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Original Article

Traditional and Novel Virologic Markers for Functional Cure and HBeAg Loss with Pegylated Interferon in Chronic Hepatitis B: A Systematic Review and Meta-analysis

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Abstract

Background and Aims: The rate of functional cure (HBsAg loss) remains unsatisfactory following pegylated interferon (PEG-IFN) treatment in chronic hepatitis B. To optimize PEG-IFN administration, this study aimed to evaluate virological markers to predict functional cure and/or hepatitis B e antigen (HBeAg) loss. ***Methods:*** Relevant studies assessing virologic markers for predicting functional cure and HBeAg loss after PEG-IFN therapy were systematically retrieved from PubMed, Embase, the Cochrane Library, and Web of Science up to November 2023. Predictive effectiveness was evaluated via the summary receiver operating characteristic curve. ***Results:*** We analyzed 38 studies (6,179 patients). HBsAg decline at week 24 had the greatest discriminative ability according to the area under the receiver operating characteristic curve (AUROC) (0.89) and sensitivity (0.88) for predicting functional cure, whereas baseline HBsAg had a comparable AUROC (0.86) and highest specificity (0.79), with both being significantly better than baseline hepatitis B core-related antigen and hepatitis B virus (HBV) RNA (all $P < 0.001$). For HBeAg loss or seroconversion, HBV RNA, HBV DNA, HBeAg, and HBeAg decline at week 12, as well as HBV DNA and HBeAg decline at week 24, all exhibited comparable predictive values (AUROC = 0.75–0.78). HBV RNA and HBeAg levels at week 24 showed optimal sensitivity (0.87), and HBeAg decline at week 12 had the highest specificity (0.83). ***Conclusions:*** HBsAg decline at week 24 and baseline HBsAg levels are better predictors of functional cure than novel virologic markers, while on-treatment HBV RNA and HBeAg levels and dynamic changes are the most reliable indicators for HBeAg loss.

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Introduction

Chronic hepatitis B (CHB) remains a significant global public health challenge, with nearly 296 million people currently living with the condition worldwide and 1.1 million deaths in 2022.[1] The primary therapeutic objective in CHB is to achieve a functional cure, defined by the clearance of hepatitis B surface antigen (HBsAg), with or without the appearance of anti-HBs antibodies. First-line antiviral therapy mainly consists of nucleos(t)ide analogs (NAs) or pegylated interferon (PEG-IFN);[2] of these, PEG-IFN-based antiviral therapy has the highest functional cure rate, but its five-year sustained HBsAg clearance rate is still modest at only 13.0%.[3] For hepatitis B e antigen (HBeAg)-positive individuals, the primary treatment objective prior to functional cure is HBeAg loss, thereby lowering the risk of developing cirrhosis or hepatocellular carcinoma.[4–6]

The conventional markers of hepatitis B virus (HBV), including HBV DNA, HBeAg, hepatitis B e antibody, and qualitative HBsAg, have traditionally served to monitor CHB and guide therapy. Several novel biomarkers, such as quantitative hepatitis B core antibody (anti-HBc), hepatitis B core-related antigen (HBcrAg), and HBV RNA,[7,8] have emerged as potential supplementary markers for monitoring CHB. Both baseline and treatment-induced variations in HBV virological markers have been reported to predict the likelihood of HBsAg loss and HBeAg seroconversion following PEG-IFN administration.[9–11] Nevertheless, the most effective virological markers for predicting treatment outcomes after PEG-IFN administration remain debated. To date, no diagnostic meta-analysis or comprehensive comparison has evaluated the value of distinct virological markers for predicting HBsAg and HBeAg seroclearance following PEG-IFN therapy.

Accordingly, this study aimed to comprehensively assess

Keywords: Chronic hepatitis B; Interferon; Functional cure; Virologic markers; Hepatitis B e antigens; Predictive value of tests.

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the predictive value of traditional and novel HBV virological markers for functional cure and HBeAg seroclearance/seroconversion in CHB patients treated with PEG-IFN. Such data are needed to tailor PEG-IFN use to patients with a high likelihood of response and avoid unnecessary treatment burden for those whose chances of functional cure are poor.

Methods

Search strategy

The present systematic review and meta-analysis adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, as provided in the Supplemental File 1. The protocol was registered with PROSPERO (www.crd.york.ac.uk/prospero; CRD42025629442). Two reviewers (ZY and WLF) independently searched the PubMed, Embase, Cochrane Library, and Web of Science databases up to November 2023. Supplementary Methods provide a full account of the search strategy (Supplemental File 2).

Inclusion and exclusion criteria

Studies were included if they: (1) enrolled well-defined patients with CHB; (2) involved ≥48 weeks of PEG-IFN therapy; (3) evaluated functional cure (HBsAg clearance or seroconversion at the end of treatment or ≥24 weeks post-treatment) as the primary endpoint; (4) assessed HBeAg loss (HBeAg clearance or seroconversion at the end of treatment or during follow-up) as the secondary endpoint; and (5) provided or allowed the calculation of true-positive, false-positive, false-negative, and true-negative values. Exclusion criteria were animal studies, case-control designs, non-original publications (letters, case reports, guidelines, reviews, conference abstracts), duplicate publications, or studies with insufficient, intractable, or irrelevant data.

Data extraction

The data were independently extracted by two reviewers (ZY and WLF) using a standardized form. The extracted information comprised study characteristics (authors, year, region, sample size, patient age, and proportion of males) and virological markers, including quantification of HBsAg, HBeAg, HBV DNA, and HBV RNA at baseline, 12, and 24 weeks of treatment; HBsAg decline at 12 and 24 weeks; and baseline levels of HBcrAg and anti-HBc. The identified cut-off values and timing of assessment were also recorded. These variables were then analyzed alongside effect estimates, such as cumulative incidence of outcomes, treatment response indicators, and diagnostic measures (true positives, false negatives, false positives, and true negatives). Partial data from ROC curves were captured using GetData Graph Digitizer (version 2.22). When key information was unavailable, the study authors were contacted by email for clarification. Differences in data evaluation were resolved through consensus and, if required, consultation with a third author (CJ).

Quality assessment

The potential for bias was determined based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2),[12] with RevMan 5.3 employed to manage and present the results. QUADAS-2 evaluates four key domains (patient selection, index test, reference standard, and flow and timing of participants through the study), with full details accessible at https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/. Each domain was assigned a bias rating ("low," "high," or "unclear") according to the responses to the relevant questions in that section. The assessments were independently conducted by two reviewers, and the findings were illustrated graphically. Disagreements were resolved through discussion, and if consensus could not be reached, a third senior researcher was consulted for arbitration.

Statistical analysis

The summary estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with 95% confidence intervals (CI) were derived via a bivariate random-effects model. The summary receiver operating characteristic curve was constructed via the same model.[13] The DOR indicates the strength of association between the biomarkers and treatment efficacy. A test demonstrates better performance when the area under the receiver operating characteristic curve (AUROC) approaches 1, and larger DOR values indicate higher AUROC.[14] The association between virological markers and clinical outcomes was quantified using the AUROC (median and range). An AUROC < 0.5 reflects no predictive capacity, 0.5–0.7 suboptimal, 0.7–0.8 good, and >0.8 excellent.[15] We aggregated true-positive, false-negative, false-positive, and true-negative data from multiple studies to compute the combined AUROC and its standard error for each virological marker. Differences between AUROCs were assessed using a Z-test, with $P < 0.05$ considered significant. Inter-study heterogeneity was evaluated using Cochran's Q test, and its magnitude was quantified by I^2, with values of 25%, 50%, and 75% corresponding to low, moderate, and high heterogeneity, respectively.[16] Meta-analysis was performed in Stata 15.0 when more than three studies applied guideline-based diagnostic criteria. Deeks' funnel plot analysis was performed to detect possible publication bias, and a *P*-value below 0.1 was taken as evidence of its presence.[17]

Results

Search results and assessment of bias

The literature search retrieved 4,362 titles and abstracts, of which 1,027 were assessed in full text. Following the application of predefined exclusion criteria, 459 studies were removed, and an additional 530 articles lacking relevant data were excluded after careful evaluation (Fig. 1). Ultimately, 38 studies (Supplementary Table 1) were included, comprising data from at least 6,179 unique patients who had discontinued PEG-IFN therapy. Among the included studies, 13 were prospective, 20 were retrospective, and 5 were randomized controlled trials. Thirty-seven studies involving 5,400 participants (87.4%) were conducted in Asian populations, including 18 (47.4%) exclusively from Mainland China. Participants were mostly middle-aged (28.2–51.6 years) with a male predominance (71.7%). Of the 24 studies reporting HBV genotypes, genotype C was the most common (51.5%), followed by genotype B (31.2%). PEG-IFN α-2a or α-2b, given alone or with NAs for 48–52 weeks, was administered to most patients, involving over 5,590 (90.5%) individuals. Assessment with QUADAS-2 revealed that seven studies did not report whether patient enrollment was consecutive. Overall, most studies demonstrated high quality, exhibiting low risk of bias and few applicability concerns (Supplementary Figs. 1, 2). The primary sources of potential bias were related to patient selection, as well as the flow and timing of the index and reference tests.

Predictive value of virological markers for functional cure

A total of 19 studies, which included 2,576 participants, as-

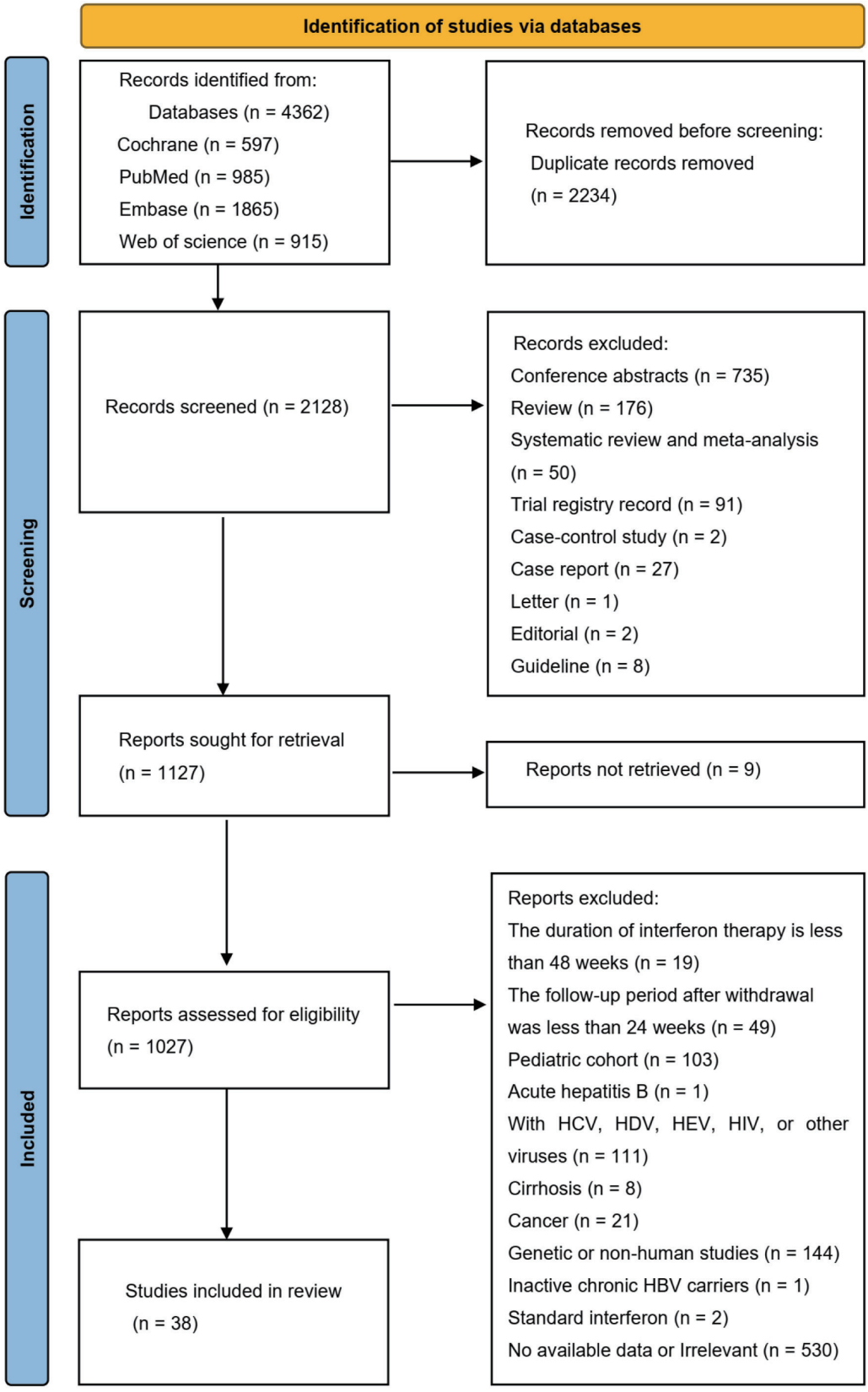

Fig. 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

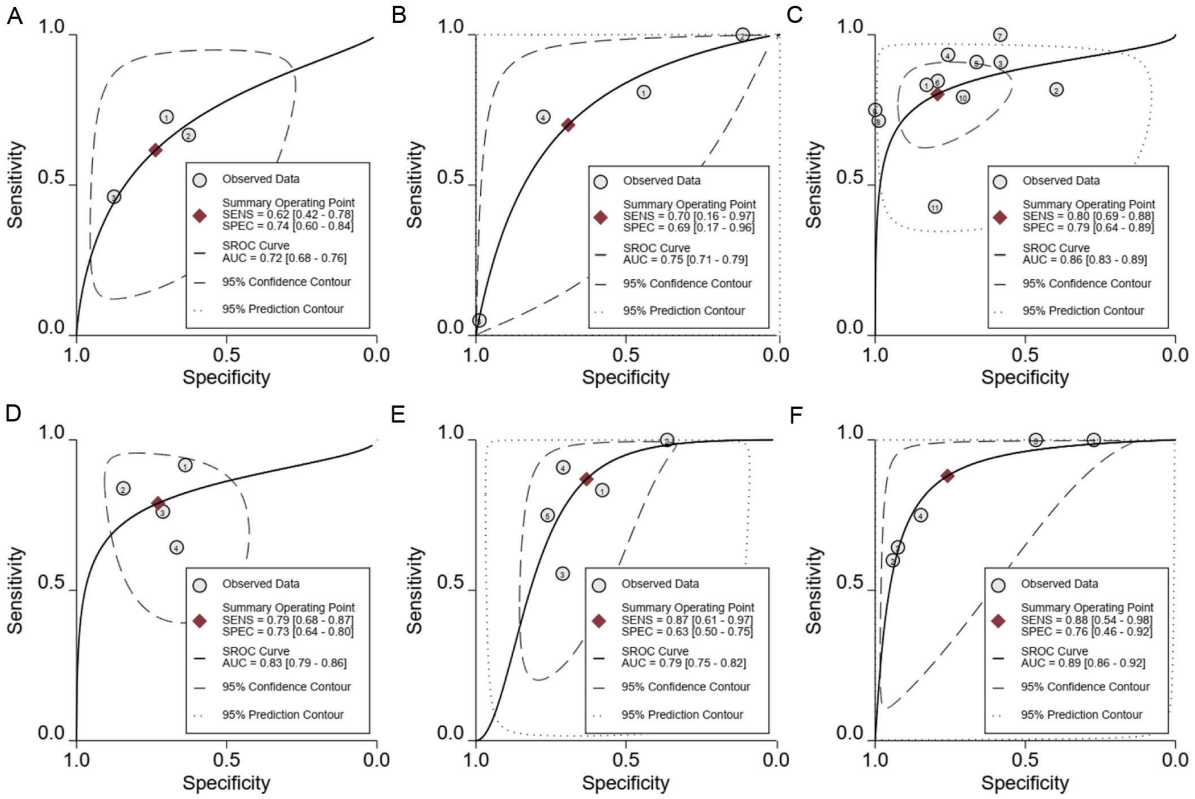

Fig. 2. The SROCs of different virological markers for predicting functional cure. (A) Baseline HBcrAg; (B) Baseline HBV RNA; (C) Baseline HBsAg; (D) HBsAg at week 12; (E) HBsAg decline at week 12; (F) HBsAg decline at week 24. AUC, area under the summary receiver operating characteristic curve; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; SROC, summary receiver operating characteristic curve; SENS, sensitivity; SPEC, specificity.

sessed virological markers for predicting functional cure in CHB. Figure 2 presents summary receiver operating characteristic curves for baseline HBcrAg, HBV RNA, and HBsAg levels, as well as HBsAg at week 12, HBsAg decline at week 12, and HBsAg decline at week 24. The summary estimates of AUROC, DOR, sensitivity, specificity, PLR, NLR, and heterogeneity (I^2) are presented in Figure 2, Table 1, and Supplementary Table 2.

Novel virologic markers: Novel virologic markers for predicting functional cure were examined across six studies including 1,379 patients. For the evaluation of the efficacy of baseline HBcrAg, the pooled sensitivity estimate was 0.62 (95% CI [0.42, 0.78], I^2 = 0%), and the pooled specificity estimate was 0.74 (95% CI [0.60, 0.84], I^2 = 69.4%) in patients with HBeAg-negative CHB (Fig. 2A). For baseline HBV RNA, the pooled sensitivity estimate was 0.64 (95% CI [0.07, 0.98], I^2 = 93.6%), and the pooled specificity estimate was 0.72 (95% CI [0.16, 0.97], I^2 = 99.2%) (Fig. 2B), with 82.7% of HBeAg-positive CHB patients likely contributing to the high heterogeneity. The median AUROCs for baseline HBcrAg (0.72, range 0.68–0.76, DOR 4.74 [2.25–10.0]) and HBV RNA (0.74, range 0.70–0.78, DOR 4.43 [1.5–13.1])

Table 1. Predictive value of virologic markers for functional cure with pegylated interferon treatment in patients with CHB

No. of studies	No. of patients	Predictors (log_{10} IU/mL)	Baseline HBeAg+ (n, %)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	I^2 (%, 95% CI)
3	296	Baseline HBcrAg	0 (0)	2.3 (1.5, 3.6)	0.52 (0.34, 0.80)	4.74 (2.25, 10.0)	48.9 (0, 100)
4	1197	Baseline HBV RNA	993 (82.9)	2.3 (1.0, 5.4)	0.50 (0.13, 1.88)	4.43 (1.5, 13.1)	98.8 (98.2, 99.4)
11	1710	Baseline HBsAg	1110 (64.9)	3.9 (2.1, 7.1)	0.25 (0.16, 0.40)	15.5 (6.52, 36.9)	94.4 (89.8, 99.1)
4	1231	HBsAg at week 12	1150 (93.4)	2.9 (2, 4.1)	0.29 (0.18, 0.47)	10.1 (4.59, 22.1)	0 (0, 100)
6	658	HBsAg decline at week 12	242 (36.8)	2.5 (1.9, 3.4)	0.25 (0.11, 0.55)	10.2 (4.43, 23.3)	90.1 (80.4, 99.8)
5	528	HBsAg decline at week 24	187 (35.4)	3.7 (1.6, 8.5)	0.16 (0.04, 0.64)	23.2 (6.66, 80.7)	96.5 (93.9, 99.1)

CHB, chronic hepatitis B; CI, confidence interval; DOR, diagnostic odds ratio; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

Table 2. Predictive value of virologic markers for predicting HBeAg loss with pegylated interferon treatment in patients with CHB

No. of studies	No. of patients	Predictors (log_{10} IU/mL)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (range)	DOR (95% CI)
HBV RNA at different time points						
4	1125	Baseline HBV RNA	0.14 (0, 0.96)	0.8 (0.43, 0.96)	0.66 (0.62–0.70)	2.25 (1.66, 3.05)
4	1125	HBV RNA at week 12	0.83 (0.47, 0.97)	0.59 (0.36, 0.79)	0.75 (0.71–0.79)	7.23 (2.46, 21.3)
3	398	HBV RNA at week 24	0.87 (0.5, 0.98)	0.5 (0.29, 0.7)	0.69 (0.65–0.73)	3.34 (2.05, 5.45)
HBsAg-related markers						
9	1941	Baseline HBsAg	0.65 (0.57, 0.73)	0.61 (0.51, 0.69)	0.67 (0.63–0.71)	2.89 (2.03, 4.13)
11	2197	HBsAg at week 12	0.76 (0.57, 0.88)	0.59 (0.43, 0.74)	0.72 (0.68–0.76)	4.54 (2.98, 6.90)
9	852	HBsAg at week 24	0.86 (0.64, 0.96)	0.59 (0.48, 0.69)	0.71 (0.67–0.75)	8.95 (3.47, 23.1)
5	1334	HBsAg decline at week 12	0.55 (0.27, 0.81)	0.71 (0.38, 0.91)	0.67 (0.63–0.71)	3.04 (1.91, 4.84)
5	631	HBsAg decline at week 24	0.54 (0.27, 0.79)	0.79 (0.41, 0.95)	0.70 (0.66–0.74)	4.57 (2.02, 10.3)
HBeAg-related markers						
4	965	Baseline HBeAg	0.47 (0.26, 0.70)	0.75 (0.52, 0.89)	0.66 (0.61–0.70)	2.68 (1.71, 4.20)
5	1131	HBeAg at week 12	0.77 (0.55, 0.90)	0.66 (0.45, 0.82)	0.77 (0.73–0.81)	6.50 (4.04, 10.5)
5	687	HBeAg at week 24	0.87 (0.74, 0.94)	0.58 (0.48, 0.67)	0.73 (0.69–0.77)	9.29 (4.84, 17.8)
3	374	HBeAg decline at week 12	0.64 (0.31, 0.87)	0.83 (0.23, 0.99)	0.77 (0.73–0.80)	4.04 (2.22, 7.34)
3	374	HBeAg decline at week 24	0.76 (0.54, 0.90)	0.63 (0.41, 0.81)	0.76 (0.72–0.79)	5.53 (3.09, 9.87)
HBV DNA-related markers						
9	2158	Baseline HBV DNA	0.48 (0.41, 0.55)	0.75 (0.64, 0.83)	0.59 (0.55–0.63)	2.75 (1.93, 3.90)
6	1174	HBV DNA at week 12	0.74 (0.50, 0.89)	0.68 (0.48, 0.82)	0.76 (0.72–0.80)	5.95 (3.41, 10.4)
7	974	HBV DNA at week 24	0.84 (0.64, 0.94)	0.54 (0.29, 0.77)	0.78 (0.75–0.82)	6.22 (3.27, 11.8)
3	374	HBV DNA decline at week 12	0.69 (0.53, 0.81)	0.63 (0.48, 0.76)	0.71 (0.67–0.75)	3.71 (2.29, 6.01)
3	374	HBV DNA decline at week 24	0.65 (0.56, 0.73)	0.73 (0.58, 0.84)	0.67 (0.63–0.71)	5.49 (3.30, 9.16)

CHB, chronic hepatitis B; AUC, area under the receiver operating characteristic curve; CI, confidence interval; DOR, diagnostic odds ratio; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

were similar (P = 0.511), and both showed good performance.

HBsAg-related markers: Nineteen studies involving 2,576 patients provided data on the quantitative HBsAg for predicting functional cure, with approximately 45.6% of the patients being HBeAg-negative CHB. As predictive markers of HBsAg clearance, different HBsAg-related markers showed excellent performance. HBsAg decline at week 24 had the greatest AUROC of 0.89 (95% CI [0.86–0.92]) and the best sensitivity of 0.88 (95% CI [0.54, 0.98], I^2 = 69.4%) (Fig. 2F), significantly surpassing HBsAg at week 12 (AUROC 0.83 [95% CI 0.79–0.86], P = 0.007) (Fig. 2D) and HBsAg decline at week 12 (AUROC 0.81 [95% CI 0.77–0.84], P = 0.002) (Fig. 2E). Compared to HBsAg decline at week 24, baseline HBsAg had a comparable AUROC of 0.86 (95% CI [0.83–0.89], P = 0.164) and the highest specificity of 0.79 (95% CI [0.64, 0.89], I^2 = 91.8%) (Fig. 2C).

A subgroup analysis was performed due to high heterogeneity, focusing on HBsAg-related markers for predicting functional cure in HBeAg-negative CHB patients, based on 11 studies comprising 882 participants (Supplementary Table 3). The decline in HBsAg at week 24 demonstrated the highest AUROC (0.91, 95% CI [0.88–0.93]) and sensitivity (0.97, 95% CI [0.28–1.0], I^2 = 77.1%), yet no significant difference was observed compared with baseline HBsAg (P = 0.088), which presented an AUROC of 0.86 (95% CI [0.82–0.88]) and the highest specificity (0.74, 95% CI [0.57–0.86], I^2 = 88.4%). With an AUROC of 0.81 (95% CI 0.77–0.84), the week-12 HBsAg decline exhibited weaker predictive ability than baseline HBsAg and the week-24 decline (P = 0.025 and P < 0.001, respectively).

Predictive value of virological markers for HBeAg loss

Twenty-three studies encompassing 4,776 patients with HBeAg-positive CHB investigated virological markers for the prediction of HBeAg loss. As shown in Table 2 and Supplementary Table 4, the pooled estimates of AUROC, DOR, sensitivity, specificity, PLR, NLR, and heterogeneity (I^2) are summarized.

HBV RNA at different time points: Four studies involving 1,125 patients used HBV RNA at different time points

for its predictive value regarding HBeAg loss. At baseline, HBV RNA showed an overall sensitivity of 0.14 (95% CI [0–0.96], I^2 = 96.9%) and a corresponding specificity of 0.80 (95% CI [0.43–0.96], I^2 = 96.2%). At week 12, sensitivity was estimated at 0.83 (95% CI [0.47–0.97], I^2 = 93.8%) with a specificity of 0.59 (95% CI [0.36–0.79], I^2 = 95.8%). At week 24, the summary sensitivity reached 0.87 (95% CI [0.50–0.98], I^2 = 87.4%), whereas specificity was 0.50 (95% CI [0.29–0.70], I^2 = 87.1%). The median AUROCs were for baseline HBV RNA of 0.66 (poor) with DOR 2.25 (1.66, 3.05), for HBV RNA at week 12 of 0.75 (good) with DOR 7.23 (2.46, 21.3), and for HBV RNA at week 24 of 0.69 (poor) with DOR 3.34 (2.05, 5.45). Compared to the AUROCs of HBV RNA at baseline and at week 24, HBV RNA at week 12 was superior for predicting HBeAg loss or seroconversion at at the end of treatment or follow-up (P < 0.001 and P = 0.011, respectively).

HBsAg-related markers: Nineteen studies with 3,889 patients provided data about HBsAg-related markers for predicting HBeAg loss. The median AUROCs were for baseline HBsAg of 0.67 (poor) with DOR 2.89 (2.03, 4.13), for HBsAg at week 12 of 0.72 (good) with DOR 4.54 (2.98, 6.90), for HBsAg at week 24 of 0.71 (good) with DOR 8.95 (3.47, 23.1), for HBsAg decline at week 12 of 0.67 (poor) with DOR 3.04 (1.91, 4.84), and for HBsAg decline at week 24 of 0.70 (good) with DOR 4.57 (2.02, 10.3). HBsAg at week 12 exhibited significantly higher predictive performance for HBeAg loss compared with baseline values (P < 0.001) and HBsAg decline at week 12 (P = 0.003), while remaining statistically indistinguishable from levels and decline at week 24 (P = 0.599 and 0.362).

HBeAg-related markers: Seven studies with 1,458 patients provided data about baseline HBeAg, HBeAg at week 12, and 24 for predicting HBeAg loss. The median AUROCs were 0.66 (poor) for baseline HBeAg with a DOR of 2.68 (1.71, 4.20), 0.77 (good) for HBeAg at week 12 with a DOR of 6.50 (4.04, 10.5), 0.73 for HBeAg at week 24 with a DOR of 9.29 (4.84, 17.8), and the best sensitivity of 0.87 (95% CI [0.74, 0.94], I^2 = 79.4%), 0.77 (good) for HBeAg decline at week 12 with a DOR of 4.04 (2.22, 7.34) and the best specificity of 0.83 (95% CI [0.23, 0.99], I^2 = 90.4%), and 0.76 (good) for HBeAg decline at week 24 with a DOR of 5.53 (3.09, 9.87).

HBV DNA-related markers: Fourteen studies with 3,025 patients provided data for predicting HBeAg loss. The median AUROCs were for baseline HBV DNA of 0.59 (poor) with DOR 2.75 (1.93, 3.90), for HBV DNA at week 12 of 0.76 (good) with DOR 5.95 (3.41, 10.4), at week 24 of 0.78 (good) with DOR 6.22 (3.27, 11.8), for HBV DNA decline at week 12 of 0.71 (good) with DOR 3.71 (2.29, 6.01), and for HBV DNA decline at week 24 of 0.67 (poor) with DOR 5.49 (3.30, 9.16). By comparing the AUROCs of different HBV DNA-related markers, it was found that HBV DNA quantification at week 24 offers a significantly better predictive value for HBeAg loss compared to baseline HBV DNA and HBV DNA decline at weeks 12 and 24 (all P < 0.05).

Comparison of different virologic markers for predicting functional cure and HBeAg loss

For predictive markers of functional cure, both HBsAg decline at week 24 and baseline HBsAg demonstrated significantly superior AUROCs compared to baseline HBcrAg and HBV RNA (all P < 0.001). In patients with HBeAg-negative CHB, baseline HBcrAg demonstrated significantly lower predictive ability for functional cure relative to baseline HBsAg and the declines observed at weeks 12 and 24 (all P < 0.05), while its specificity was comparable to that of baseline HBsAg (0.74). However, there was insufficient data for HBV RNA analysis to compare in this subgroup. For predictive markers of HBeAg loss, the performance of different virologic markers varies. At week 12, HBeAg quantification had a significantly higher AUROC than HBsAg quantification (P = 0.004) but was similar to HBV RNA (P = 0.305). Although HBV DNA at week 24 had the highest AUROC, it was not significantly different from the AUROCs of HBV DNA, HBV RNA, HBeAg, or HBeAg decline at week 12 (P = 0.136, 0.621, and 0.728, respectively). Furthermore, HBV RNA and HBeAg at week 24 demonstrated optimal sensitivity of 0.87, whereas HBeAg decline at week 12 showed the highest specificity of 0.83.

Publication bias

Assessment using Deeks' funnel plot asymmetry test (Supplementary Figs. 3–7) suggested little evidence of publication bias across most predictors. Some publication bias was observed in the three studies investigating baseline HBcrAg for its predictive value for functional cure (P = 0.018). Additionally, studies predicting HBeAg loss using baseline HBsAg, HBsAg at week 12, and HBsAg at week 24 showed potential publication bias (P = 0.054, 0.067, and 0.067, respectively).

Discussion

To inform efficacy assessment of CHB patients undergoing PEG-IFN therapy and future HBV cure clinical development, this systematic review and meta-analysis comprehensively evaluated both the baseline and dynamic changes of traditional as well as novel virologic markers as potential predictors of functional cure and of HBeAg loss and seroconversion. We found that traditional HBsAg-associated virological markers are superior to novel virological markers in predicting PEG-IFN treatment-induced functional cure, with HBsAg decline at week 24 representing the strongest predictor. Our findings agree with previous studies reporting that lower baseline HBsAg and greater HBsAg decline from baseline to weeks 12 and 24 correspond to an increased likelihood of HBsAg loss upon PEG-IFN completion.[9,18]

Baseline HBsAg levels under 500 IU/mL, particularly below 120 IU/mL, are associated with increased HBsAg clearance with Peg-IFN treatment, while levels exceeding 1,500 IU/mL predict a reduced likelihood of functional cure.[19,20] In our meta-analysis, baseline HBsAg was identified as having the highest specificity for predicting functional cure with PEG-IFN therapy, suggesting that an excessively high baseline HBsAg quantification (>1,500 IU/mL),[19] especially >3.4 log10 IU/mL,[21] may help pre-screen and exclude patients unlikely to achieve a functional cure with PEG-IFN therapy. In contrast, on-treatment biomarkers were found to be more reliable predictors of achieving functional cure compared to baseline markers. HBsAg decline at week 24 had the greatest AUROC of 0.89 and the best sensitivity of 0.88 for predicting functional cure in our study. A decrease in HBsAg of more than 1 log10 IU/mL by week 24 is predictive of subsequent HBsAg loss.[22] HBsAg declines observed at weeks 12 and 24 during PEG-IFN treatment are linked to more persistent HBsAg clearance over long-term follow-up.[23] Our findings are consistent with results from recent head-to-head studies[22,24–26] and support the clinical utility of HBsAg kinetics, particularly baseline HBsAg and HBsAg decline at week 24. Recent expert consensus recommends that low baseline HBsAg levels (<1,500 IU/mL), or early on-treatment HBsAg decline, are more likely to achieve HBsAg loss with PEG-IFN-based therapy,[27] thereby further encouraging the clinical applicability of HBsAg kinetics for optimizing functional cure–oriented treatment strategies.

A randomized controlled trial conducted in Singapore indicated that an HBsAg level under 70 IU/mL at week 8 most accurately predicted clearance 24 weeks after PEG-IFN cessation, with an AUC of 0.96.[28] Another retrospective cohort study established a model using a baseline HBsAg level of <1,000 IU/mL combined with an HBsAg decline of >0.5 log at week 12, demonstrating good predictive performance for HBsAg loss under PEG-IFN treatment, with an AUC of approximately 0.78–0.81.[29] Among CHB patients with prior NA exposure undergoing sequential PEG-IFN-α therapy, a >1 log10 IU/mL decline in HBsAg at week 12, combined with baseline anti-HBc and HBsAg levels, yielded a significantly higher AUC (0.93) than any single marker.[30] Therefore, combining multiple virologic markers may improve predictive value. Additional well-designed, prospective studies are required for validation.

HBV RNA and HBcrAg are promising on-treatment biomarkers for anticipating response to PEG-IFN therapy and identifying patients likely to achieve functional cure.[31,32] Contrary to a few prior studies reporting better performance with HBcrAg and HBV RNA as compared to traditional virological markers in predicting virological response after antiviral therapy,[33–35] our meta-analysis indicated that baseline HBV RNA and HBcrAg were significantly less effective than HBsAg-related virological markers in predicting HBsAg loss (AUROC = 0.72 vs. 0.74 vs. 0.81–0.89). Our findings are consistent with another meta-analysis reporting that HBcrAg was suboptimal for predicting HBsAg loss,[11] similar to Lim et al.,[28] who found HBV RNA and HBcrAg to be weak predictors. The independent production pathway of HBcrAg from HBsAg limits its predictive value for functional cure, and the available studies are insufficient, necessitating further validation.[11] Notably, in NA-suppressed CHB patients switched to PEG-IFN-α for 96 weeks, those with HBcrAg ≥ 5 $\log_{10}$ U/mL and HBsAg ≥ 100 IU/mL did not achieve HBsAg loss,[36] indicating the predictive value of combined HBsAg and HBcrAg markers for functional cure. However, the limited studies evaluating novel combined with traditional markers for predicting functional cure need to be further confirmed.

In HBeAg-positive patients, approximately 70% of HBcrAg is derived from HBeAg, indicating potential for predicting HBeAg seroconversion.[11] Regarding the prediction of HBeAg seroclearance, our study found that HBV DNA level and HBeAg decline at week 24, as well as HBeAg, HBeAg decline, and HBV RNA levels at week 12, are all optimal predictors of HBeAg loss or seroconversion, with AUROC values of 0.78, 0.76, 0.77, 0.77, and 0.75, respectively. Our study found that HBV DNA level at week 24 exhibits the highest AUROC for predicting HBeAg loss, exclusively in patients with detectable HBV DNA at baseline, not in those with undetectable HBV DNA at baseline. Recent research has developed a predictive model suggesting that initial and on-therapy quantitative HBeAg levels could help identify patients likely to achieve HBeAg loss during NA therapy with PEG-IFN add-on or switch.[37] HBeAg level at week 24 also demonstrated an optimal sensitivity of 0.87 and a good AUROC of 0.73 (0.69–0.77), suggesting that HBeAg level at week 24 may have superior predictive value for HBeAg loss. This is consistent with previous studies,[38,39] which also indicated that HBeAg at week 24 with a cutoff of 2.0 $\log_{10}$ S/CO provided the best prediction of HBeAg seroconversion (AUC 0.91, sensitivity 85%), markedly outperforming HBsAg and HBV DNA. However, previous studies found that low baseline HBV DNA (<50 IU/mL) favored HBeAg loss, and that on-treatment HBsAg, particularly when combined with HBeAg or HBV DNA, was useful for predicting HBeAg seroconversion after PEG-IFN therapy.[40,41] Our meta-analysis found that HBsAg-related virological markers are not optimal for predicting HBeAg loss or seroconversion, as HBeAg quantification showed significantly higher AUROC than HBsAg quantification at week 12 (P = 0.004). The inconsistencies in these studies may be due to differences in PEG-IFN treatment regimens and baseline virologic markers among the CHB populations.

Additionally, we found that among HBV RNA-related markers, HBV RNA at week 12 is the most effective predictor of HBeAg loss, while HBV RNA at week 24 with an optimal sensitivity of 0.87 shows a less favorable AUROC value (0.75). HBV RNA has been considered a potential indicator of therapeutic response, reflecting cccDNA activity and linking to intrahepatic cccDNA levels, long-term viral persistence, and likelihood of recurrence.[42–44] One study showed that HBV RNA measured at week 12 predicts HBeAg seroconversion in HBeAg-positive patients receiving PEG-IFN treatment, with an AUROC of 0.77, and performs better when combined with traditional markers like HBeAg.[45] Additionally, while HBcrAg quantification and changes during treatment have a nearly 100% negative predictive value for HBeAg seroconversion, the positive predictive value is relatively low.[24,38,46] These findings suggest that future studies should validate predictive models combining HBV RNA, HBcrAg, and HBeAg levels, along with their dynamic changes, for HBeAg loss during PEG-IFN treatment.

We also acknowledge the following limitations. First, heterogeneity across studies in patient characteristics (including age, HBV genotype, and host immune status),[47–49] treatment regimens, follow-up durations, and assay methodology may have influenced the predictive efficiency (Supplementary Table 5). Nevertheless, the consistency of multiple head-to-head studies supports the robustness of our findings despite insufficient data for stratified analyses. Studies enrolling younger patients or those with a higher proportion of HBV genotype B may show better PEG-IFN responses, which could partially account for the observed heterogeneity. Second, although the predicted values for the same indicators were combined, the optimal cutoff values could not be determined and still need to be established through further diagnostic tests. Finally, diagnostic meta-analysis could not be conducted for these markers due to the insufficient number of studies on specific virological markers, such as HBcrAg, baseline anti-HBc, and HBsAg at week 24. Moreover, emerging molecular and immunologic markers, such as CXC chemokine receptors,[50,51] represent promising candidates for investigating predictors of PEG-IFN response. However, the current evidence remains scattered, which limits robust meta-analysis and underscores the need for further comprehensive research in the future.

Conclusions

Our systematic review and diagnostic meta-analysis of 38 studies involving approximately 8,000 patients found that on-treatment HBV RNA and HBeAg levels, along with their dynamic changes, are the most reliable indicators for HBeAg loss or seroconversion, while HBsAg decline at week 24 and baseline HBsAg level were the more effective predictors of functional cure compared to novel virologic markers. These findings can help inform future HBV cure clinical development as well as patient selection and individualized strategies for the current PEG-IFN regimen in CHB patients.

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Conflict of interest

The authors declare no conflicts of interest regarding this publication.

Author contributions

Study concept and design (QZ, YZ, MHN), data acquisition (YZ, LFW), data analysis (YZ, JC), drafting of the manuscript (YZ, QC), critically revision of important intellectual content (QZ, MHN, JC), management, technical tasks, and resources (QZ, JC), and supervision (QZ, MHM). All authors substantially contributed to the study and approved the final manuscript.

Ethical statement

This study is a systematic review and meta-analysis based on previously published data, and was carried out in accordance with the Declaration of Helsinki (as revised in 2024). Since no individual patient data were collected or analyzed, ethical approval and informed consent were not required.

Data sharing statement

Supporting data are available from the corresponding author, Qi Zheng, upon reasonable request.

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