



Trabajo Original

Obesidad y síndrome metabólico

The association between atherogenic index of plasma and metabolic dysfunction-associated fatty liver disease as detected by FibroScan

Asociación entre el índice aterogénico del plasma y la enfermedad hepática grasa asociada a disfunción metabólica detectada por FibroScan

Aili Wang^{1,2}, Jialin Li¹, Li Li¹, Huiqing Ding³, Naibin Yang⁴, Miao Xu¹

¹Department of Endocrinology and Metabolism. The First Affiliated Hospital of Ningbo University; ²Health Science Center. Ningbo University; ³Department of Obstetrics and Gynecology. The First Affiliated Hospital of Ningbo University. ⁴Department of Infection and Liver Diseases. The First Affiliated Hospital of Ningbo University. Ningbo, Zhejiang. People's Republic of China

Abstract

Objectives: this study aimed to explore the potential of the atherogenic index of plasma (AIP) as a predictor of metabolic dysfunction-associated fatty liver disease (MAFLD).

Methods: a cross-sectional study, including data from 4473 participants in the National Health and Nutrition Examination Survey (NHANES) 2017-2018, was performed. A control attenuation parameter (CAP) ≥ 285 dB/m was used to confirm hepatic steatosis. Degrees of liver stiffness were confirmed according to liver stiffness measurement (LSM). Weighted multivariate logistic regression models were used to assess the association between AIP and the risk for MAFLD and liver fibrosis. Finally, receiver operating characteristic (ROC) curve analysis was used to test the accuracy of AIP in predicting MAFLD.

Results: the association between AIP and the prevalence of MAFLD was positive in all three multivariate logistic regression models (model 1, odds ratio (OR), 18.2 (95 % confidence interval (CI), 14.4-23.1); model 2, OR, 17.0 (95 % CI, 13.3-21.8); model 3, OR, 5.2 (95 % CI, 3.9-7.0)). Moreover, this positive relationship was found to be significant in patients of different sexes and whether they had diabetes. However, no significant differences were observed between AIP and significant fibrosis or cirrhosis as assessed by different liver fibrosis indices. Finally, ROC curve analysis demonstrated that the AIP index also demonstrated positive diagnostic utility (area under the ROC curve, 0.733 (95 % CI, 0.718-0.747); $p < 0.001$).

Conclusion: This study revealed a positive association between AIP and MAFLD among American adults. Furthermore, this association persisted in different sexes and whether they had diabetes.

Keywords:

National Health and Nutrition Examination Survey. Metabolic dysfunction-associated fatty liver disease. Atherogenic index of plasma. Vibration-controlled transient elastography. Diagnostics.

Received: 23/08/2023 • Accepted: 29/12/2023

Data availability statement: the data are publicly available on the Internet for researchers around the world at <http://www.cdc.gov/nchs/nhanes/>

Ethics statement: the ethics review board of the National Center for Health Statistics approved all NHANES protocols. The patients/participants provided their written informed consent to participate in this study.

Acknowledgments: the authors are grateful to the staff and the participants of the NHANES study for their valuable contributions.

Naibin Yang (maf1d2021@163.com and fyayangnaibin@nbu.edu.cn) and Miao Xu (wzmcxm@126.com and fyxumiao@nbu.edu.cn) are considered the corresponding author of this article.

Conflicts of interest: the authors declare that there are no conflicts of interest regarding this paper.

Artificial intelligence: the authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Wang A, Li J, Li L, Ding H, Yang N, Xu M. The association between atherogenic index of plasma and metabolic dysfunction-associated fatty liver disease as detected by FibroScan. *Nutr Hosp* 2024;41(2):384-392
DOI: <http://dx.doi.org/10.20960/nh.04891>

Correspondence:

Miao Xu. Department of Endocrinology and Metabolism. The First Affiliated Hospital of Ningbo University. NO. 59 Liuting Street, Haishu District. Ningbo, Zhejiang 315010. People's Republic of China
e-mails: wzmcxm@126.com; fyxumiao@nbu.edu.cn

Resumen

Objetivos: este estudio tuvo como objetivo explorar el potencial del índice aterogénico del plasma (AIP) como predictor de enfermedad hepática grasa asociada a disfunción metabólica (MAFLD).

Métodos: se realizó un estudio transversal que incluyó datos de 4473 participantes de la encuesta nacional de exámenes de salud y nutrición (NHANES) 2017-2018. Se utilizó un parámetro de atenuación de control (CAP) ≥ 285 dB/m para confirmar la esteatosis hepática. Los grados de rigidez hepática se confirmaron de acuerdo con la medición de rigidez hepática (LSM). Se utilizaron modelos de regresión logística multivariados para evaluar la asociación entre AIP y el riesgo de MAFLD y fibrosis hepática. Por último, se utilizó el análisis de la curva ROC para probar la precisión de la AIP en la predicción de la MAFLD.

Resultados: la asociación entre AIP y prevalencia de MAFLD fue positiva en los tres modelos de regresión logística multivariable (modelo 1, odds ratio (OR): 18,2 (intervalo de confianza (IC) del 95 %: 14,4-23,1); Modelo 2, OR: 17,0 (IC del 95 %: 13,3-21,8); Modelo 3, OR: 5,2 (IC del 95 %: 3,9-7,0)). Además, esta relación positiva se encontró significativa en pacientes de diferentes sexos ya tuvieran o no diabetes. Sin embargo, no se observaron diferencias significativas entre la AIP y la fibrosis o cirrosis significativa evaluada por diferentes índices de fibrosis hepática. Finalmente, el análisis de la curva ROC demostró que el índice AIP también demostró utilidad diagnóstica positiva (área bajo la curva ROC = 0,733 (IC del 95 %: 0,718-0,747); $p < 0,001$).

Conclusión: este estudio reveló una asociación positiva entre AIP y MAFLD en los adultos estadounidenses. Además, esta asociación persistió en los diferentes sexos ya tuvieran o no diabetes.

Palabras clave:

Encuesta Nacional de Exámenes de Salud y Nutrición. Enfermedad hepática grasa asociada a disfunción metabólica. Índice aterogénico del plasma. Elastografía transitoria de vibración controlada. Diagnósticos.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a complex liver disorder that can be broadly defined as the presence of steatosis and liver inflammation in more than 5 % of liver cells on liver biopsy in individuals with metabolic disorders without heavy alcohol consumption (1-3). Epidemiological studies have shown that NAFLD affects approximately 30 % of the global adult population and is the most common chronic liver disease, especially in the United States (4,5). Studies have found that NAFLD not only leads to liver cirrhosis and cancer but also increases the risk for extrahepatic complications, including type 2 diabetes mellitus (T2DM), dyslipidemia, metabolic syndrome, and cardiovascular disease (CVD) (6,7). It is worth noting that in early 2020, an international panel of experts proposed to replace NAFLD with a new term: "metabolic dysfunction-associated fatty liver disease (MAFLD)" to better reflect the underlying pathological mechanism and its close correlation with metabolic comorbidities (8). In contrast to NAFLD, the recently proposed diagnostic criteria for MAFLD incorporate one of three criteria, in addition to a pathophysiological basis for hepatic steatosis: overweight/obesity, manifestation of T2DM, or the presence of metabolic disorders (8). Although an increasing number of studies have focused on the mechanism of MAFLD and related diseases, no effective monitoring index for MAFLD has been available to date (9). Therefore, there is an urgent need for a highly sensitive and specific surveillance index to detect MAFLD early (10).

The atherogenic index of plasma (AIP)—the logarithm of molar ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C)—is a valid indicator for assessing serum lipid levels (11,12). It has demonstrated good performance in predicting metabolic diseases, including T2DM, atherosclerosis, and CVD (13,14). Moreover, MAFLD has been widely reported to co-exist with metabolic diseases (15). As such, the aim of the present study was to investigate the potential association between AIP and MAFLD. Recent studies have shown a significant association between AIP and MAFLD in cohorts from Iran and Chinese Han population (16,17). However, the association between AIP and MAFLD in American population remains unclear. This study

aimed to detect a possible link between AIP and MAFLD and explore the potential of AIP as a predictor of MAFLD.

We analyzed data from the National Health and Nutrition Examination Survey (NHANES) 2017-2018 and conducted a large cross-sectional study to investigate the relationship between AIP and MAFLD in general United States population. Additionally, we explored the relationship between AIP and liver fibrosis.

RESEARCH DESIGN AND METHODS

DATA SOURCES

Data for the present study were obtained from the NHANES, 2017-2018. Detailed information regarding NHANES data is available at www.cdc.gov/nchs/nhanes/. The Institutional Review Board of National Center for Health Statistics (NCHS) approved all NHANES survey protocols, and informed consent was obtained from each participant.

PARTICIPANTS

Among the 9254 participants included in the NHANES 2017-2018 cycle, 550 with no available data regarding mobile examination centers (MECs), 2717 participants lacked transient elastography results (including 258 identified as ineligible results and 2459 with missing transient elastography data), and 493 who underwent partial examinations with unsatisfactory and inadequate results were excluded. Furthermore, 748 individuals < 18 years of age were excluded. Moreover, 273 without available HDL-C or TG data were also eliminated. Ultimately, data from 4473 individuals were included in the final analysis.

VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE)

As a convenient, rapid, and noninvasive technique, VCTE has been widely adopted for the diagnosis of liver steatosis and fi-

brosis. The controlled attenuation parameter (CAP) was measured to assess liver steatosis, and liver stiffness measurement (LSM) was used to confirm liver fibrosis (18). Hepatic steatosis was defined as a CAP value ≥ 285 dB/m, as previously reported (19). LSM ≥ 8.2 , ≥ 9.7 and ≥ 13.6 kPa were confirmed to indicate significant fibrosis (\geq F2), advanced fibrosis (\geq F3) and cirrhosis (F4) (20,21).

NON-INVASIVE FIBROSIS ASSESSMENT

The liver fibrosis index was also determined based on NAFLD Fibrosis Score (NFS), fibrosis 4 score (FIB-4) and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) values (22).

$NFS = -1.675 + 0.037 \times \text{age (yrs)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{impaired fasting glycemia (IFG) or T2DM} + 0.99 \times \text{AST (U/L)} / \text{ALT (U/L)} - 0.013 \times \text{platelet count (PLT)} - 0.66 \times \text{albumin (g/dL)}$

$FIB-4 = (\text{age} \times \text{AST}) / (\text{PLT} \times 10^9/\text{L} \times \text{ALT}^{1/2})$

$APRI = ((\text{AST}/\text{ULN}) / \text{PLT} \times 10^9/\text{L}) \times 100$.

The published APRI threshold of 1.5, FIB-4 of 2.67, and NFS of 0.675 were first considered preferred for diagnosing advanced fibrosis (\geq F3).

DIAGNOSTIC CRITERIA

Diagnostic criteria for MAFLD incorporate one of three criteria, in addition to a pathophysiological basis for hepatic steatosis: overweight/obesity, manifestation of T2DM, or the presence of metabolic disorders (8). Metabolic abnormalities were characterized by the presence of at least two of the following conditions: 1) waist circumference $\geq 102/88$ cm in Caucasian men and women; 2) blood pressure $\geq 130/85$ mmHg or specific drug treatment; 3) plasma triglycerides ≥ 150 mg/dl or specific drug treatment; 4) plasma HDL-cholesterol < 40 mg/dl in men and < 50 mg/dl in women or specific drug treatment; 5) Prediabetes (i.e., fasting glucose levels 5.6 to 6.9 mmol/L, or HbA1c = 5.7 % to 6.4 %); 6) homeostasis model assessment of insulin resistance score ≥ 2.5 ; 7) plasma high-sensitivity C-reactive protein level > 2 mg/L (19,23).

VARIABLES

AIP was regarded to be an independent variable in this study. AIP was calculated using the following equation: $\log(\text{TG [mmol/L]} / \text{HDL-C [mmol/L]})$. Participants were separated into four groups according to AIP index: Q1 (range, -0.88 to -0.23 [$n = 1118$]), Q2 (range, -0.23 to -0.01 [$n = 1118$]), Q3 (range, -0.01 to 0.21 [$n = 1118$]), and Q4 (range, 0.21 to 1.64 [$n = 1119$]). MAFLD and liver fibrosis were considered to be dependent variables. Demographic information, including age, sex, and race/ethnicity, was obtained using self-administered questionnaires. Additional covariates, including height, weight and waist circumference, were collected during MEC. T2DM was diagnosed as previously reported (24): with any of the following 1) A self-reported diag-

nosis of diabetes; 2) Use of anti-diabetic drugs; 3) A Hemoglobin A1c (HbA1c) level $\geq 6.5\%$ (48 mmol/mol); 4) a fasting plasma glucose level of ≥ 126 mg/dL; 5) A random plasma glucose ≥ 200 mg/dl. A diagnosis of hypertension was made in any of the following situations: previous physician diagnosis; currently taking prescribed blood pressure medications; or blood pressure $\geq 140/90$ mmHg (25). Physical activity was divided into three groups based on previously published studies: < 600 , 600-7999, and ≥ 8000 metabolic equivalent task (i.e., "MET") min/week (26). The poverty to income ratio (PIR) is the official poverty measure in the United States (27), which measures an individual's economic status and family size to provide a more accurate estimate of an individual's poverty threshold. Participants were divided into three categories based on PIR: low-income (PIR < 1.30); middle-income (PIR 1.30-3.49); and high-income (PIR ≥ 3.50) (28). Significant alcohol intake was defined as > 2 standard drinks/day for women and > 3 standard drinks/day for men in the last 12 months (29). Among the studied conditions, several questions dealt with previous coronary artery disease (CAD), stroke, angina/angina pectoris and congestive heart failure (HF). CVD was defined as a previous history of CAD and/or stroke and/or angina.

STATISTICAL METHODS

All analyses were performed using the *EmpowerStats* software based on the R package version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as median (interquartile range [i.e., Q1-Q3]) and categorical variables are expressed as n (%). Weight was considered during the analysis. Differences with $p < 0.05$ were considered to be statistically significant. Multivariate logistic regression models were used to assess the association between AIP values and MAFLD in American adults. Three statistical models were established based on the unadjusted and adjusted covariates. Finally, the accuracy of the AIP index in predicting MAFLD was tested using receiver operating characteristic (ROC) curve analysis.

RESULTS

Of 4473 participants, 2189 (48.9 %) were diagnosed with MAFLD, and 2284 (51.1 %) were included in the non-MAFLD group (Table I). Compared with individuals in the non-MAFLD group, patients with MAFLD tended to be older, male, with diabetes and hypertension, and exhibited a higher body mass index (BMI), waist circumference, AST, ALT, gamma-glutamyl transferase (GGT), glycohemoglobin, TG, and HDL-C levels ($p < 0.05$). It's noteworthy that patients with MAFLD exhibited higher AIP than those in the non-MAFLD group ($p < 0.001$). However, no significant differences were found in CVD ($p = 0.852$), CHF ($p = 0.203$), PLT ($p = 0.057$) and serum creatinine ($p = 0.142$) levels between MAFLD and non-MAFLD groups.

Table I. Weight characteristics of the study participants

Parameters	Total	Non-MAFLD	MAFLD	p-value
Patients, n (%)	4473 (100 %)	2284 (51.1 %)	2189 (48.9 %)	< 0.001
CAP (dB/m)	264 (218-308)	219 (194-241)	309 (284-341)	< 0.001
LSM (kPa)	4.9 (4.0-6.1)	4.5 (3.7-5.6)	5.4 (4.4-6.8)	< 0.001
Age (years)	51 (33-64)	45 (29-62)	55 (40-65)	< 0.001
Men, n (%)	2202 (49.2 %)	1020 (44.7 %)	1182 (54.0 %)	0.003
<i>Race/Ethnicity, n (%)</i>				
Mexican American	644 (14.4 %)	238 (10.4 %)	406 (18.5 %)	< 0.001
Other Hispanic	430 (9.6 %)	222 (9.7 %)	208 (9.5 %)	
Non-Hispanic White	1533 (34.3 %)	764 (33.5 %)	769 (35.1 %)	
Non-Hispanic Black	985 (22.0 %)	346 (15.1 %)	288 (13.2 %)	
Non-Hispanic Asian	634 (14.2 %)	136 (5.9 %)	146 (6.5 %)	
Other race	247 (5.5 %)	134 (5.9 %)	113 (5.2 %)	
Diabetes, n (%)	866 (19.4 %)	216 (9.5 %)	650 (29.7 %)	< 0.001
Hypertension: n (%)	1212 (27.1 %)	483 (21.1 %)	729 (33.3 %)	< 0.001
CVD	281 (6.3 %)	145 (6.3 %)	136 (6.2 %)	0.852
CHF	112 (4.0 %)	51 (3.5 %)	61 (4.5 %)	0.203
<i>Smoking: n (%)</i>				
Current smoker	769 (17.2 %)	432 (18.9 %)	337 (15.4 %)	< 0.001
Former smoker	1028 (23.0 %)	433 (19.0 %)	595 (27.2 %)	
Nonsmoker	2676 (59.8 %)	1419 (62.1 %)	1257 (57.4 %)	
Significant alcohol intake: n (%)	733 (16.4 %)	363 (15.9 %)	370 (16.9 %)	0.362
Viral hepatitis: n (%)	87 (1.9 %)	53 (2.3 %)	34 (1.6 %)	0.063
PIR	2.6 (1.3-3.7)	2.6 (1.2-3.8)	2.6 (1.3-3.6)	0.627
<i>Education level: n (%)</i>				
Less than high school graduate	838 (19.7 %)	390 (18.4 %)	448 (20.9 %)	0.09
High school graduate or GED	997 (23.4 %)	494 (23.3 %)	503 (23.5 %)	
Some college or above	2427 (56.9 %)	1236 (58.3 %)	1191 (55.6 %)	
<i>Physical activity: n (%)</i>				
< 600 MET-minutes/week	1605 (35.9 %)	733 (32.1 %)	872 (39.8 %)	< 0.001
600~7999 MET-minutes/week	2034 (45.5 %)	1109 (48.6 %)	925 (42.3 %)	
≥ 8000 MET-minutes/week	834 (18.6 %)	442 (19.4 %)	392 (17.9 %)	
BMI (kg/m ²)	28.3 (24.6-33.1)	25.3 (22.4-28.9)	31.7 (28.0-36.1)	< 0.001
Waist circumference (cm)	98 (87-110)	89.7 (80.7-99.2)	107.0 (98.1-117.7)	< 0.001

(Continues on next page)

Table I (cont.). Weight characteristics of the study participants

Parameters	Total	Non-MAFLD	MAFLD	p-value
Laboratory indexes				
AST (IU/L)	19 (16-24)	19 (16-23)	20 (16-25)	< 0.001
ALT (IU/L)	18 (13-26)	15 (12-21)	21 (15-31)	< 0.001
GGT (IU/L)	21 (14-32)	17 (13-26)	25 (18-40)	< 0.001
Serum albumin (g/L)	41 (39-43)	41 (39-43)	40 (38-43)	< 0.001
Platelet count (10 ⁹ /L)	236 (201-279)	226 (191-270)	232 (195-276)	0.057
Serum creatinine (mg/dL)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.142
Glycohemoglobin (%)	5.6 (5.3-6.0)	5.4 (5.2-5.7)	5.7 (5.4-6.3)	< 0.001
Total Cholesterol (mg/dL)	184 (160-213)	180 (157-209)	189 (162-217)	< 0.001
Triglyceride (mg/dL)	115 (81-168)	93 (69-134)	141 (103-202)	< 0.001
HDL-cholesterol (mg/dL)	51 (42-61)	55 (47-66)	46 (40-55)	< 0.001
AIP	-0.0 (-0.2 - 0.2)	-0.1 (-0.3-0.1)	0.1 (-0.1-0.3)	< 0.001

Median (Q1-Q3) was for continuous variables. The p-value was calculated by weight linear regression model. N (%) was for categorical variables. The p-value was calculated by weighted chi-square test. Abbreviations: MAFLD: metabolic dysfunction-associated fatty liver disease; CAP: controlled attenuation parameter; LSM: liver stiffness measurement; CHF: congestive heart failure; CVD: chronic vascular disease; PIR: poverty to income ratio; BMI: body mass index; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma-glutamyl transferase; HDL: high density lipoprotein; AIP: atherogenic index of plasma.

As shown in table II, the association between AIP and the prevalence of MAFLD was positive in all three multivariate logistic regression models: model 1, odds ratio (OR), 18.2 (95 % confidence interval [CI], 14.4-23.1); model 2, OR, 17.0 [95 % CI, 13.3-21.8]; model 3, OR, 5.2 [95 % CI, 3.9-7.0]. After adjusting for all confounding covariates, a one-unit increase in AIP was associated with a 4.2-fold increase in the risk for MAFLD. Moreover, compared with the lowest quartile group (i.e., Q1), the risk for MAFLD increased more in the higher quartile groups for AIP (p for trend < 0.001).

Positive associations between AIP and MAFLD persisted in different subgroups after stratification according to sex and diabetes status after fully adjustment for confounding factors (Table III). After subgroup analysis stratified according to sex, the association remained positive both in males (OR, 5.1 (95 % CI, 3.4-7.7); p < 0.001) and females (OR, 5.3 (95 % CI, 3.5-8.2); p < 0.001). After subgroup analysis stratified according to diabetes status, the association remained positive both in diabetes (OR, 2.7 (95 % CI, 1.4-5.3); p = 0.004) and non-diabetes (OR, 5.9 (95 % CI, 4.3-8.2); p < 0.001) groups.

Table II. The association between AIP and MAFLD

Model	Model 1 OR (95 % CI), p	Model 2 OR (95 % CI), p	Model 3 OR (95 % CI), p
AIP	18.2 (14.4, 23.1) < 0.0001	17.0 (13.3, 21.8) < 0.0001	5.2 (3.9, 7.0) < 0.0001
AIP (Quartile)			
Q1 (-0.9 to -0.2)	Reference	Reference	Reference
Q2 (-0.2 to -0.0)	2.2 (1.9, 2.7) < 0.0001	2.0 (1.7, 2.5) < 0.000	1.4 (1.1, 1.8) 0.0019
Q3 (-0.0 to 0.2)	5.14 (4.27, 6.18) < 0.0001	4.61 (3.81, 5.57) < 0.0001	2.41 (1.92, 3.04) < 0.0001
Q4 (0.2 to 1.6)	9.69 (7.98, 11.76) < 0.0001	8.96 (7.30, 10.98) < 0.0001	3.57 (2.79, 4.57) < 0.0001
p for trend	< 0.001	< 0.001	< 0.001

Model 1: no covariates were adjusted. Model 2: gender, age, and race were adjusted. Model 3: gender, age, race, BMI, waist circumference, diabetes, smoking, total cholesterol, ALT, and GGT were adjusted. Abbreviations: MAFLD: metabolic dysfunction-associated fatty liver disease; AIP: atherogenic index of plasma; BMI: body mass index; ALT: alanine transaminase; GGT: gamma-glutamyl transferase.

Table III. The association between AIP and MAFLD stratified by gender or diabetes

Model	Model 1 OR (95 % CI), p	Model 2 OR (95 % CI), p	Model 3 OR (95 % CI), p
Stratified by gender			
Men	15.3 (11.1, 21.1) < 0.001	15.3 (11.0, 21.5) < 0.001	5.1 (3.4, 7.7) < 0.001
Women	22.1 (15.5, 31.6) < 0.001	19.5 (13.5, 28.2) < 0.001	5.3 (3.5, 8.2) < 0.001
Stratified by diabetes status			
Non-diabetes	17.2 (13.2, 22.3) < 0.001	16.7 (12.6, 22.0) < 0.001	5.9 (4.3, 8.2) < 0.001
Diabetes	6.8 (3.8, 12.0) < 0.001	5.3 (2.9, 9.5) < 0.001	2.7 (1.4, 5.3) 0.004

Model 1: no covariates were adjusted. Model 2: gender, age, and race were adjusted. Model 3: gender, age, race, BMI, waist circumference, diabetes, smoking, total cholesterol, ALT, and GGT were adjusted. In the analysis stratified by gender and diabetes, the model is not adjusted for gender and diabetes, respectively. Abbreviations: MAFLD: metabolic dysfunction-fatty liver disease; AIP: atherogenic index of plasma; BMI: body mass index; ALT: alanine transaminase; GGT: gamma-glutamyl transferase.

The associations between AIP and different degrees of liver fibrosis were further investigated, with data summarized in table IV. However, there were no significant differences between AIP and significant fibrosis (OR, 1.3 [95 % CI, 0.9-2.0]; $p = 0.188$), advanced fibrosis (OR, 0.9 [95 % CI, 0.6-1.6]; $p = 0.819$), or cirrhosis (OR, 0.9 [95 % CI, 0.4-2.0]; $p = 0.864$).

After adjusting for relevant confounding factors, the associations between AIP and advanced liver fibrosis ($\geq F3$) as defined by FIB-4, APRI, or NFS exhibited variations. The positive association was observed between AIP and advanced liver fibrosis ($\geq F3$)

diagnosed with FIB-4 (OR, 0.4 [95 % CI, 0.2-0.7]; $p = 0.001$), while no significant disparity was detected in NFS (OR, 1.2 [95 % CI, 0.8-1.9]; $p = 0.393$) and APRI (OR, 0.8 [95 % CI, 0.1-7.7]; $p = 0.855$). These findings are presented in table V.

The predictive ability of AIP for MAFLD diagnosis (area under the ROC curve [AUC] 0.733 [95 % CI, 0.718-0.747]; $p < 0.001$) was presented in figure 1 and table VI. At the same time, an optimal AIP cut-off of -0.02 was proposed to predict MAFLD (sensitivity, 66.99 %; specificity, 69.53 %).

Table IV. The associations between AIP and degree of fibrosis in participants

Model	Model 1: β (95 % CI), p	Model 2: β (95 % CI), p	Model 3: β (95 % CI), p
Significant fibrosis ($\geq F2$)			
LSM < 8.2	Reference	Reference	Reference
LSM \geq 8.2	3.4 (2.6, 4.6) < 0.001	3.3 (2.4, 4.5) < 0.001	1.3 (0.9, 2.0) 0.188
Advanced fibrosis ($\geq F3$)			
LSM < 9.7	Reference	Reference	Reference
LSM \geq 9.7	3.0 (2.1, 4.3) < 0.001	2.7 (1.9, 4.0) < 0.001	0.9 (0.6, 1.6) 0.819
Cirrhosis (F4)			
LSM < 13.6	Reference	Reference	Reference
LSM \geq 13.6	2.8 (1.6, 4.7) < 0.001	2.2 (1.2, 4.0) 0.007	0.9 (0.4, 2.0) 0.864

Model 1: no covariates were adjusted. Model 2: gender, age, and race were adjusted. Model 3: gender, age, race, BMI, waist circumference, diabetes, smoking, total cholesterol, ALT, and GGT were adjusted. Abbreviations: AIP: atherogenic index of plasma; LSM: liver stiffness measurement; BMI: body mass index; ALT: alanine transaminase; GGT: gamma-glutamyl transferase.

Table V. The associations between AIP and advanced liver fibrosis ($\geq F3$) defined by FIB-4, APRI or NFS

Model	Model 1: β (95 % CI), p	Model 2: β (95 % CI), p	Model 3: β (95 % CI), p
FIB-4			
FIB-4 < 2.67	Reference	Reference	Reference
FIB-4 > 2.67	0.4 (0.3, 0.8) 0.003	0.3 (0.2, 0.6) < 0.001	0.4 (0.2, 0.7) 0.001

(Continues on next page)

Table V (cont.). The associations between AIP and advanced liver fibrosis (\geq F3) defined by FIB-4, APRI or NFS

Model	Model 1: β (95 % CI), p	Model 2: β (95 % CI), p	Model 3: β (95 % CI), p
NFS			
NFS < 0.676	Reference	Reference	Reference
NFS > 0.676	1.8 (1.3, 2.5) < 0.001	2.0 (1.4, 3.0) < 0.001	1.2 (0.8, 1.9) 0.393
APRI			
APRI < 1.5	Reference	Reference	Reference
APRI > 1.5	0.8 (0.2, 4.2) 0.796	0.8 (0.1, 4.1) 0.768	0.8 (0.1, 7.7) 0.855

Model 1: no covariates were adjusted. Model 2: gender, age, and race were adjusted. Model 3: Gender, age, race, BMI, waist circumference, diabetes, smoking, total cholesterol, ALT, and GGT were adjusted. Abbreviations: AIP: atherogenic index of plasma; FIB-4: fibrosis 4 score; APRI: AST to platelet ratio index; NFS: non-alcoholic fatty liver disease fibrosis score; BMI: body mass index; ALT: alanine transaminase; GGT: gamma-glutamyl transferase.

Table VI. ROC analysis for continuous predictors

	AUC	95 % CI	Sensitivity	Specificity	Cut-off
AIP	0.7326	0.718-0.7471	0.6699	0.6953	-0.0196

AIP: atherogenic index of plasma; AUC: area under the curve.

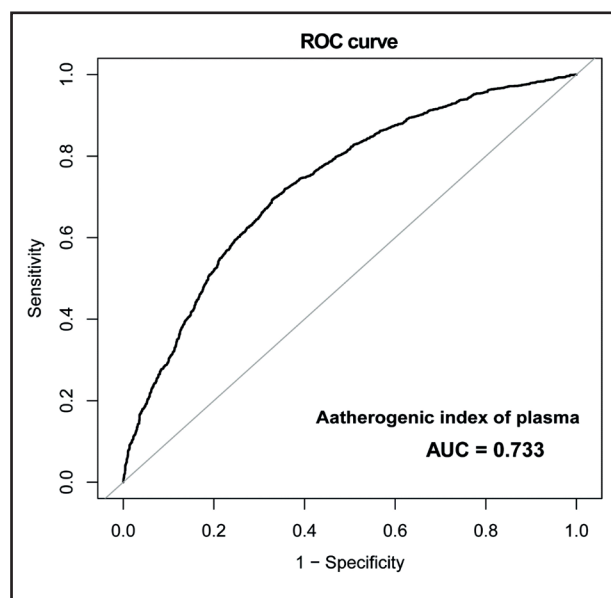


Figure 1. The ROC curve for AIP.

DISCUSSION

The current cross-sectional investigation explored the relationship between AIP and MAFLD, and aimed to identify a monitoring index for the early diagnosis of MAFLD. Our results revealed that patients with MAFLD in the United States exhibited higher AIP values than those in the non-MAFLD group. Notably,

AIP was positively associated with the risk for MAFLD. We further found that this association persisted in different sexes and whether they had diabetes or otherwise. However, no significant associations were found among significant fibrosis, advanced fibrosis, cirrhosis, and AIP in patients with MAFLD. Furthermore, our observations revealed a lack of statistical significance in the association between AIP and advanced liver fibrosis (\geq F3) as diagnosed by APRI and NFS. Finally, the ROC curve analysis revealed that AIP demonstrated good diagnostic utility for MAFLD, with an AUC of 0.733.

Recently, some investigators have focused on the association between AIP and MAFLD, although the results of studies remain controversial. A recent retrospective study of 2547 patients demonstrated a positive and significant association between AIP and risk for MAFLD (17). Duan et al. focused on 864 Chinese participants with ultrasonically diagnosed fatty liver and found that higher AIP was associated with increased odds of MAFLD in the Chinese populations after a multivariate logistic regression analysis (16). Our study validated the significant positive relationship using data from a large-scale investigation of the general United States population. However, in a cross-sectional study involving 1074 patients with NAFLD, researchers found that AIP values were more strongly associated with the risk for NAFLD in females (especially those > 65 years of age) than in males in a subgroup analysis (30). We hypothesized that this result may be due to the different inclusion criteria, resulting in the loss of estrogen protection in females > 65 years of age. While consistent with previous studies reporting the predictive role of AIP values in patients with NAFLD, there were still differences in the optimal cut-off of AIP values in our study.

For example, Samimi et al. found that the optimal cut-off point of AIP value was 0.54 (17), while Duan et al. measured the optimal value as 0.833 (16). Moreover, the influence of race should not be ignored when explaining these differences (31). Similarly, Giannini et al. demonstrated differences in TG/HDL-C ratios between different races (32). Therefore, this may, to some extent, explain the difference between our results and those reported in previous studies regarding the optimal cut-off for AIP.

Due to the imbalance in lipid metabolism in the liver, excessive accumulation of TG in the liver eventually leads to oxidative stress and hepatocyte injury, which further leads to the development of MAFLD. Although the exact mechanism has not been elucidated, it is now generally accepted that net retention of TG in the liver is necessary for the development of MAFLD (33,34). Through the transport of VLDL derived from the liver, serum TG concentration is further increased. Studies have found that elevated serum TG levels are associated with arteriosclerosis (35), and AIP is a newly proposed index reflecting the factors leading to atherosclerosis in recent years. In addition, several studies have shown that the TG/HDL-C ratio is positively correlated with homeostasis model assessment for IR (HOMA-IR), high AIP values may indicate insulin resistance, which is another important factor associated with NAFLD (36). Therefore, we hypothesized that AIP may be a predictor of NAFLD.

The greatest strength of this study is that it involved a large sample (i.e., 4473 participants). By fully adjusting for many potential confounding factors and using strict statistical methods to minimize residual confounding, the reliability of the data is strongly supported and data supporting clinical diagnosis is provided. However, this study had some limitations. First, based on the nature of this study, we could not determine the causal relationship between AIP and MAFLD, nor could we completely rule out residual confounding. Second, our assessment of fatty liver status was based on CAP values rather than the liver biopsy technique. Third, self-reported confounders may have introduced recall bias.

CONCLUSIONS

In summary, AIP values were higher in American patients with MAFLD, and a positive association between AIP and MAFLD was detected. Furthermore, this association persisted in different sexes and regardless of diabetes status. Therefore, further investigation is warranted to explore the potential of AIP as a predictive biomarker for the early diagnosis of MAFLD.

AUTHOR CONTRIBUTIONS

Naibin Yang and Miao Xu conceived the study. Naibin Yang was in charge of the execution, acquisition of data, analysis, and interpretation. Aili Wang and Jialin Li took charge of drafting and revising the manuscript. Li Li and Huiqing Ding critically reviewed the article. All authors gave final approval of the version to be

published, had agreed on the journal of which the article has been submitted. Miao Xu and Naibin Yang are co-corresponding authors, and their contributions are equal.

FUNDING

This work was supported by the Medical Health Science and Technology Project of Zhejiang Province (Grant No. 2024KY1521), the Major Science and Technology Projects for Health of Zhejiang Province (Grant No. WKJ-ZJ-2216), and the Program of Ningbo Science and Technology Bureau (CN) (Grant No. 2019F1003).

REFERENCES

- Ferguson D, Finck BN. Emerging therapeutic approaches for the treatment of NAFLD and type 2 diabetes mellitus. *Nature reviews. Endocrinology* 2021;17(8):484-95. DOI: 10.1038/s41574-021-00507-z
- Huang H, Wang Q, Shi X, Chen Y, Shen C, Zhang J, et al. Association between Monocyte to High-Density Lipoprotein Cholesterol Ratio and Nonalcoholic Fatty Liver Disease: A Cross-Sectional Study. *Mediators of inflammation* 2021;2021:6642246. DOI: 10.1155/2021/6642246
- Cobbina E, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. *Drug metabolism reviews* 2017;49(2):197-211. DOI: 10.1080/03602532.2017.1293683
- Ciardullo S, Perseghin G. Prevalence of NAFLD, MAFLD and associated advanced fibrosis in the contemporary United States population. *Liver international : official journal of the International Association for the Study of the Liver* 2021;41(6):1290-93. DOI: 10.1111/iv.14828
- Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology (Baltimore, Md.)* 2016;64(1):73-84. DOI: 10.1002/hep.28431
- The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Clinical liver disease* 2018;11(4):81. DOI: 10.1002/cld.722
- Papatheodoridi M, Cholongitas E. Diagnosis of Non-alcoholic Fatty Liver Disease (NAFLD): Current Concepts. *Current pharmaceutical design* 2018;24(38):4574-86. DOI: 10.2174/1381612825666190117102111
- Eslam M, Sanyal AJ, George J. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020;158(7):1999-2014.e1. DOI: 10.1053/j.gastro.2019.11.312
- Jahn D, Kircher S, Hermanns HM, Geier A. Animal models of NAFLD from a hepatologist's point of view. *Biochimica et biophysica acta. Molecular basis of disease* 2019;1865(5):943-53. DOI: 10.1016/j.bbdis.2018.06.023
- Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. *Journal of hepatology* 2018;68(2):268-79. DOI: 10.1016/j.jhep.2017.09.003
- Wang Q, Zheng D, Liu J, Fang L, Li Q. Atherogenic index of plasma is a novel predictor of non-alcoholic fatty liver disease in obese participants: a cross-sectional study. *Lipids in health and disease* 2018;17(1):284. DOI: 10.1186/s12944-018-0932-0
- Dong BY, Mao YQ, Li ZY, Yu FJ. The value of the atherogenic index of plasma in non-obese people with non-alcoholic fatty liver disease: a secondary analysis based on a cross-sectional study. *Lipids in health and disease* 2020;19(1):148. DOI: 10.1186/s12944-020-01319-2
- Bora K, Pathak MS, Borah P, Hussain MI, Das D. Association of the Apolipoprotein A-I Gene Polymorphisms with Cardiovascular Disease Risk Factors and Atherogenic Indices in Patients from Assam, Northeast India. *Balkan journal of medical genetics: BJMG* 2017;20(1):59-70. DOI: 10.1515/bjmg-2017-0002
- Cai G, Shi G, Xue S, Lu W. The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. *Medicine* 2017;96(37):e8058. DOI: 10.1097/md.0000000000008058
- Sun DQ, Jin Y, Wang TY, Zheng KI, Rios RS, Zhang HY, et al. MAFLD and risk of CKD. *Metabolism: clinical and experimental* 2021;115:154433. DOI: 10.1016/j.metabol.2020.154433

16. Duan SJ, Ren ZY, Zheng T, Peng HY, Niu ZH, Xia H, et al. Atherogenic index of plasma combined with waist circumference and body mass index to predict metabolic-associated fatty liver disease. *World journal of gastroenterology* 2022;28(36):5364-79. DOI: 10.3748/wjg.v28.i36.5364
17. Samimi S, Rajabzadeh S, Rabizadeh S, Nakhjavani M, Nakhaei P, Avanaki FA, et al. Atherogenic index of plasma is an independent predictor of metabolic-associated fatty liver disease in patients with type 2 diabetes. *European journal of medical research* 2022;27(1):112. DOI: 10.1186/s40001-022-00731-x
18. Siddiqui MS, Vuppalanchi R, Van Natta ML, Hallinan E, Kowdley KV, Abdelmalik M, et al. Vibration-Controlled Transient Elastography to Assess Fibrosis and Steatosis in Patients With Nonalcoholic Fatty Liver Disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2019;17(1):156-63.e2. DOI: 10.1016/j.cgh.2018.04.043
19. Tian T, Zhang J, Xie W, Ni Y, Fang X, Liu M, et al. Dietary Quality and Relationships with Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) among United States Adults, Results from NHANES 2017-2018. *Nutrients* 2022;14(21). DOI: 10.3390/nu14214505
20. Zhang X, Heredia NI, Balakrishnan M, Thrift AP. Prevalence and factors associated with NAFLD detected by vibration controlled transient elastography among US adults: Results from NHANES 2017-2018. *PloS one* 2021;16(6):e0252164. DOI: 10.1371/journal.pone.0252164
21. Sporea I, Mare R, Popescu A, Nistorescu S, Baldea V, Sirli R, et al. Screening for Liver Fibrosis and Steatosis in a Large Cohort of Patients with Type 2 Diabetes Using Vibration Controlled Transient Elastography and Controlled Attenuation Parameter in a Single-Center Real-Life Experience. *Journal of clinical medicine* 2020;9(4). DOI: 10.3390/jcm9041032
22. Alqahtani SA, Golabi P, Paik JM, Lam B, Moazez AH, Elariny HA, et al. Performance of Noninvasive Liver Fibrosis Tests in Morbidly Obese Patients with Nonalcoholic Fatty Liver Disease. *Obesity surgery* 2021;31(5):2002-10. DOI: 10.1007/s11695-020-04996-1
23. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *Journal of hepatology* 2020;73(1):202-09. DOI: 10.1016/j.jhep.2020.03.039
24. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes care* 2020;43(Suppl 1):S14-s31. DOI: 10.2337/dc20-S002
25. Vilar-Gomez E, Nephew LD, Vuppalanchi R, Gawrieh S, Mladenovic A, Pike F, et al. High-quality diet, physical activity, and college education are associated with low risk of NAFLD among the US population. *Hepatology (Baltimore, Md.)* 2022;75(6):1491-506. DOI: 10.1002/hep.32207
26. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ (Clinical research ed.)* 2016;354:i3857. DOI: 10.1136/bmj.i3857
27. Hoge C, Bowling CB, Lim SS, Drenkard C, Plantinga LC. Association of Poverty Income Ratio with Physical Functioning in a Cohort of Patients with Systemic Lupus Erythematosus. *The Journal of rheumatology* 2020;47(7):983-90. DOI: 10.3899/jrheum.190991
28. Fadeyev K, Nagao-Sato S, Reicks M. Nutrient and Food Group Intakes among U.S. Children (2-5 Years) Differ by Family Income to Poverty Ratio, NHANES 2011-2018. *International journal of environmental research and public health* 2021;18(22). DOI: 10.3390/ijerph182211938
29. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology (Baltimore, Md.)* 2018;67(1):328-57. DOI: 10.1002/hep.29367
30. Lin J, Li H, Wan Q. A Cross-Sectional Study of the Correlation Between the Atherogenic Index of Plasma and Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes. *Diabetes, metabolic syndrome and obesity: targets and therapy* 2022;15:2227-34. DOI: 10.2147/dms0.s375300
31. Huxley RR, Barzi F, Lam TH, Czernichow S, Fang X, Welborn T, et al. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease: an individual participant data meta-analysis of 23 studies in the Asia-Pacific region. *Circulation* 2011;124(19):2056-64. DOI: 10.1161/circulationaha.111.028373
32. Giannini C, Santoro N, Caprio S, Kim G, Lartaud D, Shaw M, et al. The triglyceride-to-HDL cholesterol ratio: association with insulin resistance in obese youths of different ethnic backgrounds. *Diabetes care* 2011;34(8):1869-74. DOI: 10.2337/dc10-2234
33. Li YW, Kao TW, Chang PK, Chen WL, Wu LW. Atherogenic index of plasma as predictors for metabolic syndrome, hypertension and diabetes mellitus in Taiwan citizens: a 9-year longitudinal study. *Scientific reports* 2021;11(1):9900. DOI: 10.1038/s41598-021-89307-z
34. Mahran HN, Saber LM, Alghaithy AA, Elareefy AA. The role of elevated alanine aminotransferase (ALT), FasL and atherogenic dyslipidemia in type II diabetes mellitus. *Journal of Taibah University Medical Sciences* 2017;12(1):8-13. DOI: 10.1016/j.jtumed.2016.10.002
35. Deprince A, Haas JT, Staels B. Dysregulated lipid metabolism links NAFLD to cardiovascular disease. *Molecular metabolism* 2020;42:101092. DOI: 10.1016/j.molmet.2020.101092
36. Yin B, Wu Z, Xia Y, Xiao S, Chen L, Li Y. Non-linear association of atherogenic index of plasma with insulin resistance and type 2 diabetes: a cross-sectional study. *Cardiovascular diabetology* 2023;22(1):157. DOI: 10.1186/s12933-023-01886-5