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Assessment of IL-17 and TNF- α Levels and Liver Function among Iraqi Hepatitis B Patients

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Abstract:

Hepatitis B virus (HBV) infection is a global health problem that causes liver inflammation, fibrosis, and hepatocellular carcinoma. Chemokines, such as Interleukin-17 (IL-17) and Tumor Necrosis Factor-alpha (TNF- α) are essential for immune functions but their expression profiles and associations with HBV progression in Iraqi patients are poorly understood. The purpose of the study was to compare the levels of serum IL-17 and TNF- α and their correlation with the severity of the disease with the help of liver enzymes (ALT, AST, and ALP). The case-control study was involving100 individuals: 60 acute HBV, 20 chronic HBV, 10 healthy controls and10 participants were excluded .serum levels of IL-17 and TNF-α were measured using ELISA while liver enzymes were determined by colorimetric method. Statistical analysis demonstrated significant differences ($P < 0.01$) between the study groups. Serum levels of IL-17 and TNF- α were much higher in HBV patients than in healthy controls, and are even higher in acute infection. There were also significant results of liver enzyme activities (ALT, AST, and ALP) in the acute group, in contrast to the chronic and control groups. These findings suggest that the elevated IL-17 and TNF- α levels are associated with HBV infection among Iraqi patients and the combined immunological and liver enzyme parameters can be useful indicators to monitor HBV progression and chronicity.

Keywords: hepatitis B infection; IL-17; TNF- α; Liver enzyme; Immune response.

تقييم مستويات انترلوكين-17 وعامل نخر الورم الفا ووظائف الكبد لدى المرضى العراقيين المصابين بالتهاب الكبد الفيروسي نوع ب

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الخلاصة

يعد التهاب الكبد الفيروسي ب (HBV) مشكلة صحية عالمية تسبب التهاب الكبد وتليفه وتطور سرطان للخلايا الكبدية وتعد الكيموكينات ،مثل انترلوكين 17 (IL-17) وعامل نخر الورم الفا (TNF- α) عناصر أساسية في الاستجابة المناعية الا ان انماط تعبيرها وارتباطها بتطور مرض التهاب الكبد الفيروسي ب لدى المرضى العراقيين ما تزال غير مفهومة بشكل كاف لذا هدفت هذه الدراسة الى مقارنة مستويات IL-17 و TNF- α في المصل ودراسة ارتباطها بشدة المرض بالاستعانة بإنزيمات الكبد (AST,ALT,ALP) للدلالة على تلف الكبد، تضمنت هذه الدراسة للحالات والشواهد مشاركة 100 فرد بواقع 60 مريضا مصابا بالتهاب الكبد الفيروسي ب الحاد و20 مريضا مصابا بالتهاب الكبد الفيروسي ب المزمن و10 افراد اصحاء كمجموعة سيطرة، في حين تم استبعاد 10 مشاركين. تم قياس مستويات IL-17 و TNF- α في المصل باستخدام تقنية المقايسة المناعية المرتبطة بالإنزيم (ELISA)، بينما قيست انزيمات الكبد باستخدام الطريقة اللونية (colorimetric method)، واظهر التحليل الاحصائي وجود فروق معنوية ($P < 0.01$) بين مجاميع الدراسة، وكانت مستويات IL-17 و TNF- α اعلى بصورة ملحوظة لدى مرضى التهاب الكبد الفيروسي ب مقارنة بالأصحاء، وكانت اعلى المستويات في حالات العدوى الحادة. كما أظهرت انزيمات الكبد(AST,ALT,ALP) نتائج معنوية مرتفعة في المجموعة الحادة مقارنة بالمجموعتين المزمنة والاصحاء، وتشير هذه النتائج الى ان ارتفاع مستويات IL-17 و TNF- α ترتبط بعدوى التهاب الكبد الفيروسي ب لدى المرضى العراقيين، وان الجمع بين المؤشرات المناعية وانزيمات الكبد قد يوفر مؤشرات تنبؤيه مفيدة لمتابعة المرض وتحوله الى الحالة المزمنة.

1. Introduction

Hepatitis B virus (HBV), a member of the Hepadnaviridae family, is an enveloped hepatotropic DNA virus and a major global health concern, with approximately 296 million people chronically infected as of 2019 Its lifecycle consists of conversion of the relaxed circular DNA (rcDNA) into a stable covalently closed circular DNA (cccDNA) in the hepatocyte nuclei, enabling persistent infection [1],this molecular reservoir is stable and escapes to host's immune responses and conventional antiviral treatment, allowing for continuous persistence and lifelong infection. As a result, chronic HBV infection is one of the major contributors of severe liver pathology, with 20-30% of infected individuals progressing to cirrhosis and leading to almost 45% of hepatocellular carcinoma (HCC) cases worldwide [2], Given the complex host-pathogenic relationship, new therapeutic strategies will need to be developed that involve both direct-acting antiretroviral and immune-modulatory therapies, Although novel approaches like specific cccDNA editing or epigenetic silencing offer a promising route towards a functional cure, risk stratification models, grounded in certain biomarkers, are also becoming critical to prognosis and to preventing reactivation in vulnerable groups .[3] Liver enzyme tests are essential in HBV infection, as significant alterations occur in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) make it a key biomarkers of hepatocellular injury and disease progression, supporting both diagnosis and monitoring [4] Cytokines also have a role to play, as they are potential therapeutic agents, diagnostic and disease severity and progression predictors [5].One of these cytokines is interleukin-17 (IL-17), which is a strong pro-inflammatory cytokine primarily generated by Th17 CD4+ T cells and is vital in the immune defense and in the inflammatory responses. The IL-17 in HBV infection enhances hepatic inflammation by attracting neutrophils and monocytes and activating hepatocytes, Kupffer cells, and stellate cells to secrete pro-inflammatory cytokines and chemokines such as IL-6 and TNF- α, further intensifying liver inflammation [6, 7]. Although IL-17 could play a role in the clearance of pathogens in acute infection, but high levels in chronic HBV are linked to sustained inflammation, fibrosis, and heightened risk of cirrhosis and hepatocellular carcinoma (HCC) [8]. Recent research shows that IL-17 signaling is closely associated with progression of the disease, which is a good prognostic biomarker and a potential option in the guided selection of therapeutic strategies [6]on the other hand, Tumor necrosis factor-alpha (TNF-) is a primary pleiotropic pro-inflammatory cytokine, which takes part in regulating the pathways of inflammation, cell proliferation, and programmed cell death [9] It is mainly secreted by macrophage, natural killer (NK) cells and activated T lymphocytes and is at the center stage of both acute and chronic inflammatory responses [10]. TNF- is a dual action cytokine in HBV infection, where it reinforces antiviral immunity, but also drives hepatic inflammation; chronic upkeep is linked to liver fibrosis and is linked with chronic infection and cirrhosis [11]. Recent discoveries indicate that TNF-a monitoring can give useful information on the activity of the disease and the pathogenesis of chronic HBV infection [12]. This study aims to evaluate IL-17 and TNF-α levels as predictive factors for the progression of hepatitis B virus infection, and to investigate their association with disease severity by measuring the activity of liver enzymes ALT, AST and ALP.

2. Material and Methods:

2.1.Patient and Sample Collection:

This comparative case-control study was carried out in several health clinics in Salah al-Din Governorate, in Iraq, such as Al-Mu'allimeen Primary Health Care Center, Samara General

Hospital, and Tikrit Teaching Hospital. Participants were originally recruited from November 2025 – February 2026, but excluded if they had viral co-infections (such as Hepatitis C) or recently had antiviral treatment (n=10). The final participants were ranged from 17 to 63 years, divided into three groups, acute Hepatitis B patients (36 males and 24 females), chronic Hepatitis B patients (10 males and 10 females) and apparently healthy individuals (7 males and 3 females) as control group. Specialized doctors were able to confirm the presence of HBV infection from clinical records and serological detection of Hepatitis B surface antigen antigen (HBsAg) by the ELISA technique. Socio-demographic and clinical data were obtained for all participants and those with autoimmune and metabolic liver diseases were excluded to make sure that immunological and biochemical elevations are related to Hepatitis B infection only. Laboratory Investigations consisted of the aseptic collection of 5 mL of venous blood that was placed in anticoagulant free, gel separator tubes and allowed to clot for 20–30 minutes at room temperature. After a 15-minute centrifugation at 3000 rpm, the separated sera were divided into pre-coded Eppendorf tubes and stored at -20°C for analysis.

2.2.Biochemical and Immunological Assessment:

Serum levels of liver enzymes (ALT, AST, ALP) and immunological markers (IL-17 and TNF – α) were measured in adults. The IL-17 concentration in the serum was determined by a high-sensitivity ELISA kit (Sunlong Biotech, China; Cat. No. SL0978Hu), it is based on the principle of quantitative sandwich ELISA. According to the manufacturer's specifications, this test has a detection range of 2.8–200 pg/mL and an analytical sensitivity of 0.8 pg/mL. The similar ELISA kit (Sunlong Biotech, China; Cat.No. SL1761Hu) was also employed to detect the concentration of TNF-α. The detection range of this test is 6–300 pg/mL, and the sensitivity is 2.2 pg/mL. The absorbance of both markers was measured at 450 nm using a Biotik ELISA microplate reader (USA). At the same time, the activity of three key liver enzymes was evaluated by Biolabo colorimetry kits (France). The levels of ALT, AST activity were estimated at 505 nm and ALP was estimated at 510 nm by Apel spectrometer (Japan). Biolabo references indicate that the normal range for ALT is 10–40 IU/L for males and 7–35 IU/L for females while the normal range for adults for ALT is 13-31 IU/L , whereas the normal value for ALP is 32–92 IU/L (4.5–13 kJ/dL) (using the phenylphosphate method) . In the experimental phase, all laboratory procedures were strictly followed according to manufacturers to ensure high accuracy of the results.

2.3.Statistical Analysis:

The statistical analysis was carried out using Minitab software (version 17). The data are presented as Mean ± SD (standard deviation) for continuous data. A one-way ANOVA test was used to assess significant differences among the study groups and Duncan's multiple range test was used to compare the means at a significance level of $p < 0.05$.

3. Result

Table 1 shows the difference of serum immunological markers (IL-17 and TNF-α) among the study groups. There was a significant difference in the levels of IL-17 in the serum of the studied cohorts. The highest IL-17 level was observed in acute HBV patients (138.940 ± 24.620 pg/mL), followed by chronic HBV patients (53.950 ± 10.350 pg/mL), while the lowest mean was recorded in the healthy control group (12.259 ± 2.369 pg/mL) . Also, the patient groups showed

a large and significant increase in the level of TNF-α, with the mean for acute cases being 209.010 ± 41.840 pg/mL and 84.250 ± 11.100 pg/mL for chronic cases, while for healthy individuals, the mean level of TNF-α was 16.610 ± 5.411 pg/mL. Figure 1 and 2 show distribution and variability of these markers by clinical status with an increased central tendency in the acute phase reflecting the findings presented in Table 1.

A summary of the activities of primary liver enzymes throughout the different stages of infection is presented in Table 2. The mean concentration of ALT, in both the acute and chronic groups, was significantly higher than that in the healthy group (326.500 ± 58.600 U/L and 115.840 ± 19.340 U/L, respectively in patient groups and 22.280±7.650 in healthy group), as shown in Figure 3. Similarly, each group of patients had significantly higher AST levels (265.360 ± 36.230 U/L and 85.560 ± 19.430 U/L respectively) compared with the controls (21.710 ± 4.230 U/L), as illustrated in Figure 4. Moreover, the ALP level of acute (217.490 ± 49.860 U/L) and chronic (148.460 ± 36.330 U/L) patients is significantly higher than that of healthy individuals (82.440 ± 9.160 U/L) as shown in Fig. 5.

Table1- Serum levels of immunological markers (IL-17 and TNF-α) in the study groups

Study groups	N	IL-17 (pg/mL) (Mean ± SD)	TNF-α (pg/mL) (Mean ± SD)	p-value
Healthy	10	12.25±2.369 **c**	16.61±5.411**c**	>0.001
Chronic HBV	20	53.95±10.35 **b**	84.25±11.10 **b**	>0.001
Acute HBV	60	138.94±24.62 **a**	209.01±41.84 **a**	>0.001

Not: Data are expressed as Mean± standard Deviation(SD).Different letters(a,b,c) within the same column indicate statistically significant differences at p >0.05 according to Duncan's multiple range test.

Table 2- Activities of primary liver enzymes (ALT, AST, and ALP) across the study groups

Study groups	N	ALT(U/L) (Mean ± SD)	AST (U/L) (Mean ± SD)	ALP(U/L) (Mean ± SD)	p-value
Healthy	10	22.28±7.65 **c**	21.71 ±4.235 **c**	82.44 ±9.16 **c**	
Chronic HBV	20	115.84±19.34 **b**	85.54 ±19.43 **b**	148.46 ±36.33**b**	
Acute HBV	60	326.50± 58.60 **a**	265.36 ±36.23 **a**	217.49±49.68 c	

Note: Data are expressed as Mean ± Standard Deviation (SD). Different letters (a, b, c) within the same column indicate statistically significant differences at p >0.05 according to Duncan's multiple range test

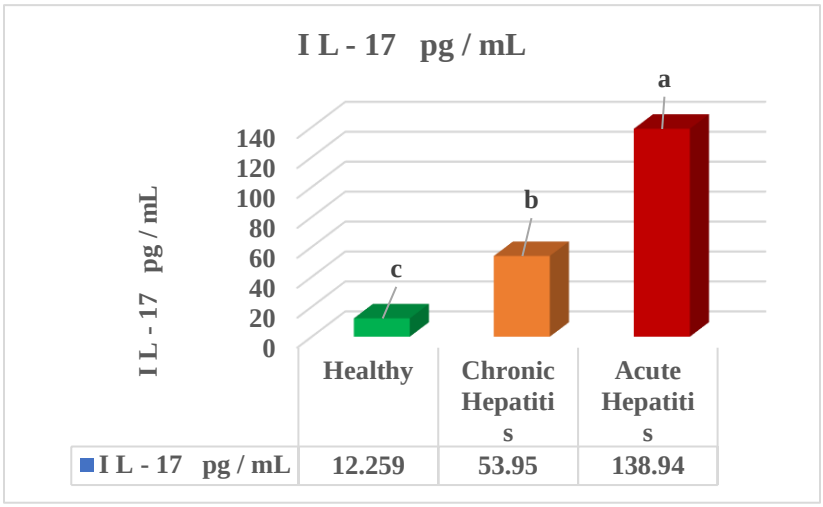

Figure-1 Mean serum concentration of IL-17 (pg/mL) across the study groups.

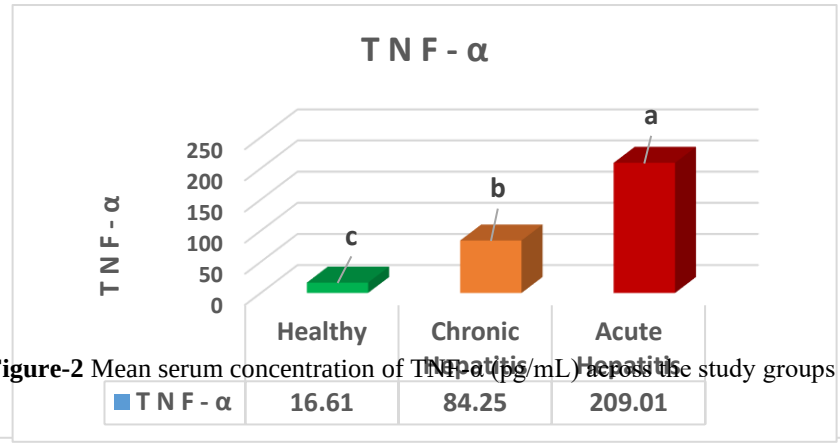

Figure-2 Mean serum concentration of TNF-α (pg/mL) across the study groups

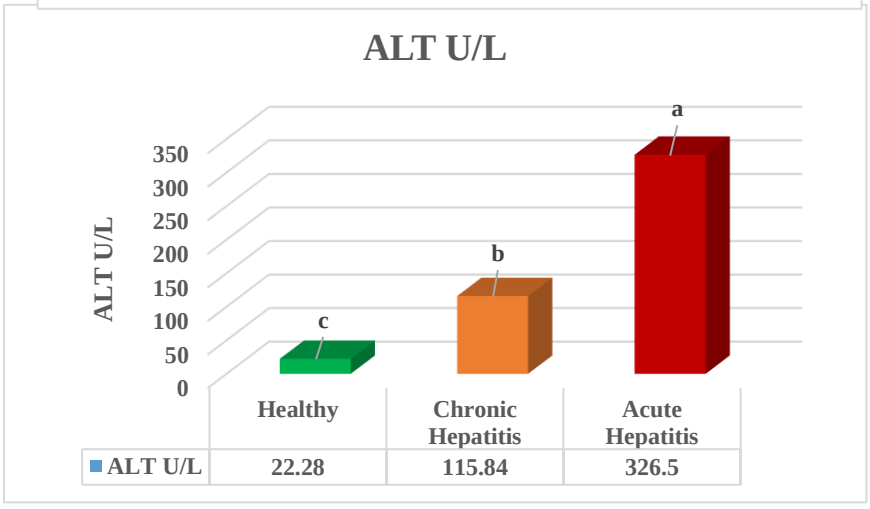

Figure-3 Activity of serum ALT enzyme (U/L) across the study groups.

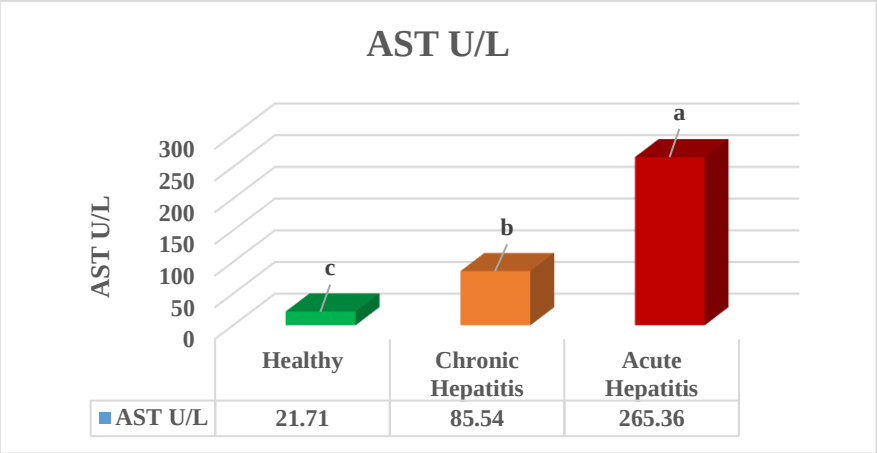

Figure-4 Activity of serum AST enzyme (U/L) across the study groups

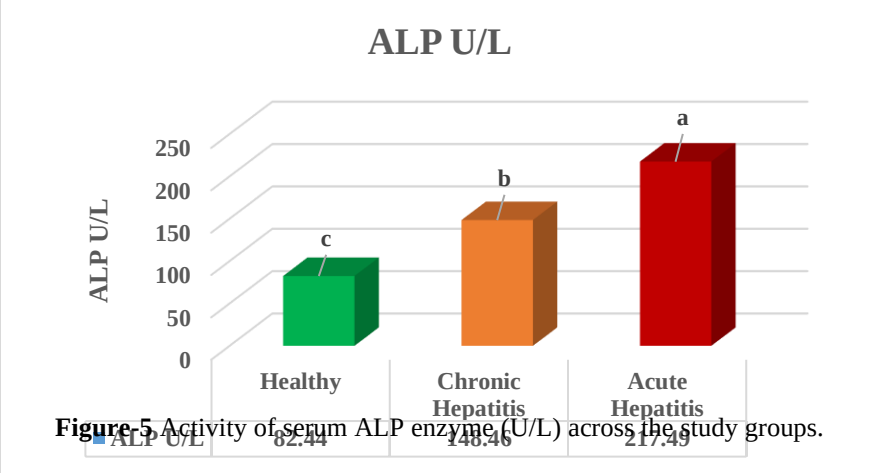

Figure-5 Activity of serum ALP enzyme (U/L) across the study groups.

4. Discussion

The significantly higher level of IL-17 in HBV patients, especially during the acute stage of the disease, may be a reflection of the activation of immune responses mediated by T helper 17 cells during viral hepatitis. IL-17 is a highly potent pro-inflammatory cytokine, which is involved in antiviral immunity and liver damage as a result of immune mechanisms. It is thought that the mechanism is that IL-17 causes the recruitment of neutrophils and monocytes and activates the hepatocytes, Kupffer cells, and hepatic stellate cells to produce inflammatory cytokines and chemokines which perpetuate hepatic inflammation. Therefore, the increased levels of IL-17 observed in the present study may be associated with the increased inflammatory response to liver damage caused by HBV infection [7] Moreover, the increased amount of IL-17 in acute HBV infection as observed in chronic infection might be due to the two-fold immune function of this cytokine during the course of HBV infection. IL-17 may contribute to the clearance of a pathogen during acute infection by promoting inflammatory cell infiltration and antiviral functions, while persistent high levels of IL-17 may lead to chronic inflammatory responses and the progression of liver disease. The activation of hepatic stellate cells and collagen deposition is linked to immune activation by IL-17[8] These findings are consistent with those of previous studies, which observed that IL-17 is significantly increased in patients

with active hepatitis B as compared to those with inactive disease and healthy controls, suggesting a role for this cytokine in immune-mediated liver damage in HBV patients [13] Similarly, other study [14] demonstrated a direct correlation of IL-17 expression with histological activity index (HAI) in HBV patients, which confirmed that IL-17 plays a role in liver inflammation and necrosis in HBV patients. These results are similar and may indicate association between IL-17 and the inflammatory activity of the disease in HBV infection and not a general immune response [13-14].The clinical implications of IL-17 could go beyond that as an inflammatory mediator. This result suggested that measuring the levels of both IL-17 and the traditional liver enzyme assays (such as ALT and AST) may improve prediction of the diagnosis of HBV-related hepatic fibrosis and early cirrhosis changes [15] which confirmed the potential use of IL-17 as a valuable tool on the alternative immunological marker in the surveillance of disease in HBV patients and in identifying those who are most likely to develop liver complications.

TNF-α is another key cytokine in the immunopathogenesis of HBV besides IL-17-mediated inflammatory response, the marked increase in the levels of TNF-α in patients with HBV, especially acute infection, may be attributed to the central immunoregulatory role of this cytokine in antiviral immune responses because TNF-α is not merely an inflammatory mediator but rather a pleiotropic cytokine involved in regulating immune activation, hepatocyte survival, and antiviral defense. Previous studies reported that significant difference in TNF-α level was found between clinical groups of HBV with highest level during recent and acute infection. All of these results agree with the present study, and indicate that the increase in production of TNF-α in early HBV infection may be a protective host response that restricts viral replication and promotes immune control of the virus [16].In the current study, it was observed that the predominance of TNF-α in acute HBV as compared to chronic infection is similar to the known HBV immunopathologies where more TNF-α responses have been seen to occur in acute HBV infections than chronic infection. Long-term or abnormal production of TNF-α could, however, play a role in chronic inflammation and disease progression [17] In addition to inflammatory control, TNF-α is involved in hepatocyte apoptosis and survival via activation of transcription factors like NF-κB. Thus, in addition to being used as inflammatory markers, raised levels of TNF-α may also be considered as markers of complex immune–hepatic interactions in the context of HBV infection[18] .The correlation between TNF-α levels and liver enzymes activity further supports this interpretation, highlighting the role of TNF-α in liver inflammatory damage and in causing liver injury [19].The clinical importance of the role of TNF-α may also include disease monitoring and prognosis, Results of a previous study showed that the level of TNF-α was significantly elevated in chronic HBV patients with high diagnostic sensitivity, which is well supported by the present results [12]. Further, chronic inflammation due to TNF-α has been linked to the progression of cirrhosis and hepatocellular carcinoma (HCC), which makes the use of TNF-α as a marker for patients at risk of worsening liver disease potential a possibility [20].

Liver enzymes were significantly elevated in HBV patients in the present study, indicating a continuing injury to and inflammatory activity in the liver. Of these enzymes, ALT is thought to be the more liver specific as it is mainly found within the hepatocyte, while AST is also found in extrahepatic tissues, and is a more sensitive marker of hepatocellular injury and viral hepatitis activity[21]The liver damage caused by HBV is mainly immunologic and not a direct effect of the virus. Increased ALT and AST levels in the present study can be attributed to the leakage of the enzymes into the bloodstream due to the cytotoxic immune response against the infected hepatocyte, which is a mechanism known to occur in infections [22]. Additionally, previous

studies correlated ALT levels with immune activation and inflammatory cytokine responses in the context of HBV infection [23] AST and ALP have both retained clinical value, but may be markers of other pathological processes in addition to hepatocellular injury. In cases of AST elevated, this may be due to necroinflammatory changes and progression of fibrosis, while ALP elevation may suggest involvement of bile ducts and cholestasis that may be affected by inflammatory cytokines [24-25] From an immunological perspective, It has also been shown that the elevated immune cytokines such as IL-17 and TNF-α in patients with chronic hepatitis led to increased bile acids, increased cholestasis, and consequently, increased ALP levels. [26] The current results are consistent with two past Iraqi studies showing significantly higher levels of ALT, AST and ALP in the HBV patients. One of them reported elevation in liver enzyme levels of HBV patients in Baghdad hospitals [4] and the other found significant changes in liver function tests related to the activity of HBV disease [27] which are in line with the current study . Liver enzymes, however, are clinically significant markers of injury to the liver, but they should be taken with other markers of immunity to assess the progression of HBV disease.

5. Conclusion

The study emphasizes the importance of immunological and physiological markers in the study of the course of HBV infection in patients in Salah al-Din Governorate, Iraq. IL-17 and TNF-α levels were significantly and substantially higher in the serum of all patient groups than in healthy controls, and were highest during the acute phase of infection. A significant rise in pro-inflammatory cytokines was correlated with a marked elevation in liver enzyme activities (ALT, AST, and ALP) indicating the degree of liver tissue damage and integrity of plasma membrane during active infection phases. Moreover, In conclusion, this research has shown that this combination of traditional liver function tests along with IL-17 and TNF-α determination is a powerful tool that allows one to follow disease progression and predict the risk of hepatitis transitioning towards chronicity, and to establish immunopathological mechanisms of hepatocyte injury. It is recommended to use these markers as clinical markers to improve the accuracy of monitoring and to make early diagnosis more easily before reaching to the complication of HBV infection among the Iraqi people.

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