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Diagnostic Potential of Inflammatory Biomarker Levels in the Serum of Patients with Hepatitis B Infection: A Retrospective Study

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Abstract: This study aimed to evaluate the diagnostic biomarker potential of C-Reactive Protein (CRP) and Procalcitonin (PCT) levels in the serum of individuals infected with the Hepatitis B Virus (HBV). The patients were divided into two age groups: Younger (<60 years) and older (≥60 years). An Electrochemiluminescence Immunoassay (ECLIA) platform was employed for the serological analysis to quantify the biomarker levels. A retrospective analysis was conducted on a cohort of HBV-infected patients and serum samples were collected from 200 individuals infected with HBV as well as from healthy controls. ECLIA revealed significantly increased levels of the pro-inflammatory markers CRP and PCT in both younger and older HBV-infected patients compared with those for participants in the healthy controls ($p<0.0001$). Importantly, the serum CRP and PCT levels were independent of age and sex. These findings provide evidence for increased serum CRP and PCT levels following HBV infection, indicating a potential correlation between these biomarkers and HBV infection. Thus, this study demonstrates the promising clinical diagnostic significance of CRP and PCT in HBV infections when assessed using ECLIA.

Keywords: C-Reactive Protein, Hepatitis B Viru, Procalcitonin, Serological Assay

Introduction

Viral hepatitis is a widespread infectious disease that impairs the host's ability to regulate and eliminate the infection, leading to a significant risk of liver cancer (60-70%) and high mortality rates. In Korea, there is a high prevalence of viral hepatitis, with 2.5-3% of the population being carriers of hepatitis B (de Souza Pires-Neto *et al*., 2020; Yang *et al*., 2022). Hepatitis B Virus (HBV) infection can cause acute liver disease, leading to acute-on-chronic liver failure and other metabolic pathological symptoms that result in liver injury. Additionally, it can lead to cirrhosis (with a mortality rate of 20-30%) and hepatocellular carcinoma (with a mortality rate of 60%) (Shin *et al*., 2018; Yang *et al*., 2022; Surial *et al*., 2021).

Inflammatory dysfunction is a common characteristic of many chronic diseases, including severe liver disease caused by hepatitis. C-Reactive Protein (CRP) and Procalcitonin (PCT) are commonly used inflammatory markers in clinical practice for diagnosing sepsis at the serological level. Typically, the levels of CRP and PCT in the serum are measured using a Chemiluminescent Immunoassay (CLIA) or a latex particle-enhanced immunoturbidimetric assay, which requires the use of a fully automatic biochemical analyzer. While these methods are accurate, they can be expensive to perform (Dong *et al.*, 2019).

CRP is an acute-phase protein synthesized by hepatocytes in response to inflammatory reactions and it is involved in promoting apoptosis and phagocytosis (Shin *et al*., 2018; Tan *et al*., 2018). Recent meta-analyses have investigated the correlation between CRP and HBV infection explaining that the elevated level is observed (Moura *et al*., 2019; Chen *et al*., 2018; Swanson *et al*., 2016). Some studies have demonstrated a correlation between serum CRP levels and the

severity of HBV infection, indicating that patients with elevated CRP levels are at a higher risk of liver damage, including cirrhosis and fibrosis (Sproston and Ashworth, 2018).

PCT is a precursor hormone to calcitonin and its levels in the serum have been reported to be elevated in patients with bacterial infections (He *et al*., 2021). Moreover, elevated serum PCT levels have been associated with pro-inflammatory effects and increased mortality rates in sepsis models (Zheng *et al*., 2018; Igna *et al*., 2022). However, inhibition of PCT expression can prevent these effects. Altered serum PCT levels have been observed in chronic liver diseases and cirrhosis. Notably, patients with HBV infection also exhibit elevated serum PCT levels. Additionally, patients with HBV tend to have higher CRP levels than healthy individuals (Moura *et al*., 2019). Nevertheless, our understanding of the correlation between serum PCT levels and liver disorders such as liver cirrhosis and hepatocellular carcinoma resulting from HBV infection remains limited (Igna *et al*., 2022; Oh *et al*., 2021; Tan *et al*., 2018). These findings highlight the involvement of CRP in the inflammatory response and its potential correlation with the severity of HBV infection. Furthermore, elevated PCT levels in patients with HBV infection suggest its association with the disease. However, further research is needed to fully comprehend the exact relationship between serum PCT levels and liver-related complications arising from HBV infection, such as liver cirrhosis and liver cancer (Liu *et al*., 2022).

We believe that the present study is necessary, given the need for reliable diagnostic biomarkers for HBV infections. Currently, accurate diagnosis of HBV infections can be challenging, especially in the early stages, as the symptoms can be non-specific. The availability of specific biomarkers could aid in the timely detection and diagnosis of HBV infections, allowing for early intervention and appropriate medical management (Liu *et al*., 2022).

The findings of this study could provide novel insights into the assessment of inflammatory markers in HBV infections. Specifically, it investigates the diagnostic potential of two inflammatory markers, CRP and PCT, in individuals with HBV infections. This study will contribute to our understanding of the clinical usefulness of CRP and PCT as specific markers for HBV infections.

By evaluating and comparing the levels of CRP and PCT in the serum of HBV-infected patients versus those in healthy controls, this study addresses the necessity for improved diagnostic tools for HBV infections. The observed CRP and PCT levels in HBV-infected individuals, independent of age and sex, support the potential use of these biomarkers as clinically valuable indicators of HBV infection. The study's results contribute to advancing the understanding and management of HBV infections, potentially leading to improved diagnostic strategies and better patient outcomes.

This study aimed to investigate the association between serum CRP and PCT levels in patients with HBV infection and healthy controls. The analysis focused on evaluating the relationship between these inflammatory biomarkers and liver infection. Furthermore, the data obtained were analyzed with respect to age and sex to determine whether serum CRP and PCT levels were independent of these factors in both HBV-infected patients and healthy controls.

Materials and Methods

Study Design and Participants

In this retrospective study, we examined patients who were diagnosed with HBV infection. The diagnosis was made based on a Reverse-Transcription quantitative Polymerase Chain Reaction (RT-qPCR) test performed using serum samples from patients from August 2022 to September 2022 at Dankook University Hospital in Cheonan Province, Republic of Korea. A total of 200 patients were enrolled in the study, of whom 104 were diagnosed with HBV infection and 96 were healthy controls. The patients were divided into two age groups: The younger group (0-59 years) and the older group (≥60 years). The mean age was 48±11 years in young individuals and 67±10 years in older adults. This study was approved by the Clinical Research Review Committee of Dankook University (Institutional Review Board DKU Certificate No. 2023-01-005). The 104 patients with HBV and 96 healthy controls were divided into two groups according to criteria that included age, sex, and infection status (positive or negative) (Osei-Boakye *et al.*, 2022; Gitimu *et al*., 2022).

Data Collection

CRP and PCT levels were measured using an Electrochemiluminescence Immunoassay (ECLIA) quantitative analyzer (cobas e 801 analytical unit; Roche Diagnostics, Mannheim, Germany). The Diagnostic Test Department at Dankook University evaluated the data according to test procedures guided by Elecsys CRP and PCT (cobas e 411 analyzers; Roche Diagnostics). Data on the inflammatory parameters were obtained from 200 HBV-positive serum samples following HBV confirmation by RT-qPCR.

Measurement of CRP and PCT Levels

The detection buffer contained an antibody combined with a fluorescent dye that specifically binds to inflammatory markers such as CRP and PCT. When the detection buffer and specimen are mixed, the antibody in the detection buffer and inflammatory-related antigen in the specimen form an antigen-antibody complex. The extent of the immune

response is converted into a fluorescence signal and the concentration is calculated by a dedicated measuring device (cobas e 801 analytical unit; Roche Diagnostics). The test results are displayed on the reader as milligrams per liter (mg/L) for CRP and nanograms per milliliter (ng/mL) for PCT. A fluorescence-labeled control protein of known quantity is included in the reaction and the intensity of this control line is measured as a quality check.

Data Evaluation

The 200 samples used in this study were received anonymously by the laboratory for routine measurement of the two inflammatory markers using ECLIA. The selected samples were within the analytical range provided by Roche Diagnostics, namely CRP concentrations between 0.1 and 300.0 mg/L and PCT concentrations between 0.1 and 100.0 ng/mL. According to the Korean Society of Laboratory Medicine, the normal ranges of CRP and PCT are <10.0 mg/L and <0.5 ng/mL, respectively.

Statistical Analyses

Normally distributed continuous data are expressed as the mean ± standard deviation and an independent t-test was used to determine the significant differences between groups. All statistical analyses were performed using GraphPad Prism (version 7.00.159; GraphPad Software, San Diego, CA, USA). Statistical significance was set at $p<0.05$.

Results

Demographic and Clinical Characteristics of Enrolled Subjects

The study enrolled a total of 200 participants: 140 individuals in the younger group (0-59 years) and 60 individuals in the older group (≥60 years) (Table 1). Among the patients with HBV infection, 79 (76%) belonged to the younger group, whereas 25 (24%) belonged to the older group. Among the 96 healthy controls, 61 (41%) were included in the younger group and 35 (59%) were included in the older group (Table 2). The study findings revealed that both younger and older individuals infected with HBV exhibited significantly increased levels of CRP and PCT compared with the levels of those without HBV infection.

HBV Infection Enhances Serum CRP and PCT Levels in Patients with HBV

The study findings demonstrated that the CRP and PCT levels were significantly higher in patients with HBV infection than in healthy individuals. The average CRP level was 5.91±0.45 mg/L in patients with HBV infection and 1.91±0.27 mg/L in healthy individuals. Similarly, the average PCT level was 0.24±0.23 ng/mL in patients with HBV infection and 0.028±0.013 ng/mL in healthy individuals (Fig. 2).

Levels of CRP and PCT in Males and Females with HBV Infection

The study findings provide additional insights into the relationship between CRP and PCT levels and HBV infection based on sex differences. The average CRP level was 4.81±0.23 mg/L in males with HBV infection and 1.41±0.43 mg/L in males without HBV infection. Similarly, the average PCT level was 0.23±0.03 ng/mL in males with HBV infection and 0.013±0.003 ng/mL in males without HBV infection. The average CRP level was 6.91±0.78 mg/L in females with HBV infection, compared with 1.48±0.25 mg/L in females without HBV infection. Similarly, the average PCT level was 0.28±0.24 ng/mL in females with HBV infection and 0.042±0.012 ng/mL in females without HBV infection (Fig. 3).

Quantification of Hepatitis B DNA Levels Based on Sex and Age Among Patients with HBV

Figure 4 provides important insights into the quantitative measurement of Hepatitis B Viral load (HBV unit) using RT-qPCR analysis in patients with HBV. The results highlight notable differences in HBV unit levels based on sex and age groups. The average HBV unit was 140,256±105,119 units in male patients and 55.93±30.58 units in female patients, indicating a considerable difference in viral load between the two sexes. Additionally, a significant difference was observed between the younger (104,697±78,641 units) and older groups (262.3±217.2 units), as depicted in Fig. 3. Importantly, as shown in Fig. 3, a significant correlation was noted between inflammatory biomarker (CRP and PCT) trends and HBV viral load in HBV units.

Table 1: Demographic features and laboratory findings of the participants based on age

		The younger group (age 0-59 years)			Older group (age≥60 years)		
Parameter		Hepatitis B virus-negative (n = 61)	Hepatitis B virus-positive (n = 79)	P_1	Hepatitis B virus-negative (n = 35)	Hepatitis B virus-positive (n = 25)	P_2
Sex	Male (%)	43 (70%)	44 (56%)	*NS*	18 (51%)	15 (60%)	*NS*
	Female (%)	18 (30%)	35 (44%)	*NS*	17 (49%)	10 (40%)	*NS*
CRP (mg/L)		1.29±0.13	4.11±1.92	<0.0001	1.18±0.26	5.44±0.15	<0.0001
PCT (ng/mL)		0.025±0.003	0.28±0.24	<0.0001	0.025±0.002	0.13±0.10	<0.0001

NS: Not significant

Table 2: Demographic features and laboratory findings of participants based on HBV infection

		Hepatitis B virus-negative			Hepatitis B virus-positive		
Parameter		Young people (age 0-59 years) (n = 61)	Older adults (age ≥60 years) (n = 35)	P_1	Young people (age 0-59 years) (n = 79)	Older adults (age ≥60 years) (n = 25)	P_2
Sex	Male (%)	43 (70%)	18 (51%)	*NS*	44 (56%)	15 (60%)	*NS*
	Female (%)	18 (30%)	17 (49%)	*NS*	35 (44%)	10 (40%)	*NS*
CRP (mg/L)		1.91±0.13	1.47±0.37	<0.0001	5.22±0.17	4.44±0.57	<0.0001
PCT (ng/mL)		0.024±0.02	0.021±0.03	<0.0001	0.21±0.12	0.24±0.17	<0.0001

NS: Not significant

Discussion

This study aimed to assess the analytical and diagnostic performance of two inflammatory markers, CRP and PCT, at the serological level using the ECLIA platform to evaluate their potential clinical utility.

Table 1 and 2 suggest that CRP and PCT may serve as reliable biomarkers for indicating the presence of HBV infection, regardless of age. The absence of a significant difference between the two age groups in terms of CRP and PCT levels indicates that the association between these biomarkers and HBV infection is independent of age. These results have important implications for the diagnosis and management of HBV infection. The elevated CRP and PCT levels in both younger and older individuals with HBV infection highlight their potential as diagnostic markers for identifying HBV-infected patients. By measuring the levels of these biomarkers, healthcare providers may be able to distinguish between individuals with HBV infection and those without, thus contributing to early detection and appropriate treatment initiation.

Furthermore, the independence of CRP and PCT levels from age suggests that these biomarkers can be used across different age groups, enhancing their clinical utility. However, it is important to note that although CRP and PCT levels are indicative of HBV infection, they may not be specific to HBV infection and their levels could potentially be elevated in other liver diseases or inflammatory conditions.

Figures 1-2 results indicate that HBV infection is associated with an enhanced inflammatory response, as evidenced by the elevated CRP and PCT levels. CRP is an acute-phase protein produced by the liver in response to inflammation, whereas PCT is a precursor hormone released during bacterial infections and inflammatory processes. The significant elevation in both CRP and PCT levels in patients with HBV infection suggests an ongoing inflammatory reaction within the liver.

Figure 3 results indicate that CRP and PCT levels are significantly increased in males and females following HBV infection. This suggests that the inflammatory response triggered by HBV affects both sexes, leading to higher levels of these biomarkers in individuals with HBV infection than in those without HBV infection. The observed differences in CRP and PCT levels between HBV-infected and uninfected individuals further emphasize the potential diagnostic value of these biomarkers in identifying HBV infection.

The sex-specific findings reveal that the CRP and PCT levels tend to be higher in females with HBV infection than in males with HBV infection. This suggests that females exhibit a stronger inflammatory response in the context of HBV infection. However, it is important to note that the study findings do not provide information on the underlying reasons for these sex differences. Further research is needed to explore the mechanisms behind the observed sex-specific differences in CRP and PCT levels in HBV infection.

The findings in Fig. 4 suggest a potential correlation between the inflammatory response, as indicated by the elevated CRP and PCT levels, and the viral replication activity of HBV, as reflected by the HBV unit measurements. The observed differences in the HBV unit levels between males and females may be attributed to various factors, such as hormonal influences, genetic variations, or differences in the immune response to HBV infection. Further research is needed to explore the underlying mechanisms responsible for these sex-related disparities in HBV viral load. The significant correlation between inflammatory biomarkers and HBV unit levels implies an association between the severity of HBV infection and the extent of liver inflammation. Elevated CRP and PCT levels could potentially serve as indicators of increased viral replication activity and liver inflammation in patients with HBV infection. However, it is important to note that the exact cause-and-effect relationship between inflammatory

biomarkers and HBV replication or liver inflammation cannot be determined solely based on these findings. Further studies are necessary to establish a more comprehensive understanding of the interplay between viral replication, inflammation, and the host immune response in HBV infection.

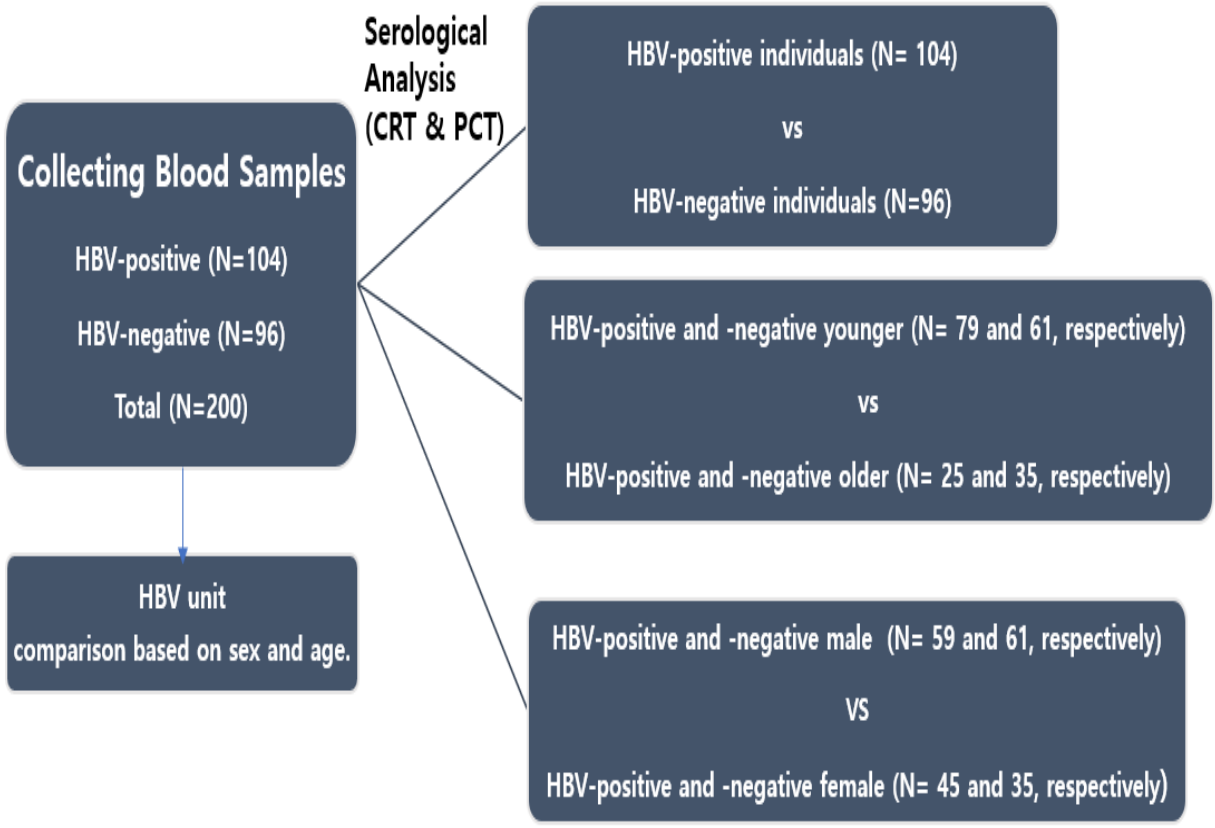

Fig. 1: Flowchart for the study methodology

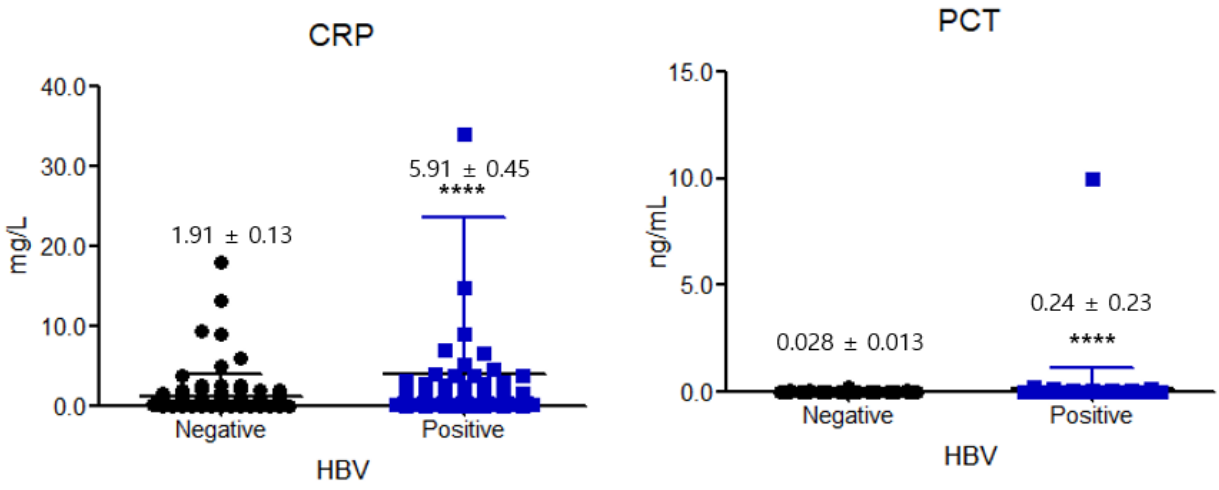

Fig. 2: Comparison of inflammatory marker levels (CRP and PCT) based on HBV infection. CRP levels ($p<0.0001$) (a) and PCT levels ($p<0.0001$) (b). CRP, C-reactive protein; PCT, procalcitonin; HBV, hepatitis B virus

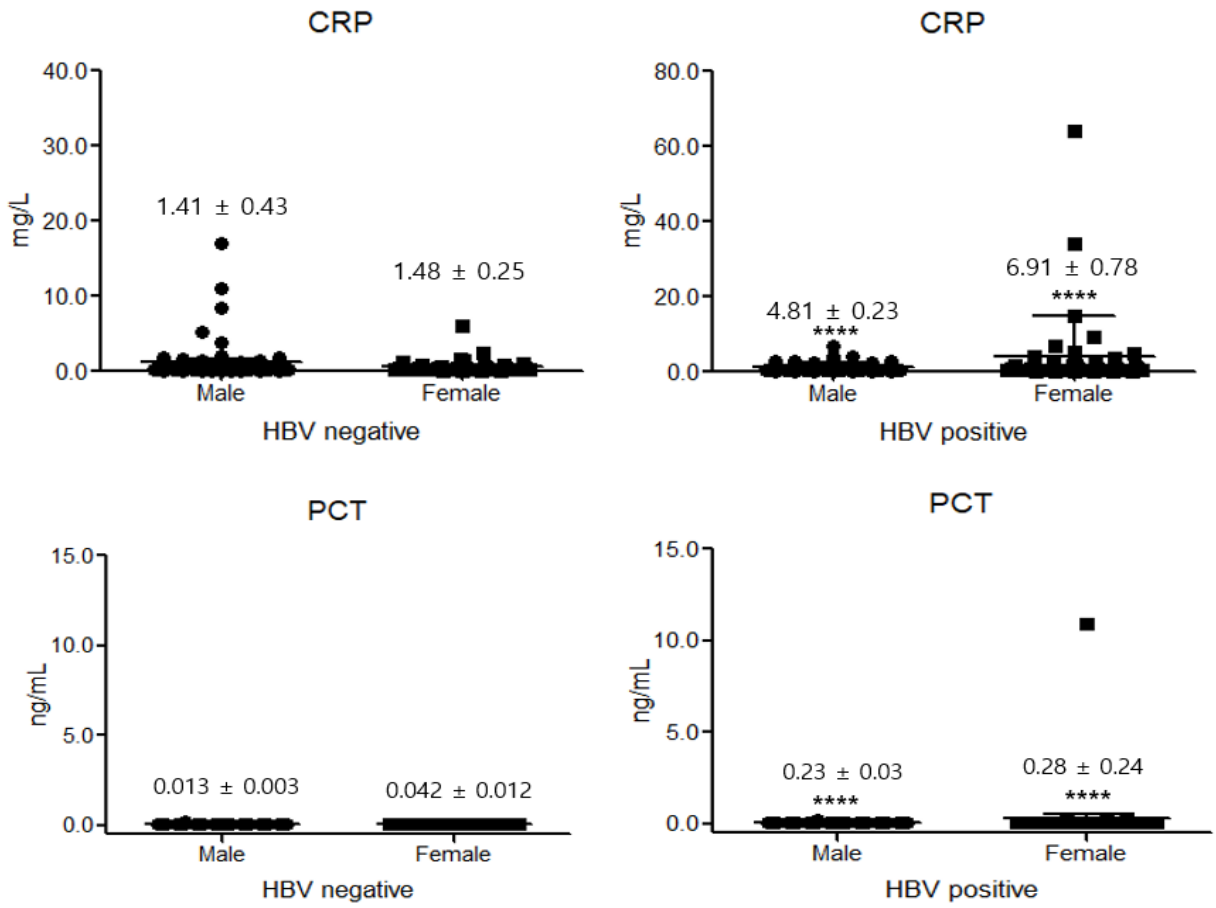

Fig. 3: Comparison of CRP and PCT levels based on sex. CRP levels in the HBV-positive group (male and female) (a), CRP levels in the HBV-negative group (male and female) (b), PCT levels in the HBV-positive group (male and female) (c), PCT levels in the HBV-negative group (male and female) (d). CRP, C-reactive protein; PCT, procalcitonin; HBV, hepatitis B virus

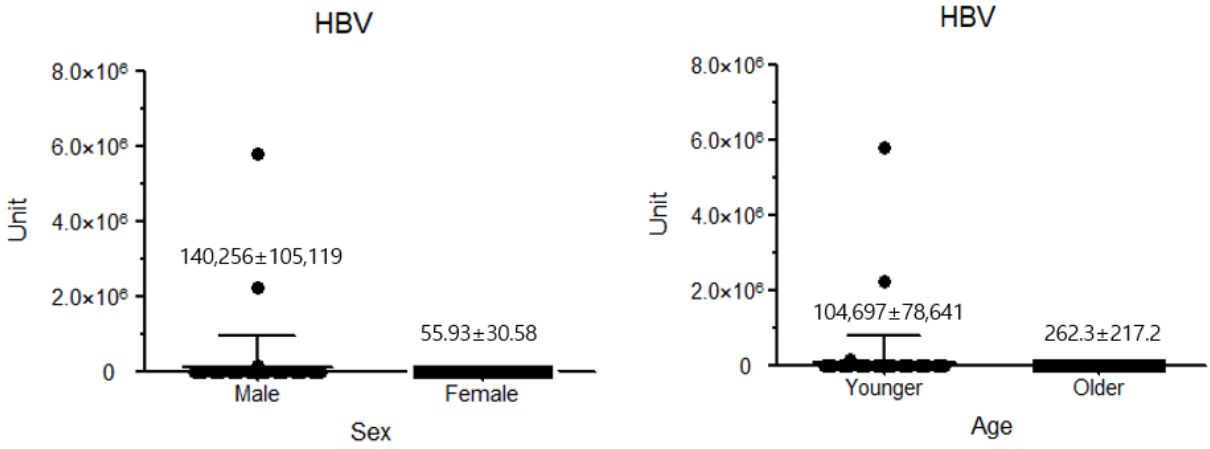

Fig. 4: Comparison of hepatitis B DNA quantitative units (HBV units) based on sex and age. HBV units based on sex in patients with HBV (a). HBV units based on age in patients with HBV (b)

Previous studies have reported conflicting findings regarding the relationship between inflammatory markers and liver function in HBV infection, with some studies indicating increased CRP levels and indeterminate increases in PCT levels (Sproston and Ashworth, 2018; Igna *et al*., 2022; Li *et al*., 2021). In our study, we observed a significant increase in both CRP and PCT levels in patients with HBV infection compared with the levels in healthy individuals, but no significant differences were found based on age or sex. Moreover, unlike CRP and PCT levels, the variation in HBV units showed age- and sex-dependent differences. The relationship between HBV infection and inflammatory markers has been a subject of debate in previous studies. For instance, Moura *et al*. (2019) suggested that hepatitis viral replication inhibits CRP production and is unrelated to HBsAg positivity (Zhiping *et al*., 2020). However, several studies have demonstrated elevated CRP and PCT levels in various liver diseases, such as hepatitis, liver carcinoma, and liver cirrhosis (Bhuiyan *et al*., 2019; Zheng *et al*., 2018; Igna *et al*., 2022; Yuan *et al*., 2013; Tan *et al*., 2018; Singh *et al*., 2021; Kang *et al*., 2021; Chen *et al*., 2020; Lu *et al*., 2021). Thus, our findings are consistent with the findings of studies supporting a significant association between inflammatory markers and hepatitis B.

We believe that the findings of the present study offer unique and novel contributions to the field. First, to assess inflammatory markers in HBV infections, this study investigated the diagnostic potential of two inflammatory markers, i.e., CRP and PCT, in individuals with HBV infections, providing valuable insights into the clinical utility of these markers, specifically in the context of HBV.

Second, the study examines CRP and PCT levels in different age groups (younger and older groups) and sexes (males and females) among both HBV-infected and healthy individuals. The observation that age and sex do not significantly affect the marker levels enhances our understanding of the inflammatory response in HBV infections and underscores the consistency of these markers across demographic variables.

Third, the correlation between inflammatory markers and HBV units was also evaluated. The study established a significant correlation between inflammatory marker (CRP and PCT) levels and HBV units via RT-qPCR analysis. This finding suggests a potential association between the severity of HBV infection (as indicated by HBV units) and the inflammatory response (as reflected by elevated CRP and PCT levels) (Zhiping *et al*., 2020).

The study's findings align with the results of previous research, indicating a significant association between elevated CRP and PCT levels and liver diseases such as hepatitis, liver carcinoma, and liver cirrhosis. By confirming this relationship in the context of HBV infections, the study reinforces our understanding of the role of inflammatory markers in HBV-related liver damage.

However, this study has some limitations. As the focus was on CRP and PCT as biomarkers for HBV infections, debates may arise concerning the specificity of these biomarkers. There might be discussions regarding the potential of additional biomarkers or a panel of biomarkers to provide more accurate and specific diagnostic information on HBV infections. Furthermore, due to the retrospective nature of data collection and study design, other inflammatory biomarkers such as D-dimer (an initial indicator of inflammatory activity (Tan *et al*., 2018)) and IL-6 (a key marker influencing the liver and neurons (Surial *et al*., 2021)) were not included. Hence, future studies should investigate the levels of these important inflammatory markers alongside CRP and PCT in serum (Dong *et al*., 2019; Li *et al*., 2021), as well as explore other potential biomarkers, including cardiac and inflammatory markers, to better understand their association with hepatitis B. Additionally, it is important to evaluate whether the observed increasing trend of CRP and PCT in serum is specific to hepatitis B or if it is also observed in other liver diseases such as liver cirrhosis and liver cancer. Comparative data on CRP and PCT levels in the serum of patients with HBV infection and other liver diseases should be included in future research to determine the specificity of this increasing trend in hepatitis B patients.

In addition, the diagnostic accuracy of CRP and PCT could be subject to debate (Tan *et al*., 2018). While the study suggests the potential value of CRP and PCT as diagnostic biomarkers for HBV infections, their accuracy, and specificity in differentiating HBV infection from other liver diseases or inflammatory conditions have not been confirmed (Zhiping *et al*., 2020). Further studies and validation are required to determine the diagnostic accuracy of CRP and PCT, specifically for HBV infections. Although the study demonstrates significantly elevated levels of CRP and PCT in HBV-infected individuals compared with healthy controls, the practical clinical utility of these biomarkers has not been established. Clinicians may discuss whether CRP and PCT alone are sufficient for HBV diagnosis or if they should be used in conjunction with other diagnostic tools or markers to enhance diagnostic accuracy (Zhang *et al*., 2021). Furthermore, the current study indicates that CRP and PCT levels in HBV-infected patients are independent of age and sex. However, this finding may ignite debates regarding the potential influence of other confounding factors or comorbidities on biomarker levels. Some may argue that a larger and more diverse sample size is necessary to confirm the independence of CRP and PCT levels from these factors. The practical implementation of the study's findings is also debatable. While the diagnostic potential of CRP and PCT using an ECLIA platform is demonstrated, the practicality

and accessibility of this specific platform in various clinical settings and resource-limited environments may be of concern. Moreover, it is worth noting that in patients with decompensated liver cirrhosis, a high PCT concentration has shown high sensitivity and specificity for bacterial infections (Yuan *et al*., 2013). However, since biomarkers such as PCT and CRP are measured after confirmation and hospitalization of patients with hepatitis B, they are considered useful for monitoring and predicting the progression of hematologic activity, such as complete blood count, erythrocyte sedimentation rate, or white blood cell count (Li *et al*., 2021; Chen *et al*., 2020). Additionally, due to administrative approaches and temporary operations of the hospital, only patients with quantitatively confirmed positive or negative hepatitis B diagnoses were managed. As a result, the presence or absence of other respiratory illnesses in inpatients and the criteria for severe or non-severe hepatitis B could not be determined based on symptoms.

These debate points open avenues for further research and discussion to enhance the diagnostic accuracy, clinical utility, and practical implementation of CRP and PCT as biomarkers for HBV infections.

Conclusion

This study evaluated the diagnostic performance of CRP and PCT as inflammatory markers for HBV infection using an ECLIA platform. We found that the CRP and PCT levels were significantly higher in HBV-infected individuals than in healthy controls, regardless of age or sex. These findings contribute to our understanding of the relationship between inflammatory markers and HBV infection, highlighting the potential clinical utility of CRP and PCT as diagnostic biomarkers for HBV infections. However, there could be debates and limitations regarding the specificity of these biomarkers, the inclusion of additional biomarkers, and the need for comparative studies with other liver diseases. Future research should address these limitations and further investigate the diagnostic accuracy, clinical utility, and practical implementation of CRP and PCT as biomarkers for HBV infections, considering the influence of confounding factors and comorbidities.

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Author's Contributions

Hyeokjun Yun and Bo Kyeung Jung: Conception the work and write the manuscript.

In Soo Rheem, Kap No Lee and Jae Kyung Kim: Designed the work and collected the data.

Ethics

This study was approved by the clinical research review committee of Dankook University (Institutional review board DKU certificate No. 2023-01-005).

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