# Correlation between quantitative HBsAg

*by* Ummi Maimunah

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# Correlation between quantitative HBsAg and quantitative HBV DNA in chronic hepatitis B patients: a systematic review and meta-analysis

Ummi Maimunah[1*], Puspa Wardhani[2], Citrawati Dyah Kencono Wungu[3], Anisa Firdausi Rahmanda[4], Andreas Agung Kurniawan[5] and Andrio Palayukan[5]

## Abstract

**Background** HBV DNA assays have several limitations including being expensive and not widely available. Detection of HBsAg in serum has been the hallmark of HBV infection. However, previous studies regarding the association between HBsAg and HBV DNA revealed contradictory results. This study aims to reassess the correlation between HBsAg and HBV DNA in chronic hepatitis B patients.

**Methods** Observational studies with näive chronic hepatitis B patients were included, while studies with other coinfections were excluded. The studies were identified by searching through Google Scholar, PubMed, ScienceDirect, and Springer Link for English and Bahasa articles from 2011 to 2021. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) was followed. Study quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal.

**Results** A total of 17 studies with 4134 participants met the criteria. The overall analysis revealed a moderate correlation between quantitative HBsAg and quantitative HBV DNA in the total sample of chronic hepatitis B patients ($r = 0.57$, 95% *CI* 0.40–0.75, $P < 0.00001$). In HBeAg + group, a moderate correlation was indicated while in HBeAg − revealed a weak association ($r = 0.55$, 95% *CI* 0.39–0.70, $P < 0.00001$ vs $r = 0.29$, 95% *CI* 0.20–0.38, $P < 0.00001$). The strongest correlation was discovered in HBeAg + chronic HBV infection phase ($r = 0.59$, 95% *CI* 0.35–0.82, $P < 0.00001$).

**Conclusion** Serum HBsAg titer supports as a predictor of serum HBV DNA levels in clinical practice with moderate strength of correlation.

**Trial registration** This review had been registered in PROSPERO (ID: CRD42023421246).

**Keywords** HBsAg, HBV DNA, Chronic hepatitis B

*Correspondence:
Ummi Maimunah
ummima@gmail.com
Full list of author information is available at the end of the article

## Introduction

Chronic hepatitis B has evolved into a global health crisis. The World Health Organization estimates that 254 million individuals worldwide have chronic hepatitis B in 2022 [1]. This condition is caused by infection with the hepatitis B virus, which leads to liver inflammation. The outcome of acute versus chronic hepatitis B infection varies [2]. If hepatitis B infection becomes chronic and is not appropriately treated, it can lead to deadly consequences such as cirrhosis of the liver and hepatocellular carcinoma (HCC) [3].

The management of chronic hepatitis B necessitates multiple tests, including HBsAg, quantitative HBV DNA, and HBeAg testing. These tests are used to estimate the replication rate of the hepatitis B virus, which is useful for diagnosis, selecting therapeutic methods, and evaluating the therapeutic response [4]. HBsAg is an antigen protein that serves as an early signal when hepatitis B infection is suspected. In order to monitor the patient's status, periodic quantitative HBV DNA testing is required because high blood HBV DNA levels have been observed to dramatically increase the risk of liver cirrhosis [5]. HBeAg + chronic HBV infection, HBeAg + chronic hepatitis B, HBeAg − chronic HBV infection, and HBeAg − chronic hepatitis B [6] are the four phases of chronic hepatitis B that patients may encounter. This phase is characterized based on the HBV DNA test, HBeAg, ALT, and the presence of liver inflammation.

Numerous studies were conducted to evaluate the link between HBsAg and HBV DNA in individuals with chronic hepatitis B, but the results were inconclusive. This systematic review and meta-analysis of quantitative HBsAg in correlation with quantitative HBV DNA in naive chronic hepatitis B patients in various phases is based on controversial results from earlier research regarding the correlation between HBsAg and HBV DNA in chronic hepatitis B patients. This review is conducted to shed light on the nature of the link between these variables and to identify the mechanisms responsible for the differences so that the findings can be used in daily medical practice, particularly in the treatment of chronic hepatitis B infection. Performing quantitative HBV DNA analysis may not be feasible in all healthcare facilities and entails significant expenses. On the other hand, quantitative HBsAg can serve as a substitute indicator for HBV DNA in several capacities, such as assessing the level of viral replication [7]. We hypothesize a link between the quantitative levels of HBsAg and HBV DNA in naïve chronic hepatitis B patients.

## Materials and methods

### Search strategy and identification of studies

We conducted a systematic review and meta-analysis to determine the relationship between HBsAg and HBV DNA in chronic hepatitis B patients with positive or negative HBeAg. The systematic review was registered in PROSPERO and reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist. Using a search keyword comprised of the terms correlation, quantitative HBsAg, HBV DNA, HBeAg, and chronic hepatitis B, literature search strategies were developed. We searched PubMed, Springer Link, ScienceDirect, and Google Scholar. Reviewers J. I. and D. F. screened abstracts based on standard inclusion and exclusion criteria. Two reviewers (A. A. and A. F.) independently assessed all studies identified for full manuscript review against inclusion criteria. The papers were either accepted or rejected, with the reasons for rejection being specified. Disagreements were resolved through dialogue between review authors.

### Selection criteria

The following inclusion criteria were in place: Observational studies (cohort, case control, or cross-sectional), studies in English and Indonesian, studies with populations of chronic hepatitis B patients who have not received therapy, studies with a quantitative HBsAg correlation test with HBV DNA, and studies that include the HBeAg status of the patients.

We excluded sources from non-research studies (review articles, conference papers, or book chapters); duplicated studies; studies with chronic hepatitis B patients who have received therapy; studies with chronic hepatitis B patients co-infected with other diseases such as hepatitis C, hepatitis D, HIV, alcoholic liver disease, or NAFLD; studies for which the full text could not be obtained; and studies with insufficient data.

### Data extraction and quality assessment

Author's name and publication year, study location and design, total sample size, male-to-female ratio, population age, quantitative HBsAg levels, quantitative HBV DNA levels, HBeAg, *P*-value, and correlation coefficient between HBsAg and HBV-DNA were extracted as variables.

The Joanna Briggs Institute (JBI) critical appraisal was used to evaluate the quality of each article collected to prevent bias [8]. The inclusion criteria included studies that have been assessed and subsequently agreed upon. Low-scoring studies were omitted to prevent bias in the validity of the results (Tables S1–S3).

### Data analysis and synthesis

On the basis of the previously mentioned points, data extraction was conducted. The data were organized in a tabular and/or descriptive format to facilitate analysis. This study analyzed the correlation between quantitative HBsAg levels and quantitative HBV-DNA in chronic naive hepatitis B patients with either positive or negative HBeAg by comparing the results of each previous study. We conducted a meta-analysis by combining data using the random-effect method to calculate a pooled correlation coefficient with 95% confidence intervals (CI) and a subgroup analysis to investigate potential sources of heterogeneity. The following is a rough guide to the interpretation of $I^2$:

- 0 to 40% suggests that heterogeneity may not be significant.
- 30 to 60% corresponds to moderate heterogeneity.
- 50 to 90% denotes substantial heterogeneity.
- 75 to 100% implies significant heterogeneity [9].

Review Manager software version 5.4.1 was used for data analysis. All statistical tests were two-tailed, and differences with $P < 0.05$ were considered statistically significant. Strong correlation represented by $r \geq 0.67$, moderate correlation by $0.33 < r < 0.67$, and weak moderate by $r \leq 0.33$. Publication bias is assessed through visualization of the funnel plot.

## Results

### Study selection and characteristics

A total of 909 citations were identified, and 47 full-text articles with matching populations and variables were examined, yielding a total of 17 studies that met the inclusion and exclusion criteria (Fig. 1). Fifteen out of 17 studies employed a cross-sectional methodology. One study utilized a cohort design and the other a case-control design. The studies included between 62 and 645 individuals as samples. The age of the samples ranged from 1 to 80 years old, with a mean age of between 33.50 and 49.30 years. Patients with chronic hepatitis B who have never received anti-HBV treatment make up all of the samples (Table 1).

### Correlation between quantitative HBsAg and quantitative HBV DNA in chronic hepatitis B

The correlation between quantitative HBsAg and quantitative HBV DNA in the total sample of chronic hepatitis B patients was examined in 10 studies (Table 2). All studies discovered significant correlations. There is a strong correlation between both variables, according to three studies. Five additional studies demonstrated a modest correlation. Two studies have identified a weak correlation between HBsAg and HBV DNA levels in patients with chronic hepatitis B.

There was substantial heterogeneity among the included studies ($I^2$ = 84%, $P$ 0.00001). Thus, a model with random effects was employed. Figure 2 illustrates the compiled results. The pooled correlation between quantitative HBsAg and quantitative HBV DNA in patients with chronic hepatitis B was 0.57 (95% confidence interval: 0.40–0.75, $P$ 0.00001), indicating a moderate strength.

### Correlation between quantitative HBsAg and quantitative HBV DNAin HBeAg + chronic hepatitis B

In addition, a subgroup analysis was conducted for the association between HBeAg+ and HBeAg− (Fig. 3) patients. The correlation between quantitative HBsAg and quantitative HBV DNA in chronic hepatitis B patients with HBeAg+ was reported in 10 studies (Table 3). One study found a moderate correlation, seven studies found a moderate correlation, and the remaining studies found a strong correlation. A meta-analysis of 10 studies utilizing a random-effects model revealed a moderate correlation ($r$ = 0.55, 95% *CI*: 0.39–0.70, $P$ 0.00001) between quantitative HBsAg and quantitative HBV DNA in HBeAg+.

### Correlation between quantitative HBsAg and quantitative HBV DNA in HBeAg − chronic hepatitis B

Two included studies found no significant correlation between quantifiable HBsAg and quantifiable HBV DNA. Three studies indicated a weak correlation, while four studies demonstrated a moderate one. None of the included studies found a strong association. In the HBeAg− group, the pooled analysis revealed a weak correlation ($r$ = 0.29, 95% *CI*: 0.20–0.38, $P$ 0.00001).

### Correlation between quantitative HBsAg and quantitative HBV DNA according to the phase of chronic hepatitis B

Additionally, we performed a subgroup analysis of the association based on the stage of chronic hepatitis B infection (Fig. 4). Chronic HBV infection is the initial phase of chronic hepatitis B. In this phase, four studies reported the correlation. One study found no correlation, one study found a moderate correlation, and two studies found a strong correlation. This group's pooled analysis revealed a moderate correlation ($r$ = 0.59, 95% confidence interval: 0.35–0.82, $P$ 0.00001). The relationship between quantitative HBsAg and quantitative HBV DNA in the second phase of HBeAg+ chronic hepatitis B was discovered by three studies. These studies found, respectively, a strong, moderate, and insignificant association. This group's pooled analysis revealed a moderate correlation ($r$ = 0.51; 95% *CI*: 0.15–0.87; $P$ 0.00001).

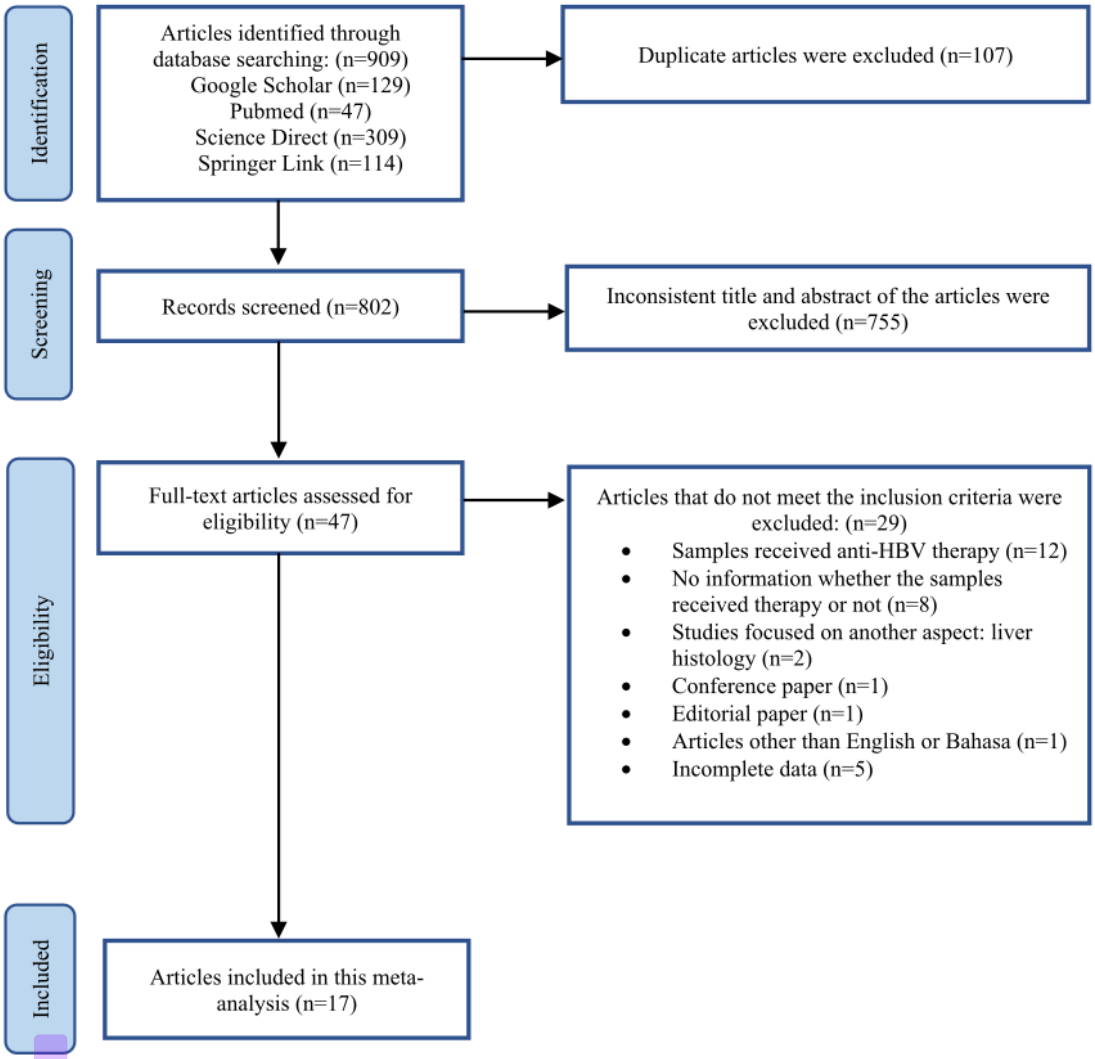


**Fig. 1** Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) study flowchart. *HBV*, hepatitis B virus

In the third phase, HBeAg-chronic HBV infection, the majority of the five studies that examined the correlation between quantitative HBsAg and quantitative HBV DNA, revealed no significant association, with the exception of one study by Alghamdi et al. There was a weak correlation discovered by Alghamdi et al. [14]. The pooled analysis of this group revealed no significant correlation ($r$ = 0.13, 95% *CI*: −0.02 to 0.27, $P$ = 0.08). All of the studies included in this review that were conducted during the fourth phase of HBeAg-chronic hepatitis B found a moderate correlation between quantitative HBsAg and quantitative HBV DNA. This group's pooled analysis revealed a moderate correlation ($r$ = 0.40, 95% *CI*: 0.27–0.53, $P$ 0.00001) (Table 4).

### Publication bias

The funnel plot revealed a possible publication bias in the pooled analysis of the correlation between quantitative HBsAg and quantitative HBV DNA in patients with chronic hepatitis B (Figs. S1–S3).

**Table 1** Study characteristics

| No | Study | Study design | Country | Total sample | Age | Genotype |
|---|---|---|---|---|---|---|
| 1 | Balkan et al. (2016) [10] | Cross-sectional | Turkey | 204 | 33.54 ± 11.74 | No data |
| 2 | Tan et al. (2014) [11] | Cross-sectional | China | 233 | 37 ± 12 | B, C |
| 3 | Cheng et al. (2013) [12] | Cross-sectional | Taiwan | 198 | 36.4 ± 10.5 | B, C |
| 4 | Keshvari et al. (2015) [13] | Cross-sectional | Iran | 151 | 40.9 ± 14.2 | D |
| 5 | Alghamdi et al. (2013) [14] | Cross-sectional | Saudi Arabia | 106 | 39.3 (21–75) | D |
| 6 | Primadharsini et al. (2013) [15] | Cross sectional | Indonesia | 62 | 42.34 ± 13.07 | No data |
| 7 | Hong et al. (2014) [16] | Cross sectional | China | 362 | 35.56 ± 9.9 | B, C |
| 8 | Goyal et al. (2014) [17] | Cross-sectional | India | 481 | 31 (14–65) | A, D |
| 9 | Antaki et al. (2012) [18] | Cross-sectional | Syria | 272 | 33 (1–76) | D |
| 10 | Turyadi et al. (2013) [19] | Cross-sectional | Indonesia | 152 | 44 (14–80) | B, C |
| 11 | Martinot-Peignoux et al. (2013) [20] | Cross-sectional | France | 406 | 40 ± 12 | A, B, C, D, E |
| 12 | Bathaix et al. (2015) [21] | Retrospective cross-sectional | West Africa | 105 | 39.01 ± 9.72 | E |
| 13 | Nasser et al. (2021) [22] | Cross-sectional | Egypt | 92 | 36.1 ± 10.5 | D |
| 14 | Puspitasari et al. (2021) [23] | Case control | Indonesia | 70 | 36.86 ± 12.732 | No data |
| 15 | Zhang et al. (2021) [24] | Retrospective cohort | China | 472 | (28–51) | No data |
| 16 | Tatar et al. (2020) [25] | Retrospective cross-sectional | Turkey | 123 | 48 ± 11.2 | D |
| 17 | Kim et al. (2011) [26] | Retrospective cross-sectional | Korea | 645 | 49.38 ± 11.85 | C |

**Table 2** Correlation between quantitative HBsAg and quantitative HBV DNA in total sample of chronic hepatitis patients

| Study | Sample (*n*) | HBsAg[a] | HBV DNA[a] | *r* | *P* | Strength of correlation |
|---|---|---|---|---|---|---|
| Antaki et al. (2012) [18] | 272 | 3.67 (3.45–3.62) log IU/mL | 3.83 (4.16–4.69) log IU/mL | 0.830 | < 0.008 | Strong |
| Balkan et al. (2016) [10] | 100 | 5150.78 ± 8473.16 IU/mL | 59,900.47 ± 140,555.35 IU/mL | 0.533 | < 0.001 | Moderate |
| Hong et al. (2014) [16] | 362 | 3.80 ± 0.58 log IU/mL | 6.05 ± 2.08 log IU/mL | 0.305 | < 0.0001 | Weak |
| Kim et al. (2011) [26] | 645 | 2.92 ± 1.26 log IU/mL | 4.41 ± 2.51 log IU/mL | 0.693 | < 0.001 | Moderate |
| Nasser et al. (2021) [22] | 92 | No data | No data | 0.750 | < 0.001 | Strong |
| Primadharsini et al. (2013) [15] | 62 | No data | No data | 0.737 | 0 | Strong |
| Puspitasari et al. (2021) [23] | 70 | No data | No data | 0.599 | < 0.001 | Moderate |
| Tan et al. (2014) [11] | 233 | 3.61 ± 0.68 log IU/mL | No data | 0.637 | < 0.001 | Moderate |
| Tatar et al. (2020) [25] | 123 | 4625.9 ± 5614.9 IU/mL | 11,377.6 ± 25,598.4 IU/mL | 0.303 | 0.001 | Weak |
| Turyadi et al. (2013) [19] | 152 | 3.25 (1.30–4.99) log IU/mL | 4.24 (0.04–8.14) log IU/mL | 0.659 | < 0.001 | Moderate |

[a] Data is presented in mean ± standard deviation or median (range)

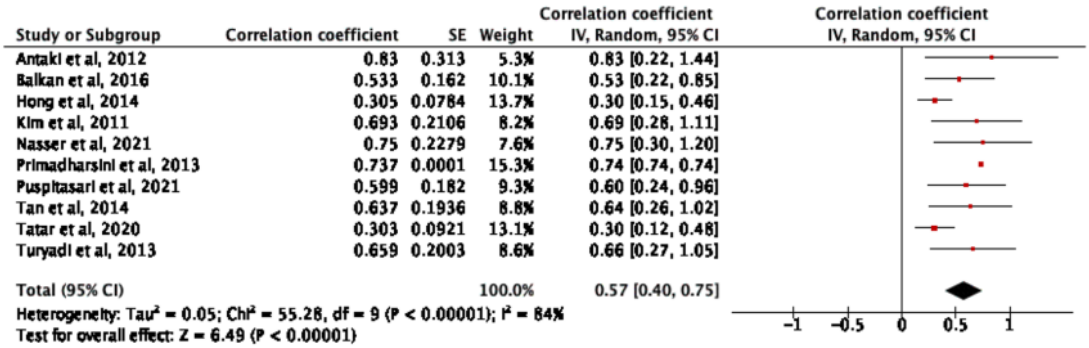


**Fig. 2** Forest plot of the correlation between quantitative HBsAg and quantitative HBV DNA in the total sample

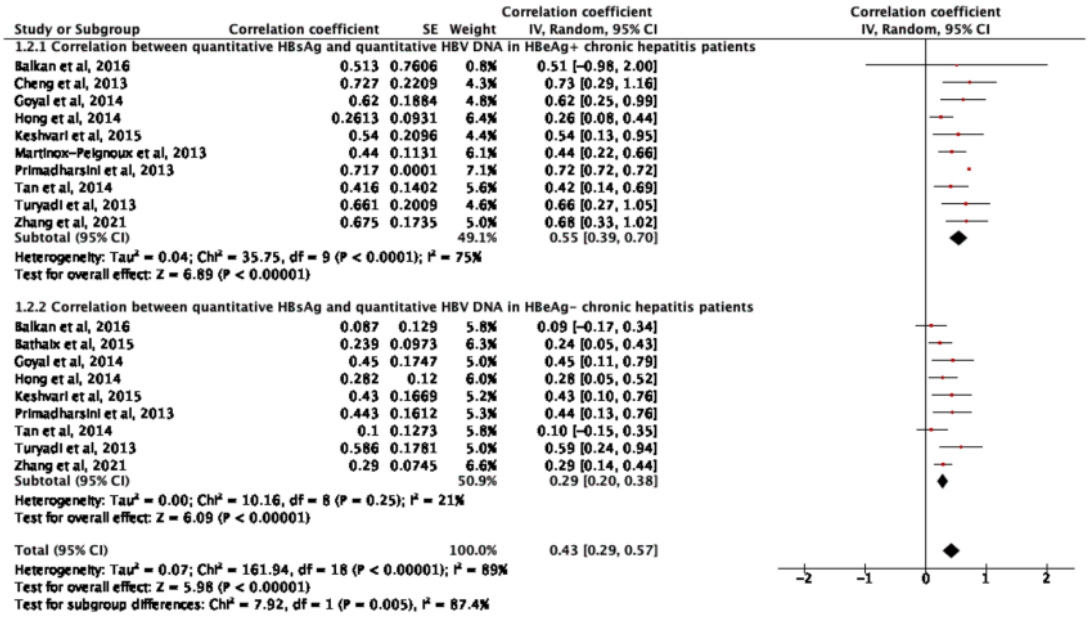


**Fig. 3** Forest plot of the correlation between quantitative HBsAg and quantitative HBV DNA in chronic hepatitis patients based on HBeAg status

**Table 3** Correlation between quantitative HBsAg and quantitative HBV DNA in chronic hepatitis patients based on HBeAg status

| Study | Sample (*n*) | HBsAg[a] | HBV DNA[a] | *r* | *P* | Strength of correlation |
|---|---|---|---|---|---|---|
| HBeAg + | | | | | | |
| Balkan et al. (2016) [10] | 38 | No data | No data | 0.513 | 0.001 | Moderate |
| Cheng et al. (2013) [12] | 198 | 4.3 (1.7–5.4) log IU/mL | 8.7 (4.8–10.0) log copies/mL | 0.727 | < 0.001 | Strong |
| Goyal et al. (2014) [17] | 126 | 4.60 (1.26–6.26) log IU/mL | 8.39 (2.10–11.56) log IU/mL | 0.62 | < 0.001 | Moderate |
| Hong et al. (2014) [16] | 210 | 3.87 ± 0.64 log IU/mL | 7.17 ± 1.45 log IU/mL | 0.2613 | 0.005 | Weak |
| Keshvari et al. (2015) [13] | 30 | 4.6 (UR) log IU/mL | 9.0 (UR) log IU/mL | 0.54 | < 0.01 | Moderate |
| Martinox-Peignoux et al. (2013) [20] | 101 | 4.24 ± 0.90 log IU/mL | 7.06 ± 1.71 log IU/mL | 0.44 | < 0.0001 | Moderate |
| Primadharsini et al. (2013) [15] | 25 | $2.81 \times 10^5 \pm 1.3 \times 10^6$ log IU/mL | $5.9 \times 10^7 \pm 5.45 \times 10^7$ copies/mL | 0.717 | 0 | Strong |
| Tan et al. (2014) [11] | 49 | 4.17 ± 0.66 log IU/mL | 7.0 ± 0. 8 log IU/mL | 0.416 | 0.003 | Moderate |
| Turyadi et al. (2013) [19] | 65 | No data | No data | 0.661 | < 0.001 | Moderate |
| Zhang et al. (2021) [24] | 241 | No data | No data | 0.675 | < 0.0001 | Moderate |
| HBeAg − | | | | | | |
| Balkan et al. (2016) [10] | 62 | No data | No data | 0.087 | 0.5 | Not significant |
| Bathaix et al. (2015) [21] | 105 | 12,111.2 ± 10,617.4 IU/mL | 4.4 e7 ± 7.5 e7 IU/mL | 0.239 | 0.014 | Weak |
| Goyal et al. (2014) [17] | 355 | 3.47 (1.11–4.66) log IU/mL | 3.40 (0.30–7.94) log IU/mL | 0.45 | < 0.01 | Moderate |
| Hong et al. (2014) [16] | 152 | 3.68 ± 0.44 log IU/mL | 4.20 ± 1.58 log IU/mL | 0.282 | 0.0188 | Weak |
| Keshvari et al. (2015) [13] | 121 | 3.6 log IU/ml | 5.1 log IU/ml | 0.43 | < 0.01 | Moderate |
| Primadharsini et al. (2013) [15] | 37 | $4.9 \times 10^3 \pm 2.05 \times 10^4$ IU/mL | $7.53 \times 10^6 \pm 2.55 \times 10^7$ copies/mL | 0.443 | 0.006 | Moderate |
| Tan et al. (2014) [11] | 64 | 3.23 ± 0.40 log IU/mL | 4.8 ± 1.0 log IU/mL | 0.1 | 0.432 | Not significant |
| Turyadi et al. (2013) [19] | 87 | No data | No data | 0.586 | < 0.001 | Moderate |
| Zhang et al. (2021) [24] | 106 | No data | No data | 0.29 | < 0.0001 | Weak |

[a] Data is presented in mean ± standard deviation or median (range)

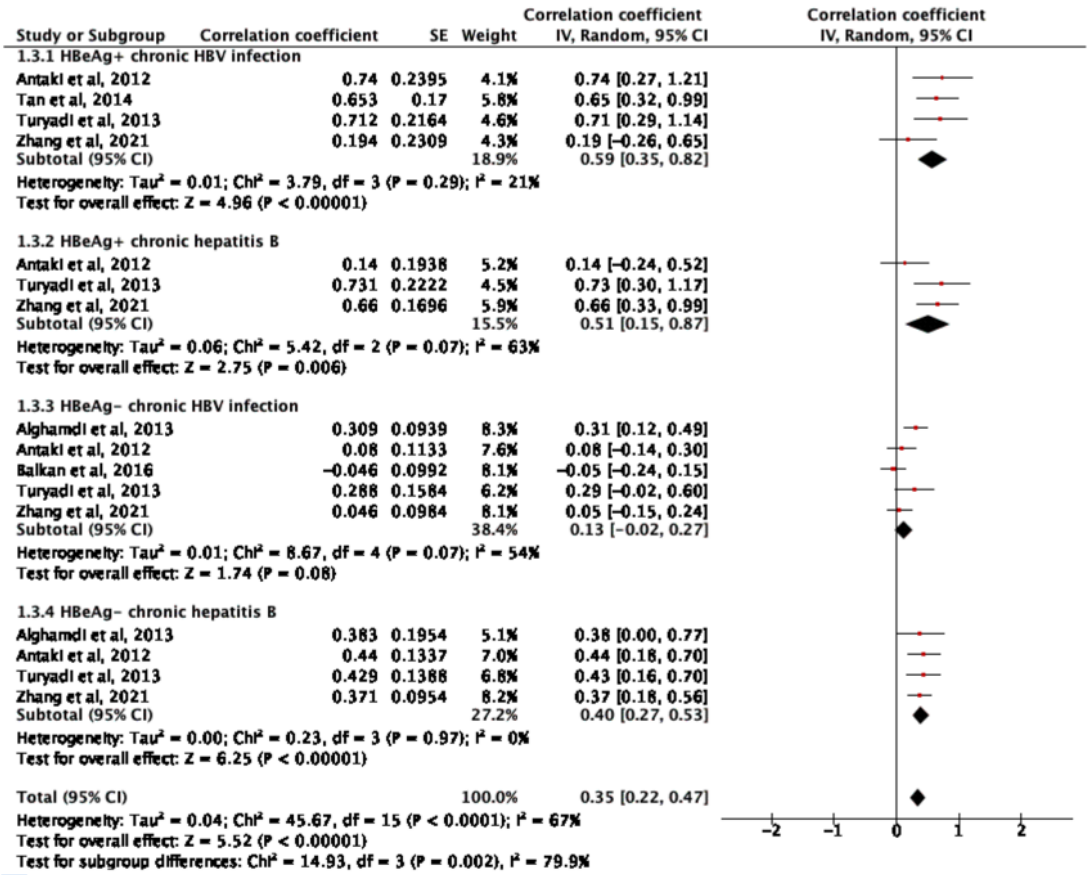


**Fig. 4** Forest plot of the correlation between quantitative HBsAg and quantitative HBV DNA in chronic hepatitis patients according to the phase of chronic hepatitis B infection course

## Discussion

This systematic review and meta-analysis sought to determine the relationship between HBsAg and HBV DNA levels in chronic hepatitis B patients. The correlation analysis could depict the dynamic of HBV DNA that reflected active replication and quantitative HBsAg that demonstrated immune control and viral transcription activity in hepatocytes (intrahepatic cccDNA). A significant correlation between the two variables would permit the substitution of quantitative HBsAg.

According to 10 studies included in this review, there is a correlation between the level of quantitative HBsAg and HBV DNA in the general population of hepatitis B patients with chronic infection. Five of 10 studies demonstrated a moderate correlation, whereas 3 and 2 studies, respectively, demonstrated a strong and weak correlation. Several factors may account for the disparities in the strength of correlation among these studies.

All studies that discovered this correlation in the total sample of patients with chronic hepatitis B had mean and median ages ranging from 30 to 50 years old. Tan et al. [11] found that age has a significant negative correlation with HBsAg level. Patients with hepatitis B who are younger are primarily in the HBeAg+chronic HBV infection phase. This phase lasts longer in vertically infected patients than in horizontally infected patients. In addition, the immune system has not yet been activated to combat the hepatitis B virus during this phase. It is manifested by an increase in HBV DNA levels with normal ALT levels and nonspecific histological changes [27]. The immune system, which is continuously active against the hepatitis B virus, will suppress the production of HBsAg as a person ages.

The variation in phenotype may influence the production of HBsAg and HBV DNA. The levels of HBeAg and HBV DNA are higher in genotypes B and C than in

**Table 4** Correlation between quantitative HBsAg and quantitative HBV DNA according to the phase of chronic hepatitis B infection course

| Study | Sample (*n*) | HBsAg[a] | HBV DNA[a] | *r* | *P* | Strength of correlation |
|---|---|---|---|---|---|---|
| HBeAg + chronic HBV infection | | | | | | |
| Antaki et al. (2012) [18] | 9 | 20,781 IU/mL | $7.6 \times 10^7$ IU/mL | 0.74 | 0.002 | Strong |
| Tan et al. (2014) [11] | 29 | 4.50 ± 0.43 log IU/mL | 7.1 ± 0.7 log IU/mL | 0.653 | 0.000123 | Moderate |
| Turyadi et al. (2013) [19] | 33 | 4.22 (−1.3–4.99) log IU/mL | 4.55 (0.78–7.82) log IU/mL | 0.712 | < 0.001 | Strong |
| Zhang et al. (2021) [24] | 21 | 4.779 log IU/mL | 7.878 log IU/mL | 0.194 | 0.4007 | Not significant |
| HBeAg + chronic hepatitis B | | | | | | |
| Antaki et al. (2012) [18] | 26 | 26,774 IU/mL | $4.1 \times 10^7$ IU/mL | 0.14 | 0.47 | Not significant |
| Turyadi et al. (2013) [19] | 32 | 3.34 (−1.3–4.99) log IU/mL | 5.13 (0.44–8.04) log IU/mL | 0.731 | < 0.001 | Strong |
| Zhang et al. (2021) [24] | 220 | 3.943 log IU/mL | 7.167 log IU/mL | 0.66 | < 0.0001 | Moderate |
| HBeAg − chronic HBV infection | | | | | | |
| Alghamdi et al. (2013) [14] | 78 | 1235.6 (0.1–34,985) log IU/mL | 371 (undetected–2123) log IU/mL | 0.309 | < 0.001 | Weak |
| Antaki et al. (2012) [18] | 131 | 2112 IU/mL | 50 IU/mL | 0.08 | 0.48 | Not significant |
| Balkan et al. (2016) [10] | 104 | 5150.78 ± 8473.16 IU/mL | $0.640 \times 10^3 \pm 0.584$ IU/mL | − 0.046 | 0.643 | Not significant |
| Turyadi et al. (2013) [19] | 34 | 2.52 (−1.3–3.93) log IU/mL | 1.73 (0.04–3.87) log IU/mL | 0.288 | 0.069 | Not significant |
| Zhang et al. (2021) [24] | 106 | 3.059 log IU/mL | 2.699 log IU/mL | 0.046 | 0.64 | Not significant |
| HBeAg − chronic hepatitis B | | | | | | |
| Alghamdi et al. (2013) [14] | 28 | 3.09 (−1–4.4) log IU/mL | 20,958 ($2.3 \times 10^3$–$1.9 \times 10^8$) log IU/mL | 0.383 | < 0.05 | Moderate |
| Antaki et al. (2012) [18] | 106 | 5184 IU/mL | 19,500 IU/mL | 0.44 | < 0.001 | Moderate |
| Turyadi et al. (2013) [19] | 53 | 3.37 (−1.3–4.65) log IU/mL | 4.83 (0.71–8.14) log IU/mL | 0.429 | 0.002 | Moderate |
| Zhang et al. (2021) [24] | 125 | 3.409 log IU/mL | 5.057 log IU/mL | 0.371 | < 0.0001 | Moderate |

[a] Data is presented in mean ± standard deviation or median (range)

genotypes A and D [28]. How genotype variation contributes to these clinical markers remains unknown. Cheng et al. [12] found that genotype B correlates with HBsAg secretion and HBV DNA replication more strongly than genotype C. While Tuaillon et al. [29] demonstrated that HBsAg tends to correlate with HBV DNA in genotype A but not in genotype D, HBsAg does not tend to correlate with HBV DNA in genotype D.

Aside from the aforementioned variables, mutations in the hepatitis B virus may also be responsible for the difference in correlation. No studies on mutations are included in this review, but mutations can influence the production of HBsAg and HBV DNA. Zafrullah et al. [30] found that mutations of the S gene affect HBsAg expression, with the exception of genotype A2. There are mutations in all open reading frames (ORFs) of the hepatitis B virus, including preS/S, polymerase, precore/core, and X. The preS/S open reading frame (ORF) encodes three different molecules that will form HBsAg, so mutations in this ORF will result in distinct HBsAg production [31].

In chronic hepatitis B, HBsAg levels are significantly higher in patients with positive HBeAg, as are HBV DNA levels [17, 22]. According to the pooled analysis, the correlation between the two variables in HBeAg-positive individuals was significant and moderately strong, whereas in HBeAg-negative individuals, the correlation was weak.

The disconnection between quantitative HBsAg levels and HBV DNA in HBeAg− patients could be due to a number of factors. First, the dynamic interaction between HBV and host immunity may stimulate HBV replication during the HBeAg− chronic HBV infection phase and vice versa. Second, the HBsAg synthesis pathway is distinct from the HBV DNA replication pathway as a result of distinct immune control mechanisms [14]. Mutations in the pre-core promoter may impair the secretion of HBV virions, the primary source of HBV DNA. Also, reducing HBsAg secretion is mutations in the pre-S region. As these mutations do not always occur simultaneously, the production of HBsAg and HBV DNA becomes unbalanced, thereby reducing the correlation between the two variables. The correlation between HBsAg and HBV DNA was observed in individuals with wild-type PreS/S sequences but not in subgroups with BCP (basal core promoter) double mutations or PreC mutations [32].

The natural progression of chronic hepatitis B in the absence of HBeAg can be highly variable and frequently unpredictable. HBsAg titers should be correlated with HBV DNA concentrations. HBsAg is an HBV replication

product [33]. This correlation may be invalidated, however, because HBV gene expression is governed by distinct mechanisms and the inhibition of HBV DNA replication. Mutations may affect the secretion of HBV virion and HBsAg, but mutations typically occur at different times, resulting in unequal production and a weakened correlation between the variables [32].

Separate dynamics govern the replication of HBV DNA and the production of HBsAg, which is an additional consideration. In the absence of viral replication, a nonessential aspect of HBV's life cycle produces HBsAg, causing the number of HBsAg to exceed that of virions. HBsAg transcription and secretion could be spared if viral replication is controlled posttranscriptionally [34].

HBsAg levels are highest during the first phase, HBeAg+chronic HBV infection; then decrease during the second phase, HBeAg+chronic hepatitis B; and continue to decline when entering the third phase, HBeAg−chronic HBV infection. When entering the fourth phase of HBeAg−chronic hepatitis B, HBsAg levels will rise again. Quantitative HBV DNA levels also exhibit a similar pattern of increase and decrease. Because HBV virions and antigens undergo minimal or no immune response at the onset of infection, their levels will be elevated. As the phase progresses, the immune system will remain active, resulting in a decline in HBsAg, which can eventually lead to seroconversion in the third phase, HBeAg-negative chronic HBV infection. In the fourth phase, the re-increase of HBsAg indicates the reactivation of the disease, which causes liver damage.

Due to differences in HBV transcription that are minimally influenced by the host immune response, quantitative HBsAg and HBV DNA may not be significantly correlated. HBsAg can also be produced not only from intrahepatic cccDNA but also from HBV sequences that have been integrated [24]. In the HBeAg−chronic HBV infection phase, the host immune system is active, suppressing HBV DNA levels; however, this phase has the potential to reactivate and transition to the HBeAg−chronic hepatitis B infection phase and vice versa. In these instances, regardless of HBsAg levels, HBV DNA levels decrease to undetectable levels. Numerous patients in this phase have undetectable HBV DNA and elevated levels of HBsAg. Antaki et al. discovered that the HBsAg/HBV DNA ratio was highest during the third phase. This suggests that immune system regulation does not always inhibit HBsAg production [18].

This investigation yielded significant heterogeneity. One possible explanation for these findings is the variation in clinical characteristics among the studies that were included. Significant disparities in age might contribute to a high level of heterogeneity. The inclusion of various research designs, such as cross-sectional, case–control, and cohort studies, in this analysis further contributes to the heterogeneity seen. Geographical variations can also exert an influence. Funnel plot asymmetry in the meta-analysis can be attributed to several variables, resulting in the majority of studies being situated near the tip of the funnel plot. These issues encompass publication bias, heterogeneity, and methodological quality in research characterized by smaller sample sizes [35].

We acknowledge that this study contains several flaws. In order to assess the maintenance of the relationship between HBsAg and HBV DNA in this context, we exclude patients receiving antiviral therapy. The correlation found in a few studies reviewed in this article was not established as the primary result. The majority of study designs were cross-sectional, so there was no sample follow-up. A further drawback is that some studies omitted variable data, which may have an impact on the analysis of the final result. To clarify this association, additional research with a larger number of samples and studies is necessary.

In this meta-analysis, studies included have various sample sizes where most of them had small sample size. This could lead to small study effect, which is a phenomenon where smaller studies may show different, often larger effects than larger ones. Smaller studies may be more susceptible to biases because they were more likely to report larger beneficial effects than larger studies [36]. Smaller studies may also overestimate the effect size, which could lead to erroneous conclusions [37].

## Conclusion

In conclusion, our study established a moderate correlation between HBsAg and HBV DNA in the entire cohort of patients with chronic hepatitis B. These findings require confirmation in larger studies with more comprehensive methods, characteristics, and criterion to reduce bias. The result of this study must be interpreted cautiously due to the possibility of publication bias and small study effect.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43066-024-00336-5.

**Additional file 1: Supplementary figures. Fig. S1.** Funnel plot Correlation between quantitative HBsAg and quantitative HBV DNA in total sample of chronic hepatitis B patients. **Fig. S2.** Funnel plot Correlation between quantitative HBsAg and quantitative HBV DNA in chronic hepatitis B patients according to the HBeAg status. **Fig. S3.** Funnel plot Correlation between quantitative HBsAg and quantitative HBV DNA based on chronic HBV infection course. **Supplementary tables: Table S1.** Cross-sectional study critical appraisal. **Table S2.** Case-control study critical appraisal. **Table S3.** Cohort study critical appraisal.

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None

**Authors' contributions**
UM: Conceptualization, project design, supervision, materials, literature search, data collection and/or processing, data analysis and/or interpretation, writing and/or review the manuscript, and final approval of the version to be submitted. PW: Conceptualization, project design, supervision, materials, literature search, data collection and/or processing, data analysis and/or interpretation, writing and/or review the manuscript, and final approval of the version to be submitted. CDKW: Conceptualization, project design, supervision, materials, literature search, data collection and/or processing, data analysis and/or interpretation, writing and/or review the manuscript, and final approval of the version to be submitted. AFR: Materials, literature search, data collection and/or processing, data analysis and/or interpretation, writing and/or review the manuscript, and final approval of the version to be submitted. AAK: Materials, literature search, data collection and/or processing, data analysis and/or interpretation, writing and/or review the manuscript, and final approval of the version to be submitted. AP: Materials, literature search, data collection and/or processing, data analysis and/or interpretation, writing and/or review the manuscript, and final approval of the version to be submitted.

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The authors confirm that the data supporting the findings of this review are available within the article and/or its supplementary materials.

## Declarations

**Ethics approval and consent to participate**
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**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1]Division of Gastroenterohepatology, Faculty of Medicine, Airlangga University, Surabaya 60286, Indonesia. [2]Department of Clinical Pathology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia. [3]Department of Physiology and Medical Biochemistry, Faculty of Medicine, Airlangga University, Surabaya, Indonesia. [4]Faculty of Medicine, Airlangga University, Surabaya, Indonesia. [5]Department of Internal Medicine, Faculty of Medicine, Airlangga University, Surabaya, Indonesia.

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