The Role of Lipopolysaccharide-Binding Protein in Hepatitis B-Related Cirrhosis: Is There a Link to Portal Hypertension?

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ABSTRACT

Background: *Bacterial translocation plays a critical role in the pathogenesis of systemic inflammation in cirrhosis, particularly in cases related to chronic Hepatitis B infection. Lipopolysaccharide-binding protein (LBP) is a key acute-phase reactant that reflects exposure to endotoxins, yet its relationship with portal hypertension remains poorly defined. This study aimed to evaluate the correlation between serum LBP levels and spleen stiffness, a non-invasive marker of portal hypertension in patients with Hepatitis B-related cirrhosis.*

Methods: *A cross-sectional study was conducted on 50 patients with Hepatitis B-related cirrhosis at Dr. Mohammad Hoesin Hospital, Palembang, between September and December 2024. Serum LBP levels were measured, and spleen stiffness was assessed using transient elastography. Laboratory parameters, clinical characteristics, and virologic profiles were analyzed. Correlation analyses were performed using Pearson's or Spearman's correlation tests, as appropriate.*

Results: *The mean serum LBP level was 20.49 ± 7.34 µg/mL, while the mean spleen stiffness was 71.69 ± 17.74 kPa. A negative but non-significant correlation was observed between serum LBP levels and spleen stiffness ($r = -0.263$, $p = 0.065$). Serum LBP levels showed significant negative correlations with total, direct, and indirect bilirubin levels, as well as transaminase levels (AST and ALT), but not with platelet count, HBV DNA levels, or coagulation parameters.*

Conclusion: *In patients with Hepatitis B-related cirrhosis, serum LBP may reflect systemic inflammatory activity rather than the severity of portal hypertension. Further studies are needed to determine its prognostic value in cirrhotic complications.*

Keywords: *Bacterial Translocation, Binding Protein, Cirrhosis, Hepatitis B, Lipopolysaccharide-Portal Hypertension, Spleen Stiffness*

ABSTRAK

Latar belakang: *Translokasi bakteri merupakan mekanisme penting dalam patogenesis inflamasi sistemik pada sirosis, khususnya pada kasus yang disebabkan oleh infeksi Hepatitis B kronik. Lipopolysaccharide-binding protein (LBP) merupakan protein fase akut yang berperan sebagai penanda paparan endotoksin. Namun, hubungan antara kadar LBP serum dan derajat hipertensi portal masih belum jelas. Penelitian ini bertujuan untuk mengevaluasi korelasi antara kadar LBP serum dan kekakuan limpa sebagai penanda non-invasif hipertensi portal pada pasien sirosis akibat Hepatitis B.*

Metode: *Penelitian potong lintang ini melibatkan 50 pasien dengan sirosis akibat Hepatitis B yang dirawat di RSUP Dr. Mohammad Hoesin Palembang pada periode September hingga Desember 2024. Kadar LBP serum diukur menggunakan metode imunologis, dan kekakuan limpa dinilai dengan transient elastography. Data laboratorium, klinis, dan virologis dianalisis. Uji korelasi dilakukan menggunakan metode Pearson atau Spearman sesuai dengan distribusi data.*

Hasil: *Rerata kadar LBP serum sebesar 20,49 ± 7,34 µg/mL dan rerata kekakuan limpa sebesar 71,69 ± 17,74 kPa. Terdapat korelasi negatif yang tidak signifikan antara kadar LBP dan kekakuan limpa (r = -0,263; p = 0,065). Kadar LBP menunjukkan korelasi negatif yang signifikan dengan kadar bilirubin (total, langsung, dan tidak langsung) serta enzim transaminase (AST dan ALT), namun tidak berhubungan secara signifikan dengan jumlah trombosit, kadar DNA HBV, atau profil koagulasi.*

Kesimpulan: *Pada pasien sirosis akibat Hepatitis B, kadar LBP serum lebih mencerminkan aktivitas inflamasi sistemik dibandingkan dengan derajat hipertensi portal. Diperlukan penelitian lebih lanjut untuk menilai potensi nilai prognostik LBP terhadap komplikasi sirosis.*

Kata kunci: *Translokasi Bakteri, Protein Pengikat, Sirosis, Hepatitis B, Lipopolisakarida-Hipertensi Portal, Kekakuan Limpa*

INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global health concern, contributing significantly to the burden of chronic liver disease and cirrhosis. According to the World Health Organization (WHO), over 296 million individuals live with chronic HBV infection worldwide, with nearly 820,000 deaths annually attributed to its complications, including cirrhosis and hepatocellular carcinoma.[1] In Indonesia, HBV prevalence is among the highest in Southeast Asia, with estimates ranging from 7% to 10% in the general population.[2] Chronic HBV infection is responsible for a substantial proportion of cirrhosis cases in Indonesia, placing a heavy burden on the healthcare system in terms of both mortality and financial cost.[3,4] Hospitalizations resulting from decompensated cirrhosis and its complications require prolonged care, advanced diagnostics, and repeated interventions, thereby contributing to rising national healthcare expenditures.[5,6]

Portal hypertension (PH) is a key and life-threatening complication of cirrhosis, often determining clinical prognosis and driving the development of variceal bleeding, ascites, and hepatic encephalopathy.[7] The pathogenesis of PH involves increased resistance to portal blood flow due to intrahepatic architectural distortion and vascular remodeling, along with splanchnic vasodilation that increases portal inflow.[8] Clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg, is associated with a marked increase in the risk of variceal hemorrhage and death.[9] However, HVPG measurement is invasive, expensive, and not widely available in routine clinical practice,[10] especially in resource-limited settings such as Indonesia. Consequently, spleen stiffness measurement (SSM) via elastography has gained attention as a non-invasive, reproducible alternative. Guidelines from the European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), and Indonesian Association for the Study of the Liver (Ina-ASL) recognize SSM as a useful surrogate marker for assessing PH in patients with Hepatitis B-related cirrhosis.[11–13]

Recent advances in understanding the gut-liver axis have highlighted the role of bacterial translocation and endotoxemia in the progression of cirrhosis and the development of its complications.[14] The impaired intestinal barrier in cirrhosis allows for gut-derived microbial products, such as lipopolysaccharide (LPS), to enter the portal circulation, triggering systemic immune activation. Lipopolysaccharide-binding protein (LBP) is a liver-derived acute-phase protein that binds to LPS and facilitates its recognition by immune cells via the CD14/TLR4 complex.[15] Elevated

serum LBP levels have been proposed as a biomarker of bacterial translocation and systemic inflammation in patients with chronic liver disease.[16] Given its hepatic origin and rapid response to endotoxemia, LBP may also reflect both hepatocellular functional integrity and the extent of immune dysregulation in cirrhosis.

Several studies have reported elevated LBP levels in cirrhotic patients, often associating them with systemic inflammation and poor outcomes. Still, their relationship with portal hypertension—a major predictor of mortality and complications in advanced liver disease—remains unclear. Agiasotelli et al found that elevated serum LBP was associated with increased short-term mortality even in cirrhotic patients without overt infection.[17] Albillos et al showed that cirrhotic patients with ascites and high LBP levels had marked immune and hemodynamic disturbances, though portal pressure was not altered by antibiotic therapy.[18] Gioia et al. demonstrated that, among patients with portal hypertension due to porto-sinusoidal vascular disorder (PSVD), elevated LPS and zonulin levels were associated with endothelial dysfunction and platelet activation, reinforcing the role of gut-derived endotoxins in portal microvascular pathology.[19] In experimental models, Chuang et al revealed that LPS triggered exaggerated renal vasoconstriction in portal vein-ligated rats, suggesting that bacterial products may exacerbate systemic vascular dysfunction in portal hypertension.[20] However, evidence regarding the association between serum LBP levels and non-invasive markers of portal hypertension, including spleen stiffness, remains limited, particularly in patients with Hepatitis B-related cirrhosis. This study therefore aims to investigate the relationship between serum LBP levels and spleen stiffness and to evaluate the potential role of LBP as a surrogate biomarker for portal hypertension in HBV-related cirrhosis.

METHODS

Study Design

This study employed a cross-sectional observational design and was conducted at the Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, between September and December 2024. The objective was to assess the correlation between serum lipopolysaccharide-binding protein (LBP) levels and spleen stiffness as a non-invasive surrogate marker for portal hypertension in patients with hepatitis B-related cirrhosis.

Ethical Considerations

The research protocol was reviewed and approved by the Health Research Ethics Committee of Dr. Mohammad Hoesin General Hospital, Palembang, under approval number DP.04.03/D.XVIII.06.08/ETIKRSMH/12/2024. Prior to participation, all subjects received detailed information regarding the study objectives, procedures, and potential risks, and provided written informed consent. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Participants and Eligibility Criteria

Subjects were enrolled consecutively from the inpatient and outpatient services of the Department of Internal Medicine, Division of Gastroenterology and Hepatology. Eligible participants were adults (≥18 years of age) with clinically and/or radiologically diagnosed cirrhosis secondary to chronic hepatitis B virus (HBV) infection. Exclusion criteria included concurrent hepatocellular carcinoma, other causes of liver disease, active infection, recent use of antibiotics or probiotics, autoimmune disorders, or a history of splenectomy.

Data Collection

Clinical data were collected through structured interviews and review of medical records. Laboratory evaluations included complete blood count, liver function tests, coagulation profiles, and quantitative HBV DNA measurement. Serum LBP levels were measured using an enzyme-linked immunosorbent assay (ELISA). Spleen stiffness was assessed using vibration-controlled transient elastography (VCTE) performed by trained sonographers, with measurements obtained under fasting conditions using a standardized technique.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0. Data normality was assessed with the Kolmogorov-Smirnov test. Normally distributed data were presented as the mean ± standard deviation, while non-normally distributed variables were expressed as the median (minimum–maximum). Correlation analyses between LBP and clinical or elastographic variables were conducted using Pearson's or Spearman's correlation tests, as appropriate. A p-value < 0.05 was considered statistically significant. To further assess the relationship between serum LBP

levels and spleen stiffness as a dependent variable, simple linear regression analysis was performed. Variables with $p < 0.25$ in bivariate correlation were considered for inclusion in the regression model. A p-value < 0.05 was considered statistically significant, with 95% confidence interval was reported where applicable.

RESULTS

Data in **Table 1** describe the general characteristics, laboratory findings, and imaging results of the 50 subjects with hepatitis B-related cirrhosis. The mean age was 55.34 ± 8.46 years, with a predominance of male subjects (68%). The average body mass index was 22.83 ± 3.87 kg/m². Clinical features included ascites (50%), esophageal varices (46%), and splenomegaly (80%), while no patients presented with hepatic encephalopathy. Based on the Child-Pugh classification, 48% of patients were classified as class A, 46% as class B, and 6% as class C.

Mean hemoglobin level was 11.32 ± 2.12 g/dL, with a mean platelet count of 98,260 ± 35,183/mm³. The median total bilirubin level was 1.25 mg/dL, the median SGOT level was 41.50 IU/L, and the mean SGPT level was 39.88 ± 17.98 IU/L. The mean serum albumin was 3.21 ± 0.75 g/dL. The mean serum LBP level was 20.49 ± 7.34 µg/mL. The mean spleen stiffness measured by elastography was 71.69 ± 17.74 kPa, and the median liver stiffness was 24.65 kPa (range 12.5–75).

As shown in **Table 2,** bivariate analysis revealed a negative correlation between serum LBP and spleen stiffness (r = –0.263), although this result did not reach statistical significance (p = 0.065). However, multivariate linear regression analysis **(Table 3)** demonstrated that serum LBP was a significant predictor of spleen stiffness (B = –0.66; 95% CI: –1.22 to –0.09; p = 0.024). Other significant predictors included hemoglobin (p = 0.001), INR (p = 0.008), and splenomegaly (p = 0.001). Female gender showed a borderline association with spleen stiffness (p = 0.061). The final regression model yielded an adjusted R^2 of 0.378. To assess multicollinearity, variance inflation factors (VIFs) were calculated for the final model and ranged from 1.018 to 1.146, indicating the absence of significant multicollinearity.

Table 1. General Characteristics, Laboratory Findings, and Imaging Results of Study Participants

Characteristics	Participants (n=50)
Age (years)	55.34±8.46
Sex	
Male (n, %)	34 (68%)
Female (n, %)	16 (32%)
Body Mass Index (kg/m²)	22.83±3.87
Clinical Manifestations	
Ascites (n, %)	25 (50%)
Esophageal Varices (n, %)	23 (46%)
Hepatic Encephalopathy (n, %)	0
Splenomegaly (n, %)	40 (80%)
Child Pugh Turcotte Score (CP)	7 (5-11)
CP Class A (n, %)	24 (48%)
CP Class B (n, %)	23 (46%)
CP Class C (n, %)	3 (6%)
Laboratory Findings	
Hemoglobin (g/dL)	11.32±2.12
Leukocyte (/mm³)	5716.20±2159.07
Platelets (/mm³)	98260±35183
Absolute Eosinophil Count (/mm³)	150.47±98.08
Absolute Neutrophil Count (/mm³)	3059.80 (989.4-8177)
Absolute Lymphocyte Count (/mm³)	1462.81±630.50
Absolute Monocyte Count (/mm³)	459 (211.80-1515.60)
Total Bilirubin (mg/dL)	1.25 (0.50-10.80)
Conjugated Bilirubin (mg/dL)	0.60 (0.20-7.70)
Unconjugated Bilirubin (mg/dL)	0.60 (0.20-3.60)
AST (IU/L)	41.50 (17-98)
ALT (IU/L)	39.88±17.98
Albumin (g/dL)	3.21±0.75
Urea (mg/dL)	25 (8-100)
Creatinine (mg/dL)	0.90 (0.50-3.10)
INR	1.27 (1.07-2.12)
Immunoserology and Virology	
HBeAg positivity (n, %)	5 (10%)
HBV DNA (IU/mL)	81800 (0-1.46x10⁷)
*Lipopolysaccharide binding protein (*ng/ml*)*	20.49±7.34
Imaging	
*Spleen Stiffness (*kPa)	71.69±17.74
Liver Stiffness (kPa)	24.65 (12.5-75)

CP: Child-Pugh; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International normalized ratio; HBV DNA: Hepatitis B virus Deoxyribonucleic acid

Table 2. Correlation between LBP and Spleen Stiffness

Variable	Spleen Stiffness (kPa)	
	r	p
*Lipopolysaccharide binding protein (*µg/ml*)*	-0.263	0.065

Table 3. Linear Regression Analysis of Predictors of Spleen Stiffness

Variable	Bivariate		Multivariate		
	r	p	B	IK95%	p
LBP (ng/ml)	-0.26	0.065[1]	**-0.66**	**-1.22 sd -0.09**	**0.024**
Age (years)	-0.08	0.559[1]			
Body Mass Index (kg/m^2)	-0.05	0.705[1]			
Skor CP	0.18	0.210[2]			
Hemoglobin (g/dL)	**-0.29**	**0.044[1]**	**-3.48**	**-5.51 sd -1.46**	**0.001**
Leukocyte (/mm^3)	-0.02	0.868[1]			
Platelets (/mm^3)	-0.01	0.973[1]			
Absolute Eosinophil Count (/mm^3)	-0.19	0.174[1]			
Absolute Neutrophil Count (/mm^3)	0.01	0.952[2]			
Absolute Lymphocyte Count (/mm^3)	-0.22	0.119[1]			
Absolute Monocyte Count (/mm^3)	0.09	0.542[2]			
Total Bilirubin (mg/dL)	0.02	0.878[2]			
Conjugated Bilirubin (mg/dL)	0.04	0.803[2]			
Unconjugated Bilirubin (mg/dL)	0.03	0.827[2]			
AST (IU/L)	0.06	0.677[2]			
ALT (IU/L)	-0.09	0.537[1]			
Albumin (g/dL)	-0.27	0.055[1]			
Urea (mg/dL)	0.08	0.560[2]			
Creatinine (mg/dL)	0.02	0.911[2]			
INR	**0.29**	**0.038[2]**	**23.97**	**6.49 sd 41.45**	**0.008**
HBV DNA (IU/mL)	-0.11	0.428[2]			
Liver Stiffness (kPa)	0.13	0.363[2]			
Female			-8.75	-17.90 sd 0.40	0.061
Clinical Splenomegaly			**16.97**	**6.98 sd 27.03**	**0.001**

LBP: Lipopolysaccharide-binding protein; CP: Child-Pugh; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International normalized ratio; HBV DNA: Hepatitis B virus Deoxyribonucleic acid. Multicollinearity assessment (final model): VIF ranged 1.018–1.146 (INR 1.071; LBP 1.061; spleen 1.018; sex 1.146; hemoglobin 1.134)

DISCUSSION

This study investigated the relationship between serum lipopolysaccharide-binding protein (LBP) and spleen stiffness (SS) in patients with hepatitis B-related cirrhosis and identified a significant inverse association between LBP and SS in a multivariate analysis. While bivariate testing did not yield statistically significant results, adjustment for key covariates revealed that higher LBP levels were associated with lower SS values. This is a notable finding, as spleen stiffness is an established non-invasive surrogate for portal pressure, and LBP is increasingly recognized as a marker of microbial translocation and systemic immune activation. These results suggest that LBP, despite being a pro-inflammatory marker, does not uniformly increase in tandem with the severity of portal hypertension severity and may instead reflect earlier or dynamic immune states in cirrhosis progression.

The negative correlation between LBP and spleen stiffness observed in multivariate models may appear counterintuitive but can be explained by the complex immunopathological landscape of chronic hepatitis B cirrhosis. In early or compensated stages, LBP may rise in response to increased exposure to gut-derived endotoxin, reflecting heightened immune surveillance and preserved hepatic synthetic function.[21,22] As the disease advances and liver function deteriorates, LBP synthesis may decline, while portal hypertension and spleen stiffness increase due to long-standing vascular resistance and fibrotic remodeling.[23] This decoupling of LBP from SS in late-stage disease may account for the lack of correlation in unadjusted analysis. Additionally, spleen stiffness, although correlated with portal pressure, can be influenced by splenic congestion, fibrosis, or inflammation—factors not directly aligned with transient changes in endotoxin-driven immune responses.[24] The non-significant association between LBP and liver stiffness in this cohort further supports the idea that LBP is more reflective of immune activation than fibrotic or hemodynamic burden alone, as reported in studies by Simbrunner et al and Albillos et al.[18,25]

Previous studies have demonstrated varying relationships between LBP and markers of portal hypertension, though consistent correlations remain elusive. For example, Albillos et al identified elevated LBP levels in ascitic cirrhotic patients, which were associated with systemic inflammatory markers (such as IL-6 and TNF-α), immune activation (e.g., sCD14), and reduced vascular resistance, suggesting hemodynamic alterations secondary to bacterial

translocation.[18] However, their study also reported that LBP levels did not correlate with portal pressure, as measured by HVPG, suggesting that LBP may reflect immune dysregulation rather than direct mechanical pressure. Similarly, Simbrunner et al found that elevated LBP was part of an early immune activation profile in compensated cirrhosis, but again, this increase was not necessarily linked to the severity of portal hypertensive severity.[25] These findings support the current study's results, where LBP was not significantly correlated with spleen stiffness in univariate analysis, but showed a significant negative association after multivariate adjustment, indicating the presence of confounding variables such as hemoglobin and INR. One plausible interpretation is that LBP elevation occurs in early disease stages, when gut-derived endotoxin exposure is high and hepatic synthesis is still preserved, while spleen stiffness — as a proxy for portal hypertension — tends to increase during later vascular remodeling and congestion.[25,26] As such, LBP and SS may represent distinct but intersecting biological processes along the cirrhosis continuum: the former reflecting immune activation and the latter reflecting long-standing portal resistance. This temporal dissociation could explain the seemingly paradoxical inverse association observed in adjusted models.

The pathophysiological relevance of LBP in cirrhosis centers on its role as a mediator of the innate immune response to circulating lipopolysaccharides (LPS), which translocate from the gut due to compromised intestinal barriers[27,28] LBP facilitates the binding of LPS to CD14 and TLR4 receptors on monocytes and macrophages, triggering the release of inflammatory cytokines such as TNF-α and IL-6.[29] These mediators contribute to systemic vasodilation, endothelial dysfunction, and further decompensation in cirrhosis, but their immediate impact on portal pressure or splenic remodeling may be modest or delayed. Thus, while LBP is a sensitive marker of microbial translocation, it may not linearly reflect the mechanical changes assessed by spleen stiffness.

Interestingly, the relationship between LBP and biochemical indices such as aminotransferases and albumin offers further insight into the state of hepatocellular function. Lower LBP levels in patients with higher Child-Pugh scores and reduced hemoglobin may reflect hepatic synthetic failure, as LBP is produced predominantly by hepatocytes.[30] This could explain why, in some cases, patients with severe portal hypertension and high SS values exhibited low LBP concentrations. The dissociation between inflammatory markers and fibrotic burden is not unique to LBP; it is also observed in other inflammatory liver conditions, where immune activation precedes structural damage.

From a clinical perspective, these findings emphasize the importance of using integrated biomarkers to assess the progression of cirrhosis. While spleen stiffness remains a promising tool for non-invasive estimation of portal pressure, its interpretation may benefit from concurrent evaluation of systemic immune markers like LBP. In settings where hepatic venous pressure gradient (HVPG) measurement is unavailable, this combination could offer a pragmatic approach to identifying patients at risk of complications related to portal hypertension. Moreover, the inclusion of LBP in predictive algorithms may enhance the stratification of patients in both research and practice, especially in chronic HBV-endemic regions.

The strength of this study lies in its focused cohort of hepatitis B-related cirrhotic patients and the use of objective spleen stiffness measurement via elastography. This reduces confounding from etiologic heterogeneity and improves internal validity. However, several limitations merit consideration. The cross-sectional design limits the ability to infer temporal or causal relationships. The modest sample size, though powered for preliminary associations, may have been insufficient to detect subtle interactions. Additionally, the exclusion of other bacterial translocation markers, such as sCD14 or endotoxin levels, restricts the ability to contextualize LBP within the broader immune landscape. Future studies should incorporate these markers and explore longitudinal trajectories of LBP in relation to spleen stiffness and portal hemodynamics. Despite these limitations, our findings contribute to the evolving understanding of the gut-liver axis in cirrhosis and suggest that serum LBP, when interpreted within a multivariable framework, may offer insight into the inflammatory dynamics associated with portal hypertension. This opens avenues for developing non-invasive, integrative models to monitor cirrhotic patients, particularly in hepatitis B-endemic areas.

CONCLUSION

Serum LBP levels were inversely associated with spleen stiffness in patients with hepatitis B–related cirrhosis, suggesting a complex relationship between bacterial translocation–related inflammation and portal hypertension rather than indicating that LBP is a direct hemodynamic marker of portal hypertension. Future

studies should use longitudinal designs and include direct portal hemodynamic assessment to clarify temporal trajectories of LBP in relation to spleen stiffness and portal pressure.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

FUNDING

This research did not receive any external funding.

ACKNOWLEDGMENT

The authors have no additional acknowledgments to declare.

AUTHOR CONTRIBUTIONS

Conceptualization, EF and SU; methodology, EF; validation, EF, SU, and L; formal analysis, L; investigation, EF and L; resources, IS; data curation, EF; writing—original draft preparation, EF and SU; writing—review and editing, SU, L, IS, VOB, MAA, and AAS; visualization, VOB; supervision, SU; project administration, SU; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript

DATA AVAILABILITY

The data that support the findings of this study are not publicly available but can be obtained from the corresponding author upon reasonable request.

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