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ORIGINAL RESEARCH

Inflammatory Indices and MAFLD Prevalence in Hypertensive Patients: A Large-Scale Cross-Sectional Analysis from China

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Objective: Hypertension development and progression are largely influenced by inflammation, which plays a critical role by activating the immune system and causing damage to the vascular endothelium. Metabolic dysfunction-associated fatty liver disease (MAFLD) is also associated with chronic low-grade inflammation, which drives disease progression via metabolic imbalances and adipose tissue dysfunction. This study investigates the relationship between inflammatory indices and MAFLD in hypertensive patients and assesses the predictive accuracy of these indices for MAFLD.

Methods: We performed a cross-sectional analysis involving 34,303 hypertensive patients from a Chinese hospital-based registry. The diagnosis of MAFLD was established using metabolic dysfunction criteria alongside evidence of hepatic steatosis confirmed through imaging. Complete blood counts were used to calculate inflammatory indices, including the monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII), and aggregate index of systemic inflammation (AISI). To assess the relationship between inflammatory indices and MAFLD, multivariable logistic regression was performed with adjustments for potential confounders. The diagnostic performance of these indices was analyzed using receiver operating characteristic (ROC) curves and area under the curve (AUC) calculations.

Results: Patients with MAFLD exhibited significantly elevated levels of all inflammatory indices compared to those without. After multivariable adjustment, each standard deviation increase in AISI, SIRI, and SII was associated with a 74%, 62%, and 58% increased odds of MAFLD, respectively. The AUC for AISI was 0.659, indicating moderate diagnostic accuracy. The AUCs for SIRI and SII were 0.626 and 0.619, respectively, while NLR, PLR, and MLR had lower AUCs of 0.593, 0.558, and 0.589, respectively.

Conclusion: In hypertensive patients, inflammatory indices, especially AISI, show a strong association with MAFLD, indicating their potential utility in risk stratification within clinical settings. Further research is needed to evaluate the effectiveness of these markers in the management of MAFLD.

Keywords: metabolic-dysfunction-associated fatty liver disease, inflammatory indices, hypertension, diagnostic accuracy

Introduction

Metabolic-dysfunction-associated fatty liver disease (MAFLD), now the preferred term replacing non-alcoholic fatty liver disease (NAFLD), represents a growing global health concern, affecting approximately 25% of the adult population.[1,2] This hepatic disorder is characterized by hepatocellular lipid accumulation and is intricately linked with metabolic comorbidities.[3,4]

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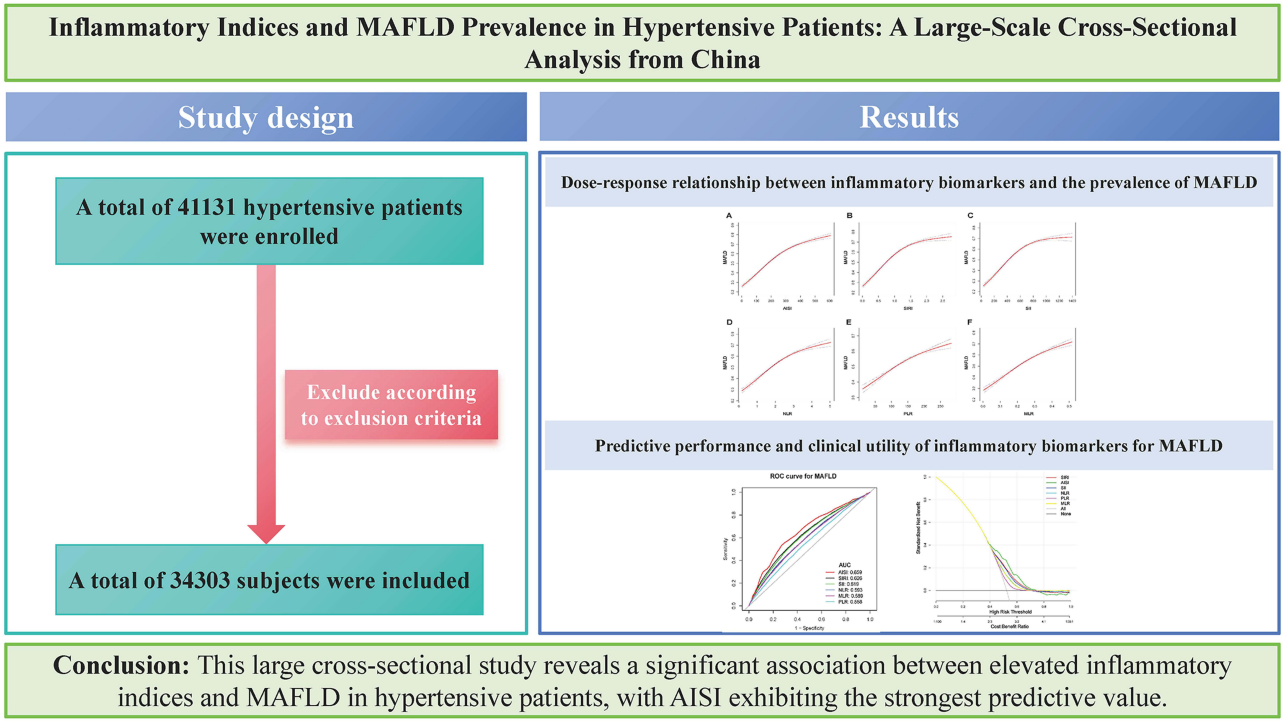
Graphical Abstract



Epidemiological analyses indicate a rising prevalence of MAFLD, particularly in regions with elevated obesity and T2DM rates, including the United States and several Asian countries.[5–7] The development of MAFLD is shaped by various metabolic factors, such as insulin resistance, dyslipidemia, and hypertension, which are key elements of metabolic syndrome.[8–10] These factors play a pivotal role in the pathogenesis and progression of MAFLD and significantly increase the risk of cardiovascular diseases.[11] Recent research has highlighted a bidirectional association between hypertension and MAFLD, indicating that MAFLD might both contribute to and arise from hypertensive states.[12] The combination of MAFLD and hypertension is linked to worse cardiovascular outcomes, emphasizing the significance of this comorbidity.[13] Therefore, the prompt identification and management of MAFLD, especially in the context of hypertension, are essential for mitigating cardiovascular risks and have significant implications for public health strategies.

Although MAFLD is highly prevalent, its pathogenesis is not yet fully clarified, and standardized, widely accepted non-invasive diagnostic methods are still lacking.[14] MAFLD often presents asymptomatically, with diagnoses typically made through abnormal liver biochemistry or imaging examinations. Imaging modalities, including ultrasound, exhibit limited sensitivity for detecting mild hepatic steatosis. In contrast, proton magnetic resonance spectroscopy offers a more definitive assessment but is costly and primarily reserved for research environments.[15] Liver biopsy, the diagnostic gold standard, is invasive and carries inherent risks, limiting its applicability in clinical practice.[16] There is an imperative need for the development of novel and robust biomarkers to enhance the diagnostic accuracy, prognostic stratification, and therapeutic monitoring of MAFLD.

One of the main contributing factors to the onset and advancement of hypertension is chronic inflammation.[17] Inflammatory processes are known to impair vascular endothelial function, promote oxidative stress, and lead to arterial stiffness, all of which play crucial roles in the pathophysiology of hypertension.[18] Furthermore, low-grade systemic inflammation, marked by increased levels of pro-inflammatory cytokines, has been associated with the progression of both hypertension and MAFLD.[19–21] Inflammation is instrumental in the progression of MAFLD, as hepatic steatosis can progress from a harmless condition to one marked by hepatocyte damage, triggering an inflammatory response and the

activation of immune cells.[22] The activation of hepatic stellate cells and the onset of fibrosis can result from the recruitment of macrophages, neutrophils, T cells, and dendritic cells, which collectively drive hepatic inflammation.[23] The hepatocyte inflammasome may link MAFLD-associated hepatocyte death to fibrotic responses and could serve as a non-invasive inflammatory biomarker.[24,25] Elevated levels of inflammatory cytokines, which contribute to persistent inflammation and accelerate disease progression, are also a defining feature of MAFLD.[26] These shared inflammatory pathways suggest a potential mechanistic link between hypertension and MAFLD, where systemic inflammation may act as a mediator exacerbating their coexistence.[27] The progression to advanced cirrhosis is also attributed to the role of systemic inflammation.[28] Timely identification and evaluation of MAFLD are crucial for effective management and making well-informed treatment choices.[22] The development of non-invasive diagnostic methodologies that leverage inflammatory biomarkers could significantly enhance patient safety and mitigate the economic burden in the clinical management of MAFLD.

In recent years, inflammation indexes derived from blood cell counts have attracted considerable interest due to their cost-effectiveness, simplicity, and ease of computation.[29–31] The monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) have been independently and notably linked to mortality in individuals with pancreatic diseases.[32] Additionally, broader indices like the systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), and aggregate index of systemic inflammation (AISI) combine data from several immune pathways, offering a more comprehensive evaluation of inflammatory status.[33] The AISI has emerged as a distinct prognostic biomarker, with studies highlighting its significant ability to differentiate idiopathic pulmonary fibrosis (IPF) patients from healthy controls and its correlation with unfavorable outcomes in both IPF and viral pneumonia.[34] The SIRI and SII have demonstrated significant predictive value for clinical outcomes and disease severity across a spectrum of conditions, including inflammatory diseases, cardiometabolic diseases, and stroke.[31,35–37] Derived from complete blood count data, these indices serve as innovative and comprehensive biomarkers, reflecting various inflammatory and immune pathways throughout the body and enabling a more holistic evaluation of systemic inflammation.

Given the established links between MAFLD and systemic inflammation, and considering the high prevalence of MAFLD among hypertensive patients, our study examines the association between six inflammatory biomarkers—MLR, PLR, NLR, SII, SIRI, and AISI—and the risk of MAFLD in individuals with hypertension. This study aims to investigate their predictive validity and potential influencing factors, offering important insights into the detection, treatment, and management of MAFLD in high-risk populations.

Materials and Methods

Study Population

This cross-sectional study, conducted from January 1, 2014, to December 31, 2023, initially enrolled 41,131 hospitalized patients. The study population was defined by applying specific exclusion criteria to ensure the accuracy of the assessment for MAFLD. Participants were excluded if they were under 18 years of age, lacked the necessary diagnostic information to confirm MAFLD, or had incomplete routine blood data. Patients with chronic hepatitis, autoimmune hepatitis, cirrhosis, or hepatectomy were also excluded to avoid confounding effects. Similarly, patients with a history of stroke, myocardial infarction, heart failure, or severe renal insufficiency were also excluded, as these conditions might affect liver function and alter the inflammatory profile. To account for factors that might influence inflammatory cell counts, we also excluded individuals with autoimmune diseases, hematological disorders, malignancies, acute or chronic infections, or those on long-term medications affecting blood counts. These exclusions were crucial to evaluate the specific impact of inflammatory biomarkers on MAFLD risk. Post-exclusion, 34,303 subjects were analyzed (Figure 1). Reporting follows the STROBE guidelines.[38]

Ethical approval for the study was obtained from the Ethics Committee of the Xinjiang Uygur Autonomous Region People's Hospital (KY2022080905), and the study complied with the ethical standards set forth in the Helsinki Declaration and its later amendments. Participants were thoroughly informed about the study's purpose and procedures, provided written consent, and were assured that their participation was voluntary and could be withdrawn at any time without any negative consequences.

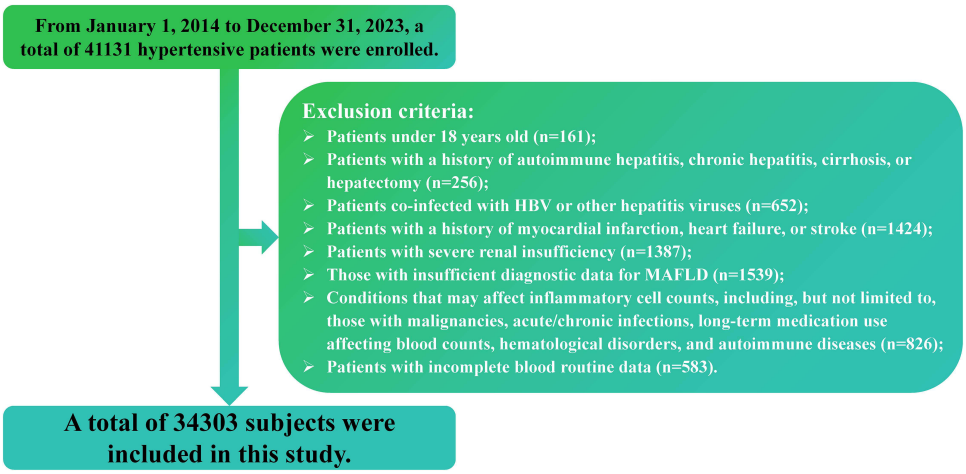


Figure 1 The flowchart of our study.

Data Collection and Definitions

For our analysis, we compiled an extensive dataset encompassing clinical data, examination findings, lifestyle factors, medical backgrounds, and medication regimens, sourced from initial electronic health records. The admission data encompassed demographics such as age and sex, anthropometrics including height, weight, body mass index (BMI), blood pressure, and waist circumference (WC). Smoking and alcohol consumption were classified as current or non-current. Detailed methodologies are delineated in the Supplementary Material.

Peripheral venous blood samples were obtained following an 8- to 10-hour overnight fast to assess a range of biochemical markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), serum creatinine (Scr), uric acid (UA), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin (HbA1c), and high-sensitivity C-reactive protein (hs-CRP). An automated analyzer was utilized for these measurements, following the manufacturer's protocols. The triglyceride and glucose (TyG) index was derived from the natural logarithm of the product of TG (mg/dL) and FBG (mg/dL), divided by 2.[39,40]

Routine blood tests, including counts of white blood cells, neutrophils, monocytes, lymphocytes, and platelets, were performed using a full blood count analyzer. We derived the following inflammatory indices from these counts: MLR, PLR, NLR, SII, SIRI, and AISI. The calculations for these indices were as follows:

- AISI = Neutrophil count × Platelet count × (Monocyte count / Lymphocyte count)
- SIRI = Neutrophil count × (Monocyte count / Lymphocyte count)
- SII = Platelet count × Neutrophil count / Lymphocyte count
- NLR = Neutrophil count / Lymphocyte count
- PLR = Platelet count / Lymphocyte count
- MLR = Monocyte count / Lymphocyte count

For comprehensive definitions of the study's comorbidities, refer to the Supplementary Material.

Diagnostic Criteria for MAFLD

MAFLD is diagnosed based on the presence of hepatic steatosis, as confirmed by imaging techniques, and the presence of metabolic dysfunction. Metabolic dysfunction is ascertained by meeting at least one of the following criteria:

1. Overweight or obesity, defined by a BMI ≥ 23 kg/m²;
2. Diabetes mellitus (DM);

3. A metabolic abnormality score ≥ 2, calculated using the following components:
- WC ≥ 90 cm in men and ≥ 80 cm in women;
- Blood pressure ≥ 130/85 mmHg or the use of antihypertensive medications;
- TG levels ≥ 150 mg/dL or the use of antidyslipidemic agents;
- HDL-C levels < 40 mg/dL in men and < 50 mg/dL in women, or the use of antidyslipidemic agents;
- FBG levels between 5.6 and 6.9 mmol/L;
- Hs-CRP levels > 2 mg/L;
- Homeostasis model assessment of insulin resistance (HOMA-IR) score ≥ 2.5.

In cases where HOMA-IR data is unavailable, the triglyceride glucose (TyG) index serves as a surrogate measure. Specifically, TyG index values above the 75th percentile are employed as an alternative to the HOMA-IR threshold for diagnosing MAFLD.[41,42] The diagnostic flowchart for MAFLD is presented in Figure S1.

Statistical Analysis

We evaluated multicollinearity via the variance inflation factor (VIF), omitting variables with VIF ≥ 10 to ensure model reliability (Figure S2). Multivariable logistic regression was utilized to evaluate the association between inflammatory biomarkers and MAFLD prevalence, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated to quantify the strength and precision of these associations. A generalized additive model (GAM) was employed to examine the dose-response relationship between biomarkers and MAFLD prevalence. Sensitivity analyses were conducted to validate the robustness of our findings, while stratified analyses identified potential modifiers of the association. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curves, with area under the curve (AUC), sensitivities, specificities, positive predictive values (PPV), and negative predictive values (NPV) calculated. A clinical decision curve analysis (DCA) assessed the net benefit of biomarkers across different risk thresholds, compared with null strategies. Statistical analyses were executed using R software, version 4.1.1, with significance set at a two-tailed P value < 0.05.

Results

Characteristics of the Study Population

The study sample was composed of 16,343 participants without MAFLD and 17,959 participants with MAFLD, with baseline traits detailed in Table 1. The mean age was slightly higher in the non-MAFLD group (51.09 ± 12.12 years) compared to the MAFLD group (50.64 ± 12.03 years; P < 0.001). A higher prevalence of male participants was observed in both groups, with no significant difference (P = 0.388). Anthropometric parameters, including BMI and WC, were significantly elevated in the MAFLD group (P < 0.001 for both). Blood pressure measurements also showed significant differences, with higher systolic and diastolic values in the MAFLD group (P < 0.001). Lifestyle factors such as current smoking were more prevalent in the MAFLD group (34.26% vs 32.11%; P < 0.001). Biochemical indices revealed significant differences in liver enzymes, cholesterol levels, and FBG, with higher values in the MAFLD group (P < 0.001 for all). Comorbidities like DM, dyslipidemia, and coronary artery disease were more frequent in the MAFLD group (P < 0.001 for all). Additionally, there was no statistically significant difference in the duration of hypertension between patients with and without MAFLD (P = 0.252). Medication use was similar between groups with no significant variations observed. Inflammatory biomarkers—AISI, SIRI, SII, NLR, PLR, and MLR—were significantly higher in the MAFLD group. Figure 2 illustrates a dose-response relationship, showing a progressive increase in MAFLD prevalence across quartiles from Q1 to Q4 for all inflammatory biomarkers, with each successive quartile associated with an increased risk of MAFLD (P for trend < 0.001).

Relationship Between Inflammatory Biomarkers and MAFLD Prevalence

The association between inflammatory biomarkers and MAFLD prevalence was rigorously assessed using a series of logistic regression models, as detailed in Table 2. The analysis uncovered significant correlations between each of the six inflammatory indices and the probability of MAFLD. Notably, a one standard deviation (SD) increment in the AISI was linked to a 74% rise in MAFLD odds within the fully adjusted Model 5, with an OR of 1.74 (95% CI, 1.69–1.80; P < 0.001).

Table 1 Characteristics of Participants with or Without MAFLD

Characteristics	Without MAFLD	With MAFLD	P-value
Sample size, n	16343	17,959	
Age, years	51.09 ± 12.12	50.64 ± 12.03	<0.001
Men, %	9375 (57.36%)	10,219 (56.90%)	0.388
Body mass index, kg/m^2	26.38 ± 3.55	27.22 ± 3.66	<0.001
Waist circumference, cm	93.99 ± 11.05	96.77 ± 11.30	<0.001
Systolic blood pressure, mmHg	142.89 ± 17.39	147.22 ± 17.77	<0.001
Diastolic blood pressure, mmHg	86.20 ± 12.35	88.98 ± 12.68	<0.001
Current smoking, %	5247 (32.11%)	6153 (34.26%)	<0.001
Current drinking, %	5107 (31.25%)	5468 (30.45%)	0.108
Duration of hypertension, %			0.252
<5 year	12203 (74.67%)	13,506 (75.20%)	
≥5 year	4140 (25.33%)	4453 (24.80%)	
Biochemical indexes			
AST/ALT	0.84 (0.65–1.08)	0.85 (0.67–1.10)	<0.001
GGT, U/L	26.47 (17.65–43.45)	28.28 (19.19–45.45)	<0.001
TBIL, umol/L	11.86 (9.02–15.66)	12.21 (9.19–16.06)	<0.001
DBIL, umol/L	4.02 (2.94–5.36)	4.08 (2.99–5.45)	<0.001
IBIL, umol/L	7.74 (5.69–10.59)	7.98 (5.76–10.81)	<0.001
Serum creatinine, μmol/L	63.73 ± 14.07	65.75 ± 14.55	<0.001
Uric acid, μmol/L	336.68 ± 89.20	347.89 ± 91.81	<0.001
Total cholesterol, mmol/L	4.39 (3.77–5.04)	4.53 (3.90–5.21)	<0.001
Triglyceride, mmol/L	1.50 (1.08–2.16)	1.56 (1.11–2.25)	<0.001
HDL-C, mmol/L	1.01 (0.86–1.19)	1.03 (0.89–1.21)	<0.001
LDL-C, mmol/L	2.69 (2.14–3.23)	2.76 (2.19–3.32)	<0.001
Fasting blood glucose, mmol/L	4.93 ± 1.02	5.08 ± 1.06	<0.001
HbA1c, %	5.82 ± 0.77	5.99 ± 0.80	<0.001
hs-CRP, mg/dL	2.59 (1.27–4.76)	2.70 (1.31–5.01)	<0.001
TyG index	7.02 ± 0.60	7.30 ± 0.66	<0.001
AISI	156.32 (107.85–228.68)	219.56 (144.34–323.31)	<0.001
SIRI	0.69 (0.49–0.96)	0.88 (0.61–1.24)	<0.001
SII	407.24 (306.51–544.36)	494.49 (367.63–664.99)	<0.001
NLR	1.78 (1.41–2.26)	2.01 (1.58–2.58)	<0.001
PLR	122.68 (98.57–152.38)	131.07 (104.99–163.76)	<0.001
MLR	0.21 (0.16–0.26)	0.23 (0.18–0.29)	<0.001
Comorbidities, %			
Diabetes mellitus	2457 (15.03%)	3034 (16.89%)	<0.001
Dyslipidemia	2672 (16.35%)	3838 (21.37%)	<0.001
Coronary artery disease	1215 (7.43%)	1950 (10.86%)	<0.001
Medications use, %			
ACEI/ARB	7556 (46.23%)	8292 (46.17%)	0.908
β-blockers	2950 (18.05%)	3134 (17.45%)	0.146
Calcium channel blockers	4165 (25.48%)	4612 (25.68%)	0.678
Diuretic	1756 (10.74%)	1939 (10.80%)	0.876
Antidiabetic agents	1210 (7.40%)	1335 (7.43%)	0.916
Lipid-lowering drugs	1901 (11.63%)	2085 (11.61%)	0.949

Notes: Categorical variables are presented as number (percentage), while continuous variables are expressed as mean ± standard deviation for normally distributed data or median (25th to 75th percentiles) for non-normally distributed data.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; hs-CRP, high sensitivity C-reactive protein; AISI, aggregate index of systemic inflammation; SIRI, systemic inflammatory response index; SII, systemic immune inflammation index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; TyG index, triglyceride glucose index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

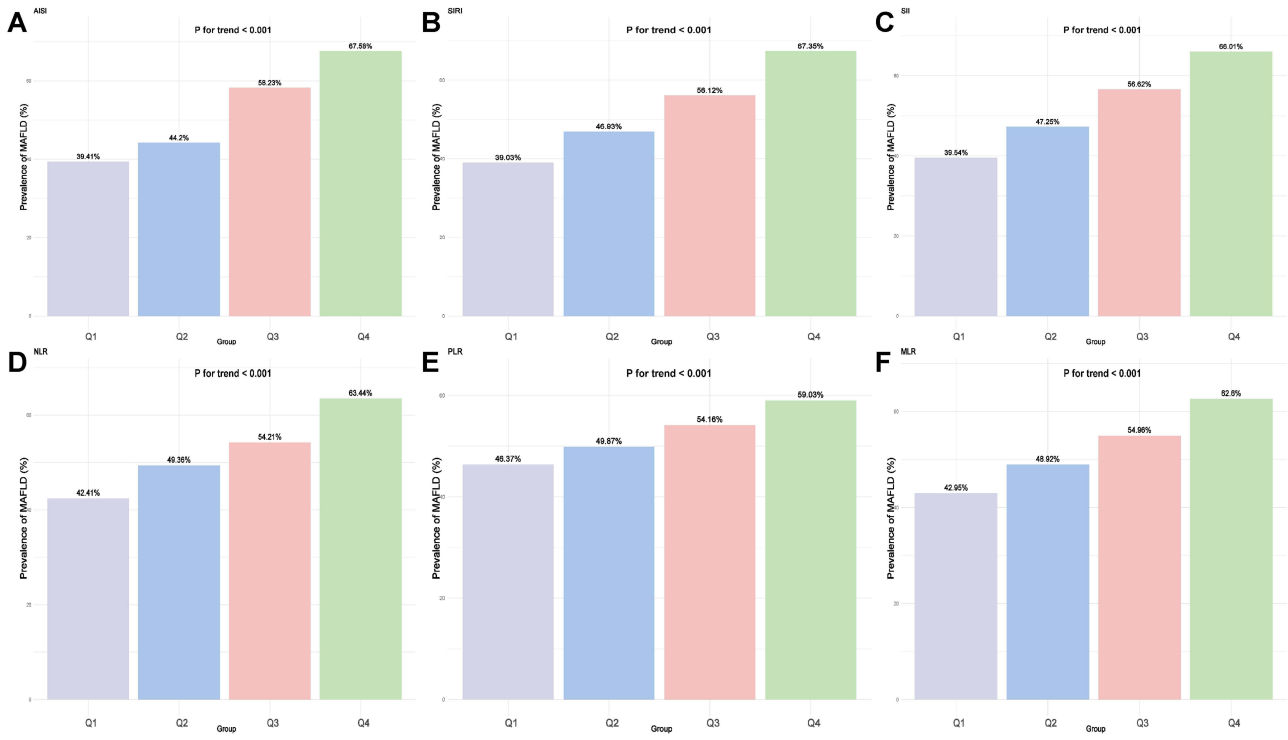


Figure 2 Correlation of inflammatory biomarkers with the prevalence of MAFLD, stratified by quartiles. (**A**) AISI; (**B**) SIRI; (**C**) SII; (**D**) NLR; (**E**) PLR; (**F**) MLR.

The SIRI and SII were similarly associated with 62% and 58% increased odds of MAFLD per SD increment, respectively (SIRI: OR, 1.62; 95% CI, 1.58–1.67; SII: OR, 1.58; 95% CI, 1.54–1.63; both P < 0.001). The NLR, PLR, and MLR also exhibited significant associations, with each SD increase corresponding to 42%, 24%, and 39% heightened odds of MAFLD, respectively (NLR: OR, 1.42; PLR: OR, 1.24; MLR: OR, 1.39; all P < 0.001). Quartile stratification of the biomarkers provided further clarity, demonstrating a progressive escalation in MAFLD odds with each ascending quartile. Specifically, the fourth quartile of AISI was associated with a tripling of MAFLD odds compared to the first quartile (OR,

Table 2 The Relationship Between Inflammatory Biomarkers and the Prevalence of MAFLD

Exposure	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
AISI (per SD increase)	1.75 (1.69, 1.80)	1.74 (1.69, 1.80)	1.74 (1.69, 1.80)	1.74 (1.69, 1.80)	1.74 (1.69, 1.80)
AISI quartiles					
Q1 (<121.91)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2 (121.91–185.83)	1.22 (1.15, 1.29)	1.22 (1.14, 1.29)	1.22 (1.15, 1.29)	1.22 (1.14, 1.29)	1.22 (1.15, 1.29)
Q3 (185.83–279.52)	2.14 (2.02, 2.28)	2.14 (2.01, 2.27)	2.14 (2.02, 2.28)	2.14 (2.01, 2.27)	2.14 (2.02, 2.28)
Q4 (≥279.53)	3.21 (3.01, 3.41)	3.19 (3.00, 3.40)	3.19 (3.00, 3.40)	3.19 (3.00, 3.40)	3.19 (3.00, 3.40)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
SIRI (per SD increase)	1.63 (1.58, 1.67)	1.62 (1.58, 1.67)	1.62 (1.58, 1.67)	1.62 (1.58, 1.67)	1.62 (1.58, 1.67)
SIRI quartiles					
Q1 (<0.55)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2 (0.55–0.78)	1.38 (1.30, 1.47)	1.38 (1.30, 1.47)	1.38 (1.30, 1.47)	1.38 (1.30, 1.47)	1.38 (1.30, 1.47)
Q3 (0.78–1.11)	2.00 (1.88, 2.12)	1.99 (1.88, 2.12)	2.00 (1.88, 2.12)	1.99 (1.88, 2.12)	2.00 (1.88, 2.12)
Q4 (≥1.11)	3.22 (3.03, 3.43)	3.21 (3.01, 3.42)	3.21 (3.02, 3.42)	3.21 (3.01, 3.42)	3.21 (3.02, 3.42)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001

(*Continued*)

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Table 2 (Continued).

Exposure	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
SII (per SD increase)	1.58 (1.54, 1.63)	1.58 (1.54, 1.62)	1.58 (1.54, 1.62)	1.58 (1.54, 1.62)	1.58 (1.54, 1.62)
SII quartiles					
Q1 (<333.66)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2 (333.68–450.17)	1.37 (1.29, 1.46)	1.37 (1.29, 1.45)	1.37 (1.29, 1.45)	1.37 (1.29, 1.45)	1.37 (1.29, 1.45)
Q3 (450.17–611.37)	2.00 (1.88, 2.12)	1.99 (1.87, 2.11)	1.99 (1.88, 2.12)	1.99 (1.87, 2.11)	1.99 (1.88, 2.12)
Q4 (≥611.39)	2.97 (2.79, 3.16)	2.95 (2.78, 3.14)	2.95 (2.78, 3.14)	2.95 (2.78, 3.14)	2.95 (2.78, 3.14)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
NLR (per SD increase)	1.42 (1.39, 1.46)	1.42 (1.38, 1.46)	1.42 (1.38, 1.46)	1.42 (1.38, 1.46)	1.42 (1.38, 1.46)
NLR quartiles					
Q1 (<1.49)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2 (1.49–1.89)	1.32 (1.25, 1.41)	1.32 (1.24, 1.40)	1.32 (1.25, 1.41)	1.32 (1.24, 1.40)	1.32 (1.25, 1.41)
Q3 (1.89–2.43)	1.61 (1.51, 1.71)	1.60 (1.51, 1.70)	1.60 (1.51, 1.70)	1.60 (1.51, 1.70)	1.60 (1.51, 1.70)
Q4 (≥2.43)	2.36 (2.22, 2.51)	2.34 (2.20, 2.49)	2.34 (2.20, 2.49)	2.34 (2.20, 2.49)	2.34 (2.20, 2.49)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
PLR (per SD increase)	1.24 (1.21, 1.27)	1.23 (1.21, 1.26)	1.23 (1.21, 1.26)	1.23 (1.21, 1.26)	1.23 (1.21, 1.26)
PLR quartiles					
Q1 (<101.92)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2 (101.92–126.79)	1.15 (1.08, 1.22)	1.15 (1.08, 1.22)	1.15 (1.08, 1.22)	1.15 (1.08, 1.22)	1.15 (1.08, 1.22)
Q3 (126.79–158.28)	1.37 (1.29, 1.45)	1.36 (1.28, 1.45)	1.36 (1.28, 1.45)	1.36 (1.28, 1.45)	1.36 (1.28, 1.45)
Q4 (≥158.28)	1.67 (1.57, 1.77)	1.66 (1.56, 1.76)	1.66 (1.56, 1.76)	1.66 (1.56, 1.76)	1.66 (1.56, 1.76)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
MLR (per SD increase)	1.39 (1.36, 1.42)	1.38 (1.35, 1.42)	1.38 (1.35, 1.42)	1.38 (1.35, 1.42)	1.38 (1.35, 1.42)
MLR quartiles					
Q1 (<0.17)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2 (0.17–0.22)	1.27 (1.20, 1.35)	1.27 (1.20, 1.35)	1.27 (1.20, 1.35)	1.27 (1.20, 1.35)	1.27 (1.20, 1.35)
Q3 (0.22–0.28)	1.62 (1.52, 1.72)	1.61 (1.52, 1.71)	1.61 (1.52, 1.71)	1.61 (1.52, 1.71)	1.61 (1.52, 1.71)
Q4 (≥0.28)	2.22 (2.09, 2.37)	2.21 (2.08, 2.35)	2.21 (2.08, 2.35)	2.21 (2.08, 2.35)	2.21 (2.08, 2.35)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001

Notes: Model 1: Unadjusted (univariate analysis). Model 2: Adjusted for age, sex, smoking status, alcohol consumption, and duration of hypertension. Model 3: Model 2 plus additional adjustments for systolic blood pressure, diastolic blood pressure, body mass index, waist circumference, diabetes mellitus, dyslipidemia, and coronary artery disease. Model 4: Model 3 plus further adjustments for AST/ALT, GGT, serum creatinine, uric acid, total cholesterol, triglyceride, HDL-C, LDL-C, fasting blood glucose, HbA1c, hs-CRP, and TyG index. Model 5: Model 4 plus adjustments for the use of antidiabetic medications, lipid-lowering agents, and antihypertensive drugs.
Abbreviations: SD, standard deviation; OR, odds ratio; CI, confidence interval. Other abbreviations are as defined in Table 1.

3.19; 95% CI, 3.00–3.40). Comparable trends were observed for SIRI, SII, NLR, PLR, and MLR, with the highest quartiles posing the most substantial risk (all P for trend < 0.001).

Figure 3 graphically represents the dose-response relationship between inflammatory markers and MAFLD prevalence. The curves' upward trend in each panel highlights the positive correlation between increasing inflammatory marker values and MAFLD prevalence, corroborating the logistic regression findings.

Sensitivity Analysis

We performed sensitivity analyses to assess the stability of the relationship between inflammatory markers and MAFLD prevalence, as presented in Supplementary Tables S1–S6. The initial sensitivity analysis, detailed in Table S1, excluded participants with any missing data. The associations remained significant across all models, indicating that missing data did not substantially affect the integrity of the observed associations. Subsequently, a sensitivity analysis excluding outliers, as shown in Table S2, was performed to evaluate the impact of extreme values. The results were congruent with the main analysis, indicating that the presence of outliers did not significantly skew the observed relationships. To address potential confounding from alcohol consumption, a third sensitivity analysis was executed, as illustrated in Table S3. Participants with

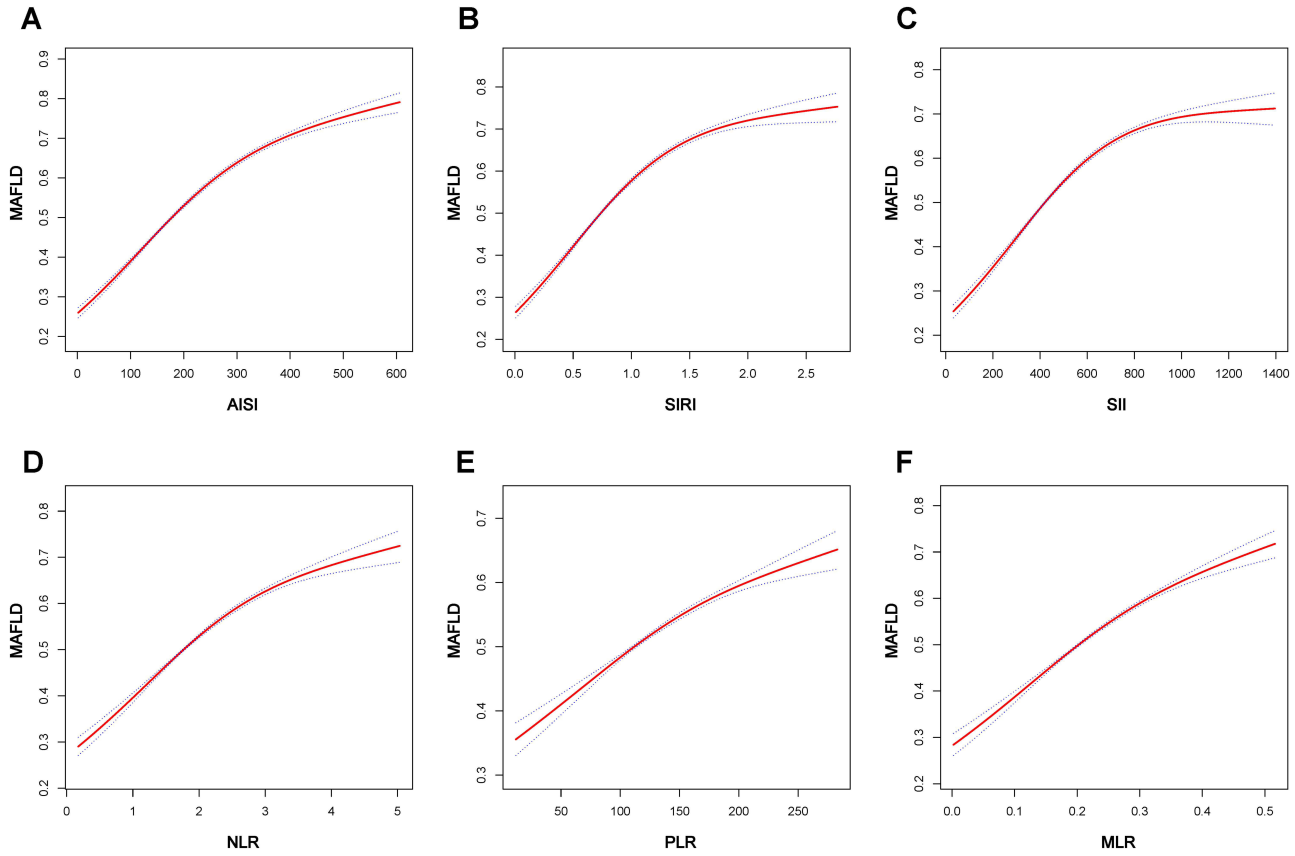

Figure 3 Dose-response relationship between inflammatory biomarkers and the prevalence of MAFLD. The solid red line represents the fit line and the dashed line represents the confidence interval. (**A**) AISI; (**B**) SIRI; (**C**) SII; (**D**) NLR; (**E**) PLR; (**F**) MLR.

excessive alcohol intake were excluded from this analysis. The findings were consistent with the primary analysis, suggesting that alcohol consumption did not significantly confound the association between the inflammatory biomarkers and MAFLD. In Table S4, participants were excluded based on a nonalcoholic fatty liver disease fibrosis score (NFS) greater than 0.676. The ORs for all inflammatory indices remained consistent across the five models, with slight variations in the point estimates that did not alter the overall significance of the findings. This suggests that the association between the inflammatory indices and MAFLD risk is not significantly influenced by the presence of severe liver fibrosis as defined by NFS. Table S5 further supports this conclusion by using a different criterion to exclude participants with severe liver fibrosis, specifically a fibrosis-4 (FIB-4) score greater than 2.67. The ORs for the inflammatory indices were also stable across the five models, with no substantial changes in the confidence intervals. This consistency in the results across different definitions of severe liver fibrosis indicates that the observed associations are robust and not confounded by the presence of advanced liver disease. Finally, Table S6 presents E-values for the inflammatory indices and MAFLD, suggesting that an unmeasured confounder would need to be strongly associated with both exposure and outcome to negate our observed associations, thus supporting the robustness of our results against unmeasured confounding.

Subgroup Analysis

The subgroup analysis of inflammatory biomarkers, as presented in Figure 4, uniformly indicates significant associations with MAFLD across a spectrum of demographic and clinical categories. The analysis was meticulously stratified to account for sex, age, smoking status, alcohol consumption, DM, dyslipidemia, and coronary artery disease, thereby offering an exhaustive view of the biomarkers' influence on MAFLD risk. While some interaction P-values suggest statistical significance, the consistent direction of effect sizes across subgroups indicates that these interactions do not alter the fundamental association. Therefore, the primary focus remains on the overall trend, which supports the utility of

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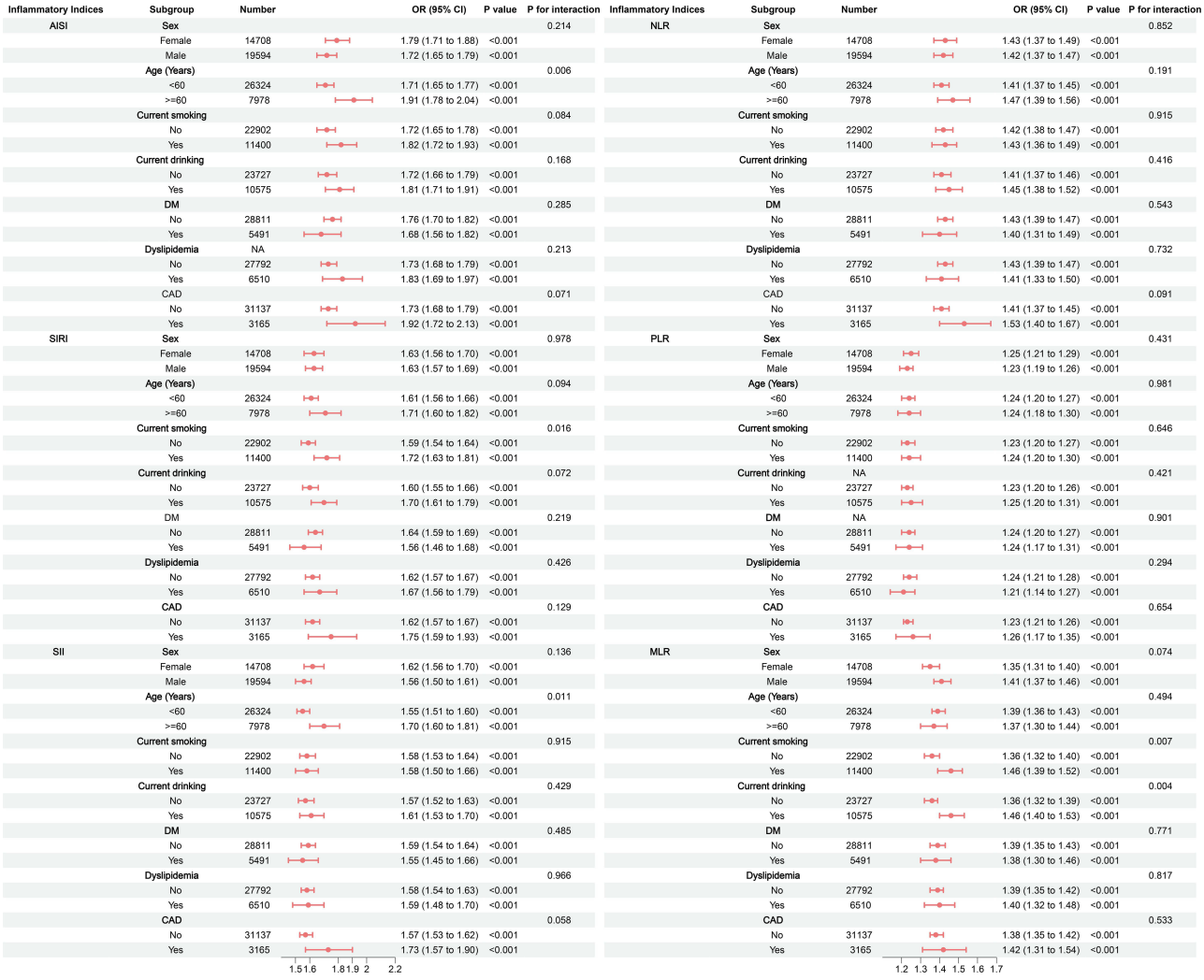

Figure 4 Stratified analysis of inflammatory biomarkers (per SD increasement) and their association with MAFLD.

these biomarkers in assessing MAFLD risk, without necessitating an overemphasis on the variations due to subgroup interactions.

Predictive Performance and Clinical Utility of Inflammatory Biomarkers for MAFLD

The predictive performance of inflammatory biomarkers for MAFLD was evaluated using ROC curves, as depicted in Figure 5, and detailed in Table 3. The diagnostic accuracy was evaluated based on the AUC, specificity, sensitivity, PPV, and NPV. The AUC, a pivotal measure of diagnostic discrimination, revealed that the AISI exhibited the highest AUC of 0.659, indicative of moderate diagnostic accuracy. This was succeeded by the SIRI and SII, with AUCs of 0.626 and 0.619, respectively, denoting a significant yet lower predictive capacity. In contrast, the NLR, PLR, and MLR displayed relatively inferior predictive performances, with AUCs of 0.593, 0.558, and 0.589, respectively. These findings underscore AISI's potential as a reliable biomarker for MAFLD diagnosis, while also highlighting the limitations of NLR, PLR, and MLR in clinical practice. The specificity and sensitivity values corroborate these results, with AISI also demonstrating the highest specificity (0.730) and a moderate sensitivity (0.534).

The DCA presented in Figure 6 offers a strategic perspective on the clinical utility of these inflammatory biomarkers. It evaluates the net benefit of incorporating these biomarkers into clinical decision-making across various threshold probabilities. The DCA indicates that AISI provides the highest net benefit across a broad spectrum of threshold

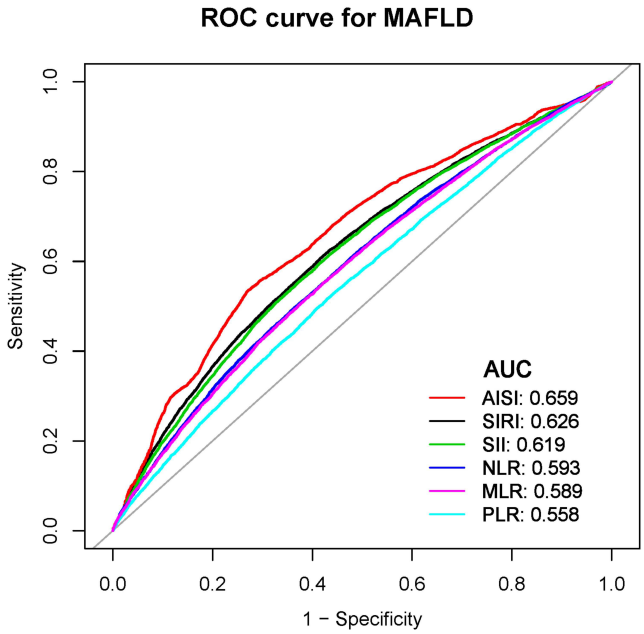

Figure 5 Receiver operating characteristic (ROC) curve analysis of inflammatory biomarkers for MAFLD.

probabilities, underscoring the importance of selecting biomarkers that maximize net benefit to enhance the accuracy and cost-effectiveness of MAFLD diagnosis.

Discussion

In this large-scale cross-sectional analysis, we investigated the relationship between six inflammatory indices—MLR, PLR, NLR, SII, SIRI, and AISI—and the risk of MAFLD in hypertensive patients. We leveraged a comprehensive dataset comprising 34,303 participants and employed multiple logistic regression models to elucidate the relationship between these inflammatory biomarkers and the prevalence of MAFLD. Our findings indicated that there was a strong link between the risk of MAFLD and higher levels of inflammatory indices, with AISI exhibiting the most pronounced association. Notably, an increment of one SD in AISI was linked to a 74% increase in the odds of MAFLD in the fully adjusted model. This correlation was further supported by a dose-response relationship, as evidenced by the generalized smooth curve analysis. The robustness and generalizability of our findings are shown by the consistency of our results across several sensitivity analyses, including those that eliminated outliers and people with possible confounding variables. By using ROC curves and DCA, the diagnostic accuracy of AISI was further supported, confirming its dependability as a MAFLD diagnostic tool. These results demonstrate the importance of inflammation in the development of MAFLD and the practicality of non-invasive biomarkers in clinical practice, positioning AISI as a useful biomarker for MAFLD risk assessment in hypertensive adults.

Table 3 Diagnostic Performance of Inflammatory Biomarkers for MAFLD

Index	AUC	95% CI Low	95% CI Upp	Specificity	Sensitivity	Positive-pv	Negative-pv
AISI	0.659	0.654	0.665	0.730	0.534	0.685	0.588
SIRI	0.626	0.620	0.632	0.584	0.607	0.616	0.575
SII	0.619	0.613	0.625	0.627	0.555	0.620	0.562
NLR	0.593	0.587	0.599	0.643	0.490	0.601	0.534
PLR	0.558	0.552	0.564	0.571	0.516	0.569	0.518
MLR	0.589	0.583	0.595	0.578	0.552	0.590	0.540

Abbreviations: AUC, area under the curve; Positive-pv, positive predictive value; Negative-pv, negative predictive value. Other abbreviations are as defined in Table 1.

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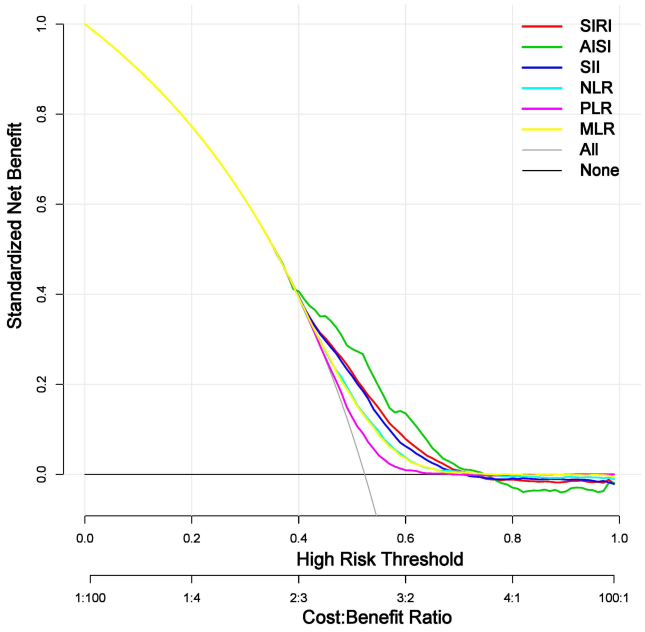

Figure 6 Decision curve analysis of inflammatory biomarkers for the prediction of MAFLD.

In recent studies, the association between inflammatory markers and hepatic steatosis has been extensively explored.[43–46] A NHANES-based study by Liu et al analyzed the relationship between systemic immune-inflammatory indices and NAFLD risk, revealing significant positive correlations for SII, NLR, and LMR after logarithmic transformation.[45] Zhao et al found a U-shaped relationship between SII and NAFLD risk, with an SII index of 422.40 associated with the lowest NAFLD prevalence.[47] Another study identified a nonlinear association between NLR and PLR with NAFLD, indicating that a PLR of 42.29 or higher may confer protection against NAFLD, while an NLR below 1.23 could be indicative of a risk factor.[48] Building on these insights, Wang et al conducted a study based on NHANES data to investigate the association between six systemic immune biomarkers and metabolic dysfunction-associated steatotic liver disease (MASLD), assessing their predictive value.[49] The study observed higher levels of SII, SIRI, NLR, and PLR in participants with MAFLD compared to those without, with a positive linear relationship existing between these markers and MAFLD risk. Arefhosseini et al reported that, with the exception of PLR, all SII components significantly varied with the severity of steatosis.[50] Changes in NLR were significantly associated with various anthropometric indices and lipid levels, and the relationship between the lipid profile and all studied SII components, particularly the monocyte-to-HDL cholesterol ratio (MHR) and the lymphocyte-to-HDL cholesterol ratio (MLR), highlighted their connection with metabolic risk factors for NAFLD. Xie et al utilized the NHANES dataset to explore the correlation between SII and hepatic steatosis and fibrosis.[43] The study demonstrated a significant positive correlation between SII and hepatic steatosis, as measured by the controlled attenuation parameter, particularly in males. However, no significant association was observed between SII and liver fibrosis, as indicated by liver stiffness measurement. The study also indicated a nonlinear, inverse U-shaped relationship between SII and hepatic steatosis, suggesting that SII may serve as a predictive marker for hepatic steatosis. In summary, these studies underscore the importance of immune-inflammatory biomarkers in the pathogenesis and risk stratification of NAFLD and MAFLD. The findings highlight the potential utility of these markers in clinical practice for the early identification and management of these conditions.

The precise biological mechanisms linking inflammatory indices to MAFLD are not yet fully understood. However, based on the current understanding of MAFLD pathophysiology and the role of inflammation in metabolic disorders, several hypotheses can be proposed. One hypothesis suggests that chronic low-grade inflammation, as indicated by elevated AISI, may contribute to hepatic steatosis by disrupting lipid metabolism and increasing the delivery of free fatty acids to the liver. This inflammation-driven metabolic disturbance could promote triglyceride accumulation in hepatocytes, a hallmark feature of MAFLD.[51–53] Secondly, the interplay between adipose tissue and the liver may represent a critical link between systemic inflammation and MAFLD. Insulin resistance can result from the production of several cytokines and adipokines by adipose

tissue in response to inflammation. These substances can disrupt insulin signaling. In the pathophysiology of MAFLD, insulin resistance is a key factor that leads to the development of nonalcoholic steatohepatitis (NASH).[54] This resistance can exacerbate hepatic lipid accumulation and the progression of MAFLD.[55–57] Oxidative stress, often associated with increased inflammatory markers, may represent another mechanism. It can cause cellular damage, activate hepatic stellate cells, and promote fibrogenesis, which are key pathogenic processes in MAFLD.[58] The potential for oxidative stress to induce hepatocyte injury and lipid peroxidation further supports its role in the pathogenesis of MAFLD.[24,59,60] The gut-liver axis is another potential pathway linking inflammation with MAFLD.[61] Increased permeability of the gut barrier in the context of systemic inflammation can lead to the translocation of bacterial products, such as lipopolysaccharide, into the portal circulation.[62] This endotoxemia can activate Kupffer cells in the liver, initiating a cascade of inflammatory responses that contribute to hepatic steatosis and injury.[63–65] Additionally, it is crucial to recognize that the relationship between inflammation and MAFLD may be bidirectional. Although inflammation can contribute to the development of MAFLD, the presence of MAFLD may also stimulate the production of inflammatory markers. Hepatic steatosis can activate hepatic immune cells, leading to the release of pro-inflammatory cytokines and perpetuating a systemic inflammatory state.[24,66,67]

This study offers an in-depth examination of the link between inflammatory biomarkers and MAFLD among a large sample size of hypertensive patients. A significant strength is the large sample size, which enhances the generalizability and statistical power to detect significant correlations. Our comprehensive data collection, covering a wide array of clinical and biochemical variables, allows for rigorous adjustment for potential confounders. Moreover, the employment of various regression models and sensitivity analyses enhances the reliability of our findings. However, interpreting our findings requires acknowledgment of several limitations. First, the cross-sectional design limits our ability to infer causality, leaving the temporality of the observed associations ambiguous. This limitation precludes us from determining whether elevated inflammatory biomarkers precede the development of MAFLD or are a consequence of the disease. Second, despite adjustments for numerous potential confounders, the possibility of residual confounding due to unmeasured factors, such as dietary habits, physical activity levels, and genetic predispositions, cannot be ruled out. These unmeasured factors could significantly impact both inflammatory status and the risk of MAFLD. Third, the cross-sectional design of this study lacks detailed records on the duration of MAFLD, thereby limiting the analysis of disease progression. Consequently, future research should consider including the duration of MAFLD as a significant covariate to more accurately assess the relationship between inflammatory indices and MAFLD, thereby providing deeper insights for clinical practice. Fourth, the demographic homogeneity of our study population, predominantly consisting of Chinese hypertensive patients, may restrict the applicability of our results. The influence of cultural, dietary, and genetic differences across diverse populations may modulate the relationship between inflammatory biomarkers and MAFLD, suggesting that our results should be cautiously extrapolated to other ethnic groups. Lastly, the diagnosis of MAFLD was based on imaging techniques, which, despite their non-invasive nature and suitability for large-scale studies, may not offer the same sensitivity and specificity as liver biopsy. The potential for misdiagnosis or misclassification could introduce bias into our prevalence estimates.

Conclusion

In conclusion, this large cross-sectional study reveals a significant association between elevated inflammatory indices and MAFLD in hypertensive patients, with AISI exhibiting the strongest predictive value. These findings underscore the potential utility of non-invasive inflammatory biomarkers in MAFLD risk stratification, warranting further prospective investigation.

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Disclosure

The authors report no conflicts of interest in this work.

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