- **Fasting glucose:** Measured in milligrams per deciliter (mg/dL).
- **Fasting triglycerides:** Measured in milligrams per deciliter (mg/dL).
- **High-density lipoprotein cholesterol (HDL-C):** Measured in milligrams per deciliter (mg/dL).
- **Waist circumference:** Measured in centimeters (cm).
- **Sex:** Recorded as male or female.

The electronic-based application uses these inputs to calculate the probability of a patient belonging to 1 of the 4 clusters: SIDD, SIRD, MOD, or MARD.

While several classification systems have been proposed, including a 5-cluster model, we chose to use the 4-cluster classification explicitly developed for the Mexican population by Bello-Chavolla et al. This model has been validated within this demographic and considers the unique clinical and biochemical characteristics prevalent in the population we studied, which can differ from those in other populations where the 5-cluster model is more commonly applied.

Biochemical Analysis

All biochemical measurements were conducted at the central laboratory of HGDMGG. Blood samples were collected after at least 10 h of fasting. The measured parameters included serum levels of AST, ALT, gamma-glutamyl transpeptidase (GGT), fasting glucose, HbA1c, total cholesterol, HDL-C, and triglycerides, analyzed using the DxC 700 AU Chemistry Analyzer (Beckman Coulter, Fullerton, CA). The Sampson et al formula calculated low-density lipoprotein cholesterol (LDL-C) [15].

Statistical Analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, NY, USA). The data were first screened for outliers, and normality was assessed using the Shapiro-Wilk test. Continuous variables were reported as mean±standard deviation for normally distributed data or as median (interquartile range) for non-normally distributed data. Categorical variables were expressed as frequencies (percentages).

Comparisons between the diabetes subgroups were made using one-way ANOVA for normally distributed continuous variables or the Kruskal-Wallis test for non-normally distributed continuous variables. The chi-square test was used for categorical variables. Binary logistic regression was used to evaluate the association between diabetes subgroups and advanced liver fibrosis (F3-F4) as determined by the FIB-4 index. The models were adjusted for potential confounders, including age, sex, hypertension, and antidiabetic medication use. Odds ratios (ORs) with 95% CIs were reported, and a *P* value of ≤0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Population

A total of 1205 patients with type 2 diabetes, without any known liver disease, were included in the study. The mean age of the patients was 59.59±14.09 years, with 67.9% being women. The mean BMI was 28.64±6.31 kg/m^2, and the median waist circumference was 89 (80-99) cm. Additionally, 51.8% had hypertension, and the median duration of type 2 diabetes

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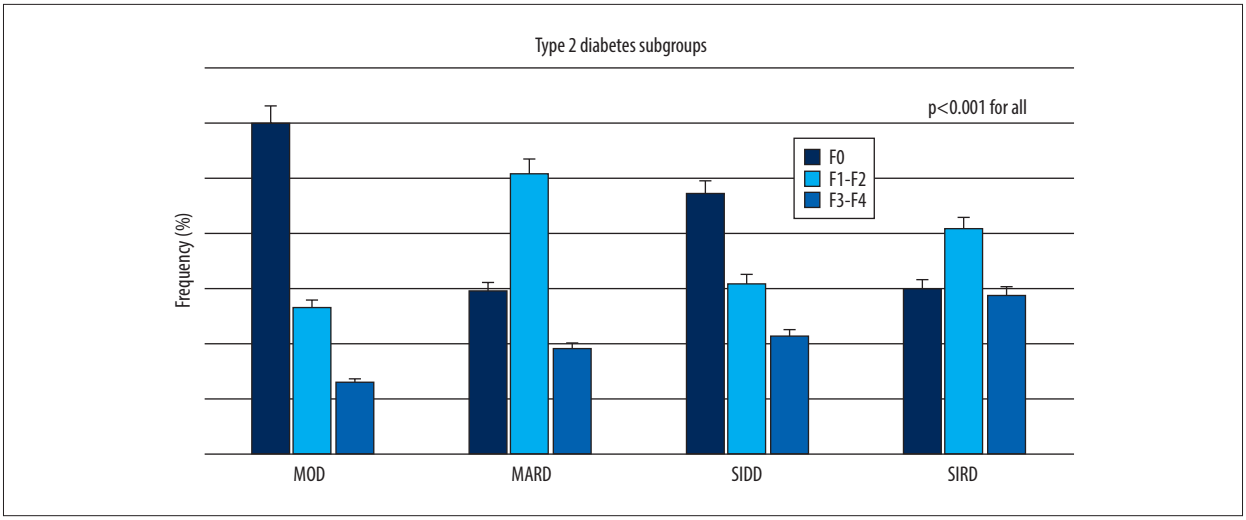

Figure 1. Type 2 diabetes subgroups distribution according to liver fibrosis stages using the Fibrosis-4 index. *P* value: chi-square test. MOD – mild obesity-related diabetes; MARD – mild age-related diabetes; SIDD – severe insulin-deficient diabetes; SIRD – severe insulin-resistant diabetes.

since diagnosis was 7 (3-14) years. The distribution of diabetes duration was as follows: 37.0% were diagnosed within 0-4 years, 25.1% within 5-9 years, and 37.8% for >10 years. Regarding medication, 80.2% were on metformin, 36.7% were using basal subcutaneous insulin, 10.8% were taking SGLT-2 inhibitors, 13.2% were on DPP-4 inhibitors, 1.2% used GLP-1 agonists, 1.6% were taking pioglitazone, 10.5% were on sulfonylureas, 20.0% were taking fibrates, and 50.9% were on statins.

Biochemical Characteristics

The median fasting glucose level was 124 (100-166) mg/dL, with 48.5% of patients having levels above 126 mg/dL. The mean HbA1c was 7.76±2.04%, with 44.0% having HbA1c below 7%, 20.9% between 7% and 7.99%, 12.2% between 8% and 8.99%, and 22.9% above 9%. The median serum creatinine was 0.88 (0.70-1.04) mg/dL. Screening for diabetic kidney disease showed a median microalbuminuria of 11.02 (2.45-50.40) mg/24 h, with 69.2% having microalbuminuria <30 mg/24 h, 20.8% between 30 and 299 mg/24 h, and 10.0% >300 mg/24 h. The mean total cholesterol level was 176±50 mg/dL, HDL-C was 43±12 mg/dL, mean LDL-C was 94±40 mg/dL, and the median triglyceride level was 164 (116-229) mg/dL. The median FLI was 61 (35-83), with 48.4% having a FLI <60.

Distribution of Diabetes Subgroups

Among the study population, 28.8% of patients were classified as SIDD, 7.7% as SIRD, 33.9% as MOD, and 29.6% as MARD.

Prevalence and Severity of Liver Fibrosis

Figure 1 illustrates the frequency of liver fibrosis across the different diabetes subgroups. The SIRD subgroup had the highest prevalence of advanced liver fibrosis among all the subgroups. The clinical and biochemical characteristics of patients according to their diabetes subgroup are summarized in **Table 1**. Since parameters such as age, age at diabetes diagnosis, waist circumference, BMI, triglycerides, and HDL-C were used to define the diabetes subgroups, significant differences were expected. Although patients with SIRD had a higher prevalence of hypertension, it was not statistically significant. Notably, metformin use was significantly lower in patients with SIDD (68.6%) than in other groups (*P*<0.001).

Association Between Diabetes Subgroups and MASLD

The frequency of MASLD varied significantly among the different subgroups: 80.6% in SIRD, 61.5% in MOD, 57.6% in SIDD, and 26.9% in MARD (*P*<0.001).

Association Between Diabetes Subgroups and Liver Fibrosis

The FIB-4 index showed significant variation across the subgroups, indicating liver stiffness. Patients in the SIRD group had a higher percentage of advanced fibrosis (*P*<0.001). **Figure 2** displays the crude and adjusted associations of type 2 diabetes subgroups with advanced liver fibrosis, using MOD as the reference group. After logistic regression analysis, MARD (OR=1.933 [95%CI 1.202-3.108]), SIDD (OR=2.169 [95%CI 1.363-3.452]), and SIRD (OR=3.526 [95%CI 1.824-6.817]) were associated with increased odds of advanced liver fibrosis.

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Table 1. Clinical and biochemical characteristics of the diabetes subgroups.

	Diabetes subgroups				*p* value
	MOD (n=408)	MARD (n=357)	SIDD (n=347)	SIRD (n=93)	
Female sex (%)	70.1	63.9	65.4	82.8	0.003
Age (years)	50.7±12.6	68.5±9.9	58.6±13.2	68.5±11.1	<0.001
BMI (kg/m^2)	30.73±7.11	25.30±3.05	28.31±6.19	33.60±5.43	<0.001
BMI categories (%) <25 25-29.9 >30	 18.1 35.8 46.1	 50.4 43.7 5.9	 34.3 30.8 34.9	 5.4 7.5 87.1	<0.001
Waist circumference (cm)	91 (83-104)	84 (78-90)	89 (81-101)	92 (89-102)	<0.001
Duration of type 2 diabetes (years)	6 (2-15)	6 (2-11)	10 (5-17)	6 (3.5-11)	<0.001
Duration of type 2 diabetes (%) 0-4 years 5-9 years >10 years	 44.4 18.4 37.3	 40.1 30.8 29.1	 25.4 25.4 49.3	 36.6 32.3 31.2	<0.001
Hypertension (%)	47.5	54.2	51.7	61.3	0.068
Metformin (%)	81.9	87.1	68.6	89.2	<0.001
Subcutaneous insulin (%)	36.3	21.3	57.3	20.4	<0.001
SGLT-2i (%)	11.3	9.5	11.5	10.8	0.828
DPP-4i (%)	15.7	9.2	15.6	8.6	0.015
GLP-1 (%)	2.5	0.6	0.6	1.1	0.058
Pioglitazone (%)	2.5	1.4	0.9	1.1	0.339
Sulfonylureas (%)	5.4	14.3	11.5	15.1	<0.001
Fibrates (%)	19.3	18.8	22.4	17.7	0.623
Statins (%)	49.6	46.4	60.3	36.8	<0.001
Fasting glucose (mg/dL)	123±47	123±41	209±99	122±31	<0.001
Fasting glucose >126 mg/dL (%)	33.3	37.5	81.0	36.6	<0.001
Hemoglobin A1c (%)	6.80±0.92	6.61±0.82	10.38±1.66	6.47±0.80	<0.001
HbA1c categories (%) HbA1c <7% HbA1c 7-7.9% HbA1c 8-8.9% HbA1c >9%	 56.4 31.4 11.5 0.7	 66.4 27.5 5.6 0.6	 0.0 0.3 22.2 77.5	 70.2 27.4 2.4 0.0	<0.001
Serum creatinine (mg/dL)	0.84 (0.67-1.04)	0.89 (0.73-1.03)	0.88 (0.70-1.07)	0.90 (0.76-1.12)	0.066
Microalbuminuria (mg/24 h)	13.0 (3.1-60.2)	4.4 (1.3-16.3)	17.6 (4.3-123)	7.1 (2.1-23)	<0.001
Microalbuminuria stages (%) <30 mg/24 h 30-299 mg/24 h >300 mg/24 h	 65.1 23.8 11.1	 81.8 13.2 4.9	 59.2 26.5 14.3	 76.9 15.4 7.7	<0.001

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Table 1 continued. Clinical and biochemical characteristics of the diabetes subgroups.

	Diabetes subgroups				*p* value
	MOD (n=408)	MARD (n=357)	SIDD (n=347)	SIRD (n=93)	
Total cholesterol (mg/dL)	175±50	170±45	184±56	173±46	0.005
Total cholesterol categories (%)					0.002
<150 mg/dL	31.1	35.6	25.1	36.6	
151-200 mg/dL	40.7	38.9	36.3	31.2	
>200 mg/dL	28.2	25.5	38.6	32.3	
HDL-C (mg/dL)	43±12	44±11	42±12	44±12	0.080
LDL-C (mg/dL)	94±40	90±39	97±42	93±38	0.128
LDL categories (%)					0.421
<70 mg/dL	30.9	34.7	25.6	29.0	
71-100 mg/dL	27.0	26.1	30.8	28.0	
101-130 mg/dL	24.3	22.4	22.8	26.9	
>130 mg/dL	17.9	16.8	20.7	16.1	
Triglycerides (mg/dL)	166 (115-233)	151 (111-203)	188 (125-260)	148 (111-198)	<0.001
Triglycerides >150 mg/dL (%)	60.3	51.5	65.1	48.4	<0.001
AST (U/L)	26 (20-38)	27 (21-38)	25 (18-39)	28 (21-41)	0.409
ALT (U/L)	26 (17-38)	24 (17-35)	25 (17-36)	25 (16-32)	0.741
GGT (U/L)	39 (21-78)	35 (22-70)	42 (23-89)	31 (18-70)	0.040
Albumin (g/dL)	3.8 (3.3-4.1)	3.9 (3.4-4.2)	3.7 (3.1-4.1)	3.9 (3.5-4.1)	0.001
Fatty liver index	65.87±26.92	41.96±22.73	61.77±27.67	74.24±19.92	<0.001
Fatty liver index >60 (%)	61.5	26.9	57.6	80.6	<0.001
FIB-4 stages (%)					<0.001
F0	60.0	29.7	47.3	30.1	
F1-F2	26.7	51.0	31.1	40.9	
F3-F4	13.2	19.3	21.6	29.0	

MARD – mild age-related diabetes; MOD – mild obesity-related diabetes; SIDD – severe insulin-deficient diabetes; SIRD – severe insulin-resistant; BMI – body mass index; SGLT-2i – sodium glucose cotransporter 2 inhibitors; DPP-4i – dipeptidyl peptidase 4 inhibitors; GLP-1 – glucagon-like peptide-1 agonists; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; AST – aspartate aminotransferase, ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; FIB-4 index – fibrosis-4 index. Variables are shown as mean±standard deviation or median (interquartile range) or percentages. *P* value: ANOVA test, Kruskal-Wallis test, or chi-square test.

Discussion

In this study, we identified significant differences in the prevalence and severity of MASLD and liver fibrosis among the various type 2 diabetes subtypes. Our findings demonstrate that advanced liver fibrosis was most prevalent in the SIRD subgroup, followed by SIDD, MARD, and MOD, which had the lowest prevalence. These results suggest that the risk of developing severe liver complications varies considerably across type 2 diabetes subgroups, highlighting the need for tailored clinical management strategies.

Our study is the first to report such variability in MASLD presentation and progression across different type 2 diabetes clusters, providing new insights into the heterogeneity of the disease [16]. These findings are consistent with those of Ahlqvist et al, who used a data-driven cluster analysis to categorize type 2 diabetes patients and identified distinct clinical

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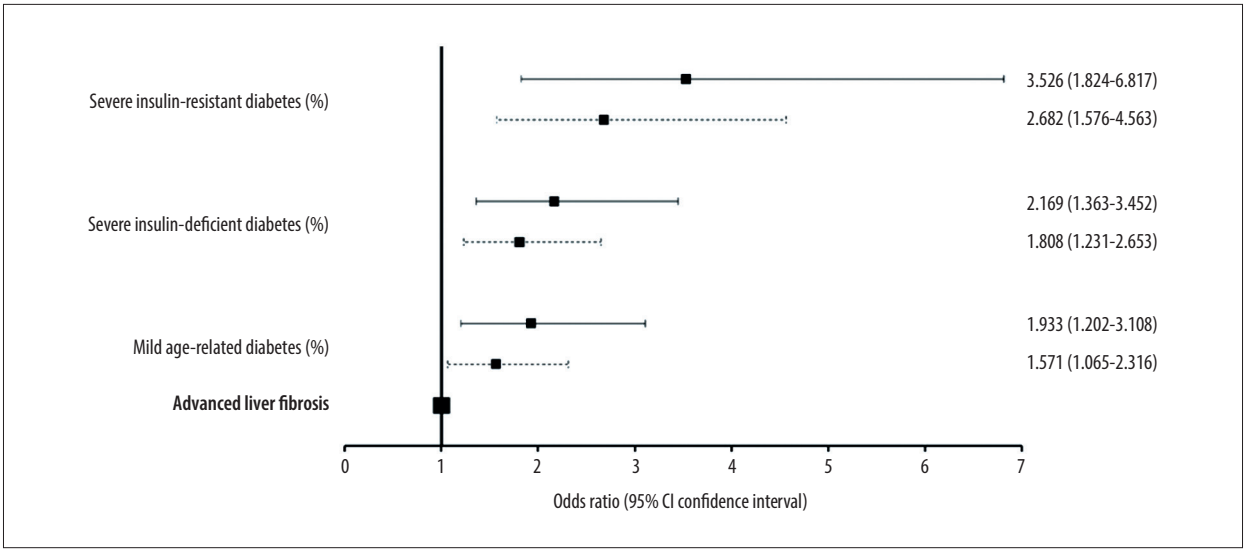

Figure 2. Association of type 2 diabetes subgroups with advanced liver fibrosis. Logistic regression analysis adjusted by hypertension, metformin, subcutaneous insulin, sodium-glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 agonists, pioglitazone, sulfonylureas, fibrates, statins, serum creatinine, and microalbuminuria. Mild obesity-related diabetes was considered as the reference group. Dashed lines represent the univariate model, and solid lines represent the multivariate model.

characteristics and risks for complications within each subgroup [3]. Precisely, our identification of the SIRD subgroup as having a significantly higher risk for advanced liver fibrosis aligns with Ahlqvist's observation of increased risks for complications, such as diabetic kidney disease, in this subgroup. Liver fibrosis and kidney disease share underlying pathogenic mechanisms, including insulin resistance and chronic inflammation, which further support the link between the SIRD subgroup and severe liver disease.

Moreover, our findings are supported by a recent study by Antonio-Villa et al (2024), which explored the association between type 2 diabetes subgroups and liver-related outcomes. Their study also found that the SIRD subgroup had a higher propensity for developing severe liver disease, including cirrhosis, underscoring the importance of recognizing type 2 diabetes heterogeneity in managing MASLD [6]. Our study's use of the 4-cluster classification, validated explicitly for the Mexican population by Bello-Chavolla et al [5], enhances the relevance of our findings to this demographic. This classification effectively captures the clinical heterogeneity of type 2 diabetes, particularly in subgroups SIRD and SIDD, which are crucial for understanding MASLD and liver fibrosis progression.

The pathophysiological basis for these findings lies in the impaired insulin function in individuals with insulin resistance, particularly in the SIRD subgroup [16]. Insulin resistance leads to uninhibited hepatic glucose production and increased lipid synthesis, contributing to liver fibrosis [17,18].

MASLD is significantly more prevalent in patients with type 2 diabetes than in the general population. Overall, between 50% and 75% of patients with diabetes have MASLD, with variations depending on ethnic origin [1,18]. Conversely, the prevalence of diabetes is also higher in patients with MASLD than in the general population. An observational study detected MASLD in 63.3% of 929 Korean patients with diabetes attending a university diabetes clinic [19]. The prevalence of MASLD appears to be related to glycemic status, being detected in 25.6% of patients with normal fasting glucose, 56.2% of patients with impaired fasting glucose, and 68% of patients with diabetes (defined as fasting blood glucose ≥126 mg/dL) [20]. Although type 2 diabetes and liver steatosis are related, it is important to note that diabetes increases the risk of steatosis, fibrosis, cirrhosis, and hepatocellular carcinoma. On the other hand, MASLD aggravates insulin resistance, which increases the risk of dyslipidemia, makes diabetes treatment more complex, and increases cardiovascular risk [21].

Liver fibrosis is a dynamic process involving the continuous activation of the healing response due to recurrent liver damage, resulting in excessive deposition of fibrillar extracellular matrix in the liver and eventually leading to cirrhosis if the cause of the damage is not removed [18,22]. Insulin resistance, hyperglycemia, and diabetes can cause hepatic fibrosis through interrelated mechanisms. Insulin resistance increases the accumulation of lipid deposits in the liver (steatosis), leading to a chronic inflammatory state and the activation of hepatic stellate cells [21]. These cells are primarily responsible for producing extracellular matrix and collagen, key components of hepatic fibrosis [21].

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Hyperglycemia further contributes to oxidative stress and the production of reactive oxygen species, which damage hepatocytes and promote the release of inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-6, and transforming growth factor-beta. These cytokines further activate hepatic stellate cells, perpetuating the cycle of inflammation and fibrosis [17,18,21,22].

Additionally, diabetes exacerbates these processes through inadequate glycemic control [17]. Persistent hyperglycemia increases the formation of advanced glycation end products, which interact with their receptors on liver cells, amplifying inflammatory and fibrogenic responses. These products and their interactions promote the activation of hepatic stellate cells and collagen production, contributing to fibrosis progression in several target organs, not only in the liver [21]. Thus, diabetes and MASLD are independent risk factors for cardiovascular disease and all-cause mortality [7,12,21]. Yet, during the progression of diabetes, MASLD can remain unnoticed and asymptomatic until the patient shows signs of advanced liver fibrosis. Insulin resistance promotes fibrosis progression in metabolic-associated steatohepatitis through a combination of mechanisms [23,24]. Our findings highlight the significance of distinguishing between distinct clusters of type 2 diabetes in patients with MASLD to potentially assess the severity of liver disease and the progression of liver fibrosis [4,11]. The various subgroups or clusters manifest differing degrees of seriousness in MASLD and the advancement of liver fibrosis, indicating that the risk of developing MASLD is not solely attributable to type 2 diabetes but is associated with each specific cluster.

This study has several strengths, including a large sample size, which enhances the generalizability of the findings. The use of validated noninvasive markers, such as the FIB-4 index and the FLI, is another key strength, as these tools are widely recognized for their accuracy in assessing liver fibrosis and steatosis, without the need for invasive procedures, such as liver biopsies. Additionally, the focus on the Mexican population, using a diabetes subgroup classification validated explicitly for this demographic, ensures that the study's findings are particularly relevant to this group. The study's emphasis on the differences in liver fibrosis progression among various type 2 diabetes subgroups provides valuable insights that can inform more personalized approaches to managing liver disease in diabetic patients.

Nevertheless, the study also has limitations. The absence of liver biopsies, which are considered the criterion standard for diagnosing liver fibrosis and steatosis, is a significant limitation. While noninvasive markers like FIB-4 and FLI are reliable, they cannot fully replace the detailed histological information provided by biopsies. The retrospective design of the study can introduce selection bias and limit the ability to establish causal relationships between diabetes subgroups and liver fibrosis progression. Additionally, the study's cross-sectional nature restricts the ability to observe changes in liver fibrosis and diabetes management over time, underscoring the need for future longitudinal research. Finally, while the study's focus on a Mexican cohort is a strength, it also limits the generalizability of the findings to other populations, as the diabetes subgroup classification used may not be directly applicable to different demographic groups.

Conclusions

This study demonstrates that advanced liver fibrosis is most prevalent in patients with SIRD, followed by those with SIDD and MARD, while being least common in those with MOD. These findings highlight the heterogeneity in the development and progression of MASLD among different type 2 diabetes subgroups, indicating that the risk of liver fibrosis is not evenly distributed. Classifying patients into specific subgroups is crucial for accurately assessing liver disease severity and the risk of fibrosis progression, which can significantly affect personalized management and treatment strategies. Recognizing these differences enables clinicians to identify high-risk patients and tailor interventions more effectively, ultimately improving clinical outcomes. Since this is the first study to report such variability in type 2 diabetes clusters concerning MASLD, further research is needed to validate these findings and explore the underlying mechanisms driving these differences.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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