

Research Article

# Association of IL-37 Levels with Liver Function Enzymes in a Sample of Iraqi HBV-Infected Patients

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## I N F O

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## A B S T R A C T

**Background:** Despite extensive efforts towards its elimination, Hepatitis B virus (HBV) continues to be a major concern, posing risk of liver cirrhosis and hepatocellular carcinoma (HCC) in those infected. Therefore, there is a need for reliable biomarkers to accurately assess the infection. While liver enzymes remain the standard diagnostic tools, the anti-inflammatory and anti-tumor interleukin-37 (IL-37) has emerged as a potential biomarker.

**Aims:** To assess the relationship between serum IL-37 and liver enzymes in HBV patients.

**Methods:** Liver enzymes were measured by Fujifilm's dry chemistry system (Fuji Dri-Chem), whereas Enzyme-Linked Immunosorbent Assay (ELISA) was utilized for determination of IL-37 levels. A total of 100 patients (37 females, 63 males; mean age: 42 years) from the Medical City in Baghdad, along with 50 age/sex-matched controls (23 females, 27 males; mean age: 38 years) were enrolled in this study.

**Results:** The study has demonstrated highly significant variation in TSB, GOT, and ALP ( $P < 0.01$ ) between patients and controls. Additionally, Sex-based differences in TSB and GOT also showed a significant variation ( $P < 0.01$ ), and the diagnostic value was confirmed by receiver operating characteristic (ROC) curve analysis. Furthermore, a high significant divergence in IL-37 levels was observed between patients and controls [ $P < 0.01$ , IQR: 32.4 vs. 61.4 Picogram/Millilitre (pg/mL), respectively], with ROC analysis supporting its clinical relevance ( $P < 0.01$ ). Also, significant variation was noted in levels of IL-37 in correlation with HBV serological markers, particularly in patients with negative HBsAg and anti-HBcAb (119.8 vs 63.16 pg/mL, respectively)

**Conclusions:** IL-37, in combination with liver enzymes, may serve as a valuable biomarker panel for monitoring HBV infection

**Keywords:** Biomarkers; Cytokines; Hepatitis B Virus; IL-37; Liver Enzymes

## Introduction

Hepatitis B virus (HBV) infection affects approximately 350 million individuals globally, posing a substantial burden on health systems. This burden is reflected in high morbidity and mortality associated with HBV-related liver complications, including chronic hepatitis, hepatic failure, cirrhosis, and hepatocellular carcinoma (HCC).<sup>1,2</sup> Despite the widespread vaccination programs, HBV was responsible for nearly one million deaths in 2020 alone.<sup>3</sup> Interestingly, HBV itself does not exert direct cytopathic effects on hepatocytes. Instead, the clinical manifestations of the infection are largely attributed to complex interactions between the host immune system and the virus.<sup>4</sup> A critical aspect of this immune response is *in vivo* cytokine milieu, which plays a pivotal role in pathogenesis and progression of HBV infection. Numerous cytokines are implicated in initiating and modulating the immune response against HBV, acting as both mediators of liver inflammation and effectors of antiviral defence.<sup>5</sup>

Interleukin-37 (IL-37, previously known as IL-1F7), a recently identified member of the IL-1 cytokine family, has garnered attention for its immunomodulatory properties.<sup>6</sup> IL-37 is produced by various human cells, including monocytes and plasma cells, and exists in five isoforms (IL-37a–e). It is synthesized as an inactive precursor that requires cleavage to achieve maturation and subsequent secretion.<sup>7–9</sup> The cellular receptor of IL-37 is composed of two subunits, the IL-18 receptor alpha chain (IL-18R $\alpha$ ) and the single immunoglobulin IL-1 receptor-related molecule (SIGIRR). Upon ligand binding, the IL-37/IL-37R complex initiates intracellular signalling cascades that result in down-regulation of pro-inflammatory gene expression and suppression of cytokine production.<sup>10</sup>

IL-37 has been shown to have broad protective effects against excessive inflammatory responses and tissue damage, as evidenced by its dysregulation in various auto-inflammatory disorders and infectious diseases.<sup>11,12</sup> IL-37 has also gained interest for its potential role in inhibiting tumor growth and metastasis, as well as in modulating tumor microenvironment.<sup>13</sup> As a result, IL-37 is being increasingly recognized as a promising biomarker and therapeutic target in both inflammatory conditions and cancers.<sup>14</sup>

The objective of the current study was to investigate the correlation between liver enzymes and IL-37 levels among HBV-infected Iraqi patients. This study, to our knowledge, is the first local study to assess serum levels of IL-37 in correlation with serological markers of HBV infection.

## Materials and Methods

### Study groups

A total of 150 participants, 100 patients attending Gastroenterology and Hepatology Hospital in Baghdad,

who were diagnosed with hepatitis B virus infection and 50 healthy controls who tested negative for hepatitis B surface antigen (HBsAg), were enrolled in the study during the period January to June 2024. Age and sex distribution of the participants were as follows. Ratio of female and male patients was 37% and 63%, respectively; mean age was 44 and 41 years, respectively, Female and male matching apparently healthy controls were 46% and 54%, with mean age 37 and 36 years, respectively.

### Sample Collection

Blood samples (5 mL, each) were collected from all participants. From each specimen, 3 mL was centrifuged to obtain serum, which was then divided into aliquots and stored at  $-20^{\circ}\text{C}$  until further analysis. HBV infection was confirmed by four viral serological markers plus testing for presence of HBsAg in the study groups. These markers are anti-hepatitis B surface antigen (anti-HBs), Anti-Hepatitis B envelope antigen (anti-HBe), Anti-Hepatitis B core antigen-IgM (anti-HBc IgM); (InTec products, China), and Total Anti-HBc (Fortress diagnostics, UK). All of these immunological tests were conducted using enzyme linked immunosorbent assay (ELISA) technique according to the manufacturer's instructions. The status of infection in patients was: + total anti-HBc= 96%; + HBsAg=97%; + anti-HBc IgM= 90%; + anti-HBe= 87%; and + anti-HBs= 65%.

### Liver Function Enzymes

Assessment of liver function enzymes including aspartate aminotransferase (AST/GOT), alanine aminotransferase (ALT/GPT), alkaline phosphatase (ALP), and total serum bilirubin (TSB) was performed using the automated Fuji Dri-Chem Slide system (FUJIFILM™, Japan). All procedures were carried out in accordance with the manufacturer's instructions.

### Measurement of IL-37 Levels

Serum concentrations of interleukin-37 were determined using ELISA technique following the protocol provided by the manufacturer (BT-Lab™, China). Microtiter plate washing and absorbance readings were carried out using an automated ELISA reader and washer (Biobase™, China).

### Ethical consideration

Study protocol was reviewed and approved by the College of Science Research Ethics Committee/University of Baghdad (Ref: CSEC/1023/0094).

### Statistical Analysis

Data obtained from the study were analyzed to assess the normality of distribution using the Shapiro–Wilk test, the Kolmogorov–Smirnov test, and the Kruskal–Wallis test. These statistical methods were also employed to determine the significance of differences among various

groups and parameters. Furthermore, Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance and classification accuracy of selected biomarkers. All statistical tests were performed using standard software, with a significance level set at  $P < 0.05$ .

## Results

### Estimation of Liver Function Enzymes

The findings related to liver function enzymes (Figure 1) demonstrate elevated levels across all measured parameters in HBV patient group compared to healthy controls. Notably, the most significant differences were observed in the mean values of total serum bilirubin, alkaline phosphatase (ALP), and aspartate aminotransferase (AST/GOT), with statistical significance at  $P < 0.01$ . Additionally, liver function parameters exhibited sex-based variability among both HBV patients and healthy controls. This variation was particularly evident in total serum bilirubin (TSB) and aspartate aminotransferase (AST/GOT) levels, which showed statistically significant differences between male and female participants ( $P < 0.01$  and  $P < 0.035$ , respectively), as illustrated in Figure 2.

### Determination of Diagnostic Validity of Liver Enzymes

Regarding the diagnostic sensitivity and specificity of liver function tests, serum bilirubin and GOT (AST) demonstrated the highest association with hepatic infection, as indicated by the Area Under the Curve (AUC) in the Receiver Operating Characteristic (ROC) analysis (AUC = 0.9891 and 0.6571, respectively), followed by alkaline phosphatase (ALP) and alanine aminotransferase (ALT/GPT) (AUC = 0.6315 and 0.5125, respectively) (Figure 3). The sensitivity of the tests was 0.98, 0.81, 0.56, and 0.89, while the specificity values were 0.90, 0.46, 0.68, and 0.18, respectively. Statistically significant differences were observed for TSB, GOT, and ALP ( $P < 0.01$ ), but no significant difference was found for GPT ( $P = 0.803$ ).

### Measurement of Interleukin-37

In addition to liver function tests, IL-37 levels were measured across all study participants, both patients and controls. The results revealed a significant decrease in IL-37 levels in HBV-infected patients compared to the healthy controls ( $P < 0.001$ ), as shown in Table 1 Figure 4. Moreover, a significant variation in IL-37 levels was observed between both sexes ( $P < 0.0001$ ), with male patients had a higher median concentration (23.40 pg/mL) compared to females. Interestingly, levels of IL-37 in healthy female controls surpassed the male controls with a median level of 127.2 (pg/mL) versus 88.56 (pg/mL), respectively.

### Determination of IL-37 Diagnostic Validity and Correlation with HBV Markers

The levels of IL-37 were further analysed in correlation with immunologic markers that indicate the precise infective and replicative stage of the hepatic virus in the patients. These markers are presented in Figure 5 and include: HBsAg; HBsAb; Anti-HBc IgM/Total; and Anti-HBe Ab. Moreover, the highest levels of IL-37 (in pg/mL) were associated with HBsAg negative (119.8), negative anti-HBc total/IgM (63.16 and 51.71, respectively), and anti-HBe/anti-HBs positive (38.34 pg/mL). However, the most drastically decreased levels of IL-37 were observed in patients with negative anti-HBe and anti-HBe/anti-HBs (14.52 and 15.52 pg/mL, respectively). Moreover, the ROC curve analysis has shown a reliable diagnostic value in discriminating HBV patients from controls at  $P < 0.0001$ , with AUC = 0.9382 as depicted in Figure 4.

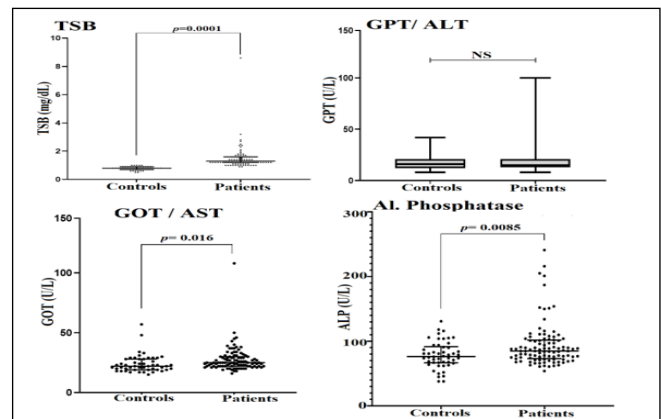


Figure 1. Distribution of liver tests levels among HBV infected patients and controls

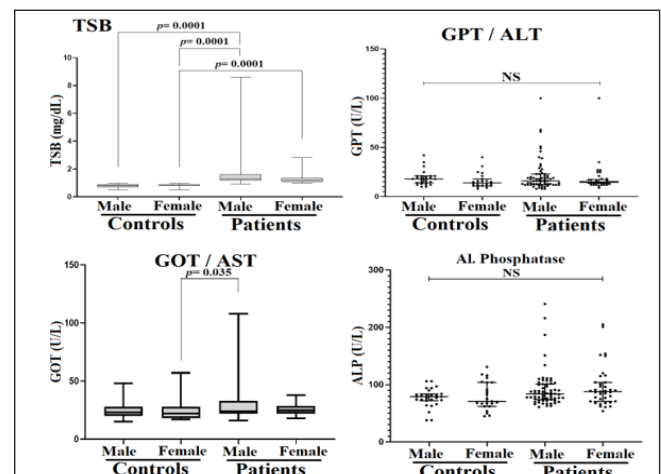


Figure 2. Distribution of liver tests according to the sex of patients and controls.

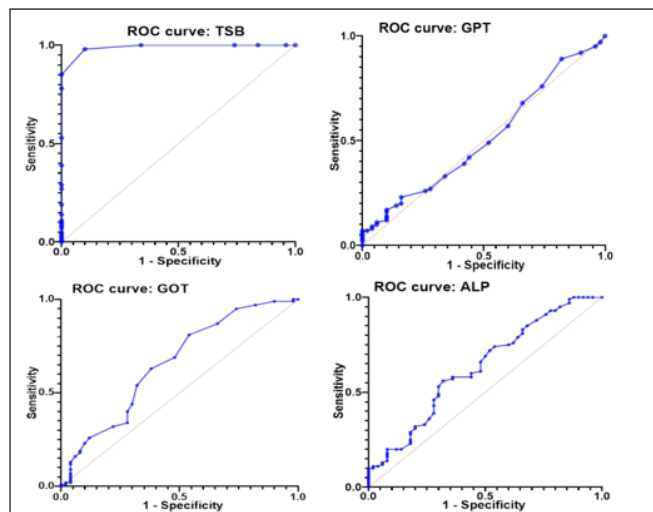


Figure 3. ROC curve analysis of liver tests demonstrating sensitivity and specificity of the enzymes with HBV infection.

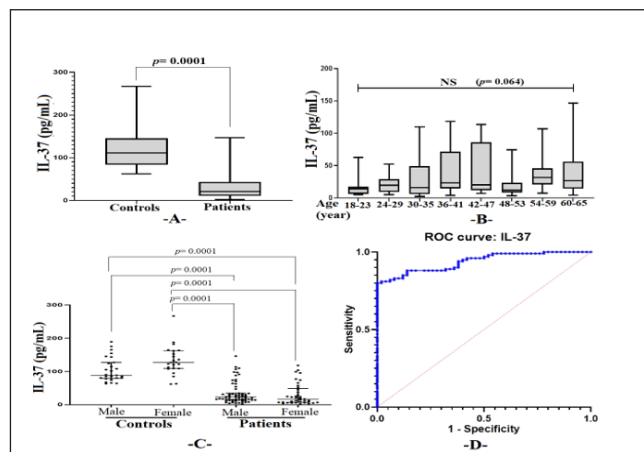


Figure 4. Statistical analysis of IL-37 according to different parameters. A-IL-37 levels variation in patients and controls; B-levels of IL-37 by age groups; C-IL-37 levels distribution between sexes; D-ROC curve showing the sensitivity and specificity

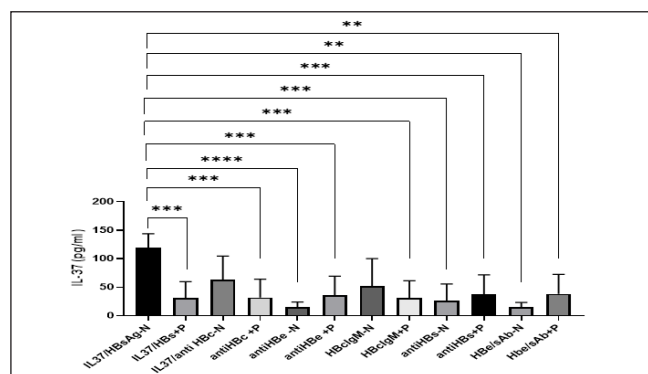


Figure 5. Serum levels of IL-37 in correlation with HBV serologic markers (presented as mean  $\pm$  SD., P=positive, N=Negative)

Table I. Distribution of IL-37 according to different categories (patients/controls, sex, & age)

Statistical test	Category	Parameter				P value
		75% Percentile	Median (pg/ml)	Std. Deviation	Interquartile Range	
Mann-Whitney (Patients & Controls)	Patients	43.48	20.75	32.76	32.43	**
	Controls	145.1	111.0	42.24	61.44	<0.001
Kruskal-Wallis (sex distribution)	Male Patients	34.70	23.40	32.86	20.54	** <0.001
	Female Patients	48.95	17.00	32.91	41.91	
	Male Controls	127.4	88.56	36.39	48.3	
	Female Controls	162.4	127.2	44.22	53.3	

Kruskal-Wallis (age groups, years)	18 - 23	17.41	14.00	15.68	11.312	0.064 NS
	24 - 29	29.20	19.60	14.59	19.835	
	30 - 35	49.34	15.95	34.31	43.342	
	36 - 41	71.50	23.23	35.28	56.92	
	42 - 47	86.10	20.10	39.55	74.05	
	48 - 53	23.50	11.75	21.94	15.225	
	54 - 59	45.80	31.70	28.90	24.85	
	60 - 65	56.15	26.70	40.34	41.64	
ROC	Area	Cut off value	Sensitivity	Specificity	95% confidence interval	Std. Error
	0.9382	< 59.95	0.8	1	0.903-0.973	0.01788
	P value*** <0.0001					
* Significant; NS= Non-Significant						

## Discussion

The findings of this study are consistent with those of previous studies that have reported a positive correlation between HBV-related liver damage and elevated levels of liver enzymes.<sup>15,16</sup> However, Mohsen et al. (2019) observed that among liver enzymes, only alkaline phosphatase exhibited a statistically significant difference between HBV patients and healthy controls.<sup>17</sup> Furthermore, Wei et al. reported that the absence of a significant difference in alanine aminotransferase (ALT/GPT) levels between HBV-infected individuals and controls may, paradoxically, reflect more advanced hepatic injury.<sup>18</sup> This phenomenon could be attributed to the progression of liver damage beyond the inflammatory phase, wherein reduced enzyme leakage into the bloodstream may result from impaired hepatocyte function or an on-going tissue repair and regeneration process.

This study revealed a sex-dependent variation in liver enzyme levels, suggesting that liver function and the progression of HBV infection may be influenced by sexual physiology. Several studies have indicated that HBV infection is responsive to sex hormones, which may contribute to differential immune responses and liver injury between males and females.<sup>19,20</sup> Contrastingly, some studies demonstrated insignificant differences in liver enzyme levels based on sex in either HBV or HCV infections.<sup>21,22</sup> These discrepancies may reflect variability in study populations, disease stages, or regional differences in epidemiology. Also, results showed a high diagnostic value for total serum bilirubin (TSB), and aspartate aminotransferase (AST/GOT) with a lesser, yet notable, association. These findings align with previous research, which has emphasized the utility of TSB and GOT as reliable biomarkers for diagnosing liver infection.<sup>16,21</sup> However, these results contrast with those from a study by Mohsen (2023), who found no

significant diagnostic value for the TSB test.<sup>23</sup> The observed discrepancies between studies could be attributed to various factors, including the stage of infection, viral load, and the patient's treatment status, all of which may influence enzyme levels.

In addition to liver function tests, the results revealed a significant decrease in IL-37 levels in the HBV-infected patients compared to the healthy controls. As suggested by the aforementioned findings, the down-regulated levels of this anti-inflammatory cytokine may be influenced by several factors, including the acute phase of HBV infection, which, in turn, could exacerbate liver damage through intensified cytotoxicity of CD8+ T-cells.<sup>24</sup> This phenomenon has also been observed in the progression of the disease toward hepatocellular carcinoma, highlighting the critical protective role of IL-37. Similar trends have been documented in diseases such as severe acute respiratory syndrome, allergic rhinitis, asthma, and urticaria, where levels of IL-37 were notably reduced.<sup>26,27</sup> This reduction suggests a potential role for IL-37 in modulating the immune response during HBV infection and highlights its potential as a novel biomarker for disease progression and severity. However, during the progression of HBV infection from the acute to chronic phase, IL-37 levels were significantly upregulated, surpassing the healthy threshold levels<sup>28</sup>. The pattern of elevation has also been observed in other health conditions, including rheumatoid arthritis and autoimmune thyroiditis.<sup>29,30</sup>

Although no statistically significant variation in circulating IL-37 levels was observed across different age groups, a distinct elevation was noted in patients in their third and fourth decades compared to both younger and older cohorts. This periodic variation in cytokine expression might be attributed to the combined effects of aging, immune function, and disease status. While older individuals are generally experience a decline in immune function,

younger individuals may experience a greater impact of HBV infection on their developing immune systems, leading to lower IL-37 levels. In line with these findings, some studies have explicitly pointed out the influence of age on the circulating levels of IL-37.<sup>31</sup>

Previous studies have also highlighted sex-based differences in IL-37 levels, particularly in relation to conditions such as coronary artery disease and diabetes.<sup>32,33</sup> This disparity may reflect the impact of sex hormones on cytokine expression. However, male participants in both patients and control groups demonstrated fewer irregularities in IL-37 levels, with values closer to the reference plasma range (84 pg/mL) established by Santarelli et al. suggesting a better overall health status and disease resolution.<sup>34</sup>

Lastly, the analysis of the ROC curve confirmed the exceptional utility of IL-37 as both a diagnostic and a monitoring tool for hepatic infections, consistent with previous research.<sup>28</sup> The level of IL-37 was further analysed in correlation with immunological markers that indicate the precise infective and replicative stage of the hepatic virus in the patients. The findings indicate that regulation of IL-37 may be influenced by the replicative phase of the virus, which is indicated by the decreased levels of IL-37 during the sero-conversion and clearance of HBeAg35. Moreover, the notable elevation in the titre of the cytokine upon the development of protective immunity through the anti-HBs represents an extra support to restoration of cytokine homeostasis after clearance of the infective virus.

## Conclusions

The study underscores the critical role of biochemical tests in the follow-up surveillance of hepatitis B patients, particularly highlighting the increase in serum bilirubin and alkaline phosphatase levels, along with the potential misinterpretation of normal GPT/ALT levels. Furthermore, the study emphasizes the significant potential role of IL-37 as a diagnostic and therapeutic biomarker in monitoring progression of HBV infection.

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**Conflict of Interest:** None

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