Original Article

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Prevalence of Hepatitis B Associated Chronic Nephropathy in Baghdad, Iraq for the Year 2023

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ABSTRACT

Background: The correlation between hepatitis B virus (HBV) and nephropathy presents a significant public health issue in Iraq. **Aim**: This study systematically investigates the association between hepatitis B surface antigen (HBsAg) serology and chronic kidney disease among residents of Baghdad, Iraq. **Methods**: We evaluated the clinical characteristics and serologic profiles of 609 patients with adult-onset HBV-related membranous nephropathy. **Results**: Individuals who are HBsAg (+) have a slightly increased risk of developing eGFR < 60 ml/min/1.73m^2 or proteinuria compared to HBsAg (-) individuals. **Conclusion**: The study emphasizes the substantial impact of HBV on chronic kidney disease, independent of viral replication or inflammation. The findings underscore the importance of understanding the epidemiology and clinical implications of HBV infection in the context of renal complications, revealing potential immunological and pathological mechanisms. Further studies are recommended to elucidate the complex relationship between HBV infection and kidney impairment.

Keywords: Hepatitis B, chronic kidney disease, HBV-associated nephropathy, proteinuria, eGFR

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INTRODUCTION

Hepatitis B virus (HBV) is the most common cause of liver disease.[1] cirrhosis, and primary liver cancer. The annual toll of HBV-related mortality is around 1 million worldwide, translating to an alarming rate of approximately 2 deaths per minute. Depending on the virus sequence homogeneity, at least 10 genotypes (A to J) and various sub-genotypes have been identified. Genotype D has a global presence but is most prevalent in the Middle East and Southern Europe.[2] Genotype E, on the other hand, is primarily confined to West Africa, while Genotype F is prevalent in Central and South America.[3] Hepatitis B viral variants can vary in their virulence, serologic reactivity, pathogenicity, therapeutic response, and global distribution. The frequency of hepatitis B virus (HBV) infection in Iraq is a major public health problem, significantly contributing to the incidence of hepatitis B-associated chronic nephropathy in the nation. Multiple studies have emphasized the occurrence of HBV infection in various areas of Iraq, with rates ranging from around 1% in the northern region to 3.5% in the southern region.[4,5] Baghdad, however, has low epidemicity.[6] Moreover, the genetic diversity of HBV

has been examined in individuals with chronic infection in Iraq, highlighting the need to examine HBV genotypes in relation to chronic nephropathy.[7,8] The correlation between HBV infection and chronic nephropathy has been extensively documented, with HBV being associated with several renal symptoms, such as membranous nephropathy and mesangiocapillary glomerulonephritis.[9,10] Additionally, the prevalence of HBV infection has been investigated in specific populations, such as blood donors and pregnant women, pre-marital exams, and chronic hereditary hemoglobinopathies, shedding light on the widespread nature of the virus in Iraq.[11,5] Overall, the incidence of hepatitis B-associated nephropathy in Iraq is a multifaceted issue influenced by the prevalence of HBV infection, the genetic diversity of the virus, and its impact on renal complications. Understanding the epidemiology, clinical implications, and molecular aspects of HBV infection is crucial for developing effective strategies to prevent and manage HBV-associated chronic nephropathy in Iraq. This study aimed to determine the prevalence of chronic kidney disease (CKD) among Iraqi patients with Hepatitis B in Baghdad, the capital of Iraq. To do this, the researchers assessed glomerular filtration rate (GFR), proteinuria, urine dipstick test, body mass index (BMI), glucose level, and systolic blood pressure.

MATERIALS AND METHODS

A total of 320,069 patients were screened. Patients with a documented cancer history (n = 3,667), ultrasound confirmation of inflammatory liver disease, and pre-existing chronic kidney disease (n = 14,548) were included in the study. Following the elimination of the first 19,645, the total number of participants who fulfilled the requirements was 300,424 individuals (170,214 men and 130,210 women). Additionally, 301 individuals were excluded from the research due to insufficient baseline data, such as their HBsAg serology, estimated glomerular filtration rate, body mass index, glucose level, systolic blood pressure, or urine dipstick test. This resulted in a final sample size of 299,913 unique individuals (169,994 men and 129,919 women). The data were obtained from regular health screenings. The study was approved by the review committees at Baghdad Teaching Hospital, Al Yarmouk Teaching Hospital, and Al Kadhmia Teaching Hospital. As part of the comprehensive health evaluation, a standardized self-administered questionnaire was used to collect information on each participant's medical and family history, medication, smoking, socioeconomic status, and level of physical activity. Participants' vital signs were routinely taken by a qualified expert in a controlled environment at regular intervals. Abdominal ultrasonography was also conducted as part of the normal health screening. At each visit, participants were evaluated for viral hepatitis B serology, complete blood count, blood biochemistry, and urine examination for proteinuria. Blood samples were drawn for testing HBs Ag using electrochemiluminescent immunoassay. In this analysis, chronic kidney disease (CKD) was defined as having an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73m² or below, and/or the presence of proteinuria. Periodic evaluations of estimated glomerular filtration rate (eGFR) and proteinuria were conducted to monitor the progression of chronic kidney disease (CKD). Hazard ratios (HRs) and confidence intervals (CIs) were used to compare individuals with and without HBsAg. Other information, such as smoking and alcohol use, formal educational achievements, physical activity, and BMI, was recorded as part of the general history taking. Informed consent from the patients regarding participation in the study was obtained during the visit.

RESULTS

We determined hazard ratios and confidence intervals (CI) for the occurrence of chronic renal disease by comparing patients with and without HBsAg. Patients without HBsAg served as the control group (CKD). We utilized the following three models, each with a different degree of adjustment, to account for the impact of any possible confounding variables: In the initial model, we considered age, gender, study site, and the estimated glomerular filtration rate (eGFR) at the beginning of the procedure. For our second model, we included variables like smoking history, alcohol use, educational attainment, degree of physical activity, and body mass index. A spline-based parametric survival model was then used to predict the smooth lines of the cumulative incidence curves (Fig. 1). Among the 11,209 individuals who tested positive for HBsAg, there were 609 cases of chronic kidney disease (CKD), while there were 13,315 CKD cases among the 288,704 individuals who tested negative for HBsAg (the incidence rates were 9.3 and 8.3 per 1,000 person-years, respectively.). The hazard ratio for the comparison between individuals who had a positive HBsAg and those who did not was 1.11 (95% CI: 1.03–1.21).

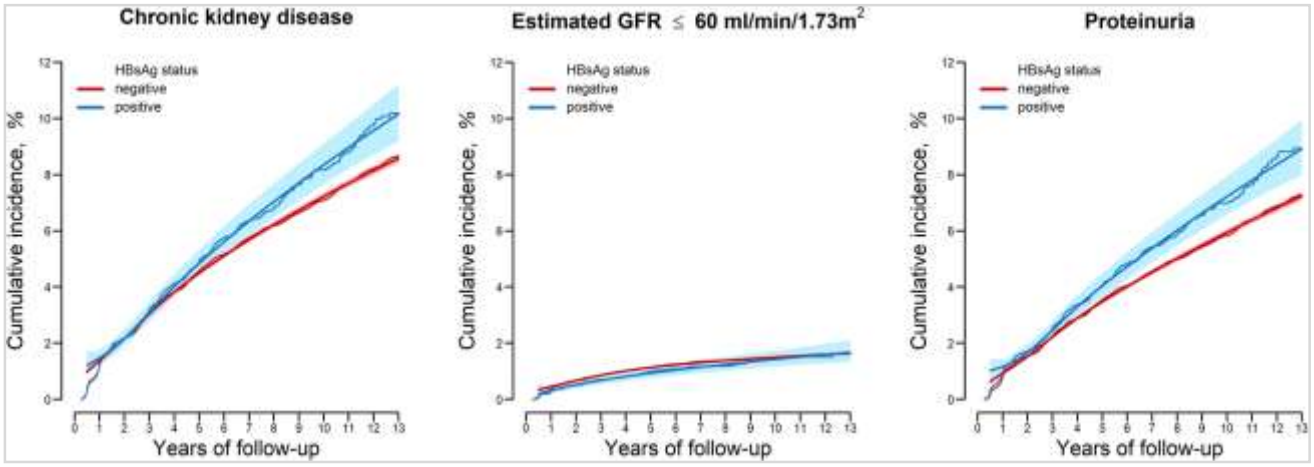

Figure 1: Adjusted cumulative incidence of chronic kidney disease (CKD) based on the presence of hepatitis B surface antigen (HBsAg) in the first blood sample.

Table 1: Hazard ratios (HR) for incident CKD by HBsAg serology (n = 299,913).

	No. of incident cases (person-years)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
eGFR < 60 ml/min/1.73m²ml/min/1.73m2 or proteinuria				
HBsAg (−)	13,315 (1,608,299.2)	1.00 (reference)	1.0 (reference)	1.00 (reference)
HBsAg (+)	609 (65,401.8)	1.07 (0.99–1.16)	1.09 (1.00–1.18)	1.11 (1.03–1.21)
eGFR < 60 ml/min/1.73m²ml/min/1.73m2				
HBsAg (−)	31063,106 (1,641,700.4)	1.00 (reference)	1.00 (reference)	1.00 (reference)
HBsAg (+)	119 (67,044.5)	0.91 (0.76–1.09)	0.87 (0.72–1.05)	0.89 (0.73–1.07)
Proteinuria				
HBsAg (−)	10,560 (1,621,635.3)	1.00 (reference)	1.00 (reference)	1.00 (reference)
HBsAg (+)	512 (65,806.8)	1.17 (1.07–1.28)	1.20 (1.10–1.31)	1.23 (1.12–1.35)

DISCUSSION

Among this large group of individuals who did not exhibit any overt symptoms of renal illness, those who tested positive for HBsAg had a significantly increased chance of developing chronic kidney disease (CKD). Proteinuria was the primary contributor to the increased risk, even though only a small percentage of individuals who tested positive for HBsAg had an eGFR lower than 60 ml/min/1.73 m². After excluding patients with cirrhosis or positive HBV antibodies from the tri al, the findings remained consistent, regardless of whether the baseline level of liver enzymes was elevated or normal. According to the research findings, the widespread prevalence of chronic hepatitis B infection likely contributes to the global burden of chronic kidney diseases. It is not entirely clear whether an infection with hepatitis B plays a crucial role in the development of chronic renal disease, due to a lack of adequate data to substantiate either theory. Despite considerable variability among studies, a meta-analysis.[12] including four cohort studies revealed that individuals with HBV infection had a pooled HR of 2.2 (95% CI: 0.95–3.50) for chronic kidney disease(CKD).[13] Despite significant opportunities for modification, this remained the case. Additional meta-analyses.[14] conducted on cohort, cross-sectional, and case-control studies in Asian populations have not discovered any association between HBsAg serology and a reduction in eGFR (adjusted risk ratio 0.95; 95% CI 0.72–26) or proteinuria (adjusted risk ratio 1.00; 95% CI 0.83–1.20). Relevant meta-analyses conducted on Iraqi populations,

encompassing cohort, cross-sectional, and case-control studies, have consistently reached the same conclusion, finding a strong association between chronic HBV infection and the development of both incident CKD and incident end-stage renal disease (ESRD), as indicated by significantly high hazard ratios (HRs). No correlation was found between a positive HBsAg serology and an increased risk of existing proteinuria in any of the three cross-sectional studies conducted consistently in East Asian nations. These studies.[15] employed the same methodology. Conversely, the present investigation discovered a noteworthy association between HBsAg serology and the occurrence of CKD. Nevertheless, this connection was attributed to the development of proteinuria rather than a decrease in the estimated glomerular filtration rate (eGFR). HBsAg serology is a blood test used to identify the presence of the hepatitis B surface antigen. Based on our thorough investigation, it was shown that a higher occurrence of proteinuria is primarily responsible for the heightened susceptibility to chronic kidney disease (CKD) observed in individuals who are positive for HBsAg. This conclusion was reached after careful analysis. HBV-associated nephropathies, such as membranous nephropathy and membranoproliferative glomerulonephritis, are characterized by the presence of proteinuria or nephrotic syndrome. This conclusion was derived after considering any possible confounding factors. After excluding 215 individuals who reported receiving treatment for viral hepatitis at the beginning or during the study and recalculating the hazard ratio, we found an increased risk of developing chronic kidney disease in HBsAg-positive individuals. This result was evident in the comparison of individuals who were positive for HBsAg and those who were negative for HBsAg. Another key finding is that our research participants who had ALT levels outside of the normal range at the start of the trial were at a greater risk of developing CKD than those whose ALT levels were within the normal range. HBV-associated nephropathy is more likely to arise during the inactive carrier phase of hepatitis, characterized by low levels of hepatitis viral load and liver enzyme levels. This contrasts with the immune-tolerant or immunological clearance phases, where there is active replication of the virus or active inflammation in liver cells. Our study findings indicate that individuals with HBV infection are at a heightened risk of kidney injury, regardless of whether there is active viral replication or inflammation. This was true even in the absence of any evidence for either condition. This suggests that the relationship between positive HBV serology and the occurrence of CKD was consistent, independent of the initial ALT level of an individual. A prior investigation conducted in 2019.[16] on the rural population of China produced comparable findings. Du et al. postulated that chronic kidney disease was more strongly associated with hepatitis B virus (HBV) infection compared to hepatitis B alone.[13] The natural progression of HBV infection is influenced by the interplay between the host's immune response and HBV replication.[17,18]. Although these observations have provided valuable information, the exact mechanisms by which HBV-related nephropathy develops remain unclear. Research has demonstrated that the serum of individuals with persistent HBV infection triggers apoptosis in renal tubular cells.[19,20] Furthermore, there is a correlation between HBV infection and the presence of oxidative stress and insulin resistance.[21,22] Immunohistochemical investigations have confirmed that HBV antigens are expressed in kidney tissues, which can lead to persistent immunologic damage and direct viral-induced pathological changes. While it is well-accepted that the presence of HBV antigens and host antibodies in the kidneys is a key factor in causing kidney damage, there is currently no consensus on the specific viral antigen primarily responsible for this. Notably, HBe Ag has been recognized as the main antigen in HBV-associated membranous nephropathy (MN), with the presence of HBsAg, Hepatitis B Core Antigen (HBc Ag), and HBe Ag deposits detected. Renal tubular epithelial cells expressing HBs Ag and HBc Ag may enhance the activation of complement-mediated inflammatory gene pathways, leading to kidney damage.[17].

CONCLUSIONS

Our conclusions are supported by the outcomes of the investigations conducted as part of our fundamental research. Immunological processes, particularly the deposition of immunological complexes in the kidney, are the key mechanisms responsible for the development of HBV-associated nephropathy. In addition to causing harm to the kidney via immunologic processes, the virus may also inflict damage through apoptosis or directly through its own activity. Studies have shown that HBV DNA may be found in both glomerular and tubular cells. It has been suggested that HBV can enhance apoptosis of renal tubular cells by activating the fast pathway. To fully understand the nature of the cause-and-effect relationship between HBV

infection and kidney impairment, further research is necessary.

Conflict of interest:

The authors declare no conflicts of interest regarding the publication of this review article. No financial or personal relationships with individuals or organizations have influenced the content or presentation of the manuscript. This includes employment, consultancies, honoraria, and any other financial or non-financial interests. The authors affirm their commitment to unbiased and objective reporting in the field under consideration.

Author contribution:

Prof. Adam Dawoud Salim played a pivotal role in conceiving the structure and focus of the research article, outlining the key themes, and establishing the overall direction of the manuscript. Ali Abduljabbar Razooqi contributed significantly to the composition of the research, conducting thorough literature reviews, synthesizing data, and providing critical analysis of existing research to shape the narrative. Prof. Bakri Yousif Nour and Ali Abduljabbar Razooqi were instrumental in revising and refining the manuscript, ensuring coherence, clarity, and adherence to academic standards. They also finalized the article for submission.

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