European Review for Medical and Pharmacological Sciences 2024; 28: 2288-2296

Analysis of the effect of elevated systemic immuno-inflammation index on hepatic steatosis based on the NHANES database

H.-J. XIA, J. HE, D.-W. ZHANG, X. DING

Department of Emergency, Eastern Hepatobiliary Surgery Hospital, Third Affiliated Hospital of Naval Medical University, Shanghai, China

Abstract. – OBJECTIVE: Based on data from the National Health and Nutrition Examination Survey (NHANES), this study aimed to investigate the effect of high levels of systemic immune inflammation (SII) on hepatic steatosis by conducting a population-based cross-sectional survey of research subjects.

SUBJECTS AND METHODS: The population included 5,119 participants from the NHANES 2017-2020 cycle who were selected as the research subjects. We used (neutrophil count × platelet count)/lymphocyte count as the formula for calculating SII. The formula for calculating HSI levels was 8 × the ratio of [alanine aminotransferase (ALT) / aspartate aminotransferase (AST)] + body mass index (BMI) + 2 (with diabetes mellitus) + 2 (for women). HSI=36 was taken as the cut-off value for evaluating hepatic steatosis. Multivariate logistic regression analysis was used to evaluate the relationship between hepatic steatosis and SII in different models. Subgroup analysis was used to explore the relationship between different subgroups of SII and hepatic steatosis. Interaction analyses were used to assess the heterogeneity.

RESULTS: Out of a total of 5,119 participants, hepatic steatosis was observed in 2,742 individuals. Multivariate logistic regression showed that the independent risk factor for hepatic steatosis was a high SII level (OR=1.33, 95% CI: 1.11-1.49, $p<0.05$). After adjusting for differences in BMI and HSI using propensity score matching (PSM), bariatric surgery also reduced SII risk.

CONCLUSIONS: There is a correlation between SII and hepatic steatosis, and bariatric surgery can effectively reduce SII risk in the hepatic steatosis population.

Key Words:

Hepatic steatosis, Systemic immuno-inflammation, Non-alcoholic fatty liver disease, National health and nutrition examination survey, Bariatric surgery.

Introduction

Hepatic steatosis is the appearance of fat droplets in the cytoplasm of liver hepatocytes when hypoxia, ischemia, poisoning, infection, and other factors affect the balance of fat metabolism in liver cells[1]. The causes of hepatic steatosis include lipoprotein synthesis disorder, excessive neutral fat synthesis, fatty acid oxidation, or lipid disorder[2]. Hepatic steatosis is a reversible injury that can return to normal after the cause is eliminated. Severe hepatic steatosis can cause fatty liver, hepatomegaly, painful pressure, abnormal liver function, liver cell necrosis, fibrous hyperplasia, and even liver cirrhosis[3]. Fatty liver is now an important cause of liver transplantation in the United States and Europe[4]. The global incidence of fatty liver is as high as 25%. In the United States, it is estimated that more than 64 million people suffer from non-alcoholic fatty liver disease (NAFLD), and the annual direct medical cost is about 103 billion US dollars[5].

According to relevant research[4] data in 2018, the prevalence of fatty liver diagnosed by abdominal color Doppler ultrasound in China has increased significantly. In just 10 years, the prevalence has risen from 15% at the beginning to more than 31% now. The incidence of liver cirrhosis in patients with steatohepatitis can be as high as 15%-25% during 10-15 years of follow-up, with the disease progressing rapidly. The severity of liver fibrosis directly correlates with the risk of mortality from liver disease. According to the study[4], the risk of death escalates by approximately 11.13 times with advanced liver fibrosis. Moreover, projections suggest that by 2030, the cumulative number of deaths attributed to liver diseases related to fatty liver in China will surpass those in the United States, potential-

Corresponding Author: Xian Ding, MD; e-mail: XianDing8611@163.com

ly reaching an alarming 103,800 cases[6,7]. Therefore, hepatic steatosis is an important factor that determines the progression of liver disease and has always been a hot spot and difficulty in the prevention and treatment of fatty liver.

In recent years, more and more scholars have paid attention to the inflammatory indicators that can reflect the state of the whole body, such as systemic immune inflammation index (SII), monocyte/lymphocyte ratio (MLR), prognostic nutritional index (PNI) and neutrophil/lymphocyte ratio (NLR)[1]. SII, first defined in 2014, is an index based on lymphocyte, peripheral neutrophil, and platelet counts; the formula of SII is (P×N)/L, where P, L, and N are the platelet count, lymphocyte count, and neutrophil count, respectively. SII is a potential indicator that can establish a balance between the host's inflammatory state and immune state[8]. SII is more often used as a prognostic indicator in cancer research[9,10]. Hu et al[11] analyzed postoperative patients with hepatocellular carcinoma (HCC) and found that the median overall survival (OS) in the low SII group and high SII group was 63.3 months and 37.3 months, respectively, and the disease-free survival (DFS) was 61.3 months and 26.4 months, respectively, suggesting that SII is a strong predictor of poor prognosis in HCC patients. HCC patients with elevated SII levels have an increased risk of recurrence and shorter, suggesting that SII can become a new independent prognostic indicator for HCC. Estes et al[4] showed that preoperative SII ≥226 was negatively correlated with the prognosis of liver transplantation patients with HCC, and was better than platelet lymphocyte ratio (PLR), MLR, and NLR in predicting OS. Therefore, SII is closely related to the prognosis of HCC patients and has certain predictive value.

Nonetheless, there is a limited amount of research concerning the impact of SII on hepatic steatosis. Therefore, we aimed to investigate whether elevated SII level has predictive value on hepatic steatosis participants by conducting a population-based survey through the National Health and Nutrition Examination Survey (NHANES).

Subjects and Methods

Data Sources

The data for this study came from the NHANES. NHANES is a continuous Centers for Disease Control and Prevention (CDC) cross-sectional study that collects population-based data on the prevalence of chronic disease through surveys that allow estimates of previously undiagnosed, known, and reported conditions. Detailed statistics can be accessed at https://www.cdc.gov/nchs/nhanes/.

The study's team consisted of medical technicians, doctors, and health investigators. Participation in the survey is voluntary, and participants will undergo standardized examinations and personal interviews. The NHANES interview portion of the population includes questions related to socioeconomic, demographic, health, and dietary aspects, and the examination portion includes medical, physiological, and dental measurements, as well as laboratory tests performed on the population by medical personnel. In this study, we included the population of the NHANES 2017-2020 cycle as the research subjects. There were 15,560 participants in total. Among these participants, we excluded 8,278 age-inappropriate participants (age <18, >65 years), 84 participants who were pregnant, 911 participants lacking SII, 1,054 participants without hepatic steatosis index (HSI), 13 participants with no education, and 101 participants with hepatitis B. Finally, 5,119 participants were included in the study (Figure 1).

Definition of SII

Lymphocyte and platelet counts as well as neutrophils (expressed in units of $\times 10^3$ cells/μl) were measured by complete blood count. SII levels were calculated as (platelet count × neutrophil count)/lymphocyte count[12].

Outcome Variable

Since the relationship between the degree of hepatic steatosis and HSI has been demonstrated, hepatic steatosis index (HSI)>36 indicates NAFLD[13]. Therefore, we use HSI=36 as the critical value for evaluating hepatic steatosis. The level of HSI is calculated using the following formula: 8 x [alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratio] + body mass index (BMI) + 2 (with diabetes) + 2 (for women)[14].

Covariate

We screened for some covariates that might influence the relationship between hepatic steatosis and SII. Demographic data include age, education level, gender, race, body mass index, and smoking. The biochemical profile includes total cholesterol (TC) and glycated hemoglobin. A health risk factor is diabetes.

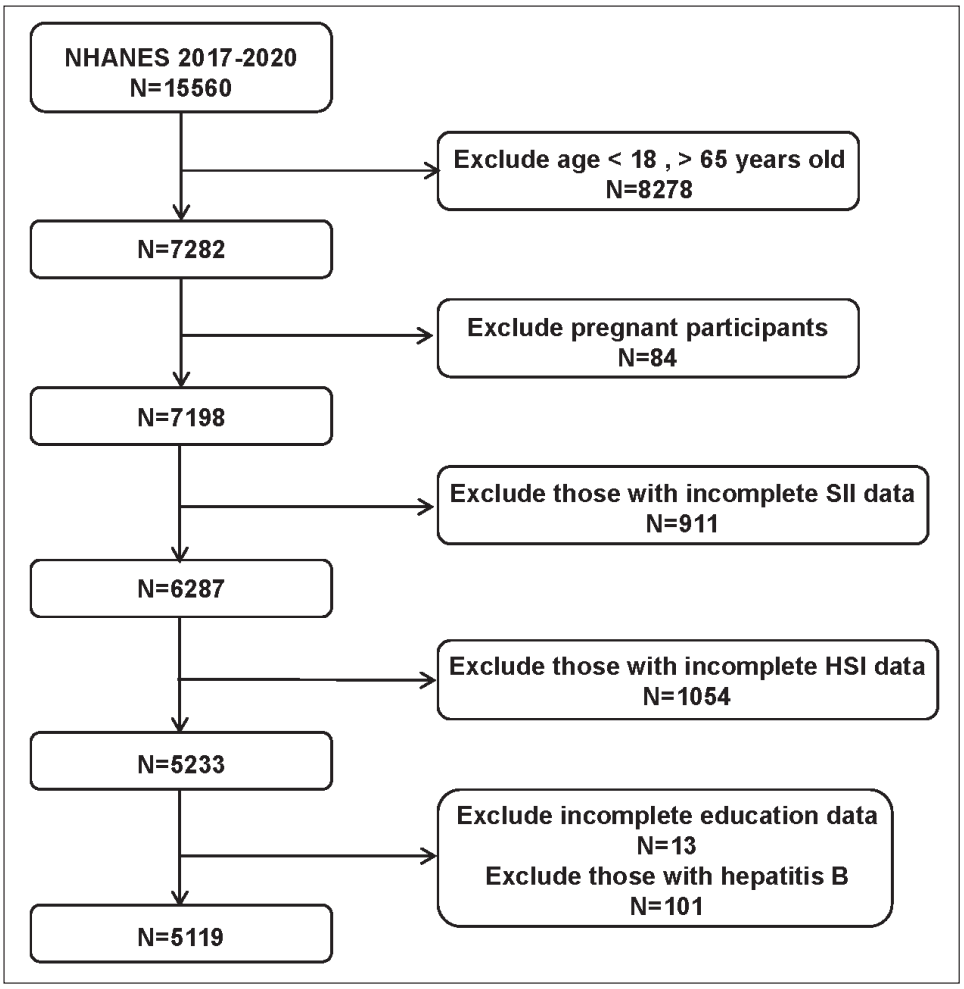

Figure 1. Flowchart of the participants' selection from NHANES 2017-2020.

Data Sources for Bariatric Surgery Patients

Studies confirm that bariatric surgery can effectively reduce hepatic steatosis[15,16]. Therefore, we compared those with steatosis who did and did not undergo bariatric surgery in the NHANES database and explored the association between bariatric surgery and hepatic steatosis.

Statistical Analysis

Due to the complexity of the sample survey, we conducted a weighted analysis according to the NHANES recommendation. The Chi-square test was used to compare differences in characteristics between the normal group and the hepatic steatosis group. Multivariate logistic regression analysis evaluated the correlation between hepatic steatosis and SII levels in different models. Model 1: original unadjusted variables. Model 2: adjusting for age, education, race, and smoking status. Model 3: adjusting for age, education, sex, race, diabetes, smoking status, and Hemoglobin A1c (HbA1c). Subgroup analysis explored the relationship between different subgroups of hepatic steatosis and SII. Stratification factors were gender, age, and diabetes. Interaction analysis was used to assess heterogeneity between subgroups. This study further explores the impact of bariatric surgery on the relationship between hepatic steatosis and SII. The "MatchIt" package for R was used for propensity score matching (PSM) analysis to eliminate bias and control for potential confounding variables. The "nhanesR" package for R was used to extract, analyze, and perform calculations on the data. R/Bioconductor package for extracting, combining, processing, and comparing omics datasets from different and diversely localized sources and their metadata, is available at https://www.bioconductor.org/packages/release/bioc/html/RGMQL.html. $p<0.05$ was considered statistically significant.

Results

Basic Characteristics of Participants

A total of 5,119 participants were included in our study. There were 2,377 participants without hepatic steatosis (normal group), with an average age of 41.24±0.62 years. Females accounted for 50.64%, and males accounted for 49.36%. There were 2,742 participants with hepatic steatosis (hepatic steatosis group), with the average age of 44.31±0.94 years, women accounted for 51.05%, and men accounted for 48.95%. There were significant differences in terms of age, education level, diabetes mellitus (DM), smoking status, BMI, SII, TC, ALT, and glycohemoglobin between the normal group and hepatic steatosis group (p<0.05), and the mean value of SII was significantly different (Figure 2). Gender and AST were not statistically different between the two groups. Biochemical characteristics and clinical data of all participants are shown in Table I.

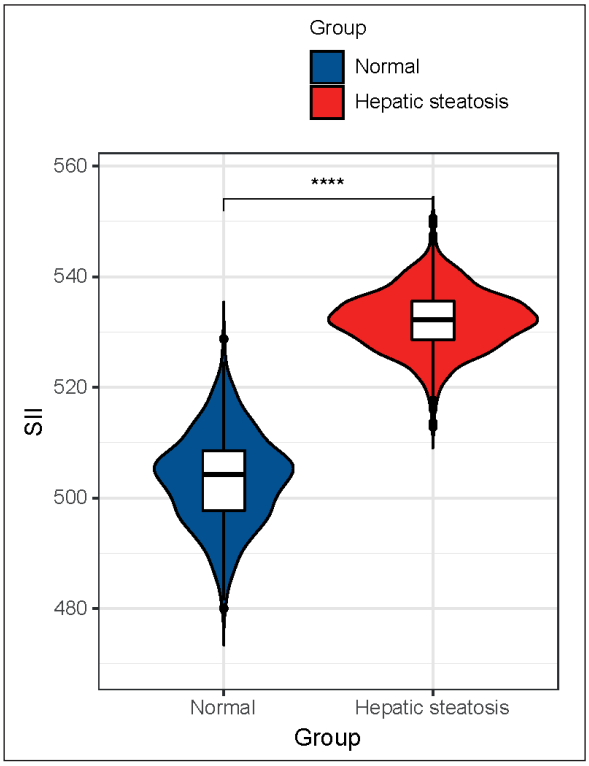

Figure 2. Comparing violin plots of SII. ****p<0.0001.

Independent Effect of SII on Hepatic Steatosis

Logistic regression analysis showed that SII level was independently associated with hepatic steatosis in different models. Univariate analysis showed that high SII level was a risk factor (OR=1.40, 95% CI: 1.22-1.56, p<0.05) (Table II). After continuing to adjust for age, sex, educa-

Table I. Basic characteristics of participants (n=5,119) in the NHANES 2017-2020.

Outcomes	Normal (n=2,377)	Hepatic steatosis (n=2,742)	*p*-value
Age	41.24±0.62	44.31±0.94	0.000
Sex			0.82
Female	50.64 (48.21,52.28)	51.05 (49.40,53.12)	
Male	49.36 (46.15,51.84)	48.95 (46.30,50.66)	
Education			0.000
> High school	21.45 (19.54,24.09)	25.04 (23.71,28.01)	
< High school	12.23 (10.49,13.97)	13.87 (11.24,15.33)	
BMI (kg/m²)	23.56±0.11	34.20±0.17	0.000
Diabetes Mellitus			0.000
Yes	8.56 (6.15,9.48)	22.89 (20.74,24.22)	
No	91.44 (88.98,93.48)	77.11 (75.65,90.13)	
Smoke			0.000
Former	22.04 (20.01,24.76)	25.84 (24.11,28.48)	
Never	56.82 (56.15,59.55)	54.21 (53.08,57.69)	
Now	21.14 (19.48,23.14)	19.95 (15.75,20.41)	
SII	503.48±8.22	532.15±5.42	0.000
ALT (U/L)	20.50±0.32	27.59±0.35	0.000
AST (U/L)	23.85±0.23	24.28±0.21	0.21
TC (mmol/L)	4.68±0.06	4.89±0.05	0.000
Glycohemoglobin (%)	5.39±0.03	5.91±0.02	0.000

Mean±SD was used for continuous variables. The percentage (95% confidence interval) was for categorical variables. NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; SII, systemic immune-inflammation index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol.

Table II. Association between SII and hepatic steatosis.

SII	OR	95% CI	*p*
Model 1			
< 445.2	Reference		
≥ 445.21	1.40	1.40 (1.22,1.56)	0.000
Model 2			
< 445.2	Reference		
≥ 445.21	1.42	1.42 (1.25,1.60)	0.000
Model 3			
< 445.2	Reference		
≥ 445.21	1.33	1.33 (1.11,1.49)	0.000

SII, systemic immune-inflammation index; OR, odds ratio; CI, confidence interval.

tion level, smoking status, DM, AST, TC, ALT, and glycosylated hemoglobin, high SII level was shown to be also an independent risk factor (OR=1.33, 95% CI: 1.11-1.49, $p<0.05$).

Subgroup Analysis

Subgroup analyses showed an inconsistent relationship between SII level and hepatic steatosis (Figure 3). A strong correlation between SII and hepatic steatosis was found in a subgroup of sex ($p<0.05$). In participants under 45 years old without DM, a statistically significant association was found ($p<0.05$). Interaction tests revealed no significant differences in the relationship between hepatic steatosis and SII in the two subgroups of sex and DM, suggesting that these factors did not significantly contribute to this positive relationship ($p>0.05$). However, age may be a factor influencing the association between hepatic steatosis and SII ($p<0.05$).

PSM Analysis

To assess the association between SII level and bariatric surgery in participants with hepatic steatosis, we analyzed the data by PSM. The basic characteristics of the participants who underwent bariatric surgery and those who did not undergo bariatric surgery are shown in Table III. PSM analysis of the data did not reveal differences in these characteristics. There was a statistical difference between SII and ALT among the participants with hepatic steatosis who received or

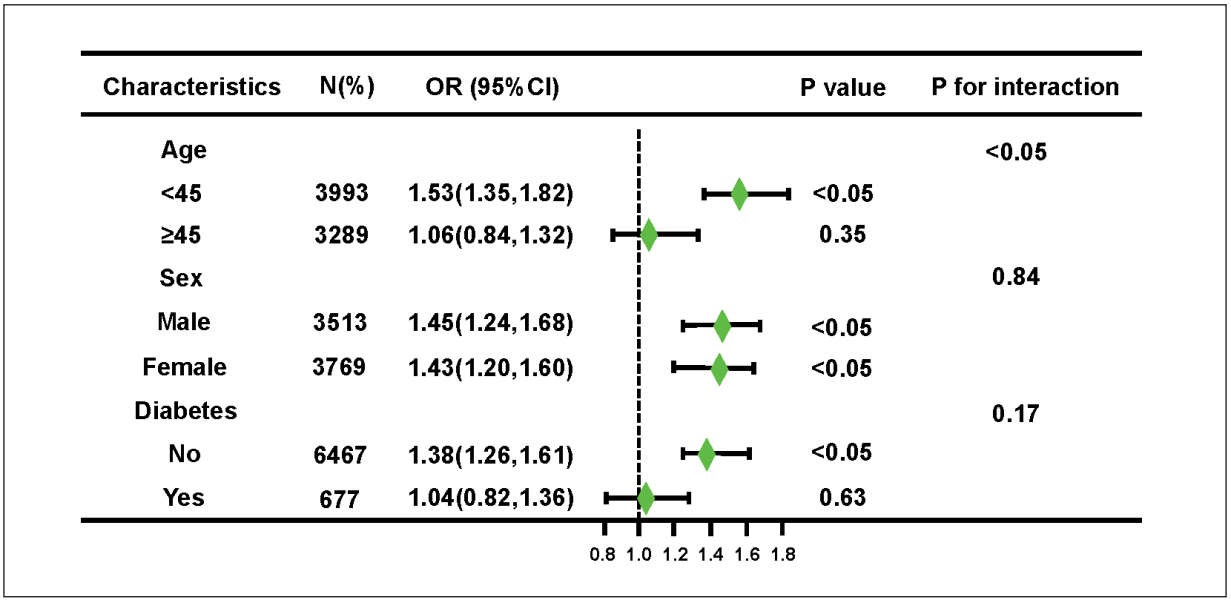

Figure 3. Subgroup analysis for the association between SII and hepatic steatosis. Weighted univariate logistic regression was used for subgroup analysis.

Table III. Basic characteristics of participants with hepatic steatosis with/without bariatric surgery after PSM analysis in the NHANES 2017-2020.

Outcomes	Hepatic steatosis without bariatric surgery (n=459)	Hepatic steatosis with bariatric surgery (n=27)	*p*-value
Age	48.25±1.06	48.43±0.51	0.94
Sex			0.53
Female	83.49 (79.68,85.26)	80.52 (77.67,84.01)	
Male	16.51 (8.87,21.45)	19.48 (15.86,21.39)	
Education			0.71
> High school	25.72 (22.35,29.05)	27.60 (18.48,33.84)	
< High school	2.05 (0.56,4.55)	2.32 (1.08,3.69)	
BMI (kg/m^2)	37.05±0.66	37.98±0.48	0.40
Diabetes Mellitus			0.21
Yes	28.80 (24.59,31.20)	30.22 (25.17,37.48)	
No	71.20 (69.44,76.59)	69.78 (63.50,78.56)	
Smoke			0.75
Former	29.23 (23.42,33.08)	22.37 (16.59,35.45)	
Never	61.02 (58.48,64.88)	60.87 (51.49,71.50)	
Now	9.75 (7.20,12.56)	16.76 (11.05,25.04)	
SII	550.62±11.26	506.21±5.15	0.000
ALT (U/L)	25.05±1.05	20.42±0.35	0.000
AST (U/L)	22.98±1.02	21.07±0.14	0.15
TC (mmol/L)	4.82±0.07	4.56±0.02	0.20
Glycohemoglobin (%)	5.98±0.10	5.32±0.03	0.54

Mean±SD was for continuous variables. The percentage (95% confidence interval) was for categorical variables. NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; SII, systemic immune-inflammation index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol.

did not receive bariatric surgery (p<0.05). The differences in SII levels are shown in Figure 4. The rest of the characteristics did not differ. It was found that bariatric surgery reduced the high SII levels associated with hepatic steatosis, with no correlation with BMI.

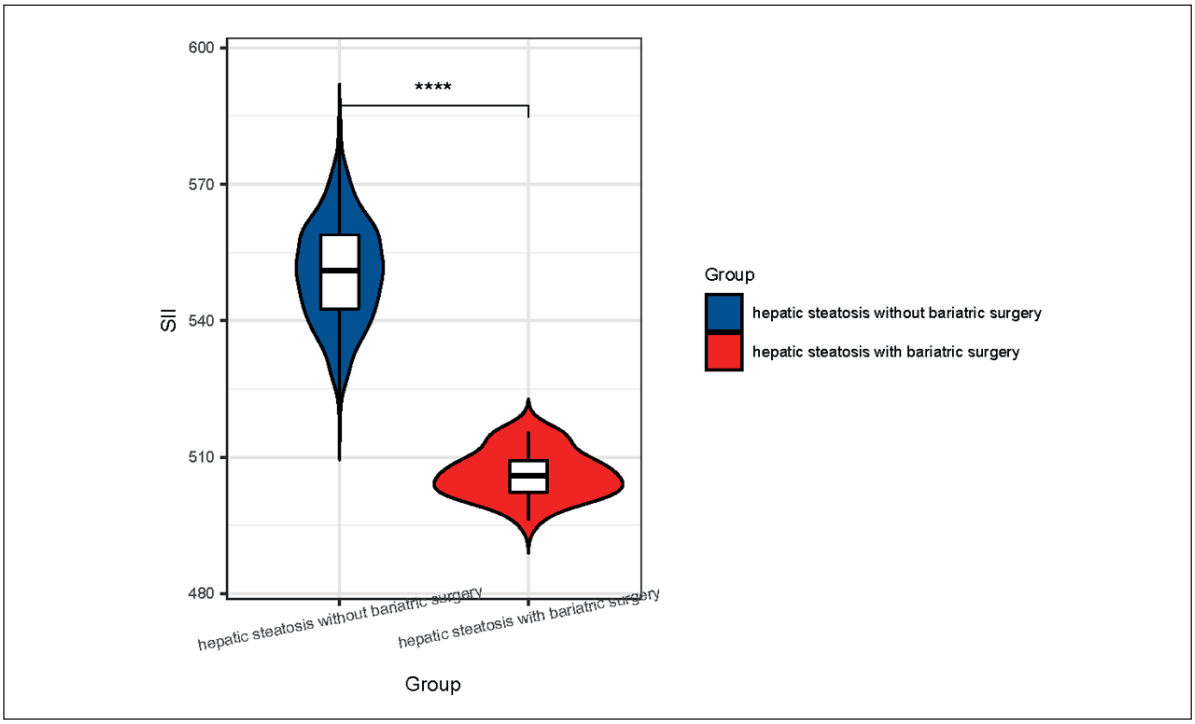

Figure 4. Comparing violin plots of SII. ****p<0.0001.

Discussion

According to the Global Burden of Chronic Liver Disease Database, the number of deaths from chronic liver diseases in the world in 2017 increased by 11.4% compared to that in 2012, and the growth rate of the number of deaths from HCC (16%) was higher than that of liver cirrhosis (8.7%)[5]. In 2015, 62.6% of global liver disease deaths and 72.7% of HCC deaths occurred in Asia, and China was the most serious. With urbanization, modernization (sedentary life and lack of exercise), and westernization of dietary patterns, the prevalence of NAFLD and its associated end-stage liver disease will continue to increase over the next few decades[17]. The causes of hepatic steatosis include lipoprotein synthesis disorder, excessive neutral fat synthesis, fatty acid oxidation, or lipid disorder. Hepatic steatosis is a reversible injury that can return to normal after the cause is eliminated. Severe hepatic steatosis, also called fatty liver, can cause hepatomegaly, painful pressure, and abnormal liver function. At present, NAFLD has affected 33% of Asian adults. Whether in Europe, America, or Asia, the impact of NAFLD on the quality of life and disease burden of patients has surpassed that of other chronic liver diseases[18]. Studies[19] have demonstrated a correlation between SII and liver disease. In NHANES 2016-17, a population-based study[19] found a significant association between SII and higher BMI. While our subgroup analysis showed similar results, participants with hepatic steatosis were at higher risk of SII, suggesting that patients with hepatic steatosis should receive more attention, especially those with NAFLD.

So far, the relationship between high levels of SII and hepatic steatosis is unclear. At present, it mainly involves several theories in cancer to explain this phenomenon, mainly involving the following aspects: (a) neutrophils can activate parenchymal cells and endothelial cells, thereby promoting distant tumor metastasis and enhancing the adhesion of circulating tumor cells. It can also participate in tumor metastasis and proliferation by releasing inflammatory factors such as neutrophil elastase, interleukin-8 (IL-8), and matrix metalloproteinase 9[20]. In addition, granulocytes, especially neutrophils, can secrete substances that promote angiogenesis[21]. (b) In tumor cells, the interaction between platelets and tumor cells directly activates nuclear factor tissue growth factor beta (TGF-β)/Smad and nuclear factor kappa B (NF-κB) signal transduction pathways, thereby inducing epithelial-mesenchymal transition and promoting the metastasis of tumor cells to distant sites. In addition, platelets can act as a protective "cloak" to protect circulating tumor cells from immune destruction; thus, platelets play a major role in the survival and metastasis of tumor cells[22,23]. (c) Lymphocytes can control tumor growth by inducing cytokine secretion and toxic cell death and inhibiting tumor cell migration and proliferation[24]. In addition, low levels of lymphocytes are associated with poor survival in cancer patients, possibly because the host's anti-cancer immunity is weakened with decreased levels of lymphocytes[25]. Based on this information, higher levels of SII may be associated with tumor angiogenesis, invasion, and metastasis, resulting in poorer survival. Thus, elevated SII is associated with poor survival in cancer patients. Our study found that higher SII was independently associated with a higher risk of hepatic steatosis, suggesting that SII may have an independent adverse effect on hepatic steatosis.

Type 2 diabetes mellitus (T2DM), obesity, and dyslipidemia are the risk factors most closely related to metabolism-associated fatty liver disease (MAFLD). Cardiovascular disease (CVD) is the leading cause of death in patients with MAFLD[26]. In 2018, my country's NAFLD prevention and treatment guidelines proposed that the main treatment target is liver disease and related metabolic complications, and the secondary target is to reduce liver lipid deposition and avoid liver inflammation and acute-on-chronic liver failure caused by "additional blows". Patients with liver inflammation and liver fibrosis also need to prevent the progression of liver disease to reduce the occurrence of liver cirrhosis, liver cancer, and complications[27]. In 2020, the Asia-Pacific Society for the Study of Liver Diseases pointed out that the ideal treatment method for MAFLD should not only effectively reduce hepatic steatosis and related liver damage, but also improve the metabolic and cardiovascular risk factors and complications of MAFLD patients.

Hence, the primary approach and fundamental strategy for managing MAFLD remain centered around implementing a structured intervention program. This program includes dietary restrictions, dietary adjustments, increased physical activity, and lifestyle modifications. A recent study[28] of 293 cases of MAFLD treated with lifestyle changes showed that the improvement rate of steatohepatitis was 58% in those who lost more than 5% of their weight, and the improvement

rate of steatohepatitis in those who lost more than 10% was as high as 90%. It was accompanied by a reduction in the degree of fibrosis[29]. Because weight loss through lifestyle changes and exercise requires long-term perseverance and it is difficult to maintain weight loss, surgical weight loss has become popular. In a recent prospective study[30] monitoring liver biopsies, it was observed that after a weight loss intervention, the rates of improvement for steatohepatitis and liver disease at the five-year mark were 84% and 70.2%, respectively. Furthermore, the decrease in liver fibrosis began within the first year following bariatric surgery and demonstrated continued improvement over time. Studies[15,16] find bariatric surgery effective in reducing liver steatosis. According to our study on the relationship between hepatic steatosis and bariatric surgery, the results suggest that SII is a valid marker for evaluating the efficacy of bariatric surgery.

Due to its predictive power, SII is considered to have great potential. We selected a representative sample size and we eliminated some confounding variables in the study to obtain more reliable results. However, there are still many variables that we cannot exclude one by one, making it impossible for us to determine the causality of the research.

Conclusions

In conclusion, this study confirmed that there is a correlation between SII and hepatic steatosis and that bariatric surgery can effectively reduce SII, but larger studies are needed to confirm the further relationship between high levels of SII and hepatic steatosis.

Authors' Contributions

Hongjuan Xia and Jian He conceived the structure of the manuscript. Dewen Zhang did the experiments and made the figures. Xian Ding reviewed and edited the manuscript. All authors read and approved the final manuscript.

Funding

None.

Availability of Data and Materials

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

Conflict of Interest

The authors declare that they have no competing interests.

ORCID ID

Xian Ding: 0000-0002-9540-6753

Informed Consent

The data was from a public dataset; therefore, the informed consent of patients was not applicable.

Ethics Approval

The data was from a public dataset; therefore, the ethics approval was not applicable.

References

1) Larussa T, Abenavoli L, Procopio AC, Iannelli C, Polimeni N, Spagnuolo R, Doldo P, Luzza F. The role of gluten-free diet in nonalcoholic fatty liver disease development. Eur Rev Med Pharmacol Sci 2021; 25: 6613-6618.
2) Guo W, Cai S, Zhang F, Shao F, Zhang G, Zhou Y, Zhao L, Tan F, Gao S, He J. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected non-small cell lung cancer. Thorac Cancer 2019; 10: 761-768.
3) Peksen C, Aktokmakyan TV, Savas OA, Ediz B, Sumer A. Comparison of laparoscopic evaluation of hepatosteatosis with ultrasound findings. Eur Rev Med Pharmacol Sci 2023; 27: 9067-9075.
4) Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, Colombo M, Craxi A, Crespo J, Day CP, Eguchi Y, Geier A, Kondili LA, Kroy DC, Lazarus JV, Loomba R, Manns MP, Marchesini G, Nakajima A, Negro F, Petta S, Ratziu V, Romero-Gomez M, Sanyal A, Schattenberg JM, Tacke F, Tanaka J, Trautwein C, Wei L, Zeuzem S, Razavi H. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol 2018; 69: 896-904.
5) Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the Global Burden of Chronic Liver Diseases From 2012 to 2017: The Growing Impact of NAFLD. Hepatology 2020; 72: 1605-1616.
6) Shao YL, Fan JG. [Prevalence and harm of non-alcoholic fatty liver disease]. Zhonghua Gan Zang Bing Za Zhi 2019; 27: 10-13.
7) Zhao ZH, Liu XL, Fan JG. [Research on the natural history of non-alcoholic fatty liver disease should be taken seriously]. Zhonghua Gan Zang Bing Za Zhi 2017; 25: 81-84.
8) Hong YM, Yoon KT, Cho M. Systemic immune-inflammation index predicts prognosis of sequential

therapy with sorafenib and regorafenib in hepatocellular carcinoma. BMC Cancer 2021; 21: 569.

9) Fu H, Zheng J, Cai J, Zeng K, Yao J, Chen L, Li H, Zhang J, Zhang Y, Zhao H, Yang Y. Systemic Immune-Inflammation Index (SII) is Useful to Predict Survival Outcomes in Patients After Liver Transplantation for Hepatocellular Carcinoma within Hangzhou Criteria. Cell Physiol Biochem 2018; 47: 293-301.
10) Ren A, Li Z, Cheng P, Zhang X, Deng R, Ma Y. Systemic Immune-Inflammation Index Is a Prognostic Predictor in Patients with Intrahepatic Cholangiocarcinoma Undergoing Liver Transplantation. Mediators Inflamm 2021; 2021: 6656996.
11) Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, Zhang X, Wang WM, Qiu SJ, Zhou J, Fan J. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014; 20: 6212-6222.
12) Qin Z, Li H, Wang L, Geng J, Yang Q, Su B, Liao R. Systemic Immune-Inflammation Index Is Associated With Increased Urinary Albumin Excretion: A Population-Based Study. Front Immunol 2022; 13: 863640.
13) Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, Kim YJ, Yoon JH, Cho SH, Sung MW, Lee HS. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010; 42: 503-508.
14) Shih KL, Su WW, Chang CC, Kor CT, Chou CT, Chen TY, Wu HM. Comparisons of parallel potential biomarkers of 1H-MRS-measured hepatic lipid content in patients with non-alcoholic fatty liver disease. Sci Rep 2016; 6: 24031.
15) Song Y, Guo W, Liu S, Li Z, Guo D, Li Y. Individuals Undergoing Bariatric Surgery Ameliorate Hepatic Steatosis: Evidence from NHANES 2015-2018. Obes Surg 2022; 32: 3811-3814.
16) Song Y, Ni Z, Li Y, Li Z, Zhang J, Guo D, Yuan C, Zhang Z, Li Y. Exploring the landscape, hot topics, and trends of bariatric metabolic surgery with machine learning and bibliometric analysis. Ther Adv Gastrointest Endosc 2022; 15: 26317745221111944.
17) Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, Zheng MH, Shiha G, Yilmaz Y, Gani R, Alam S, Dan YY, Kao JH, Hamid S, Cua IH, Chan WK, Payawal D, Tan SS, Tanwandee T, Adams LA, Kumar M, Omata M, George J. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020; 14: 889-919.
18) Zhang J, Lin S, Jiang D, Li M, Chen Y, Li J, Fan J. Chronic hepatitis B and non-alcoholic fatty liver disease: Conspirators or competitors. Liver Int 2020; 40: 496-508.
19) Zhang Z, Chen Z. Higher Systemic Immune-Inflammation Index is Associated With Higher Likelihood of Peripheral Arterial Disease. Ann Vasc Surg 2022; 84: 322-326.
20) Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar S, Jia J, Tian Q, Aggarwal R, Muljono DH, Omata M, Ooka Y, Han KH, Lee HW, Jafri W, Butt AS, Chong CH, Lim SG, Pwu RF, Chen DS. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 2020; 5: 167-228.
21) Eslam M, Sanyal AJ, George J. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020; 158: 1999-2014.e1.
22) Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol 2017; 67: 862-873.
23) Zhang X, Wong GL, Wong VW. Application of transient elastography in nonalcoholic fatty liver disease. Clin Mol Hepatol 2020; 26: 128-141.
24) Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, Racila A, Hunt S, Beckerman R. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016; 64: 1577-1586.
25) Roderburg C, Krieg S, Krieg A, Demir M, Luedde T, Kostev K, Loosen SH. Non-alcoholic fatty liver disease (NAFLD) is associated with an increased incidence of chronic kidney disease (CKD). Eur J Med Res 2023; 28: 153.
26) Méndez-Sánchez N, Valencia-Rodríguez A. Caveats for the implementation of global strategies against non-alcoholic fatty liver disease. J Hepatol 2020; 73: 220.
27) Önnerhag K, Dreja K, Nilsson PM, Lindgren S. Increased mortality in non-alcoholic fatty liver disease with chronic kidney disease is explained by metabolic comorbidities. Clin Res Hepatol Gastroenterol 2019; 43: 542-550.
28) Espina S, Casas-Deza D, Bernal-Monterde V, Domper-Arnal MJ, García-Mateo S, Lué A. Evaluation and Management of Nutritional Consequences of Chronic Liver Diseases. Nutrients 2023; 15: 3487.
29) Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, Friedman SL, Diago M, Romero-Gomez M. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology 2015; 149: 367-378.e5; quiz e14-15.
30) Lassailly G, Caiazzo R, Ntandja-Wandji LC, Gnemmi V, Baud G, Verkindt H, Ningarhari M, Louvet A, Leteurtre E, Raverdy V, Dharancy S, Pattou F, Mathurin P. Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. Gastroenterology 2020; 159: 1290-1301.e5.