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Association of platelet to albumin ratio with metabolic dysfunction-associated steatotic liver disease based on the National Health and Nutrition Survey 2017–2018

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The prevalence and incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) are significantly increasing globally, but the index of non-invasive disease is limited. Platelet-albumin ratio(PAR) is a non-invasive biomarker of inflammation, the aim of this study was to evaluate the relationship between PAR and MASLD. This population-based cross-sectional retrospective study analyzed data extracted from the National Health and Nutrition Survey (NHANES) database from 2017 to 2018. Multivariate logistic regression analysis was used to evaluate the correlation between PAR and MASLD in different models. Model I was unadjusted, model II adjusted for race, sex and age, and model III was adjusted based on model II plus smoking status, hypertension, and diabetes. Further subgroup analysis was carried out according to sex, age, hypertension and diabetes status. The study involved 3287 participants, of whom 873 (26.5%) were diagnosed with MASLD. The PAR level in MASLD group was significantly higher than non-MASLD group ($P < 0.05$). Multivariate logistic regression revealed that high PAR level was an independent risk factor for MASLD (OR = 2.58, 95%CI: 1.26–5.27, $P = 0.03$), which adjusted for sex, age, race, smoking status, hypertension, and diabetes.The same results were observed in multiple subgroups of further subgroup analysis, and it can effectively predict the risk of MASLD (AUC = 0.842, 95% CI: 0.826–0.859). In conclusion, the new biomarker PAR shows a positive correlation with the risk of MASLD in the population, and can be used as a biomarker of MASLD to help clinicians identify people at high risk of MASLD.

Keywords Metabolic dysfunction-associated steatotic liver disease, Steatosis, PAR, NHANES

Chronic liver disease (CLD) is currently a growing problem and burden worldwide. Compared with cirrhosis caused less than 0.899 million deaths in 1990, the deaths in 2017 had exceeded 1.32 million[1]. The prevalence and incidence of non-alcoholic fatty liver disease (NAFLD) have increased significantly worldwide. Currently, the global prevalence of NAFLD in the general population is estimated to be 25%, with the highest prevalence in western countries (17–46%), where it is the most common CLD in adults[2,3]. NAFLD is a potentially progressive liver disease that can lead to cirrhosis, hepatocellular carcinoma and death[4]. NAFLD is the cause of the fastest increase in liver-related deaths worldwide because of its high prevalence, although less than 10% of them have liver-related complications[5]. Therefore, the early detection and evaluation of NAFLD is very important for improving the prognosis of the disease and choosing appropriate treatment for patients. In June 2023, NAFLD has been renamed as metabolic dysfunction-associated steatotic liver disease (MASLD)[6].

The pathogenesis of MASLD involves a variety of endogenous and exogenous factors, such as insulin resistance, lipid metabolism, body fat accumulation, chronic inflammation, intestinal microflora changes,

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lifestyle and nutritional intake[7–9]. Overnutrition is the main driving factor, which leads to the imbalance of lipid metabolism through the expansion of fat pool and the accumulation of ectopic fat. The imbalance of lipid metabolism can lead to cell stress (oxidative stress and endoplasmic reticulum stress), inflammatory body activation and apoptotic cell death due to increased lipotoxic lipid formation, followed by inflammation, tissue regeneration and fibrosis. at this time, hepatocytes are also exposed to oxidative stress and inflammation due to lipid accumulation[10].

Recent studies have shown that platelet to albumin ratio (PAR) can be used as a potential marker of inflammation in patients, which is a cost-effective and easily available indicator using platelet count and albumin value, and can be used as a prognostic factor or progression indicator for many diseases[11,12]. Therefore, as a new inflammatory index, PAR has attracted great attention. However, there is no research on PAR and MASLD at present. For this reason, we aim to explore the correlation between PAR and MASLD.

Methods

Study design and data source

The data in this study come from the National Health and Nutrition Examination Survey (NHANES) database (https://www.cdc.gov/nchs/nhanes/index.htm). Data collection is conducted by the National Center for Health Statistics (NCHS), using a hierarchical, multi-stage and probabilistic cluster design to assess the health status of the American people. The study used NHANES data from 2017 to 2018. The preliminary search for the expected study period retrieved the data of 9254 people. n our analysis, the exclusion criteria were as follows: (1) participants without complete vibration controlled transient elastography (VCTE); (2) < 18 years old; (3) pregnant women; (4) positive serological markers of hepatitis B or C virus; (5) self-reported autoimmune liver disease; (6) malignant tumor; (7) excessive drinking (m defined as male average daily drinking > 30 g, female average daily drinking > 20 g); (8) lack of albumin or platelet data. Finally, a total of 3287 participants were enrolled in this study. The inclusion and exclusion criteria for study participants were shown in Fig. 1. The Ethical Review Committee of the National Centre for Health Statistics approved the NHANES agreement and obtained the informed consent of all participants.

Study variables

Diagnosis of MASLD

The controlled attenuation parameter (CAP) of VCTE was used to measure hepatic steatosis. steatotic liver disease (SLD) was defined as having a CAP ≥ 302 dB / m[13]. VCTE outcomes were considered valid when participants with a fasting time of ≥ 3 h, with more than 10 complete liver stiffness measurement (LSM) readings, or a liver stiffness interquartile (IQR) range/median LSM of less than 30%[14]. MASLD was defined as having SLD plus the presence of one of the following cardiometabolic adult criteria without other causes of hepatic steatosis or excessive alcohol consumption[6]. Cardiometabolic adult criteria were defined as the following: (1) BMI ≥ 25 kg/m^2 (23 kg/m^2 for Asia) or waist circumference (WC) > 94 cm for males and > 80 cm for females; (2) Fasting blood glucose(FBG) ≥ 100 mg/dL or 2-hour post-load glucose levels ≥ 140 mg/dL or glycated hemoglobin (HbA1c) ≥ 5.7% or type 2 diabetes or treatment for type 2 diabetes; (3) blood pressure ≥ 130/85 mmHg or specific antihypertensive drug treatment; (4) plasma triglycerides (TG) ≥ 1.70 mmol/L or lipid lowering treatment; and (5) plasma high-density lipoprotein cholesterol (HDL-C) ≤ 1.0 mmol/L for males and ≤ 1.3 mmol/L for females or lipid lowering treatment[6].

Measurement of PAR

The Beckman Coulter DxH 800 instrument in the NHANES mobile examination center produces a CBC on blood specimens and the method to measure albumin concentration utilizes the dye bromcresol purple. Calculate PAR using the same blood sample and the following formula: platelet count (1000 cells/ul) / albumin (g / dL).

Covariates

Including demographic variables (age, sex, ethnicity, smoking and drinking habits), body measurements, past history (hypertension, diabetes status) and laboratory variables.

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg or a physician diagnosis of hypertension. The diagnosis of diabetes was based on any of the following criteria: HbA1c ≥ 6.5%, FBG ≥ 100 mg/dL; doctor diagnosing diabetes; using insulin. Impaired fasting glucose (IFG) was defined by HbA1c between 5.7% and 6.4%, FBG between 100 and 125 mg/dl.

Statistical methods

Considering the complex sampling design of NHANES, all analyses were sample weighted. The continuous variable was expressed as the survey weight median ± standard error (SE), the classified variable was expressed as unweighted number and weighted ratio. Multivariate logistic regression analysis was used to evaluate the correlation between PAR and MASLD in different models. Model I was unadjusted, model II adjusted for race, sex and age, and model III was adjusted for sex, age, race, smoking status, hypertension, and diabetes. Subgroup analysis was used to explore the relationship between PAR and MASLD in different subgroups, stratification factors included gender, age, hypertension and diabetes status. Restricted cubic spline (RCS) was employed to reveal the dose-response relationship between PAR and MASLD. Associations between PAR and MASLD were evaluated by using the area under the receiver operating characteristics (AUROC). Double-tailed $P < 0.05$ was considered to be statistically significant. All analyses were performed using R software (version 4.3.0).

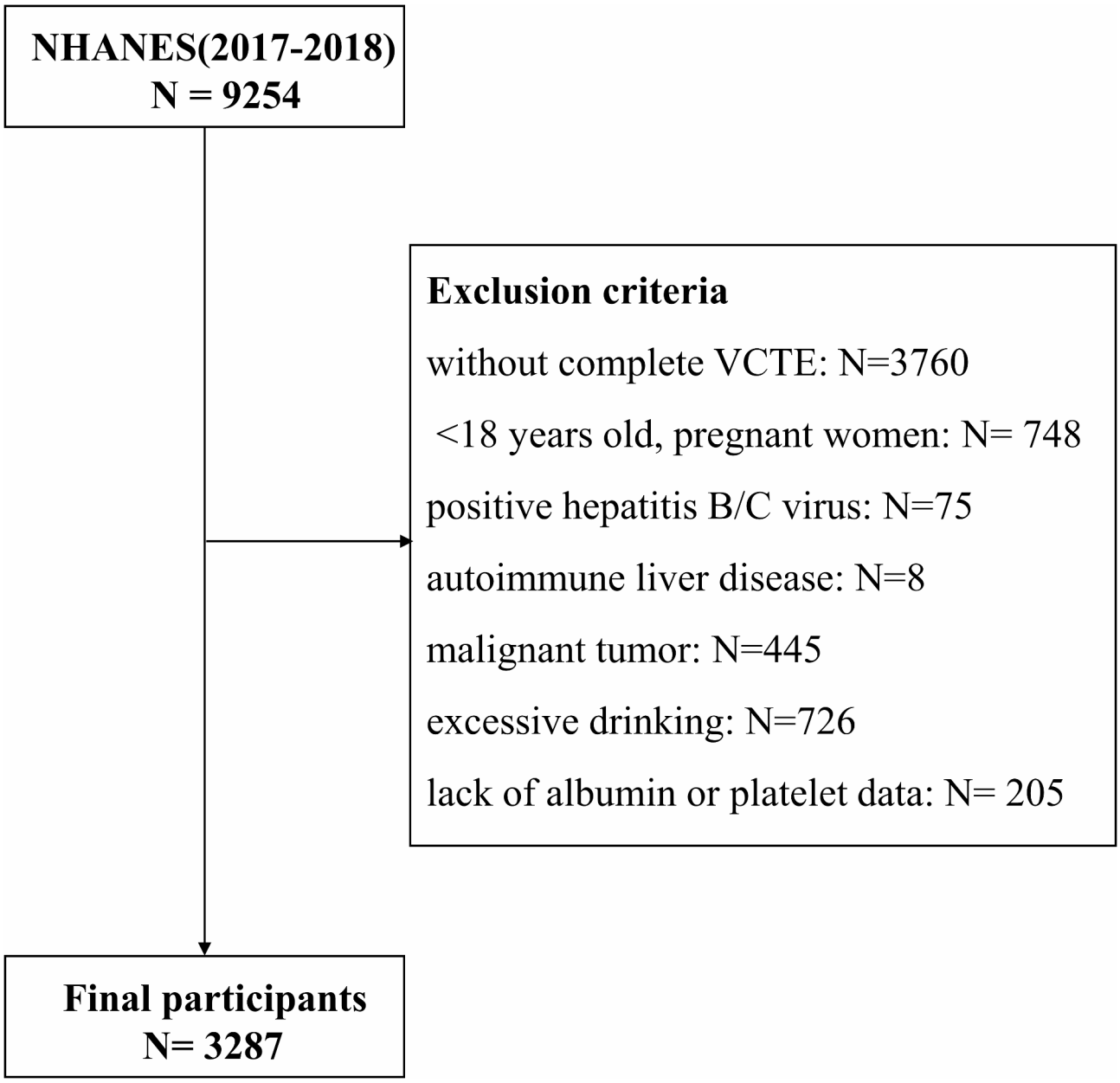

Fig. 1. Flow-chart of the MASLD participants. NHANES, National Health and Nutrition Examination Survey; VCTE, vibration controlled transient elastography.

Results

Participant characteristics

A total of 3287 individuals were enrolled in this study, including 1574 males and 1713 females. The baseline characteristics of participants were shown in Table 1. The prevalence of MASLD was 26.5%. Overall, patients with MASLD were older and had significantly higher rates of smoking and hypertension and diabetes than non-MASLD patients ($P < 0.05$). Furthermore, participants with MASLD had higher of body mass index (BMI), waist circumference, PAR, TG, hypersensitive-c-reactive-protein(hs-CRP) and lower HDL levels.

Logistic regression analysis

The association between PAR quartiles and MASLD was showed in Table 2. Compared with participants in the lowest PAR quartile, those in the highest PAR quartile (OR: 2.58 ,95% CI: 1.26–5.27, $P = 0.03$) had a significantly higher risk of MASLD after adjusting for the confounders of sex, age, race, smoking status, hypertension status, and diabetes status.

Characteristic	Non-MASLD $N=2414$	MASLD $N=873$	*P*-value
Age (years)	45 ± 18	54 ± 15	< 0.001
Sex (n, %)			< 0.001
Female	1343 (55%)	370 (42%)	
Male	1071 (45%)	503 (58%)	
Race			0.072
Mexican American	289 (7.8%)	147 (10%)	
Hispanic	234 (7.5%)	85 (6.4%)	
Non-Hispanic White	720 (60%)	300 (64%)	
Non-Hispanic Black	620 (13%)	159 (8.8%)	
Non-Hispanic Asian	418 (7.2%)	136 (6.4%)	
Others	131 (4.9%)	48 (4.3%)	
BMI (kg/m^2)	27 ±(6)	34 ±(7)	< 0.001
Waist circumference (cm)	94 ±(15)	114 ±(15)	< 0.001
Smoking status (n, %)			0.004
Never	1,606 (66%)	509 (57%)	
Former	475 (22%)	257 (31%)	
Current	331 (12%)	109 (11%)	
Drinking status (n, %)			0.2
Never	306 (8.6%)	108 (12%)	
Former	368 (17%)	137 (16%)	
Current	1,738 (74%)	630 (72%)	
Diabetes status (n, %)			< 0.001
No	1,207 (56%)	220 (27%)	
IFG	962 (38%)	384 (46%)	
Yes	243 (5.8%)	271 (27%)	
Hypertension	483 (15%)	257 (26%)	< 0.001
PAR	5.64 ±(1.74)	5.92 ±(1.71)	0.003
HDL(mmol/L)	1.40 ±(0.37)	1.16 ±(0.32)	< 0.001
Triglyceride (mmol/L)	0.89 ±(0.98)	1.42 ±(1.53)	< 0.001
LDL (mmol/L)	2.74 ±(0.93)	2.92 ±(0.90)	0.12
Hs-CRP (mg/L)	1.3 ± 4.4	2.7 ± 9.3	< 0.001

Table 1. Basic characteristics of participants. Continuous variables are presented as mean ± SE; categorical variables are presented as unweighted counts (weighted percentage). BMI, Body mass index; PAR, platelet-albumin ratio; IFG, impaired fasting glucose; HDL, high density lipoprotein; TG, Triglyceride; LDL, low density lipoprotein; Hs-CRP, hypersensitive-c-reactive-protein; MASLD, metabolic dysfunction-associated steatotic liver disease.

PAR	Model I OR, (95%CI), *P*-value	Model II OR, (95%CI), *P*-value	Model III OR, (95%CI), *P*-value
Q1 (PAR < 4.88) ($N=821$)	Reference	Reference	Reference
Q2 (4.88 ≤ PAR < 5.73) ($N=825$)	1.23, (0.81–1.86), 0.3	1.39(0.85–2.26),0.15	1.37,(0.61–3.11),0.2
Q3 (5.73 ≤ PAR < 6.95) ($N=820$)	1.24, (0.86–1.79), 0.2	1.60, (0.98–2.60), 0.058	1.59, (0.69–3.66), 0.14
Q4 (PAR ≥ 6.95) ($N=821$)	1.71, (1.34–2.18), < 0.001	2.62, (1.75–3.93), 0.002	2.58, (1.26–5.27), 0.03

Table 2. Association of PAR with MASLD. Model I, unadjusted. Model II, adjusted for age, sex, race. Model III, adjusted for model II plus smoke status, diabetes status, hypertension status. OR, odds ratio; CI, confidence interval; PAR, platelet-albumin ratio.

Subgroup analysis

Figure 2 showed the association between PAR and MASLD risk stratified by sex, age, diabetes status and hypertension status. As for the subgroup stratified by sex, age, diabetes, and hypertension, connection with statistical significance was observed among those participants with both male and female, age < 60 years, IFG and without hypertension ($P < 0.05$).

Subgroups	Total (N)	OR (95% CI)	P-value
Male			
Q1	559	Reference	
Q2	469	1.47 (0.95-2.35)	0.1
Q3	343	1.56 (0.96-2.52)	0.067
Q4	203	1.71 (1.22-2.39)	0.004
Female			
Q1	262	Reference	
Q2	356	1.90 (0.46-2.57)	0.8
Q3	477	1.50 (0.79-2.80)	0.2
Q4	618	2.83 (1.55-5.15)	0.003
Age≥60			
Q1	337	Reference	
Q2	272	1.00 (0.58-1.73)	>0.9
Q3	255	1.00 (0.55-1.84)	>0.9
Q4	204	1.18 (0.71-1.98)	0.5
Age<60			
Q1	484	Reference	
Q2	553	1.44 (0.91-2.28)	0.11
Q3	565	1.45 (0.95-2.21)	0.082
Q4	617	2.14 (1.57-2.90)	<0.001
Hypertension			
Q1	199	Reference	
Q2	181	2.12 (0.95-4.75)	0.064
Q3	187	1.10 (0.47-2.56)	0.8
Q4	173	1.12 (0.49-2.52)	0.8
Witnout hypertension			
Q1	622	Reference	
Q2	644	1.01 (0.62-1.67)	>0.9
Q3	633	1.28 (0.84-1.96)	0.2
Q4	648	1.91 (1.48-2.45)	<0.001
Diabetes			
Q1	140	Reference	
Q2	126	1.97 (0.80-4.88)	0.13
Q3	108	0.93 (0.32-2.73)	0.9
Q4	140	2.00 (0.93-4.30)	0.071
IFG			
Q1	314	Reference	
Q2	333	1.54 (0.75-3.16)	0.2
Q3	351	1.88 (1.11-3.20)	0.023
Q4	348	2.18 (1.37-3.47)	0.003
Without diabetes			
Q1	367	Reference	
Q2	366	0.84 (0.50-1.41)	0.5
Q3	361	0.93 (0.51-1.69)	0.8
Q4	333	1.08 (0.61-1.90)	0.8

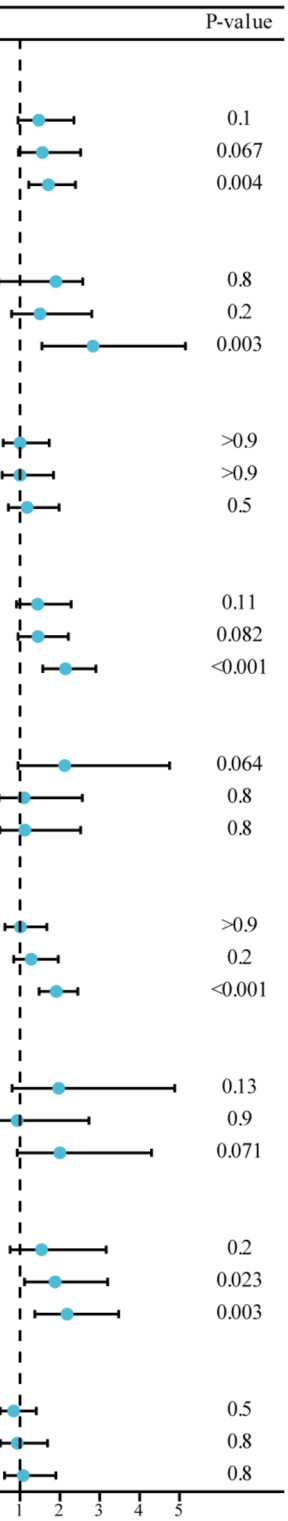

Fig. 2. Subgroup analysis for the association between PAR and MASLD. OR, odds ratio; CI, confidence interval.

Nonlinear associations between PAR level and the prevalence of MASLD

Multivariate adjusted RCS regression method was used to show the non-linear correlation between PAR and the prevalence of MASLD. As shown in Fig. 3, PAR level was nonlinearly and positively correlated with the risk of MASLD (P for nonlinearity = 0.003), with inflection points of 5.75. The nonlinear positive correlation between PAR and MASLD risk was also observed in the subgroup analysis based on age, sex, hypertension and diabetes status (Fig. 4).

ROC analysis

The receiver operating characteristic curve of the PAR to anticipate MASLD risk was illustrated in Fig. 5. The AUC for PAR in the ROC analysis was 0.842 (95% CI: 0.826–0.859), and the cut-off value was 5.78. This indicates that PAR had a good predictive efficacy for the risk of MASLD.

Discussion

As far as we know, this is the first study to explore the relationship between PAR and MASLD. In this cross-sectional study of 3287 participants, we found that the prevalence of MASLD in the high PAR group was significantly higher than that in the low PAR group. The unadjusted model showed that there was a significant correlation between PAR level and MASLD ($P < 0.05$). After fully adjusting for sex, age, race, smoke status, diabetes status, hypertension status, PAR was still a risk factor for MASLD (OR = 2.58, $P = 0.03$). Then we conducted a further subgroup analysis, the same conclusion was observed in both male and female, age < 60 years, IFG and without hypertension ($P < 0.05$).

Albumin is the most abundant plasma protein, which plays a key role in regulating plasma colloid osmotic pressure[15]. In addition, as an effective scavenger, antioxidant and immunomodulator, albumin plays a variety of dynamic balance functions[16]. CLD often affects albumin levels, and the ensuing malnutrition and disturbances in amino acid metabolism accelerate the development of other complications[17,18]. Previous studies have shown that there is a close correlation between ALB and inflammation[19]. Studies have shown that hypoproteinemia causes the release of a range of inflammatory cytokines[20]. More importantly, ALB is an important index for predicting the prognosis of patients with liver cirrhosis[21,22]. Platelet can promote the secretion of cytokines by interacting with a variety of immune cells (including IL-1, IL-6, INF- γ and TNF α), which can be used as a rough indicator of inflammatory activity[23,24], and it has also been proved to be closely related to the prognosis of liver diseases in many studies[25,26]. From the above research results, it is not difficult to see the importance of

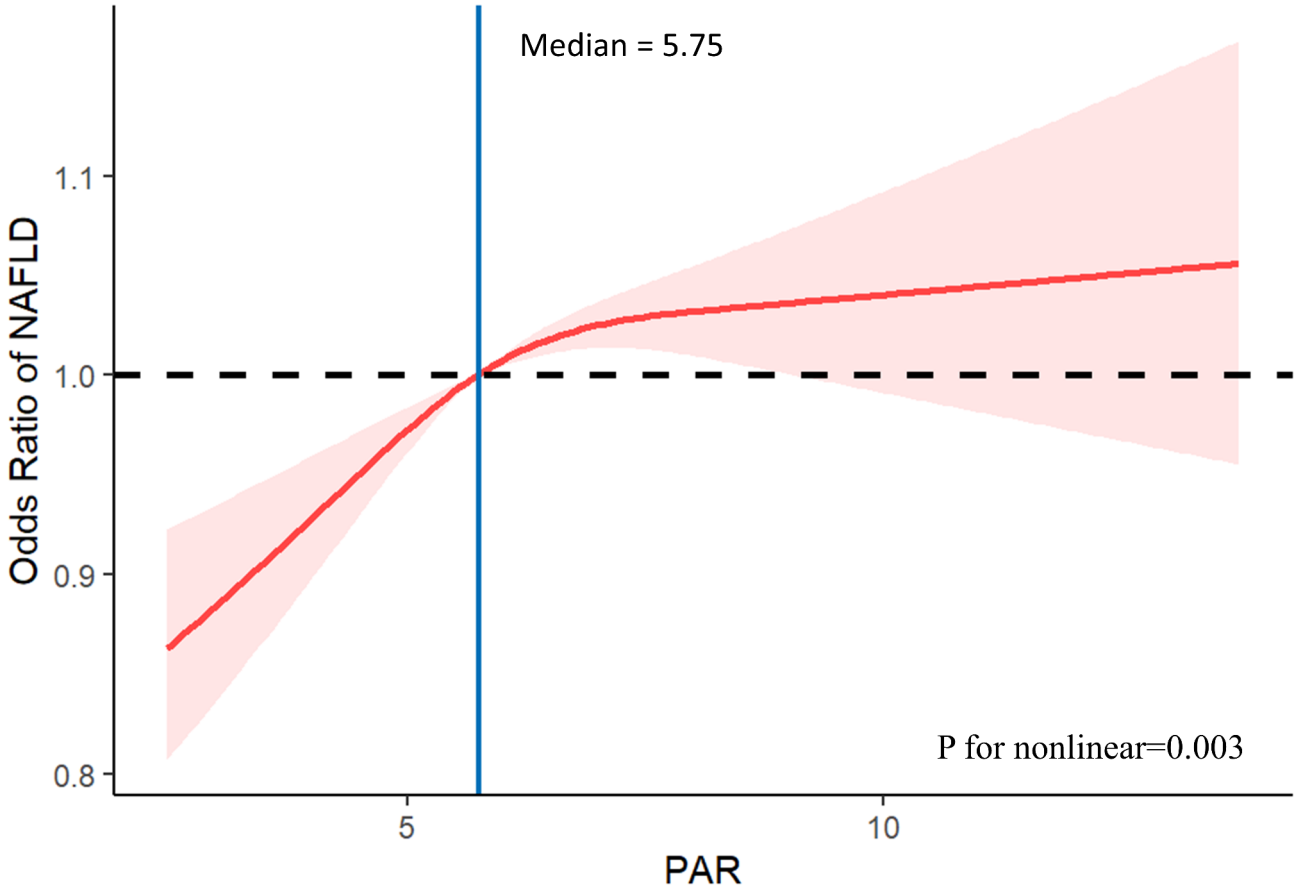

Fig. 3. Associations between PAR and the prevalence of MASLD. The model was adjusted for sex, age, race, smoking status, hypertension, and diabetes. PAR, platelet-albumin ratio.

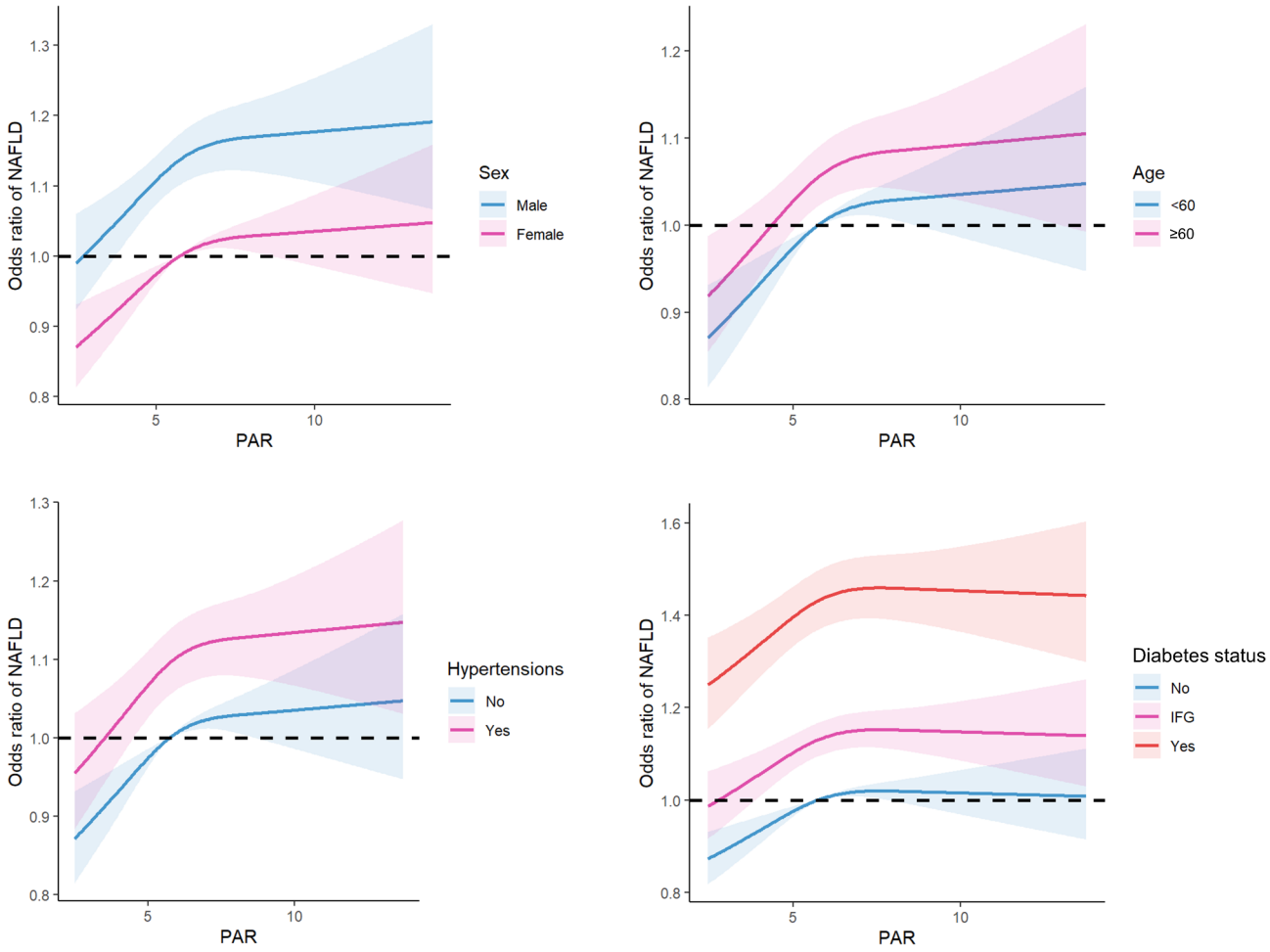

Fig. 4. Stratified analyses of MASLD by PAR levels. PAR, platelet-albumin ratio; IFG, impaired fasting glucose.

monitoring albumin and platelet levels in liver diseases. PAR is less likely to be affected by various physiological or disease conditions than PLT and ALB alone, and it is proposed as a more reliable new indicator to assess systemic inflammation and immunonutrition status.

The role of chronic inflammation in the pathogenesis of MASLD may range from simple steatosis to non-alcoholic steatohepatitis (NASH), advanced liver fibrosis, liver cirrhosis, and finally end-stage liver disease and hepatocellular carcinoma[27]. However, the exact mechanism of the relationship between inflammation and hepatic steatosis is not clear. The causes of liver inflammation may originate outside the liver (adipose tissue or digestive tract) and inside organs (lipotoxicity, innate immune response, mitochondrial dysfunction and endoplasmic reticulum stress)[28]. The characteristics of the new model of MASLD progress no longer emphasize lipotoxicity as the main driving factor, but put more emphasis on the interaction between intestinal tract, liver and adipose tissue[29]. The contribution of adipokines and inflammatory cytokines released by inflammatory adipose tissue in promoting insulin resistance and steatosis has been fully confirmed[30]. As an easily available and non-invasive inflammatory marker, PAR has been used to predict the prognosis of severe fever with thrombocytopenia syndrome[31] and colorectal cancer[32]. In our study, we also confirmed PAR can be used as a direct, non-invasive indicator to identify high-risk patients with MASLD. We can detect the dynamic changes of PAR to indicate the high-risk group of MASLD, in order to provide lifestyle or drug interventions to them as early as possible, and to reduce the physical and economic burdens caused by MASLD. In summary, PAR was a simple and practical clinical indicator that can be used as an independent predictor of MASLD. This may help clinicians to implement more aggressive treatment strategies.

The main highlight of our study is the relatively large and well-designed population-based samples, which are representative of the population. Due to the strong standardization of the NHANES research program, the measurement and information deviation is very low, so the analysis results have good reliability and stability.

However, there are some limitations in our research. First of all, the cross-sectional study design makes it impossible for us to establish causality, which should be further explored through future prospective studies or randomized controlled studies. In addition, although we have adjusted the relevant confounding factors included, we cannot completely rule out the impact of other potential confounding variables (e.g., metabolic or lifestyle variables) on the results.

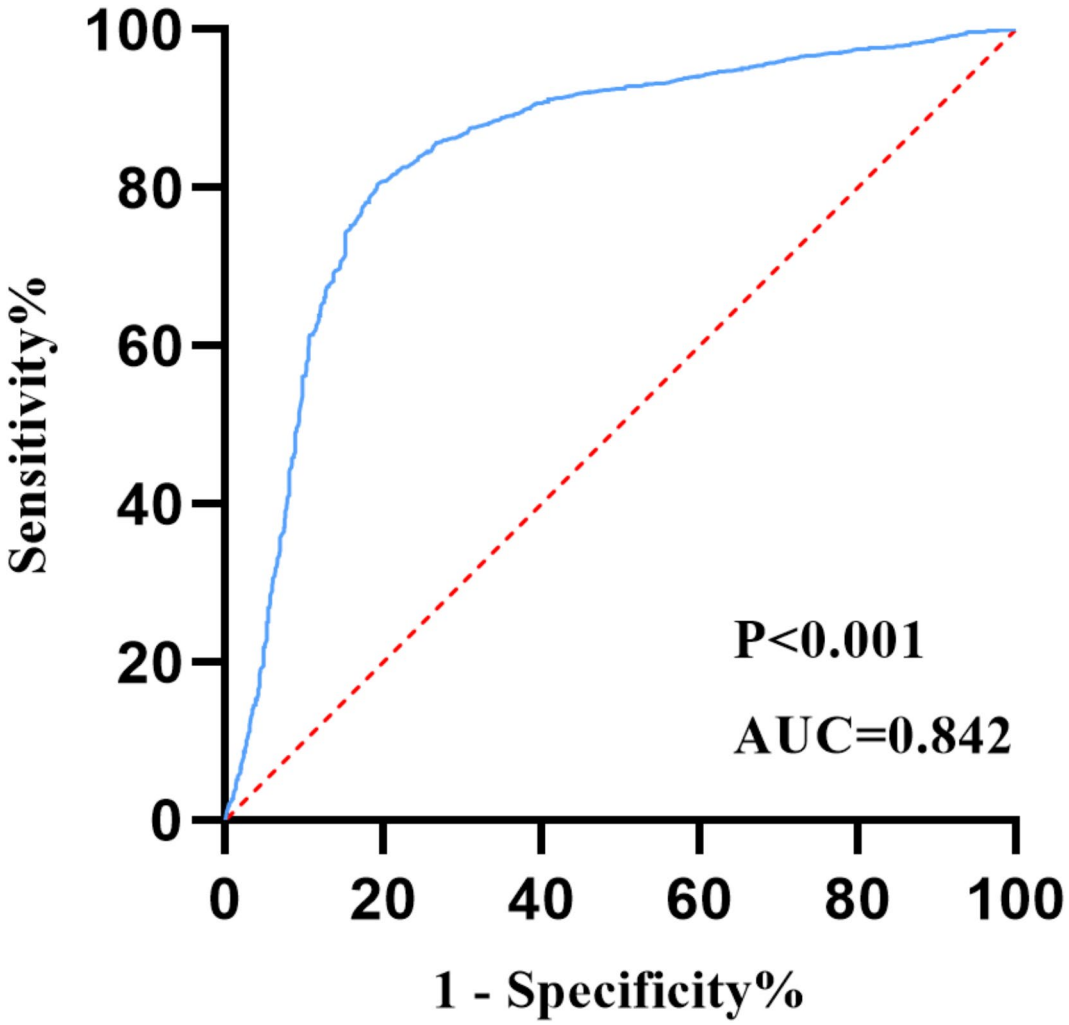

Fig. 5. ROC curve of PAR for predicting the risk of MASLD.

Data availability

Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/Nchs/Nhanes/.

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Declarations

Ethics approval
The studies involving human participants were reviewed and approved by the Research Ethics Review Board of the NCHS. The patients/participants provided their written informed consent to participate in this study.

Competing interests
The authors declare no competing interests.

Additional information
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