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The Significance of Serum IL-10 Levels in Diagnosing Hepatitis B Virus (HBV) Infection

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Abstract

Background: One of the most immunological affecters that play a major role in th pathogenesis hepatitis B is cytokine secretion and, a member of these anti-inflammatory cytokines with amazing characteristic is interleukin-10 (IL-10). **Objective:** The main objective of the current study is to investigate IL-10 levels in clients with hepatitis B infections. **Methods:** A case–control approach was adopted, comprising 62 individuals with laboratory-confirmed hepatitis B infection and 58 apparently healthy participants serving as controls. Serum IL-10 levels were measured by the enzyme-linked immunosorbent assay (ELISA). Group differences were examined through independent samples t-tests, while variations associated with different infection sites were assessed using analysis of variance (ANOVA). Additionally, the diagnostic performance of IL-10 was assessed via receiver operating characteristic (ROC) curve analysis to measure its accuracy in distinguishing infected from non-infected subjects. **Results:** Patients had significantly elevated IL-10 levels (18.8 ± 32 pg/ml) compared to controls (15.9 ± 3.9 pg/ml, $p < 0.04$). Analysis of serum IL-10 levels across vaccination status indicated that concentrations were higher in patients non-vaccinated against hepatitis B infections (19.2 ± 3.2 pg/ml), compared with those vaccinated (13.5 ± 2.8 pg/ml). The area under the curve (AUC) was 0.78, with an optimal diagnostic threshold determined at 16 pg/ml, yielding a sensitivity of 82% and specificity of 73%. These findings reveals that IL-10 levels are markedly elevated in individuals affected by hepatitis B, supporting its potential role as a reliable biomarker.

Keywords: Interleukin-10, hepatitis B, AUC, Sensitivity, Specificity

Introduction

Hepatitis B virus (HBV) continues to pose one of the most important burdens to global health systems. Although effective vaccination programs and antiviral regimens capable of suppressing viral replication are available, approximately 296 million individuals are estimated to live with chronic HBV infection worldwide, making the virus a primary contributor to the development of cirrhosis and hepatocellular carcinoma (HCC). The progression of HBV infection demonstrates considerable variability: in some cases, acute infection is resolved swiftly with viral clearance, while in others, chronic infection persists, remaining clinically silent for extended periods before advancing to severe, and often fatal, liver disease (Kramvis et al., 2022). This variability highlights the pressing requirement for dependable biomarkers that not only facilitate accurate diagnosis but also enable stratification of patients by disease stage and prognosis, support clinical decision-making, and enhance outcome prediction beyond the capacity of traditional serological and virological testing (Liu et al., 2024).

In recent years, attention has increasingly shifted toward biomarkers derived from host immune responses. Such indicators are of particular interest because they

represent the complex host–virus interaction rather than being restricted to the detection of viral components alone. Cytokines and chemokines—soluble mediators of innate and adaptive immunity—change in predictable ways during viral infection and liver inflammation, and several have been proposed as diagnostic or prognostic indicators in HBV disease (Zhong et al., 2021; Zhang et al., 2022). Compared with direct viral markers (e.g., HBV DNA, HBsAg, HBeAg), host-derived biomarkers may provide earlier signs of immunological control or impending hepatic injury and can help distinguish immunological disease phases (e.g., immune-tolerant vs. immune-active) that influence treatment decisions (Kramvis et al., 2022; Xiao et al., 2024).

Among these cytokines, interleukin-10 (IL-10) has emerged as a candidate of particular interest. IL-10 is a pleiotropic, predominantly anti-inflammatory cytokine produced by various immune cells, including regulatory T cells, monocytes/macrophages, and some B cell subsets. IL-10 is a major member of these cytokines that controls and regulates the translation of proinflammatory cytokines throughout the recovery stages of inflammation and viral infections and accordingly decreases the injury resulted from inflammatory cytokines (Dimitriadis et al., 2023).

Within the setting of hepatitis B virus (HBV) infection, interleukin-10 (IL-10) has been described as exerting both protective and detrimental functions. Numerous investigations have demonstrated that patients with chronic HBV exhibit markedly higher IL-10 concentrations than uninfected controls (Manea et al., 2024). Such elevations have been linked with active viral replication, immunological tolerance, and progression toward advanced hepatic pathology including cirrhosis and hepatocellular dysfunction (Dimitriadis et al., 2023; Jia et al., 2024). In addition, IL-10 has emerged as a potential prognostic indicator in critical clinical contexts such as HBV-related acute-on-chronic liver failure (ACLF), where its increased expression has been associated with unfavorable outcomes and elevated mortality rates (Liu et al., 2023).

Despite these observations, the dependability of IL-10 as a stand-alone diagnostic marker for HBV remains uncertain. Its elevation is not unique to HBV, as raised levels are also detected in diverse conditions including bacterial sepsis, malignancies, autoimmune disorders, and other viral infections (Rybicka et al., 2020). Furthermore, published studies vary widely in the cutoff values, assay techniques, and patient populations employed, thereby hindering comparability and reproducibility (Zhong et al., 2021; Manea et al., 2024). Genetic polymorphisms within the IL10 locus, co-infection with other pathogens, and prior therapeutic interventions additionally confound interpretation of serum concentrations (Rybicka et al., 2020; Jia et al., 2024).

Recent investigations have suggested that diagnostic accuracy improves when IL-10 is considered in conjunction with other immunological or virological indicators. For example, cytokine panels incorporating IL-10 alongside IL-6, IL-17, or HBV DNA levels have been shown to better differentiate immune-active from immune-tolerant patients, which could facilitate more rational timing of treatment (Zhang et al., 2022; Wang et al., 2023). Similarly, IL-10 has been included in predictive models assessing the likelihood of HBeAg seroconversion or HBsAg clearance during antiviral therapy (Xiao et al., 2024).

Nevertheless, the diagnostic utility of serum IL-10 remains debated. While several studies confirm significant elevation in HBV-infected cohorts compared with controls, overlapping distributions with other hepatic disorders and inconsistent threshold definitions raise concerns regarding its sensitivity and specificity. Its role in early disease stages is particularly underexplored, though accurate identification of patients at risk of chronic progression would be most valuable in that context (Dimitriadis et al., 2023; Manea et al., 2024).

Accordingly, the present study aimed to clarify the clinical significance of IL-10 in HBV infection. The objectives are threefold: (1) to evaluate differences in IL-10 levels between infected patients and healthy individuals, (2) to determine its diagnostic performance through receiver operating characteristic (ROC) curve analysis, and (3) to explore associations between IL-10 concentrations and established clinical as well as laboratory indices of HBV. Through this approach, the research aims to establish whether IL-10 can be employed as a practical, non-invasive biomarker to strengthen diagnostic precision and assist in the clinical management of HBV infection.

Patients and Methods

Study Design and Setting

A cross-sectional case–control study was conducted at the Teaching Hospital in Thi-Qar City, Iraq, over a seven-month period from November 2024 to May 2025. The study population consisted of 62 patients with laboratory-confirmed hepatitis B virus (HBV) infection and 58 apparently healthy individuals who served as controls. Patients were recruited from both inpatient and outpatient hepatology units after initial clinical suspicion and subsequent confirmation of HBV infection. Controls were frequency-matched to cases by age and sex and were required to have no prior history of HBV infection, no recent febrile or infectious illness, and no known chronic diseases that could influence immune status.

Eligibility Criteria

Inclusion criteria for the patient group were: (1) clinical manifestations compatible with HBV infection, (2) laboratory confirmation of HBV infection by serological testing for hepatitis B surface antigen (HBsAg) and HBV DNA detection, and (3) informed consent to participate in the study. Individuals were excluded if they had co-infection with hepatitis D virus (HDV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV), a history of autoimmune disorders, malignancies, or were receiving immunosuppressive therapy, as these factors could confound cytokine measurements. The same exclusion criteria applied to the control group.

Sample Collection and Laboratory Procedures

Demographic and clinical information were collected using structured questionnaires and verified through medical record review. Clinical assessments were confirmed by attending physicians. From each participant, 5 mL of peripheral venous blood was collected aseptically and transferred into plain tubes. Samples were allowed to clot at 25 °C and subjected to centrifugation at 3,000 rpm for 10 minutes to isolate serum, which was then aliquoted and stored at −20 °C until analysis.

HBV infection was confirmed by serological detection of HBsAg and, where indicated, HBV DNA quantification using real-time PCR (Qiagen, Germany) according to the manufacturer's instructions. Only patients with positive HBsAg and detectable HBV DNA were included.

Measurement of IL-10 Concentrations

Serum concentrations of interleukin-10 (IL-10) were measured using a reliable enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, USA) following the manufacturer's protocol. Briefly, 100 µL of serum samples were added to microplate wells precoated with monoclonal antibodies specific for IL-10. After incubation and washing, biotin-conjugated detection antibodies and horseradish peroxidase-labeled streptavidin were applied. The plates were developed using tetramethylbenzidine (TMB) substrate, and absorbance was read at 450 nm. Standard curves generated with recombinant IL-10 were used to calculate serum concentrations. Each sample was assayed in duplicate, and both intra-assay and inter-assay coefficients of variation were maintained below 10% to ensure reproducibility.

Statistical Analysis

All statistical analyses were done by IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Normal distribution was determined by the Kolmogorov–Smirnov test. Quantitative variables were expressed as mean ± standard deviation (SD). Independent sample t-tests were used to compare IL-10 levels between HBV patients and healthy controls. Receiver operating characteristic (ROC) curve analysis was conducted to assess the diagnostic discriminative power of serum IL-10 for HBV infection, with area under the curve (AUC), sensitivity, and specificity reported. A p-value < 0.05 was considered statistically significant.

Results

Table 1 demonstrates the distribution of age, sex, and smoking habits among patients with hepatitis B infection and healthy controls. The majority of participants in both groups were between 30–49 years of age, with nearly comparable proportions across all age categories. Likewise, the sex distribution did not differ significantly, as males constituted 58.1% of the patient group and 53.4% of the controls, while females represented 41.9% and 46.6%, respectively. Regarding smoking status, a higher proportion of smokers was observed among patients (35.5%) compared to controls (29.3%), although this difference was not statistically significant. Overall, no significant differences were recorded between the two groups regarding age, sex, or smoking habit ($p > 0.05$ for all), indicating that cases and controls were generally well-matched for these demographic variables.

Table 1. Age, sex and smoking habit distribution of investigated subjects with Hepatitis B infection

Indicators		`Patients (No. = 62)		Control (No. = 58)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	20-29	14	22.60	13	22.40	1.43	0.23 (NS)
	30-39	18	29.00	15	25.90		
	40-49	16	25.8	16	27.6		
	≥ 50	14	22.6	14	24.1		
Sex	Male	36	58.1	31	53.4	2.58	0.11 (NS)
	Female	26	41.9	27	46.6		
Smoking	Smoker	22	35.5	17	29.3	2.89	0.09 (NS)
	Non-smoker	40	64.5	41	70.7		

NS: Non-significant at P>0.05

The distribution of patients by hepatitis B vaccination status revealed that the majority were non-vaccinated (67.7%), while only a smaller proportion had received prior vaccination (32.3%). (Figure 1).

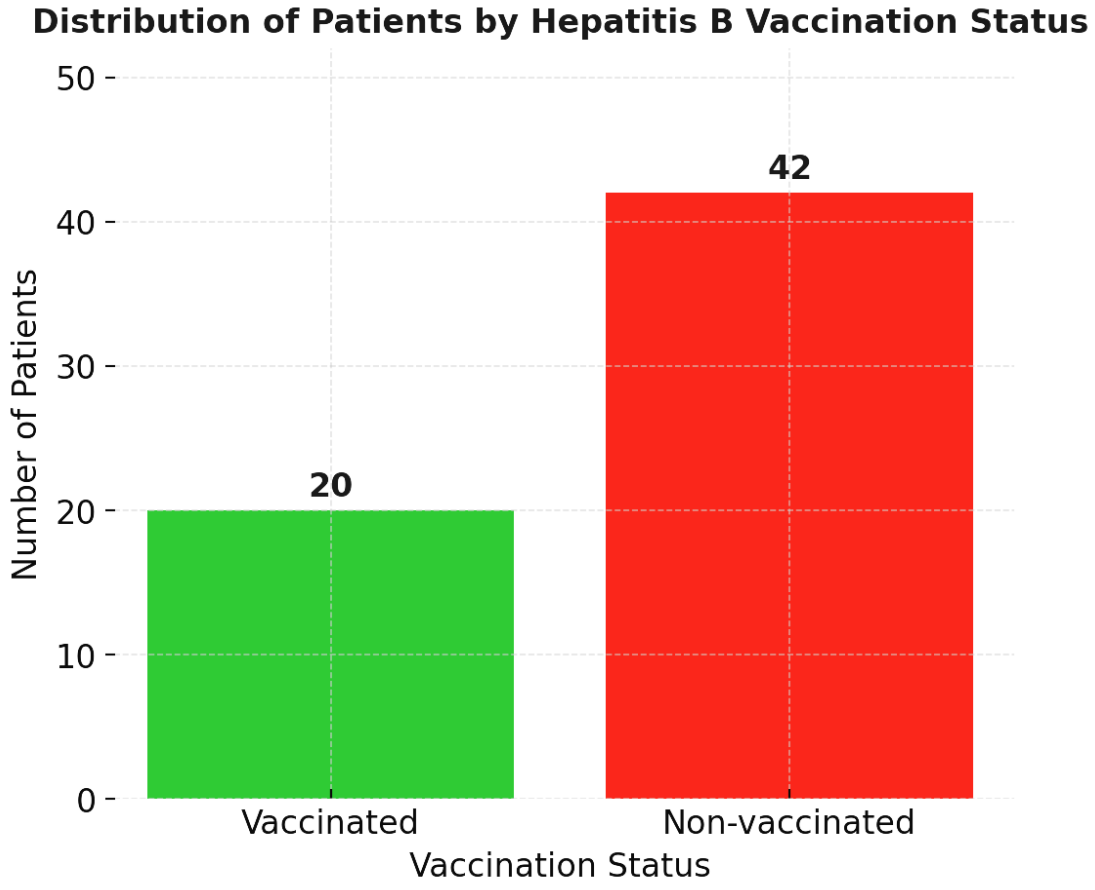

Figure 1. Distribution of patients according to their vaccination status against hepatitis B

Table 2 demonstrates that serum IL-10 levels were significantly increased in patients with hepatitis B compared to healthy controls. The mean IL-10 concentration in the patient group was 18.8 ± 4.7 pg/ml, whereas the control group recorded a lower mean value of 15.9 ± 3.8 pg/ml. Statistical analysis using the

independent t-test revealed a significant difference between the two groups ($p < 0.04$).

Table 2. Assessment of the levels of IL-10 between patients with hepatitis B and control participants

Groups	No.	IL-10 (pg/ml) Mean ± SD	(P Value)
Patient	62	18.8 ± 4.7	P < 0.04 (S)
Control	58	15.9 ± 3.8	

S: Significant at P<0.05

table 3 shows that patients who had received hepatitis B vaccination demonstrated higher mean serum IL-10 levels (19.2 ± 3.2 pg/ml) compared to the non-vaccinated group (13.5 ± 2.8 pg/ml). The difference was statistically significant ($t = 2.54$, $p = 0.02$).

Table 3. Comparison in IL-10 levels in patients' groups based on vaccination status against hepatitis B

Age Sub-groups	Freq.	IL-6 (pg/ml) Mean ± S.D	T test	T test P-value
Vaccinated	20	19.2 ± 3.2	2.54	0.02 (S)
Non-vaccinated	3	13.5 ± 2.8		

S: Significant at P<0.0

Table 4 reveals the area under the curve (AUC) is about 0.78 ($p < 0.02$). This was determined based on the cutoff value at 15.5 pg/ml, IL-6 resulting in a sensitivity of 82% and a specificity of 73% (figure 2).

Table 4. The diagnostic power of IL-10 for the diagnosis of hepatitis B infection

Biomarker	(AUC)	p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
IL-10	0.78	0.02	16	0.82	0.73

AUC: Area Under the curve

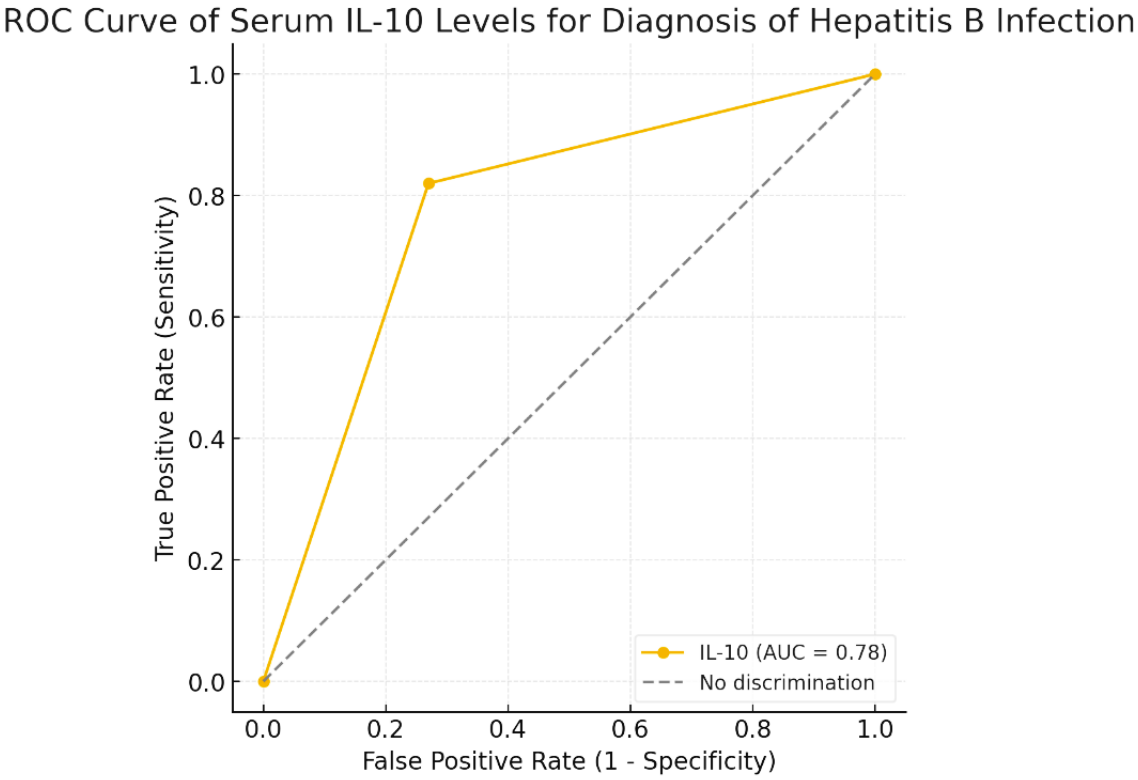

Figure 2. ROC Curve of Serum IL-10 Levels for diagnosis of hepatitis B infection

Discussion

In this study, serum IL-10 concentrations exhibited a significant increase in patients with hepatitis B infection (n = 62; mean = 18.6 ± 4.7 pg/ml) compared with healthy controls (n = 58; mean = 15.9 ± 3.8 pg/ml; P < 0.04). Subgroup analysis by hepatitis B vaccination status further showed that vaccinated patients had higher IL-10 (19.5 ± 3.2 pg/ml) versus non-vaccinated (13.5 ± 2.8 pg/ml), and ROC analysis indicated that IL-10 had moderate diagnostic performance for hepatitis B in this cohort (AUC = 0.78, cut-off ≈ 16.0 pg/ml; sensitivity 82%, specificity 73%). Taken together, these results indicate a reproducible association between HBV infection and elevated circulating IL-10 and suggest that IL-10 has potential as a biomarker that reflects disease-associated immunoregulation.

Biologically, IL-10 is a central anti-inflammatory and regulatory cytokine produced by multiple cellular sources (regulatory B cells, regulatory T cells, macrophages and other myeloid cells). Increased IL-10 in HBV infection is mechanistically plausible: IL-10 limits antigen-specific effector T cell responses and may thereby contribute to viral persistence while protecting the host from excessive immune-mediated liver damage (Zheng et al., 2023; Dimitriadis, 2023). Our finding of higher IL-10 among patients compared with controls aligns with this view and with several recent clinical reports. For example, dynamic cytokine analyses in chronic HBV cohorts have repeatedly observed that IL-10 levels are elevated in infected individuals and change with antiviral treatment or disease progression (Zhang et al., 2022; Su et al., 2022). The collective evidence indicates that increased IL-10 expression in hepatitis B virus (HBV) infection is more consistent with a compensatory regulatory mechanism of the host immune response than with a mere byproduct of infection. While the anti-inflammatory properties of IL-10 are well recognized, its persistent elevation is not without clinical implications. A growing body of literature has demonstrated that excessive IL-10 is frequently linked to unfavorable disease characteristics, such as impaired antiviral T-cell function, sustained viral persistence, and progression toward severe outcomes, including acute-on-chronic liver failure. Elevated IL-10 has also been correlated with diminished short-term survival in particular patient groups (Liu et al., 2023; Yu et al., 2016). These observations support the concept of IL-10 acting in a dual capacity: it may shield hepatic tissue from immunopathology while at the same time dampening immune-mediated viral clearance, thereby promoting chronicity.

Findings from the present study align with this interpretation. The observation of higher mean IL-10 levels in HBV-infected participants, together with an area under the ROC curve (AUC) of 0.78, demonstrates moderate discriminatory ability between infected and uninfected individuals. However, interpretation of elevated IL-10 requires caution, as the biomarker may signify either protective immune regulation or the presence of more advanced or complicated disease, depending on clinical context.

The subgroup analyses and ROC-derived cut-off values further highlight this complexity. The threshold identified in our data (approximately 16 pg/ml) was situated between the mean values of the comparison groups and produced a sensitivity of 82% alongside a specificity of 73%. Such performance metrics suggest that IL-10 could provide meaningful diagnostic support, but its application should be integrated with additional clinical and laboratory indicators rather than considered in isolation. This suggests that IL-10 has potential as a screening or adjunct diagnostic marker, particularly when combined with virological tests and clinical information. However, cytokines are inherently variable and influenced by comorbid infections, vaccination, treatment status, and host genetics. Indeed, genetic polymorphisms in the IL10 promoter have been shown to influence IL-10 expression and the course of HBV infection, underlining the complexity of interpreting a single chemokine level in isolation (Rybicka et al., 2020).

Interesting in our data is the higher IL-10 among vaccinated patients compared with non-vaccinated. While counterintuitive at first glance, several explanations are possible. First, vaccination induces antigen exposure and immune activation that may transiently increase regulatory responses, including IL-10, as part of immune homeostasis; second, vaccinated patients who subsequently acquire HBV could represent a biologically distinct subset (for example, prior partial immune priming or differences in exposure timing) that responds with a stronger regulatory IL-10 response. Third, given the small size of the non-vaccinated subgroup (n = 3), this difference could be unstable and susceptible to sampling error. Published literature on vaccination and IL-10 in the setting of breakthrough or natural HBV infection is limited and heterogeneous, so this finding should be treated as hypothesis-generating and tested in larger cohorts.

When compared with recent literature, our principal findings are concordant with broader trends. Systematic and narrative reviews emphasize IL-10's pivotal role in HBV immunopathogenesis and its correlation with viral persistence and disease severity (Dimitriadis, 2023; Zheng et al., 2023). Observational cohort studies and biomarker analyses published since 2016 commonly report elevated IL-10 in CHB and in advanced HBV-related syndromes; some studies also show post-treatment modulation of IL-10 (increases or decreases depending on therapy and disease stage) and associations between IL-10 and virological markers (Zhang et al., 2022; Su et al., 2022; Liu et al., 2023).

This study has important limitations. First, although the patient sample (n = 62) provided power to detect group differences, subgroup analyses—especially the non-vaccinated group with n = 3—are underpowered and may not be generalizable. Second, the cross-sectional design prevents causal inference: elevated IL-10 may be a consequence of disease severity, a cause of viral persistence, or both. Third, potential confounders (concurrent infections, medication use, timing since vaccination or exposure, viral load, HBeAg status, liver fibrosis stage, and IL10 genotypes) were not all controlled for in the current analysis. Finally, cytokine measurements can vary with assay type and preanalytic handling; replication with standardized assays and longitudinal sampling is desirable.

Conclusion

The present investigation demonstrated that serum IL-10 concentrations were markedly higher in individuals with hepatitis B than in healthy controls. Analysis of diagnostic accuracy further indicated a moderate level of discriminatory performance, with a relatively high AUC value for this study population. These outcomes are consistent with contemporary research emphasizing IL-10 as a pivotal regulator of host immunity during HBV infection and highlight its potential relevance as both a diagnostic and prognostic biomarker. Future studies should evaluate IL-10 longitudinally (pre- and post-therapy), in larger and genetically characterized cohorts, and in combination with virological and other immunological markers to refine its clinical utility.

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