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Aggregate index of systemic inflammation tied to increased fatty liver disease risk: insights from NHANES data

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Abstract

Background Fatty liver disease (FLD), characterized by hepatic lipid accumulation, impairs quality of life and can progress to cirrhosis and hepatocellular carcinoma, imposing a healthcare burden. This study investigates the association between the aggregate index of systemic inflammation (AISI) and FLD prevalence, evaluating AISI's potential as an early biomarker for risk assessment.

Methods Data were obtained from the National Health and Nutrition Examination Survey (NHANES) database, which encompasses the years 2017 through 2020. Participants were chosen based on the availability of controlled attenuation parameter (CAP) scores derived from transient elastography (TE), a technique utilized for assessing liver steatosis. The formula employed to compute the AISI is as follows: $AISI = N \times P \times M / L$, where N, P, M, and L refer to neutrophils, platelets, monocytes, and lymphocytes, respectively. Additionally, demographic, socioeconomic, dietary, and health-related information was gathered. Logistic regression models were utilized to pinpoint risk factors associated with FLD, and a nomogram was created to forecast FLD risk.

Results Of the 3,961 participants, 2,377 (60.0%) were diagnosed with FLD based on a CAP score ≥ 248 dB/m. Elevated AISI was significantly associated with FLD ($P = 0.021$). Other significant risk factors included sex, age, BMI, race, marital status, hypertension, and diabetes. The nomogram demonstrated excellent discriminatory performance with an AUC of 0.814 (95% CI: 0.800, 0.827) and good calibration.

Conclusion This study reveals a significant, independent association between elevated AISI and increased FLD risk in the U.S. population, even after adjusting for confounders. AISI demonstrated good discriminative performance for FLD, but its effect size suggests it should supplement, not replace, existing clinical risk assessment tools. AISI, a cost-effective biomarker, holds potential for enhancing FLD screening, particularly in resource-limited settings.

Keywords Aggregate index of systemic inflammation, Fatty liver disease, NHANES, Inflammation, Complete blood cell count-derived inflammatory indicator

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Introduction

Fatty liver disease (FLD) has emerged as a major global public health challenge. Over the past three decades, its prevalence has significantly increased from 25.3 to 38.2%, closely linked to the epidemics of obesity and metabolic syndrome [1]. As the global obesity problem intensifies, the clinical and economic burdens associated with FLD are expected to rise further, placing immense pressure on healthcare systems. Moreover, the risk of disease progression cannot be overlooked, as approximately 7% of patients develop cirrhosis or hepatocellular carcinoma, significantly increasing liver-related mortality (0.77 per 1000 person-years) [2]. Significant bottlenecks currently exist in FLD screening: conventional ultrasound has a high miss rate and is operator-dependent, the cost of MRI limits its application, and the invasiveness and sampling variability of liver biopsy preclude its widespread use for early screening. Therefore, there is a pressing requirement to create more efficient and economically viable approaches for screening and assessing risk levels [3].

Chronic low-grade inflammation is considered a key driver of metabolic dysfunction. By activating immune cells and releasing pro-inflammatory factors, it triggers insulin resistance, lipid metabolism disorders, and adipose tissue dysfunction, ultimately promoting the development and progression of FLD [4, 5]. In obesity, for example, activation of the TLR4/NF-κB pathway can induce the polarization of adipose tissue macrophages towards the M1 phenotype. These macrophages then release pro-inflammatory factors such as tumor necrosis factor-α (TNF-α), which intensifies the inflammatory response and contributes to the dysregulation of hepatic lipid metabolism [6]. This vicious cycle between inflammation and metabolism is highly associated with the development and progression of FLD [7, 8]. In recent years, Complete blood cell count-derived inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammatory index (SII), and aggregate index of systemic inflammation (AISI), have provided new avenues for assessing systemic inflammation. These indices are widely used for diagnosis, prognostic assessment, and monitoring treatment efficacy in various chronic inflammatory diseases. Research indicates that both NLR and SII are significantly linked to the likelihood of developing FLD. Furthermore, elevated NLR is positively correlated with the severity of liver fibrosis, indicating its potential utility in predicting FLD risk and its progression [9–11]. AISI, by integrating additional cellular parameters, holds promise for more comprehensively reflecting the systemic inflammatory state and has demonstrated good predictive power in research on various chronic diseases [12, 13]. While AISI has been associated with FLD among hypertensive individuals [14], large population-based evidence is still lacking. Our study addresses this gap with the general U.S. population.

Therefore, based on the National Health and Nutrition Examination Survey (NHANES) database, this study employed multivariable logistic regression to systematically analyze the association between AISI and FLD, and developed a risk prediction model for FLD. The objective was to evaluate the potential utility of AISI in FLD screening and risk assessment, thereby providing new evidence and theoretical support for the clinical application of inflammatory markers.

Methods

Data sources and population selection

The information utilized in this research was exclusively derived from the NHANES. NHANES is an ongoing health and nutrition assessment program for U.S. adults and children, conducting surveys on demographics, socioeconomic status, dietary habits, and health issues. NHANES has received approval from the National Center for Health Statistics Ethics Review Board (https://www.cdc.gov/nchs/nhanes/about/erb.html). All participants provided informed consent prior to their involvement in the study.

This analysis utilized information from the NHANES cycles spanning March 2017 to March 2020, focusing on data from 2017 to 2018 and March 2019 to March 2020. The COVID-19 pandemic limited data collection in 2020, necessitating the combination of these cycles for robust analysis.

This study utilized liver transient elastography (TE). Participants were divided into FLD and non-FLD groups using a controlled attenuation parameter (CAP) criterion of ≥248 dB/m. We selected participants from the initial 24,814 individuals in the NHANES database (2017–2020). The screening process involved excluding individuals for the following reasons: missing the CAP data (n = 9,168); being under 18 years old (n = 2,210); missing education status (n = 664); missing marital status (n = 7); missing economic status (n = 1,696); missing height and weight data (n = 95); missing smoking and drinking information (n = 1,444); missing hypertension and diabetes history (n = 303); and missing blood cell count data (n = 5,266). Due to the NHANES protocol, not all participants underwent CAP scoring or blood cell count testing each year, leading to significant data gaps for these measures [15]. Ultimately, our analysis included 3,961 participants (Fig. 1).

Outcome variable: FLD

TE of the liver is widely used for the screening of FLD due to its high accuracy and non-invasive nature. In the NHANES program, CAP data were obtained using a FibroScan® 502 V2 Touch device by health technicians

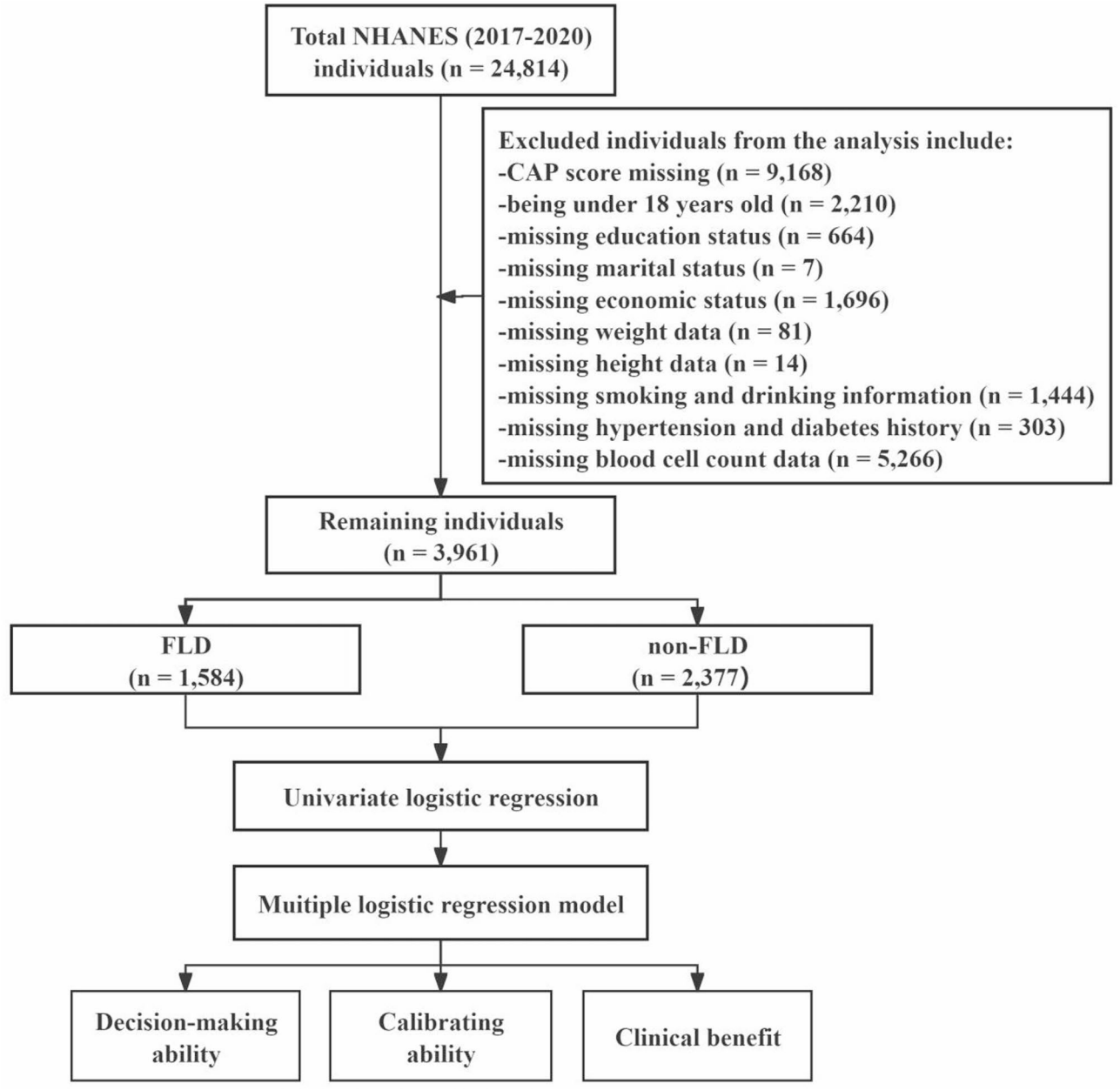

Fig. 1 Participant selection flowchart

who were uniformly trained and certified. In this study, a CAP value of ≥ 248 dB/m was used as the threshold to differentiate between FLD and non-FLD groups. This threshold has been widely validated for effectively identifying hepatic steatosis at stage S1 or above [16, 17], making it suitable for large-scale epidemiological screening and reducing the risk of missed diagnoses of early-stage FLD.

Exposure variable: AISI

Following an overnight fasting period, venous blood specimens were obtained in the morning at the mobile examination center of NHANES. AISI is clinically important as it indicates the body's inflammatory status and helps in diagnosing diseases, assessing conditions, monitoring treatments, and evaluating prognosis. AISI is defined as AISI = N × P × M / L, where L, M, N, and P denote lymphocytes, monocytes, neutrophils, and platelets, respectively.

Covariates

To control for potential confounding biases in this study, we selected covariates from the NHANES database based on clinical practice and previous literature: sex, age,

weight, height, body mass index (BMI), race, poverty income ratio (PIR), education level, marital status, alcohol consumption, smoking status, and histories of hypertension and diabetes.

Age was stratified into < 60 years and ≥ 60 years. BMI categories were defined as normal (< 25 kg/m^2), overweight (25–30 kg/m^2), or obese (≥ 30 kg/m^2). The racial categories encompassed individuals identifying as Mexican American, members of other Hispanic groups, non-Hispanic Whites, non-Hispanic Blacks, as well as those belonging to other races or having a mixed-race background. PIR was categorized as < 1.5, 1.5–3.5, or ≥ 3.5. Education levels were grouped into less than high school, high school/GED, and some college/AA degree or higher. Marital status was dichotomized as married/living with a partner or living alone. A questionnaire was used to collect data on alcohol consumption, smoking, and histories of hypertension and diabetes. "Drinkers" were defined as individuals who consumed at least 12 drinks annually or drank more than twice in the past 12 months, whereas "non-drinkers" were those who drank fewer than 12 times annually or less than twice in the past 12 months. Individuals classified as "smokers" were those who had consumed over 100 cigarettes in their lifetime. Histories of hypertension and diabetes were based on diagnoses by physicians or healthcare professionals.

Statistics analysis

Statistical analyses were performed using R version 4.3.2. Continuous variables are presented as mean ± standard deviation, and categorical variables as frequencies (percentages). Between-group comparisons were conducted using independent samples *t*-tests or chi-square tests. Univariate logistic regression was used for preliminary screening of variables associated with FLD; variables with $P < 0.05$ were included in the multivariate model to assess the independent association between AISI and FLD risk. To improve the predictive model, a backward stepwise regression was employed to derive the final model and construct a nomogram. Given the skewed distribution of raw AISI data, log2 transformation was applied to enhance statistical power while preserving interpretability of the original AISI values. Results were reported as odds ratios (OR) with their 95% confidence intervals (CI). The area under the curve (AUC) of the receiver operating characteristic (ROC) was used to evaluate the model discrimination performance. Calibration of the nomogram was validated by calibration curves using 1,000 bootstrap resamples. Decision curve analysis (DCA) was conducted to quantify the clinical net benefit of the model across different threshold probabilities. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Fundamental characteristics

Table 1 outlines the core attributes of NHANES carried out between 2017 and 2020. There were 3,961 participants, among whom 2,377 were diagnosed with FLD. This group comprised 1,313 males (55.24%) and 1,064 females (44.76%). The mean age was 47.11 ± 18.46 years for the non-FLD group, and 53.21 ± 16.03 years for the FLD group. The non-FLD group had a mean BMI of 25.90 ± 5.24, as opposed to 32.66 ± 7.31 for the FLD group. In contrast to individuals without FLD, those diagnosed with FLD tended to be older and exhibited elevated weight and BMI. Additionally, the two groups showed significant differences in height, race, marital status, education, smoking status, and medical histories of hypertension and diabetes ($P < 0.05$). The two groups showed no significant differences in family PIR, or alcohol consumption. Patients with FLD showed significantly higher average values for both the AISI and log2-AISI. This disparity was notable when compared to the non-FLD population.

Univariate logistic regression examination

Table 2 showed that the univariate logistic regression analysis identified several factors significantly associated with FLD incidence. The AISI and log2-AISI were significantly correlated with an increased risk of developing FLD. Moreover, factors such as sex, age, weight, height, BMI, ethnic background, education, marital situation, smoking, hypertension, and diabetes were associated with the development of FLD.

Multiple logistic regression models

Figure 2 showed a multiple logistic regression model. In this model, the primary variable was log2-AISI, with sex, age, BMI, race, education, marital status, alcohol use, hypertension, and diabetes serving as covariates. After accounting for the multiple logistic regression model, the AISI score was still an important marker of FLD risk. Individuals with higher log2-AISI values had an increased likelihood of developing FLD (OR = 1.08, 95% CI: 1.01, 1.16, $P = 0.021$). Age (OR = 1.02, 95% CI: 1.02, 1.03, $P < 0.001$) and BMI (OR = 1.23, 95% CI: 1.21, 1.25, $P < 0.001$) were positively correlated with increased FLD risk. Women had a lower FLD risk than men (OR = 0.64, 95% CI: 0.54, 0.74, $P < 0.001$). Compared to Mexican American, FLD risk was significantly lower in Other Hispanic (OR = 0.63, 95% CI: 0.45, 0.88, $P = 0.006$), Non-Hispanic White (OR = 0.52, 95% CI: 0.40, 0.69, $P < 0.001$), and Non-Hispanic Black (OR = 0.27, 95% CI: 0.20, 0.36, $P < 0.001$). Unmarried individuals exhibited a notably reduced FLD risk compared to those who were married or living with partner (OR = 0.83, 95% CI: 0.71, 0.98, $P = 0.024$). Patients with a history of hypertension

Table 1 Baseline characteristics

Variables	Overall (*n* = 3,961)	Non-FLD group (*n* = 1,584)	FLD group (*n* = 2,377)	*P*-value
Sex, n (%)				**< 0.001**
Male	2,058 (51.96%)	745 (47.03%)	1,313 (55.24%)	
Female	1,903 (48.04%)	839 (52.97%)	1,064 (44.76%)	
Age, years, mean(SD)	50.77 ± 17.30	47.11 ± 18.46	53.21 ± 16.03	**< 0.001**
< 60years	2,512 (63.42%)	1,105 (69.76%)	1,407 (59.19%)	**< 0.001**
≥ 60years	1,449 (36.58%)	479 (30.24%)	970 (40.81%)	
Weight, kg, mean(SD)	84.05 ± 22.53	72.03 ± 16.04	92.07 ± 22.68	**< 0.001**
Height, cm, mean(SD)	167.28 ± 9.75	166.64 ± 9.54	167.71 ± 9.86	**< 0.001**
BMI, kg/m^2, mean(SD)	29.95 ± 7.34	25.90 ± 5.24	32.66 ± 7.31	**< 0.001**
Race, n (%)				**< 0.001**
Mexican American	513 (12.95%)	139 (8.78%)	374 (15.73%)	
Other Hispanic	359 (9.06%)	132 (8.33%)	227 (9.55%)	
Non-Hispanic White	1,563 (39.46%)	610 (38.51%)	953 (40.09%)	
Non-Hispanic Black	864 (21.81%)	423 (26.70%)	441 (18.55%)	
Other race (including multi-racial)	662 (16.71%)	280 (17.68%)	382 (16.07%)	
Family PIR				0.511
< 1.5	1,300 (32.82%)	531 (33.52%)	769 (32.35%)	
1.5–3.5	1,415 (35.72%)	549 (34.66%)	866 (36.43%)	
≥ 3.5	1,246 (31.46%)	504 (31.82%)	742 (31.22%)	
Education, n (%)				**0.029**
Less than high school	673 (16.99%)	240 (15.15%)	433 (18.22%)	
High school or GED	972 (24.54%)	386 (24.37%)	586 (24.65%)	
Some college or AA degree above	2,316 (58.47%)	958 (60.48%)	1,358 (57.13%)	
Marital status, n (%)				**< 0.001**
Married/Living with partner	2,350 (59.33%)	868 (54.80%)	1,482 (62.35%)	
Living alone	1,611 (40.67%)	716 (45.20%)	895 (37.65%)	
Alcohol user, n (%)				0.099
Yes	2,642 (66.70%)	1,081 (68.24%)	1,561 (65.67%)	
No	1,319 (33.30%)	503 (31.76%)	816 (34.33%)	
Smoking status, n (%)				**0.002**
Yes	1,857 (46.88%)	694 (43.81%)	1,163 (48.93%)	
No	2,104 (53.12%)	890 (56.19%)	1,214 (51.07%)	
Hypertension, n (%)				**< 0.001**
Yes	1,499 (37.84%)	417 (26.33%)	1,082 (45.52%)	
No	2,462 (62.16%)	1,167 (73.67%)	1,295 (54.48%)	
Diabetes, n (%)				**< 0.001**
Yes	632 (15.96%)	116 (7.32%)	516 (21.71%)	
No	3,329 (84.04%)	1,468 (92.68%)	1,861 (78.29%)	
AISI	392.15 ± 383.54	346.37 ± 331.30	422.65 ± 411.97	**< 0.001**
log2-AISI	8.16 ± 1.13	8.00 ± 1.12	8.27 ± 1.12	**< 0.001**

(OR = 1.22, 95% CI: 1.02, 1.47, $P = 0.030$) or diabetes (OR = 1.79, 95% CI: 1.39, 2.31, $P < 0.001$) were at increased risk of FLD.

Nomogram to predict FLD

Based on significant risk factors identified through multivariate logistic regression analysis, we developed a nomogram (Fig. 3) to predict FLD risk. The model demonstrated a C-index of 0.814 and an AIC value of 4015.7, with no multicollinearity among the variables (Supplementary Table 1) nor interaction effects (Supplementary Table 2). The results showed that higher AISI, male, older age, obesity, Mexican American, married/living with partner, hypertension, and diabetes were risk factors for FLD. Clinicians could obtain corresponding scores from the nomogram based on the patient's specific characteristics. By summing these scores, the probability associated with the total score could be used to estimate the risk of developing FLD. A higher total score indicated a greater risk, which can aid in implementing stratified management and personalized interventions.

Nomogram demonstrated good discriminatory performance, with an AUC of 0.814 (95% CI: 0.800, 0.827) (Fig. 4). Compared to the model excluding log2-AISI

Table 2 Univariate logistic regression examination of FLD

Variables	OR(95%CI)	*P*-value
Sex, n (%)		
Male	Reference	
Female	0.72 (0.63, 0.82)	**< 0.001**
Age, years, mean(SD)	1.02 (1.02, 1.02)	**< 0.001**
< 60years	Reference	
≥ 60years	1.59 (1.39, 1.82)	**< 0.001**
Weight, kg, mean(SD)	1.06 (1.06, 1.06)	**< 0.001**
Height, cm, mean(SD)	1.01 (1.00, 1.02)	**< 0.001**
BMI, kg/m^2, mean(SD)	1.22 (1.20, 1.24)	**< 0.001**
Race, n (%)		
Mexican American	Reference	
Other Hispanic	0.64 (0.48, 0.85)	**0.003**
Non-Hispanic White	0.58 (0.47, 0.72)	**< 0.001**
Non-Hispanic Black	0.39 (0.31, 0.49)	**< 0.001**
Other race (including multi-racial)	0.51 (0.40, 0.65)	**< 0.001**
Family PIR		
< 1.5	Reference	
1.5–3.5	1.09 (0.93, 1.27)	0.277
≥ 3.5	1.02 (0.87, 1.19)	0.839
Education, n (%)		
Less than high school	Reference	
High school or GED	0.84 (0.69, 1.03)	0.096
Some college or AA degree above	0.79 (0.66, 0.94)	**0.008**
Marital status, n (%)		
Married/Living with Partner	Reference	
Living alone	0.73 (0.64, 0.83)	**< 0.001**
Alcohol user, n (%)		
No	Reference	
Yes	0.89 (0.78, 1.02)	0.092
Smoking status, n (%)		
No	Reference	
Yes	1.23 (1.08, 1.40)	**0.002**
Hypertension, n (%)		
No	Reference	
Yes	2.34 (2.04, 2.68)	**< 0.001**
Diabetes, n (%)		
No	Reference	
Yes	3.50 (2.84, 4.35)	**< 0.001**
AISI	1.00 (1.00, 1.00)	**< 0.001**
log2-AISI	1.20 (1.13, 1.27)	**< 0.001**

(AUC = 0.807, 95% CI: 0.794, 0.821), the inclusion of log2-AISI provided a statistically meaningful improvement in predictive accuracy. The optimal cutoff value was 0.082, with the maximum Youden index of 0.459, yielding a sensitivity of 74.9% and a specificity of 71.0% for prediction. The calibration curve results (Fig. 5) showed a high level of agreement between the model's predicted probabilities and the actual observed probabilities, with a mean absolute error of only 0.021, indicating that the model was well-calibrated. DCA (Fig. 6) demonstrated that the nomogram offered a greater net benefit compared to both the "treat-all" and "treat-none" approaches over a threshold probability range from 10 to 95%, confirming its clinical utility in routine practice.

Correlation between AISI and CAP

To clarify the correlation between AISI and the severity of hepatic steatosis, this study employed Spearman's rho analysis to assess the association between AISI and CAP. The findings indicated a significant positive correlation between AISI and FLD ($R = 0.13$, $P < 0.001$) (Fig. 7).

Relationship between AISI and FLD

In the overall population, univariate logistic regression results showed a positive association between AISI and FLD (OR: 1.24, 95% CI: 1.17, 1.32, $P < 0.001$). This association persisted after adjusting for age, sex, and race (Model 2: OR 1.23, 95% CI: 1.16, 1.31, $P < 0.001$) and after full covariate adjustment (Model 3: OR 1.09, 95% CI: 1.01, 1.16, $P = 0.021$). When log2-AISI was divided into quartiles (Q1–Q4), the Q1 group was the reference in logistic regression. In Model 1, the Q4 group had a significantly higher OR than Q1 (OR: 1.82, 95% CI: 1.51, 2.18, $P < 0.001$). In Model 3, patients in the highest log2-AISI quartile had a 26% higher disease odds than the reference group (OR: 1.26, 95% CI: 1.01, 1.57, $P = 0.044$). Complete results are provided in Table 3.

Restricted cubic spline (RCS) analysis revealed a significant linear association between AISI and FLD risk (Fig. 8). Threshold analysis after full adjustment in Model 3 identified an AISI inflection point at 8.12. FLD risk remained low below this threshold but increased significantly when AISI exceeded 8.12.

Discussion

FLD has emerged as a major global public health burden due to its high prevalence, insidious symptoms, and close associations with chronic conditions such as cardiovascular diseases and diabetes [18]. Based on the large-scale NHANES cohort, this study is the first to systematically identify a significant independent association between AISI and FLD risk (per one-unit increase in log2-AISI was associated with an 8% elevated FLD risk; OR = 1.08, 95% CI: 1.01, 1.16, $P = 0.021$). Furthermore, after incorporating AISI into the multivariate risk model, its discriminative ability reached an AUC of 0.814 (95% CI: 0.800, 0.827). Fatty Liver Index (FLI) and Hepatic Steatosis Index (HSI) are two widely used serum-based non-invasive methods for predicting FLD. External validation studies have shown that the AUCs of FLI and HSI in different populations often range from 0.69 to 0.86 [19, 20]. In comparison, the diagnostic efficacy of the prediction model in this study falls within a similar range, suggesting its potential clinical predictive value and providing a new reference dimension for clinical risk assessment of FLD.

Variable		N	Odds ratio	*P*-value
log2-AISI		3961	1.08 (1.01, 1.16)	0.021
Sex	Male	2058	Reference	
	Female	1903	0.64 (0.54, 0.74)	<0.001
Age		3961	1.02 (1.02, 1.03)	<0.001
BMI		3961	1.23 (1.21, 1.25)	<0.001
Race	Mexican American	513	Reference	
	Other Hispanic	359	0.63 (0.45, 0.88)	0.006
	Non-Hispanic White	1563	0.52 (0.40, 0.69)	<0.001
	Non-Hispanic Black	864	0.27 (0.20, 0.36)	<0.001
	Other race, including multi-racial	662	0.82 (0.60, 1.10)	0.187
Education	Less than high school	673	Reference	
	High school or GED	972	1.07 (0.83, 1.38)	0.600
	Some college or AA degree above	2316	1.04 (0.82, 1.30)	0.762
Marital status	Married/Living with partner	2350	Reference	
	Living alone	1611	0.83 (0.71, 0.98)	0.024
Alcohol user	No	1319	Reference	
	Yes	2642	1.18 (1.00, 1.40)	0.053
Hypertension	No	2462	Reference	
	Yes	1499	1.22 (1.02, 1.47)	0.030
Diabetes	No	3329	Reference	
	Yes	632	1.79 (1.39, 2.31)	<0.001

Fig. 2 Multiple logistic regression analysis of FLD

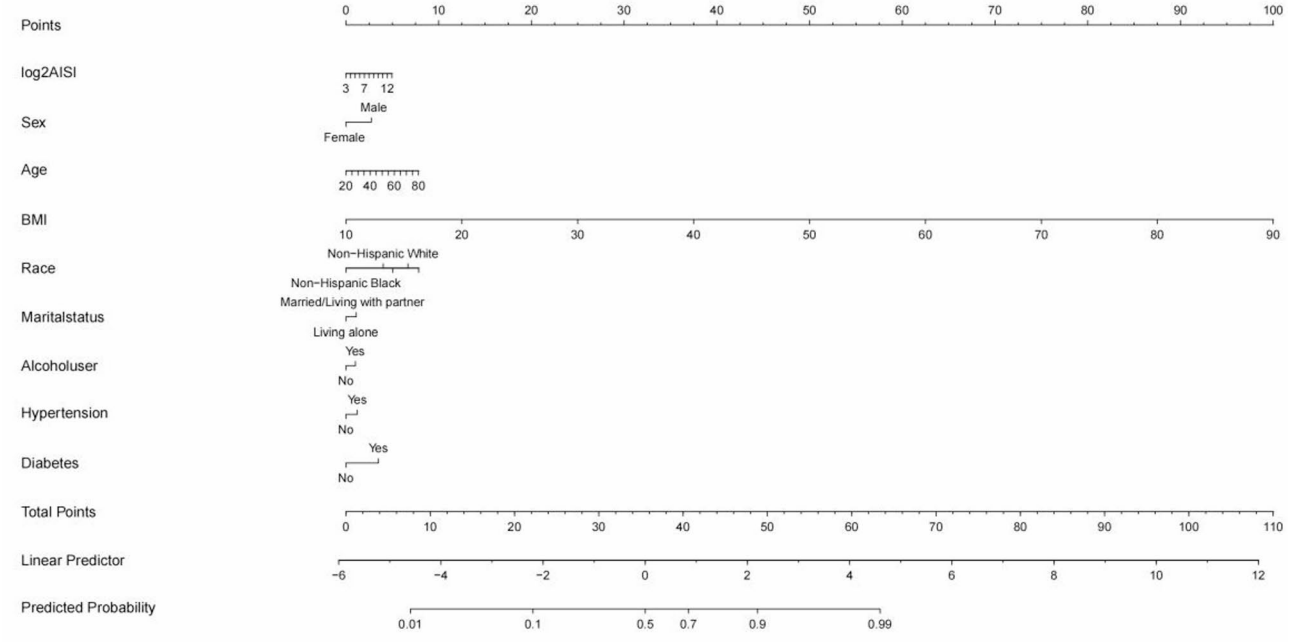

Fig. 3 Nomogram of FLD

Chronic inflammation plays a pivotal role in FLD; however, not all clinical inflammatory biomarkers exhibit pathophysiological relevance to this condition. In FLD—a disease characterized by complex inflammatory mechanisms—the utility of traditional single inflammatory markers remains contentious. While white blood cell count (WBC) has been inconsistently associated with FLD across diverse populations, C-reactive protein (CRP) demonstrates limited diagnostic efficacy for distinguishing disease severity [21–23]. Furthermore, CRP suffers from low specificity due to interference from other inflammatory states and incurs higher testing costs

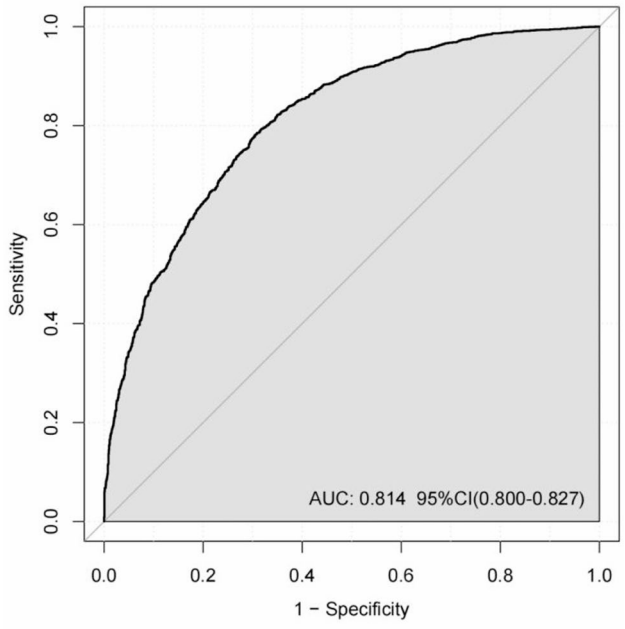

Fig. 4 AUC value of multiple logistic regression model

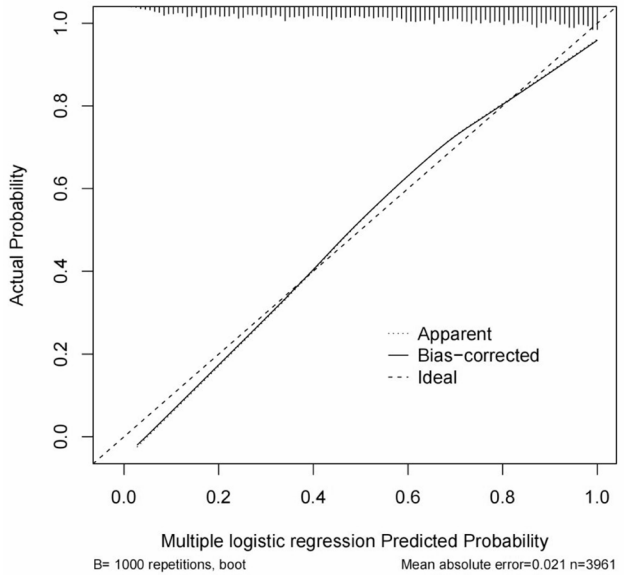

Fig. 5 Calibration profile of multiple logistic regression model

compared to routine blood tests [24]. By contrast, AISI possesses a theoretical basis to more comprehensively reflect the body's complex chronic inflammatory process because it integrates information from multiple types of immune cells. A recent cohort study involving 34,303 Chinese adults with hypertension further validated the value of AISI in FLD risk assessment. Results showed that each standard deviation increase in AISI was associated with a 74% higher FLD risk (OR = 1.74, 95% CI: 1.69, 1.80), with the highest quartile group having three times the risk of the lowest quartile. AISI demonstrated the highest diagnostic performance (AUC = 0.659, 95% CI: 0.654, 0.665) among multiple inflammatory indices, indicating its superior predictive advantage for FLD risk [14]. It is important to note that a study has demonstrated a negative correlation between AISI and the risk of liver fibrosis in patients with psoriasis. This finding may indicate pathophysiological differences between early steatosis and advanced fibrosis [25]. Specifically, while a high AISI value indicates heightened systemic inflammation and an increased FLD risk, progression to significant fibrosis may involve depletion or exhaustion of immune and inflammatory cells, resulting in a decrease in measurable AISI values. Therefore, the clinical utility of AISI may vary depending on the stage of liver disease, underscoring the need for longitudinal studies to elucidate its dynamic role throughout the disease course. This study, based on the NHANES database, is the first to assess the association between AISI and FLD risk in the U.S. population. The findings revealed a statistically significant association between AISI and FLD. While the effect size was relatively modest, AISI—a simple and readily accessible marker from routine blood tests—still holds potential as a supplementary tool for early screening.

Multivariate regression analysis showed that male, older age, higher BMI, Mexican American, hypertension, and diabetes are all independent risk factors for FLD, consistent with previous epidemiological evidence [26–30]. The reduced risk observed in women could be linked to the protective properties of estrogen and the lower occurrence of detrimental lifestyle choices, such as tobacco use and alcohol consumption [26]. Mexican Americans have a significantly higher FLD risk compared to other ethnic groups, and potential mechanisms include visceral fat distribution, specific genetic polymorphisms (such as PNPLA3 and TM6SF2), and sociodemographic factors (such as diet and access to healthcare) [29]. It should be noted that these risk factors are not entirely independent but act synergistically to promote the onset and progression of FLD through complex interactions. For example, aging not only directly leads to metabolic disorders and systemic inflammation, but also significantly increases the risk of hypertension and diabetes [27]. BMI is a key predictor of FLD, with an incidence as high as 42% among individuals with a high BMI (BMI ≥ 25 kg/m^2), significantly higher than the 26% observed in people of normal weight [28]. Obesity, diabetes, and FLD share chronic inflammation and insulin resistance as a common pathological basis. Chronic, low-grade inflammation associated with obesity can enhance hepatic insulin resistance and lipid accumulation through increased macrophage infiltration and the release of inflammatory mediators, including TNF-α and Interleukin-6 (IL-6), thus accelerating the progression of the disease [31].

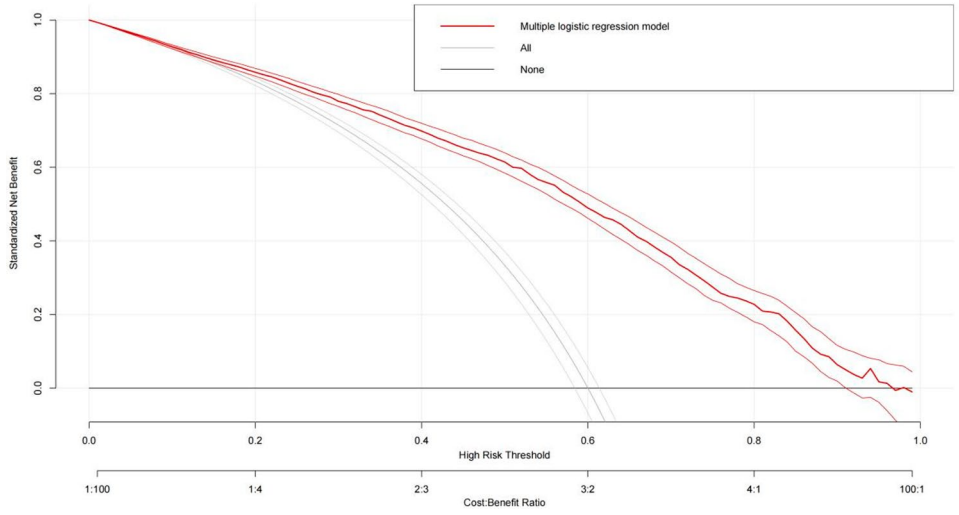

Fig. 6 Decision graph of multiple logistic regression model

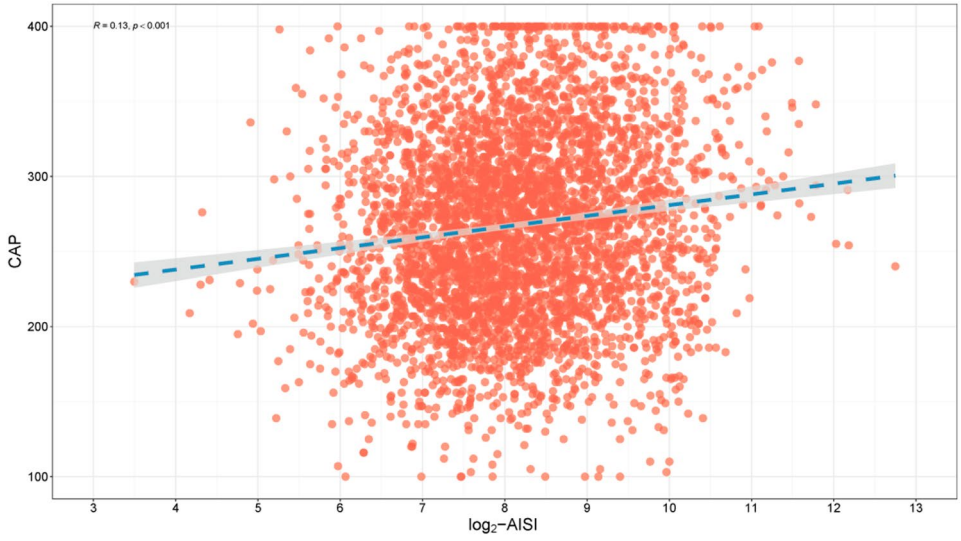

Fig. 7 Scatter plot of Log2-AISI and CAP

Table 3 Relationship between AISI and FLD risk was examined using logistic regression analyses

	Model 1		Model 2		Model 3	
	OR(95% CI)	***P***	**OR(95% CI)**	***P***	**OR(95% CI)**	***P***
log2-AISI	1.24 (1.17, 1.32)	< 0.001	1.23 (1.16, 1.31)	< 0.001	1.09 (1.01, 1.16)	0.021
log2-AISI(quartile)						
Q1(< 7.39)	Reference		Reference		Reference	
Q2(7.39 ~ 8.12)	1.17 (0.98, 1.40)	0.083	1.15 (0.95, 1.38)	0.147	0.96 (0.7, 1.19)	0.723
Q3(8.12 ~ 8.92)	1.49 (1.24, 1.78)	< 0.001	1.44 (1.19, 1.74)	< 0.001	1.05 (0.84, 1.30)	0.688
Q4(> 8.92)	1.82 (1.51, 2.18)	< 0.001	1.78 (1.48, 2.16)	< 0.001	1.26 (1.01, 1.57)	0.044
P for trend	< 0.001		< 0.001		0.033	

OR, odds ratio; CI, Confidence interval

Model 1: No covariates were included in the adjustment

Model 2: Adjusted for age, sex, and race

Model 3: Adjusted for age, sex, race, BMI, family PIR, education, marital status, alcohol user, smoking status, hypertension, and diabetes

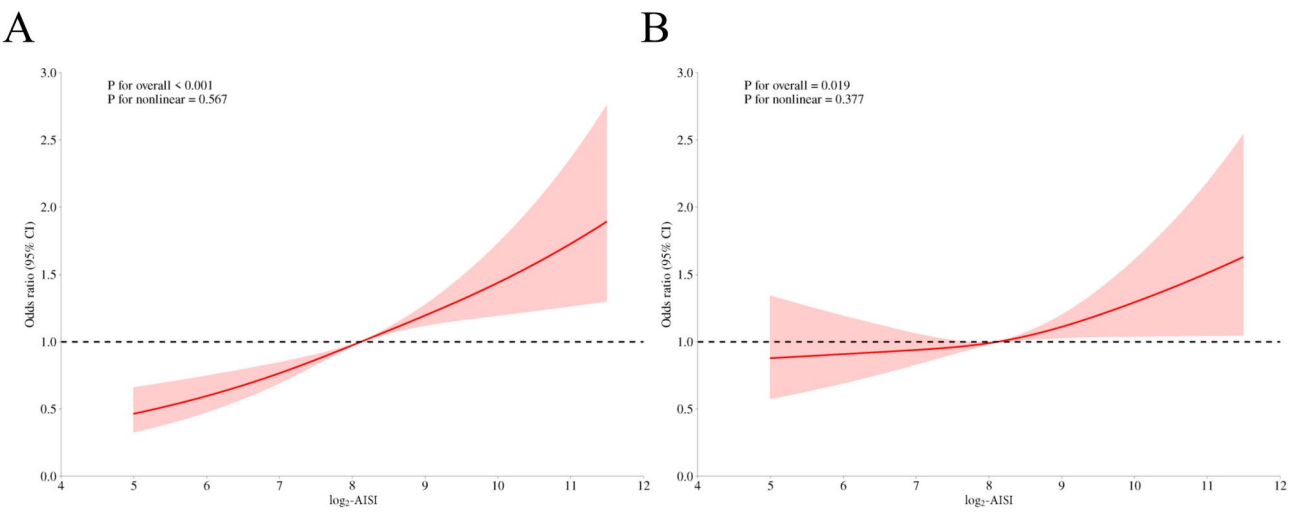

Fig. 8 Decision graph of multiple logistic regression model (**A**) Pre-adjustment RCS prediction chart; (**B**) Adjusted RCS prediction chart

The mechanisms by which elevated AISI increases FLD risk remain under investigation. Studies suggest that neutrophils worsen liver inflammation and hasten the progression from simple steatosis to steatohepatitis via releasing reactive oxygen species and pro-inflammatory factors like TNF-α and IL-6 [32, 33]. In lymphocytes, the infiltration of CD8 + T cells and their secretion of interferon-γ (IFN-γ) and TNF-α intensify hepatic inflammation and fibrosis [34, 35]. Activated B cells, stimulated by oxidative stress and activating factors, produce antibodies and pro-inflammatory mediators that drive liver fibrosis [36]. Monocytes infiltrate the liver and differentiate into macrophages, which further induce hepatic lipid accumulation and tissue damage by secreting inflammatory mediators like interleukin-1β (IL-1β) and TNF-α, while modulating lipid metabolism-related signaling pathways [37, 38]. Beyond their traditional pro-coagulant role, platelets amplify immune signaling and promote hepatic inflammatory cascades by releasing mediators such as platelet factor 4 (PF4) and transforming growth factor β (TGF-β), as well as forming heterotypic aggregates with leukocytes [39]. It should be noted that most of these mechanisms are derived from animal or in vitro studies, with limited clinical evidence in human populations.

This study isn't without several limitations. First, the cross-sectional nature of the study limits it to demonstrating the correlation between AISI and FLD, rather than establishing a definitive causal relationship, and lacks long-term follow-up to observe the progression of the disease. Second, the diagnostic criteria did not incorporate clinical diagnosis, liver function indicators, or pathological staging information, which may affect the accuracy of disease classification. Third, due to considerations such as cost-effectiveness and participant compliance, this study had a relatively high sample exclusion rate, leading to a higher prevalence of FLD in the sample and resulting in some selection bias. Fourth, the study data were derived from a U.S. population, without accounting for differences in laboratory standards or genetic backgrounds across regions, which limits the generalizability of the findings. Fifth, although various confounding factors were adjusted for in the statistical analysis, the absence of data on important variables such as diet, physical activity, and medication history could still lead to residual confounding. Sixth, the effect size of AISI as an independent risk factor is relatively limited, and its actual value and feasibility for clinical application require further supporting evidence.

Based on the above limitations, future research can be pursued in the following areas. First, large-sample prospective cohort studies should be conducted to clarify the temporal relationship between AISI and the onset and progression of FLD. Second, the predictive capacity of AISI for FLD should be further validated in multi-center studies and diverse ethnic populations, with exploration of appropriate reference intervals. Third, combining more accurate diagnostic tools for FLD can improve the precision and credibility of research findings. At the same time, it is necessary to analyze in depth the specific roles of each component of AISI in the staging and pathogenesis of fatty liver. Furthermore, exploring risk models that combine AISI with other biomarkers or imaging characteristics may help enhance the accuracy of FLD risk assessment. Finally, it is also important to evaluate the actual effects of AISI-targeted novel anti-inflammatory intervention strategies in the prevention and treatment of fatty liver.

Conclusion

This study establishes a significant independent association between elevated AISI and increased FLD risk in the U.S. population, even after adjusting for demographic, metabolic, and lifestyle confounders. Incorporating AISI into the prediction model demonstrated good discriminative performance (AUC = 0.814). While its effect size is limited when predicting FLD risk alone, it is not yet sufficient to completely replace existing clinical risk assessment tools. Nevertheless, our findings suggest that AISI, as a cost-effective and readily accessible biomarker, has the potential to supplement existing screening systems, particularly in primary care settings or resource-limited scenarios where rapid initial screening is needed.

Abbreviations

FLD	Fatty liver disease
TNF-α	Tumor necrosis factor-α
NLR	Neutrophil-to-lymphocyte ratio
SII	Immune-inflammatory index
AISI	Aggregate index of systemic inflammation
NHANES	National Health and Nutrition Examination Survey
TE	Transient elastography
CAP	Controlled attenuation parameter
BMI	Body mass index
PIR	Poverty income ratio
AUC	Area under the curve
ROC	Receiver operating characteristic
DCA	Decision curve analysis
RCS	Restricted cubic spline
FLI	Fatty liver index
HSI	Hepatic steatosis index
WBC	White blood cell count
CRP	C-reactive protein
IL-6	Interleukin-6
IFN-γ	Interferon-γ
IL-1β	Interleukin-1β
PF4	Platelet factor 4
TGF-β	Transforming growth factorβ

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

MZ and YY contributed to the study design, manuscript drafting, and critical revision. CW participated in data visualization. YH and MF were responsible for data curation, software implementation. XL contributed to methodology development and manuscript review. ZQ oversaw project administration, funding acquisition, and final manuscript approval. All authors contributed to the article and approved the submitted version.

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Data availability

The data used in this study were obtained from the NHANES, which is provided by the Centers for Disease Control and Prevention (CDC). NHANES data can be accessed publicly through the CDC website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

Declarations

Ethics approval and consent to participate

The NCHS research ethics review board approved the NHANES study involving human subjects, and participants provided written informed consent upon enrollment. The studies were carried out in compliance with local regulations and institutional guidelines.Participants gave written informed consent before joining the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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