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ORIGINAL RESEARCH

Dynamic Status of Systemic Immune Inflammation Index Is Associated With Metabolic Dysfunction-Associated Steatotic Liver Disease: An Evidence From a Ten-Year Prospective Longitudinal Cohort Study

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Objective: Previous research studies have linked the systemic immune inflammation index (SII), derived from a complete blood count, to metabolic dysfunction-associated steatotic liver disease (MASLD). However, evidence on the relationship between longitudinal changes in SII and MASLD remains limited. This study aimed to explore distinct SII trajectories and their association with MASLD incidence.

Methods: A longitudinal study analyzed 25,600 individuals who underwent periodic health assessments at a Dalian City hospital between 2014 and 2023. MASLD was diagnosed via ultrasound. The SII was calculated using the formula SII = (platelet count × neutrophil count) / lymphocyte count. Group-based trajectory modeling was used to identify SII trajectories, and restricted cubic spline (RCS) analysis was employed to assess the dose-response relationship. Stratified analyses and sensitivity analyses were also conducted.

Results: Three SII trajectories were identified: "low stable" (50.6%), "moderate stable" (35.1%), and "high stable" (8.9%). After adjustments, the hazard ratios (*HR*) for MASLD incidence were 1.118 (95% *CI*: 1.057–1.182, $P<0.001$) for the "moderate stable" group and 1.284 (95% *CI*: 1.172–1.408, $P<0.001$) for the "high stable" group. These associations persisted after adjusting for lifestyle factors. A significant non-linear relationship between SII and MASLD risk was found in both the overall population and among different genders. Subgroup and sensitivity analyses consistently confirmed these findings.

Conclusion: Elevated SII levels are significantly associated with an increased risk of MASLD, particularly among individuals under 45 and women. Regular SII monitoring may improve risk stratification and facilitate targeted prevention strategies for those at higher risk of MASLD.

Keywords: systemic inflammation, dynamic status, long-term trajectories, metabolic dysfunction-associated steatotic liver disease, prospective cohort

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), introduced in 2023, builds on the concept of non-alcoholic fatty liver disease (NAFLD) to emphasize the role of metabolic dysfunction and reduce stigma. Unlike NAFLD, MASLD can coexist with alcohol consumption, other liver diseases, or secondary causes of liver steatosis.[1,2] According to Global Burden of Disease (GBD) data, MASLD has a global prevalence of 32.4% (95% *CI*: 29.9%-34.9%), with higher

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rates in men (39.7%) than women (25.6%).[3] In China, the prevalence of MASLD is approximately 29.71%.[4] Recent evidence indicates that nearly 99% of former NAFLD cases meet the criteria for MASLD.[5] The spectrum of MASLD ranges from simple hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis and hepatocellular carcinoma (HCC). In addition to liver-related complications, MASLD is associated with various extrahepatic conditions, including stroke, cardiovascular diseases (CVD), and chronic kidney disease (CKD).[6–9] While liver-related deaths account for only 7% of total mortality in MASLD patients, CVD and extrahepatic malignancies are the leading causes of death.[10] As the global metabolic burden continues to rise, the prevalence of MASLD and its associated complications is expected to increase further, underscoring the urgent need for improved risk stratification tools.[11]

MASH is characterized by hepatic inflammation, hepatocyte ballooning, and fibrosis, marking a critical stage in the progression of MASLD.[12] This inflammatory process is primarily driven by lipotoxicity, which leads to endoplasmic reticulum stress, oxidative stress, organelle dysfunction, and ferroptosis.[13] Previous studies have emphasized the importance of inflammation-related cells and molecular mediators in various biological functions, including tissue healing, metabolism, thermogenesis, and neural function.[14] Inflammatory indices derived from routine serum biochemical tests are considered both cost-effective and reliable indicators, reflecting local immune responses and systemic inflammatory states.[15] Despite advances in understanding MASLD, the dynamic and multifaceted nature of inflammation in MASLD remains poorly understood. The systemic inflammation index (SII), computed as platelet count × neutrophil count/lymphocyte count, is an inflammatory biomarker that has shown prognostic value in cancer and cardiovascular diseases.[16,17] However, significant gaps in MASLD research remain, particularly regarding the application of SII. Most studies focus on single-timepoint measurements of the SII, which fail to capture the chronic nature and fluctuations of inflammation over time.[18–20] This limitation highlights the need for longitudinal studies to better understand the role of systemic inflammation in MASLD progression and its potential as a therapeutic target. To address these gaps, our research aims to utilize a population-based trajectory model (GBTM) to investigate the long-term trajectories of systemic inflammation, as measured by the SII index, in relation to the incidence of MASLD across a diverse population. By understanding how inflammatory status evolves over time, we hope to identify potential biomarkers for early diagnosis and predictive risk assessments, ultimately improving outcomes for patients at risk for MASLD and its complications.

Materials and Methods

Study Population

The subjects of this investigation were sourced from the Dalian Health Management Cohort (DHMC) (ChiCTR2300073363). This DHMC is a substantial, ongoing prospective cohort study initiated in 2014 at the Second Affiliated Hospital of Dalian Medical University. Enrollment necessitated the completion of comprehensive questionnaires, a standardized health evaluation, and laboratory procedures to obtain biochemical parameters. The study population included 37,191 adults aged 18 and older, with a maximum age of 90, all of whom participated in at least three consecutive annual health assessments between 2014 and 2023. Exclusion criteria included participants diagnosed with MASLD at baseline (n=11,072), those with a history of excessive alcohol intake (males exceeding 420 grams/day, females exceeding 350 grams/day) (n=74),[21,22] individuals with a history of cancer (n=17), and those affected by other liver pathologies such as autoimmune hepatitis, viral hepatitis, cirrhosis, or nephrosis (n=242). Furthermore, subjects with incomplete complete blood count data (n=203) were also excluded. Finallly, our study consisted 25,600 individuals over (Figure 1). The baseline time was defined as the date of the first visit, and the follow-up endpoint was the occurrence of new-onset MASLD or the last follow-up before December 31, 2023, for those without the outcome event. Follow-up visits involved patients returning to the hospital for physical exams every six months to one year, during which data were collected on abdominal ultrasound and blood markers, including lipids, blood glucose, and complete blood count. Participants were free to withdraw from the study at any time. Ethical clearance was granted by the ethical review committee of the Second Affiliated Hospital of Dalian Medical University (grant number: 2,022,064), and all participants provided written informed consent.

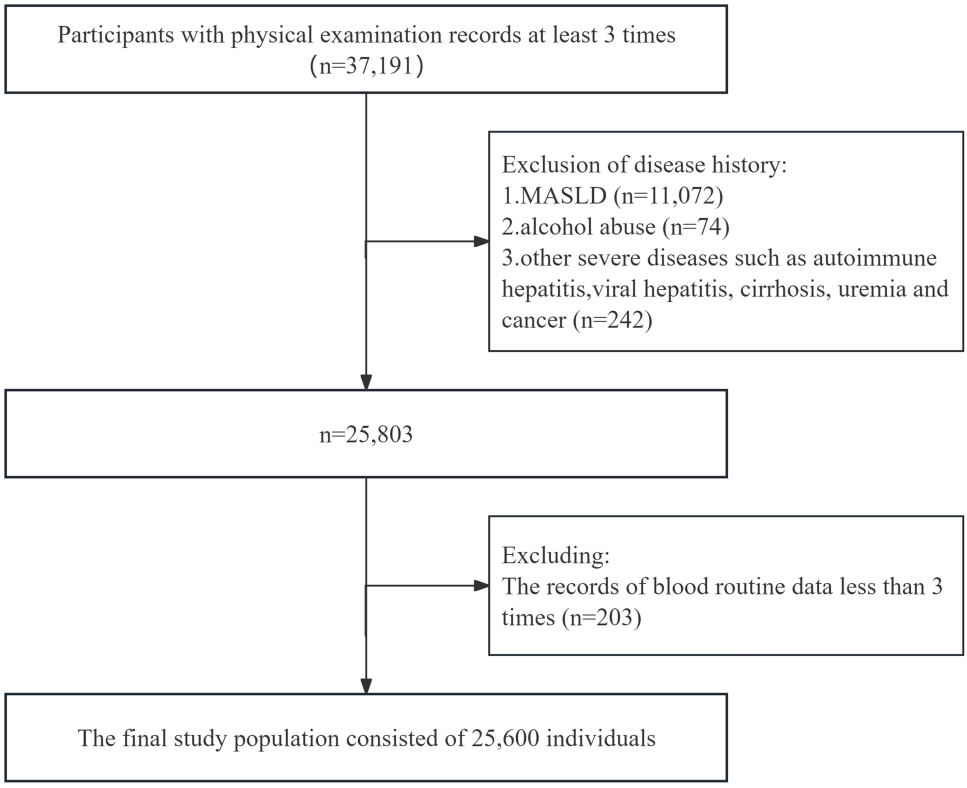

Figure 1 Flowchart of the study population selection.
Abbreviations: SII, systemic inflammation index; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease.

Data Collection and Definitions

Demographic characteristics, including sex, age, medical history, daily hours of sleep, daily amount of physical activity, vegetable consumption, fruit consumption, milk intake and weekly consumption of sugary beverages and alcohol consumption status, were gathered via questionnaires. Dietary intake was assessed using a 24-hour dietary recall and a semi-quantitative food frequency questionnaire, which provided information on the variety of foods ingested. Solid food consumption was quantified in grams (g), and liquid intake was recorded in milliliters (mL). Participants' height and weight height and weight were measured while wearing light clothing and no shoes. Blood pressure was measured with anron electronic sphygmomanometer (HBP9020, Japan) after a 5-minute rest period. Laboratory assessments included a fasting venous blood draw (≥8 hours prior) and the analysis of biochemical markers using a fully automated biochemical immunoassay instrument. The following blood parameters were evaluated: white blood cell (WBC) count, neutrophil (N) count, lymphocyte (L) count, monocyte (M) count, red blood cell (RBC) count, hemoglobin (Hb), platelet (PLT) count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), globulin (GLB), gamma-glutamyl transferase (GGT), total bilirubin (TBil), direct bilirubin (DBil), blood urea nitrogen (BUN), serum uric acid (SUA), serum creatinine (SCr), fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

The SII was calculated using the formula: SII = (peripheral platelet count × neutrophil absolute value) / lymphocyte absolute value.[23] Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Smoking status was assessed by asking participants"Do you smoke?" Responses were categorized as either "never smoked" or "former/current smoker." Alcohol consumption was evaluated with the question"How often do you drink alcohol?" Participants with a daily alcohol intake exceeding 420 grams for males or 350 grams for females were excluded from the study. Sugary beverage consumption was gauged by asking"How many bottles of sugary drinks do you consume per week?" Responses were classified into two groups: "less than once per week or none" and "two or more bottles per week." Vegetable intake was deemed adequate at 300 grams per day. Intake below this level was classified as "insufficient vegetable intake" while intake at or above

300 grams was considered "sufficient vegetable intake." Fruit intake was considered adequate at 200 grams per day. Intake below this threshold was classified as "insufficient fruit intake" and intake at or above 200 grams was categorized as "sufficient fruit intake." Milk intake was considered adequate at 250 milliliter per day. Intake below this threshold was classified as "insufficient milk intake" and intake at or above 250 milliliter was categorized as "sufficient milk intake." Sleep duration was standardized to 7 hours per night. Less than 7 hours was categorized as "insufficient sleep" and more than 7 hours was classified as "sufficient sleep." Physical activity intensity was quantified using the metabolic equivalent of task (MET). A MET value below 3 was considered "insufficient exercises" a MET value of 3 or more was classified as "moderate exercise" and a MET value greater than 6 was classified as "sufficient exercise.".[24] Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, use of antihypertensive medications, or self-reported hypertension.[25] Diabetes was considered if participants were using antidiabetic medications or insulin, had a history of diabetes, or had FPG ≥7 mmol/L or glycated hemoglobin ≥6.5%.[26] Dyslipidemia was defined as TG ≥150 mg/dL and/or TC ≥200 mg/dL and/or LDL-C ≥130 mg/dL and/or HDL-C ≤40 mg/dL.[27]

Diagnostic Criteria for MASLD

MASLD was diagnosed based on hepatic steatosis detected by ultrasonography while excluding other potential causes or excessive alcohol consumption (≥420 g/week for males and ≥350 g/week for females). Abdominal ultrasonography was performed by two trained physicians using an ultrasonography system. Fatty liver was identified based on at least one of the following criteria: high-intensity bright liver, hepato-renal contrast, vascular obscuration, or deep attenuation in the liver.[28] Additionally, participants were required to have at least one of the following five cardiovascular and metabolic risk factors: (1) BMI ≥23 kg/m^2 for both males and females or waist circumference ≥90/80 cm; (2) FPG ≥5.6 mmol/L or glycated hemoglobin ≥5.7%, or a history of type 2 diabetes mellitus (T2DM) or ongoing T2DM treatment; (3) blood pressure ≥130/85 mmHg or receiving specific antihypertensive medications; (4) TG ≥1.70 mmol/L or receiving lipid-lowering therapy; (5) For men, HDL-C <1.0 mmol/L, and for women, <1.3 mmol/L or receiving lipid-lowering treatment.[6]

Method and Statistic

All statistical analyses were performed using Stata version 17.0 and R version 4.3.2. A two-sided P value of <0.05 was regarded as statistically significant. Normally distributed variables were presented as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median (P25, P75). Comparisons between groups were conducted using independent sample t-tests, analysis of variance (ANOVA), and Wilcoxon rank-sum tests. Categorical variables were reported as frequencies and percentages, with differences assessed using x^2 tests. The multiple comparisons were corrected using the false discovery rate (FDR) method. During data preparation, the winsorization technique was applied to handle outliers at both ends of the distribution, with a 1% threshold for robustness. Missing covariates were imputed using the k-nearest neighbors (KNN) method.[29]

Group-Based Trajectory Modeling (GBTM) is utilized to identify distinct subgroups within longitudinal datasets based on similar developmental trajectories. To analyze the trajectory of the SII, we analyzed 2 to 5 patterns, including linear, quadratic, and cubic trends. The optimal model was selected based on the minimum absolute value of the bayesian information criterion (BIC), ensuring that each trajectory had at least 5% representation and higher average posterior probabilities (0.70).[30] Based on this analysis, we determined that categorizing the trajectories into three distinct groups was the most appropriate approach (Figure 2). Additional details on the modeling approach are provided in Supplementary Table S1.

Kaplan-Meier analysis was used to determine the cumulative incidence rate of MASLD, with the Log rank test employed to compare intergroup discrepancies. Cox proportional hazards regression analysis was utilized to evaluate the association between all trajectory groups and MASLD risk. Model 1 was unadjusted, Model 2 was adjusted for baseline age and sex, while Model 3 was further adjusted for baseline levels BMI, Hb, ALT, AST, ALB, GLB, GGT, TBil, BUN, SCr, SUA, T2DM, hypertension, dyslipidemia, smoking. The dose-response relationship between SII and MASLD risk was explored using a restricted cubic spline Subgroup analyses based on age, sex, BMI, hypertension, T2DM, and dyslipidemia were conducted to further investigate the potential link between SII and MASLD risk.

To ensure the robustness of our findings, four sensitivity analyses were conducted. First, we excluded subjects with incomplete data, particularly those missing information on BMI, ALT, AST, GGT, SUA, SCr, TC, TG, HDL-C, and

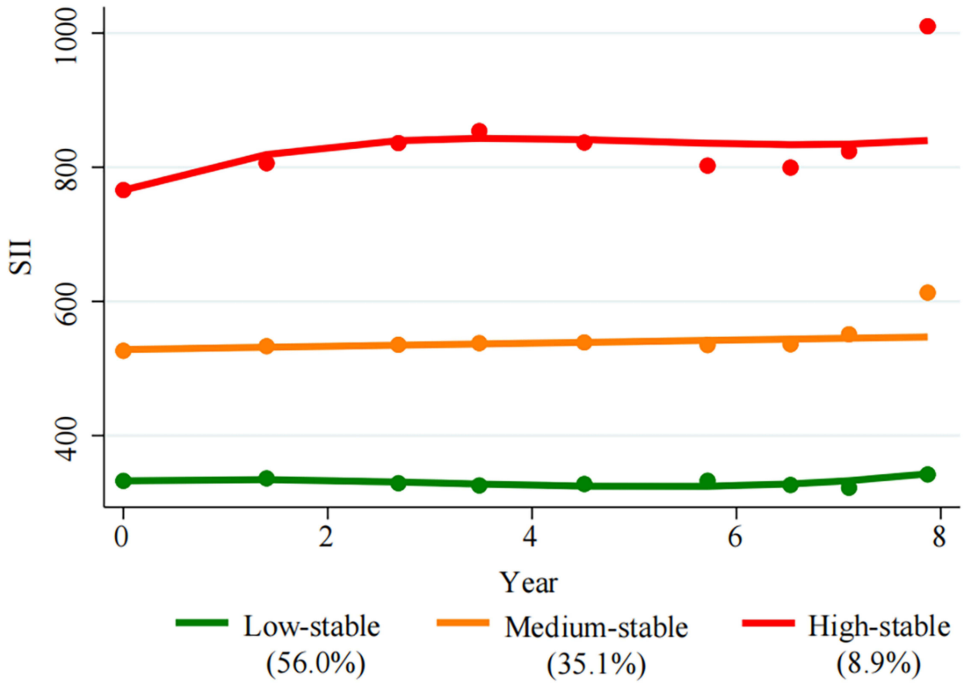

Figure 2 Dynamic trajectory of SII.
Abbreviation: SII, systemic inflammation index.

LDL-C (n=8,078), and recalculated the GBTM model. Second, we excluded participants who developed MASLD within two years (n=4,384) to reduce the likelihood of reverse causation. Third, we examined the impact of pharmacological interventions by excluding subjects using medications for lipid-lowering, blood pressure control, and blood sugar management to assess their influence on the results. Finally, in participants with available lifestyle data (n=4,255), we categorized SII into quartiles and further adjusted for dietary and physical activity variables to evaluate their effect on the association between SII levels and MASLD incidence.

Results

Baseline Characteristics

In this study, participants had a mean age of 40.12 years, with 41.5% males in the cohort. A total of 5,843 new cases of MASLD were recorded with an average follow-up period of 3.98 years. As illustrated in Figure 2, we identified three distinct SII trajectory groups among the 25,600 participants: "Low-Stable" (n=14,482, 50.6%), "Medium-Stable" (n=8,854, 35.1%), and "High-Stable" (n=2,264, 8.9%). Baseline characteristics stratified by SII trajectory groups are summarized in Table 1. A comparison between the "Low-Stable" group and the "High-Stable" group showed that the "High Stable" group to be younger and predominantly female. This group also exhibited lower levels of L, RBC, Hb, ALT, AST, ALB, TBil, DBil, BUN, SUA, TC, HDL-C, and LDL-C. Conversely, they had higher SBP, DBP, WBC, N, M, TP, GLB, and TG. Additionally, this group had a higher prevalence of hypertension but lower smoking rates, dyslipidemia prevalence, and diabetes history. The baseline characteristics of individuals excluded due to MASLD diagnosis at enrollment and those included in the study cohort were comprehensively compared in Supplementary Table S2.

Associations Between SII Trajectories and the Risk of MASLD

SII trajectories were significantly associated with the incidence of MASLD. All covariates successfully passed the multicollinearity test, with Variance Inflation Factor (VIF) values < 4 (Supplementary Table S3). After adjusting for potential confounders, the *HR* for MASLD in the medium-stable and high-stable trajectory groups were 1.118 (95% *CI*: 1.057–1.182, *P*<0.001) and 1.284 (95% *CI*: 1.172–1.408, *P*<0.001), respectively (Table 2). Cumulative Hazard Function analysis revealed a significantly higher MASLD incidence among individuals in the medium-stable and high-stable SII

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Table 1 The Baseline Characteristics of the Population Grouped by SII Trajectories

Variable	Low Stable[a] (N=14,470)	Moderate Stable[a] (N=8,883)	High Stable[a] (N=2,267)	*P*-value	q-value[b]
Age (Years)[a]	39.00 (30.00, 50.00)	37.00 (30.00, 46.00)	38.00 (30.00, 46.00)	<0.001[c]	<0.001
Sex[n(%)]				<0.001[4]	<0.001
Male	6,762 (47%)	3,196 (36%)	671 (30%)		
Female	7,708 (53%)	5,667 (64%)	1,596 (70%)		
SBP(mmHg)[a]	123.00 (113.00, 134.00)	122.00 (113.00, 133.00)	124.00 (113.00, 135.00)	<0.001[c]	<0.001
DBP(mmHg)[a]	74.00 (67.00, 81.00)	74.00 (67.00, 81.00)	75.00 (68.00, 82.15)	0.001[c]	0.001
BMI (kg/m²)[a]	22.68 (20.69, 24.77)	22.68 (20.70, 24.76)	22.86 (20.82, 24.91)	0.070[c]	0.070
WBC(10^9/L)[a]	5.46 (4.68, 6.35)	6.08 (5.23, 7.05)	6.62 (5.65, 7.74)	<0.001[c]	<0.001
N(10^9/L)[a]	2.95 (2.45, 3.56)	3.70 (3.10, 4.42)	4.34 (3.60, 5.25)	<0.001[c]	<0.001
L(10^9/L)[a]	2.03 (1.70, 2.40)	1.86 (1.57, 2.20)	1.71 (1.41, 2.03)	<0.001[c]	<0.001
M (10^9/L)[a]	0.29 (0.23, 0.37)	0.31 (0.25, 0.39)	0.33 (0.27, 0.41)	<0.001[c]	<0.001
RBC (10^9/L)[a]	4.73 (4.43, 5.07)	4.68 (4.43, 5.01)	4.66 (4.41, 4.95)	<0.001[c]	<0.001
Hb(g/L)[a]	142.00 (132.00, 155.00)	139.00 (130.00, 151.00)	137.00 (127.62, 147.00)	<0.001[c]	<0.001
PLT (10^9/L)[a]	218.00 (190.00, 248.00)	255.00 (225.00, 288.00)	286.00 (250.00, 327.00)	<0.001[c]	<0.001
ALT (U/L)[a]	16.97 (12.80, 23.00)	15.96 (12.00, 22.00)	15.10 (11.56, 20.74)	<0.001[c]	<0.001
AST(U/L)[a]	19.00 (16.62, 22.18)	18.09 (16.00, 21.00)	17.97 (15.60, 21.00)	<0.001[c]	<0.001
TP(g/L)[a]	74.45 (72.42, 76.40)	74.64 (72.63, 76.70)	74.69 (72.75, 76.80)	<0.001[c]	<0.001
ALB(g/L)[a]	46.84 (45.35, 48.45)	46.66 (45.16, 48.22)	46.37 (44.87, 47.95)	<0.001[c]	<0.001
GLB(g/L)[a]	27.53 (25.65, 29.35)	27.94 (26.10, 29.74)	28.33 (26.40, 30.21)	<0.001[c]	<0.001
GGT (U/L)[a]	14.55 (10.78, 21.94)	14.00 (10.47, 21.04)	13.91 (10.58, 21.00)	<0.001[c]	<0.001
TBil(U/L)[a]	14.15 (11.53, 17.44)	13.25 (10.68, 16.39)	12.47 (9.96, 15.55)	<0.001[c]	<0.001
DBil(U/L)[a]	4.51 (3.64, 5.67)	4.23 (3.40, 5.33)	3.97 (3.19, 5.02)	<0.001[c]	<0.001
BUN(μmol/L)[a]	4.84 (4.11, 5.57)	4.61 (3.92, 5.39)	4.51 (3.80, 5.30)	<0.001[c]	<0.001
SUA(μmol/L)[a]	314.45 (261.30, 375.39)	304.68 (256.00, 366.00)	299.16 (250.55, 356.85)	<0.001[c]	<0.001
SCr(μmol/L)[a]	64.25 (54.78, 75.77)	59.87 (52.64, 72.00)	58.20 (51.42, 69.02)	<0.001[c]	<0.001
FPG(mmol/L)[a]	5.34 (5.06, 5.71)	5.33 (5.05, 5.68)	5.34 (5.06, 5.71)	0.034[c]	0.035
TC(mmol/L)[a]	4.76 (4.22, 5.35)	4.71 (4.17, 5.29)	4.67 (4.15, 5.26)	<0.001[c]	<0.001
TG(mmol/L)[a]	1.18 (0.87, 1.63)	1.20 (0.87, 1.65)	1.24 (0.90, 1.67)	<0.001[c]	<0.001
HDL-C(mmol/L)[a]	1.39 (1.18, 1.62)	1.37 (1.18, 1.59)	1.36 (1.18, 1.56)	<0.001[c]	<0.001
LDL-C(mmol/L)[a]	2.49 (2.07, 2.93)	2.47 (2.04, 2.91)	2.42 (2.03, 2.90)	0.006[c]	0.007
T2DM[n(%)]	1,282 (8.9%)	703 (7.9%)	177 (7.8%)	0.02d[d]	0.026
Hypertension[n(%)]	2,466 (17%)	1,533 (17%)	471 (21%)	<0.001[d]	<0.001
Dyslipidemia[n(%)]	3,893 (27%)	2,267 (26%)	530 (23%)	<0.001[d]	<0.001
Smoking[n(%)]	477 (3.7)	206 (3.1)	27 (2.1)	0.003[d]	0.003

Notes: [a]Median (Q1, Q3); n (%). [b]False discovery rate correction for multiple testing. [c]Kruskal–Wallis rank sum test. [d]Pearson's Chi-squared test.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WBC, white blood cell; N, neutrophil; L, lymphocyte; M, monocyte; RBC, red blood cell; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; GLB, globulin; GGT, gamma-glutamyl transferase; TBil, total bilirubin; DBil, direct bilirubin; BUN, blood urea nitrogen; SUA, serum uric acid; SCr, serum creatinine; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; T2DM, type 2 diabetes mellitus.

Table 2 Association Between SII Trajectory With Incidence of MASLD

Trajectory groups	Model 1		Model 2		Model 3	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Low stable	1 (Reference)		1 (Reference)		1 (Reference)	
Moderate stable	1.077(1.019,1.138)	0.009	1.215(1.150,1.284)	<0.001	1.118(1.057,1.182)	<0.001
High stable	1.161(1.061,1.271)	0.001	1.383(1.262,1.514)	<0.001	1.284(1.172,1.408)	<0.001

Notes: Model 1: unadjusted. Model 2: Adjusted for baseline age and sex. Model 3: Model 2 plus additional adjustments for BMI, Hb, ALT, AST, ALB, GLB, GGT, TBil, BUN, SCr, SUA, T2DM, hypertension, dyslipidemia, smoking.
Abbreviations: HR hazard ratio, CI confidence interval. Other abbreviations are as defined in Table 1.

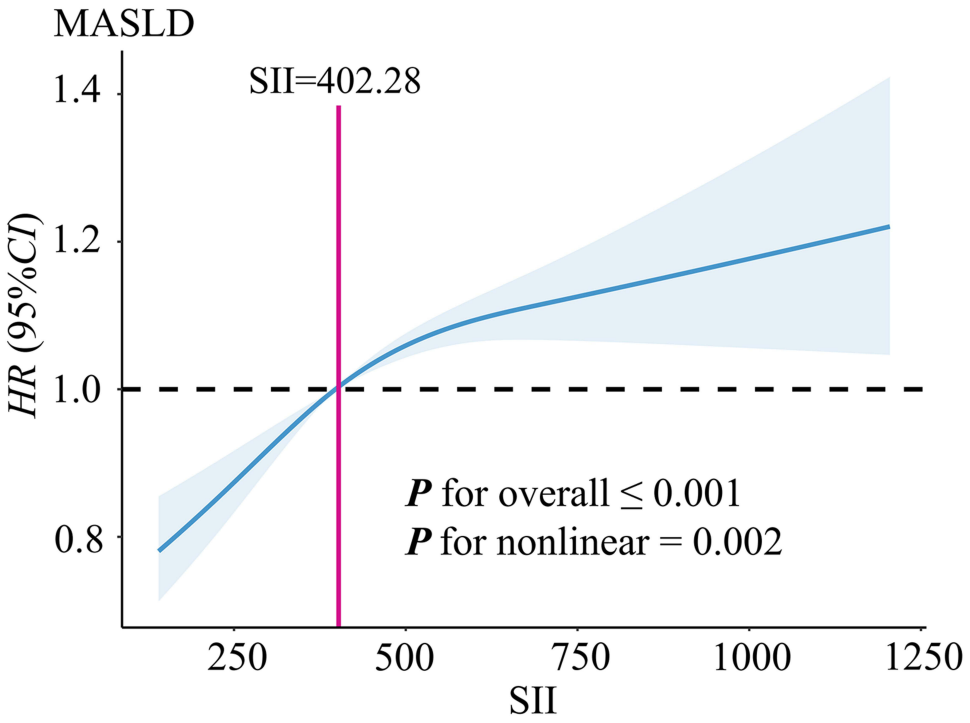

Figure 3 The association between baseline SII and MASLD risk Restricted cubic spline analyses were conducted with 3 knots to assess the nonlinear relationship between baseline SII and MASLD on a continuous scale. The *HR* were depicted by solid lines, while the 95% *CIs* were indicated by shaded areas. The analysis was adjusted for several factors, including age, sex, BMI, Hb, ALT, AST, ALB, GLB, GGT, TBil, BUN, SCr, SUA, T2DM, hypertension, dyslipidemia, and smoking.

trajectory groups compared to those in the low-stable group ($P<0.001$), as illustrated in Supplementary Figure S1. Furthermore, a nonlinear relationship was identified between baseline SII and the incidence of MASLD after adjusting for other covariates (*P* for nonlinear trend = 0.018) (Figure 3). When stratified by sex, the study revealed a significant nonlinear correlation in both male and female cohorts. Specifically, the male cohort (*P* for nonlinear trend = 0.026) and the female cohort (*P* for nonlinear trend = 0.006) exhibited statistical significance. Importantly, the cutoff point for the male cohort was lower than that of the female cohort, with SII values of 370.20 and 423.68, respectively, as shown in Supplementary Figure S2.

Stratified Analysis

Subgroup analyses were conducted based on sex, age, BMI, hypertension, and dyslipidemia. Figure 4 delineates the baseline risk of MASLD across these diverse subgroups. The incidence of MASLD was significantly lower in females (14.63%) than in males (34.35%), with a pronounced sex discrepancy observed in the medium-stable and high-stable trajectory groups. Males had *HR* of 1.07 (95% *CI*: 1.00–1.15) and 1.15 (95% *CI*: 1.01–1.30), whereas females had higher *HR* of 1.24 (95% *CI*: 1.13–1.35) and 1.50 (95% *CI*: 1.32–1.71). Participants under 45 years had a lower MASLD incidence (20.07%) compared to those aged ≥ 45 years (28%). In younger individuals, the medium-stable and high-stable trajectories were associated with a significantly elevated MASLD risk (*HR* = 1.19, 95% *CI*: 1.11–1.28; *HR* = 1.64, 95% *CI*: 1.46–1.84). However, in older participants, no significant differences were observed across the SII trajectory groups. MASLD prevalence was three times higher in individuals with BMI ≥23 kg/m² (36.28%) compared to those with BMI <23 kg/m^2 (11.32%). Among participants with BMI <23, the medium-stable and high-stable trajectories were linked to increased MASLD risk (*HR* = 1.14, 95% *CI*: 1.02–1.27; *HR* = 1.33, 95% *CI*: 1.11–1.58). In those with BMI ≥ 23, the *HR* for the medium-stable and high-stable groups were 1.11 (95% *CI*: 1.04–1.18) and 1.26 (95% *CI*: 1.13–1.41), respectively. Among participants with hypertension, MASLD incidences were 20.67% (non-hypertensive) and 32.95% (hypertensive). In non-hypertensive participants, the *HR* for the medium-stable and high-stable trajectories were 1.16 (95% *CI*: 1.09–1.24) and 1.38 (95% *CI*: 1.24–1.53). In non-dyslipidemic participants, the *HR* were 1.16 (95% *CI*: 1.08–1.25)

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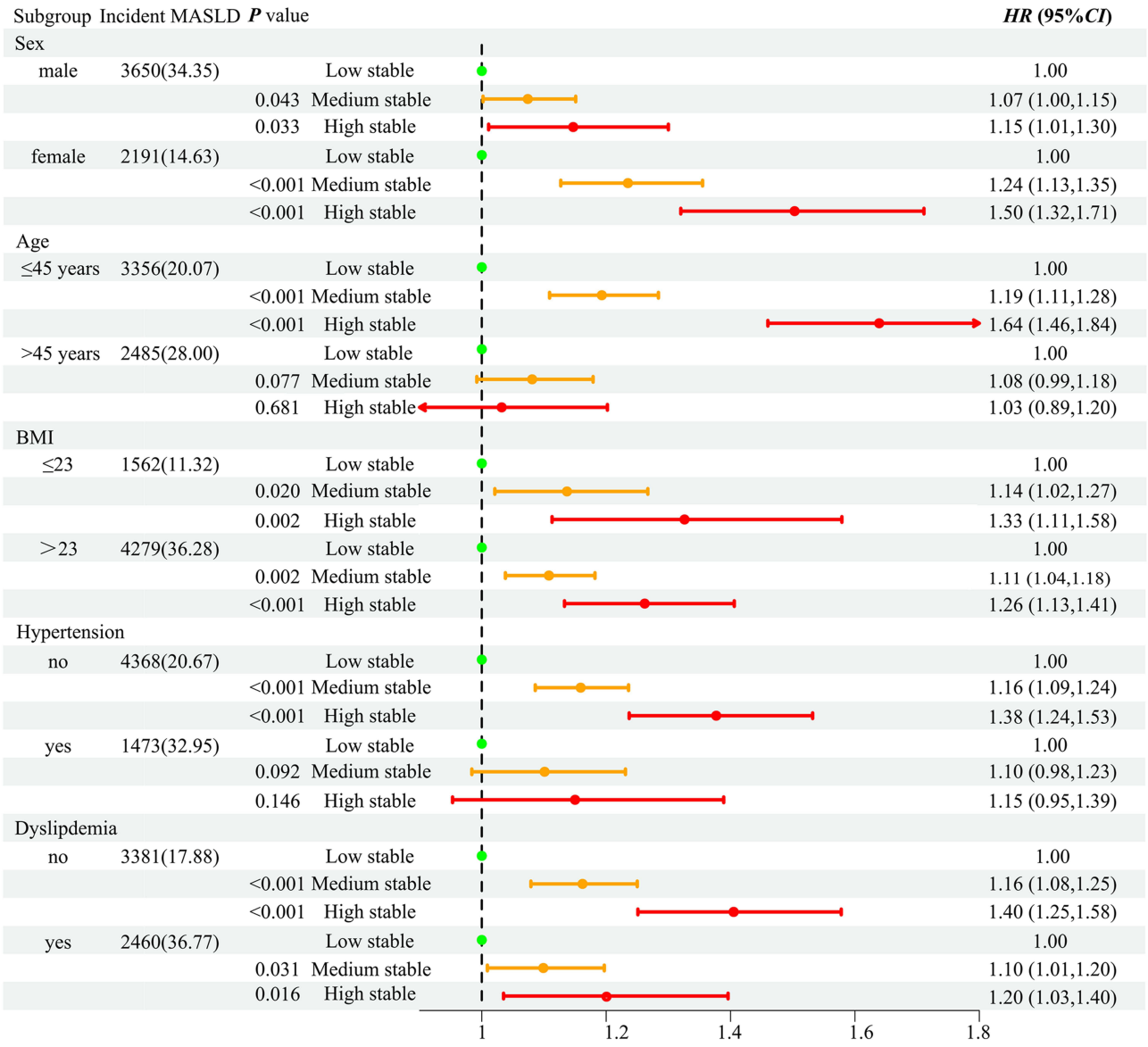

Figure 4 Adjusted *HR* for incident of MASLD in different trajectories by stratified analyses.

and 1.40 (95% *CI*: 1.25–1.58), while for those with dyslipidemia, the *HR* were 1.10 (95% *CI*: 1.01–1.20) and 1.20 (95% *CI*: 1.03–1.40).

Sensitivity Analyses

A series of four sensitivity analyses confirmed the robustness of the findings. (Supplementary Table S4-5). First, recalibrating the GBTM model after excluding participants with critical missing covariates demonstrated consistent results. Second, the association between SII trajectory and MASLD remained stable even after excluding individuals who developed MASLD within the first two years. Third, after removing participants on antihypertensive medications, antidiabetic agents, and lipid-lowering treatments, the significant association between SII trajectory and MASLD risk persisted. Finally, among individuals who completed the lifestyle questionnaires and had no missing covariate data, the detailed dataset is presented in the baseline characteristics table (Supplementary Table S6). Stratification of the SII into four quartiles revealed that the *HR* for quartiles 2, 3, and 4, when compared to the lowest inflammation index group, were 1.211 (95% *CI*: 0.957–1.532, *P*=0.111), 1.333 (95% *CI*: 1.056–1.682, *P*=0.016), and 1.382 (95% *CI*: 1.096–1.753,

P=0.006), respectively. These findings highlight a significant association between an elevated inflammation index and the incidence of MASLD, after adjusting for lifestyle variables (Supplementary Table S5).

Discussion

Our findings utilized a dataset from a cohort of participants undergoing health examinations to examine the association between SII trajectories and the incidence of MASLD. After adjusting for potential confounders, our findings revealed a significant positive correlation, indicating that elevated SII levels are associated with an increased risk of developing MASLD. The association persisted in models futher adjusted for lifestyle factors, including daily sleep duration, physical activity levels, sugar-sweetened beverages, and vegetable and fruit consumption. Further analysis using multivariate-adjusted RCS demonstrated a significant non-linear positive correlation between SII and the relative risk coefficient for MASLD. Additionally, subgroup analyses demonstrated that SII significantly enhanced the risk of MASLD within strata defined by sex, BMI, age, and dyslipidemia status. Notably, elevated levels of SII were found to be significantly associated with an increased risk of MASLD within the subsets of participants younger than 45 years and among females. Sensitivity analyses conducted subsequently confirmed the validity of these findings, thereby partly mitigating concerns regarding reverse causality.

The SII, initially introduced as an accessible and cost-effective biomarker for systemic inflammation, has garnered substantial attention in clinical research since its inception. A growing body of evidence has confirmed its prognostic and diagnostic relevance across various pathological conditions, including cardiovascular diseases, metabolic disorders like diabetes mellitus, and different forms of cancer.[31–33] However, the associations between SII levels and disease manifestation remain unclear. A cross-sectional study by Wu et al revealed a U-shaped correlation, indicating that both low and high SII levels may be linked to an increased risk of MASLD.[34] In contrast, our findings align with the non-linear positive correlation reported by Liu et al in their cross-sectional study of European populations.[15,19] The differences in results may be attributed to several factors, including racial variations in previous studies and differences in methodology. While many earlier studies relied on cross-sectional designs and estimations based on the hepatic steatosis index (HSI), our prospective cohort study used standardized B-ultrasound diagnostics, currently considered the most reliable non-invasive method for assessing hepatic fat.[35,36] These methodological differences extend beyond diagnostic criteria. The longitudinal design of our study allowed for the assessment of SII fluctuations over time in relation to MASLD progression, overcoming the limitations of cross-sectional studies, which capture only a single time point. Additionally, our analysis incorporated multivariate adjustments for various potential confounders, including dietary habits and lifestyle factors, providing deeper insights into the observed differences across populations. These methodological improvements reinforce our conclusion of a consistent, positive association between elevated SII levels and the incidence of MASLD within the studied demographic group.

Previous epidemiological studies have showed that males, the elderly, and those with hypertension or dyslipidemia are at a higher risk of MASLD. However, our findings indicate that the SII *HR* is significantly higher in females and individuals under 45 years of age, compared to male patients and older individuals. This suggests that the prognostic predictive value of SII may be more pronounced in females and individuals under 45. Stratified RCS analysis revealed differing cutoff points for the male and female, with SII values at 370.20 and 423.68, respectively, indicating variations in the reference values for each gender. Hormonal factors may play a role in the sex disparity observed in MASLD. Previous research has demonstrated that estrogen can regulate immune cell activity and the extent of inflammatory responses, potentially reducing the incidence of chronic conditions, including MASLD.[37,38] Moreover, these studies have highlighted that postmenopausal women experience a higher incidence of MASLD than elderly men.[39] Our findings highlight an important trend: as the SII increases, the relative HR of MASLD in females is higher than in males, indicating a greater susceptibility to inflammation in females. The RCS revealed that the cutoff point for the male cohort was lower than that for the female cohort. It is crucial to further explore the underlying pathophysiological mechanisms that contribute to this discrepancy.

These findings suggest that increased SII levels are significantly associated with an elevated risk of developing MASLD. The progression of MASLD is driven by metabolic and inflammatory processes, with potential mechanisms involving immune cell activity.[40] Previous research indicated that neutrophil infiltration serves as a marker of liver

inflammation. Neutrophils release cytokines, proteases, and inflammatory mediators, which recruit macrophages, worsen hepatocellular damage, and contribute to the progression of MASLD.[41] Additionally, platelets play a critical role in MASLD progression, contributing to prothrombotic and proinflammatory states that facilitate disease progression. Platelets facilitate the release of substantial chemokines by sinusoidal endothelial cells and augment the aggregation of immune cells within the liver, intensifying local inflammation and liver injury, which in turn accelerates the advancement of MASLD.[42] Conversely, certain lymphocyte subsets provide protective effects against MASLD progression. For instance, regulatory T cells (Tregs) can effectively mitigate liver inflammation and fibrosis by secreting interleukin-10 (IL-10), an anti-inflammatory cytokine. This regulatory function aids in delaying the development and progression of liver steatosis and fibrosis.[43,44] Similarly, regulatory B cells help suppress inflammatory responses and fibrosis associated with liver steatosis.[45]

The research is strengthened by a substantial sample size and an extended follow-up period, providing valuable insights for the proactive diagnosis and management of inflammation and MASLD. Moreover, our study used B-ultrasound for MASLD diagnosis, which proved to be more accurate than the previous HSI and USFLI indices.[35] Previous studies on the correlation between inflammatory indices and MASLD have often overlooked lifestyle and dietary factors. However, our study accounted for these confounders and still found significant results, further confirming the strong association between inflammatory indices and MASLD onset. Additionally, our research, conducted in an Asian population, expands on prior studies regarding the link between the SII and MASLD in Asian populations, while also exploring gender differences and revealing that SII cut-off values differ between men and women. However, our study does have some limitations. First, the data was sourced exclusively from the northern region of China, and the sample is predominantly of Asian descent, which introduces potential regional and racial biases. Second, lifestyle information was based on self-reported questionnaires, making it vulnerable to recall bias. Third, the diagnosis of MASLD was based on ultrasonic examination without considering the severity of MASLD, which may have led to missed diagnoses in patients with mild MASLD. Finally, despite adjusting for certain known confounders, the study may have overlooked other potential factors, such as acute inflammatory biomarkers like C-reactive protein, which could affect the accuracy of the findings.

Conclusion

In conclusion, our study demonstrates that elevated SII levels are significantly associated with an increased risk of MASLD, suggesting that SII could be a valuable tool for identifying individuals at higher risk of this condition. By incorporating lifestyle factors into the analysis and using more precise diagnostic methods, our findings provide a clearer understanding of the relationship between inflammation and MASLD. However, further research is needed to elucidate the precise mechanisms through which SII contributes to MASLD progression and to validate these results in more diverse populations.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author (Song Leng) on reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University (2,022,064). Informed consent was obtained from all patients to be included in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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