

Evaluation of inflammatory and biochemical indicators in dialysis patients infected with hepatitis B virus

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Abstract

Viral hepatitis B is a causative factor in the development of various forms of extrahepatic vasculitis that can lead to acute kidney injury and chronic kidney disease (CKD). This study aimed to evaluate the effects of anti-inflammatory and pro-inflammatory cytokines on hepatitis B virus (HBV)-associated renal failure prevalence and progression in the dialysis unit of Ramadi Teaching Hospital. 88 men and women participated in the study from July 2023 to February 2024: 72 patients with kidney failure and 16 healthy people (controls) between 25 and 70 years old. Age, sex, and kidney and liver function laboratory data were recorded. All participants were screened for hepatitis B surface antigen (HBsAg) by enzyme-linked immunosorbent assay. The dialysis patients comprised 38 men (56.8%) and 34 women (47.2%) (mean age: 53.4 years old). 30 patients were HBsAg-positive: 19 men (63.3%) and 11 women (36.7%). 42 patients were HBV-negative: 23 men (54.8%) and 19 women (45.2%). The patients had significantly increased levels of urea, creatinine, liver enzymes (alanine transaminase, aspartate transaminase, and alkaline phosphatase), and cytokines (interleukin [IL]-10 and IL-17) compared to the healthy controls ($P < 0.0001$). The urea, creatinine, IL-10, and IL-17 levels were not significantly different between HBV-positive and HBV-negative patients. In conclusion, IL-10 and IL-17 may be potential biomarkers to predict HBV-associated renal failure prognosis and progression.

Keywords: dialysis, renal failure, hepatitis B virus, interleukin-10, interleukin-17

Резюме

Вирусният хепатит В е причинител на развитието на различни форми на екстрахепатален васкулит, който може да доведе до остро бъбречно увреждане и хронично бъбречно заболяване (ХБЗ). Това проучване има за цел да оцени ефектите на противовъзпалителните и провъзпалителните цитокини върху разпространението и прогресията на бъбречната недостатъчност, свързана с вируса на хепатит В (HBV), в диализното отделение на Учебната болница „Рамади“. Общо 88 мъже и жени участваха в проучването от юли 2023 г. до февруари 2024 г.: 72 пациенти с бъбречна недостатъчност и 16 здрави хора (контролна група) на възраст между 25 и 70 години. Записани са възраст, пол и лабораторни данни за бъбречната и чернодробната функция. Всички участници са скринирани за повърхностен антиген на хепатит В (HBsAg) чрез ензимно-свързан имуносорбентен анализ. Пациентите на диализа са 38 мъже (56.8%) и 34 жени (47.2%) (средна възраст: 53.4 години). 30 пациенти са HBsAg-позитивни: 19 мъже (63.3%) и 11 жени (36.7%). От всички пациенти 42 са HBV-отрицателни: 23 мъже (54.8%) и 19 жени (45.2%). Пациентите са със значително повишени нива на урея, креатинин, чернодробни ензими (аланин трансаминаза, аспартат трансаминаза и алкална фосфатаза) и цитокини (интерлевкин [IL]-10 и IL-17) в сравнение със здрави контроли ($P < 0.0001$). Нивата на урея, креатинин, IL-10 и IL-17 не се различават значително между HBV-позитивни и HBV-отрицателни пациенти. В заключение, IL-10 и IL-17 могат да бъдат потенциални биомаркери за прогнозиране на прогресията на бъбречна недостатъчност, свързана с HBV.

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Introduction

Hepatitis B virus (HBV) belongs to the Hepadnaviridae family and is a noncytopathic enveloped virus with a partially double-stranded circular DNA genome (Seeger *et al.*, 2020). The HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. The virus can lead to severe liver disease, such as fulminant hepatitis, cirrhosis, or hepatocellular carcinoma (HCC) (Ringe-han *et al.*, 2017). The HBV-related liver disease pathogenesis is largely due to the immune-related liver damage induced by active viral replication (Tourkochristou *et al.*, 2022).

An estimated two billion people worldwide are infected with HBV, and an estimated 350 million have chronic, lifelong infections. Thus, HBV infection is a severe global public health issue. Between 15 and 40% of patients with chronic HBV develop cirrhosis, HCC, or liver failure (Umego *et al.*, 2018). A Dialysis Outcomes and Practice Patterns Study data analysis demonstrated 0–6.6% HBV prevalence across dialysis facilities in Western Europe, Japan, and the United States (Jadoul *et al.*, 2019). Furthermore, viral hepatitis has been implicated as a causative factor in the development of various forms of extrahepatic vasculitis that can lead to acute kidney injury and chronic kidney disease (CKD) (Fabrizi *et al.*, 2019).

The antibody response to the HBV envelope antigens is T-cell-dependent and may explain why patients with advanced CKD are more susceptible to infections (Soi *et al.*, 2019). Patients infected by HBV, particularly those with the hepatitis e antigen, have a higher incidence of developing membranous nephropathy (Jaryal *et al.*, 2016). Polyarteritis nodosa is a systemic necrotising disorder that affects small- and medium-sized arteries and is associated with chronic HBV (Meng *et al.*, 2021). Despite treating these underlying disease processes, the chronic disease may progress, which leads to dialysis dependence. The kidneys filter the blood by removing waste and excess fluid from the body. The waste is sent to the bladder to be eliminated through urination. Dialysis performs the function of the kidneys if they have failed (Udomkarnjananun *et al.*, 2020). The National Kidney Foundation stated that end-stage kidney failure occurs when the kidneys are performing at only 10–15% of their normal function (Levey *et al.*, 2014).

A study that evaluated 1068 cirrhotic patients with end-stage renal disease (ESRD) compared with a control group without renal diseases reported that the patients had an almost doubled hazard

ratio (Elahi *et al.*, 2020). The one- and three-year mortality rates of 48.5% and 73.1% of patients in the ESRD group were significantly greater than that of 32.9% and 55.6% of the control group, respectively (Hung *et al.*, 2016). Regardless of dialysis modality, liver cirrhosis is an independent risk factor for death in patients. Both peritoneal dialysis and haemodialysis patients had equivalent adverse outcomes after adjustment for this condition (Kim *et al.*, 2016). Therefore, this study aims to evaluate the relationship of interleukins IL-10 and IL-17 and some biochemical indicators in renal failure patients infected and uninfected with hepatitis B virus (HBV) to predict the progression of the disease.

Materials and Methods

Study design and patients

This study was conducted on kidney failure patients undergoing dialysis in the dialysis unit at Ramadi Teaching Hospital in Ramadi City, Al-Anbar Province, Iraq, from July 2023 to February 2024. This study had 88 participants (42 men and 46 women; age: between 25 and 70 years old). All patients were on regular dialysis under access to permanent dialysis for over 15 months, and the dialysis cycle was three times per week. The patients were divided into HBV-infected and HBV-uninfected groups.

Sample collection and preparation

Venous blood (5 ml) was collected from sixteen healthy individuals and seventy-two kidney patients (infected and uninfected with HBV). The blood was placed in gel tubes containing clotting activators, and centrifuged for 15 minutes at 3000 rpm to separate the serum. The serum was stored at -20°C to determine the biochemical parameters and inflammatory markers.

Determination of HBsAg

Serum screening for hepatitis B surface antigen (HBsAg) was performed using ELISA kits (CTK Biotech, USA). Automated washing of 96-well ELISA plates was performed by a microplate washer (BioTek™ 50TS, USA), and the absorbance was measured at 450 nm using an ELISA reader (BioTek 800TS), located in the virology laboratory of Ramadi Teaching Hospital. Testing was performed on the same day following the manufacturer's instructions.

Detection of serum interleukins (IL-10 and IL-17) levels

The serum IL-10 and IL-17 levels were detected by enzyme-linked immunosorbent assay

(ELISA) kits from R&D Systems (Minneapolis, MN, USA). The measurements were conducted and results were recorded following the manufacturer's instructions using an ELISA washer-50TS and reader-800TS (BioTek™, USA).

Determination of biochemical parameters

The levels of urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) in all serum specimens were measured using the Mindray BS-240 Fully Automatic Biochemistry Analyser (China), located in the biochemistry laboratory of Ramadi Teaching Hospital.

Statistical analysis

Data are expressed as the mean $\pm$ SD. The comparisons between healthy subjects and HBV-positive and HBV-negative dialysis patients of males and females using unpaired t-tests. The comparison tests were conducted for the statistical analysis using OriginPro 8 (Origin Lab Inc., USA). A confidence level of $P < 0.05$ was considered statistically significant for all analyses.

Results

Participant distribution according to age and gender

This study involved 88 participants (42 men and 46 women). The controls comprised nine men (56.2%) and seven women (43.8%) (mean age: 47.6 ± 8.2 years old). Based on their clinical history, 72 haemodialysis patients were diagnosed with renal failure at the kidney care centre. The patients

comprised 38 men (56.8%) and 34 women (47.2%) (mean age: 53.4 ± 14.9 years old). Thirty patients were HBsAg-positive (19 men, 63.3%; 11 women, 36.7%; mean age: 54.7 ± 19.5 years old), while forty-two patients were HBsAg-negative (23 men, 54.8%; 19 women, 45.2%; mean age: 52.4 ± 10.7 years old). Table 1 presents the participants' demographic characteristics.

Evaluation of participants' serum biochemical tests

Table 2 presents the mean $\pm$ SD values of the participants' biochemical parameters. The patients had significantly increased urea, creatinine, ALT, AST, and ALP levels compared to the controls ($P < 0.0001$).

Assessment of biochemical tests in HBV-negative and HBV-positive patient serum

Table 3 presents the mean $\pm$ SD biochemical parameters of the HBV-positive and HBV-negative patients. The HBsAg-positive patients had significantly increased ALT and ALP ($P < 0.0001$) and AST levels ($P < 0.05$) compared the HBsAg-negative patients. Contrastingly, the statistical analysis results of the male and female patients did not exhibit any significant difference in the urea and creatinine levels between the HBsAg-positive and HBsAg-negative patients.

The relationship between serum IL-10 and IL-17 levels

Figures 1 and 2 present the participants' mean $\pm$ SD serum IL-10 and IL-17 levels. The patients had a significantly increased ($P < 0.0001$) mean se-

Table 1. Demographic characteristics of patients and controls

Characteristic	Patients (N=72)	HBV-positive (N=30)	HBV-negative (N=42)	Controls (N=16)
Age, years (mean $\pm$ SD)	53.4 $\pm$ 14.9	54.7 $\pm$ 19.5	52.4 $\pm$ 10.7	47.6 $\pm$ 8.2
Male gender, N (%)	38 (56.8%)	19 (63.3%)	23 (54.8%)	9 (56.2%)
Female gender, N (%)	34 (47.2%)	11 (36.7%)	19 (45.2%)	7 (43.8%)

Abbreviations: HBV, hepatitis B virus; SD, standard deviation.

Table 2. Participants' biochemical results

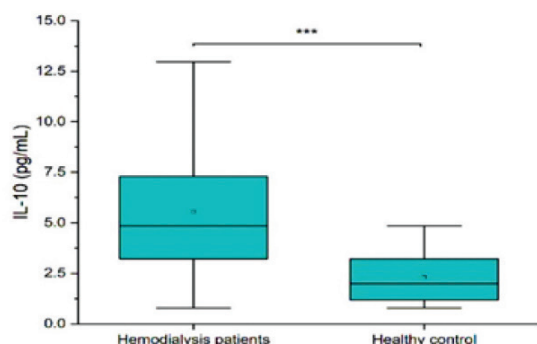
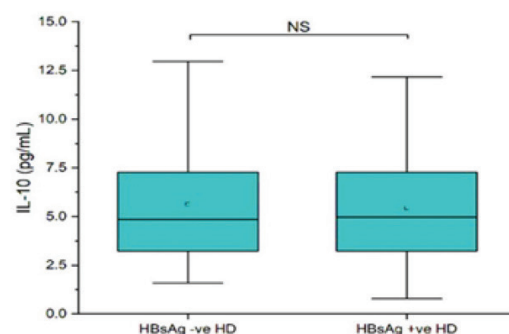
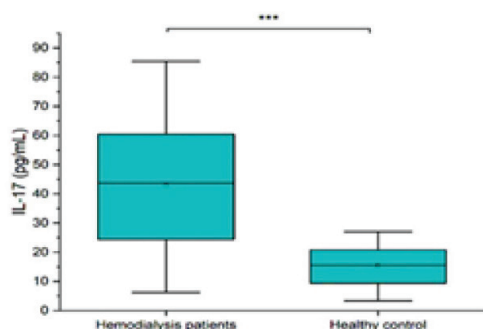
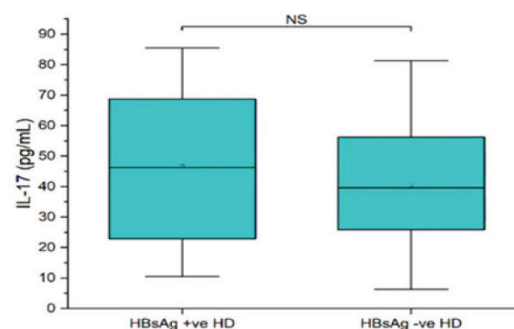
Parameters, Mean $\pm$ SD	Patients (N=72)	Controls (N=16)	P-value
Urea (mg/dL)	118.0 $\pm$ 26.0	27.5 $\pm$ 4.9	<0.0001
Creatinine (mg/dL)	5.9 $\pm$ 1.8	0.74 $\pm$ 0.18	<0.0001
AST (U/L)	38.0 $\pm$ 13.7	18.8 $\pm$ 5.4	<0.0001
ALT (U/L)	33.5 $\pm$ 15.8	17.5 $\pm$ 6.4	<0.0001
ALP (U/L)	183.5 $\pm$ 102.4	94.1 $\pm$ 5.8	<0.0001

Note: $P < 0.0001$ was considered highly significant. Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase

Table 3. Biochemical tests of HBV-positive and HBV-negative patients

Parameters, Mean±SD	HBsAg-positive (N=30)	HBsAg-negative (N=42)	P-value
Urea (mg/dL)	122.5±29.1	114.7±23.3	0.2
Creatinine (mg/dL)	6.2±2.2	5.7±1.4	0.2
AST (U/L)	42.8±17.4	34.6±9.0	<0.05
ALT (U/L)	41.7±18.6	27.6±10.3	<0.0001
ALP (U/L)	183.5±102.4	94.1±23.5	<0.0001

Note: P<0.05 was significant; P<0.0001 was highly significant. Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; HBsAg, hepatitis B surface antigen.

**Fig. 1.** IL-10 concentration in the serum of patients and controls**Fig. 3.** Serum IL-10 level in HBV-negative and HBV-positive haemodialysis patients**Fig. 2.** IL-17 concentration in the serum of patients and controls**Fig. 4.** Serum IL-17 level in HBV-positive and HBV-negative haemodialysis patients

rum IL-10 level (5.54 ± 2.95 pg/mL) compared to the controls (2.30 ± 1.32 pg/mL) (Fig. 1). Similarly, the patients had a significantly increased ($P < 0.0001$) serum IL-17 level (42.9 ± 21.6 pg/mL) compared to the controls (15.4 ± 7.4 pg/mL) (Fig. 2).

Estimation of serum IL-10 and IL-17 levels of HBV-positive and HBV-negative patients

Figures 3 and 4 present the mean $\pm$ SD serum IL-10 and IL-17 levels in the HBV-positive and HBV-negative patients. The results demonstrated that the mean serum IL-10 level was not significantly different ($P = 0.7$) between the HBsAg-positive patients (5.43 ± 3.05 pg/mL) and HBsAg-negative patients (5.61 ± 2.91 pg/mL) (Fig. 3). Similarly, the mean serum IL-17 level was significantly different ($P = 0.2$) between the HBsAg-positive patients (46.6 ± 23.9 pg/mL) and HBsAg-negative patients (40.3 ± 19.6 pg/mL) (Fig. 4).

Discussion

Patients with chronic renal failure (CRF) on haemodialysis are at higher risk for acquiring HBV. Compared to patients without renal failure, haemodialysis patients have a higher tendency of becoming chronic HBV carriers. Globally, HBV is prevalent among 0–58% and 0–22.7% of haemodialysis patients and blood donors, respectively (Mohamed *et al.*, 2020). As HBV infection prevalence in Iraq is intermediate, the rate of HBV is proportionally low to moderate in different regions in Iraq. Thus, an important measure should be implemented to control hepatitis in all dialysis departments.

Despite an effective vaccine against HBV infection, HBV-related acute and chronic liver disease is one of the leading causes of death. The HBsAg assay is most frequently used to analyse the presence of HBV infection. The HBsAg test screening

was implemented for further strategy programs to prevent HBV infectious disease spread (Nicolini *et al.*, 2019). Kidney failure associated with HBV infection causes abnormal kidney function tests in patients. A virus infection of the kidneys may lead to glomerular or tubular dysfunction, or any combination thereof (Shi *et al.*, 2016). In this study, the urea and creatinine tests did not reveal a strong relationship between the HBV-positive and HBV-negative patients. The results agreed with some studies that reported that HBV can slightly affect urea and creatinine activity (Hussein *et al.*, 2020; Alayadi *et al.*, 2024).

The liver is pivotal in regulating many physiological processes, degrading or modifying toxic substances, and metabolising drugs (Hasan *et al.*, 2021). Many medications can affect liver function, damage it, or both. Some medications, such as kidney failure or viral infection medications, can increase liver enzyme levels (AST and ALT) and cause liver damage (minor damage), which is asymptomatic (Gara *et al.*, 2012; Mutar *et al.*, 2019; Almakhatreh *et al.*, 2020). The results revealed that renal failure increased ALT, AST, and ALP and decreased urea and creatinine in the kidney. These results were consistent with those of de Oliveira Liberato *et al.* (2012), who reported that elevated liver enzymes indicate deteriorating liver function due to widespread inflammation, as observed in the dialysis group. The HBV-infected patients had increased ALT, where these tests are used in the general population to detect chronic liver disease. In haemodialysis patients, the ALT has a poor diagnostic value as it tends to be below the baseline (Lin *et al.*, 2021).

Haemodialysis is an effective treatment for most patients with renal failure and an alternative to kidney transplantation. Thus, haemodialysis improves the patient's quality of life with adequate dialysis and even prolongs their lifespan. Nevertheless, viral diseases are among the most important factors leading to an increased mortality rate and restricting the quality of life of dialysis patients. Specifically, HBV is a serious public health issue globally. Furthermore, an extremely high rate of CKD patients are exposed to HBV infections (Elahi *et al.*, 2020).

Generally, more than half of the infected patients on dialysis become persistent, asymptomatic HBsAg carriers without biochemical evidence of hepatitis. Additionally, the appearance of HBV serological markers may be delayed by as long as 6–12 months (Treger *et al.*, 2016). Some dialysis

centres have reported outbreaks of fulminant HBV infection, which indicate that immunocompromised hosts, such as end-stage kidney disease patients on dialysis, may develop severe disease from HBV infection (Fabrizi *et al.*, 2019). The HBV spread relies on HBV infection endemicity, inadequate dialysis unit management, familial HBV infection, and contaminated blood transfusion. In India, the reported HBV and HCV infection prevalence among haemodialysis patient varies. Bhaumik and Debnath, (2012) reported that 5.9% of patients on haemodialysis were HCV-positive, while 1.4% of patients had HBV infection and 3.7% had HBV and HCV co-infection. Al-Hegami *et al.* (2015) reported that 7.46% and 37.10% of CKD, or renal transplant or haemodialysis patients had HBV, HCV, and co-infection of both viruses, respectively.

The results corresponded to Fyneface *et al.* (2018), who reported that the mean serum urea values in all male and female patients were increased before haemodialysis when compared to the mean values after haemodialysis. Generally, urea accumulation in the serum of kidney failure patients arises from the degradation of food and tissues, such as muscle. The high urea level in the blood can lead to extreme illness unless the kidneys remove it from the bloodstream (Beier *et al.*, 2011). Nonetheless, creatinine clearance is the best method for examining kidney function. Analysis results demonstrated that all haemodialysis patients had lower serum creatinine after dialysis, which indicated that age, sex, and physical status affect serum creatinine levels (Canaud *et al.*, 2014).

The data were similar to the results of Fyneface *et al.* (2020), who reported that haemodialysis positively affected renal failure patients, where serum creatinine levels were significantly reduced. The reduced creatinine level during haemodialysis is also used as a surrogate marker of dialysis inadequacy. However, both men and women in the 41- and 60-year-old age group are more prone to kidney failure, which might be due to hypertension, diabetes or other age-related changes. Liver enzymes are naturally secreted from the liver in small quantities, and accelerate vital processes in the body and convert food into energy (Sette and de Almeida Lopes, 2014). This study demonstrated that dialysis led to liver dysfunction in renal failure patients through increased serum liver enzyme levels (ALT, AST, ALP) and increased urea and creatinine levels.

The HBV infection is a major health issue in Iraq, which has moderate or high HBV endemicity rates. Therefore, this study investigated the preva-

lence of HBV infections in kidney failure patients receiving dialysis. Furthermore, the effect of viral infection on the response of anti-inflammatory cytokines (IL-10) and pro-inflammatory cytokines (IL-17) in dialysis patients, and on the effectiveness of their liver and kidney functions, was evaluated.

This study investigated the response to anti-inflammatory cytokines (IL-10) and pro-inflammatory cytokines (IL-17) in dialysis patients. The results demonstrated that the patients had significantly increased IL-10 and IL-17 levels compared to the control. The results were consistent with other studies that observed diverse responses to anti-inflammatory and pro-inflammatory cytokines associated with monocyte activation in dialysis patients and patients with chronic renal failure (Taraz *et al.*, 2012; Tbahriti *et al.*, 2013).

The results suggested that IL-10 and IL-17 may be critical in CKD pathogenesis and in HBV-infected patients. Therefore, the prognostic significance of elevated IL-10 and IL-17 levels is independent of and additive to the prognostic impact of the classical markers of renal function, which include creatinine and urea (Yu *et al.*, 2015; Mathew *et al.*, 2016). Patients with kidney disease, particularly those with viral hepatitis, had significantly higher levels of inflammatory cytokines, such as IL-10 and IL-17. A simple explanation for the finding is that a decreased GFR typically significantly decreases the clearance of these cytokines. Additionally, the circulating levels of these cytokines continue to increase as the body continues to secrete them (Ortega and Fornoni, 2010).

In this study, the HBV-positive patients had elevated IL-10 and IL-17 levels compared with the controls. The roles of IL-17 in stimulating appropriate immune responses against viral infections are controversial. The IL-17 may have a positive role in antiviral immune responses in many diseases (Mills, 2023). Nevertheless, IL-17 is positively regulated in HBV-induced inflammation in chronic hepatitis B infection, and may be relevant to liver fibrosis and HCC development (Du *et al.*, 2013). The IL-17 can also significantly stimulate monocytes and dendritic cells (DCs) to express its ligand (IL-17R) and produce pro-inflammatory cytokines, such as IL-1 β , TNF- α , IL-10, and IL-6 (Zhong *et al.*, 2021; Abdelnabi *et al.*, 2024). These cytokines are important for liver damage during the development of chronic HBV. Despite the evidence supporting the important immunological role of IL-10 and IL-17, many other functions of these interleukins in the liver and kidney require further research. Fur-

thermore, the role of IL-10 and IL-17 in complex immune systems requires further investigation. The limitation of this study is that it involved a small number of cases and few cytokines. Therefore, further studies with expanded samples and extended follow-up should be conducted. In conclusion, this study detected high IL-10 and IL-17 levels in kidney failure patients. The HBV infection remains common in patients receiving dialysis, and will increase the burden on patients with kidney failure, affect their immune system, and cause serious complications. The IL-10 and IL-17 are potential biomarkers to predict renal failure development, and their elevated levels may contribute to spontaneous HBV clearance (Abdelnabi *et al.*, 2024).

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