Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Atherogenic Combined Index is Independently Associated with MASLD in Type 2 Diabetes: A Cross-Sectional Study

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Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is commonly associated with metabolic disorders such as obesity, diabetes and dyslipidemia. Previous studies have explored the relationship between traditional lipid parameters and MASLD. The atherogenic combined index (ACI), a novel non-traditional lipid marker, has recently been proposed as a potential indicator of coronary artery disease. The relationship between the ACI and MASLD remains unclear. This study aims to investigate this relationship in patients with type 2 diabetes (T2D).

Methods: This cross-sectional study analyzed 2703 patients with T2D. Ultrasound was used to assess MASLD. The clinical and biochemical data were gathered. The ACI was calculated as the base-10 logarithm of the product of triglyceride and non-high-density lipoprotein cholesterol divided by high-density lipoprotein cholesterol. Statistical analyses explored the association between the ACI and MASLD.

Results: Compared to the non-MASLD group, the ACI was higher in the MASLD group ($P < 0.001$). Spearman correlation analysis revealed a positive association between ACI and MASLD ($P < 0.001$). Logistic regression analysis showed that the ACI was independently associated with MASLD. Compared with participants in the lowest ACI quartile (Q1), Q4 (OR: 3.636, 95% CI: 2.361–5.601) showed significantly increased risks of MASLD ($P < 0.001$). Subgroup analyses confirmed that the significant association between ACI and MASLD was consistent across sex (females and males), body mass index (BMI < 24 kg/m² and BMI ≥ 24 kg/m²) and age groups (age < 60 years and age ≥ 60 years).

Conclusion: The ACI is independently correlated with MASLD in T2D patients, supporting its potential as a useful marker for MASLD screening and management in this population.

Keywords: atherogenic combined index, metabolic dysfunction-associated steatotic liver disease, type 2 diabetes

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) was introduced in 2023 through a multi-society Delphi consensus statement to replace the term nonalcoholic fatty liver disease (NAFLD).[1] MASLD is defined by the presence of hepatic steatosis along with at least one cardiometabolic risk factor.[2] This new terminology more accurately describes the underlying pathogenic mechanisms of the disease and highlights the pivotal role of cardiometabolic risk factors. In the context of the global epidemics of type 2 diabetes (T2D), MASLD has become a prevalent chronic liver condition.[3,4] Epidemiological studies estimate that nearly 69% of individuals with T2D have MASLD.[5] This coexistence poses a significant clinical concern, heightening the risk of diabetic complications and accelerating MASLD progression to cirrhosis, hepatocellular carcinoma, and liver-related mortality.[6] Consequently, identifying the risk factors associated with MASLD in T2D patients is crucial. MASLD is closely associated with various metabolic disorders, including

Received: 27 February 2025
Accepted: 28 July 2025
Published: 25 August 2025

obesity, lipid metabolism abnormalities and insulin resistance (IR),[7,8] in which lipid metabolism plays a pivotal role in the pathogenesis of MASLD, influencing processes such as lipogenesis, IR and inflammation.[9] Although liver biopsy is considered the gold standard for diagnosing MASLD, its invasiveness and cost limit its widespread use. Therefore, identifying reliable biomarkers, particularly lipid-related indices, is essential for early screening of MASLD in T2D patients. In our previous study, we explored the relationship between IR surrogate markers, including the insulin resistance metabolic score (METS-IR) and the single-point insulin sensitivity estimator (SPISE), and MASLD, highlighting the crucial role of metabolic parameters in the diagnosis of MASLD.[10,11] However, the role of lipid metabolism-related indicators in MASLD, particularly in the context of T2D, remains underexplored and warrants further investigation.

Atherogenic dyslipidemia, characterized by elevated plasma triglyceride (TG) levels, an increase in small and dense low-density lipoprotein (LDL-c) and a reduction in high-density lipoprotein cholesterol (HDL-c) levels, is commonly observed in patients with MASLD.[12] The prevalence of atherogenic dyslipidemia in MASLD patients ranges from 20% to 80%.[13] Although traditional lipid parameters such as TG, LDL-c, and HDL-c have been closely associated with MASLD,[14] their predictive utility remains controversial. Some studies suggest that certain lipid ratios may provide better predictive value for MASLD, as traditional single lipid parameters cannot fully reflect the complexity and dysregulation of lipid metabolism.[15]

In recent years, several non-traditional lipid parameters have been proposed as potential biomarkers for metabolic risk, including the lipid combination index (LCI), residual cholesterol (RC), castelli risk index I (CRI-I), castelli risk index II (CRI-II), non-high-density lipoprotein cholesterol (non-HDL-c), atherogenic index of plasma (AIP). Although several studies have investigated the relationship between these lipid indices and MASLD, and non-traditional lipid indices have shown promise in predicting MASLD risk, the results remain inconsistent.[16–18]

The atherogenic combined index (ACI), a novel composite marker derived from TG, non-HDL-c, and HDL-c, has been proposed as a potential indicator for coronary artery disease.[19] Unlike the lipoprotein ratios studied previously, ACI integrates both pro-atherogenic and anti-atherogenic components through logarithmic transformation, potentially providing a more nuanced reflection of lipid metabolism dysregulation. However, to date, studies on ACI remain limited, and its potential association with MASLD has yet to be investigated. Given the common underlying mechanisms shared by MASLD and cardiovascular disease, including chronic inflammation, IR and dyslipidemia.[20] This study aims to assess the independent association between ACI and MASLD and evaluate its stability across different sex, BMI, and age subgroups.

Methods

Research Participants

This study included hospitalized patients with T2D, aged 18 years and above, who were admitted to the Department of Endocrinology at Linyi People's Hospital between January 2020 and March 2023. According to the American Diabetes Association (ADA) guidelines,[21] T2D was defined as a fasting blood glucose (FBG) ≥7.0 mmol/L, and/or a 2-hour blood glucose ≥11.1 mmol/L during an oral glucose tolerance test, and/or a glycosylated hemoglobin (HbA1c) ≥6.5%, and/or the use of insulin or oral hypoglycemic agents, along with a self-reported history of physician-diagnosed T2D. Exclusion criteria: (1) patients with other types of diabetes; (2) patients with a history of severe hepato-renal dysfunction, acute infection and stress condition; (3) participants who did not undergo the liver ultrasonography or had incomplete clinical data, such as total cholesterol (TC), HDL-c, TG and LDL-c.

It is essential to highlight that some of the participants in this study were also included in our prior research.[10,11] Despite the overlap in the study population, the focus of this study differs from that of previous investigations. The previous study focused on exploring IR markers and their correlation with MASLD, whereas the present study aims to specifically examine the relationship between ACI, a novel non-traditional lipid marker, and MASLD in patients with T2D, an area not addressed in the previous work. Ultimately, a total of 2703 adults with T2D were enrolled in this study.

Clinical Data and Anthropometric Measurement

Clinical data, including age, sex, diabetes duration and self-reported smoking status, were obtained based on the medical records. The height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by standardized methods. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. An Omron DUALSCAN BIA machine (Omron HDS-2000, Kyoto, Japan) was used for measuring the visceral fat area (VFA) and subcutaneous fat area (SFA). Overweight/obesity was defined as a BMI $\geq$ 24 kg/m^2.

Biochemical Measurements

After an overnight fast, fasting venous blood samples were collected for the measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), serum albumin (Alb), uric acid (UA), serum creatinine (Scr), TG, TC, HDL-c, LDL-c, FBG, HbA1c, urinary albumin-to-creatinine ratio (UACR), fasting C-peptide (FCP) and fasting serum insulin (FINS) levels. A detailed description of the equipment and procedures employed in this study can be found in our previous work.[10,11]

Definition of MASLD

According to the 2023 consensus proposed by three large multinational liver associations, MASLD is defined as hepatic steatosis confirmed by imaging or biopsy, accompanied by at least one of the following five cardiometabolic risk factors: elevated BMI or waist circumference, impaired glucose tolerance or T2D, elevated blood pressure or use of antihypertensive medication, dyslipidemia or use of lipid-lowering agents.[1] In this study, the diagnosis of MASLD was based on the presence of hepatic steatosis detected by ultrasound and the presence of T2D. The ultrasound diagnostic criteria for hepatic steatosis included vascular blurring, deep attenuation, abnormal hepatorenal echo contrast and increased hepatic echogenicity.

Parameter Calculations

(1) non-HDL-c = TC (mg/dL) – HDL-c (mg/dL);[22]
(2) ACI = $\log_{10}$ [TG (mg/dL) × non-HDL-c (mg/dL)/HDL-c (mg/dL)];[19]
(3) LCI = TC (mg/dL) × TG (mg/dL) × LDL-c/HDL-c (mg/dL);[19]
(4) AIP = $\log_{10}$ (TG/HDL-c) (mg/dL);[23]
(5) RC = TC (mg/dL) – HDL-c (mg/dL) – LDL-c (mg/dL);[24]
(6) CRI-I = TC (mg/dL)/HDL-c (mg/dL);[25]
(7) CRI-II = LDL-c (mg/dL)/HDL-c (mg/dL);[25]

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, USA). Normally distributed continuous variables were presented as mean ± SD, while abnormally distributed continuous variables were presented as median and interquartile ranges. Independent-samples *t*-test and Mann–Whitney *U*-test were used to compare normally and abnormally distributed continuous variables, respectively. Analysis of variance (ANOVA) and Student–Newman–Keuls tests were performed for multiple and pairwise comparisons of normally distributed data. Categorical variables were presented as frequencies (n) with proportions (%) and compared using the chi-square test. To avoid multicollinearity, TC, LDL and non-traditional lipid indices such as ACI, non-HDL-c, LCI, AIP RC, CRI-I and CRI-II were transformed into quartile-based variables. Univariate correlation analysis and binary logistic regression were then performed to evaluate the associations between MASLD and the covariates. To test the stability of the analysis results in different subgroups, stratified analyses were conducted based on baseline sex, age (<60 years and ≥60 years) and BMI (<24 kg/m^2 and ≥24 kg/m^2).

Results

General Characteristics of the Study Subjects

Table 1 shows the general characteristics of study subjects. Compared with the non-MASLD group (n = 1610), the BMI, VFA, SFA, SBP, DBP, Alb, AST, ALT, GGT, UA, FBG, FCP, FINS, TG, TC, LDL-c, non-HDL-c, ACI, LCI, AIP, RC,

Table 1 Comparison of Clinical and Biochemical Characteristics Between Non-MASLD and MASLD Groups

Variables	All	Non-MASLD Group	MASLD Group	P
Number (n)	2703	1610	1093	
Age (years)	55.9 ± 13.0	57.7 ± 12.5	53.3 ± 13.4	<0.001
Diabetes duration (years)	7.00 (2.00~12.00)	8.00 (3.00~15.00)	5.00 (1.00~10.00)	<0.001
Sex (males)	1367 (50.6%)	769 (47.8%)	598 (54.7%)	<0.001
Smoking (n, %)	525 (19.4%)	276 (17.2%)	249 (22.8%)	0.003
BMI (kg/m^2)	25.47 ± 3.87	24.20 ± 3.54	27.35 ± 3.55	<0.001
VFA (cm^2)	91.00 (64.00~121.00)	75.00 (51.00~103.00)	111.00 (87.00~138.00)	<0.001
SFA (cm^2)	180.00 (137.00~228.00)	157.00 (119.00~199.00)	213.00 (173.00~257.00)	<0.001
SBP (mmHg)	129.1 ± 18.5	127.6 ± 19.2	131.4 ± 17.2	<0.001
DBP (mmHg)	80.7 ± 11.8	78.7 ± 11.7	83.6 ± 11.4	<0.001
Alb (g/L)	43.32 ± 4.85	42.49 ± 4.97	44.57 ± 4.38	<0.001
AST (U/L)	17.3 (13.9~22.5)	16.8 (13.6~21.2)	18.1 (14.6~25.1)	<0.001
ALT (U/L)	17.9 (13.1~26.9)	16.2 (12.1~23.7)	21.2 (15.2~33.9)	<0.001
GGT (U/L)	22.0 (15.2~32.0)	19.0 (13.1~27.0	27.0 (20.0~40.9)	<0.001
UA (μmolL)	292.00 ± 98.58	277.08 ± 97.09	313.97 ± 96.67	<0.001
Scr (μmol/L)	65.81 ± 20.65	66.33 ± 22.04	65.05 ± 18.39	0.103
UACR (mg/g)	11.15 (5.90~39.48)	12.15 (6.00~52.70)	10.00 (5.70~30.08)	0.001
FBG (mmol/L)	9.28 ± 3.91	8.99 ± 4.07	9.72 ± 3.62	<0.001
FCP (ng/mL)	0.91 (0.54~1.49)	0.71 (0.45~1.17)	1.27 (0.80~1.90)	<0.001
FINS (mU/L)	16.34 (10.37~22.70)	15.73 (9.09~22.35)	17.15 (11.65~22.93)	0.001
HbA1c (%)	9.48 ± 2.28	9.48 ± 2.43	9.49 ± 2.05	0.885
TG (mg/dL)	124.04 (87.71~187.83)	108.09 (76.20~154.16)	155.05 (111.64~241.88)	<0.001
HDL-c (mg/dL)	44.97 ± 12.10	46.97 ± 12.56	42.03 ± 10.72	<0.001
LDL-c (mg/dL)	117.75 ± 40.42	114.75 ± 40.27	122.16 ± 40.26	<0.001
TC (mg/dL)	187.52 ± 49.48	182.47 ± 47.96	194.96 ± 50.74	<0.001
Non-HDL-c (mg/dL)	142.54 ± 48.31	135.50 ± 46.17	152.92 ± 49.52	<0.001
ACI	2.61 ± 0.42	2.50 ± 0.39	2.78 ± 0.40	<0.001
LCI ($x10^{-3}$)	60.83 (30.10~122.58)	46.27 (23.29~89.78)	86.32 (50.19~163.71)	<0.001
AIP	0.46 (0.26~0.68)	0.37 (0.18~0.57)	0.59 (0.39~0.80)	<0.001
RC	0.51 (0.29~0.79)	0.45 (0.24~0.69)	0.61 (0.39~0.95)	<0.001
CRI-I	4.41 ± 1.57	4.10 ± 1.38	4.87 ± 1.38	<0.001
CRI-II	2.76 ± 1.08	2.58 ± 1.06	3.01 ± 1.06	<0.001

Notes: Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions. The Independent-Samples *T* test and Mann–Whitney *U*-test were used for comparisons of normally and abnormally distributed continuous variables between non-MASLD and MASLD groups, respectively. Categorical variables were presented as percentage (%) and were compared by chi-square test. Statistical differences were defined by P (two-tailed) less than 0.05.

Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, serum albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-Glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; UACR, urinary albumin to creatinine ratio; FBG, fasting blood glucose; FCP, fasting c-peptide; FINS, fasting serum insulin; HbA1c, glycated hemoglobin; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; ACI, atherogenic combined index; LCI, lipoprotein combined index; AIP, atherogenic index of plasma; RC, remnant cholesterol; CRI-I, castelli risk index-I; CRI-II, castelli risk index-II; MASLD, metabolic dysfunction-associated steatotic liver disease.

CRI-I, CRI-II and percentages of males and smoking were significantly increased in the MASLD group (n = 1093), while the age, diabetes duration, UACR and HDL-c were significantly decreased (all $P < 0.05$). The HbA1c and Scr were no significant difference between the two groups (all $P > 0.05$).

Quartile cut-off points for the ACI were determined based on the distribution within our study population, using the 25th, 50th (median), and 75th percentiles of the data. Accordingly, the participants were divided into four groups: Q1 (1.38–2.33), Q2 (2.33–2.60), Q3 (2.60–2.87) and Q4 (2.87–4.49) (Table 2). As ACI quartiles increased, the BMI, VFA, SFA, SBP, DBP, Alb, AST, ALT, GGT, UA, Scr, UACR, FBG, FCP, FINS, HbA1c, TG, LDL-c, TC, non-HDL-c, LCI, AIP, RC, CRI-I, CRI-II and percentages of males, smoking and MASLD were gradually increased, while the age,

Table 2 Comparison of Variables According to the Categories of the ACI

Variables	Q1 (1.38–2.33)	Q2 (2.33–2.60)	Q3 (2.60–2.87)	Q4 (2.87–4.49)	P
Age (years)	59.98 ± 11.86	59.28 ± 10.84	56.91 ± 12.52[a]	51.55 ± 14.27[abc]	< 0.001
Diabetes duration (years)	10.00 (5.00~15.00)	10.00 (3.00~13.00)[a]	6.00 (2.00~10.00)[a]	5.00 (2.00~10.00)[abc]	< 0.001
Sex (males, n, %)	313 (46.3%)	339 (50.1%)	330 (49.0%)	385 (56.9%)	< 0.001
Smoking (n, %)	101 (14.9%)	119 (17.6%)	133 (19.7%)	172 (25.4%)	< 0.001
BMI (kg/m^2)	23.71 ± 3.47	24.95 ± 3.58[a]	26.19 ± 3.71[ab]	27.03 ± 3.86[abc]	< 0.001
VFA (cm^2)	66.00 (41.00~95.75)	86.00 (63.00~113.00)[a]	97.00 (76.00~124.00)[ab]	111.50 (85.00~137.25)[abc]	< 0.001
SFA (cm^2)	148.00 (111.00~190.00)	174.00 (134.00~214.00)[a]	192.00 (148.00~238.25)[ab]	205.00 (166.00~250.00)[abc]	< 0.001
SBP (mmHg)	127.6 ± 19.1	127.4 ± 18.0	130.4 ± 18.5[ab]	131.1 ± 18.1[ab]	< 0.001
DBP (mmHg)	77.9 ± 11.7	79.6 ± 11.0[a]	81.7 ± 12.1[ab]	83.7 ± 11.7[abc]	< 0.001
Alb (g/L)	42.67 ± 5.07	43.50 ± 4.18[a]	43.48 ± 4.38[a]	43.65 ± 5.59[a]	0.001
AST (U/L)	17.80 (14.40~22.88)	16.70 (13.60~20.55)[a]	16.80 (13.40~21.80)[a]	18.00 (14.20~25.98)[abc]	< 0.001
ALT (U/L)	17.10 (12.78~24.70)	16.80 (12.70~26.60)	18.00 (12.88~26.60)	20.60 (14.25~35.00)[abc]	< 0.001
GGT (U/L)	17.00 (12.00~24.00)	19.65 (15.00~27.00)[a]	24.00 (17.00~32.63)[ab]	30.00 (21.00~46.00)[abc]	< 0.001
UA (μmolL)	259.52 ± 89.70	279.46 ± 93.09[a]	296.71 ± 87.56[ab]	332.35 ± 108.01[abc]	< 0.001
Scr (μmol/L)	63.61 ± 18.31	65.21 ± 21.01	65.77 ± 19.41	68.65 ± 23.25[abc]	< 0.001
UACR (mg/g)	9.90 (5.00~36.20)	9.55 (5.70~25.75)	11.70 (6.15~38.70)	15.00 (6.60~74.00)[abc]	< 0.001
FBG (mmol/L)	8.12 ± 3.85	8.80 ± 3.51[a]	9.38 ± 3.46[ab]	10.84 ± 4.24[abc]	< 0.001
FCP (ng/mL)	0.61 (0.38~1.03)	0.77 (0.50~1.30)[a]	1.02 (0.65~1.54)[ab]	1.31 (0.80~1.97)[abc]	< 0.001
FINS (mU/L)	15.17 (8.58~22.02)	15.43 (9.16~22.10)	17.04 (11.44~22.22)[a]	17.77 (12.32~24.37)[ab]	0.001
HbA1c (%)	9.00 ± 2.24	9.42 ± 2.40[a]	9.47 ± 2.19[a]	10.04 ± 2.19[abc]	< 0.001
TG (mg/dL)	69.11 (57.59~83.28)	105.43 (91.26~122.27)	146.19 (124.93~171.00)	259.60 (206.44~350.86)	< 0.001
HDL-c (mg/dL)	54.49 ± 13.13	46.39 ± 9.82[a]	41.72 ± 8.60[ab]	37.29 ± 8.98[abc]	< 0.001
LDL-c (mg/dL)	91.65 ± 30.76	114.92 ± 32.71[a]	128.57 ± 36.29[ab]	135.85 ± 45.52[abc]	< 0.001
TC (mg/dL)	156.93 ± 38.53	177.86 ± 38.44[a]	192.90 ± 40.99[ab]	222.33 ± 53.69[abc]	< 0.001
Non-HDL-c (mg/dL)	102.44 ± 30.90	131.47 ± 31.69[a]	151.18 ± 35.57[ab]	185.04 ± 49.98[abc]	< 0.001
LCI ($x10^{-3}$)	19.56 ± 9.17	46.86 ± 15.10[a]	87.95 ± 28.46[ab]	278.63 ± 30.58[abc]	< 0.001
AIP	0.13 (0.02~0.23)	0.36 (0.28~0.44)[a]	0.55 (0.47~0.63)[ab]	0.85 (0.72~1.01)[abc]	< 0.001
RC	0.26 (0.13~0.42)	0.43 (0.25~0.58)[a]	0.58 (0.41~0.75)[ab]	1.05 (0.79~1.38)[abc]	< 0.001
CRI-I	2.93 ± 0.56	3.87 ± 0.59[a]	4.68 ± 0.80[ab]	6.15 ± 1.72[abc]	< 0.001
CRI-II	1.72 ± 0.55	2.50 ± 0.59[a]	3.12 ± 0.81[ab]	3.69 ± 1.11[abc]	< 0.001
MASLD	120 (17.8%)	230 (34.0%)	322 (47.8%)	422 (62.2%)	< 0.001

Notes: Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions which were log-transformed (base 10) before parametric tests. Analysis of variance (ANOVA) and Student–Newman–Keuls tests were performed for multiple and pairwise comparisons of normally distributed data. Categorical variables were presented as percentage (%), and were compared by chi-square test. Statistical differences were defined by P (two-tailed) less than 0.05.[a] P<0.05 versus Q1; [b] P<0.05 versus Q2; [c] P<0.05 versus Q3.

Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, serum albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-Glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; UACR, urinary albumin to creatinine ratio; FBG, fasting blood glucose; FCP, fasting c-peptide; FINS, fasting serum insulin; HbA1c, glycated hemoglobin; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; ACI, atherogenic combined index; LCI, lipoprotein combined index; AIP, atherogenic index of plasma; RC, remnant cholesterol; CRI-I, castelli risk index-I; CRI-II, castelli risk index-II; MASLD, metabolic dysfunction-associated steatotic liver disease.

diabetes duration and HDL-c were gradually decreased (all $P < 0.05$). The change in MASLD prevalence stratified by ACI quartiles is shown in Figure 1.

Spearman Correlation Analysis

To control potential multicollinearity, TC, LDL and non-traditional lipid indices such as ACI, non-HDL-c, LCI, AIP RC, CRI-I and CRI-II were transformed into quartile-based variables. Table 3 shows the correlations between MASLD and each variable. According to the Spearman correlation analysis, MASLD was positively related to the smoking, BMI, VFA, SFA, SBP, DBP, Alb, AST, ALT, GGT, UA, FBG, FCP, FINS, TG, TC quartile, LDL-c quartile, non-HDL-c quartile, ACI quartile, LCI quartile, AIP quartile, RC quartile, CRI-I quartile and CRI-II quartile, but negatively correlated with sex, age, diabetes duration, HDL-c and UACR (all $P < 0.05$). The HbA1c and Scr were not related to MASLD (both $P > 0.05$). Figure 2 displays the Spearman correlation coefficients between the variables, which span from −1.0 to 1.0. A value of 1.0 indicates a perfect positive correlation, while −1.0 signifies a strong negative correlation.

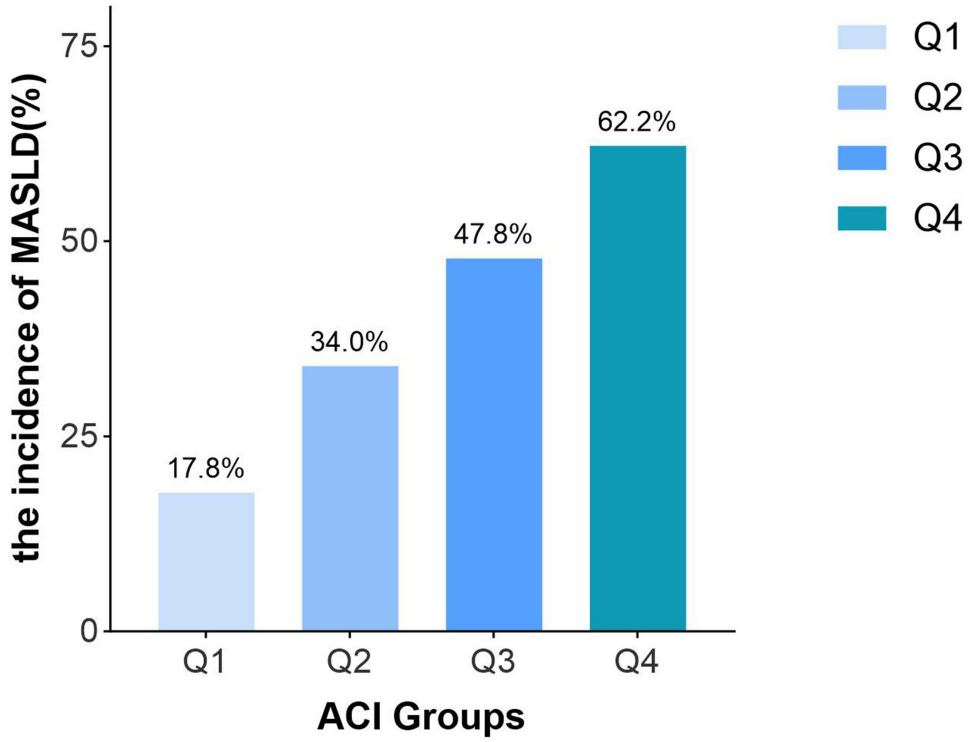

Figure 1 The bar chart shows the prevalence of MASLD stratified by ACI quartiles.

Multivariate Analysis

MASLD was served as the dependent variable, the smoking, BMI, VFA, SFA, SBP, DBP, Alb, AST, ALT, GGT, UA, FBG, FCP, TG, TC quartile, LDL-c quartile, non-HDL-c quartile, ACI quartile, LCI quartile, AIP quartile, RC quartile, CRI-I quartile, CRI-II quartile, sex, age, diabetes duration, HDL-c and UACR were set as the independent variables, the logistic regression analysis was performed and the results were presented in Table 4. Finally, we found that among the numerous lipid indicators, only the ACI quartile entered the regression equation. Compared with the first quartile (Q1) of ACI, subjects in the highest quartile (Q4) had a 3.636-fold increased risk of MASLD (OR: 3.636, 95% CI: 2.361–5.601).

Table 3 The Correlation Between MASLD and Different Variables by Univariate Analysis

	Correlation Coefficient	P
Age	−0.165	<0.001
Diabetes duration	−0.203	<0.001
Sex	−0.068	<0.001
Smoking	0.077	<0.001
BMI	0.420	<0.001
VFA	0.431	<0.001
SFA	0.421	<0.001
SBP	0.113	<0.001
DBP	0.214	<0.001
Alb	0.228	<0.001
AST	0.134	<0.001
ALT	0.249	<0.001

(*Continued*)

Table 3 (Continued).

	Correlation Coefficient	P
GGT	0.347	<0.001
UA	0.208	<0.001
Scr	0.017	0.363
UACR	−0.063	0.001
FBG	0.134	<0.001
FCP	0.370	<0.001
FINS	0.080	0.001
HbA1c	0.026	0.189
TG	0.338	<0.001
HDL-c	−0.209	<0.001
LDL-c quartile	0.095	<0.001
TC quartile	0.111	<0.001
Non-HDL-c quartile	0.180	<0.001
ACI quartile	0.335	<0.001
LCI quartile	0.308	<0.001
AIP quartile	0.324	<0.001
RC quartile	0.211	<0.001
CRI-I quartile	0.258	<0.001
CRI-II quartile	0.217	<0.001

Notes: Correlation coefficients between MASLD and different variables were determined by Spearman correlation analysis.

Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, serum albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ- Glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; UACR, urinary albumin to creatinine ratio; FBG, fasting blood glucose; FCP, fasting c-peptide; FINS, fasting serum insulin; HbA1c, glycated hemoglobin; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; ACI, atherogenic combined index; LCI, lipoprotein combined index; AIP, atherogenic index of plasma; RC, remnant cholesterol; CRI-I, castelli risk index-I; CRI-II, castelli risk index-II; MASLD, metabolic dysfunction-associated steatotic liver disease.

And FCP (OR: 1.251, 95% CI: 1.033–1.515), Alb (OR: 1.060, 95% CI: 1.024–1.096), VFA (OR: 1.011, 95% CI: 1.007–1.016), SFA (OR: 1.008, 95% CI: 1.005–1.011), DBP (OR: 1.028, 95% CI: 1.012–1.046) and diabetes duration (OR: 0.976, 95% CI: 0.956–0.998) were also independently related to MASLD.

Subgroup Analysis

We further stratified all subjects based on BMI, sex and age to explore the relationship between lipid parameters and MASLD in different populations (Figure 3). After adjusting for covariates based on the Spearman analysis results in each subgroup, ACI was found to be independently associated with MASLD across all subgroups.

Discussion

In this study, we found that the ACI was positively associated with MASLD in patients with T2D. After adjusting for potential confounders, the ACI remained an independent risk factor for MASLD. Notably, this association was significant across various subgroups.

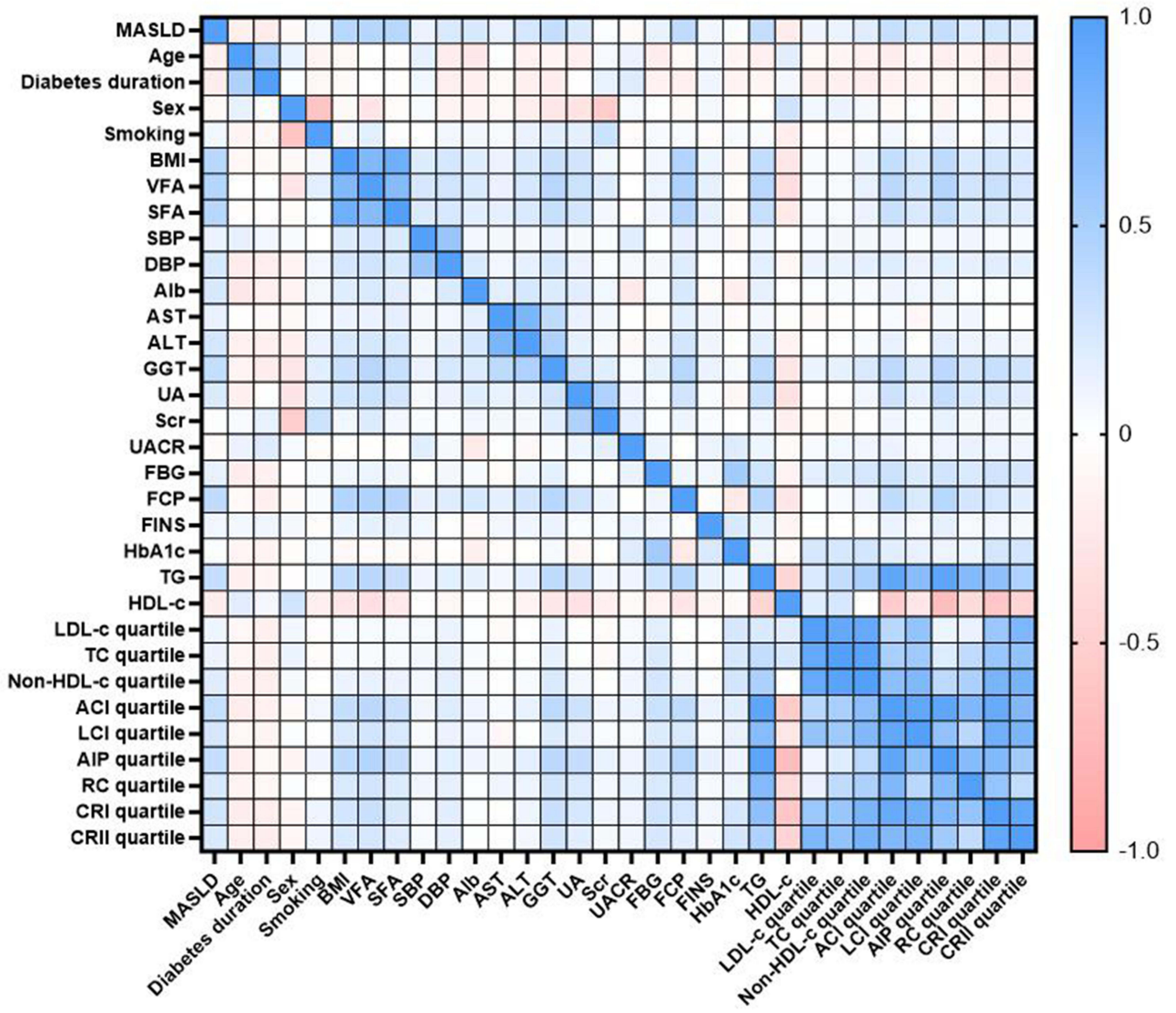

Figure 2 The heatmap illustrates the Spearman correlation coefficients between the variables. A blue color indicates a strong positive correlation (near +1), while red signifies a strong negative correlation (close to −1). White represents either a weak correlation or no significant correlation (approaching 0).

Currently, large-scale epidemiological studies on MASLD are limited. However, emerging evidence shows a high concordance between NAFLD and MASLD definitions, with about 99% of NAFLD patients meeting MASLD criteria.[26] Thus, findings from NAFLD studies remain relevant and can serve as a reference for MASLD research. MASLD is a liver disease closely associated with obesity, IR, T2D, hypertension, dyslipidemia, and metabolic syndrome.[27] In previous studies, we analyzed the relationship between IR surrogate markers and MASLD.[10,11] Building on these findings, the current study shifts its focus to explore the relationship between dyslipidemia and MASLD. Dyslipidemia is known to play a critical role in both the onset and progression of MASLD.[14] Previous studies have explored the relationship between lipid levels and lipid ratios with MASLD, with results suggesting that lipid ratios are more effective at detecting MASLD than single lipid parameters. This may be since lipid ratios reflect the interactions between lipid components.[28]

The ACI is a recently proposed lipid marker for predicting coronary artery disease,[19] incorporating TG, HDL-c and non-HDL-c. Our research found it is closely associated with MASLD. Elevated TG levels are known to lead to liver fat accumulation,[29] while reduced HDL-c impairs the liver's ability to clear excess lipids and protect against oxidative stress.[19] Non-HDL-c, which includes LDL-c and very-low-density lipoprotein (VLDL), has been shown to contribute to

Table 4 The Relative Risk for MASLD by Logistic Regression Analysis

Variables	B	SE	Wald	P	OR	95.0% CI for OR
ACI quartile						
Q1 (1.38–2.33)	–	–	34.674	<0.001	–	–
Q2 (2.33–2.60)	0.617	0.210	8.588	0.003	1.853	1.227–2.799
Q3 (2.60–2.87)	0.670	0.208	10.399	0.001	1.955	1.301–2.938
Q4 (2.87–4.49)	1.291	0.220	34.326	<0.001	3.636	2.361–5.601
FCP	0.224	0.098	5.260	0.022	1.251	1.033–1.515
Alb	0.058	0.017	11.110	0.001	1.060	1.024–1.096
VFA	0.011	0.002	21.757	<0.001	1.011	1.007–1.016
SFA	0.008	0.001	27.214	<0.001	1.008	1.005–1.011
DBP	0.028	0.008	11.247	0.001	1.028	1.012–1.046
Diabetes duration	−0.024	0.011	4.733	0.030	0.976	0.956–0.998

Notes: The independent variables for MASLD were assessed by logistic regression analysis.
Abbreviations: ACI, atherogenic combined index; FCP, fasting c-peptide; Alb, serum albumin; VFA, visceral fat area; SFA, subcutaneous fat area; DBP, diastolic blood pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; SE, standard error; CI, confidence interval; OR, odd ratio.

atherogenic processes, facilitating lipid deposition in the liver.[15] The individual components of ACI are highly correlated with MASLD through the pathways described above, which supports its utility in predicting the occurrence of MASLD.

Research on ACI is limited, and its potential association with MASLD has yet to be investigated. This study is the first to reveal the association between ACI and MASLD, thereby extending the potential utility of ACI beyond cardiovascular diseases to liver metabolic disorders. This extension may be attributed to the common underlying mechanisms shared by MASLD and cardiovascular disease, including chronic inflammation, insulin resistance and dyslipidemia.[20] Furthermore, the results show that none of the individual components of ACI were included in the regression equation, suggesting that ACI, as a comprehensive index, is more valuable than individual indicators in predicting MASLD. Additionally, several non-traditional lipid parameters such as RC, AIP, CRI-I, CRI-II and LCI have also been shown to be closely related to metabolic diseases such as diabetes, MASLD and metabolic syndrome.[15,30,31] Unlike previous studies, this research not only included the aforementioned non-traditional lipid parameters but also incorporated the latest lipid index, ACI, providing a more comprehensive analysis. After adjusting for other variables,

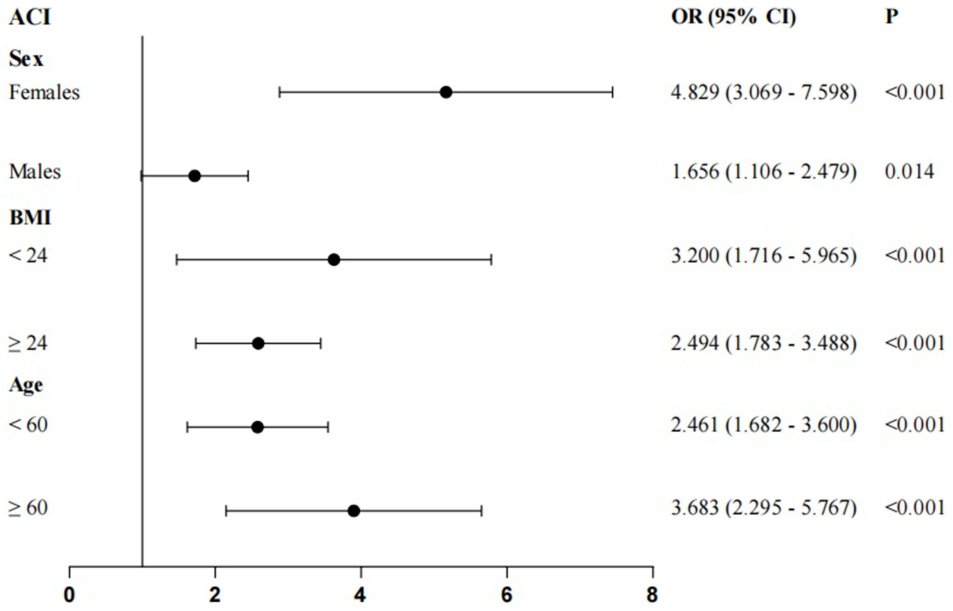

Figure 3 The forest plot shows the independent association between ACI and MASLD after stratification by sex, BMI, and age.

https://doi.org/10.2147/DMSO.S523139

only ACI remained independently associated with MASLD, further suggesting that the relationship between ACI and MASLD may be stronger than that of other lipid indices, highlighting its potential clinical value. As a novel lipid index, ACI proved to be a more valuable screening tool for MASLD than previously studied lipid parameters and may assist clinicians in the early identification and management of MAFLD risk in patients with T2D.

Notably, the association between the ACI and MASLD was significantly present in various subgroups. This consistent association underscores the robustness of ACI as a risk factor of MASLD regardless of differences in sex, BMI or age. During the subgroup analysis, several interesting results were also observed: (1) The association between ACI and MASLD was stronger in individuals with BMI <24 than in those with BMI ≥24, which may seem counterintuitive. However, similar findings have been reported in previous studies, suggesting that non-traditional lipid indices may better predict MASLD risk in low-weight individuals.[28] Moreover, several recent studies have highlighted that non-obese individuals are also susceptible to metabolic disturbances, which may be linked to gut microbiota dysbiosis and genetic predisposition.[28,32] It is also noteworthy that approximately 40% of MASLD patients worldwide are classified as non-obese. These findings underscore the need to include individuals with lower BMI in MASLD risk assessment and to implement early, targeted interventions to mitigate disease burden. (2) The results indicated that ACI was more strongly associated with MASLD in female patients. One possible explanation is the hormonal and age-related characteristics of our female participants, with an average age of 57.56 ± 12.71, suggesting most were likely postmenopausal. Due to the decreased secretion of ovarian estrogen after menopause, the inhibition of visceral fat accumulation is reduced. This may lead to an increase in visceral obesity, weight gain, and lipid metabolism disorders, which in turn increases susceptibility to MASLD.[33,34] This underscores the importance of analyzing and considering the reproductive cycle when analyzing sex-based differences in clinical studies of MASLD.

Furthermore, we found that several clinical factors, including obesity indicators (VFA and SFA), DBP, diabetes duration, serum Alb and FCP levels, were independently associated with MASLD. Obesity, particularly VFA, reflects visceral fat accumulation and insulin resistance, and is closely related to MASLD.[35] Our study also indicates that DBP is an independent risk factor for MASLD, with hypertension linked to increased fibrosis progression.[36] Inhibition of the renin-angiotensin-aldosterone system may help improve NASH and liver fibrosis.[37] This study further confirms that a shorter duration of diabetes is associated with MASLD, consistent with previous reports.[38] Furthermore, the FCP levels, reflecting insulin secretion, were independently associated with MASLD risk.[39] Although low serum Alb levels are usually associated with poor prognosis in MASLD, this study found that high serum Alb levels were independently associated with MASLD. This finding is consistent with previous studies, which showed that elevated Alb levels were linked to metabolic diseases, including insulin resistance, MASLD and metabolic syndrome.[40–42] This phenomenon may be related to factors such as patient characteristics, lifestyle and early disease diagnosis. Future research should further explore the relationship between Alb levels and MASLD, especially in patients at different stages of the disease.

Limitations

First, while our findings show a strong association between ACI and MASLD, MASLD may also contribute to lipid metabolism changes, rather than just resulting from dyslipidemia. The cross-sectional design limits our ability to clarify the causal relationship, emphasizing the need for future prospective research to establish the temporal sequence. Second, MASLD was assessed using ultrasound, which may miss mild hepatic steatosis compared to liver biopsy. Future studies could incorporate more precise methods, such as transient elastography with controlled attenuation parameters (CAP), MRI-proton density fat fraction (MRI-PDFF) or liver biopsy, to ensure accurate diagnosis and enhance result reliability. Finally, potential confounders such as lipid-lowering medication (statins), dietary patterns, physical activity, and anti-diabetic treatments (insulin or sulfonylureas) were not systematically collected or controlled, which may have influenced lipid levels and confounded the observed association between ACI and MASLD. Prospective studies with comprehensive data collection and adjustment for these factors are needed to validate our findings.

Conclusion

In conclusion, this study found that ACI is significantly associated with MASLD in patients with T2D and serves as an independent risk factor. Moreover, ACI demonstrated stable associations across different sex, age, and BMI subgroups,

further supporting its potential predictive value for MASLD. Future studies should further validate the application of ACI in the screening and management of MASLD in T2D patients.

Ethics Approval and Consent to Participate

The study received approval from the Human Ethics Committee of Linyi People's Hospital. All procedures followed the ethical guidelines outlined in the Declaration of Helsinki. Informed consent was obtained from all participating patients.

Funding

This study was funded by the Postdoctoral Program of the Affiliated Hospital of Jining Medical University (JYFY322152), and the Key Research and Development Program of Linyi City (2024YX004).

Disclosure

The authors declare no competing interests related to this study. Jie Sheng and Shuwei Shi contributed equally to this work and are co-first authors.

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