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Original Article

Systemic immune-inflammation index as a prognostic marker for chronic Hepatitis B with non-alcoholic fatty liver disease.

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Abstract

Introduction: This study investigates the association between high-level systemic immune-inflammatory index (SII) and cirrhosis progression in patients with chronic hepatitis B (CHB) and non-alcoholic fatty liver disease (NAFLD).

Methodology: A total of 272 CHB patients with NAFLD treated at Jincheng General Hospital between January 2018 and January 2023 were included. The study endpoint was the development of cirrhosis. The optimal SII cut-off value for predicting cirrhosis progression was determined as 1024 using ROC curve analysis and Youden index. Based on this cut-off, patients were classified into low SII (n = 159) and high SII (n = 113) groups. Univariate and multivariate Cox regression analyses were performed to identify independent predictors of cirrhosis progression and assess the relationship with SII.

Results: Univariate Cox analysis revealed that SII was a significant risk factor for cirrhosis progression in CHB with NAFLD (HR = 2.062, 95% CI: 1.717-3.941, $p < 0.001$). Multivariate Cox regression analysis demonstrated a significant association between elevated SII levels and increased incidence of cirrhosis, with patients in the high SII group having an 88.5% higher risk (HR = 1.885, 95% CI: 1.167-3.045, $p = 0.010$). Kaplan-Meier survival analysis further confirmed the higher risk of cirrhosis in patients with high SII levels (log-rank $p < 0.001$) within 60 months.

Conclusions: This study suggests that SII is a relevant risk factor for cirrhosis development in CHB individuals with NAFLD, emphasizing the importance of considering SII in current clinical management.

Key words: Chronic viral hepatitis B; non-alcoholic fatty liver disease; systemic immune-inflammatory index; cirrhosis.

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Introduction

The global burden of chronic hepatitis B (CHB) is substantial, with an estimated 350-400 million people worldwide grappling with this persistent public health challenge [1]. Individuals with hepatitis B are at risk of developing severe liver-related complications, including cirrhosis, hepatocellular carcinoma (HCC), and even mortality, resulting in approximately 0.5-1.2 million deaths annually [2]. Concurrently, there has been a surge in the occurrence of non-alcoholic fatty liver disease (NAFLD) among individuals with CHB, attributed to changes in lifestyle, enhanced living standards, and the escalating prevalence of obesity and metabolic syndrome (MetS) worldwide [3]. NAFLD manifests as a range of liver impairments, including simple steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. It has now become one of the most prevalent chronic liver diseases globally, with a prevalence rate of 25.24% [4]. Approximately 25-30% of patients with CHB demonstrate hepatic steatosis [5]. Studies have established a correlation between NAFLD and CHB, suggesting that hepatic steatosis may confer protection against CHB by reducing HBV viral markers. However, CHB individuals with coexisting NAFLD face an escalated risk of developing advanced liver disease [6].

In CHB, the immune system detects and responds to HBV infection by activating immune cell responses and signaling pathways, which stimulate the production of pro-inflammatory cytokines, chemokines, interferons, and autoantibodies. These immune responses aim to defend against HBV infection by eliminating virus-infected cells. However, this immune activation also triggers liver inflammation and exacerbates liver damage. The persistent inflammation eventually leads to liver fibrosis, as continuous viral exposure induces the secretion of numerous pro-inflammatory and fibrotic factors [7]. Moreover, it is important to note that in NAFLD, hepatocellular metabolic dysfunction and injury are further aggravated

by lipid deposition. This lipid buildup in the liver initiates inflammatory pathways, triggers the generation of reactive oxygen species, leads to mitochondrial dysfunction, and induces endoplasmic reticulum stress [8]. In summary, the immune response is believed to have a crucial role in the unfavorable prognosis of NAFLD individuals with CHB. Histological examination through liver biopsy is the benchmark for diagnosis and evaluation of inflammatory severity in hepatic conditions. However, it is a surgical intervention that carries a risk of complications. Therefore, the utilization of biomarkers that accurately reflect the immune response would offer significant advantages for clinical management purposes.

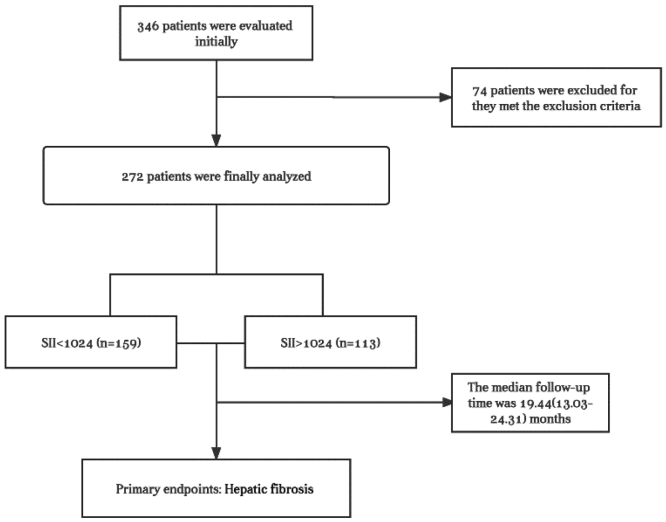
The systemic immune-inflammation index (SII) provides a more comprehensive assessment of the inflammatory and immune homeostasis within the organism. The index is a multifaceted measure of inflammation, combining the levels of neutrophils, lymphocytes, and platelets. Therefore, SII can be considered a biomarker for evaluating the inflammatory and immune status of the organism [9,10]. However, there have been limited studies exploring the impact of SII on the prognosis of patients with CHB and NAFLD. Therefore, this study examines the relationship between SII and cirrhosis, as well as the individual risk factors for cirrhosis in patients with CHB and NAFLD. The aim is to provide valuable insights as a reference for the prevention and treatment of CHB and NAFLD.

Methodology

Data sources

This study conducted a retrospective selection of patients with CHB combined with NAFLD who were treated at the Department of Infectious Diseases of Jincheng General Hospital between January 2018 and January 2023.

Figure 1. Flow chart of patient inclusion.



Inclusion criteria: (1) Individuals 18 years of age or older; (2) patients diagnosed with CHB combined with NAFLD; (3) persistence of serum HBsAg for a duration of six months or more.

Exclusion criteria: (1) acute hepatitis B; (2) drug-induced hepatitis, autoimmune hepatitis, or other types of hepatitis besides hepatitis B; (3) malignant tumors, including hepatocellular carcinoma (HCC); (4) alcoholic fatty liver; (5) patients with significant organ damage from other diseases; (6) incomplete clinical case information.

This research was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. The Jincheng General Hospital's Medical Ethics Committee granted ethical clearance for this study, and the requirement for informed consent was exempted due to the use of anonymized retrospective information (ethics approval code: 2023072501).

In accordance with the aforementioned criteria, a total of 272 patients were enrolled, as illustrated in Figure 1. General and laboratory data were collected for these patients, including (1) General information such as age, gender, and past medical history, and (2) laboratory data comprising HBV-DNA level, hepatitis B e antigen (HBeAg), blood routine, and blood biochemistry indexes, such as white blood cell count (WBC), platelet count, lymphocyte count (Lymph), neutrophil count (NEUT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs), etc.

Diagnostic criteria and definitions

We defined patients with CHB combined with NAFLD as individuals who were newly diagnosed with NAFLD or had pre-existing NAFLD during the follow-up period. The diagnostic criteria for NAFLD were based on the 2018 Guidelines for the Management of Non-Alcoholic Fatty Liver Disease [11]. These criteria involved the confirmation of diffuse hepatic steatosis through imaging or histological evidence, while excluding other potential causes of hepatic steatosis such as alcohol abuse, HCV infection, autoimmune hepatitis, Wilson's disease, drug-induced hepatitis, among others. CHB was identified by a sustained detection of serum hepatitis B virus surface antigen (HBsAg) lasting longer than six months.

The imaging diagnosis of hepatic steatosis includes the following criteria: (1) ultrasound-based: the liver parenchyma shows diffuse enhancement of near-field

echoes, gradual attenuation of far-field echoes, and reduced definition of liver structures such as blood vessel walls; (2) CT-based: the ratio of CT values between the liver and spleen is ≤ 1.0; and (3) MR-based: the proton density fat fraction is ≥ 5%.

BMI is calculated using height and weight. Overweight is defined as a BMI ≥ 23 kg/m^2 [12], based on the standard for Asian populations.

Endpoint events

The endpoint event in this study was defined as the progression to cirrhosis. The diagnosis of cirrhosis was based on the 2019 Chinese guidelines for the diagnosis and treatment of cirrhosis [13].

Follow-up visits

The primary methods of follow-up in this study included the extraction of case system records, outpatient follow-up, and telephone follow-up. The final follow-up date for the study was July 2023. Among 272 eligible patients, the median follow-up duration was 20.21 (13.17-25.95) months.

SII formula

The following formula was used: SII = platelets × (neutrophils/lymphocytes).

Statistical Analysis

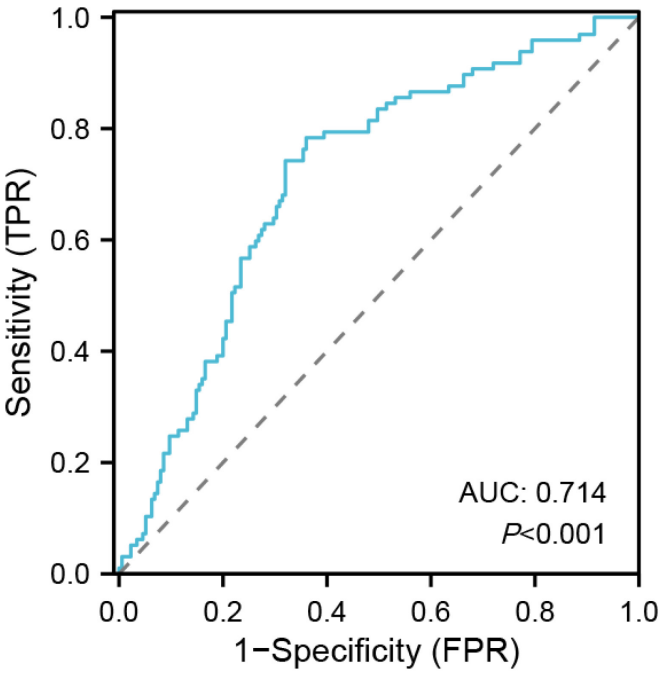
Data analysis was conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The liver cirrhosis endpoint events were used as the state variable to construct the ROC curve. The corresponding Youden index was calculated to ascertain the critical value for the endpoint event, facilitating the classification of patients into categories with either a high or low SII. The optimal cutoff value for the occurrence of liver cirrhosis events, determined by the endpoint occurrence variable, was found to be 1024 (AUC = 0.740, $p < 0.001$). Patient data was gathered and summarized, presenting continuous variables as mean ± SD or as medians with interquartile ranges, as appropriate. Continuous variables adhering to normality and equal variance were analyzed with the t-test, while the Mann-Whitney U test was applied when these conditions were not met. Categorical data were expressed as frequencies (percentages) and examined using chi-square or Fisher's exact test, according to the situation. To assess the cumulative incidence of long-term clinical outcomes, Kaplan-Meier analysis was conducted, with the log-rank test comparing outcomes across different groups. Kaplan-Meier curves graphically illustrated the association between the SII and the incidence of liver cirrhosis. A multivariate Cox proportional hazards model was developed to evaluate the endpoint events, with covariates initially chosen based on univariate analysis findings. Factors that were statistically significant in the univariate analysis were incorporated into the multivariate model. The backward stepwise approach was utilized to pinpoint independent predictors of CHB in conjunction with NAFLD. Statistical significance was determined at a p value threshold of less than 0.05. To visually convey the relationship between SII, incident liver cirrhosis, and various independent factors identified in the Cox model, forest plots were created using GraphPad Prism 8.

Results

Baseline characteristics

The study incorporated 272 patients who satisfied the established inclusion and exclusion guidelines and had follow-up data on record. Patients were stratified into low and high SII groups based on the threshold values obtained from the ROC curves and the Youden index, as illustrated in Figure 2. Table 1 presents the distribution of patients in each group. Regarding the endpoint of cirrhosis development, patients were divided into two groups: those with a low SII (SII < 1024, n = 159) and those with a high SII (SII ≥ 1024, n = 113). Statistical analysis revealed notable differences between the two groups in age, WBC, neutrophil count,

Figure 2. ROC curves of SII predicting the incidence of cirrhosis events in patients with CHB and NAFLD.



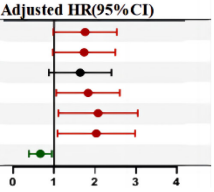
lymphocyte count, albumin levels, and the use of interferon for antiviral treatment ($p < 0.05$). However, no notable correlation was found between levels of alanine ALT, AST, the presence of hypertension, and triglyceride and cholesterol levels, with the advancement of NAFLD in patients with CHB to cirrhosis ($p \geq 0.05$).

Relationship between SII and cirrhosis of the liver

Univariate Cox regression analysis was conducted to analyze the occurrence of cirrhosis as the outcome variable (Table 2). Findings identified multiple risk factors significantly linked to the onset of cirrhosis in patients with concurrent CHB and NAFLD ($p < 0.05$). The identified risk factors for progression to cirrhosis in patients with concurrent CHB and NAFLD included being over 60 years of age, a history of diabetes, elevated WBC, increased neutrophils, high levels of alkaline phosphatase, elevated HBV-DNA, increased SII, decreased prothrombin activity, prolonged INR, extended thrombin time, BMI, and the use of interferon therapy. On the other hand, a higher lymphocyte count and the administration of NAs were associated with a protective effect. The study, however, did not establish a significant association between ALT or AST levels, the presence of hypertension, and the levels of triglycerides and cholesterol with the progression to cirrhosis in patients affected by both CHB and NAFLD.

Figure 3. Results of multivariate Cox regression analysis for cirrhosis.

Variables	Multivariate analysis		
	Adjusted *P*-value	Adjusted HR(95%CI)	Adjusted HR(95%CI)
Age	0.031	1.644(1.045-2.584)	
WBC	0.036	1.621(1.032-2.549)	
Lym	0.087	1.520(0.940-2.457)	
BMI	0.016	1.794(1.075-2.695)	
PTA	0.007	1.926(1.192-3.110)	
SII	0.01	1.885(1.167-3.045)	
NAs	0.032	0.628(0.411-0.960)	



Variables that were significant in the univariate Cox regression model were subsequently included in the multivariate analysis shown in Figure 3, employing a backward stepwise regression technique. This analysis pinpointed independent prognostic factors for cirrhosis progression in CHB patients with NAFLD ($p < 0.05$), encompassing factors such as being over 60 years old,

Table 1. Clinical and laboratory characteristics according to the SII (cirrhosis).

Characteristics	SII < 1024 (n = 159)	SII > 1024 (n = 113)	*p*
Demographics			
Age (years)	39 (28-49)	48 (39-55)	0.017
Gender, n (%)			
Males	118 (74.2)	85 (75.2)	0.851
Females	41 (25.8)	28 (24.8)	
BMI	25.34 (23.23-28.26)	26.45 (22.78-28.29)	0.828
Comorbidities, n (%)			
Coronary heart disease	49 (30.8)	36 (31.9)	0.855
Hypertensive	95 (59.7)	69 (61.1)	0.827
Diabetes	43 (27.0)	36 (31.9)	0.389
Cerebrovascular disease	22 (13.8)	21 (18.6)	0.290
Laboratory parameters			
WBC, 10^9 /L	5.85 (4.37-7.26)	5.24 (4.01-6.21)	0.024
RBC, 10^{12} /L	4.97 (4.81-5.41)	4.92 (4.42-5.39)	0.072
HB, g/L	158 (152-168)	153 (139-166)	0.105
PLT, 10^9 /L	189 (143-237)	177 (143-215)	0.556
Neut, 10^9 /L	3.30 (2.58-5.15)	7.08 (5.49-9.57)	0.001
Lymph, 10^9 /L	2.14 (1.66-2.61)	1.64 (1.22-1.96)	0.001
TC (mmol/L)	4.08 (3.37-4.56)	3.79 (3.34-4.42)	0.594
TG (mmol/L)	1.53 (1.23-2.14)	1.42 (0.97-1.93)	0.414
HDL-C (mmol/L)	0.97 (0.78-1.17)	0.90 (0.735-1.22)	0.462
LDL-C (mmol/L)	2.15 (1.70-2.88)	2.19 (1.64-2.81)	0.885
ALB (g/dL)	47.9 (44.6-50.5)	44.8 (40.2-48.5)	0.013
LDH (U/L)	181.00 (164.50-210.00)	179.00 (151.15-204.50)	0.329
ALP (U/L)	81.00 (73.50-91.50)	95.00 (70.00-134.75)	0.185
GGT (U/L)	52.00 (28.50-89.00)	54.50 (35.70-98.00)	0.629
AST (U/L)	32.00 (22.00-55.00)	33.50 (22.00-69.00)	0.583
ALT (U/L)	40.00 (27.00-80.00)	38.00 (27.40-90.00)	0.730
HBeAg (positive),([%])	61 (38.4)	38 (33.6)	0.424
HBV DNA (log10 IU/mL)	2.75 (2.70-4.12)	2.87 (2.72-4.83)	0.719
Drug use, n (%)			
NAs	33 (20.8)	34 (30.1)	0.07
Interferon	21 (13.2)	37 (32.7)	0.001

BMI: body mass index; WBC: white blood cell; RBC: red blood cell; HB: hemoglobin; PLT: platelet; NEUT: neutrophil count; Lymph: lymphocyte count; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ALB: serum albumin; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Nas: nucleotide analogues).

WBC, BMI, PTA, and SII. Notably, age over 60, white blood cell count, BMI, PTA, and SII emerged as independent predictors of cirrhosis risk, whereas the employment of NAs appeared protective. Lymphocyte count, however, did not exhibit a significant association with cirrhosis progression in the multivariate analysis ($p \geq 0.05$). Additionally, the analysis identified that a high SII level (SII ≥ 1024) corresponded with an 88.5% heightened risk of cirrhosis development in these patients (HR = 1.885, 95% CI: 1.167-3.045, $p = 0.010$) during the observation period.

Kaplan-Meier survival analysis

Outcomes from the Kaplan-Meier survival analysis, presented in Figure 4, indicate a statistically significant distinction between the high and low SII groups (log-rank $p < 0.001$). There was a considerably increased occurrence of cirrhosis advancement within the high SII group relative to the low SII group.

Discussion

This research assessed the potential of the SII as an independent prognostic marker for cirrhosis in subjects with CHB and NAFLD. Patients with elevated SII demonstrated an 88.5% surge in the likelihood of

Figure 4. Cumulative Kaplan–Meier estimates of the time to the first adjudicated occurrence of cirrhosis.

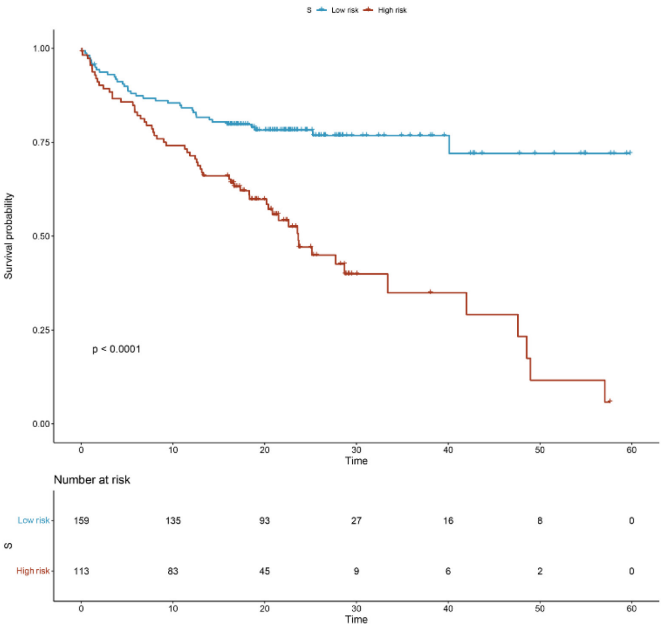


Table 2. Results of univariate COX regression analysis of cirrhosis.

Variables	*β*	*SE*	*Waldχ2*	Crude HR (95% CI)	Crude *p* value
Age	0.413	0.215	3.703	1.512 (0.102-2.303)	0.049
Gender	-0.044	0.241	0.034	0.616 (0.450-0.844)	0.853
Hypertensive	0.121	0.229	0.279	1.129 (0.720-1.768)	0.597
Diabetes	0.652	0.23	8.02	1.920 (1.222-3.014)	0.005
Cerebrovascular disease	0.461	0.335	1.896	1.585 (0.823-3.055)	0.169
WBC	0.814	0.21	15.024	2.256 (1.495-3.405)	0.001
RBC	-0.251	0.232	1.17	0.778 (0.493-1.226)	0.279
HB	0.349	0.232	2.263	1.418 (0.900-2.234)	0.133
PLT	0.415	0.353	1.386	1.514 (0.759-3.022)	0.239
Neut	0.718	0.208	11.937	2.050 (1.364-3.081)	0.001
Lymph	-0.689	0.213	10.515	0.502 (0.331-0.761)	0.001
TC	0.064	0.336	0.037	1.066 (0.5552-2.058)	0.848
TG	0.116	0.216	0.286	1.123 (0.735-1.716)	0.593
LDH (U/L)	0.18	0.223	0.654	1.198 (0.774-1.854)	0.419
ALP (U/L)	0.893	0.305	8.602	2.443 (1.345-4.437)	0.003
GGT (U/L)	0.303	0.224	1.841	1.354 (0.874-2.099)	0.175
AST (U/L)	0.036	0.206	0.031	0.859 (0.693-1.553)	0.859
ALT (U/L)	0.204	0.221	0.858	1.227 (0.796-1.891)	0.354
HBV DNA (log10 IU/mL)	0.565	0.238	5.657	1.759 (1.105-2.803)	0.017
SII	0.956	0.212	20.363	2.602 (1.717-3.941)	0.001
TT	0.733	0.265	7.631	2.081 (1.237-3.501)	0.006
PTA	0.656	0.237	7.668	1.927 (1.211-3.066)	0.006
INR	0.732	0.226	10.47	2.078 (1.334-3.237)	0.001
APTT	0.198	0.222	0.798	1.219 (0.789-1.882)	0.372
FIB	0.298	0.461	0.418	1.348 (0.546-3.329)	0.518
PT	1.237	1.006	1.513	3.446 (0.480-24.735)	0.219
BMI	0.482	0.224	4.647	1.619 (1.045-2.510)	0.031
NAs	-0.548	0.215	6.511	0.578 (0.379-0.81)	0.011
Interferon	0.834	0.213	15.356	2.303 (1.517-3.495)	$p < 0.001$

WBC: white blood cell; RBC: red blood cell; HB: hemoglobin; PLT: platelet; NEUT: neutrophil count; Lymph: lymphocyte count; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ALB: serum albumin; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; SII: systemic immune-inflammatory index; TT: thrombin time; PTA: prothrombin activity; INR: international normalized ratio; APTT: activated partial thromboplastin time; FIB: fibrinogen; PT: prothrombin time; BMI: body mass index; NAs: nucleotide analogues).

developing cirrhosis (HR = 1.885, 95% CI: 1.167-3.045, $p = 0.010$). This investigation is at the forefront of exploring the relationship between SII levels and the outcomes of CHB patients with NAFLD.

Factors influencing the progression of CHB with NAFLD to cirrhosis

NAFLD is widely acknowledged as the hepatic manifestation of MetS, which is characterized by the abnormal accumulation of fat in the liver due to excessive fat intake and synthesis. Obesity, being a significant component of MetS, is also recognized as a major factor contributing to the development of NAFLD. Abdominal obesity affects the transport of free fatty acids between the periphery and the liver, disrupting their breakdown and metabolism, thereby leading to the occurrence of fatty liver [14]. Co-infection with HBV stimulates immune mechanisms, resulting in heightened liver damage and activation of hepatic stellate cells. This activation, coupled with the deposition of collagen, sets off a series of events that ultimately leads to the progression of liver fibrosis. Within our study, we identified obesity as a significant independent risk factor for the development of liver cirrhosis in individuals with both CHB and NAFLD. Additionally, a cohort study conducted in a prospective manner in Korea demonstrated a positive correlation between weight gain in NAFLD patients and the risk of fibrosis progression [15]. Therefore, it is crucial for patients with CHB and NAFLD to actively take measures to maintain a healthy weight level in order to reduce the risk of liver cirrhosis.

Hepatic steatosis is more prevalent in elderly individuals compared to younger people. This can be attributed to increased intake of free fatty acids (FFAs) and impaired beta-oxidation capacity of fatty acids in the elderly [16]. Additionally, the aging process leads to insulin resistance and ectopic lipid deposition, contributing to the secretion of pro-inflammatory cytokines and the establishment of a state of systemic low-grade chronic inflammation. In the context of chronic HBV infection, aging individuals experience a diminished capacity to effectively clear senescent cells due to weakened surveillance mechanisms [17]. Consequently, chronic inflammatory reactions occur, further promoting disease progression. Within our study, we found that an age of ≥ 60 years was a significant independent risk factor for the progression to liver cirrhosis in individuals with chronic HBV infection and NAFLD. A large-scale cohort study demonstrated a significant increase in the risk of liver cirrhosis with advancing age among individuals with chronic HBV infection [18].

Our research indicates that NAs medications can slow the progression of liver cirrhosis in patients with both CHB and NAFLD, possibly due to their ability to effectively reduce HBV-DNA levels, inhibit virus replication and proliferation. Therefore, proactive antiviral therapy is crucial for maintaining low HBV-DNA levels in these patients, providing additional protective effects. Moreover, PTA serves as a critical indicator of liver coagulation function. Our findings identify PTA as a significant independent risk factor in patients with concurrent CHB and NAFLD. Consequently, it is recommended that PTA levels be routinely monitored in clinical practice, serving as a standard parameter for assessing liver function.

CHB and NAFLD synergize to cause liver disease progression

In our study, single-factor COX regression analysis indicated that HBV-DNA level and diabetes were found to be risk factors for cirrhosis in individuals with CHB and NAFLD. However, these two factors were not included in the multifactor COX regression model fitting, possibly due to confounding variables or multicollinearity. In the multivariate COX regression analysis, significant risk factors for cirrhosis in individuals with CHB and NAFLD were identified as age ≥ 60 years, WBC count, BMI, and SII, PTA, while the use of NAs was found to be a protective factor. This finding may be attributed to dysregulated nutrient metabolism and the impact of HBV infection. HBV infection might contribute to the progression of NAFLD towards severe hepatic steatosis by interfering with lipid biosynthesis. Hepatitis B protein X (HBx) has been demonstrated to induce the activation of PPARs and signaling pathways (PI3K/AKT, NF-κβ, SREBP), thereby impacting lipid metabolism homeostasis, liver lipogenesis, alterations in cholesterol metabolism, and liver steatosis [19–22]. However, in mice with NAFLD induced by HBV virus antigens (HBsAg and HBcAg), Miyake *et al*. observed that the saturated fatty acid palmitic acid could impair the function of hepatic dendritic cells (DC), leading to the failure to activate antigen-specific immune cells, hindering HBV clearance, and causing the progression of liver disease [23]. In summary, HBV infection may disrupt liver cholesterol metabolism, resulting in the progression of NAFLD towards more severe steatosis, while NAFLD may hinder HBV clearance within the body, thereby contributing to the progression of liver disease. Increased expression levels of long non-coding RNAs

(lncRNAs) have been detected in individuals with CHB and NASH [19,24]. Elevated levels of lncRNAs can exacerbate liver tissue damage by enhancing the hepatitis response [25].

During chronic HBV infection, immune cells in the liver are activated due to continuous viral exposure, leading to the secretion of a multitude of pro-inflammatory and pro-fibrotic factors. This process results in hepatic inflammation and fibrosis. NAFLD, which is primarily associated with obesity and metabolic disorders, serves as the main hepatic manifestation. In individuals with NAFLD, HBV infection exacerbates the severity of hepatic steatosis. This exacerbation leads to dysfunction in mitochondria and peroxisomes, oxidative stress, the production of harmful fatty acid metabolites, and the activation of inflammatory cytokines (IL-1, IL-11, TGF, TNF, CCL2, CCL11) [26,27]. The combined impact of metabolic factors and HBV infection contributes to progressive liver inflammation and fibrosis. Consequently, CHB and NAFLD act synergistically in driving the progression of liver disease.

SII response in CHB combined with NAFLD

SII, as a comprehensive novel biomarker of inflammation, has been shown to reflect local immune responses and systemic inflammation throughout the body, as reported by Hu *et al.* in their 2014 study [28]. Previous investigations have utilized SII to predict and assess the prognosis of various solid tumors, such as esophageal cancer [29], gastric cancer [30], osteosarcoma [31], and others. Recent studies have demonstrated the significant value of the SII in predicting the prognosis of cardiovascular diseases, chronic kidney diseases, and cerebrovascular diseases [32,33]. In patients with CHB coexisting with NAFLD, inflammation serves as an indicator of disease progression, with the recruitment of inflammatory cells and upregulation of inflammatory mediators playing crucial roles in fibrosis development. Compared to other markers, SII provides a more comprehensive assessment of inflammation and immune status. Recent research has demonstrated the predictive value of SII in patients with chronic liver diseases. Additionally, when combined with HBsAg testing, SII holds significant clinical significance in distinguishing HBeAg-negative chronic hepatitis from HBeAg-positive chronic hepatitis [34]. Similarly, SII exhibits a favorable predictive value in assessing the degree of hepatic steatosis and prognosis in patients with NAFLD [35]. However, at present, there is a paucity of research investigating the association between SII and the co-occurrence of CHB and NAFLD.

SII can reflect both inflammation and immunity in the body. Elevated SII levels, attributed to increased neutrophil and platelet counts, as well as decreased lymphocyte levels, typically indicate an augmented inflammatory response and a compromised immune response in the patient.

During systemic inflammation, there is a rise in circulating neutrophils and platelets, coupled with a decrease in lymphocyte count. The coexistence of NAFLD and HBV infection results in modifications of peripheral blood leukocytes, with notable accumulation of neutrophils in the liver, which is a hallmark of inflammation in different liver diseases. Neutrophil infiltration is frequently observed in patients with NAFLD or CHB, and these neutrophils play a detrimental role by fostering macrophage recruitment and releasing inflammatory mediators such as elastase and myeloperoxidase [36]. Studies have confirmed that activated hepatic stellate cells can prolong the survival of neutrophils and further enhance the ongoing inflammatory response by generating reactive oxygen species (ROS), thereby promoting liver fibrosis [37]. However, recent research has shown that neutrophils can, in turn, inhibit the activation of hepatic stellate cells and play a protective role in the progression of chronic liver inflammation towards fibrosis [38].

Studies have indicated that long-term chronic liver disease can lead to a decrease in lymphocyte synthesis and an increase in apoptosis. Through the measurement of cytotoxic T cell production and proliferation, Barber *et al.* discovered that although effector T cells were generated in early HBV-infected mice, they gradually lost their normal function [39]. Persistent elevation of antigen levels leads to T-cell exhaustion, impairing their potent effector and proliferative functions, thus rendering them unable to eliminate the virus. In prolonged infections, the inability to eradicate the virus is a consequence of T-cell exhaustion [40]. These findings, along with our study, suggest that SII may serve as a useful indicator of the prognosis for patients with NAFLD combined with CHB.

The crucial role of platelets in maintaining hemostasis and facilitating thrombosis is widely acknowledged. However, platelet activity can also be heightened in the presence of inflammation. Activated platelets release soluble mediators like TGF-β and TXA2, as well as microRNA-containing vesicles, which can provoke chronic inflammation and promote tissue fibrosis [41]. Similarly, the activation of platelet-derived growth factor (PDGF) can stimulate the

proliferation and differentiation of HSCs, the production and deposition of collagen mediated by HSCs, and the transformation of HSCs into myofibroblasts, all of which contribute to liver injury and fibrosis [42]. In an HBV transgenic mouse model, a study revealed that platelet activation played a role in the accumulation of specific CD8 T cells and non-specific inflammatory cells in the liver. The use of two specific platelet activation inhibitors (clopidogrel and aspirin) resulted in a reduction of inflammation and immune cell infiltration [43].

Recently, there has been growing recognition of the significant role that platelets play in the development and progression of liver disease. There is a notable increase in the inflammatory transcription of platelets in the peripheral blood of NAFLD patients compared to individuals without the condition [44]. However, it is worth noting that studies have consistently shown a correlation between advanced liver fibrosis and thrombocytopenia, where a platelet count below $15 \times 10^4/\mu L$ is associated with a poorer prognosis in NAFLD patients [45]. These findings contrast with the results of our study. Our study found that a higher SII was independently associated with an increased incidence of liver cirrhosis in individuals with coexisting NAFLD and CHB. These results suggest that the comprehensive index SII can indicate the balance between the immune and inflammatory responses in the body. SII has demonstrated good predictive ability in various studies and serves as a non-invasive, cost-effective, and convenient method. Therefore, SII holds excellent potential for clinical application in NAFLD with CHB.

However, it is essential to acknowledge the limitations of this study. Firstly, it was a retrospective study conducted with a relatively small sample size, which may have introduced bias and limited the generalizability of the findings. Further confirmation is required through larger sample sizes and multicenter studies in both basic and clinical research settings. Secondly, we did not utilize liver biopsy for the diagnosis of NAFLD and liver cirrhosis, and routine assessment of NAFLD activity score (NAS) was not feasible in our study. As a result, we were unable to identify patients with NASH within the NAFLD population. In our study cohort, non-invasive imaging examinations (including ultrasound, CT, and MRI) and laboratory tests were utilized for diagnosis. While liver biopsy serves as the gold standard for diagnosing these conditions, non-invasive diagnostic tools offer superior safety, better patient tolerance, greater acceptability, and the ability for repeat testing as needed. Furthermore, given our specific focus on patients with concurrent CHB and NAFLD, we did not conduct comparative studies involving individuals who solely had CHB or NAFLD. This is an area we intend to explore in future research.

Conclusions

In conclusion, our findings indicate that a high SII level serves as an independent risk indicator for cirrhosis in individuals with CHB and NAFLD. It is expected to function as an inflammatory marker for predicting a poor prognosis in this patient population and holds significant guiding implications for follow-up and treatment.

Author contributions

Bo Xue: Contributed to formal analysis, initial draft writing, editing, and data curation. Zeyu Wang: Provided writing review, editing assistance, formal analysis, and data curation. Jianguo Li: Responsible for writing review, methodology, and conceptualization.

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Conflict of interests

No conflict of interests is declared.

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