



## OPEN Monocytes to Apolipoprotein A1 ratio is associated with metabolic dysfunction-associated fatty liver disease in type 2 diabetes mellitus

Wei Wang<sup>1,2</sup>, Lian Huang<sup>1,2</sup>, Xiu Ping Qiu<sup>1</sup>, Mei Tu<sup>1</sup> & Xiu Li Guo<sup>1</sup>✉

The monocyte-to-Apolipoprotein A1 ratio (MAR) emerges as a potentially valuable inflammatory biomarker indicative of metabolic dysfunction-associated fatty liver disease (MASLD). Accordingly, this investigation primarily aims to assess the correlation between MAR and MASLD risk. A cohort comprising 957 individuals diagnosed with type 2 diabetes mellitus (T2DM) participated in this study. The relationship between MAR and MASLD was analyzed through binomial logistic regression analysis and restricted cubic splines (RCS). Furthermore, a comparative assessment of MAR and monocyte to high-density lipoprotein ratio (MHR) in identifying MASLD efficacy was conducted using receiver operating characteristic curve analysis. Remarkably, even after adjusting for metabolic parameters and hepatic functional markers, MAR stood out as an independent predictor for MASLD (*OR* 1.58, 95% CI 1.36–1.84; *P* < 0.001) and displayed a nonlinear positive association with MASLD risk according to RCS analysis (*P* for nonlinearity and overall < 0.001). Notably, MAR exhibited superior diagnostic accuracy for identifying MASLD compared to MHR (AUC: 0.772 vs 0.722, *P* < 0.001). In summary, MAR emerges as a promising inflammatory indicator for MASLD, demonstrating potential as a valuable screening tool to bolster the management of MASLD within the T2DM population.

**Keywords** Metabolic dysfunction-associated fatty liver disease, Monocyte to Apolipoprotein A ratio, Inflammatory marker, Type 2 diabetes mellitus

Monocytes, essential components of the innate immune system originating from bone marrow progenitors and disseminated via the circulatory system to extrinsic tissues, play inherent roles in systemic inflammation by instigating and amplifying inflammatory cascades<sup>1</sup>. Multiple clinical investigations have highlighted an upsurge in peripheral monocyte levels across diverse inflammatory and immune pathologies such as cardiovascular maladies<sup>2</sup>, inflammatory bowel disease<sup>3</sup>, metabolic syndrome<sup>4</sup>, and nonalcoholic fatty liver disease (NAFLD)<sup>5</sup>. Apolipoprotein A1 (APOA1), a paramount constituent of high-density lipoprotein (HDL-c) assembly, stands as a prognostic indicator for acute cardiac events, acknowledged for its capacity to sequester lipid moieties and facilitate cholesterol efflux. Noteworthy, APOA1 has exhibited immunoregulatory, anti-inflammatory, antioxidant, and anti-thrombotic properties<sup>6,7</sup>. Recent advancements in lipid metabolism and inflammation research have unveiled the repressive influence of APOA1 on monocyte activation, progenitor cell propagation, and differentiation<sup>8</sup>. Furthermore, empirical evidence from clinical examinations has affirmed an inverse correlation between ApoA1 serum concentrations and the inflammatory profile of monocytes<sup>9</sup>. Monocytes exert proinflammatory effects, while APOA1 acts as a mitigating factor during the inflammatory process. The ratio of serum monocytes to APOA1 levels (MAR) has the potential to serve as an indicator for identifying inflammatory and immune disorders.

Metabolic dysfunction-associated fatty liver disease (MASLD), formerly recognized as NAFLD, showcases hepatic triglyceride accumulation alongside assorted metabolic aberrations, embodying a spectrum of liver conditions spanning from steatosis to metabolic dysfunction-associated steatohepatitis. Global epidemiological inquiries into metabolic disorders throughout the period from 2000 to 2019 have unveiled a mounting prevalence of both Type 2 diabetes mellitus (T2DM) and MASLD over the last two decades<sup>10</sup>. Particularly noteworthy is the escalating incidence of MASLD among individuals afflicted with T2DM. A recent survey delineated a global prevalence rate of 55.2% (95% CI 47.3–63.7) for MASLD in the realm of T2DM<sup>11</sup>. The liver plays crucial roles in energy metabolism and inflammatory signaling, and the presence of MASLD significantly

<sup>1</sup>Longyan First Affiliated Hospital of Fujian Medical University, Longyan 364000, Fujian, China. <sup>2</sup>Wei Wang and Lian Huang contributed equally to this work. ✉email: 1256339602@qq.com

impacts individuals with T2DM. In addition to its well-recognized association with liver injury, MASLD is considered to synergistically increase the risk of unfavorable extra-hepatic clinical outcomes in T2DM<sup>12</sup>. Given its pervasive nature and severe implications, MASLD has emerged as a burgeoning quandary necessitating attention to prevention and therapeutic modalities. Unveiling efficacious diagnostic and prognostic markers for MASLD holds the promise of facilitating early interventions to avert these deleterious outcomes in the populace grappling with T2DM.

The intricate pathogenesis of MASLD remains enshrouded in a convoluted tapestry of dysmetabolic processes yet to be entirely unraveled. This hallmark entails perturbations in energy metabolism and activation of inflammatory signaling cascades orchestrated by immune cells. Clinical studies have observed a decrease in serum monocyte levels in patients with MASLD<sup>13</sup>. Conversely, both T2DM and MASLD exhibit disturbances in lipid metabolism, leading to reduced serum levels of APOA1 and HDL-c. While several studies have investigated the diagnostic value of the monocyte to HDL-c ratio (MHR) in MASLD<sup>14</sup>, limited research has been conducted on the diagnostic capacity of MAR in this context. This study evaluated the association between MAR and MASLD risk in T2DM. Additionally, this study also sought to compare the diagnostic performance between MAR and MHR in identifying MASLD.

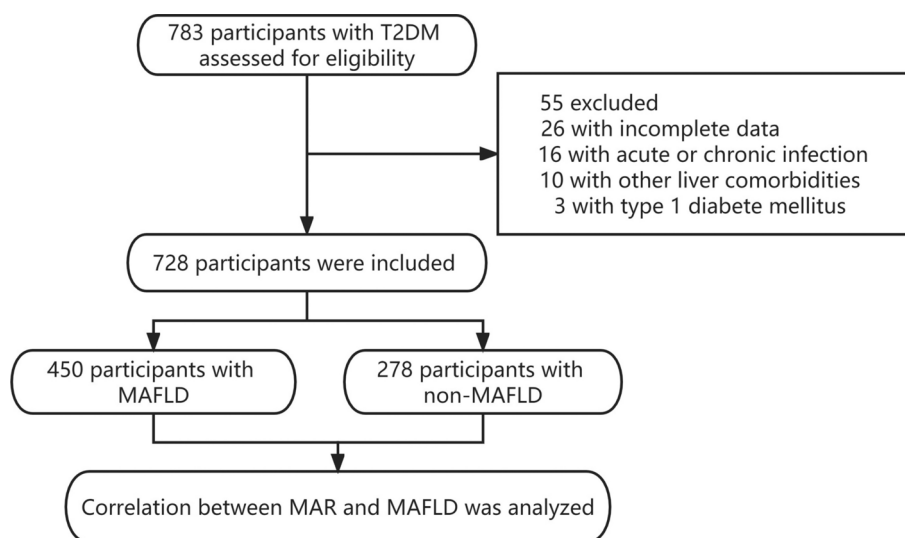
## Methods

### Study population

This prospective study recruited a total of 1078 consecutive participants with T2DM who were admitted to the inpatient ward at Longyan First Hospital between July 2022 and September 2023. All participants provided informed consent, and the study was approved by the Ethical Committee of Longyan First Hospital (IC-2022-009). All procedures were conducted in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants. The diagnosis of T2DM was based on the criteria set forth by the Chinese Diabetes Society<sup>15</sup>. To ensure the validity of the results, strict exclusion criteria were applied. Participants with other liver comorbidities that could contribute to fatty liver, such as liver malignancy, were excluded. Individuals with a history of excessive alcohol consumption ( $\geq 210$  g per week for males and  $\geq 140$  g per week for females) were also excluded. Moreover, participants with underlying conditions that could interfere with circulating monocyte count, such as acute or chronic infections, anemia, hemolytic diseases, and bleeding, were excluded. Additionally, individuals with acute illnesses that may disrupt lipid metabolism and those unable to undergo a complete CT scan, such as pregnant women or those with severe spinal curvature, were excluded. After applying the exclusion criteria, a total of 957 participants with T2DM were included in the final analysis. Of these, 342 participants (35.7%) were newly diagnosed with T2DM. Among the remaining participants, 386 were treated with metformin, 108 with thiazolidinediones (TZDs), 168 with sodium-glucose cotransporter-2 inhibitors (SGLT-2), 98 with glucagon-like peptide-1 receptor agonists (GLP-1RAs), 124 with glucosidase inhibitor, 156 with dipeptidyl peptidase-4 inhibitors, and 98 with insulin. A flowchart illustrating the process of participant selection is provided in Fig. 1.

### Data collection and laboratory assessments

Demographic information, including gender, age, duration of diabetes, medication histories, medical background, and alcohol and tobacco use, were collected during hospitalization through standardized medical history questionnaires administered by trained interviewers. Smoking and drinking habits were determined based on participants' current smoking or excessive alcohol consumption status. Additionally, anthropometric measurements such as height, weight, waist circumference, and blood pressure (BP) were taken by trained research nurses. Body mass index (BMI) was calculated as body weight (kg) divided by height squared ( $m^2$ ).



**Fig. 1.** The flowchart illustrates the process of study population enrollment.

All laboratory assessments were performed at the key laboratory using fasting blood samples. Automated biochemical analysis was conducted to measure various biomarkers, including creatinine, alanine aminotransferase, albumin, uric acid (UA), aspartate aminotransferase (AST), fasting blood glucose (FBG), TG, total cholesterol (TC), HDL-c, low-density lipoprotein cholesterol (LDL-c), and APOA1. Hemoglobin A1c (HbA1c) levels were quantified using the HPLC method. Monocyte and platelet counts were determined using the Coulter LH 780 Analyzer. Insulin resistance (IR) was defined as a homeostasis model assessment-insulin resistance (HOMA-IR) value of  $\geq 2.5$ . HOMA-IR was calculated using the following formula: fasting serum insulin ( $\mu\text{U/ml}$ )  $\times$  FBG (mmol/l)/22.5<sup>16</sup>. MAR and MHR were computed using the formulas: monocytes/APOA1 (mmol/l) and HDL-c (mmol/l).

### Evaluation of fatty liver

To assess fatty liver, unenhanced abdominal CT scans were conducted on all participants. The image reconstruction was performed using the standard algorithm, resulting in 5 mm thick continuous slices. Two experienced radiologists, who were blinded to clinical data, independently evaluated the presence of fatty liver using CT liver-spleen attenuation measurement ( $\text{CT}_{\text{L-S}}$ ). To obtain measurements, the radiologists selected the slice that provided the clearest view of the liver and spleen and then manually drew regions of interest around these structures to calculate average attenuation values. The  $\text{CT}_{\text{L-S}}$  value was determined as the ratio of the average liver attenuation to the average spleen attenuation. Participants with a  $\text{CT}_{\text{L-S}}$  value less than 1.0 were classified as having fatty liver.

### Assessment of MASLD and progressive liver fibrosis score

According to the current guidelines for diagnosing MASLD, individuals with T2DM who exhibit hepatic steatosis detected through imaging or liver pathology and no other discernible cause are classified as having MASLD<sup>17</sup>. In this study, the diagnosis of MASLD was based on the assessment of  $\text{CT}_{\text{L-S}}$  to detect the presence of fatty liver. To evaluate advanced liver fibrosis, the nonalcoholic fatty liver disease fibrosis score (NFS) was calculated. The NFS formula for individuals with T2DM was as follows<sup>18</sup>:  $-0.545 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} - 0.013 \times \text{PLT (10}^9\text{/L)} - 0.66 \times \text{albumin (g/dl)} + 0.99 \times \text{AST/ALT ratio}$ .

### Definitions

Metabolic dysfunction was characterized by the presence of specific metabolic disorders, which were defined as follows: (1) Abdominal obesity, indicated by a WC  $\geq 90$  cm in males and  $\geq 80$  cm in females. (2) Elevated BP, evidenced by multiple measurements  $\geq 130/85$  mmHg or the use of prescribed antihypertensive medications. (3) Increased serum TG levels  $\geq 1.70$  mmol/L or the use of medications targeted at managing elevated TG levels. (4) Low levels of serum HDL-c, specifically  $< 1.0$  mmol/L in males or  $< 1.3$  mmol/L in females, or the use of medications addressing low HDL-c levels. (5) Elevated serum UA levels  $\geq 420$   $\mu\text{mol/L}$  or the use of medications aimed at controlling UA levels. (6) Presence of insulin resistance (IR), determined by a HOMA-IR value  $\geq 2.5$ . (7) Diagnosis of prediabetes or diabetes.

### Statistical analysis

Data analysis was performed using SPSS 26.0 (SPSS Inc., IBM) software. The statistical differences among the MAR quartiles were assessed using either the analysis of variance or the Kruskal–Wallis test. Categorical variables were compared across groups using the chi-squared test. To determine the associations between MAR and  $\text{CT}_{\text{L-S}}$  as well as the NFS, Pearson correlation analysis was conducted. These correlations were further evaluated through multiple regression analysis, with MAR serving as the independent variable, and  $\text{CT}_{\text{L-S}}$  and NFS as the dependent variables. Adjustments were made for potential confounders in the regression models. The impact of MAR on the presence of MASLD was examined by the binomial logistic regression analysis and Restricted cubic splines (RCS) after controlling for confounding variables across different models. Furthermore, a receiver operating characteristic (ROC) curve analysis was performed to compare the diagnostic performance of MAR and MHR in identifying MASLD. Statistical significance was defined as  $P < 0.05$ .

## Results

### Comparison of clinical characteristics between MASLD and non-MASLD groups

A comparison of clinical characteristics between MASLD and non-MASLD groups was conducted, and the findings are presented in Table 1. The overall prevalence of MASLD among participants was 56.4%. Comparing the characteristics based on MASLD status, it was observed that individuals in the MASLD group exhibited higher SBP, DBP, BMI, WC, TG, ALT, UA, AST, monocyte count, and HOMA-IR levels. Conversely, the results also demonstrated lower levels of HDL-c and APOA1 than those in the non-MASLD group. Notably, inflammatory markers such as MHR and MAR were significantly increased in the MASLD group ( $P < 0.05$ ).

### Metabolic profiles and liver functional indexes according to MAR quartile

Table 2 displays the metabolic profiles and liver functional indexes classified according to the MAR quartile. The MAR values for the respective quartiles were as follows: 1.26–3.35, 3.36–4.23, 4.24–5.14, and 5.15–10.84. The findings indicated that higher MAR quartile groups exhibited elevated WC, TG, UA, SBP, DBP, and HOMA-IR levels, and a higher proportion of hypertension while demonstrating lower HDL-c and  $\text{CT}_{\text{L-S}}$  levels ( $P < 0.05$ ). Figure 2A shows that the proportion of participants with 5, 6, and 7 metabolic dysfunctions is higher in the upper MAR quartiles than in the lower MAR quartiles. Additionally, this study also observed a positive correlation between the MAR quartile and MASLD prevalence ( $P < 0.05$ ), denoted by an increase from 24.6% in the first quartile to 47.1%, 69.7%, and 84.9% in the subsequent higher quartiles (Fig. 2B).

Characteristics	Total (n = 957)	MASLD (n = 540)	Non-MASLD (n = 417)	P value
Age (year)	54.0 ± 8.1	53.9 ± 8.2	54.0 ± 8.1	0.972
Male, n (%)	483 (50.5)	279 (51.7)	204 (48.9)	0.400
Duration (year)	7.7 ± 3.1	7.8 ± 3.2	7.7 ± 3.0	0.539
BMI (kg/m <sup>2</sup> )	24.2 ± 3.0	25.3 ± 3.1	22.9 ± 2.4	<0.001
WC (cm)	85.3 ± 6.9	87.7 ± 7.0	82.1 ± 5.5	<0.001
SBP (mmHg)	132.8 ± 18.1	139.1 ± 16.9	124.7 ± 14.6	<0.001
DBP (mmHg)	81.4 ± 9.3	84.5 ± 8.5	77.3 ± 8.9	<0.001
HbA1c (%)	8.76 ± 1.05	8.76 ± 1.02	8.75 ± 1.09	0.983
TG (mmol/L)	2.18 ± 1.36	2.58 ± 1.46	1.67 ± 1.02	<0.001
TC (mmol/L)	5.30 ± 1.19	5.23 ± 1.18	5.38 ± 1.25	0.068
HDL-c (mmol/L)	1.09 ± 0.24	1.00 ± 0.21	1.20 ± 0.23	<0.001
LDL-c (mmol/L)	3.52 ± 0.94	3.56 ± 0.93	3.47 ± 0.95	0.135
APOA1 (g/L)	0.99 ± 0.19	0.91 ± 0.17	1.09 ± 0.21	<0.001
UA (umol/L)	349.0 ± 85.1	369.5 ± 88.2	321.4 ± 73.0	<0.001
Creatinine (umol/L)	68.9 ± 13.1	68.3 ± 13.2	69.7 ± 12.9	0.105
ALT (IU/L)	37.6 ± 8.8	39.1 ± 9.3	35.7 ± 7.9	<0.001
AST (IU/L)	31.3 ± 6.9	32.3 ± 7.5	30.1 ± 5.7	<0.001
Albumin (g/L) (g/L)	40.1 ± 4.9	40.0 ± 4.1	40.3 ± 4.6	0.788
Platelets (10 <sup>9</sup> /L)	187.1 ± 68.2	187.1 ± 62.7	189.1 ± 47.6	0.892
Monocyte (10 <sup>8</sup> /L)	4.75 ± 1.01	4.35 ± 1.04	3.89 ± 0.95	<0.001
HOMA-IR	3.10 ± 1.74	3.59 ± 1.79	2.46 ± 1.44	<0.001
MAR (10 <sup>8</sup> /g)	4.39 ± 1.43	4.93 ± 1.37	3.69 ± 1.17	<0.001
MHR (10 <sup>8</sup> /mmol)	4.07 ± 1.52	4.56 ± 1.53	3.43 ± 1.26	<0.001
Hypertension, n (%)	271 (37.2)	253 (46.9)	90 (21.6)	<0.001
Drinking, n (%)	229 (29.6)	163 (30.2)	120 (28.8)	0.636

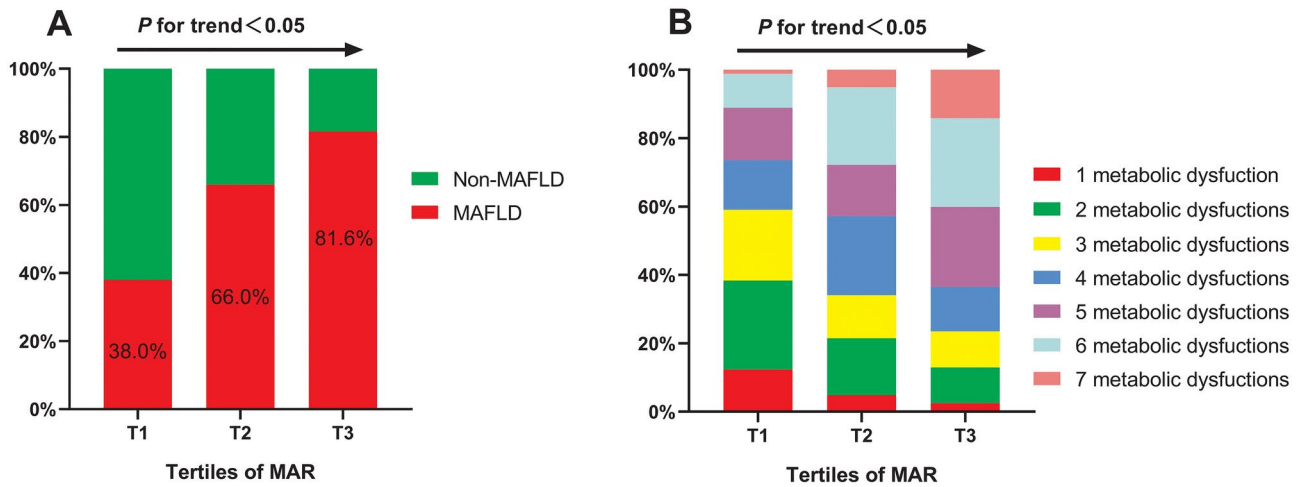
**Table 1.** Comparison of clinical characteristics between MASLD and non-MASLD groups.

Characteristics	MASLD (n = 540)				P value
	Q1(1.61–3.35)	Q2(3.36–4.23)	Q3(4.24–5.14)	Q4(5.15–10.84)	
WC (cm)	82.1 ± 5.1	84.5 ± 6.0	85.1 ± 5.9	89.4 ± 8.2	<0.001
SBP (mmHg)	122.7 ± 15.9	130.2 ± 15.1	134.6 ± 19.5	143.6 ± 15.1	<0.001
DBP (mmHg)	76.5 ± 8.8	79.9 ± 6.5	83.4 ± 9.2	85.8 ± 9.9	<0.001
Hypertension, n (%)	37(15.4)	74(30.3)	91(38.9)	141(59.0)	<0.001
HbA1c (%)	8.82 ± 1.00	8.67 ± 1.01	8.63 ± 0.96	8.91 ± 1.21	0.010
TG (mmol/L)	1.50 ± 0.89	1.87 ± 0.97	2.31 ± 1.24	3.06 ± 1.70	<0.001
HDL-c (mmol/L)	1.24 ± 0.23	1.13 ± 0.22	1.03 ± 0.19	0.95 ± 0.21	<0.001
HOMA-IR	2.37 ± 1.47	2.81 ± 1.46	3.27 ± 1.47	3.97 ± 2.08	<0.001
UA (umol/L)	310.2 ± 73.0	341.2 ± 72.2	360.9 ± 75.2	384.2 ± 99.7	<0.001
ALT (IU/L)	37.9 ± 7.5	37.7 ± 9.1	38.1 ± 9.5	38.2 ± 8.8	0.336
AST (IU/L)	31.0 ± 5.9	31.4 ± 5.6	31.6 ± 6.6	31.5 ± 8.6	0.382
CT <sub>L-S</sub>	1.13 ± 0.24	1.01 ± 0.20	0.92 ± 0.23	0.73 ± 0.24	<0.001

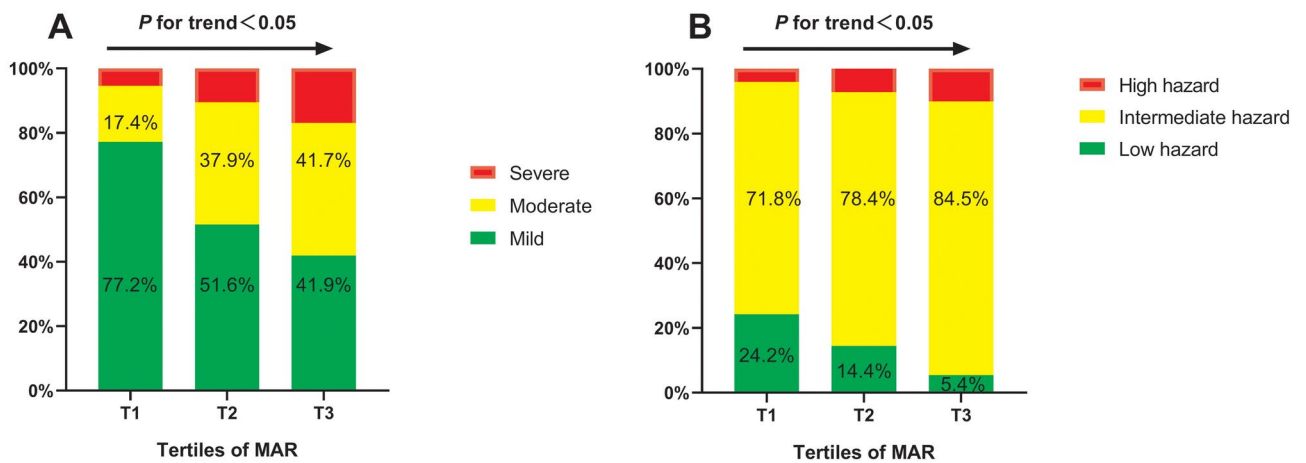
**Table 2.** Metabolic profiles and liver functional indexes according to MAR (10<sup>8</sup>/g) quartile. WC Waist circumference, SBP Systolic blood pressure, DBP Diastolic blood pressure, HbA1c Glycated hemoglobin, TG Triglyceride, HDL-c High-density lipoprotein cholesterol, HOMA-IR Homeostasis model assessment insulin resistance, UA Uric acid, ALT Alanine aminotransferase, AST Aspartate aminotransferase, MAR Monocyte to APOA1 ratio, MASLD Metabolic dysfunction-associated fatty liver disease.

### Correlation of MAR with CT<sub>L-S</sub> and NFS

Figure 3 illustrates the correlation between the MAR and CT<sub>L-S</sub> (Fig. 3A) and the NFS (Fig. 3B) assessed through Pearson correlation analysis. In individuals with MASLD, MAR displayed a positive correlation with NFS ( $r=0.158$ ,  $P<0.05$ ), while in the entire study population, an inverse association was observed between MAR and CT<sub>L-S</sub> ( $r=-0.369$ ,  $P<0.05$ ). Table 3 presents the results of the correlation of MAR with CT<sub>L-S</sub> and NFS analyzed by the multiple linear regression analysis. Significant correlations of MAR with CT<sub>L-S</sub> were observed



**Fig. 2.** MASLD prevalence (A) and metabolic dysfunctions distribution (B) based on MAR quartile. *MAR* Monocytes to Apolipoprotein A1 ratio, *MASLD* Metabolic dysfunction-associated fatty liver disease.



**Fig. 3.** Correlation of *MAR* with  $CT_{L-S}$  and NFS. (A) the negative association between *MAR* and  $CT_{L-S}$  ( $r = -0.369$ ,  $P < 0.001$ ). (B) the positive association between *MAR* and NFS ( $r = 0.158$ ,  $P < 0.001$ ). *NFS* Nonalcoholic fatty liver disease fibrosis score, *MAR* Monocytes to Apolipoprotein A1 ratio.

after adjusting potential confounders in Model 1 (including adjustments for gender, age, diabetic duration, and drinking). Subsequently, in Model 2, additional adjustments were made for metabolic profiles such as SBP, DBP, WC, BMI, HbA1c, TG, HDL-c, UA, and HOMA-IR based on Model 1. Moreover, even after further adjusting for liver functional indicators like ALT and AST, as well as the usage of hypoglycemic agents that may influence MASLD like metformin, TZDs, SGLT-2, and GLP-1RAs (Model 3), *MAR* exhibited significant correlations with both  $CT_{L-S}$  ( $\beta = -0.222$ ,  $P < 0.001$ ) and NFS ( $\beta = 0.086$ ,  $P = 0.008$ ).

### Correlation of *MAR* with MASLD risk

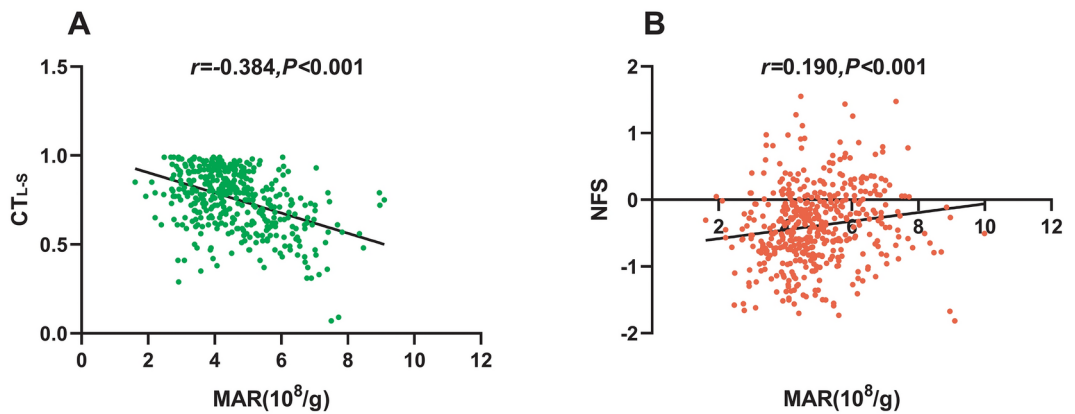
Figure 4 illustrates the correlation between the *MAR* and the presence of MASLD determined through binomial logistic regression analysis. The findings demonstrate a significant association between higher *MAR* levels and an increased risk of MASLD in both Model 1 and Model 2. Importantly, even after full adjustments in Model 3, this association remains consistent (OR 1.58, 95% CI 1.36–1.84;  $P < 0.001$ ). Figure 5 illustrates the relationship between *MAR* and MASLD analyzed using RCS. The results indicate a nonlinear association between *MAR* and MASLD risk after accounting for full adjustments in Model 3 ( $P$  for nonlinearity = 0.018).

### Comparison of MASLD identifying value between *MAR* and MHR

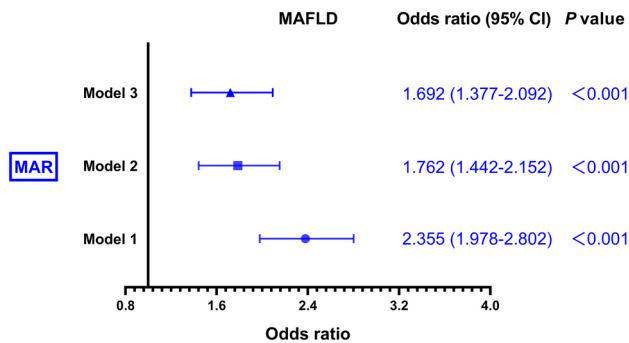
Figure 6 illustrates the performance comparison between *MAR* and MHR in identifying MASLD, as determined through ROC curve analysis. The results demonstrated that *MAR* (AUC:0.772, 95%CI 0.742–0.802) exhibits superior performance in identifying MASLD compared to MHR (AUC:0.772 vs 0.722,  $P < 0.001$ ). The optimal cut-off value of *MAR* was  $4.05 \times 10^8/g$  (sensitivity: 75.6%, specificity: 68.8%).

Variable	Model 1		Model 2		Model 3	
	$\beta$	<i>P</i>	$\beta$	<i>P</i>	$\beta$	<i>P</i>
NFS	0.142	<0.001	0.106	<0.001	0.086	0.008
CT <sub>L-S</sub>	-0.324	<0.001	-0.278	<0.001	-0.222	<0.001

**Table 3.** Multivariate linear regression analysis of the association between MAR and NFS, CT<sub>L-S</sub>. Model 1: adjustment for age, gender, diabetic duration, and drinking. Model 2: further adjustment for waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, hemoglobin A1c, triglycerides, high-density lipoprotein, homeostasis model assessment of insulin resistance, and uric acid based on Model 1. Model 3: additional adjustment for alanine aminotransferase and aspartate aminotransferase, as well as the usage of hypoglycemic agents like metformin, thiazolidinediones, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists based on Model 2. MAR Monocyte to apolipoprotein A1 ratio, NFS Nonalcoholic fatty liver disease fibrosis score.



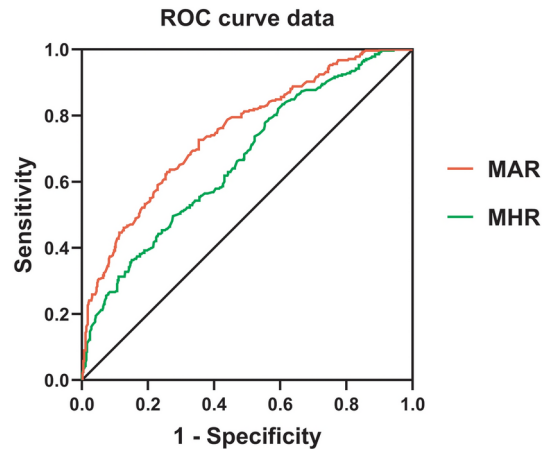
**Fig. 4.** The independent correlation of MAR with MASLD in different Models. Model 1: adjustment for age, gender, diabetic duration, and drinking. Model 2: further adjustment for waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, hemoglobin A1c, triglycerides, high-density lipoprotein, homeostasis model assessment of insulin resistance, and uric acid based on Model 1. Model 3: additional adjustment for alanine aminotransferase and aspartate aminotransferase, as well as the usage of hypoglycemic agents like metformin, thiazolidinediones, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists based on Model 2. MASLD Metabolic dysfunction-associated fatty liver disease, MAR Monocytes to Apolipoprotein A1 ratio.



**Fig. 5.** Restricted cubic splines analysis of the association between MAR and MASLD after accounting for full adjustments in Model 3. MASLD Metabolic dysfunction-associated fatty liver disease, MAR Monocytes to Apolipoprotein A1 ratio.

**Sensitivity analysis**

Sensitivity analyses were conducted in newly diagnosed T2DM (n = 342) to minimize the impact of hypoglycemic agents on the association between MAR and MASLD. Following full adjustments in Model 3, MAR persisted in significant correlations with CT<sub>L-S</sub> ( $\beta = -0.269, P < 0.001$ ), NFS ( $\beta = 0.088, P = 0.004$ ), MASLD (OR 2.10,



**Fig. 6.** ROC analysis for comparing MASLD identifying value between MAR and MHR. *MASLD* Metabolic dysfunction-associated fatty liver disease, *MAR* Monocytes to Apolipoprotein A1 ratio, *MHR* Monocytes to high-density lipoprotein, *BMI* Body mass index, *WC* Waist circumference, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *HbA1c* Glycated hemoglobin, *TG* Triglyceride, *TC* Total cholesterol, *HDL-c* High-density lipoprotein cholesterol, *LDL-c* Low-density lipoprotein cholesterol, *APOA1* Apolipoprotein A1, *UA* Uric acid, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase. *HOMR-IR* Homeostasis model assessment insulin resistance, *MAR* Monocyte to APOA1 ratio, *MHR* Monocyte to HDL-c ratio, *MASLD* Metabolic dysfunction-associated fatty liver disease.

95% CI 1.54–2.87;  $P < 0.001$ ). Furthermore, MAR demonstrated superior performance in identifying MASLD compared to MHR (AUC:0.817 vs 0.758,  $P < 0.001$ ).

## Discussion

Metabolic dysfunctions, exacerbated by chronic inflammation, constitute a pivotal aspect in the pathogenesis of MASLD. Emerging evidence substantiates the proinflammatory nature of monocytes while underscoring the anti-inflammatory attributes of APOA1 in this context. This study elucidated that MAR emerged as an independent variable for  $CT_{L-S}$ , NFS, and MASLD, even after adjustments for metabolic profiles and hepatic functional markers. A notable correlation was also unveiled between elevated MAR levels and an increased risk of MASLD. Noteworthy, MAR displayed superior efficacy in detecting MASLD compared to MHR, suggesting its potential as an innovative inflammatory biomarker for MASLD.

Inflammation and hepatocyte injury serve as the prominent features of MASLD. The activation of innate immune cells is a crucial factor contributing to liver inflammation in cases of MASLD<sup>19,20</sup>. Monocytes have been recognized as markers of inflammatory status since they facilitate the expression of inflammation. The activation and differentiation of monocytes into monocyte-derived macrophages are key drivers in the pathogenesis of chronic low-grade inflammation diseases<sup>21,22</sup>. Recent studies utilizing innovative experimental techniques have shed light on the significant involvement of innate monocyte subsets in aggravating liver inflammation and contributing to the progression of MASLD through the recruitment and accumulation of inflammatory cells, including monocyte-derived macrophages, within the hepatic tissue<sup>23,24</sup>. Consequently, an elevation in circulating monocytes is observed in individuals with MASLD. Perturbations in metabolic homeostasis serve as the main underlying factors for the progression and heightened risk of MASLD. Individuals with MASLD commonly exhibit suboptimal control over their metabolic profiles. Dysregulated lipid metabolism represents a major manifestation of the metabolic dysfunctions associated with MASLD. The activation of innate immunity further contributes to alterations in hepatic lipid metabolism, particularly characterized by elevated TG and decreased levels of APOA1 and HDL-c, which are essential for arterial wall protection and the prevention of atherosclerotic plaque formation<sup>25,26</sup>. Accordingly, an increase in plasma TG levels accompanies a decrease in APOA1 and HDL-c levels in the MASLD group.

$CT_{L-S}$  has proven to be a valuable tool for categorizing liver fat content and assessing the extent of intrahepatic inflammation<sup>27</sup>. Intriguingly, this study identifies a noteworthy inverse and independent association between MAR and  $CT_{L-S}$ , even after meticulous adjustments for metabolic profiles and liver functional indexes. These findings suggest that MAR could serve as a reliable indicator of both liver fat content and intrahepatic inflammation severity. Liver fibrosis stands as the most robust predictor of long-term clinical outcomes in individuals with MASLD. Current MASLD-related guidelines widely endorse using non-invasive indices, such as the NFS, for risk stratification in patients with liver-related morbidity and mortality, as they demonstrate comparable effectiveness to liver biopsy<sup>28</sup>. Mounting evidence highlights monocyte-derived macrophages in the progression of liver inflammation and fibrosis. Inhibition of CCR2+ monocyte recruitment through pharmacological means has been shown to efficiently accelerate this progression<sup>29,30</sup>, further supporting the critical role of monocytes in liver fibrosis. Interestingly, although MAR exhibits a positive correlation with NFS in linear regression analysis, its significance persists even after additional adjustments for metabolic profiles and liver functional indexes. This suggests that an elevated MAR may be associated with an increased risk of

progressive liver fibrosis. Currently, it is widely recognized that MASLD arises from a state of chronic inflammation induced by systemic metabolic dysfunction<sup>31</sup>. In accordance with our previous study<sup>32</sup>, this study also revealed a consistent pattern whereby individuals with higher MAR exhibited a greater number of metabolic dysfunctions. Among these metabolic dysfunctions, notable contributors to liver inflammation comprise heightened hepatic triglyceride TG accumulation, IR, and adipose tissue expansion<sup>33</sup>. This study observed that higher MAR quartile groups exhibited elevated TG, HOMA-IR, and WC. The existing data concerning the connection between various monocyte-related inflammatory markers and MASLD demonstrate consistency. Previous studies have independently identified a correlation between MASLD and monocyte-related inflammatory markers such as MHR and lymphocyte-to-monocyte ratio<sup>34,35</sup>. Corresponding to these monocyte-related inflammatory markers, this study also revealed a significant and sustained correlation between MAR and MASLD, even after accounting for potential confounding factors through binomial logistic regression analysis. Furthermore, results from the RCS analysis demonstrated a nonlinear association between MAR and MASLD risk. This relationship persists even after accounting for potential confounding factors, indicating that the risk of developing MASLD escalates with rising MAR levels. These findings establish MAR as an independent variable for MASLD and suggest its potential utility as an inflammatory marker of MASLD.

MHR has been recognized as an inflammatory predictor for several chronic inflammatory diseases, such as metabolic syndrome<sup>36</sup>, MASLD<sup>14</sup>, and cardiovascular disease<sup>37</sup>. This study conducted a comparison between MAR and MHR in identifying MASLD using Receiver ROC curve analysis. Notably, the results revealed that MAR exhibited superior performance in identifying MASLD compared to MHR. Regarding the underlying mechanisms, the biological features of APOA1 offer a plausible explanation for these findings. Apart from its well-established role in cardioprotection, APOA1 plays essential roles in HDL-c biogenesis and function. Importantly, the beneficial anti-inflammatory properties of APOA1 extend beyond its cardioprotective functions<sup>7</sup>. It is worth noting that HDL-c functionality depends not only on serum HDL-c levels but also on the apolipoprotein and lipid content functions. Recent studies have demonstrated that APOA1 can modulate cellular inflammation and oxidative stress<sup>38,39</sup>. For instance, Iqbal A. et al. revealed that apoA1 reduced the recruitment of adoptively transferred monocytes to sites of inflammation in vivo and mice<sup>8</sup>. Among different monocyte subsets, classical monocytes are believed to possess a greater potential for migration to injured or inflamed tissues compared to intermediate and non-classical subpopulations. Moreover, Patel V et al. revealed that serum APOA1 levels but not HDL-c were inversely correlated with classical monocyte subset recruitment marker profiles<sup>40</sup>.

To our knowledge, this study is pioneering in examining the link between MAR and MASLD. However, it is crucial to acknowledge several limitations inherent in this investigation. Firstly, this study did not establish a direct causal relationship between MAR and MASLD. Secondly, the study participants were limited to individuals with T2DM, which inherently increases the incidence of MASLD and elevates serum monocyte levels. Therefore, the observed association between MAR and MASLD might not be generalizable to other populations. Thirdly, this study did not delve into further exploration of the underlying mechanisms driving this association.

In conclusion, this study demonstrates that MAR not only serves as an independent variable for CT<sub>L-S</sub>, NFS, and MASLD. Additionally, MAR exhibits superior performance in identifying MASLD compared to MHR. These findings underscore the paramount clinical significance of MAR as a promising inflammatory marker for MASLD. Consequently, incorporating MAR as an adjunctive screening tool can meaningfully enhance the management of MASLD in T2DM.

## Data availability

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

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## Author contributions

W. W. and L. H. took charge of the software and contributed to the original draft. M. T. and X. P. Q. conducted the investigation. X. L. Guo and W. W. contributed to data curation and writing editing.

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## Declarations

### Competing interests

The authors report no conflicts of financial and non-financial interests in this work.

### Additional information

**Correspondence** and requests for materials should be addressed to X.L.G.

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