

Correlation of Quantitative HBsAg and Quantitative HBeAg with HBV DNA in Treatment-naïve Chronic Hepatitis B Patients at Prof. Dr. R. D. Kandou Hospital Manado

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Abstract

Introduction: Chronic hepatitis B (CHB) causes cirrhosis and hepatocellular carcinoma. Although HBV DNA quantification is essential for monitoring, molecular testing remains costly and inaccessible in some healthcare facilities. **Objective:** To assess correlations between quantitative hepatitis B surface antigen (qHBsAg), quantitative hepatitis B e antigen (qHBeAg), and HBV DNA in treatment-naïve CHB patients. **Method:** This cross-sectional study enrolled 30 treatment-naïve adults at Prof. Dr. R. D. Kandou Hospital, Manado, between October 2025 and February 2026. qHBsAg was measured by chemiluminescent microparticle immunoassay, qHBeAg by cut-off index, and HBV DNA by real-time PCR. Spearman correlation was applied. **Results and Discussion:** Median qHBsAg, qHBeAg, and HBV DNA were 2,359.67 IU/mL, 0.397 COI, and 124,500 IU/mL, respectively. HBV DNA correlated moderately with qHBsAg ($r=0.479$; $p=0.007$) and strongly with qHBeAg ($r=0.674$; $p<0.001$). **Conclusion:** Both antigens correlated significantly with HBV DNA, suggesting potential adjunctive value, but not replacement of molecular testing, where molecular testing capacity remains severely limited.

Introduction

Hepatitis B virus (HBV) infection remains a primary etiology of human liver diseases worldwide, progressing from acute and chronic hepatitis to fulminant hepatic failure, liver cirrhosis, and hepatocellular carcinoma (HCC). The global burden of chronic hepatitis B is substantial, with an estimated 240 million chronic carriers worldwide and over 780,000 annual deaths resulting from complications of HBV-related end-stage liver disease and liver malignancies. In Indonesia, national health surveillance reports an overall hepatitis prevalence of 0.12%, with North Sulawesi Province documenting an above-average prevalence of 0.17%. This heightened regional disease burden highlights the critical need to strengthen local diagnostic, risk-stratification, and treatment pathways to support hepatitis B elimination targets. (Badan Kebijakan Pembangunan Kesehatan, 2023)

Serum HBV DNA level directly reflects active viral replication in hepatocytes and represents the established gold standard for determining disease phase, guiding the initiation of antiviral therapy, and monitoring clinical outcomes (Walensky et al., 2023). Nevertheless, molecular quantification by real-time polymerase chain reaction (RT-PCR) requires sophisticated laboratory infrastructure, expensive instrumentation, and substantial operational costs, rendering routine HBV DNA testing inaccessible or severely delayed in many resource-limited and secondary healthcare centers across developing nations (Maimunah et al., 2024); (Nguyen et al., 2023). In response, international and national guidelines, including the updated 2026 Indonesian Association for the Study of the Liver (PPHI) consensus and WHO 2024 recommendations, underscore the urgent clinical utility of reflex testing and serological surrogate markers to bridge diagnostic disparities and facilitate timely antiviral treatment (Gani et al., 2026; World health Organization, 2024)

Hepatitis B surface antigen (HBsAg) quantification (qHBsAg) and Hepatitis B envelope antigen (HBeAg) quantification (qHBeAg) represent attractive, widely accessible surrogate markers. While qualitative assays only confirm the presence of viral antigens, quantitative assays numerically reflect the underlying biology of HBV infection. Quantitative HBsAg mirrors the transcriptional reservoir of intrahepatic covalently closed circular DNA (cccDNA) and integrated viral genomic sequences, whereas HBeAg serves as an accessory viral protein reflecting active core and pre-genomic transcription and viral infectivity (Liu et al., 2024; Nasser et al., 2023; Padarath et al., 2023). Prior investigations have yielded varying degrees of correlation between these serological markers and serum HBV DNA levels, influenced by disease phase, HBeAg serostatus, viral genotypes, and host immune dynamics (Maimunah et al., 2024; Yilmaz et al., 2025). Furthermore, literature evaluating both qHBsAg and qHBeAg concurrently against viral load in treatment-naïve chronic hepatitis B populations in Eastern Indonesia remains scarce. Therefore, this study aimed to determine the correlation between qHBsAg and qHBeAg with HBV DNA levels in treatment-naïve chronic hepatitis B patients at Prof. Dr. R. D. Kandou Central General Hospital, Manado, to provide local clinical evidence supporting their use as potential adjunctive diagnostic tools when molecular viral load testing is unavailable.

Method

An analytical cross-sectional study was conducted at the Gastroenterohepatology Outpatient and Inpatient Units of Prof. Dr. R. D. Kandou Central General Hospital, Manado, Indonesia, from October 2025 to February 2026. Ethical approval was obtained from the hospital's Health Research Ethics Committee, and all participants provided written informed consent. The minimum sample size was calculated using a correlation coefficient of 0.57, a significance level of 0.05, and 80% statistical power, yielding 22 participants. To ensure adequate enrollment, 30 patients were consecutively recruited (Maimunah et al., 2024). Eligible participants were adults aged ≥ 18 years with chronic hepatitis B (CHB), confirmed by HBsAg positivity for ≥ 6 months, who had never received nucleos(t)ide analogues or pegylated interferon. Patients with hepatitis C or HIV coinfection or a history of antiviral or immunosuppressive treatment were excluded.

Venous blood samples were collected aseptically. Serum qHBsAg was measured using chemiluminescent microparticle immunoassay (CMIA) on an Architect i2000 analyzer (Abbott Diagnostics) and expressed in IU/mL. HBeAg was assessed using the Architect CMIA assay and reported as a semi-quantitative cut-off index (COI), with values < 1.00 indicating non-reactivity and ≥ 1.00 indicating reactivity. HBV DNA was quantified using real-time PCR on a Cobas 6800 system (Roche Molecular Systems) and expressed in IU/mL. ALT, AST, and routine laboratory data were obtained from medical records.

Statistical analyses were performed using IBM SPSS Statistics version 26. Normality was assessed using the Kolmogorov-Smirnov test. Data were presented as mean $\pm$ standard deviation or median and range, according to distribution. Spearman's rank correlation evaluated associations between serological markers and HBV DNA, with 95% confidence intervals estimated using Fisher's z-transformation. Multivariable and subgroup analyses were not performed because of the limited sample size. Statistical significance was set at $p < 0.05$.

Result and Discussions

1. Result

A total of 30 adult patients with treatment-naïve chronic hepatitis B met the eligibility criteria and completed all study procedures. The demographic, hematological, biochemical, and virological baseline characteristics of the study participants are summarized in Table 1.

Table 1
Demographical Characteristics of Study Participants (N = 30)

Variable	Mean $\pm$ SD / N (%)	Median (Min – Max)
Age (years) (19-81)	47.10 $\pm$ 15.73	
Sex (N=30)		
Male	22 (73.3%)	
Female	8 (26.7%)	
Hemoglobin (g/dL)	13.76 $\pm$ 2.66	
Leukocyte count ($\times 10^3/\text{mm}^3$)		7.75 (4.50 – 17.80)
Platelet count ($\times 10^3/\text{mm}^3$)		273.50 (84.00 – 726.00)
AST / SGOT (U/L)		30.50 (19.00 – 121.00)
ALT / SGPT (U/L)		31.00 (15.00 – 252.00)

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qHBeAg (COI)	0.397 (0.073 – 7.590.00)
HbeAg status (N=30)	
HbeAg Reactive (≥ 1)	14 (46.7%)
HbeAg Non-reactive (< 1)	16 (53.3%)
qHBsAg (IU/mL)	2.359.67 (12.52 – 107.915.70)
HBV DNA (IU/mL)	124.500.00 (16.00 – 544.000.000.00)

Source: Primary Data 2026.

The mean age of the participants was 47.10 ± 15.73 years (range: 19 to 81 years). The majority of participants were male ($n = 22$, 73.3%), while females accounted for 26.7% ($n = 8$). Routine hematological profiles were predominantly preserved within normal physiological ranges, with a mean hemoglobin of 13.76 ± 2.66 g/dL, a median leukocyte count of $7.75 \times 10^3/\text{mm}^3$ (range: $4.50 - 17.80 \times 10^3/\text{mm}^3$) and a median platelet count of $273.50 \times 10^3/\text{mm}^3$ (range: $84.00 - 726.00 \times 10^3/\text{mm}^3$). Hepatic transaminase evaluation revealed median AST and ALT values of 30.50 U/L (range: 19.00 – 121.00 U/L) and 31.00 U/L (range: 15.00 – 252.00 U/L), respectively. Virological quantification demonstrated wide distribution, with a median serum qHBsAg of 2,359.67 IU/mL (range: 12.52 – 107,915.70 IU/mL) and a median viral load of 124,500.00 IU/mL (range: 16.00 – 544,000,000.00 IU/mL). Median qHBeAg was 0.397 COI (range: 0.073 – 7,590.00 COI), with 14 patients (46.7%) categorized as HBeAg reactive ($\text{COI} \geq 1$) and 16 patients (53.3%) categorized as HBeAg non-reactive ($\text{COI} < 1$). Because the Kolmogorov-Smirnov test confirmed non-normal distribution for qHBsAg, qHBeAg, and HBV DNA ($p < 0.05$), non-parametric bivariate correlation analysis using Spearman's rank correlation test was performed. As shown in Table 2, both quantitative serological markers demonstrated statistically significant positive correlations with viral DNA load.

Table 2
Bivariate Correlation Analysis Between Quantitative Serological Markers and HBV DNA (N = 30)

Correlated Variables	Spearman's rho (r)	95% Confidence Interval (95% CI)	p-value
qHBeAg (COI) and HBV DNA (IU/mL)	0.674	0.417 – 0.832	< 0.001
qHBsAg (IU/mL) and HBV DNA (IU/mL)	0.479	0.146 – 0.715	0.007

Source: Statistical analysis output 2026

Specifically, serum qHBeAg exhibited a statistically significant, strong positive correlation with serum HBV DNA ($r = 0.674$, CI 0.417 – 0.832, $p < 0.001$). Quantitative HBsAg also demonstrated a statistically significant, moderate positive correlation with HBV DNA ($r = 0.479$, CI 0.146 – 0.715, $p = 0.007$).

2. Discussion

The mean age of participants in this study was 47.10 ± 15.73 years. This observation aligns closely with global epidemiological transitions reported by Gnyawali et al. (2022), who documented a progressive upward shift in the median age of chronic hepatitis B cohorts from the fourth into the fifth decade of life (Gnyawali et al., 2022). While slightly older than cohorts evaluated by Yilmaz et al. (2025) (mean age 41.04 ± 13.78 years), this

demographic profile reflects the protracted natural history of CHB in endemic Asia-Pacific regions, where primary transmission occurs perinatally or during early childhood, transitioning to symptomatic or clinically recognized disease in mature adulthood (Yilmaz et al., 2025).

Baseline hematological parameters remained within reference intervals in our cohort, with mean hemoglobin levels (13.76 ± 2.66 g/dL) slightly higher than reports in advanced chronic liver disease cohorts where anemia affects approximately 24% of patients (Wobiarueri Moore-Igwe & Ezra, 2025). Hematological indices in CHB without decompensated cirrhosis generally exhibit preserved erythropoiesis although chronic viral persistence, host immune exhaustion, and intrahepatic sequestration can induce subclinical lymphopenia and neutrophil fluctuations (Ahsan et al., 2024; Iannacone & Guidotti, 2022). Furthermore, median ALT and AST concentrations were 31.00 U/L and 30.50 U/L, which are notably lower than cohorts in high-activity immune clearance phases experiencing hepatic necroinflammatory flares (Yilmaz et al., 2025). This finding is clinically pertinent because updated treatment guidelines, such as the 2026 PPHI consensus and WHO 2024 algorithms, recommend initiating antiviral therapy based on surrogate markers, significant fibrosis (APRI > 0.5), or detectable viral load even when transaminases remain near normal limits (Gani et al., 2026; World health Organization, 2024).

The present study revealed a strong, highly significant positive correlation between quantitative HBeAg and HBV DNA ($r = 0.674$, $p < 0.001$). This finding is consistent with foundational virological mechanisms: HBeAg is synthesized from precore mRNA transcripts that share the same translational framework as pregenomic RNA, which serves as the direct template for reverse transcription into viral DNA (Nasser et al., 2023). Consequently, active HBeAg secretion frequently reflects intense virion assembly and high viral load (Borgaonkar & Shahapur, 2019; Padarath et al., 2023). Our findings corroborate prior evidence from Nguyen et al. (2023), who demonstrated that HBeAg reactivity was associated with a 57.5-fold increased odds of high viremia (>200,000 IU/mL) and provided superior diagnostic sensitivity compared to qHBsAg (Nguyen et al., 2023). Mathai et al. (2017) and Borgaonkar & Shahapur (2019) similarly reported that HBeAg-positive status corresponds to significantly higher median HBV DNA loads (>20,000 IU/mL) compared to low-viremic HBeAg-negative states (Borgaonkar & Shahapur, 2019; Mathai et al., 2017). Because HBeAg testing is technically simpler, widely standardized, and markedly less costly than real-time PCR assays, quantitative or qualitative HBeAg represents an may serve as a useful tool for identifying highly infectious patients requiring immediate antiviral therapy (Liu et al., 2024; Nguyen et al., 2023).

Regarding surface antigen quantification, our analysis demonstrated a moderate, statistically significant positive correlation between qHBsAg and HBV DNA ($r = 0.479$, $p = 0.007$). This correlation magnitude aligns with findings from meta-analysis by Maimunah et al. (2024), which reported a summary correlation coefficient of $r = 0.57$ (Maimunah et al., 2024). The biological basis of this correlation rests upon the fact that both HBsAg production and viral DNA replication are driven by transcriptionally active intrahepatic cccDNA reservoirs (Nasser et al., 2023).

Nonetheless, the correlation between qHBsAg and HBV DNA remains moderate rather than strong, reflecting fundamental virological discordances that have been extensively documented. Unlike HBV DNA synthesis which strictly requires intact

encapsidation, active viral polymerase reverse transcriptase activity, and cccDNA transcription, HBsAg can be excessively produced and transcribed not only from cccDNA but also from defective viral genome fragments integrated into the host hepatocyte chromosomes (Walensky et al., 2023). Consequently, subviral non-infectious spheres and filaments composed exclusively of HBsAg circulate in serum in massive excess relative to mature infectious Dane virions. Furthermore, viral precore / basal core promoter mutations, host immunological pressure, and genotype-dependent dynamics alter virion release independently of surface envelope secretion. In particular, Wanjari et al. (2018) noted that while qHBsAg correlates with HBV DNA during high-replicative HBeAg-positive phases, this correlation weakens during late immune control phases (Maimunah et al., 2024; Wanjari et al., 2018).

The clinical implications of these findings are substantial. In low- and middle-income regions where real-time PCR quantification of HBV DNA is hampered by financial and geographic constraints, quantitative HBeAg and qHBsAg offer potential as adjunctive markers. Quantitative HBeAg exhibits potential utility in active, high-level viremia, whereas qHBsAg complements clinical assessment by reflecting the overall intrahepatic antigenemic and cccDNA transcriptional burden. Integrating these accessible serological biomarkers into clinical practice allows timely therapeutic decision-making in concordance with 2026 PPHI consensus guidelines (Gani et al., 2026).

Study Limitations

Firstly, the relatively small sample size limits the statistical power required to conduct granular subgroup analyses across distinct hepatitis B disease phases or multivariable regression adjustments. Secondly, serum qHBeAg was evaluated using the instrument cut-off index (COI) rather than an internationally standardized quantitative unit assay, although continuous COI values correlate monotonically with viral replication and rank order is preserved for Spearman analysis, upper-end saturation effects across extreme signal ranges cannot be completely excluded without formal auto-dilution protocols. Thirdly, HBV genotyping and mutation sequencing for precore and BCP variants were not performed, precluding direct assessment of genetic variants on antigen kinetics. Future prospective investigations involving larger, multicenter cohorts with predefined clinical subgroup allocations, viral sequencing, and elastographic correlation are warranted to narrow precision estimates and establish definitive clinical cut-off values.

Conclusion

In treatment-naïve adult patients with chronic hepatitis B at Prof. Dr. R. D. Kandou Central General Hospital, Manado, quantitative HBeAg demonstrated a significant, strong positive correlation with serum HBV DNA ($r = 0.674$, $p < 0.001$), while quantitative HBsAg exhibited a significant, moderate positive correlation with HBV DNA ($r = 0.479$, $p = 0.007$). These findings confirm that serum qHBeAg and qHBsAg reliably reflect viral replication activity. In conclusion, qHBeAg and qHBsAg are positively correlated with serum HBV DNA in treatment-naïve chronic hepatitis B patients, with qHBeAg showing a stronger correlation. Both serological markers demonstrate biological association with viral replication and have potential as adjunctive markers to guide antiviral initiation and monitoring where molecular testing is inaccessible.

Reference

- Ahsan, A., Tariq, M. D., Zafar, M., Hamza, H. M., & Kaleem, F. (2024). Analysis of Hematological Profiles in Hepatitis B Patients; Understanding the Interplay Between Viral Infections and Blood Parameters. In *J Nur Healthcare* (Vol. 9, Number 2).
- Badan Kebijakan Pembangunan Kesehatan. (2023). *Survei Kesehatan Indonesia (SKI) 2023 Dalam Angka*. Kementerian Kesehatan Republik Indonesia.
- Borgaonkar, R., & Shahapur, P. R. (2019). Serological markers hbsag and hbeag in chronic hepatitis B carriers and their correlation with viral DNA by polymerase chain reaction. *Journal of Pure and Applied Microbiology*, 13(3), 1645–1651. <https://doi.org/10.22207/JPAM.13.3.38>
- Gani, R. A., Hasan, I., Sulaiman, A. S., Lesmana, C. R. A., Kurniawan, J., & Purnomo, H. D. (2026). *Konsensus Nasional Penatalaksanaan Hepatitis B di Indonesia* (J. Kurniawan, S. H. H. Nababan, & K. F. Kalista, Eds.). Perhimpunan Peneliti Hati Indonesia.
- Gnyawali, B., Pusateri, A., Nickerson, A., Jalil, S., & Mumtaz, K. (2022). [Epidemiologic and socioeconomic factors impacting hepatitis B virus and related hepatocellular carcinoma](https://doi.org/10.3748/wjg.v28.i29.3793). *World Journal of Gastroenterology*, 28(29), 3793. <https://doi.org/10.3748/wjg.v28.i29.3793>
- Iannacone, M., & Guidotti, L. G. (2022). [Immunobiology and pathogenesis of hepatitis B virus infection](https://doi.org/10.1038/s41577-021-00549-4). *Nature Reviews Immunology*, 22(1), 19-32. <https://doi.org/10.1038/s41577-021-00549-4>
- Liu, Y., Wu, D., Zhang, K., Ren, R., Liu, Y., Zhang, S., ... & Huang, J. (2024). [Detection technology and clinical applications of serum viral products of hepatitis B virus infection](https://doi.org/10.3389/fcimb.2024.1402001). *Frontiers in Cellular and Infection Microbiology*, 14, 1402001. <https://doi.org/10.3389/fcimb.2024.1402001>
- Maimunah, U., Wardhani, P., Wungu, C. D. K., Rahmanda, A. F., Kurniawan, A. A., & Palayukan, A. (2024). [Correlation between quantitative HBsAg and quantitative HBV DNA in chronic hepatitis B patients: a systematic review and meta-analysis](https://doi.org/10.1186/s43066-024-00336-5). *Egyptian Liver Journal*, 14(1). <https://doi.org/10.1186/s43066-024-00336-5>
- Mathai, F., Otieno Ngayo, M., Muturi Karanja, S., Kalebi, A., & Lihana, R. (2017). Correlation of quantitative assay of HBsAg and hepatitis B virus DNA levels among chronic HBV patients attending pathologist lancet laboratory in Nairobi, Kenya. *Archives of Clinical Infectious Diseases*, 12(4). <https://doi.org/10.5812/archcid.13306>
- Nasser, N., Tonnerre, P., Mansouri, A., & Asselah, T. (2023). [Hepatitis-B virus: replication cycle, targets, and antiviral approaches](https://doi.org/10.1016/J.COVIRO.2023.101360). *Current Opinion in Virology*, 63, 101360. <https://doi.org/10.1016/J.COVIRO.2023.101360>
- Nguyen, M. N., Nguyen, T. T. H., Pham, T. D. H., Khuu, V. N., Hoang, Q. C., Nguyen, V. T., & Tran, N. H. (2023). [HBeAg testing is better than quantitative HBsAg assay as an alternative to HBV DNA assay among HBV-infected pregnant women](https://doi.org/10.3855/jidc.17516). *Journal of Infection in Developing Countries*, 17(10), 1489–1492. <https://doi.org/10.3855/jidc.17516>
- Padarath, K., Deroubaix, A., & Kramvis, A. (2023). [The complex role of HBeAg and its precursors in the pathway to hepatocellular carcinoma](https://doi.org/10.3390/v15040857). *Viruses*, 15(4), 857. <https://doi.org/10.3390/v15040857>

- Walensky, R. P., Bunnell, R., Kent, C. K., Gottardy, A. J., Leahy, M. A., Martinroe, J. C., ... & Johnson, L. (2023). [Morbidity and mortality weekly report prevalence and characteristics of autism spectrum disorder among children aged 8 years-autism and developmental disabilities monitoring network, 11 sites, United States, 2020](#) *Surveillance Summaries Centers for Disease. MMWR Surveill Summ*, 72(2), 1-14.
- Wanjari, S., Maharshi, S., Gupta, G. K., Jain, M., Nijhawan, S., & Sharma, S. S. (2022). [Correlation Between Quantitative HBsAg and Serum HBV DNA Levels in Treatment Naïve Chronic Hepatitis B Patients](#). *Tropical Gastroenterology*, 43(3), 144-149. <https://doi.org/10.7869/tg.686>
- Wobiarueri Moore-Igwe, B., & Ezra, G. (n.d.). The prevalence and hematological impact of Hepatitis B and C, with a focus on anemia, platelet abnormalities, and blood cell morphology in patients at the University of Port Harcourt Teaching Hospital. *African Journal of Laboratory Haematology and Transfusion Science*, 2025(1), 44–50. <https://doi.org/10.59708/ajlhts.v4i1.2508>
- World health Organization. (2024). *Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection*.
- Yılmaz, T., Özdemir, E., Düzenci, D., & Bahçecioğlu, İ. H. (2025). [Clinical and Histopathological Correlation of Quantitative HBsAg Levels in Chronic Hepatitis B](#). *International Journal of Hepatology*, 2025(1). <https://doi.org/10.1155/ijh/9096871>