Diagnostic Performance of Osteopontin Serum Levels in Detecting Liver Fibrosis Among Chronic Hepatitis B Patients

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Abstract

Objectives: To evaluate the diagnostic performance of serum Osteopontin (OPN) levels in determining the liver fibrosis in patients with chronic hepatitis B.

Methods: This study was an analytical observational research employing a cross-sectional design. The study subjects consisted of 83 patients with chronic hepatitis B who underwent laboratory examinations and transient elastography (TE) between August and September 2025. Serum OPN levels were measured using the enzyme-linked immunosorbent assay (ELISA) method with a Rayto RT-2100C microplate reader and analyzed using diagnostic performance tests based on the area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likehood ratio (PLR), negative likehood ratio (NLR), and accuracy.

Results: Median serum OPN was higher in the significant fibrosis (SF) group (25.1 ng/mL; 5.19–653.84) than in the non-significant group (9.13 ng/mL; 5.63–105.15) ($p < 0.001$). The AUC was 0.876 (95% CI: 0.794–0.957; $p < 0.001$). At a 14.61 ng/mL cut-off , sensitivity was 84.1%, specificity 82.5%, PPV 84.1%, NPV 82.5%, PLR 4.81, and NLR 0.19, and accuracy 83.3%

Conclusions: Serum OPN levels were significantly higher in chronic hepatitis B patients with SF, indicating its potential as a reliable non-invasive diagnostic biomarker for assessing liver fibrosis. Further research is warranted to validate and strengthen the role of OPN as a non-invasive diagnostic marker for liver fibrosis, particularly in resource-limited healthcare settings.

Keywords: Osteopontin, Liver fibrosis, Chronic hepatitis B, Transient elastography

Introduction

Hepatitis B virus (HBV) infection remains a major global health burden, causing significant morbidity and mortality. More than two billion people have been infected worldwide, with over 350 million developing chronic HBV infection, leading to 1–2 million deaths annually due to hepatocellular carcinoma[1]. Indonesia ranks among countries with the highest HBV prevalence in Southeast Asia, ranging from 4.0% to 20.3%, with higher rates outside Java Island. According to the 2021 National Health Survey (RISKESDAS), one in ten Indonesians is infected with hepatitis B or C [2]. In Central Java, HBV prevalence remains moderate (6–7%), with 1,543 reported cases in 2022. In Indonesia, 43% of patients with chronic hepatitis B who were examined using transient elastography (TE) were found to have significant liver fibrosis.[3] Limited public awareness of the asymptomatic nature of HBV contributes to delayed diagnosis, leading to advanced chronic stages by the time of detection[4].

Chronic HBV infection can progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma[5]. Persistent viral replication and immune-mediated liver inflammation drive hepatocyte injury and extracellular matrix (ECM) accumulation, leading to fibrotic remodeling[6,7]. The diagnosis of chronic HBV infection is established by persistent HBsAg positivity for more than six months, supported by serological and molecular markers such as HBeAg, anti-HBc, and HBV DNA levels[8]. Assessing liver fibrosis is essential to guide treatment initiation and long-term monitoring, traditionally performed through liver biopsy, but its invasiveness limits repeated assessments.

Non-invasive techniques, such as TE, have emerged as reliable alternatives for fibrosis assessment. TE measures liver stiffness as a surrogate for fibrosis severity and demonstrates good diagnostic performance for detecting significant fibrosis (SF) and cirrhosis[9,10]. However, TE availability remains limited in resource-constrained settings, and skilled operators are required for accurate interpretation[11]. These limitations underscore the need for accessible laboratory-based biomarkers capable of accurately reflecting the degree of hepatic fibrosis in chronic HBV patients.

Osteopontin multifunctional glycoprotein involved in inflammation and hepatic stellate cell (HSC) activation, has been proposed as a potential biomarker of liver fibrosis[12,13]. Osteopontin is expressed by hepatocytes, Kupffer cells, and activated HSC, as well as immune cells including T and B lymphocytes, macrophages, and dendritic cells. Several studies have demonstrated elevated serum OPN levels in patients with significant liver fibrosis, showing strong correlations with histological fibrosis stages[14,15,16]. Nevertheless, diagnostic performance data of serum OPN in chronic HBV-related fibrosis remain limited and inconsistent across populations. Therefore, this study aims to evaluate the diagnostic performance of serum OPN levels for detecting liver fibrosis in patients with chronic hepatitis B, providing a safer and more practical alternative to existing diagnostic methods.

Methods

This analytical observational study employed a cross-sectional design to evaluate the diagnostic performance of serum OPN levels in assessing liver fibrosis among patients with chronic hepatitis B. The study was conducted at the Clinical Pathology Laboratory of Dr. Moewardi General Hospital, Surakarta, in collaboration with the Faculty of Medicine, Universitas Sebelas Maret, from August to September 2025. The study population consisted of patients aged 18 years or older who had been diagnosed with chronic hepatitis B, defined by persistent positivity for hepatitis B surface antigen (HBsAg) for more than six months, with or without clinical symptoms or abnormalities in liver function tests. Eligible participants were enrolled consecutively until the required sample size of 83 subjects was achieved. Patients were excluded if they had co-infection with hepatitis C virus, hepatitis D virus, a history of alcohol consumption, autoimmune disease, chronic kidney disease, an HIV-infected person, a person with tuberculosis, other causes of chronic liver disease; or if they were receiving or had recently (within the previous six months) received antiviral therapy or hepatotoxic medication.

Venous blood sample of 3–5 ml is collected into a tube without anticoagulant, centrifuged, and the serum aliquots were stored at −80°C until analysis. Serum OPN concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Elabscience® Human OPN ELISA Kit) on a Rayto RT-2100C microplate reader according to the manufacturer's instructions. Liver stiffness was assessed using TE (FibroScan®), and fibrosis severity was categorized according to the World Health Organization (2024) criteria: non-significant fibrosis (NSF) if liver stiffness <7.0 kPa (<F2) and significant fibrosis (SF) if ≥7.0 kPa (≥F2). Internal quality control procedures were implemented to ensure analytical precision and reliability, using control samples provided by the manufacturer and maintaining coefficient of variation values within acceptable limits.

This study aims to measure diagnostic performance of serum OPN levels compared to TE results for diagnosing of liver fibrosis. Data analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The descriptive characteristics of respondents were analyzed. The categorical data were presented in percentage (%). Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum) depending on data distribution, which was evaluated using Kolmogorov–Smirnov test ($p > 0.05$ was significant). Comparisons between the NSF and SF groups were made using the Chi-Square test, Independent *t*-test or Mann–Whitney *U* test, as appropriate. Sensitivity and specificity tests from numeric data were presented in the Receiver Operating Characteristics (ROC) curve. OPN cut-off values were obtained by processing ROC curve data in Excel. Obtained data was entered into a 2x2 table and then calculated manually to obtain sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive

likelihood ratio (PLR), and negative likelihood ratio (NLR). A *p*-value <0.05 was considered statistically significant.

Ethical approval for this study was obtained from the Health Research Ethics Committee of Dr. Moewardi General Hospital, Surakarta (approval number: 1.829/ VIII/HREC/2025). All participants provided written informed consent prior to enrollment, and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Results

A total of 83 patients with chronic hepatitis B were included in this study, consisting of 43 (51.8%) with significant fibrosis (SF), and 40 (48.2%) with non-significant fibrosis (NSF). The baseline characteristics of the study subjects are presented in Table 1. The mean age of patients in the SF group was significantly higher than that in the NSF group (50.70 ± 11.32 vs 41.18 ± 15.27 years, $p = 0.002$). There were no statistically significant differences in gender distribution or body mass index and duration of HBV detection between the two groups ($p > 0.05$). Laboratory parameters showed significantly lower platelet counts and albumin levels in the SF group (186.97 ± 93.74 × 10^3/µL vs 244.50 ± 64.38 × 10^3/µL, $p = 0.005$; and 3.90 vs 4.40 g/dL, $p = 0.001$, respectively). The median AST and liver stiffness measurements were significantly higher in the SF group ($p < 0.001$), while Alanine Aminotransaminase (ALT) and HBV DNA levels were not significantly different between groups ($p > 0.05$).

Table 1: Baseline characteristics of study subject

Characteristic	Total 83 (100%)	SF (≥7.0 kPa) 43 (51.8%)	NSF (7.0 kPa) 40 (48.2%)	p
Age (years)		50.70±11.32	41.18±15.27	0.002#*
Gender				0.474$
Male	50 (60.2%)	28 (65.1%)	22 (55.0%)	
Female	33 (39.8%)	15 (34.9%)	18 (45.0%)	
Body Mass Index (BMI)				0.301$
Underweight	9 (10.8%)	3 (33.3%)	6 (66.7%)	
Normal weight	27 (32.5%)	14 (51.9%)	13 (48.1%)	
Overweight	17 (20.5%)	7 (41.2%)	10 (58.5%)	
Obesity 1	25 (30.1%)	17 (68.0%)	8 (32.0%)	
Obesity 2	5 (6.0%)	2 (40.0%)	3 (60.0%)	
Duration of HBV detection (months)		9.0 (6-48)	9.5 (6-48)	0.539^
Laboratory parameters				
Platelet count(x10^3/uL)	71 (85.5%)	186.97±93.74	244.50±64.38	0.005#*
Albumin (g/dL)		3.90 (2.5-6.0)	4.40 (2.8-7.2)	0.001^*
AST (IU/L)	82 (98.8%)	37 (10-79)	23.0 (10-84)	0.001^*
ALT (IU/L)		28 (5-89)	20.5 (7-141)	0.298^
Viral load HBV DNA (copies/mL)	77 (92.8%)	1420 (10-8.3x10^8)	500.05 (10-3.1x10^8)	0.440^
Liver stiffness measurement (kPa)		13.60 (7-53.2)	4.7 (2.7-6.8)	0.001^*

*Abbreviations : SF, significant fibrosis; NSF, Non Significant fibrosis; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransaminase; #: Independent T-test; $: Chi-square; ^: Mann-whitney; *: significance p<0,05*

Serum OPN levels were markedly elevated in patients with SF compared with those with NSF [25.05 (5.19–161.06) ng/mL vs 9.13 (5.63–105.15) ng/mL, $p = 0.001$]. The median OPN concentration demonstrated a strong positive association with the degree of liver stiffness on TE (Table 2).

Table 2: Baseline characteristics of OPN

Characteristics	Total (n = 83)	SF (≥7.0 kPa)	NSF (7.0 kPa)	p
OPN (ng/mL)	83 (100%)	25.05 (5.19-161.06)	9.13 (5.63-105.15)	0.001^*

Abbreviations : SF, *significant fibrosis*; NSF, *Non Significant fibrosis*; ^: *Mann-whitney; *: significance p<0,05*

Further analysis according to fibrosis stages revealed a significant stepwise increase in OPN levels across fibrosis grades (F0–F4), as shown in Table 3. Patients in stages F3 and F4 exhibited notably higher median OPN levels compared to those in early stages (F0–F1, $p < 0.001$). The Kruskal–Wallis test confirmed that the differences in OPN levels among fibrosis grades were statistically significant, supporting its potential as a marker reflecting fibrosis progression.

Table 3: Comparison of liver fibrosis stages based on serum OPN levels

Fibrosis stage (TE)	Serum OPN level (ng/mL)	p
F0-F1	9.13 (5.63 – 105.15)	0.001*¥
F2	18,87 ± 10.31	
F3	22.61 ± 6.66	
F4	27.8 (9.28 – 161.06)	

Abbreviations : OPN, Osteopontin; Transient elastography (TE); ¥: Kruskal-Wallis test; *: significance p<0,05

The relationship between OPN levels and fibrosis severity was further analyzed according to TE stages. Table 3 and Figure 1 demonstrate a progressive increase in serum OPN across fibrosis stages (F0–F4), with a significant difference observed among the groups ($p = 0.001$, Kruskal–Wallis test). The median OPN level increased stepwise from 9.13 ng/mL in F0–F1 to 27.58 ng/mL in F4, suggesting that OPN concentration correlates positively with fibrosis advancement. Figure 1 shows this trend clearly, where the boxplot visualizes the upward distribution of OPN values along increasing fibrosis stages, reinforcing its potential as a biomarker that mirrors fibrogenic progression in chronic hepatitis B patients.

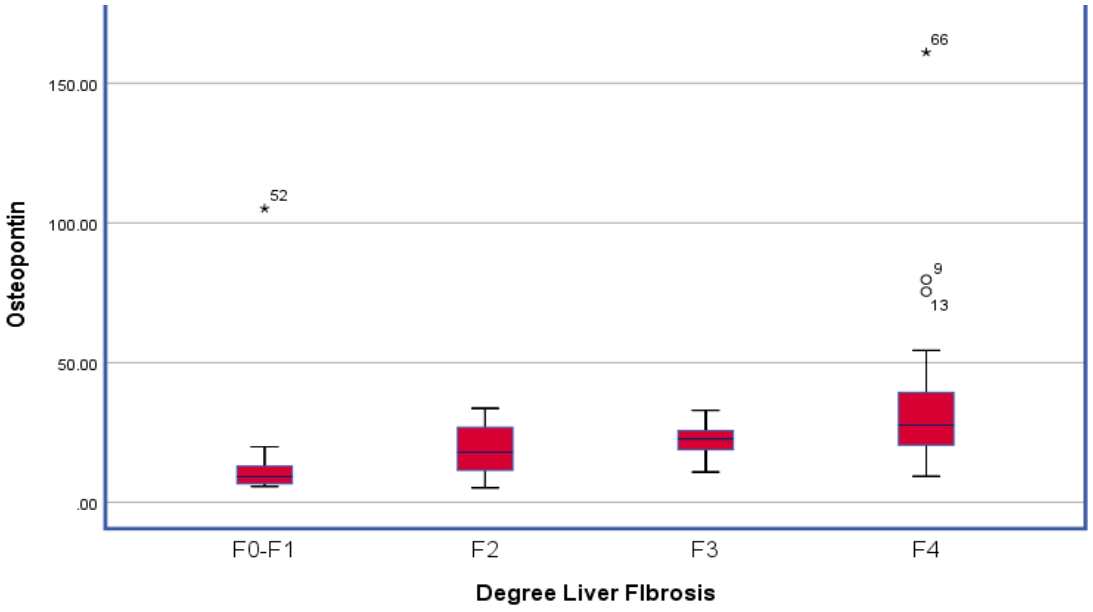

Figure 1: Boxplot of serum OPN levels according to liver fibrosis stages (F0–F4).

To evaluate its diagnostic accuracy, ROC analysis was performed to determine the discriminative ability of OPN in predicting significant fibrosis (SF). Figure 2 illustrates the ROC curve pattern, showing that the OPN line lies well above the diagonal reference line, confirming its strong discriminative ability in differentiating significant from non-significant fibrosis (NSF). These findings collectively indicate that serum OPN has high potential as a reliable non-invasive biomarker to assess liver fibrosis severity in chronic hepatitis B patients, particularly in settings where TE is unavailable.

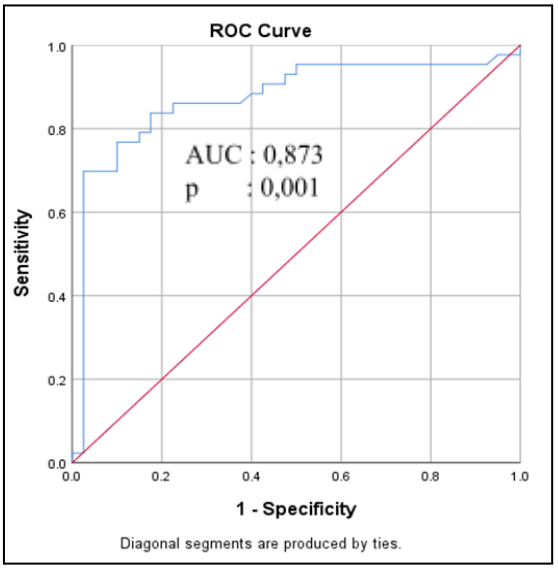

Figure 2. Receiver operating characteristic (ROC) curve of serum osteopontin

The ROC curve, shown in Figure 2, revealed an area under the curve (AUC) of 0.873 (95% CI: 0.789–0.956; $p < 0.001$), indicating excellent diagnostic performance. Diagnostic performance of serum OPN level at a cut-off point of 14.61 ng/mL, OPN achieved a sensitivity of 83.7% and specificity of 82.5%, with PPV of 83.7% and NPV of 82.5% shown in table 4 below.

Table 4: Diagnostic performance of serum OPN levels compared with TE (Dahlan, 2022)

Osteopontin Level	SF (≥7.0 kPa)	NSF (<7.0 kPa)	Total
≥ 14.61 ng/mL	36 (43.4%)	7 (8.4%)	43 (51.8%)
< 14.61 ng/mL	7 (8.4%)	33 (39.8%)	40 (48.2%)
Total	43 (51.8%)	40 (48.2%)	83 (100%)

Abbreviations : OPN, Osteopontin; Transient elastography (TE); SF, *significant fibrosis*; NSF, *Non Significant fibrosis*; ¥: Kruskal-Wallis test; *: significance p<0,05

The overall diagnostic performance metrics of serum OPN accuracy reached 83.1%, with a positive likelihood ratio (PLR) of 4.78 and negative likelihood ratio (NLR) of 0.19, shown in table 5 below.

Table 5: Diagnostic performance metrics of serum OPN

Variable	AUC (%)	p-*value*	Diagnostic performance						
			Sens	Spec	PPV	NPV	PLR	NLR	Accuracy (%)
Osteopontin	87.3 (78,9-95.6)	0.001*	83.7 (70.0-91 .9)	82.5 (68.1-91 .3)	83.7 (70.0-9 1.9)	82.5 (68.1-9 1.3)	4.78 (2.41-9. 49)	0.19 (0.09-0. 39)	83.13 (73.3-90.5)

Abbreviations: OPN, osteopontin; AUC, area under the curve; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.
Note: Significant at $p < 0.05$.

Discussion

The present study demonstrated that serum OPN levels were significantly elevated in patients with significant fibrosis (SF) compared with those without, and that OPN exhibited excellent diagnostic accuracy in identifying liver fibrosis among patients with chronic hepatitis B. The strong correlation between serum OPN concentrations and TE values suggests that OPN may reflect the degree of liver stiffness and fibrogenic activity, reinforcing its potential role as a non-invasive biomarker for liver fibrosis assessment.[17,18.] These findings are consistent with those of Sobhy et al. and Osman et al., who reported similar diagnostic performance of OPN in Chronic Hepatitis B patients[19,20.]

The high sensitivity and specificity observed in this study align with previous reports by Philips et al.[21] and Sheiko and Yurko[22], who demonstrated that plasma OPN levels increased progressively with advancing fibrosis stages.[23,24] This trend may be explained by the biological role of OPN as a multifunctional glycoprotein that modulates inflammation and HSC activation, leading to excessive ECM deposition[25,26] In chronic HBV infection, OPN secretion by hepatocytes and immune cells contributes to persistent hepatic injury and tissue remodeling, thereby linking inflammatory signaling to fibrogenesis.[27,28.]

Interestingly, the correlation strength between OPN and fibrosis observed in this study ($r = 0.63$) was comparable to that reported in prior research involving both HBV and HCV patients[29,30]. This suggests that OPN acts as a fibrosis-related marker independent of viral etiology, likely reflecting common downstream fibrogenic pathways such as TGF-β–mediated stellate cell activation and ECM accumulation. Moreover, the diagnostic performance of OPN in this study (AUC = 0.997) exceeded that of conventional non-invasive markers such as APRI and FIB-4, as reported in other studies[31,32]. This indicates a promising role for OPN as a more accurate and reliable biomarker for early detection of liver fibrosis.

The findings of this study position serum osteopontin as a promising non-invasive biomarker for liver fibrosis in chronic hepatitis B.[33,34] Beyond its statistical performance, osteopontin reflects key fibrogenic pathways involving hepatic stellate cell activation and extracellular matrix deposition.[36,37] While the diagnostic accuracy observed was high, these results should be interpreted as preliminary evidence. Future multicenter studies with larger and more diverse populations, standardized assay platforms, and direct comparison with established non-invasive indices are required to validate clinical applicability and define universal cut-off values.[38,39]

Despite the promising diagnostic performance observed, the clinical implementation of serum osteopontin (OPN) requires further standardization, as variations in assay methods, sample handling, and patient characteristics may contribute to interstudy variability in diagnostic cut-off values[40]. The single-center, cross-sectional design and relatively small sample size limit causal inference and external validity. In addition, ethnic and geographic variability may influence serum OPN levels; therefore, the generalizability of these findings beyond the Indonesian population should be interpreted with caution. Liver biopsy was not performed; however, due to its invasive nature, transient elastography was used as an accepted non-invasive reference standard for fibrosis assessment.[41] Finally, comparative non-invasive fibrosis indices, such as APRI or FIB-4, were not evaluated, and OPN measurement relied on a single ELISA platform, which may affect reproducibility.[42] Nevertheless, these findings provide valuable preliminary evidence supporting serum OPN as an adjunctive non-invasive biomarker for liver fibrosis assessment, particularly in resource-limited settings, and warrant validation in larger multicenter studies.

Conclusion

This study demonstrated that serum osteopontin OPN levels are significantly correlated with the degree of liver fibrosis among patients with chronic hepatitis B infection. Elevated serum OPN levels were consistently observed in individuals with significant and advanced fibrosis, reflecting the progressive nature of hepatic fibrogenesis.

Diagnostic evaluation revealed an excellent discriminative performance, with an AUC of 0.873 and an optimal cut-off value of 14.61 ng/mL, achieving a balanced sensitivity and specificity. These findings underscore the potential utility of serum OPN levels as a reliable, non-invasive biomarker for the detection and

staging of liver fibrosis in chronic hepatitis B. Incorporating serum OPN levels assessment into clinical practice may enhance early identification of fibrosis progression, particularly in healthcare settings where access to TE is limited.

Disclosure

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