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Association of Complete Blood Count-Derived Inflammatory Indices with Necroinflammatory Activity and Fibrosis Stages in Biopsy-Proven Chronic Hepatitis B: A Retrospective Cross-Sectional Study

Biyopsiyle Doğrulanan Kronik Hepatit B'de Tam Kan Sayımından Elde Edilen Enflamatuvar İndekslerin Nekroenflamatuvar Aktivite ve Fibrozis Evresi ile İlişkisi: Retrospektif Kesitsel Bir Çalışma

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ABSTRACT

Background: The aim of this study is to evaluate the association between inflammatory indices calculated from complete blood count (CBC) results and necroinflammatory activity and fibrosis stages determined by liver biopsy in patients with chronic hepatitis B (CHB).

Materials and Methods: This retrospective study included 529 patients with biopsy-confirmed CHB. Fibrosis was staged with the Ishak system (F0-6); necroinflammatory activity was graded with the modified Histological Activity Index (mHAI, 0-18). Systemic immune-inflammation index (SII), systemic inflammation response index, aggregate index of systemic inflammation (AISI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio were calculated from the CBC results. For statistical analysis, patients were divided into two groups based on fibrosis stage: mild fibrosis (F0–2) and advanced fibrosis (F3–6), and based on necroinflammatory activity: low activity (mHAI <6) and high activity (mHAI ≥6). Statistical analyses included group comparisons, correlation and receiver operating characteristic analyses, and multivariate logistic regression.

Results: Advanced fibrosis and high necroinflammatory activity were present in 29.5% and 23.8% of patients, respectively. SII, AISI, NLR, and PLR were significantly lower in advanced fibrosis ($p < 0.050$ for all) and showed weak negative correlations $r = -0.090$ to -0.183, $p < 0.050$ for all). In multivariate models, logPLR, logSII, and logAISI remained independently associated with advanced fibrosis ($p < 0.001$, $p = 0.002$, and $p = 0.015$, respectively). However, the area under the curve (95% confidence interval) was 0.623 (0.570-0.676) for PLR, 0.601 (0.548-0.655) for SII, and 0.559 (0.505-0.612) for AISI, indicating a low degree of discriminatory performance. None of the indices calculated for high necroinflammatory activity showed statistically significant differences between groups, nor were any independently associated.

Conclusion: SII, AISI, and PLR are independently associated with advanced fibrosis in CHB. However, their low discriminatory power alone limits their clinical use. These indices should be considered complementary biological indicators rather than primary diagnostic tools for histological staging.

Keywords: Chronic hepatitis B, complete blood count, inflammation, liver biopsy, liver fibrosis, necroinflammatory activity

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ÖZ

Amaç: Bu çalışmanın amacı, kronik hepatit B (KHB) hastalarında tam kan sayımı (TKS) sonuçlarından hesaplanarak elde edilen inflamatuar indeksler ile karaciğer biyopsisi ile belirlenen nekroenflamatuvar aktivite ve fibrozis evreleri arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, biyopsi ile doğrulanmış KHB'li 529 hasta dahil edildi. Fibrozis, Ishak sistemi (F0-6) ile; nekroenflamatuvar aktivite ise modifiye Histolojik Aktivite İndeksi (mHAI, 0-18) ile derecelendirildi. TKS sonuçlarından, sistemik immün-enflamasyon indeksi (SII), sistemik inflamasyon yanıt indeksi, sistemik inflamasyonun agrege indeksi (AISI), nötrofil-lenfosit oranı (NLO), trombosit-lenfosit oranı (TLO) ve lenfosit-monosit oranı hesaplandı. İstatistiksel analiz için hastalar fibrozis evresine göre hafif fibrozis (F0–2) vs. ileri fibrozis (F3–6) olarak, nekroenflamatuvar aktiviteye göre ise düşük aktivite (mHAI <6) vs. yüksek aktivite (mHAI $\geq$ 6) olarak iki gruba ayrıldı. İstatistiksel analizler; grup karşılaştırmalarını, korelasyon analizini, ROC analizini ve çok değişkenli lojistik regresyonu içermektedir.

Bulgular: İleri fibrozis ve yüksek nekroenflamatuvar aktivite, sırasıyla hastaların %29,5 ve %23,8'inde mevcuttu. SII, AISI, NLO ve TLO, ileri fibroziste anlamlı derecede daha düşüktü (tümü için p<0,050) ve zayıf negatif korelasyonlar gösterdi r = -0,090 ile -0,183 arası tümü için p < 0,050). Çok değişkenli modellerde log TLO, log SII ve log AISI, ileri fibrozis ile bağımsız olarak ilişkili kalmaya devam etti (sırasıyla p < 0,001, p = 0,002 ve p = 0,015). Ancak TLO için AUC (%95 güven aralığı) 0,623 (0,570-0,676), SII için 0,601 (0,548-0,655) ve AISI için 0,559 (0,505-0,612) olup, düşük ayırt edici performans gösterdi. Yüksek nekroenflamatuvar aktivite ile hesaplanan indekslerin hiçbiri, gruplar arasında istatistiksel olarak anlamlı farklılık göstermedi veya bağımsız olarak ilişkili bulunmadı.

Sonuç: SII, AISI ve TLO, KHB'de ileri fibrozis ile bağımsız ilişkiler göstermektedir. Bununla birlikte, düşük derecede ayırt edici güçleri tek başlarına klinik kullanımlarını sınırlamaktadır. Bu indeksler, histolojik evreleme için birincil tanı araçları yerine tamamlayıcı biyolojik göstergeler olarak değerlendirilmelidir.

Anahtar Kelimeler: Kronik hepatit B, tam kan sayımı, inflamasyon, karaciğer biyopsisi, karaciğer fibrozisi, nekroenflamatuvar aktivite

Introduction

Chronic hepatitis B (CHB) remains a major global health problem, affecting approximately 296 million people worldwide and leading to significant morbidity and mortality due to cirrhosis and hepatocellular carcinoma (1). The progression of CHB is determined by two key histological components: the extent of liver fibrosis and the degree of necroinflammatory activity. While fibrosis reflects cumulative structural damage and is a major predictor of long-term outcomes and treatment decisions, necroinflammatory activity represents ongoing immune-mediated hepatocellular injury and current disease activity (2). Liver biopsy remains the gold standard for assessing fibrosis severity and necroinflammatory activity. However, its invasive nature, sampling variability, and limited feasibility for repeated assessments have prompted the search for reliable non-invasive biomarkers in patients with CHB (3).

In recent years, inflammatory indices derived from routine complete blood count (CBC) parameters have attracted significant interest as potential non-invasive biomarkers in chronic diseases (4,5). Composite indices reflecting the balance between different immune cell populations, such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI), are readily obtainable and inexpensive (3,4,6). CHB is characterized by complex immunological and metabolic changes that develop throughout disease progression. While inflammation plays a central role in hepatic damage and fibrogenesis, advanced fibrosis and cirrhosis are often accompanied by hematological changes such as immune depletion, hypersplenism, thrombocytopenia and leukocyte changes (7). Consequently, inflammatory indices derived from CBC may also be non-invasive biomarkers for CHB.

While previous studies have examined some of these indices individually in CHB, most have relied on indirect or non-histological indicators of fibrosis, evaluated a limited number of indices, or failed to simultaneously assess their association with both fibrosis severity and necroinflammatory activity (3,6,8-12). Furthermore, the findings are heterogeneous, with some studies reporting strong positive associations (13,14), while others have identified inverse or null associations (6,8-12), underlining the need for a comprehensive, biopsy-based assessment in a well-defined CHB cohort.

This study aims to address this gap by simultaneously evaluating six CBC-derived inflammatory indices (NLR, PLR, lymphocyte-monocyte ratio LMR, SII, SIRI, and AISI) in a large cohort of 529 patients with biopsy-confirmed CHB, using histological fibrosis staging and necroinflammatory grading as reference outcomes, and by applying multivariate logistic regression to assess the independent association of each index.

Materials and Methods

Study Design and Population

This retrospective study was conducted at University of Health Sciences Türkiye, Ankara Training and Research Hospital and reported according to the STROBE checklist. Consecutive adult patients (≥18 years) who underwent percutaneous liver biopsy and were diagnosed with biopsy-confirmed CHB between January 1, 2014, and June 1, 2024, were screened for inclusion in the study. All patient data were obtained from the hospital information system, including the laboratory information system and electronic medical records.

CHB was defined as persistent hepatitis B surface antigen positivity for ≥6 months along with detectable serum hepatitis B virus (HBV) DNA, according to the European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines. In accordance with these criteria, HBV DNA positivity was confirmed at biopsy in all patients included in this study. Patients with other chronic liver diseases, viral co-infections (hepatitis D virus; hepatitis C virus; human immunodeficiency virus), a history of hepatocellular carcinoma or other malignancy, systemic inflammatory or autoimmune diseases, primary hematological disorders, or missing laboratory data necessary for index calculation were excluded from the study.

A total of 529 consecutive eligible patients were included in the study. Due to the retrospective design, no prior sample size calculation was performed. Potential sources of bias include the retrospective design and the single-center nature of the study.

This study was approved by the Institutional Ethics Committee of Ankara Training and Research Hospital (decision number: 532/2025, date: 18.06.2025). Due to the retrospective design of the study, the requirement for informed consent was waived by the Institutional Ethics Committee.

Histopathological Assessment

All liver biopsies were performed percutaneously using a 16G or 18G Tru-Cut needle under ultrasound guidance. Adequate samples were defined as those containing at least six complete portal tracts. Biopsy specimens were evaluated by an experienced pathologist who was blinded to the patients' laboratory and clinical data. Fibrosis was staged according to the Ishak scoring system (F; 0–6), and necroinflammatory activity was graded using the modified Histological Activity Index (mHAI; 0–18 points) (2).

For statistical analysis, patients were categorized as follows (2):

- Fibrosis stage: Low fibrosis (none or mild; F0–2) vs. high fibrosis (moderate to advanced; F3–6)
- Necroinflammatory activity: Low (mHAI <6) vs. high (mHAI ≥6)

Laboratory Data and Inflammatory Indices

Peripheral blood samples were taken 24 hours before or on the same day as the liver biopsy. CBC parameters, including hemoglobin (Hb), hematocrit, neutrophil, lymphocyte, monocyte, basophil, eosinophil, and platelet counts, and routine biochemical tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, direct bilirubin, alpha-fetoprotein (AFP), and international normalized ratio (INR) were recorded. Inflammatory indices (SII, SIRI, AISI, NLR, PLR, and LMR) were calculated using the formulas presented in Table 1.

CBC and biochemical analyses were performed using an automated hematology analyzer (Sysmex XN-10, Sysmex Corporation, Japan) and a standard automated chemistry analyzer (Cobas 8000, Roche Diagnostics, Germany), respectively.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 20.218 (MedCalc Software Ltd., Ostend, Belgium).

Data distributions were assessed using the Kolmogorov-Smirnov test, and skewness and excess kurtosis were calculated for each continuous variable. Continuous variables with a normal distribution were summarized as mean ± standard deviation, while continuous variables without a normal distribution were summarized as median (25^{th}-75^{th} percentile). Categorical variables were presented as frequencies and percentages. Group comparisons were performed using the independent samples t-test or Mann-Whitney U test, as appropriate. The Spearman rank correlation coefficient was used to evaluate the relationships between continuous variables and histological scores.

The discriminative performance of individual CBC-derived inflammatory indices was evaluated using receiver operating characteristic (ROC) curve analysis. ROC curves were constructed using the continuous values of each index as classifiers. For indices showing statistical significance ($p < 0.050$), the area under the curve (AUC), 95% confidence interval (CI), optimal cut-off values (Youden index), sensitivity, and specificity were reported.

Table 1. Formulas used to calculate inflammatory and fibrosis indices.

Name of the inflammatory indice	Formula
Systemic immune-inflammation index (SII)	SII = (P × N) / L
Systemic inflammation response index (SIRI)	SIRI = (N × M) / L
Aggregate index of systemic inflammation (AISI)	AISI = (P × N × M) / L
Neutrophil-to-lymphocyte ratio (NLR)	NLR = N / L
Platelet-to-lymphocyte ratio (PLR)	$\mathrm{PLR} = \frac{P}{L}$
Lymphocyte-to-monocyte ratio (LMR)	$\mathrm{LMR} = \frac{L}{M}$
AST-to-platelet ratio index (APRI)	$\mathrm{APRI} = (\frac{\mathrm{AST}}{\mathrm{AST_{ULN}}} \div P) \times 100$
Fibrosis-4 index (FIB-4)	$\text{FIB-4} = \frac{\mathrm{Age} \times \mathrm{AST}}{\mathrm{P} \times \sqrt{\mathrm{ALT}}}$

ALT, alanine aminotransferase; AST, aspartate aminotransferase; $\mathrm{AST_{ULN}}$, upper limit of normal for AST; L, lymphocyte count; M, monocyte count; N, neutrophil count; P, platelet count.

Univariate logistic regression analysis was performed to identify variables associated with advanced fibrosis and high necroinflammatory activity. For variables found to be statistically significant ($p < 0.050$) in the univariate analysis, a backward stepwise elimination procedure with an exclusion threshold of $p > 0.100$ was applied to obtain a reduced clinical model. Subsequently, CBC-derived inflammatory indices, APRI, and FIB-4 were added separately to the clinical model. Because these indices are calculated using formulas that share common parameters—both with the tests already included in the model and with one another—they were entered separately to avoid multicollinearity. In addition, multicollinearity among covariates was assessed using variance inflation factors (VIFs). Because AST and ALT were strongly collinear (VIF >10; Pearson r = 0.97), they were combined into the De Ritis ratio (AST/ALT) in the multivariate model for necroinflammatory activity. Logarithmic transformation was applied to the indices to reduce skewness and improve model stability. Odds ratios (ORs) with 95% CIs and p values are reported for all variables in each model. Variables with $p < 0.050$ are considered statistically significant.

Results

A total of 529 patients were included in the analysis. Of these, 156 (29.5%) had advanced fibrosis (F3–F6) and 126 (23.8%) had high necroinflammatory activity (mHAI ⩾6) (Table 2). Demographic, clinical, and laboratory characteristics stratified by fibrosis stage and necroinflammatory activity are presented in Table 2.

Patients with advanced fibrosis were older and demonstrated significant differences in lymphocyte, basophil, eosinophil, and platelet counts, Hb, AST, ALT, GGT, total and direct bilirubin levels, AFP, INR, APRI, and FIB-4 values. Among the inflammatory indices, SII, AISI, NLR, and PLR showed significant differences between the fibrosis groups. Similarly, patients with high necroinflammatory activity were older and showed significant differences in basophil and platelet counts, levels of AST, ALT, GGT, albumin, and total and direct bilirubin, and in AFP, INR, APRI, and FIB-4 values. However, most composite inflammatory indices did not show a significant difference between mHAI groups.

Fibrosis severity showed weak but statistically significant negative correlations with SII ($r = -0.151$, $p < 0.001$), PLR ($r = -0.183$, $p < 0.001$), NLR ($r = -0.097$, $p = 0.026$), and AISI ($r = -0.090$, $p = 0.039$). APRI ($r = 0.168$, $p < 0.001$) and FIB-4 ($r = 0.198$, $p < 0.001$) demonstrated positive correlations with fibrosis severity. In contrast, correlations between inflammatory indices derived from CBC and necroinflammatory activity were generally weak and non-significant, except for APRI ($r = 0.272$, $p < 0.001$) and FIB-4 ($r = 0.207$, $p < 0.001$), which showed significant positive correlations with mHAI score.

The discriminative performance of individual inflammatory indices derived from CBC with APRI and FIB-4 is presented in Table 3. For advanced fibrosis, PLR, SII, NLR, AISI, FIB-4 and APRI showed statistically significant discriminative ability; however, none reached the acceptable diagnostic accuracy threshold (AUC ⩾0.700) (15).

Table 2. Baseline demographic, clinical, and laboratory characteristics according to fibrosis stage and necroinflammatory activity.

	Fibrosis stage			Necroinflammatory activity		
	Low fibrosis (F0-F2)	High fibrosis (F3-F6)	p	Low mHAI (<6)	High mHAI (≥6)	p
n (%)	373 (70.5%)	156 (29.5 %)		403 (76.2%)	126 (23.8%)	
Age (year)	40.40 ± 12.31	44.04 ± 11.82	0.002	40.79 ± 12.01	43.66 ± 12.90	0.022
WBC (×10⁹/L)	6.96 ± 1.94	7.04 ± 1.74	0.662	6.94 ± 1.79	7.13 ± 2.14	0.308
Neutrophil (×10⁹/L)	4.03 (3.07-5.02)	3.88 (3.27-4.78)	0.513	3.96 (3.09-4.95)	3.89 (3.30-5.01)	0.815
Lymphocyte (×10⁹/L)	2.07 ± 0.64	2.21 ± 0.68	0.026	2.10 ± 0.62	2.13 ± 0.76	0.705
Monocyte (×10⁹/L)	0.49 (0.39-0.59)	0.49 (0.39-0.60)	0.141	0.49 (0.39-0.59)	0.49 (0.39-0.61)	0.269
Basophil (×10⁹/L)	0.01 (0.002-0.04)	0.02 (0.007-0.05)	0.002	0.01 (0.002-0.04)	0.02 (0.008-0.04)	0.019
Eosinophil (×10⁹/L)	0.10 (0.05-0.19)	0.10 (0.07-0.2)	0.017	0.10 (0.06-0.19)	0.10 (0.06-0.19)	0.200
Platelet (×10⁹/L)	234.0 (198.0-279.0)	213.5 (180.5-260.0)	0.002	234.0 (194.0-274.0)	214.0 (178.0-262.5)	0.013
RBC (×10¹²/L)	5.02 ± 0.54	5.08 ± 0.56	0.202	5.04 ± 0.55	5.04 ± 0.51	0.896
Hemoglobin (g/dL)	14.36 (13.19-15.61)	14.91 (13.78-15.81)	0.034	14.48 (13.28-15.66)	14.72 (13.58-15.72)	0.483
Hematocrit (%)	43.06 ± 4.78	43.90 ± 4.44	0.060	43.29 ± 4.64	43.36 ± 4.88	0.883
AST (U/L)	23.45 (19.10-30.50)	27.88 (21.37-41.33)	<0.001	23.45 (19.37-29.90)	30.75 (21.28-56.00)	<0.001
ALT (U/L)	24.77 (17.47-39.94)	31.12 (20.53-59.00)	<0.001	24.52 (17.59-36.12)	37.40 (21.33-76.66)	<0.001
GGT (U/L)	20.48 (15.10-29.50)	24.80 (16.18-41.66)	<0.001	20.48 (15.22-29.35)	25.50 (16.38-48.20)	<0.001
Albumin (g/L)	44.92 (42.63-46.96)	44.42 (42.09-46.99)	0.807	44.96 (42.80-47.05)	44.10 (41.91-46.02)	0.011
Total bilirubin (mg/dL)	0.57 (0.43-0.71)	0.64 (0.48-0.82)	0.005	0.57 (0.43-0.73)	0.65 (0.46-0.82)	0.017
Direct bilirubin (mg/dL)	0.13 (0.09-0.19)	0.16 (0.11-0.23)	<0.001	0.13 (0.09-0.19)	0.17 (0.12-0.23)	<0.001
AFP (µg/L)	2.45 (1.68-3.72)	2.97 (2.04-4.98)	0.002	2.50 (1.78-3.69)	3.03 (1.79-5.54)	0.009
INR	1.02 (0.96-1.07)	1.04 (0.99-1.09)	0.005	1.01 (0.96-1.07)	1.05 (1.00-1.11)	<0.001
SII	466.8 (346.66-632.21)	390.3 (289.80-553.65)	<0.001	453.7 (333.87-610.80)	421.2 (307.85-611.37)	0.267
SIRI	0.91 (0.68-1.36)	0.90 (0.63-1.27)	0.544	0.88 (0.67-1.28)	0.94 (0.66-1.59)	0.196
AISI	213.1 (149.40-336.41)	196.5 (123.20-292.30)	0.033	208.1 (143.86-303.62)	216.5 (128.36-344.16)	0.860
NLR	1.96 (1.50-2.55)	1.83 (1.39-2.33)	0.042	1.90 (1.47-2.47)	1.96 (1.52-2.45)	0.693
PLR	119.00 (97.57-143.43)	103.20 (84.43-126.02)	<0.001	115.78 (95.04-140.31)	111.36 (84.61-139.70)	0.089
LMR	4.25 (3.42-5.25)	4.23 (3.57-5.23)	0.650	4.27 (3.51-5.33)	4.15 (3.28-5.02)	0.089
APRI	0.29 (0.23-0.40)	0.36 (0.26-0.62)	<0.001	0.30 (0.23-0.40)	0.39 (0.26-0.74)	<0.001
FIB-4	0.80 (0.57-1.13)	0.97 (0.73-1.40)	<0.001	0.81 (0.59-1.13)	1.01 (0.67-1.50)	<0.001

Normally distributed variables are presented as mean ± standard deviation, non-normally distributed variables as median (25^{th}–75^{th} percentile). Group comparisons were performed using the Mann–Whitney U test for variables with non-normal distributions and the independent-samples t-test for variables with normal distributions. A p value of < 0.050 was considered statistically significant. AFP, alpha-fetoprotein; AISI, aggregate index of systemic inflammation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4 score; GGT, gamma-glutamyl transferase; INR, international normalized ratio; LMR, lymphocyte-to-monocyte ratio; mHAI, modified histological activity index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RBC, red blood cell count; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

For necroinflammatory activity, no individual inflammatory index demonstrated statistically significant discriminatory ability. Only APRI and FIB-4 demonstrated significant discriminative ability. 95% confidence intervals, cut-off values, sensitivity, specificity, and detailed AUC values are presented in Table 3.

In univariate logistic regression analyses, several clinical and laboratory variables, including age (p = 0.002), lymphocytes (p = 0.027), basophils (p = 0.009), eosinophils (p = 0.010), platelets (p = 0.003), ALT (p = 0.031), GGT (p = 0.001), direct bilirubin (p < 0.001), AFP (p = 0.020), INR (p = 0.002), and FIB-4 (p < 0.001), were significantly associated with advanced fibrosis. Among inflammatory indices, PLR (p < 0.001), SII (p = 0.003), and AISI (p = 0.027) showed significant associations.

Table 4 presents multivariate logistic regression models for advanced fibrosis. Candidate clinical variables were selected from univariate analysis. Among these, lymphocytes

Table 3. ROC curve analysis of individual CBC-derived inflammatory indices for prediction of advanced fibrosis (F3–F6) and high necroinflammatory activity (mHAI ⩾6).

Index	Advanced fibrosis (F3–F6)					High necroinflammatory activity (mHAI ⩾6)				
	AUC (95% CI)	Cut-off	Sens (%)	Spec (%)	p	AUC (95% CI)	Cut-off	Sens (%)	Spec (%)	p
SII	0.601 (0.548–0.655)	⩽449.29	64.1	55.2	<0.001	0.533 (0.473–0.593)	—	—	—	0.267
AISI	0.559 (0.505–0.612)	⩽320.68	82.7	28.4	0.033	0.505 (0.444–0.567)	—	—	—	0.860
PLR	0.623 (0.570–0.676)	⩽112.93	62.8	58.7	<0.001	0.550 (0.489–0.612)	—	—	—	0.089
NLR	0.556 (0.502–0.610)	⩽1.317	21.2	88.2	0.042	0.512 (0.452–0.571)	—	—	—	0.693
SIRI	0.517 (0.463–0.571)	—	—	—	0.545	0.538 (0.477–0.599)	—	—	—	0.196
LMR	0.512 (0.459–0.565)	—	—	—	0.656	0.550 (0.492–0.609)	—	—	—	0.087
APRI	0.619 (0.565–0.672)	⩾0.493	34.0	85.2	<0.001	0.640 (0.579–0.701)	⩾0.491	41.3	85.3	<0.001
FIB-4	0.633 (0.582–0.684)	⩾0.727	78.2	43.1	<0.001	0.618 (0.557–0.678)	⩾1.697	24.6	95.5	<0.001

ROC curves were constructed using the continuous values of each index as the classifiers. Optimal cut-off values were determined using the Youden index (sensitivity + specificity−1). For the CBC-derived inflammatory indices, which were inversely associated with fibrosis, values ⩽ the cut-off (indicated by "⩽") were associated with the outcome, whereas for APRI and FIB-4 values ⩾ the cut-off (indicated by "⩾") were associated with the outcome. "—" indicates that the index did not achieve statistical significance (p ⩾ 0.050) and cut-off, sensitivity, and specificity values are therefore not reported. AUC, area under the curve; CI, confidence interval; Sens, sensitivity; Spec, specificity; SII, systemic immune-inflammation index; AISI, aggregate index of systemic inflammation; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammation response index; LMR, lymphocyte-to-monocyte ratio; APRI, AST-to-platelet ratio index; FIB-4, fibrosis-4 index.

Table 4. Multivariate logistic regression models for advanced fibrosis.

Variable	Model 1		Model 1 + logSII		Model 1 + logAISI		Model 1 + logPLR	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.017 (0.998–1.036)	0.075†	1.017 (0.998–1.036)	0.074†	1.016 (0.997–1.035)	0.087†	1.016 (0.997–1.035)	0.086†
Eosinophil (×10⁹/L)	7.016 (1.066–46.177)	0.043*	4.625 (0.680–31.466)	0.117	7.605 (1.149–50.324)	0.035*	3.449 (0.483–24.632)	0.217
ALT (U/L)	0.997 (0.994–1.000)	0.083†	0.997 (0.994–1.000)	0.081†	0.997 (0.994–1.000)	0.075†	0.998 (0.994–1.001)	0.119
GGT (U/L)	1.010 (1.000–1.021)	0.058†	1.010 (0.999–1.021)	0.081†	1.011 (1.000–1.022)	0.051†	1.008 (0.998–1.019)	0.121
Direct Bilirubin (mg/dL)	7.467 (0.987–56.462)	0.051†	7.364 (0.942–57.602)	0.057†	7.708 (1.002–59.276)	0.050*	7.050 (0.900–55.222)	0.063†
AFP (µg/L)	1.051 (0.998–1.106)	0.058†	1.049 (0.996–1.105)	0.070†	1.051 (0.997–1.108)	0.063†	1.045 (0.993–1.099)	0.092†
INR	18.307 (1.635–205.043)	0.018*	13.588 (1.152–160.249)	0.038*	15.750 (1.371–180.948)	0.027*	15.814 (1.352–185.035)	0.028*
Log SII	—	—	0.485 (0.307–0.766)	0.002*	—	—	—	—
Log AISI	—	—	—	—	0.661 (0.474–0.921)	0.015*	—	—
Log PLR	—	—	—	—	—	—	0.338 (0.180–0.637)	<0.001*

Model 1 (clinical model) was derived using backward stepwise elimination (removal threshold p > 0.100); candidate variables from univariate analysis (age, eosinophil count, ALT, GGT, direct bilirubin, AFP, INR) were all retained in the final model. Each of Model 1+logSII, Model 1+logAISI, and Model 1+logPLR was constructed by adding a logarithmically transformed inflammatory index to Model 1. Each index was evaluated in a separate model.

and platelets were excluded due to mathematical overlap with PLR, SII, and AISI. After backward stepwise elimination, Model 1 retained seven variables: age, eosinophil count, ALT, GGT, direct bilirubin, AFP, and INR. Eosinophil count and INR were independently and significantly associated with advanced fibrosis ($p < 0.050$). When PLR, SII, and AISI were logarithmically transformed and added separately to Model 1, all three indices remained independently associated with advanced fibrosis after adjustment for clinical covariates (Table 4).

In univariate logistic regression analyses for high necroinflammatory activity, the following variables age ($p = 0.023$), eosinophil count ($p = 0.048$), platelet count ($p = 0.014$), AST ($p < 0.001$), ALT ($p < 0.001$), GGT ($p < 0.001$), albumin ($p = 0.003$), direct bilirubin ($p < 0.001$), AFP ($p = 0.006$), INR ($p < 0.001$), APRI ($p < 0.001$), and FIB-4 ($p = 0.002$) were significantly associated with the outcome: SIRI ($p = 0.034$) showed a significant association in the univariate analysis, while the other indices did not.

Multivariate models for high necroinflammatory activity are presented in Table 5. Following backward stepwise elimination, the reduced clinical model (Model 2) retained the De Ritis ratio (AST/ALT), direct bilirubin, and INR, all of which were independently associated with high necroinflammatory activity (Table 5). A lower De Ritis ratio—reflecting the ALT-predominant enzyme pattern typical of active hepatocellular injury—was associated with higher odds of elevated necroinflammatory activity. When log SIRI was added to the reduced clinical model (De Ritis ratio, direct bilirubin, and INR), it remained not statistically significant after adjustment ($p = 0.48$). Therefore, CBC-derived inflammatory indices did not provide independent predictive value for necroinflammatory activity beyond conventional biochemical markers.

APRI and FIB-4 were evaluated in separate add-on models for advanced fibrosis (Table 6) and high necroinflammatory activity (Table 7). When APRI was added to Model 3 for advanced fibrosis, it did not maintain its independent statistical significance after adjustment ($p = 0.232$). Similarly, FIB-4 was not independently significant in Model 4 ($p = 0.151$). When APRI was added to the reduced Model 5 for elevated necroinflammatory activity, it reached independent statistical significance ($p = 0.043$); however, FIB-4 did not reach it when added to Model 6 ($p = 0.090$).

Table 5. Multivariate logistic regression models for high necroinflammatory activity (mHAI ≥6).

Variable	Model 2		Model 2 + logSIRI	
	OR (95% CI)	p	OR (95% CI)	p
De Ritis Ratio (AST/ALT)	0.480 (0.250-0.920)	0.028*	0.490 (0.250-0.935)	0.031*
Direct Bilirubin (mg/dL)	11.090 (2.020–60.940)	0.006*	10.770 (1.970–58.990)	0.006*
INR	57.500 (5.230–632.600)	0.001*	56.950 (5.180–626.140)	0.001*
Log SIRI	–	–	1.140 (0.790–1.640)	0.476

Model 2 (clinical model)was derived using backward stepwise elimination(removal threshold $p > 0.100$). After elimination of age, eosinophil count, albumin, GGT, and AFP from the model, the final model retained De Ritis Ratio(AST/ALT),direct bilirubin, and INR. Model 2 (+ log SIRI) included the log-transformed SIRI in the clinical model.

Table 6. Multivariate logistic regression models including APRI and FIB-4 for advanced fibrosis (F3–F6).

Variable	Model 3 + APRI		Model 4+ FIB-4	
	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.015 (0.997–1.034)	0.105	–	–
Eosinophil ($\times 10^9$/L)	6.841 (1.039–45.042)	0.046*	8.734 (1.362–56.009)	0.022*
ALT (U/L)	0.994 (0.987–1.000)	0.054	–	–
GGT (U/L)	1.012 (1.000–1.024)	0.056	1.005 (0.995–1.014)	0.338
Direct Bilirubin (mg/dL)	7.352 (0.959–56.352)	0.055	5.592 (0.730–42.816)	0.097
AFP (µg/L)	1.042 (0.988–1.099)	0.125	1.045 (0.987–1.106)	0.130
INR	17.053 (1.492–194.898)	0.022*	10.440 (0.967–112.772)	0.053
APRI	1.359 (0.822–2.248)	0.232	–	–
FIB-4	–	–	1.270 (0.917–1.759)	0.151

Model 3 included all variables from Model 1 plus APRI. APRI is calculated as (AST/upper limit of normal AST) ÷ platelet count × 100. Model 4 included variables from Model 1 except age and ALT, because they are integral components of the FIB-4 formula (FIB-4 = Age × AST / [Platelet × √ALT]); their simultaneous inclusion alongside FIB-4 would introduce collinearity. *A p value <0.050 was considered statistically significant.

Table 7. Multivariate logistic regression models including APRI and FIB-4 for high necroinflammatory activity (mHAI ≥6).

Variable	Model 5 + APRI		Model 6 + FIB-4	
	OR (95% CI)	p	OR (95% CI)	p
ALT (U/L)	1.002 (0.997–1.008)	0.392	–	–
Direct Bilirubin (mg/dL)	4.689 (0.620–35.484)	0.135	6.983 (1.070–45.592)	0.042*
INR	30.353 (2.623–351.184)	0.006*	54.878 (5.031–598.661)	0.001*
APRI	1.883 (1.021–3.473)	0.043*	–	–
FIB-4	–	–	1.225 (0.969–1.550)	0.090

Model 5 included variables from Model 2 except AST because it is an integral component of the APRI formula (APRI = [AST / upper limit of normal AST] ÷ platelet count × 100); its simultaneous inclusion alongside APRI would introduce collinearity. Model 6 included variables from Model 2 except AST and ALT, because they are components of the FIB-4 formula (FIB-4 = Age × AST / [Platelet × √ALT]). *A p value <0.050 was considered statistically significant.

Discussion

This biopsy-based study on patients with CHB found that PLR, SII, and AISI—among the inflammatory indices derived from CBC—were independently associated with advanced fibrosis. Additionally, an inverse relationship was found between fibrosis severity and SII, AISI, PLR, and NLR. However, the discriminatory performance of these indicators alone in detecting advanced fibrosis was found to be poor and remained below generally accepted threshold values for clinical use. Furthermore, no indices were independently associated with necroinflammatory activity.

The relatively low AUC values in this study can be explained by several fundamental pathophysiological and cohort-based factors: First, these inflammatory indices obtained from CBCs are not derived from liver tissue-specific inflammatory cells but rather reflect systemic immune activation. These indices have been associated with inflammation and adverse outcomes in a wide variety of chronic conditions, including cardiovascular, metabolic, and malignant diseases (5,16). Decreased composite inflammatory indices in advanced fibrosis reflect hematological changes triggered by structural liver damage (cytopenias due to hypersplenism and bone marrow suppression) and alterations in circulating immune cell populations, rather than ongoing fibrogenesis at the tissue level. Progressive fibrosis and cirrhosis are often accompanied by hypersplenism, decreased thrombopoietin production, and peripheral cytopenias, particularly thrombocytopenia (7). Since the SII, AISI, PLR, and NLR indices include platelet or neutrophil counts in their numerators, decreased cell counts in advanced fibrosis may lead to lower index values. Furthermore, research on immune dysfunction associated with cirrhosis describes a paradoxical shift in systemic immune regulation in end-stage liver disease characterized by immune depletion and disorganized leukocyte homeostasis (7,17). This can be seen as relatively preserved or proportionally increased lymphocyte counts relative to neutrophil counts. Since the SII, AISI, PLR, and NLR indices include lymphocyte counts in their denominators, this may lead to lower values in these indices.

Second, 70.5% of patients in our cohort had mild fibrosis (F0-F2). The successive clinical boundaries between mild and advanced fibrosis stages (e.g., the transition from F2 to F3) create substantial gray areas that are heterogeneous within the hematological circulation. As a matter of fact, APRI and FIB-4, the most used formulas in screening for fibrosis in the literature (18,19), showed similarly low AUC values (0.619 and 0.633, respectively) in our cohort, precisely due to this disease heterogeneity.

In our study, although logPLR, logSII, and logAISI remained independently significant in multivariate analyses for association with advanced fibrosis, the AUC values obtained in the ROC analysis remained between 0.559 and 0.623, indicating poor differential diagnostic performance, which may appear to be a statistical contradiction at first glance. However, this is a phenomenon that, as is well known in the biostatistical literature (20), variables that show a statistically significant, independent association with a disease (significant OR and p value) do not necessarily achieve high diagnostic classification power (AUC ≥0.70). Which is theoretically expected. While logistic regression analysis reflects the change in average risk on a population basis, AUC reflects the overlap of these distributions between individuals.

High necroinflammatory activity (mHAI ≥6) was independently associated with the De Ritis ratio (AST/ALT), INR, and direct bilirubin in a multivariate model. CBC-derived inflammatory indices did not retain their significance after adjustment, consistent with a previous study in patients with CHB (8). This finding suggests that routine liver enzymes and markers of synthetic function more accurately reflect ongoing hepatocellular damage than CBC-derived measures of systemic inflammation. Necroinflammatory activity represents active hepatic damage, while CBC-

derived indices appear to reflect broader systemic or chronic immunohematological changes.

Previous CHB studies have reported lower NLR values in patients with advanced fibrosis, with some suggesting that this indicates a reasonable diagnostic performance (8-12). Consistent with these findings, NLR was also lower in the advanced fibrosis group in our study. However, the association was weak; NLR failed to maintain its independent significance in regression analysis, and its discriminatory performance was limited. In our cohort, PLR, AISI, and SII showed stronger univariate associations with advanced fibrosis than did NLR, and only PLR, AISI, and SII were included in the main multivariate models.

In our study, SIRI did not show a significant difference between fibrosis stages; this contradicts reports from NAFLD where high SIRI is associated with advanced fibrosis and adverse outcomes (13). This discrepancy likely reflects differences in underlying disease mechanisms and suggests that the behavior of systemic inflammatory indices may be etiology-specific rather than homogeneous across chronic liver diseases.

In a study on CHB by Shen et al. (3), the AUC for SII in detecting fibrosis was reported as 0.98, while in our study this value was 0.60. There may be several methodological reasons for this significant difference. While Shen et al. assessed fibrosis using transient elastography (FibroScan), our study used liver biopsy as the reference standard. Their cohort consisted of 120 patients and a healthy control group (n = 28), and the reported AUC of 0.982 reflects the ability to distinguish any degree of fibrosis from healthy controls. In contrast, our analysis included 529 biopsy-confirmed CHB patients and compared different stages of fibrosis without a healthy comparator. Patient classification also differed: Shen et al. (3) used a four-group classification (non-fibrosis, mild-moderate, severe, cirrhosis), whereas we applied a binary classification (F0-2 vs. F3-6).

APRI and FIB-4 scores were elevated in both the high fibrosis and high mHAI groups, consistent with previous reports (18,19). However, in our multivariate analysis, neither APRI nor FIB-4 showed independent significance for advanced fibrosis. For necroinflammatory activity, only APRI showed independent statistical significance ($p = 0.043$). These findings suggest that the predictive information conveyed by these composite scores largely overlaps with that of conventional biochemical variables already present in the model, supporting their role as complementary rather than independent predictors.

The strengths of this study include the use of liver biopsy as a reference standard, a large number of patients, and the simultaneous evaluation of multiple classical and novel inflammatory indices in a homogeneous HBV population, and the use of multiple regression analysis.

Study Limitations

Our study has several limitations that must be considered. This study was designed as a retrospective, cross-sectional, single-center study. The predominance of early-stage fibrosis may have impaired discriminative performance. HBeAg status, quantitative HBV DNA levels, and antiviral treatment data, which are well-known determinants of CHB progression, were not available and could not be evaluated. Likewise, detailed medication data (e.g., corticosteroid or immunosuppressant use) and the presence of acute intercurrent infection, recent surgery, or trauma at the time of sampling could not be systematically ascertained from the available records; therefore, residual hematological confounding of the CBC-derived indices cannot be fully excluded. Prospective studies should include these variables to provide a more comprehensive assessment.

Conclusion

This study reveals that in patients with biopsy-confirmed CHB, CBC-based systemic inflammatory indices (particularly PLR, SII, and AISI) are significantly associated with advanced fibrosis, independent of age, bilirubin, and classical liver enzyme profiles. This decrease in inflammatory indices likely reflects the pathophysiological consequences of hypersplenism related to portal hypertension, splenic cellular pooling, and bone marrow dysfunction. However, their limited diagnostic discrimination at the individual level (low AUC values) prevents these indices, both mathematically and clinically, from being used alone as primary diagnostic tools that provide a definitive judgment for histological staging. This lack of disease specificity limits their clinical usefulness in CHB alone and reinforces the conclusion that they should be interpreted as complementary biological indicators of fibrosis rather than as primary diagnostic markers. Future multicenter prospective studies will more clearly reveal the potential role and net clinical benefit of these systemic biomarkers in composite risk models when integrated with other clinical, laboratory, and radiological metrics.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Ankara Training and Research Hospital (decision number: 532/2025, date: 18.06.2025).

Informed Consent: Due to the retrospective design of the study, the requirement for informed consent was waived by the Institutional Ethics Committee.

Footnotes

Authorship Contributions

Concept: E.F.Y., M.A., M.Ş., Design: E.F.Y., M.A., M.Ş., Data Collection or Processing: E.F.Y., H.A.T., M.A., Y.H.P., L.F., M.Ş., Analysis or Interpretation: E.F.Y., H.A.T., M.A., M.Ş., Literature Search: E.F.Y., M.A., M.Ş., Writing: E.F.Y.

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References

1. Hsu YC, Huang DQ, Nguyen MH. Global burden of hepatitis B virus: current status, missed opportunities and a call for action. Nat Rev Gastroenterol Hepatol. 2023;20:524-537. [Crossref]
2. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22:696-699. [Crossref]
3. Shen J, Dai S, Huang Y, Fan X, Zhao S, Wang Z. Correlation between related inflammation indicators and the degree of liver fibrosis in patients with chronic hepatitis B. Medicine (Baltimore). 2025;104:e43545. [Crossref]
4. Bai X, Cheng L, Wang H, Deng Y, Tong X, Wen W, et al. The aggregate index of systemic inflammation (AISI) and the risk of all-cause, cardiovascular, and cardio-cerebrovascular mortality in congestive heart failure patients: results from NHANES 1999-2018. Sci Rep. 2025;15(1):18282. [Crossref]
5. Liu Y, Liu Y, Fan S, Yang J, Xu M, Zhao L, et al. Correlation between CBC-derived inflammatory indicators and all-cause mortality with rheumatoid arthritis: a population-based study. Front Med (Lausanne). 2025;12:1538710. [Crossref]
6. Xue J, Dong P, Pida M, Ma K, Zhao H, Chen J, et al. Evaluation of peripheral blood neutrophil extracellular traps as fibrotic markers in patients with chronic hepatitis B. Arab J Gastroenterol. 2026;27:102-107. [Crossref]
7. Lingas EC. Hematological abnormalities in cirrhosis: a narrative review. Cureus. 2023;15:e39239. [Crossref]
8. Ercin C, Dogru T, Sertoglu E. Neutrophil-to-lymphocyte ratio as a predictor of fibrosis in inactive hepatitis B carriers. Eur J Gastroenterol Hepatol. 2015;27:475-476. [Crossref]
9. Shivalingappa UU, Ramasamy AA, Muhammed KS, A A, N A. Neutrophil to lymphocyte ratio and correlation with hepatic fibrosis in patients with chronic hepatitis B. Int J Res Med Sci. 2022;10:1710-1714. [Crossref]
10. Kekilli M, Tanoglu A, Sakin YS, Kurt M, Ocal S, Bagci S. Is the neutrophil to lymphocyte ratio associated with liver fibrosis in patients with chronic hepatitis B? World J Gastroenterol. 2015;21:5575-5581. [Crossref]
11. Demiröz H, Bayram M, Irak K, Yıldırım Ö, Kumbasar A, Tabak Ö. Comparison of liver histopathology with non-invasive inflammation markers as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and mean platelet volume in chronic hepatitis B patients. Viral Hepat J. 2021;27:1-5. [Crossref]
12. Ding R, Zhou X, Huang D, Wang Y, Li X, Yan L, et al. Predictive performances of blood parameter ratios for liver inflammation and advanced liver fibrosis in chronic hepatitis B infection. Biomed Res Int. 2021;2021:6644855. [Crossref]
13. Yin Y, Zhu W, Xu Q. The systemic inflammation response index as a risk factor for hepatic fibrosis and long-term mortality among individuals with metabolic dysfunction-associated steatotic liver disease. Nutr Metab Cardiovasc Dis. 2024;34:1922-1931. [Crossref]
14. Ma Y, Wang J, Du L, Tang H. Association between the systemic immune-inflammation index and the outcome of liver fibrosis in patients with chronic hepatitis C. Front Med (Lausanne). 2024;11:1486503. [Crossref]
15. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010;5:1315-1316. [Crossref]
16. Chen L, Chen X. The role of different systemic inflammatory indexes derived from complete blood count in differentiating acute from chronic calculus cholecystitis and predicting its severity. J Inflamm Res. 2024;17:2051-2062. [Crossref]
17. Zheng P, Dou Y, Wang Q. Immune response and treatment targets of chronic hepatitis B virus infection: innate and adaptive immunity. Front Cell Infect Microbiol. 2023;13:1206720. [Crossref]
18. Sha FR, Pk MU, Abuelezz NZ, Pervin R, Talukder RI, Begum M, et al. Investigating the efficiency of APRI, FIB-4, AAR and AARPRI as non-invasive markers for predicting hepatic fibrosis in chronic hepatitis B patients in Bangladesh. Open Microbiol J. 2019;13:34-40. [Crossref]
19. Parikh P, Ryan JD, Tsochatzis EA. Fibrosis assessment in patients with chronic hepatitis B virus (HBV) infection. Ann Transl Med. 2017;5:40. [Crossref]
20. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol. 2004;159:882-890. [Crossref]