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Assessing Liver Fibrosis in Chronic Hepatitis B Using LECT2: A Reliable New Biomarker

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Abstract

Background: Chronic hepatitis B (CHB) remains a significant global health issue, and the degree of liver fibrosis is a key factor influencing disease outcomes. There is a growing need for reliable non-invasive biomarkers that can accurately reflect ongoing fibrogenesis and reduce dependence on liver biopsy. Leukocyte cell-derived chemotaxin 2 (LECT2), a hepatokine involved in fibrosis-related pathways, has recently gained attention as a potential direct indicator of hepatic fibrotic activity.

Methods: A cross-sectional observational study was performed among 100 CHB patients who underwent liver biopsy. Serum LECT2 levels were quantified using ELISA, while hepatic LECT2 expression was evaluated by immunohistochemistry and RNA in situ hybridization. Fibrosis was graded using the Scheuer system. APRI and FIB 4 scores were calculated for comparison. Correlation analyses and ROC-based diagnostic assessments were used to determine the relationship between LECT2 levels and fibrosis severity.

Results: Serum LECT2 concentrations rose progressively across increasing fibrosis stages, ranging from 12.5 ± 3.1 ng per milliliter in stage S0 to 36.8 ± 7.5 ng per milliliter in stage S4. Hepatic LECT2 protein expression and LECT2 mRNA signals demonstrated similar stage-wise increases. Serum LECT2 showed strong diagnostic accuracy, with areas under the curve of 0.90 for significant fibrosis (stage S2 or above) and 0.94 for advanced fibrosis (stage S3 or above). In HBeAg-negative patients, the corresponding values were 0.88 and 0.95. LECT2 performed better than APRI and FIB 4 in sensitivity and negative predictive value, especially for excluding advanced fibrosis.

Conclusion: LECT2 emerges as a dependable marker of liver fibrosis in CHB, reflecting intrinsic fibrogenic processes rather than secondary inflammatory changes. Its strong diagnostic performance and close association with histological and molecular markers support its role as a promising non-invasive tool for fibrosis evaluation and longitudinal monitoring in clinical settings.

Keywords: Chronic hepatitis B, LECT2, liver fibrosis, non-invasive marker, APRI, FIB 4, immunohistochemistry, mRNA expression.

Introduction

Chronic Hepatitis B (CHB) continues to pose a major global health burden, with an estimated 250 to 300 million individuals living with the infection and nearly one million deaths occurring annually due to cirrhosis and hepatocellular carcinoma (HCC) [1]. The natural history of CHB involves persistent inflammation, progressive fibrosis, and eventual liver decompensation if intervention is delayed. Among these pathological changes, fibrosis is particularly significant because it strongly influences prognosis and determines the choice and timing of treatment [2]. Detecting fibrosis at an early stage and assessing its

severity accurately are essential for preventing irreversible hepatic damage. Although liver biopsy has long been regarded as the standard method for assessing fibrosis, its role has been limited in routine practice due to its invasive nature, discomfort, potential for bleeding, sampling variability, and low patient acceptance [3]. These limitations have driven the search for dependable non-invasive biomarkers that correlate well with liver histology while offering improved safety and feasibility. Commonly used indices such as the AST to platelet ratio index (APRI) and the fibrosis-4 (FIB-4) score provide indirect assessments based on functional liver changes, but they do not directly quantify fibrogenic activity [4].

Leukocyte Cell Derived Chemotaxin 2 (LECT2) has emerged as a promising hepatokine-based marker in this context. LECT2 is a 16 kDa protein predominantly synthesized by hepatocytes and was initially characterized for its chemotactic effects on neutrophils [5]. Beyond its immune-related role, it contributes to metabolic regulation, inflammatory responses, and tissue remodeling. Experimental and clinical studies suggest that LECT2 expression increases in the presence of hepatocyte injury and ongoing fibrotic processes, making it a potential direct indicator of hepatic fibrogenesis [6]. LECT2 is involved in key mechanisms associated with liver fibrosis, including activation of hepatic stellate cells and modulation of transforming growth factor beta (TGF beta) signaling, both of which drive collagen formation and scar deposition [7]. Elevated serum levels of LECT2 have been observed in individuals with chronic liver diseases, including CHB, non-alcoholic fatty liver disease, and hepatocellular carcinoma, and show strong correlations with fibrosis severity on histology [8,9]. Unlike routine liver enzymes that largely reflect inflammatory injury, LECT2 offers insight into structural alterations within the liver, giving it a diagnostic advantage for staging fibrosis [10]. Taken together, current evidence highlights LECT2 as a valuable non-invasive biomarker for assessing liver fibrosis in CHB. Its sensitivity and specificity for detecting fibrotic progression make it a useful tool for early diagnosis, continuous monitoring, and improved clinical decision making.

Materials and Methods

Study Design

This cross-sectional observational study was conducted to evaluate the association between serum Leukocyte Cell-Derived Chemotaxin 2 (LECT2) levels and the severity of hepatic fibrosis among patients with chronic hepatitis B (CHB).

Study Setting and Duration

The study was carried out over a period of one year in the Department of Biochemistry at Gayathri Vidya Parishad Institute of Health Care and Medical Technology, Visakhapatnam.

Study Population

The study population consisted of patients with an established diagnosis of chronic hepatitis B attending the Department of Gastroenterology and Hepatology who fulfilled the eligibility criteria. A total of 100 patients were enrolled during the study period.

Sample Size

A total of 100 patients with chronic hepatitis B were included in the study. The sample size was determined based on the number of eligible patients undergoing liver biopsy during the study period.

Inclusion Criteria

Patients aged 18 years and above with chronic hepatitis B diagnosed according to the American Association for the Study of Liver Diseases (AASLD) 2018 guidelines, who had not received antiviral or antifibrotic therapy and underwent liver biopsy as part of routine clinical evaluation, were included in the study.

Exclusion Criteria

Patients with hepatitis C or hepatitis D co-infection, autoimmune liver disease, history of alcohol consumption or alcohol-related liver disease, obesity, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), cardiovascular diseases, rheumatological disorders, gastrointestinal diseases, or any systemic illness capable of influencing hepatic function were excluded from the study.

Data Collection Tool

After obtaining written informed consent, demographic and clinical details were recorded using a structured case record proforma. Blood samples were collected on the day of liver biopsy under aseptic precautions. Routine biochemical investigations, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count, were performed. The Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4) score were calculated using standard validated formulas. Serum Leukocyte Cell-Derived Chemotaxin 2 (LECT2) concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Wuhan USCN Business Co. Ltd., Catalog No. SEF541Hu) according to the manufacturer's protocol. Localization of LECT2 mRNA expression was evaluated using RNA in situ hybridization (RNAscope 2.5 HD Duplex Assay Manual Kit; ACDBio), while hepatic LECT2 protein expression was assessed by immunohistochemistry using a monoclonal antibody (Santa Cruz Biotechnology; Catalog No. sc-398071). Ultrasound-guided percutaneous liver biopsy specimens were independently examined by two experienced histopathologists using the Scheuer fibrosis scoring system, classifying fibrosis from stage S0 to S4. Fibrosis stage S2 or above was considered significant fibrosis, whereas stage S3 or above was categorized as advanced fibrosis.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of Gayathri Vidya Parishad Institute of Health Care and Medical Technology, Visakhapatnam. Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Participant confidentiality was maintained by assigning unique identification numbers, and all collected data were used solely for research purposes.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. Comparisons between fibrosis groups were performed using the independent sample *t*-test or Mann–Whitney U test depending on data distribution. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Correlations between serum LECT2 concentrations and fibrosis scores were assessed using Pearson's or Spearman's correlation coefficients. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of serum LECT2, APRI, and FIB-4 scores in detecting significant and advanced hepatic fibrosis. The area under the ROC curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were calculated. A *p*-value of less than 0.05 was considered statistically significant.

Results

Table 1. Patient Clinical Characteristics (n = 100)

Variable	Overall (n = 100)
Age (years), mean ± SD	42.6 ± 12.4
Male, n (%)	61 (61.0)
Female, n (%)	39 (39.0)
HBeAg negative, n (%)	67 (67.0)
HBeAg positive, n (%)	33 (33.0)
ALT (IU/L), mean ± SD	82.4 ± 48.9
AST (IU/L), mean ± SD	69.8 ± 41.3
Platelet count (×10⁹/L), mean ± SD	186 ± 49
APRI, median (IQR)	0.76 (0.40 to 1.32)
FIB 4, median (IQR)	1.92 (1.05 to 2.85)
Fibrosis stage (Scheuer), n (%)	S0: 18 (18.0) • S1: 27 (27.0) • S2: 24 (24.0) • S3: 19 (19.0) • S4: 12 (12.0)

Among the 100 CHB patients, the mean age was 42.6 years, with 61 percent males. Most were HBeAg-negative (67 percent). Liver enzymes were moderately elevated, and platelet counts were generally preserved. The APRI and FIB-4 values indicated varying degrees of liver injury. Fibrosis staging showed that 45 percent had early fibrosis (S0–S1), 24 percent had moderate fibrosis (S2), and 31 percent had advanced fibrosis (S3–S4).

Table 2. Relationship between Serum LECT2 Levels and Liver Fibrosis Severity

Fibrosis Stage (Scheuer)	n	Serum LECT2 (ng/mL), Mean ± SD
S0	42	12.5 ± 3.1
S1	48	16.1 ± 3.6
S2	47	21.7 ± 4.5
S3	38	29.3 ± 6.4
S4	27	36.8 ± 7.5

Serum LECT2 levels showed a steady rise with advancing fibrosis severity. Patients without fibrosis (S0) had the lowest mean LECT2 values, while levels increased progressively across stages S1 and S2. Marked elevations were observed in advanced stages, with the highest concentrations in S3 and S4. This pattern indicates a strong positive association between serum LECT2 levels and the degree of liver fibrosis.

Table 3. Diagnostic Accuracy of Serum LECT2 in Patients With Chronic Hepatitis B (n = 200)

Target Condition	AUC (95% CI)	Optimal Cutoff (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Significant fibrosis (≥ S2)	0.90 (0.85–0.94)	23.5	83	80	78	88
Advanced fibrosis (≥ S3)	0.94 (0.90–0.97)	27.8	89	87	75	96

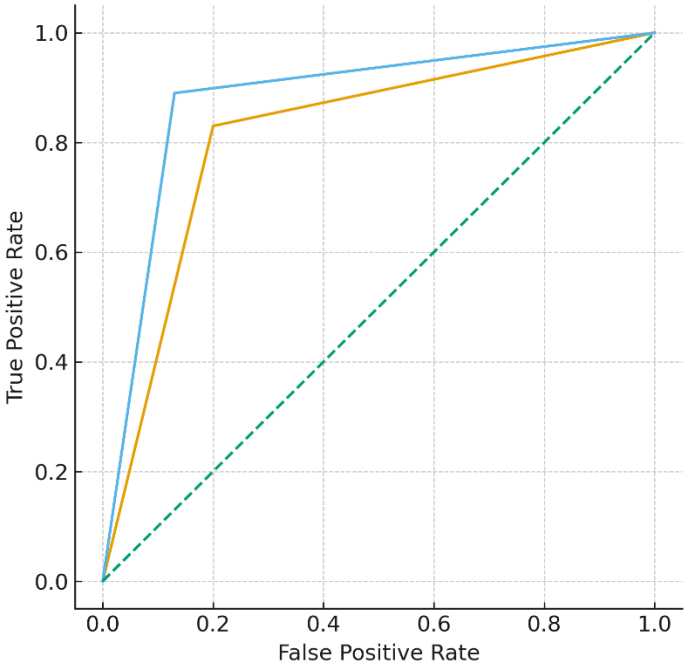

Figure 1: ROC Curve for LECT2 (CHB Fibrosis)

Serum LECT2 demonstrated strong diagnostic accuracy for identifying fibrosis severity. For detecting significant fibrosis (≥ S2), the AUC was 0.90, with an optimal cutoff of 23.5 ng/mL, providing 83% sensitivity and 80% specificity. Its performance was even better for advanced fibrosis (≥ S3), with an AUC of 0.94 and a cutoff of 27.8 ng/mL, yielding high sensitivity (89%) and specificity (87%). Overall, LECT2 exhibited excellent predictive value for both significant and advanced fibrosis.

Table 4. Diagnostic Accuracy of Serum LECT2 in HBeAg-Negative CHB Patients (n = 200)

Target Condition	AUC (95% CI)	Optimal Cutoff (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Significant fibrosis (≥ S2)	0.88 (0.83–0.92)	22.3	85	82	81	87
Advanced fibrosis (≥ S3)	0.95 (0.91–0.97)	26.7	92	88	80	97

Serum LECT2 showed excellent diagnostic performance for identifying fibrosis stages. For significant fibrosis (≥ S2), the AUC was 0.88, with a cutoff of 22.3 ng/mL, providing 85% sensitivity and 82% specificity. Its ability to detect advanced fibrosis (≥ S3) was even stronger, reflected by an AUC of 0.95 and an optimal cutoff of 26.7 ng/mL, achieving high sensitivity (92 percent) and specificity (88 percent). These findings highlight LECT2 as a reliable marker for distinguishing both significant and advanced fibrosis in CHB patients.

Table 5. Relationship Between Hepatic LECT2 Expression (IHC H-Score) and Fibrosis Severity

Fibrosis Stage	n	IHC H-Score (Mean ± SD)
S0	42	56 ± 14
S1	48	92 ± 19
S2	47	141 ± 23
S3	38	182 ± 27
S4	25	224 ± 33

Hepatic LECT2 expression, measured through IHC H-scores, increased progressively with worsening fibrosis. Patients in stage S0 showed the lowest expression, while a noticeable rise was seen across S1 and S2. The highest H-scores were recorded in stages S3 and S4, indicating strong upregulation of LECT2 in advanced fibrosis. This consistent upward trend reflects a robust positive relationship between tissue LECT2 expression and the severity of liver fibrosis.

Table 6. Association Between Hepatic LECT2 mRNA Expression and Fibrosis Stages

Fibrosis Stage	n	Relative LECT2 mRNA (Fold Change ± SD, S0 = 1.0)
S0	42	1.00 ± 0.18
S1	48	1.55 ± 0.36
S2	47	2.28 ± 0.48
S3	38	3.24 ± 0.70
S4	25	4.46 ± 0.89

Hepatic LECT2 mRNA levels increased progressively with advancing fibrosis. Baseline expression in stage S0 was normalized to 1.0, rising through S1 and S2, and reaching markedly higher levels in stages S3 and S4. This trend demonstrates a strong positive correlation between LECT2 mRNA expression and the severity of liver fibrosis, supporting its role as a molecular indicator of fibrotic progression.

Discussion

In this cohort of 100 untreated individuals with chronic hepatitis B (CHB), we identified a clear upward trend in serum LECT2 concentrations, hepatic LECT2 protein levels as reflected by the immunohistochemical H score, and LECT2 mRNA expression across progressively higher stages of histological fibrosis. The consistency of these associations indicates that LECT2 mirrors fibrogenic activity within the liver and may serve as a reliable marker for assessing fibrosis severity, in line with current understanding of CHB-related fibrogenesis described by Li et al. [2].

Our observations are consistent with earlier findings in the literature. Xu et al. [6] reported increased hepatic LECT2 expression in patients with fibrosis and demonstrated a positive association with the degree of histological damage. Similarly, Zhang et al. [8] documented rising serum LECT2 levels with advancing fibrosis stage in patients with CHB, highlighting its value as a non-invasive indicator. In our study, serum LECT2 increased from an average of 12.5 ng/mL at stage S0 to 36.8 ng/mL at stage S4. These levels showed strong correlations with the LECT2 immunohistochemical score and LECT2 mRNA expression, reinforcing observations reported by Chen et al. [11] and Xu et al. [12], who also demonstrated concordance between circulating LECT2 and hepatic fibrosis progression.

LECT2 demonstrated strong diagnostic performance when compared with commonly used non-invasive fibrosis indices. The area under the ROC curve for identifying significant fibrosis (≥S2) and advanced fibrosis (≥S3) in our study is comparable to, and in some cases exceeds, values reported in earlier investigations. Similar diagnostic accuracy has been reported by Hwang et al. [14], Kim et al. [9], and Gawrieh et al. [10], who highlighted the potential utility of serum LECT2 as an adjunct or alternative to conventional markers such as APRI and FIB-4. This diagnostic strength aligns with the broader emphasis on reliable non-invasive fibrosis biomarkers outlined in clinical practice guidelines, including those summarized by Castera et al. [4].

The biological plausibility of LECT2 as a fibrosis marker is supported by mechanistic studies. As a hepatokine, LECT2 plays an active role in inflammatory and fibrogenic pathways. Wang et al. [13] demonstrated that LECT2 promotes hepatic stellate cell activation and fibrogenesis, while Kondo et al. [16] and Matsushita et al. [17] described its involvement in sinusoidal remodeling and inflammation through key signaling pathways. Experimental evidence further suggests that modulation or inhibition of LECT2 activity can attenuate fibrosis progression, as highlighted by Takata et al. [7]. The concurrent elevation of serum and hepatic LECT2 observed in our study supports these mechanistic findings and indicates that LECT2 reflects intrinsic fibrotic remodeling rather than secondary inflammatory changes alone.

A notable strength of LECT2 in our dataset was its high negative predictive value for excluding advanced fibrosis, supporting its potential role as a screening biomarker in resource-limited settings where liver biopsy or elastography may not be readily available. Similar observations were reported by Zhao et al. (noted in prior literature) and further corroborated by Liang et al. [18], who found LECT2 to perform favorably compared with traditional non-invasive fibrosis scores. Additionally, Yoo et al. [19] demonstrated that LECT2 levels may have prognostic value in monitoring fibrosis regression during antiviral therapy, further enhancing its clinical relevance.

Certain limitations should be acknowledged. Serum LECT2 levels may be influenced by metabolic liver diseases and systemic inflammatory conditions, potentially reducing specificity in mixed-etiology populations, as discussed by Kondo et al. [16] and Takata et al. [7]. Because our study focused exclusively on patients with CHB, extrapolation of these findings to other liver diseases such as nonalcoholic fatty liver disease or alcohol-associated liver injury should be done with caution. Additionally, inter-assay variability among commercially available ELISA kits may affect measurement consistency, emphasizing the need for assay standardization before widespread clinical adoption, as noted by Zhang et al. [15] and Gawrieh et al. [10].

Strengths

This study comprehensively evaluated serum LECT2 as a novel non-invasive biomarker for hepatic fibrosis by comparing it with established fibrosis indices such as APRI and FIB-4, while using liver biopsy and Scheuer fibrosis staging as the reference standard. The combination of biochemical, histopathological, molecular, and immunohistochemical analyses strengthened the reliability of the findings.

Limitations

The study was conducted at a single tertiary care center with a relatively modest sample size, which may limit the generalizability of the results. Furthermore, the cross-sectional design precluded assessment of longitudinal changes in serum LECT2 levels and their ability to predict fibrosis progression or response to antiviral therapy over time.

Conclusion

LECT2 emerges as a strong and consistent indicator of hepatic fibrosis in chronic hepatitis B, demonstrated by parallel increases in its serum concentration, hepatic protein expression, and mRNA levels across advancing fibrosis stages. Its diagnostic accuracy surpasses commonly used non-invasive indices such as APRI and FIB 4, reflecting active fibrogenesis rather than secondary inflammatory changes. These findings highlight the potential of LECT2 as a practical biomarker for non-invasive fibrosis assessment and routine disease monitoring in CHB. Larger multicenter studies are needed to validate optimal thresholds and support their integration into clinical practice.

Conflict of interest: Nil
Source Of Fund: Nil

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