



OPEN ACCESS

EDITED BY

Roxana Adriana Stoica,
Carol Davila University of Medicine and
Pharmacy, Romania

REVIEWED BY

Mousumi Chaudhury,
Agricultural Research Service (USDA),
United States
Maroof Alam,
University of Michigan, United States
Mostafa Vaghari-Tabari,
Tabriz University of Medical Sciences, Iran

*CORRESPONDENCE

Mingchen Zhang
✉ zhangmc1015@wmu.edu.cn

RECEIVED 06 May 2025

ACCEPTED 12 August 2025

PUBLISHED 29 August 2025

CITATION

Liu J, Wang Y, Zhou X, Wen Z, Chen Y, Sun Y,
Su S, Lin W, Shen R, Sun X, Li H, Yu X and
Zhang M (2025) $ISI_{matsuda}$ as a potential
predictor of metabolic
dysfunction-associated steatotic liver disease
in patients with type 2 diabetes mellitus.
Front. Med. 12:1623808.
doi: 10.3389/fmed.2025.1623808

COPYRIGHT

© 2025 Liu, Wang, Zhou, Wen, Chen, Sun, Su,
Lin, Shen, Sun, Li, Yu and Zhang. This is an
open-access article distributed under the
terms of the [Creative Commons Attribution
License \(CC BY\)](#). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that the
original publication in this journal is cited, in
accordance with accepted academic
practice. No use, distribution or reproduction
is permitted which does not comply with
these terms.

$ISI_{matsuda}$ as a potential predictor of metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus

Jing Liu^{1,2}, Yueqiu Wang², Xinghang Zhou³, Zaixin Wen³,
Yu Chen³, Yiqiong Sun², Shuaiying Su⁴, Weiwei Lin⁵,
Ruiting Shen², Xiaoyu Sun³, Hongru Li³, Xia Yu³ and
Mingchen Zhang^{1,2*}

¹Cixi Biomedical Research Institute, Wenzhou Medical University, Wenzhou, Zhejiang, China,

²Department of Endocrinology and Metabolism, Ningbo No.2 Hospital, Ningbo, Zhejiang, China,

³College of Information Science and Engineering, Northeastern University, Shenyang, Liaoning, China,

⁴College of Medicine, Shaoxing University, Shaoxing, Zhejiang, China, ⁵College of Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

Background: This study aimed to determine the most efficacious insulin resistance (IR) indices to predict metabolic dysfunction-associated steatotic liver disease (MASLD) in patients with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study included 1,587 patients with T2DM. MASLD was defined by abdominal ultrasound findings. Liver fibrosis risk was assessed with FIB-4. All participants underwent a 100 g standard steamed bread meal test. We analyzed basal IR indices (HOMA-IR, QUICKI, IAI, Bennett ISI) and post-stimulation IR indices ($ISI_{matsuda}$, $ISI_{0,120}$) to explore their associations with MASLD and liver fibrosis.

Results: Participants were categorized into four groups according to IR indices quartiles. Among post-stimulation IR indices, MASLD detection rates in $ISI_{matsuda}$ Q1–Q4 groups were 65.7, 54.2, 37.0, and 22.2%, respectively. Logistic regression analysis revealed significantly increased odds ratios (ORs) for MASLD in $ISI_{matsuda}$ Q1–Q3 groups compared to the Q4 group (OR = 3.63, 2.53, and 1.53, respectively; all $p < 0.05$). Similar results were observed across other IR indices (all $p < 0.05$). There were no statistically significant differences in the detection rates of liver fibrosis or the ORs among the quartile groups of the IR indices (all $p > 0.05$). ROC curve analysis showed that $ISI_{matsuda}$ had superior predictive power for MASLD in patients with T2DM (AUC = 0.701). Based on these findings, a risk prediction model for MASLD in the T2DM population was constructed using age, body mass index (BMI), alanine aminotransferase (ALT), triglycerides (TG), and 2-h postprandial C-peptide (2 h CP).

Conclusion: Among the IR indices, $ISI_{matsuda}$ demonstrated the strongest correlation and highest predictive value for MASLD in T2DM.

KEYWORDS

insulin resistance, Matsuda index, metabolic dysfunction associated steatotic liver disease, type 2 diabetes mellitus, liver fibrosis

1 Introduction

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) globally continues to rise, now exceeding 30%, with approximately 11% of cases progressing to liver fibrosis (1–3). Among those with type 2 diabetes mellitus (T2DM), the incidence of MASLD ranges from 50 to 80%, with 17 to 36% of patients experiencing progressive liver fibrosis (4–6).

Insulin resistance (IR) is recognized as a central pathophysiological mechanism in the development of both T2DM and MASLD (7). IR not only constitutes the fundamental pathogenic basis of T2DM but also persists throughout the entire course of the disease. IR promotes hepatic *de novo* lipogenesis (DNL) and enhances lipolysis, leading to increased influx of free fatty acids (FFA) into the liver, which drives the development and progression of steatotic liver disease (8). The progression from IR to “second hits” has become the widely accepted framework for the pathogenesis of fatty liver disease. Patients with diabetes frequently have coexisting fatty liver disease, which progresses more rapidly in this population. However, the status of IR, especially post-stimulation IR, in patients with both diabetes and fatty liver disease remains underexplored. As some antidiabetic agents can improve IR, accurately assessing IR in this high-risk population not only helps elucidate underlying pathophysiological mechanisms but also facilitates more precise therapeutic decision-making.

The hyperinsulinemic euglycemic clamp (HEC) technique is regarded as the gold standard for assessing IR; however, its clinical application is limited by its invasiveness, high cost, and complex procedure (9). Clinically, IR assessment indices are categorized into basal indices and post-stimulation indices. Basal indices encompass the homeostasis model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), Lee index (IAI), and Bennett insulin sensitivity index (Bennett ISI), while post-stimulation indices include the Matsuda index (ISI_{Matsuda}) and Gutt index ($ISI_{0,120}$) (10, 11). Current research primarily focuses on fasting IR, particularly the association between HOMA-IR and hepatic steatosis, with relatively little attention paid to post-stimulation IR. Furthermore, the relationship between IR and the progression of liver fibrosis remains unclear. This study aims to investigate the relationship between IR indices and the risk of MASLD and liver fibrosis in patients with T2DM.

2 Methods

2.1 Subjects of study

This cross-sectional study adhered to the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of Ningbo No. 2 Hospital (ethics approval number: YJ-NBET-KY-2022-130-01) and waived individual informed consent as

only anonymized data were utilized. A total of 4,776 diabetic patients consecutively admitted to the Department of Endocrinology at Ningbo No. 2 Hospital between June 2019 and March 2022 were selected. Inclusion criteria included the following: (1) age ≥ 18 years; (2) diagnosis of diabetes in accordance with the 1999 WHO diagnostic criteria (12); (3) complete inpatient medical records. Exclusion criteria included the following: (1) type 1 diabetes, other types of diabetes, or unclear diagnosis ($n = 119$); (2) history of other chronic liver diseases (e.g., viral, autoimmune), liver cirrhosis, tumors, or other major diseases ($n = 444$); (3) acute diabetic complications or severe infections ($n = 170$); (4) history of long-term alcohol consumption ($n = 35$); (5) repeated hospitalizations ($n = 577$); (6) missing clinical data including BMI, fasting and 2-h postprandial plasma glucose and C-peptide ($n = 1,844$). Ultimately, 1,587 patients with T2DM were included in the study (Figure 1).

2.2 Data collection and processing

2.2.1 General information

Clinical data were collected from electronic medical records, including age, gender, height, weight, diabetes history, and liver ultrasound results. The body mass index (BMI) was subsequently calculated. Serum biomarkers, such as total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (γ -GGT), and glycated hemoglobin (HbA1c), were also measured.

2.2.2 The 100 g standard steamed bread meal test

The carbohydrate content of a 100 g steamed bread meal is approximately equivalent to 75 g of glucose. Research conducted by the Chinese Islet Beta-Cell Function Collaborative Research Group demonstrated that the 100 g steamed bread meal test showed good reproducibility and tolerability for assessing β -cell function, in comparison to the oral glucose tolerance test (OGTT) (13). Consequently, we employed the 100 g steamed bread meal test to measure fasting plasma glucose (FPG), 2-h postprandial glucose (2 h PG), fasting C-peptide (FCP), and 2-h postprandial C-peptide (2 h CP). C-peptide levels were quantified using a magnetic microparticle chemiluminescence assay.

2.2.3 Evaluation of IR

Due to the administration of insulin therapy to some patients during their hospital stay, C-peptide and insulin are co-secreted in equimolar ratios (14). Consequently, this study employed FPG and FCP measurements to calculate HOMA-IR, QUICKI, IAI, and Bennett ISI to assess basal IR. Additionally, fasting and 2-h post-meal blood glucose and C-peptide following the steamed bread meal test were used to compute ISI_{Matsuda} and $ISI_{0,120}$ to evaluate post-stimulation IR status. The formulas for these calculations are detailed in Supplementary Table S1.

2.2.4 MASLD and liver fibrosis assessment criteria

The diagnosis of MASLD was determined through abdominal ultrasound findings indicating fatty liver or discharge diagnosis codes, such as K76.0. According to the American Association of Clinical

Abbreviations: IR, Insulin resistance; MASLD, Metabolic dysfunction associated steatotic liver disease; T2DM, Type 2 diabetes mellitus; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; QUICKI, Quantitative Insulin Sensitivity Check Index; IAI, Li Guangwei index; Bennett ISI, Bennett insulin sensitivity index; ISI_{Matsuda} , Matsuda index; $ISI_{0,120}$, Gutt index; BMI, Body mass index; FIB-4, Fibrosis-4 index; FCP, Fasting serum C-peptide; 2 h CP, 2-h Postprandial C-peptide; FPG, Fasting plasma glucose; 2 h PG, 2-h Postprandial glucose.

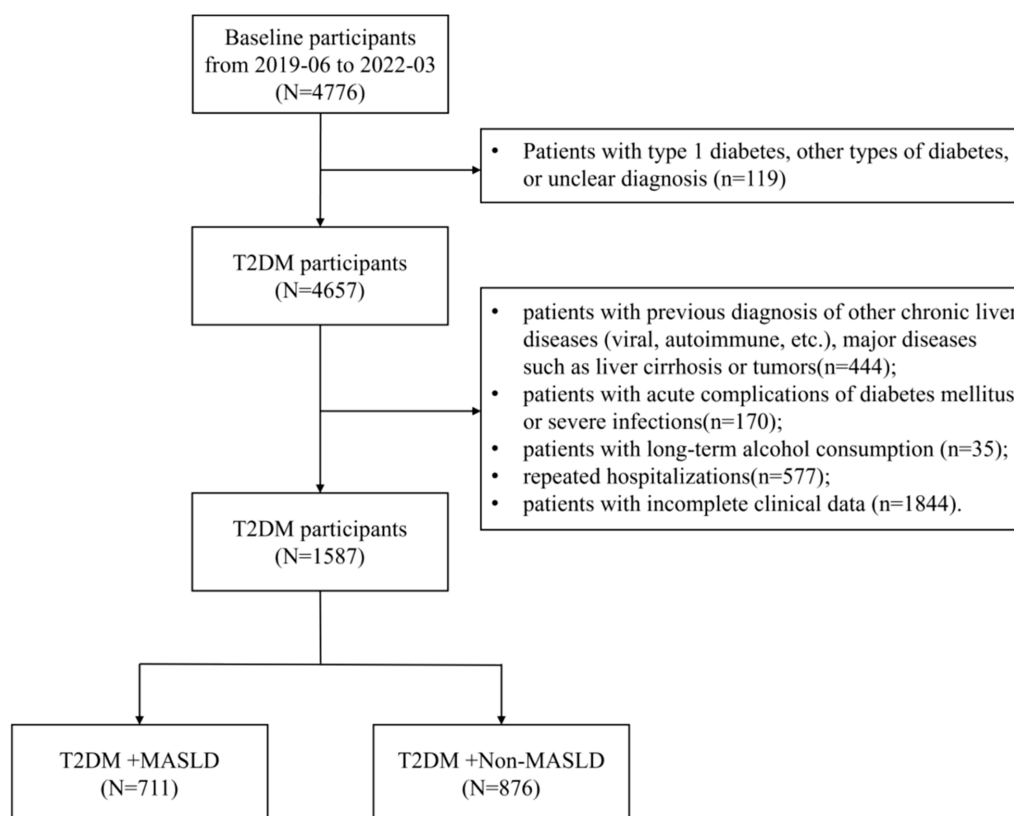


FIGURE 1
Flow diagram of patient selection.

Endocrinology (AACE) clinical practice guideline for the management of non-alcoholic fatty liver disease (NAFLD), the fibrosis risk in T2DM patients with MASLD was assessed using the non-invasive fibrosis-4 index (FIB-4) (15). $FIB-4 < 1.3$ indicated low risk, $1.3 \leq FIB-4 \leq 2.67$ indicated intermediate risk, and $FIB-4 > 2.67$ indicated high risk.

The FIB-4 calculation formula was: $FIB-4 = (Age \text{ (years)} \times AST \text{ (U/L)}) / (PLT \text{ (} 10^9/L) \times ALT \text{ (U/L)}^{1/2})$.

2.3 Statistical analysis

Statistical analysis and graphical plotting were performed using SPSS version 26.0 (IBM Corp, NY, USA) and R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Categorical data were expressed as frequency (%), and group comparisons were conducted using the χ^2 test. Continuous variables with a normal distribution were expressed as mean \pm standard deviation ($\bar{x} \pm s$), and comparisons between two groups were performed using an independent samples t-test. For multiple group comparisons, one-way analysis of variance (ANOVA) was applied. Non-normally distributed data were presented as M (P25, P75), and comparisons between two groups were performed using the Mann–Whitney U test, while comparisons among multiple groups were conducted using the Kruskal–Wallis H test.

The participants were categorized into four groups according to the quartiles of IR indices: Q1 (<25%), Q2 (25–50%), Q3 (50–75%),

and Q4 ($\geq 75\%$). Multicollinearity was assessed via variance inflation factors (VIF). After adjusting for potential confounders, logistic regression analysis was employed to examine the relationship between IR levels and the occurrence of MASLD and liver fibrosis. The diagnostic value of different IR indices for the onset of MASLD and liver fibrosis in patients with T2DM was assessed using receiver operating characteristic (ROC) curves.

Moreover, a predictive model for the risk of MASLD among the T2DM population was developed using logistic regression, incorporating age, BMI, ALT, and TG. The effectiveness of the model, before and after adding 2 h CP, was assessed using the concordance index (C-index), net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Specifically, the NRI measures the extent to which the addition of a new variable improves the correct reclassification of individuals into clinically relevant risk categories, while the IDI reflects the improvement in the model's ability to discriminate between cases and non-cases. The nomogram for the model was generated using the “rms” package. A p -value of < 0.05 was considered statistically significant.

3 Results

This study encompassed 1,587 patients with T2DM, with an average age of 51.86 ± 13.07 years. Of these, 642 (40.45%) were female and 945 (59.55%) were male. A total of 711 (44.80%) patients with T2DM were diagnosed with MASLD, of which 271 (38.12%) were at

intermediate risk of liver fibrosis and 46 (6.47%) were at high risk for liver fibrosis.

3.1 Comparison of clinical characteristics between T2DM patients with and without MASLD

Patients were divided into two groups based on the presence of MASLD: those with T2DM and MASLD (DM + MASLD group, $n = 711$) and those with T2DM but without MASLD (DM + Non-MASLD group, $n = 876$). Compared with the DM + Non-MASLD group, the DM + MASLD group was younger (55.07 vs. 60.66, $p < 0.001$) and had significantly higher levels of BMI (25.92 vs. 22.98), AST (24 vs. 20), ALT (27 vs. 18), γ -GGT (33 vs. 22), FPG (8.86 vs. 8.39), FCP (1.69 vs. 1.12), and 2 h CP (6.10 vs. 4.07) (all $p < 0.01$). Moreover, a higher proportion of the DM + MASLD group was overweight/obese (69.90%) compared with the DM + Non-MASLD (34.36%) group ($p < 0.001$). There were no significant differences in gender or HbA1c levels between the two groups ($p > 0.05$).

Compared with the DM + Non-MASLD group, in the fasting state, the DM + MASLD group showed significantly higher HOMA-IR (0.63 vs. 0.37) and lower values for QUICKI (0.20 vs. 0.21), IAI (0.07 vs. 0.12), and Bennett ISI (0.40 vs. 0.45) (all $p < 0.001$). Following a 100 g steamed bread meal stimulus, the DM + MASLD group demonstrated lower ISI_{matsuda} (1.14 vs. 1.82) and $ISI_{0,120}$ (16.13 vs. 16.80) values (all $p < 0.001$). (Table 1).

3.2 Comparison of clinical characteristics between T2DM patients with and without MASLD at different BMI levels

According to the BMI, T2DM patients were grouped into three categories: BMI $< 24 \text{ kg/m}^2$ ($n = 789$), $24 \leq \text{BMI} < 28 \text{ kg/m}^2$ ($n = 575$), and BMI $\geq 28 \text{ kg/m}^2$ ($n = 223$). The differences in IR between the DM + MASLD and DM + Non-MASLD groups were compared at each BMI level. As shown in Supplementary Table S2, in the BMI $< 24 \text{ kg/m}^2$ and $24 \leq \text{BMI} < 28 \text{ kg/m}^2$, the DM + MASLD group exhibited higher HOMA-IR (0.51 vs. 0.32; 0.63 vs. 0.44) and lower values for QUICKI (0.21 vs. 0.22; 0.20 vs. 0.21), IAI (0.09 vs. 0.14; 0.07 vs. 0.10), Bennett ISI (0.17 vs. 0.19; 0.17 vs. 0.18), ISI_{matsuda} (1.32 vs. 2.08; 1.15 vs. 1.52), and $ISI_{0,120}$ (16.09 vs. 16.88; 16.09 vs. 16.69) (all $p < 0.05$). In the BMI $\geq 28 \text{ kg/m}^2$, the DM + MASLD group showed a significantly lower ISI_{matsuda} (0.91 vs. 1.12, $p = 0.011$), while no significant differences were found in other IR indices ($p > 0.05$).

3.3 Comparison of clinical characteristics among T2DM patients with MASLD at different liver fibrosis risk groups

Liver fibrosis risk stratification was performed in the DM + MASLD population according to the FIB-4 index: low risk group ($n = 394$), moderate risk group ($n = 271$), and high risk group ($n = 46$). Supplementary Table S3 shows that compared with the

low- and moderate-risk groups, the high-risk group had significantly elevated levels of age (65.91 vs. 48.72; 65.91 vs. 62.46), AST (44 vs. 22; 44 vs. 26), ALT (35 vs. 28; 35 vs. 25), and γ -GGT (62 vs. 33; 62 vs. 31) (all $p < 0.01$). There were no significant differences observed among the three groups for BMI, HbA1c, FCP, 2 h PG, 2 h CP, or the prevalence of overweight/obesity (all $p > 0.05$). Furthermore, no significant differences in HOMA-IR, QUICKI, IAI, Bennett ISI, ISI_{matsuda} , or $ISI_{0,120}$ were observed across the different fibrosis risk groups (all $p > 0.05$).

3.4 Detection rates of MASLD and liver fibrosis at different IR levels

The participants were divided into four groups (Q1, Q2, Q3, Q4) based on the quartiles of HOMA-IR, QUICKI, IAI, Bennett ISI, ISI_{matsuda} , and $ISI_{0,120}$, respectively.

The findings indicated that for the basal IR indices, the MASLD detection rates for HOMA-IR Q1–Q4 were 21.77, 40.95, 55.03, and 61.36%, respectively. Conversely, the detection rates for QUICKI, IAI, and Bennett ISI decreased progressively across their quartile groups (all $p < 0.001$). Regarding post-stimulation IR indices, the MASLD detection rates for ISI_{matsuda} Q1–Q4 were 65.74, 54.16, 37.03, and 22.22%, respectively ($p < 0.001$). The MASLD detection rates for $ISI_{0,120}$ Q1–Q4 were 50.25, 45.73, 45.96, and 37.30%, respectively ($p = 0.003$) (Figure 2).

For T2DM patients with MASLD, there were no significant differences in the detection rates of liver fibrosis across the quartile groups of HOMA-IR, QUICKI, IAI, Bennett ISI, ISI_{matsuda} , and $ISI_{0,120}$ (all $p > 0.05$) (Supplementary Figure S1).

3.5 Relationship between IR indices and the risk of MASLD and liver fibrosis in T2DM patients

Logistic regression analysis was conducted with MASLD as the dependent variable, and HOMA-IR, QUICKI, IAI, Bennett ISI, ISI_{matsuda} , and $ISI_{0,120}$ were each included separately as independent variables. Multicollinearity was assessed using VIF, and all covariates had VIFs < 3 , indicating no significant multicollinearity (Supplementary Table S4). In Model 2, after adjusting for gender, age, BMI, FPG, and 2 h PG, for the basal IR indices, the risks of MASLD in the Q2–Q4 groups of HOMA-IR, compared with the Q1 group, were 1.89 (95% CI: 1.35–2.64), 2.75 (95% CI: 1.95–3.89), and 3.08 (95% CI: 2.11–4.48), respectively. QUICKI, with the Q4 group as reference, the Q1–Q3 groups' risks of MASLD were 3.06 (95% CI: 2.10–4.45), 2.77 (95% CI: 1.96–3.92), and 1.88 (95% CI: 1.35–2.64), respectively. Similar results were observed for IAI and Bennett ISI (all $p < 0.001$). For post-stimulation IR indices, compared with the Q4 group, the risks of MASLD for the Q1–Q3 groups for ISI_{matsuda} were 3.63 (95% CI: 2.55–5.16), 2.53 (95% CI: 1.81–3.54), and 1.53 (95% CI: 1.09–2.13), respectively, and for $ISI_{0,120}$ they were 8.63 (95% CI: 4.34–17.16), 3.89 (95% CI: 2.37–6.40), and 3.06 (95% CI: 2.07–4.52) (all $p < 0.001$) (Figure 3). Similar results were obtained in Model 3, which additionally adjusted for gender, age, BMI, FPG, 2 h PG, TC, TG, HDL-C, LDL-C, UA, and hypertension status (Supplementary Table S5).

TABLE 1 Clinical characteristics of T2DM patients with and without MASLD.

Variables	DM + MASLD (n = 711)	DM + Non-MASLD (n = 876)	$\chi^2/t/Z$	p-value
Age (Years, $\bar{x} \pm s$)	55.07 \pm 13.36	60.66 \pm 12.27	8.60	<0.001
Male (%)	435 (61.18)	510 (58.22)	1.43	0.232
BMI (kg/m ² , $\bar{x} \pm s$)	25.92 \pm 3.32	22.98 \pm 3.13	−18.12	<0.001
BMI			234.41	<0.001
Underweight, N (%)	1 (0.14)	48 (5.48)		
Normal weight, N (%)	213 (29.96)	527 (60.16)		
Overweight, N (%)	328 (46.13)	247 (28.20)		
Obesity, N (%)	169 (23.77)	54 (6.16)		
TC (mmol/L, $\bar{x} \pm s$)	4.51 \pm 1.19	4.20 \pm 1.14	−5.26	<0.001
TG (mmol/L, M (P25, P75))	1.45 (1.06, 2.13)	1.04 (0.78, 1.51)	−10.36	<0.001
HDL-C (mmol/L, $\bar{x} \pm s$)	1.04 \pm 0.26	1.10 \pm 0.33	3.48	<0.001
LDL-C (mmol/L, $\bar{x} \pm s$)	2.79 \pm 0.87	2.52 \pm 0.87	−6.05	<0.001
AST [IU/L, M (P25, P75)]	24.00 (19.00, 33.00)	20.00 (15.00, 24.00)	−11.01	<0.001
ALT [IU/L, M (P25, P75)]	27.00 (18.00, 41.00)	18.00 (13.00, 25.00)	−13.49	<0.001
γ -GGT [IU/L, M (P25, P75)]	33.00 (23.00, 59.75)	22.00 (15.00, 34.00)	−12.75	<0.001
HbA1c (% , $\bar{x} \pm s$)	9.32 \pm 2.05	9.38 \pm 2.52	0.43	0.664
FPG (mmol/L, $\bar{x} \pm s$)	8.86 \pm 2.86	8.39 \pm 3.33	−3.05	0.002
2 h PG (mmol/L, $\bar{x} \pm s$)	15.55 \pm 4.16	16.68 \pm 4.22	5.33	<0.001
FCP [ng/mL, M (P25, P75)]	1.69 (1.07, 2.54)	1.12 (0.64, 1.75)	−11.61	<0.001
2 h CP [ng/mL, M (P25, P75)]	6.10 (4.06, 9.25)	4.07 (2.40, 6.37)	−11.65	<0.001
IR indices				
HOMA-IR	0.63 (0.38, 0.97)	0.37 (0.21, 0.67)	−12.24	<0.001
QUICKI	0.20 (0.19, 0.21)	0.21 (0.20, 0.22)	−12.24	<0.001
IAI	0.07 (0.05, 0.12)	0.12 (0.07, 0.21)	−12.24	<0.001
Bennett ISI	0.40 (0.36, 0.45)	0.45 (0.38, 0.53)	−10.54	<0.001
ISI _{matsuda}	1.14 (0.81, 1.71)	1.82 (1.14, 2.83)	−13.50	<0.001
ISI _{0,120}	16.15 (14.18, 18.74)	16.82 (14.63, 19.86)	−3.35	<0.001

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ -GGT, gamma-glutamyl transpeptidase; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; 2 h PG, 2-h postprandial glucose; FCP, fasting C-peptide; 2 h CP, 2-h postprandial C-peptide; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; IAI, Li Guangwei index; Bennett ISI, Bennett insulin sensitivity index; ISI_{matsuda}, Matsuda index; ISI_{0,120}, Gutt index.

In the DM + MASLD group, with liver fibrosis as the dependent variable and HOMA-IR, QUICKI, IAI, Bennett ISI, ISI_{matsuda}, and ISI_{0,120} as independent variables, logistic regression analysis indicated no significant differences in the risk of liver fibrosis across different indicator groups (all $p > 0.05$) (Supplementary Figure S2).

3.6 Predictive power of IR indices for MASLD in patients with T2DM

ROC curve analysis showed that the areas under the curves (AUC) for HOMA-IR, QUICKI, IAI, Bennett ISI, ISI_{matsuda}, and ISI_{0,120} were 0.678, 0.678, 0.678, 0.654, 0.701, and 0.549, respectively. Notably, ISI_{matsuda} demonstrated the highest AUC at 0.701, with an optimal cutoff value of 1.480. The sensitivity was 67.7% and the specificity was 63.6% (Figure 4).

3.7 Development of a risk prediction model for MASLD in the T2DM population

We utilized clinically readily accessible indices—age, BMI, ALT, and TG—integrated into a logistic regression to develop a MASLD risk prediction model for the T2DM population. Based on our prior findings, the relationship between post-stimulation IR and MASLD was pronounced. Upon integrating 2 h CP into the MASLD risk prediction model, the C-index increased from 0.78 to 0.79. This enhancement substantially improved the model’s discriminatory power and risk reclassification (IDI 0.01, 95% CI: 0.00–0.02, $p < 0.001$; NRI 0.17, 95% CI: 0.06–0.29, $p = 0.003$), as shown in Supplementary Figure S3.

A nomogram was constructed based on age, BMI, ALT, TG, and 2 h CP to predict the probability of MASLD occurrence in patients with diabetes. This nomogram provided a visual method to calculate the total score based on the values of each predictor, offering an

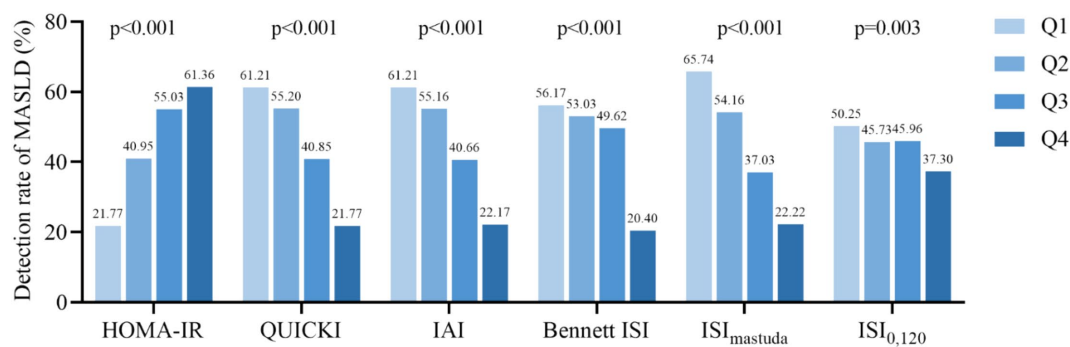


FIGURE 2 Detection rate of MASLD according to the quartiles of IR indicators. HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; IAI, Li Guangwei index; Bennett ISI, Bennett insulin sensitivity index; ISI_{matsuda}, Matsuda index; ISI_{0.120}, Gutt index.

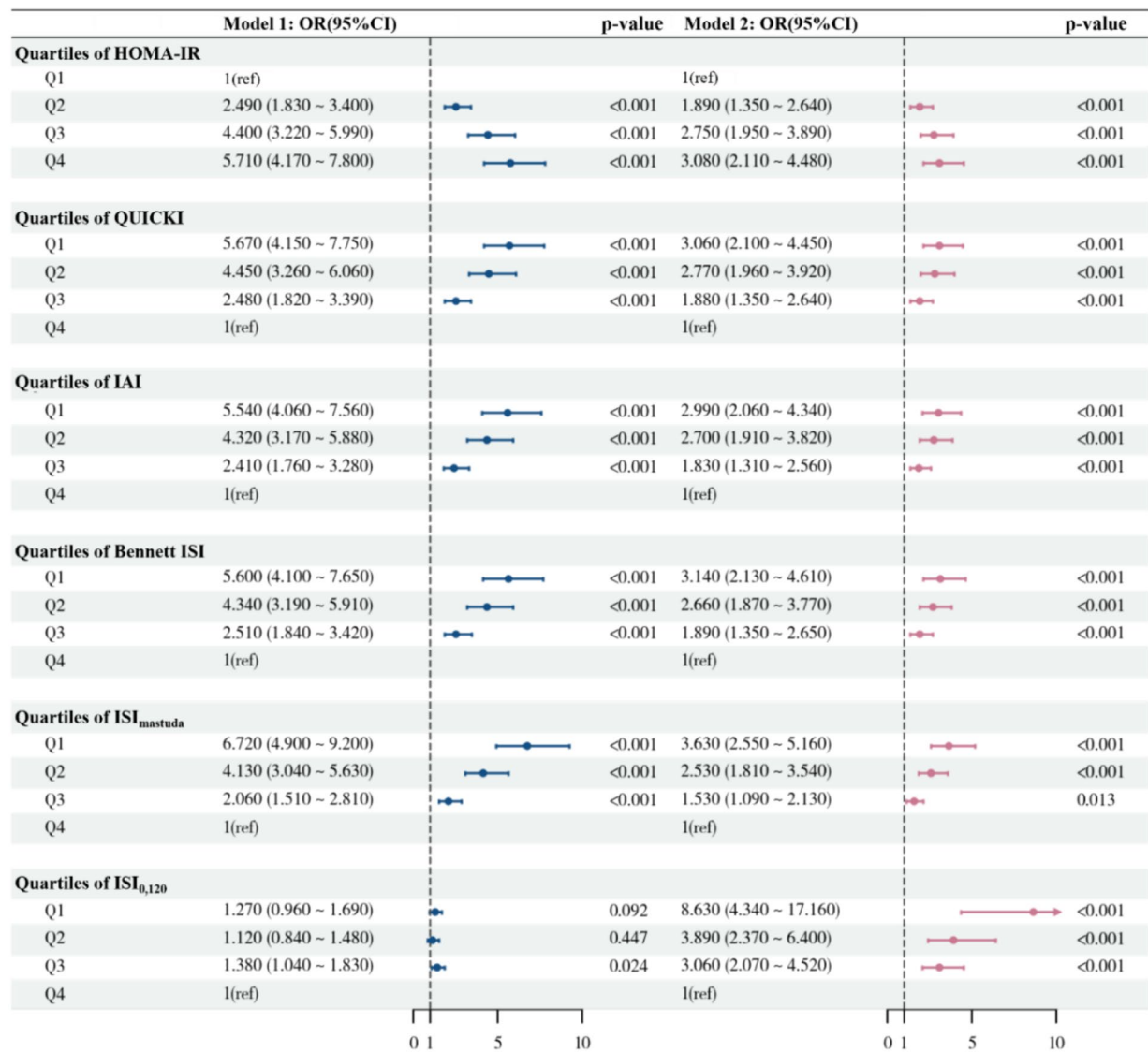
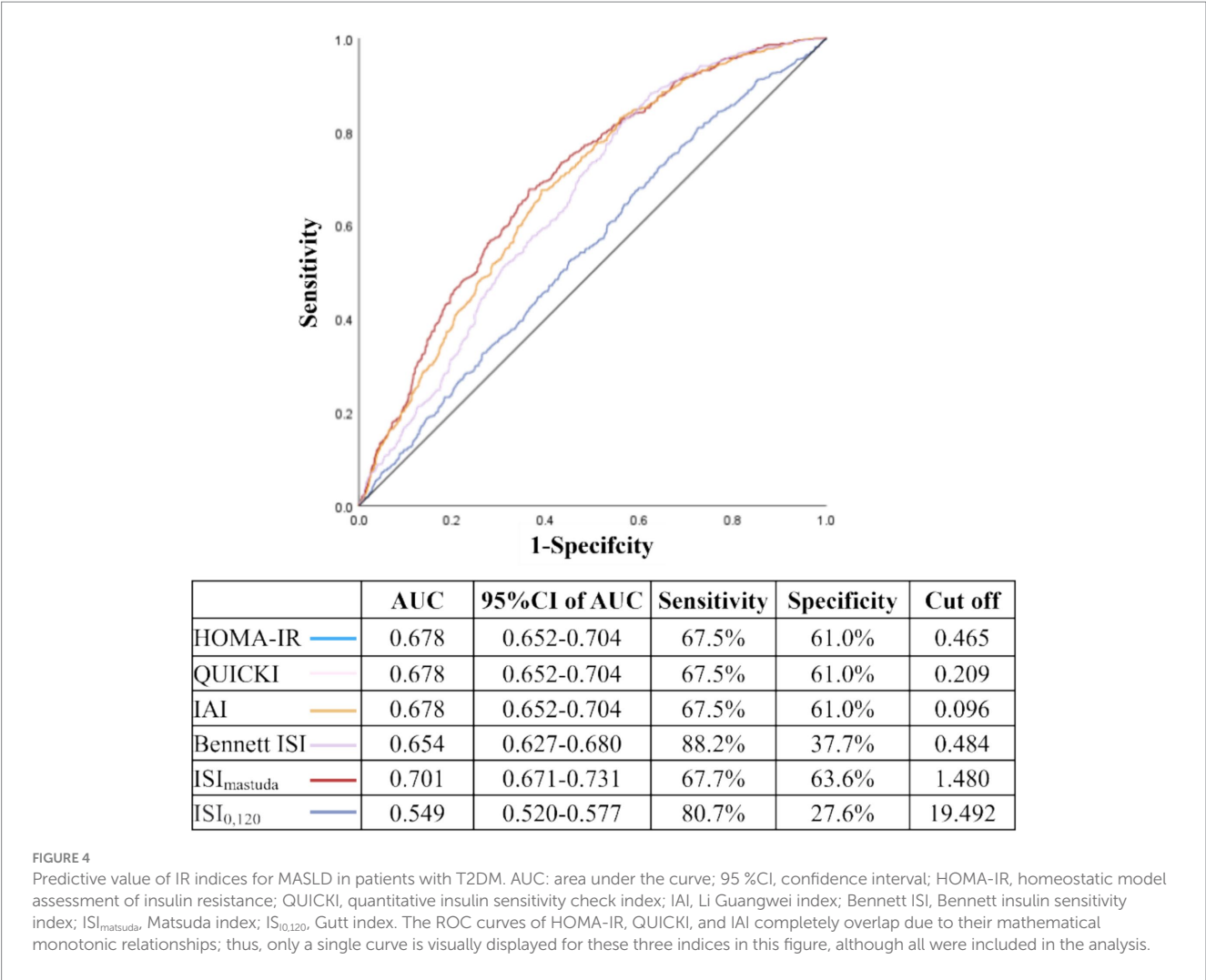


FIGURE 3 Logistic regression model for the association between IR indices and the risk of MASLD. Model 1, unadjusted; Model 2, adjusted for gender, age, BMI, FPG, 2 h PG. OR, odd ratio; 95 %CI, confidence interval; Ref, reference; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; IAI, Li Guangwei index; Bennett ISI, Bennett insulin sensitivity index; ISI_{matsuda}, Matsuda index; ISI_{0.120}, Gutt index.



intuitive estimate of the likelihood of MASLD (Figure 5A). For example, as shown in Figure 5B, a T2DM patient aged 51 years with a BMI of 27.2 kg/m², ALT of 28 IU/L, TG of 2 mmol/L, and 2 h CP of 8.80 ng/mL, the estimated probability of MASLD was 76.6%.

4 Discussion

Previous studies have demonstrated a close association between IR and the occurrence of MASLD, as well as the severity of liver involvement. In a small sample study of 56 patients with T2DM, Gala et al. identified that HOMA-IR was independently associated with the development of MASLD (OR = 1.5, 95% CI: 1.03–2.1, *p* = 0.033) (16). Similarly, Khamseh et al. conducted an investigation with 644 adult patients with T2DM and demonstrated that HOMA-IR (AUC = 0.713), QUICKI (AUC = 0.713), and Bennett ISI (AUC = 0.714) could all predict the onset of MASLD (17). In alignment with these findings, our research also revealed that the basal IR indices, including HOMA-IR, QUICKI, IAI, and Bennett ISI, were strongly associated with the occurrence of MASLD and had diagnostic value for MASLD. Clinical studies have also confirmed that insulin-sensitizing agents, such as thiazolidinediones (TZDs), can ameliorate T2DM with MASLD (18).

In addition, our observations revealed that compared with basal IR markers, post-stimulation IR indices such as ISI_{0,120} (OR = 8.63, 95%CI:4.34–17.16) and ISI_{matsuda} (OR = 3.63, 95%CI: 2.55–5.16) had stronger associations with MASLD. In our study, the highest MASLD detection rate was observed in the high IR group (Q1), as assessed by ISI_{matsuda}, reaching 65.74%; ROC curve analysis demonstrated that the AUC of ISI_{matsuda} was significantly higher than that of the other IR indices (*p* < 0.01; Supplementary Table S6), suggesting that ISI_{matsuda} provides stronger diagnostic performance for MASLD. It is noteworthy that although ISI_{0,120} exhibited the highest OR, its AUC was the lowest among all IR indices, indicating that a strong association does not necessarily translate into good discriminative ability. Therefore, clinical evaluation of IR indices should incorporate multiple metrics, including both OR and AUC, to comprehensively assess their diagnostic and predictive value. Previous studies have shown that ISI_{matsuda} was significantly correlated with “gold-standard” HEC data (*r* = 0.73, *p* < 0.0001), outperformed HOMA-IR, and was capable of assessing both hepatic and peripheral insulin sensitivity simultaneously (19). In small sample studies using liver biopsy as the “gold standard” for diagnosing fatty liver, Kato et al. confirmed that ISI_{matsuda} was significantly correlated with the degree of hepatic steatosis

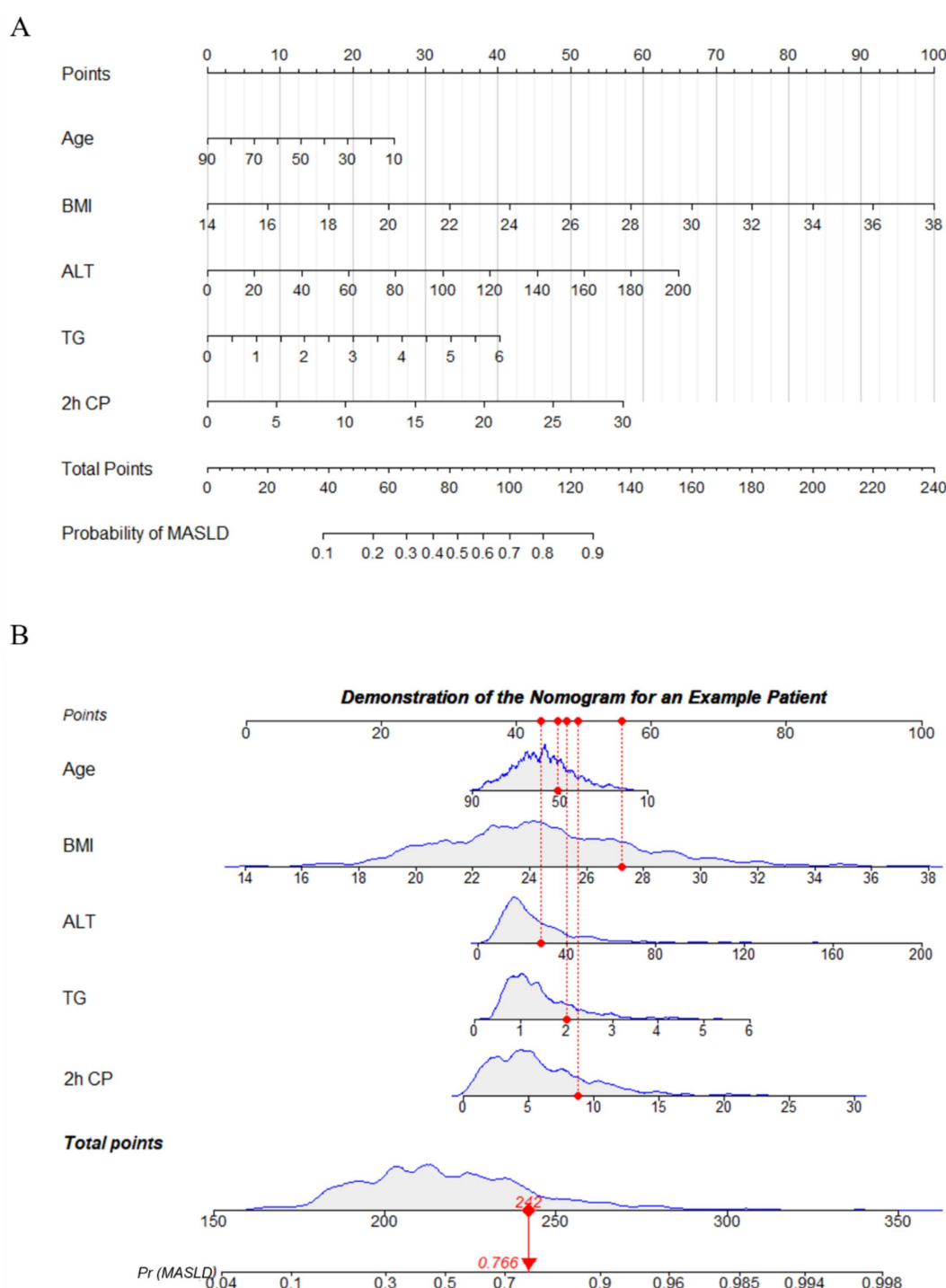


FIGURE 5

Nomogram to predict the risk of MASLD in diabetic patient. **(A)** To use the nomogram, the patient's value for each variable (age, BMI, ALT, TG, 2 h CP) is located on its respective axis, and a vertical line is drawn upward to the "Points" axis to determine the corresponding score. The points for all variables are then summed to obtain the total score. Next, on the "Total Points" axis, the corresponding total is located, and a vertical line is drawn downward to the "Probability of MASLD" axis to obtain the patient's predicted risk of MASLD. **(B)** Demonstration of nomogram use for an example patient. BMI, body mass index; ALT, alanine aminotransferase; TG, triglycerides; 2 h CP, 2-h postprandial C-peptide.

($r = -0.45$, $p < 0.001$) (20). In a prospective study of 37 patients with fatty liver who underwent metabolic surgery, $ISI_{matsuda}$ was found to be superior to HOMA-IR in predicting the regression of NASH post-surgery (AUC = 0.98), highlighting its central

role in the reversal of NASH (21, 22). Furthermore, in a study of 141 patients with T2DM using the proton magnetic resonance spectroscopy ($[^1H]$ -MRS) technique to quantify liver fat content (LFC), Wang et al. found an inverse correlation between

increased LFC and ISI_{matsuda} ($r = -0.214, p < 0.001$) (23). To date, no large-scale clinical study has systematically compared the performance of basal versus post-stimulation IR indices in the diagnosis of MASLD, especially among high-risk populations with T2DM. Our research, involving 1,587 patients with T2DM, is the first to confirm that ISI_{matsuda} shows the most robust correlation with MASLD among indices used to assess IR. This suggests that post-stimulation IR may play a more critical role in the pathogenesis of fatty liver compared to basal IR. The underlying mechanism may involve the exacerbation of IR following stimulation, where postprandial hyperglycemic and hyperlipidemic states cause a “second hit,” facilitating an increased influx of FFA into the liver and thus accelerating the formation of fatty liver.

Under chronic hyperinsulinemia, the PI3K–Akt–FoxO1 pathway responsible for suppressing hepatic glucose production (HGP) becomes desensitized first, whereas the SREBP-1c branch that promotes DNL remains relatively intact. As a result, postprandial and nocturnal insulin levels are often above the threshold required to inhibit gluconeogenesis, but precisely within the range that maximally stimulates lipogenesis. This leads to the simultaneous occurrence of persistent hepatic glucose overproduction and increased triglyceride synthesis (24). This so-called “insulin window” mechanism is highly consistent with our clinical findings, which showed that lower ISI_{matsuda} values were associated with increased MASLD risk. In addition, the heterogeneity of hepatic metabolic zonation further exacerbates this metabolic imbalance. Studies using $Gls2^{\text{CreER}}$ (periportal, PP) and $Cyp1a2^{\text{CreER}}$ (pericentral, PC) insulin signaling knockout mouse models have demonstrated that PP hepatocytes predominantly mediate the inhibitory effect of insulin on HGP. Selective IR in the PP region alone can lead to impaired glucose tolerance and a complete loss of insulin-mediated regulation of HGP. However, DNL is jointly driven by both PP and PC regions, and disruption of insulin signaling in either region can reduce overall hepatic DNL levels and attenuate the risk of high-fat-diet-induced hepatic steatosis (25). These findings underscore the importance of dynamic assessment of postprandial IR and the implementation of targeted intervention strategies in the management of patients with T2DM. Evaluating IR solely by fasting insulin measurement may underestimate the true degree of IR in patients with diabetes and concomitant fatty liver. For patients with IR and fatty liver, choosing medications that can improve IR, such as TZDs, SGLT-2 inhibitors, or GLP-1 receptor agonists, may provide greater clinical benefits. Notably, in a phase II clinical trial, nearly 60% of NASH patients achieved histological remission after 48 weeks of semaglutide treatment, further highlighting its translational potential (26).

Currently, diagnostic models for fatty liver disease are predominantly developed for the general population, with a significant paucity of large-scale studies concentrating specifically on patients with T2DM. For instance, Cen et al. conducted a cross-sectional study involving 21,468 Chinese individuals, employing clinical indices such as BMI, diastolic blood pressure (DBP), UA, FPG, TG, and ALT to construct a clinical diagnostic model for MASLD, achieving an AUC of 0.857 (27). Katarzyna and colleagues, in their investigation of 1,735 diabetic patients,

utilized eight clinical indices—age, BMI, type of diabetes, ALT, AST, hyperuricemia, platelet count, and metformin treatment—combined with a machine-learning approach, successfully developed an identification model for MASLD (AUC = 0.84) (28). Using simple clinical indices to predict the likelihood of fatty liver in diabetic populations can effectively conserve clinical resources. We selected age, BMI, TG, and ALT. Additionally, due to the complex calculation of ISI_{matsuda} , we further incorporated the postprandial 2 h CP to establish a diagnostic model for MASLD in the population with T2DM, and found that adding 2 h CP markedly improved the model’s performance. Based on these indices, we constructed a nomogram to predict the probability of MASLD occurrence. Unlike previous research, our model simplifies the indices and, for the first time, includes postprandial 2 h CP as a critical predictive marker in MASLD diagnosis, highlighting the pivotal role of post-stimulation insulin levels in the development of MASLD.

The existing literature investigating the relationship between IR and the progression of liver fibrosis in patients with MASLD is limited. A longitudinal prospective cohort study conducted in South Korea, which included 10,030 adults, demonstrated that although the Homeostatic Model Assessment of HOMA-IR could predict the onset of fatty liver, it did not show a significant correlation with advanced liver fibrosis, defined as an FIB-4 score of 2.67 or higher (29, 30). Conversely, studies involving patients with biopsy-confirmed fatty liver, such as the work by Fujii et al., suggested that HOMA-IR (OR = 2.85, 95% CI: 1.21–7.19; $p = 0.016$) served as an independent risk factor for progressive liver fibrosis (31). Thus, the relationship between IR and liver fibrosis in MASLD patients remains contentious within the general population. Furthermore, there is a notable scarcity of related research specifically addressing individuals with T2DM. A study involving 483 patients with T2DM found no significant association between HOMA-IR and the presence of liver fibrosis, defined by a Liver Stiffness Measurement (LSM) of ≥ 8.0 kPa (32). Similarly, research conducted by Seeberg et al. on severely obese patients with T2DM (BMI ≥ 33 kg/m²) revealed no notable correlation between HOMA-IR, ISI_{matsuda} , and levels of liver fibrosis (33). These findings align with the conclusions drawn from our study. To elucidate the relationship between IR and the progression to liver fibrosis in patients with T2DM comorbidity with MASLD, further investigation through large-scale, prospective cohort studies is warranted.

In conclusion, this study demonstrates that IR is an independent risk factor for the development of MASLD in patients with T2DM. Importantly, our research is the first to establish that post-stimulus IR indices, specifically ISI_{matsuda} and $ISI_{0,120}$, are more strongly associated with MASLD than basal indices. Nonetheless, no clear relationship is identified between IR indices and the progression of liver fibrosis in T2DM patients with fatty liver.

5 Limitation

This study explored the correlation between commonly utilized IR indices and the progression of MASLD and liver fibrosis in patients with T2DM. However, several limitations should be acknowledged. The cross-sectional design precludes the

establishment of a causal relationship between IR and MASLD in patients with T2DM. Additionally, the study participants were exclusively hospitalized patients with T2DM from a tertiary hospital in eastern Zhejiang Province. Although there were no explicit geographical restrictions during recruitment, the single-center nature of this study limits the external generalizability of our findings, necessitating further validation in multicenter, geographically diverse prospective cohorts. Furthermore, MASLD diagnosis was based on abdominal ultrasonography, and liver fibrosis was assessed using the FIB-4 index; although these approaches are consistent with current clinical guidelines and appropriate for large-scale retrospective analyses, they may underestimate mild steatosis or early-stage fibrosis. Future studies should therefore integrate MRI-based proton density fat fraction (MRI-PDFF) and selective liver biopsy for more accurate validation. Finally, given the strictly retrospective nature of this analysis, detailed data on dietary habits, physical activity, and specific medication use were unavailable from existing medical records, limiting deeper exploration of the relationship between IR and MASLD. Prospective studies systematically incorporating these variables are essential to enhance study rigor and strengthen the reliability of conclusions.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: In view of privacy and data security concerns, the complete raw data cannot be publicly disclosed; however, they are available from the corresponding author upon reasonable request. Requests to access these datasets should be directed to zhangmc1015@wmu.edu.cn.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Ningbo Second Hospital (approval no. YJ-NBET-KY-2022-130-01). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JL: Writing – original draft, Conceptualization, Writing – review & editing, Formal analysis, Validation, Methodology. YW: Investigation, Validation, Formal analysis, Writing – review & editing. XZ: Software, Writing – review & editing, Formal analysis, Visualization. ZW: Writing – review & editing, Software, Formal analysis, Visualization. YC: Formal analysis, Software, Visualization, Writing – review & editing. YS: Investigation, Data curation, Writing – review & editing. SS: Investigation, Writing – review & editing, Data curation. WL: Investigation, Writing – review & editing, Data curation. RS: Writing – review & editing, Investigation, Data curation. XS:

Data curation, Writing – review & editing. HL: Writing – review & editing, Data curation. XY: Data curation, Writing – review & editing. MZ: Supervision, Writing – review & editing, Conceptualization, Project administration.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Natural Science Foundation of China [grant no. 72274189], Medical and Health Science and Technology Program of Zhejiang Province [grant nos. 2023KY281; 2020KY262], the Scientific Research Project of Huamei Fund of Ningbo No.2 Hospital [grant nos. 2022HMZD02; 2024HMZD08; 2024HMKYA17], and the Zhu Xiushan Endowment for Talent Development Cultivation Program of Ningbo No.2 Hospital [grant no. 2023HMYQ19F].

Acknowledgments

The authors thank all participants for participating in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2025.1623808/full#supplementary-material>

References

- European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL–EASD–EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol.* (2024) 81:492–542. doi: 10.1016/j.jhep.2024.04.031
- Kim WR, Mannaithara A, Charu V, Chung N, Kwong A, Kwo PY, et al. Optimal population screening strategies for liver fibrosis associated with metabolic dysfunction-associated steatotic liver disease. *Am J Gastroenterol.* (2025). doi: 10.14309/ajg.0000000000003268
- Man S, Deng Y, Ma Y, Fu J, Bao H, Yu C, et al. Prevalence of liver steatosis and fibrosis in the general population and various high-risk populations: a Nationwide study with 5.7 million adults in China. *Gastroenterology.* (2023) 165:1025–40. doi: 10.1053/j.gastro.2023.05.053
- Ajmera V, Cepin S, Tesfai K, Hofflich H, Cadman K, Lopez S, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. *J Hepatol.* (2023) 78:471–8. doi: 10.1016/j.jhep.2022.11.010
- En Li Cho E, Ang CZ, Quek J, Fu CE, Lim LKE, Heng ZEQ, et al. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. *Gut.* (2023) 72:2138–48. doi: 10.1136/gutjnl-2023-330110
- Hamblin PS, Russell AW, Talic S, Zoungas S. The growing range of complications of diabetes mellitus. *Trends Endocrinol Metab.* (2025) 3:S1043–2760. doi: 10.1016/j.tem.2024.12.006
- Zhao H, Zhai B-W, Zhang M-Y, Huang H, Zhu HL, Yang H, et al. Phlorizin from *Lithocarpus litseifolius* [Hance] Chun ameliorates FFA-induced insulin resistance by regulating AMPK/PI3K/AKT signaling pathway. *Phytomedicine.* (2024) 130:155743. doi: 10.1016/j.phymed.2024.155743
- Ferguson D, Finck BN. Emerging therapeutic approaches for the treatment of NAFLD and type 2 diabetes mellitus. *Nat Rev Endocrinol.* (2021) 17:484–95. doi: 10.1038/s41574-021-00507-z
- Elahi D. In praise of the hyperglycemic clamp. A method for assessment of beta-cell sensitivity and insulin resistance. *Diabetes Care.* (1996) 19:278–86. doi: 10.2337/diacare.19.3.278
- Li G, Hu Y, Yang W, Jiang Y, Wang J, Xiao J, et al. Effects of insulin resistance and insulin secretion on the efficacy of interventions to retard development of type 2 diabetes mellitus: the DA Qing IGT and diabetes study. *Diabetes Res Clin Pract.* (2002) 58:193–200. doi: 10.1016/S0168-8227(02)00175-4
- Otten J, Åhrén B, Olsson T. Surrogate measures of insulin sensitivity vs the hyperinsulinaemic-euglycaemic clamp: a meta-analysis. *Diabetologia.* (2014) 57:1781–8. doi: 10.1007/s00125-014-3285-x
- Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* (1998) 15:539–53. doi: 10.1002/(SICI)1096-9136(199807)15:7<3.0.CO;2-S
- Huang H, Zheng X, Wen X, Zhong J, Zhou Y, Xu L. Visceral fat correlates with insulin secretion and sensitivity independent of BMI and subcutaneous fat in Chinese with type 2 diabetes. *Front Endocrinol (Lausanne).* (2023) 14:1144834. doi: 10.3389/fendo.2023.1144834
- Yosten GL, Maric-Bilkan C, Luppi P, Wahren J. Physiological effects and therapeutic potential of proinsulin C-peptide. *Am J Physiol Endocrinol Metab.* (2014) 307:E955–68. doi: 10.1152/ajpendo.00130.2014
- Leung PB, Davis AM, Kumar S. Diagnosis and Management of Nonalcoholic Fatty Liver Disease. *JAMA.* (2023) 330:1687–8. doi: 10.1001/jama.2023.17935
- Gutierrez-Buey G, Núñez-Córdoba JM, Llaverio-Valero M, Gargallo J, Salvador J, Escalada J. Is HOMA-IR a potential screening test for non-alcoholic fatty liver disease in adults with type 2 diabetes? *Eur J Intern Med.* (2017) 41:74–8. doi: 10.1016/j.ejim.2017.03.006
- Khamseh ME, Malek M, Jahangiri S, Nobarani S, Hekmatdoost A, Salavatizadeh M, et al. Insulin resistance/sensitivity measures as screening indicators of metabolic-associated fatty liver disease and liver fibrosis. *Dig Dis Sci.* (2024) 69:1430–43. doi: 10.1007/s10620-024-08309-9
- Cusi K. Treatment of patients with type 2 diabetes and non-alcoholic fatty liver disease: current approaches and future directions. *Diabetologia.* (2016) 59:1112–20. doi: 10.1007/s00125-016-3952-1
- Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care.* (1999) 22:1462–70. doi: 10.2337/diacare.22.9.1462
- Kato K, Takeshita Y, Misu H, Zen Y, Kaneko S, Takamura T. Liver steatosis is associated with insulin resistance in skeletal muscle rather than in the liver in Japanese patients with non-alcoholic fatty liver disease. *J Diabetes Investig.* (2015) 6:158–63. doi: 10.1111/jdi.12271
- Hwang J, Hwang H, Shin H, Kim BH, Kang SH, Yoo JJ, et al. Bariatric intervention improves metabolic dysfunction-associated steatohepatitis in patients with obesity: a systematic review and meta-analysis. *Clin Mol Hepatol.* (2024) 30:561–76. doi: 10.3350/cmh.2023.0384
- Russo MF, Lembo E, Mari A, Angelini G, Verrastro O, Nanni G, et al. Insulin resistance is central to long-term reversal of histologic nonalcoholic steatohepatitis after metabolic surgery. *J Clin Endocrinol Metab.* (2021) 106:750–61. doi: 10.1210/clinem/dgaa892
- Ren W, Feng Y, Feng Y, Li J, Zhang C, Feng L, et al. Relationship of liver fat content with systemic metabolism and chronic complications in patients with type 2 diabetes mellitus. *Lipids Health Dis.* (2023) 22:11. doi: 10.1186/s12944-023-01775-6
- Cook JR, Hawkins MA, Pajvani UB. Liver insulinization as a driver of triglyceride dysmetabolism. *Nat Metab.* (2023) 5:1101–10. doi: 10.1038/s42255-023-00843-6
- He B, Copps KD, Stöhr O, Liu B, Hu S, Joshi S, et al. Spatial regulation of glucose and lipid metabolism by hepatic insulin signaling. *Cell Metab.* (2025) 37:1568–1583.e7. doi: 10.1016/j.cmet.2025.03.015
- Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratzliff V, et al. A placebo-controlled trial of subcutaneous Semaglutide in nonalcoholic steatohepatitis. *N Engl J Med.* (2021) 384:1113–24. doi: 10.1056/NEJMoa2028395
- Cen C, Wang W, Yu S, Tang X, Liu B, Liu Y, et al. Development and validation of a clinical and laboratory-based nomogram to predict nonalcoholic fatty liver disease. *Hepatol Int.* (2020) 14:808–16. doi: 10.1007/s12072-020-10065-7
- Nabrdalik K, Kwiendacz H, Irlík K, Hendel M, Drożdż K, Wijata AM, et al. Machine learning identifies metabolic dysfunction-associated Steatotic liver disease in patients with diabetes mellitus. *J Clin Endocrinol Metab.* (2024) 109:2029–38. doi: 10.1210/clinem/dgae060
- Lee JH, Kwon YJ, Park K, Lee HS, Park HK, Han JH, et al. Metabolic score for insulin resistance is inversely related to incident advanced liver fibrosis in patients with non-alcoholic fatty liver disease. *Nutrients.* (2022) 14:3039. doi: 10.3390/nu14153039
- Lee JH, Park K, Lee HS, Park HK, Han JH, Ahn SB. The usefulness of metabolic score for insulin resistance for the prediction of incident non-alcoholic fatty liver disease in Korean adults. *Clin Mol Hepatol.* (2022) 28:814–26. doi: 10.3350/cmh.2022.0099
- Fujii H, Imajo K, Yoneda M, Nakahara T, Hyogo H, Takahashi H, et al. HOMA-IR: an independent predictor of advanced liver fibrosis in nondiabetic non-alcoholic fatty liver disease. *J Gastroenterol Hepatol.* (2019) 34:1390–5. doi: 10.1111/jgh.14595
- Kalavalapalli S, Leiva EG, Lomonaco R, Chi X, Shrestha S, Dillard R, et al. Adipose tissue insulin resistance predicts the severity of liver fibrosis in patients with type 2 diabetes and NAFLD. *J Clin Endocrinol Metab.* (2023) 108:1192–201. doi: 10.1210/clinem/dgac660
- Seeberg KA, Hofso D, Borgeraas H, Grimnes JO, Fatima F, Seeberg LT, et al. Association between hepatic steatosis and fibrosis with measures of insulin sensitivity in patients with severe obesity and type 2 diabetes – a cross-sectional study. *BMC Gastroenterol.* (2022) 22:448. doi: 10.1186/s12876-022-02550-0