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Predictors of relapse after cessation of nucleos(t)ide analog treatment in HBeAg-negative chronic hepatitis B patients: A meta-analysis

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ABSTRACT

Objectives: The aim of this study was to identify the predictors of relapse after the withdrawal of nucleos(t)ide analog (NA) therapy in patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB).

Methods: The PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science databases were searched through January 2019. A random-effects model meta-analysis was performed, with hazard ratios (HR) and 95% confidence intervals (CI) used as summary statistics.

Results: Seventeen studies were included in the meta-analysis. Age (HR = 1.022 per year), baseline hepatitis B surface antigen (HBsAg) (HR = 1.509 per log IU/l), end of treatment (EOT) HBsAg level (HR = 1.896 per log IU/l), EOT HBsAg level ≥1000 IU/ml (HR = 1.749), and HBsAg decline from baseline to EOT (HR = 0.748 per log IU/l) were associated with virological relapse. The predictors of clinical relapse were baseline HBsAg level (HR = 1.312 per log IU/l), EOT HBsAg level (HR = 1.458 per log IU/l), EOT HBsAg level ≥100 IU/ml (HR = 3.199) or ≥1000 IU/ml (HR = 1.810), and duration of consolidation therapy (HR = 0.991 per month).

Conclusions: This meta-analysis indicates that age, the duration of consolidation therapy, and levels of baseline and EOT HBsAg were factors predictive of relapse in HBeAg-negative CHB patients who discontinued NA treatment.

Introduction

Hepatitis B virus (HBV) infection is one of the most common infections, with more than 350 million chronic carriers worldwide, and this rate is estimated to increase by four million per year (Schweitzer et al., 2015). Chronic hepatitis B (CHB) may present either as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative. The latter, which is characterized by the absence of HBeAg, recurrent fluctuations in HBV DNA expression level, and repeatedly elevated levels of alanine aminotransferase (ALT), occurs during the late phase of HBV infection (Hadziyannis and Papatheodoridis, 2006). Patients with this type of CHB are reported to be at higher risk of liver fibrosis, cirrhosis, and liver cancer (Hadziyannis and Papatheodoridis, 2006).

In recent years, the introduction of nucleos(t)ide analogs (NAs) for oral antiviral therapy has dramatically improved the clinical outcomes of patients with CHB, due to the ability of these drugs to profoundly inhibit HBV replication and prevent disease progression to cirrhosis and liver cancer. For patients with HBeAg-negative CHB, the guidelines of European Association for the Study of the Liver (EASL, update 2017) (ref. European Association for the Study of the Liver, 2017) and the American Association for the Study of Liver Diseases (AASLD, update 2015) (Terrault et al., 2016) recommend long-term NA therapy until hepatitis B surface antigen (HBsAg) seroclearance has been achieved. However, the clearance of HBsAg seldom occurs, so this end-point seems unrealistic. Therefore, the guidelines of the Asian Pacific Association for the Study of the Liver (APASL) suggest that the

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discontinuation of NA therapy in patients with HBeAg-negative CHB can be considered after at least 2 years of treatment, if the HBV DNA level remains undetectable after three tests conducted 6 months apart (Sarin et al., 2016). Nonetheless, approximately 25% to 50% of the patients may still develop hepatitis relapse after NA discontinuation, even if they have been treated according to the recommendations of the APASL guidelines (Papatheodoridis et al., 2016).

To date, a number of studies have investigated host and viral factors that predict virological or clinical relapse after NA treatment cessation in HBeAg-negative CHB (Chen et al., 2018; Chen et al., 2015; Chen et al., 2014; Chi et al., 2015; Ge et al., 2015; Ha et al., 2012; Hung et al., 2017; Jeng et al., 2016; Jeng et al., 2013; Jin et al., 2012; Jung et al., 2016; Kang et al., 2017; Lee et al., 2015; Liu et al., 2018a, b; Liu et al., 2011; Papatheodoridis et al., 2018; Patwardhan et al., 2014). Patient characteristics, such as age, sex, and baseline levels of ALT, HBV DNA, and HBsAg, have been analyzed. Additionally, treatment-related factors, including the duration of consolidation therapy, level of HBsAg at the end of treatment (EOT), types of NA, and virus-related factors, such as genotype and mutations, have also been considered. However, these factors and their relationship with relapse are still uncertain because of the various designs, populations, patient characteristics, and sample sizes of the individual studies. Therefore, this systematic review and meta-analysis was performed to evaluate the factors predictive of relapse after the termination of NA therapy in patients with HBeAg-negative CHB. Data from this review might be clinically useful for doctors in the planning of suitable operation schemes.

Methods

With reference to the generally accepted methodology recommendations, this meta-analysis was performed according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The protocol for this study has been published in the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42016037996).

Literature search

A computerized search was performed by two independent investigators (Y.L. and Y.F.F.) in the PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science databases to identify relevant articles published up to January 30, 2019. The following terms were used for the literature search: (“nucleoside analog” or “Nuc” or “lamivudine” or “entecavir” or “adefovir” or “telbivudine” or “tenofovir”) AND (“hepatitis B” or “chronic-hepatitis-B” or “HBV” or “HBeAg-negative”) AND (“relapse” or “recurrence” or “reappear” or “recur”). The limits were “human” and “English”. Studies retrieved from both PubMed and EMBASE were imported into RefWorks (version 1.0; RefWorks, Bethesda, MD, USA), where duplicate articles were manually deleted. Citations initially selected in the systematic search were first retrieved as titles and/or abstracts and screened independently by two reviewers (Y.L. and M.L.J.). The full texts of the potentially relevant reports were then read to determine whether the articles met the necessary inclusion criteria. Moreover, the reference lists of original reports and review articles retrieved by the search were reviewed for additional studies not yet included in the computerized databases.

Trial selection

Studies fulfilling the following inclusion criteria were included in the meta-analysis: (a) original human studies published in English; (b) adult patients with HBeAg-negative CHB before NA treatment; (c) studies providing at least one defined predictor for relapse (e.g., biochemical, clinical, virological relapse) after the cessation of NA treatment; and (d) NA (e.g., lamivudine, adefovir, entecavir, telbivudine) therapy for a minimum mean or median duration of $\geq$6 months. Exclusion criteria were as follows: (a) article types including letters, comments, correspondence, review articles, or case reports; (b) studies based on a small sample size (<10 patients); and (c) articles providing insufficient data or examining irrelevant outcomes. If multiple studies were found to share an identical population, only the most recent publication was included.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (Y.L. and M.L.J.) to acquire the necessary information. The following information was retrieved from each of the included articles: first author’s name, publication year, geographic location of the study, sample size, types of NAs, treatment duration and cessation criteria, definition of relapse, and all factors related to relapse. Any discrepancies between the reviewers regarding the results were resolved after discussion with another author (W.J.).

Quality assessment

The bias within and across studies was assessed by two investigators (Y.L. and M.L.J.) based on the ROBINS-I criteria in Non-Randomized Studies of Interventions by the Cochrane Bias Methods Group (BMG) (Sterne et al., 2016). In reference to the criteria, the overall bias was judged as moderate for all included studies. In the case of disagreement, a third investigator (S.D.W.) was consulted. Studies were considered low quality if they had at least one serious risk of bias and as high or acceptable quality if their risk of bias was low or moderate, respectively.

Statistical analysis

Effect estimates presented as either the hazard ratio (HR) or relative risk (RR) and the associated 95% confidence intervals (CI) for each risk factor and outcome of interest were extracted. When available, the effect estimates from multivariate Cox or logistic regression models were used for this study analysis. For each model, risk factors were only included within the meta-analysis if relevant data from a minimum of two studies were provided. A random-effects model was selected prior to statistical testing for heterogeneity, because the included study protocols varied in potentially important ways (e.g., recruitment setting, length of follow-up). The Chi-square test, tau^2, and the Higgins I^2 test were used to assess heterogeneity (Higgins et al., 2003). The I^2 test is a method for quantifying inconsistency across studies and describes the percentage of variability in effect estimates that is due to heterogeneity. As the patients included in most studies were Asian, subgroup analyses were performed to assess the predictors for the Asian population. A value greater than 50% is considered substantial heterogeneity. A p-value of <0.05 was considered statistically significant. The statistical analysis was performed using Stata software version 10 (Stata Corp., College Station, TX, USA).

Results

Study selection

The study selection process is shown in Figure 1. A total of 1218 publications were potentially relevant to the search terms. After

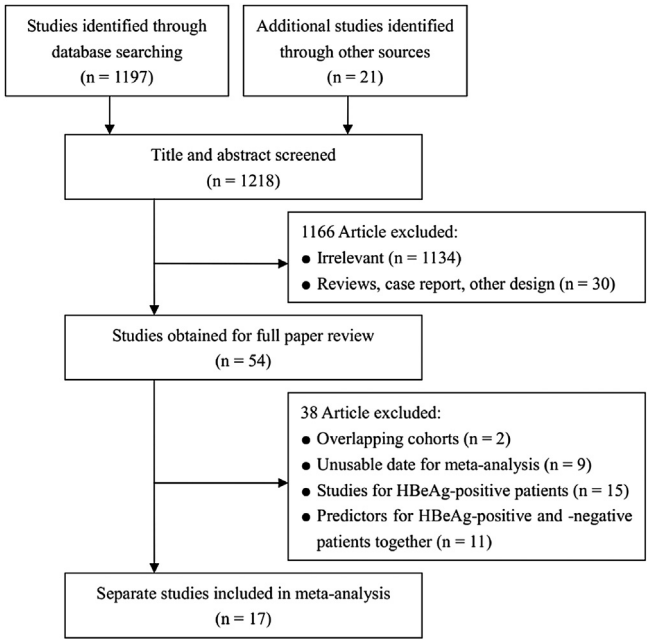

Figure 1. Flow diagram showing the selection of studies for the meta-analysis.

title and abstract screening, 54 potentially relevant studies remained for full review. Of these, 37 were excluded: 15 studies considered HBeAg-positive patients, 11 studies considered HBeAg-positive and HBeAg-negative HBV patients together, nine studies did not provide data suitable for meta-analysis, and two were duplicate studies. Finally, 17 studies were included in the meta-analysis (Chen et al., 2018; Chen et al., 2015; Chen et al., 2014; Chi et al., 2015; Ge et al., 2015; Ha et al., 2012; Hung et al., 2017; Jeng et al., 2016; Jeng et al., 2013; Jin et al., 2012; Jung et al., 2016; Kang et al., 2017; Lee et al., 2015; Liu et al., 2018a, b; Liu et al., 2011; Papatheodoridis et al., 2018; Patwardhan et al., 2014).

Characteristics and quality of the studies

Supplementary Material Table S1 summarizes the main characteristics and quality of the publications included in this meta-analysis. All studies were cohort studies (four prospective (Ha et al., 2012; Liu et al., 2018a, b; Liu et al., 2011; Papatheodoridis et al., 2018), two retrospective–prospective (Jeng et al., 2016; Jeng et al., 2013), and 11 retrospective (Chen et al., 2018; Chen et al., 2015; Chen et al., 2014; Chi et al., 2015; Ge et al., 2015; Hung et al., 2017; Jin et al., 2012; Jung et al., 2016; Kang et al., 2017; Lee et al., 2015; Patwardhan et al., 2014)). The studies were published between 2011 and 2018 and included a total of 1753 patients. Among the 17 included studies, 11 were conducted in China (Chen et al., 2018; Chen et al., 2015; Chen et al., 2014; Ge et al., 2015; Ha et al., 2012; Hung et al., 2017; Jeng et al., 2016; Jeng et al., 2013; Lee et al., 2015; Liu et al., 2018a, b; Liu et al., 2011), three in Korea (Jin et al., 2012; Jung et al., 2016; Kang et al., 2017), one in the USA (Patwardhan et al., 2014), one in Canada/Netherlands (Chi et al., 2015), and one in Greece/Taiwan (Papatheodoridis et al., 2018). The sample size of each study varied greatly, ranging from 33 to 204 patients.

Undetectable HBV DNA was a key biomarker at NA cessation in almost all studies. In more than half of the studies, the cessation criteria were according to the guidelines of the APASL. The mean or median length of follow-up after NA cessation differed among studies, ranging from 12 to 66.8 months. The findings of the risk assessment for bias are summarized in Supplementary Material Table S2. The risk of bias was scored as moderate for 13 studies (Chen et al., 2018; Chen et al., 2015; Chen et al., 2014; Ha et al., 2012; Jeng et al., 2013; Jin et al., 2012; Jung et al., 2016; Kang et al., 2017; Lee et al., 2015; Liu et al., 2018a, b; Liu et al., 2011; Papatheodoridis et al., 2018; Patwardhan et al., 2014) and serious for four studies (Chi et al., 2015; Ge et al., 2015; Hung et al., 2017; Jeng et al., 2016).

Meta-analysis

The following risk factors were examined: age (per year), age (≥40 years vs. <40 years), sex (male vs. female), race (Asian vs.

Table 1
Meta-analysis of predictors of relapse after discontinuation of nucleos(t)ide analog therapy.

Predictors	Virological relapse			Clinical relapse		
	No. study	HR (95% CI)	*p*-Value	No. study	HR (95% CI)	*p*-Value
Age (per year)	10	1.022 (1.001, 1.043)	0.036*	3	1.009 (0.992, 1.027)	0.307
Age (≥40 years vs. <40 years)	3	2.787 (0.658, 11.805)	0.164	–	–	–
Sex (male vs. female)	12	1.035 (0.800, 1.339)	0.794	5	1.101 (0.696, 1.741)	0.681
Race (Asian vs. Caucasian)	2	1.209 (0.208, 7.032)	0.833	–	–	–
Genotype (B vs. C)	4	0.996 (0.794, 1.249)	0.971	2	1.342 (0.443, 4.070)	0.603
Liver cirrhosis (yes vs. no)	4	0.912 (0.489, 1.701)	0.772	–	–	–
Antiviral agents (ETV/TDF vs. LAM/ADV/TBV)	5	0.810 (0.558, 1.177)	0.269	3	0.830 (0.561, 1.229)	0.353
Baseline ALT (per IU/l)	8	1.000 (1.000, 1.000)	0.991	3	0.999 (0.998, 1.001)	0.386
Baseline AST (per IU/l)	3	0.999 (0.996, 1.001)	0.313	–	–	–
Baseline HBV DNA (per log copies/ml)	8	1.006 (0.860, 1.177)	0.942	3	1.059 (0.916, 1.224)	0.440
Baseline HBV DNA ($\geq 2 \times 10^5$ IU/ml vs. $< 2 \times 10^5$ IU/ml)	–	–	–	2	1.732 (0.389, 7.717)	0.471
Baseline HBsAg (per log IU/l)	3	1.509 (1.272, 1.789)	<0.001*	2	1.312 (1.033, 1.666)	0.026*
Total treatment time (per month)	9	1.002 (0.997, 1.008)	0.377	4	1.000 (0.990, 1.010)	0.951
Time to undetectable HBV DNA (per month)	4	1.011 (0.989, 1.035)	0.329	2	0.999 (0.980, 1.019)	0.910
Consolidation therapy duration (per month)	6	0.997 (0.988, 1.006)	0.436	2	0.991 (0.986, 0.995)	<0.001*
Combination with IFN (yes vs. no)	2	1.394 (0.712, 2.732)	0.333	–	–	–
ALT normalization by 3 months (yes vs. no)	–	–	–	2	0.470 (0.143, 1.544)	0.214
HBsAg at month 12 of treatment (per log IU/l)						
EOT HBsAg (per log IU/l)	6	2.057 (1.612, 2.625)	<0.001*	2	1.458 (1.092, 1.946)	0.011*
EOT HBsAg (≥100 IU/ml vs. <100 IU/ml)	2	1.220 (0.609, 2.444)	0.575	3	3.199 (1.755, 5.829)	<0.001*
EOT HBsAg (≥1000 IU/ml vs. <1000 IU/ml)	3	1.749 (1.227, 2.495)	0.002*	2	1.810 (1.008, 3.250)	0.047*
HBsAg decline from baseline to EOT (per log IU/l)	3	0.748 (0.587, 0.954)	0.019*	–	–	–

HR, hazard ratio; CI, confidence interval; ETV, entecavir; TDF, tenofovir; LAM, lamivudine; ADV, adefovir; TBV, telbivudine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; INF, interferon; EOT, end of treatment.
* Significant association with relapse.

Caucasian), baseline ALT (per IU/l), baseline aspartate aminotransferase (AST, per IU/l), baseline HBV DNA (per log copies/ml), baseline HBV DNA ($\geq 10^5$ IU/ml vs. $< 10^5$ IU/ml), baseline HBsAg (per log IU/l), liver cirrhosis (yes vs. no), antiviral agents (entecavir (ETV)/(tenofovir) TDF vs. lamivudine (LAM)/adefovir (ADV)/LDT), total treatment time (per month), time to undetectable HBV DNA (per month), genotype (B vs. C), combination with interferon (IFN) (yes vs. no), duration of consolidation therapy (defined as continued treatment after the first undetectable HBV DNA, per month), ALT normalization within 3 months on-therapy (yes vs. no), EOT HBsAg (per log IU/l), EOT HBsAg (≥100 IU/ml vs. <100 IU/ml) and EOT HBsAg (≥1000 IU/ml vs. <1000 IU/ml), HBsAg at month 12 of treatment (per log IU/l), and HBsAg decline from baseline to EOT (per log IU/l).

Table 1 presents the pooled estimates for all associated factors reported in two or more studies. From the pooled analyses, age (per year; HR = 1.022, 95% CI 1.001 to 1.043; Figure 2), baseline HBsAg (per log IU/l; HR = 1.509, 95% CI 1.272 to 1.789; Figure 3), EOT HBsAg level (per log IU/l; HR = 1.896, 95% CI 1.513 to 2.377; Figure 4), EOT HBsAg level ≥1000 IU/ml (HR = 1.749, 95% CI 1.227 to 2.495; Supplementary Material Figure S1), and HBsAg decline from baseline to EOT (per log IU/l; HR = 0.748, 95% CI 0.587 to 0.954; Supplementary Material Figure S2) were associated with virological relapse. Moreover, the predictors of clinical relapse were baseline HBsAg level (per log IU/l; HR = 1.312, 95% CI 1.033 to 1.666; Figure 3), EOT HBsAg level (per log IU/l; HR = 1.458, 95% CI 1.092 to 1.946; Figure 4), EOT HBsAg level ≥100 IU/ml (HR = 3.199, 95% CI 1.755 to 5.829; Supplementary Material Figure S3) or ≥1000 IU/ml (HR = 1.810, 95% CI 1.008 to 3.250; Supplementary Material Figure S1), and duration of consolidation therapy (per month; HR = 0.991, 95% CI 0.986 to 0.995; Figure 5). Furthermore, similar results were observed in subgroup analyses focusing on the Asian population (Table 2).

There were many risk factors for relapse among the selected studies for which the data could not be pooled because they were reported in only one study. Supplementary Material Table S3 details these risk factors for each outcome studied.

Discussion

Based on published data from 14 articles, the meta-analysis showed that older age, higher levels of HBsAg at baseline and EOT, and shorter duration of consolidation therapy are factors predictive of relapse after off-therapy NAs in HBeAg-negative CHB patients. Moreover, similar results were observed in subgroup analyses focusing on the Asian population. This meta-analysis provides important information for physicians determining whether or not to discontinue NAs.

An important finding of the meta-analysis was that age may serve as an independent predictive factor for virological relapse in HBeAg-negative CHB patients after NA discontinuation. One explanation for this result may be that younger age simply means a shorter period of infection and therefore easier viral clearance. On the other hand, younger patients have a more powerful immune system than older patients, which is responsible for the final eradication of the virus (Liu et al., 2011). However, the cutoff value of age for NA cessation was still inconsistent. Age ≥40 years was not identified as a predictor in the current meta-analysis, which included three studies. Ha et al. (Ha et al., 2012) demonstrated that the discontinuation of adefovir may be considered for patients aged <25 years after receiving a minimum course of 24 months and achieving undetectable HBV DNA for at least 18 months before cessation. In another prospective study conducted in China, Liu et al. (2011) suggested that age 20 years may serve as a cutoff value for a sustained response in HBeAg-negative CHB patients after lamivudine withdrawal according to

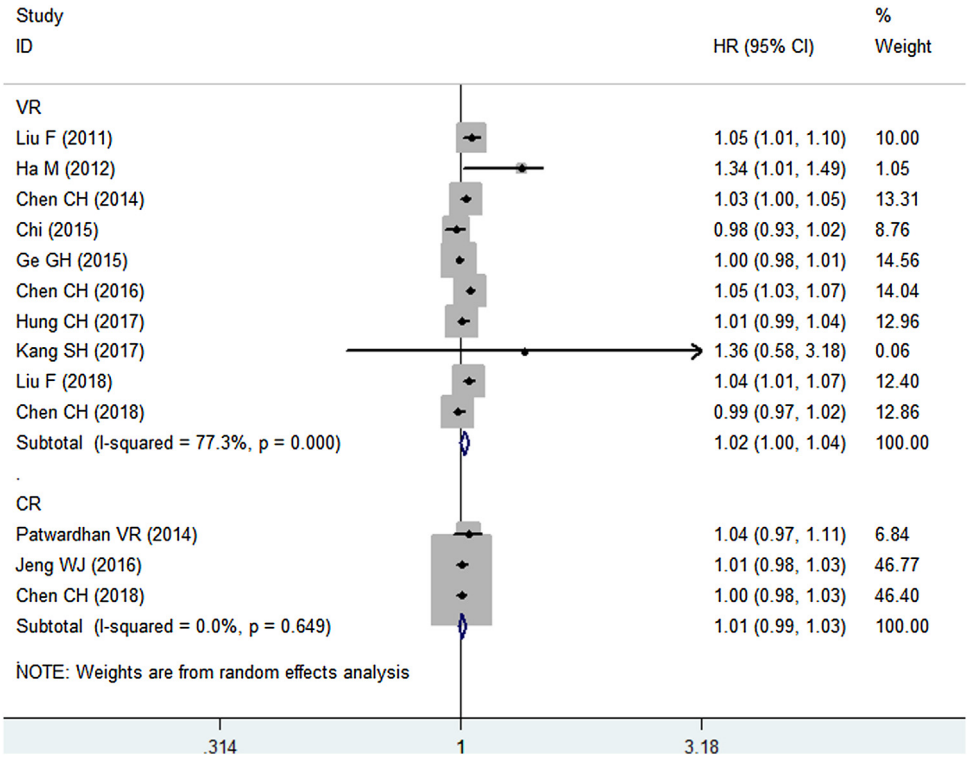

Figure 2. Forest plots for the association of age with virological relapse (VR) and clinical relapse (CR).

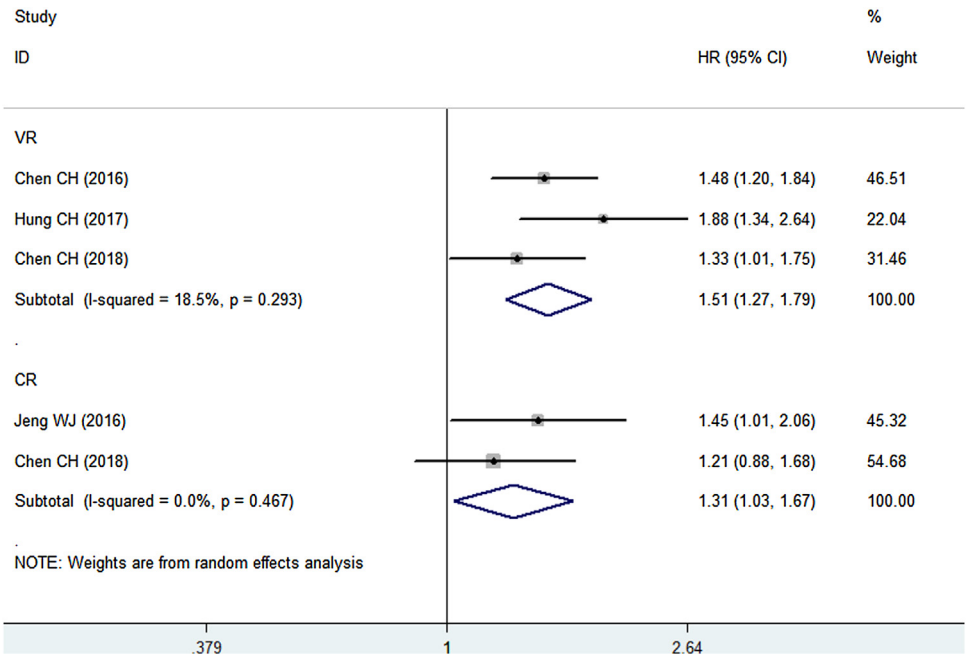

Figure 3. Forest plots for the association of the baseline level of HBsAg (per $\log_{10}$ IU/l) with virological relapse (VR) and clinical relapse (CR).

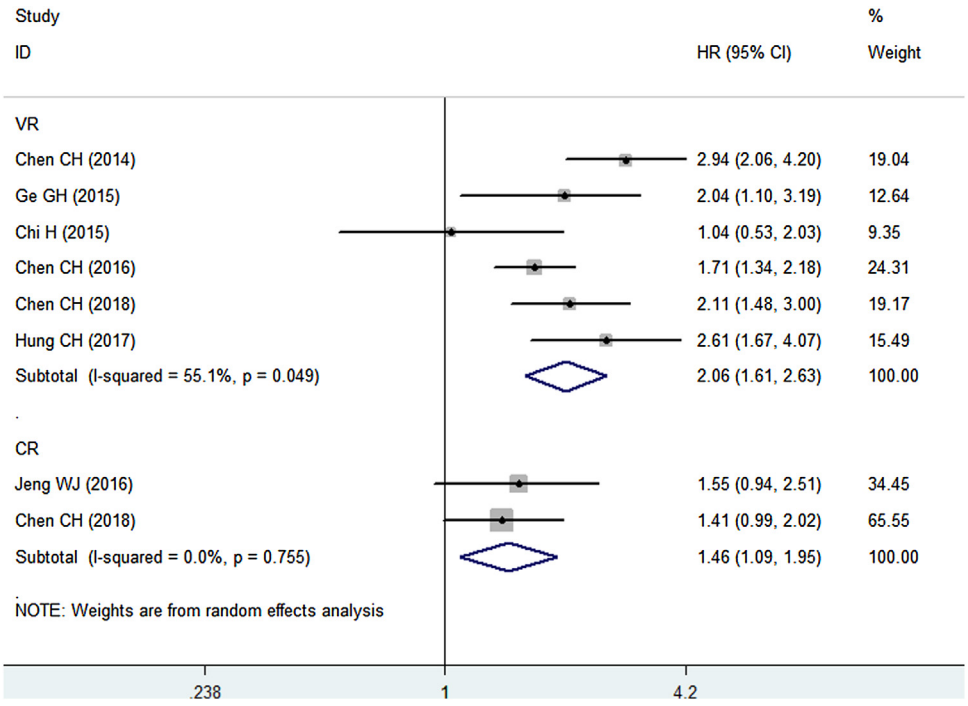

Figure 4. Forest plots for the association of end of treatment HBsAg level (per $\log_{10}$ IU/l) with virological relapse (VR) and clinical relapse (CR).

cessation criteria similar to Ha et al. Therefore, identifying an optimal cutoff value for age is essential to predict post-treatment HBV relapse in HBeAg-negative patients.

HBsAg loss and/or HBsAg seroconversion is considered the closest to a cure outcome in chronic HBV infection and the gold standard of current therapies, particularly in difficult-to-treat patients with HBeAg-negative CHB (European Association for the Study of the Liver, 2017; Sarin et al., 2016; Terrault et al., 2016). The ability of HBsAg to predict relapse is probably attributed to its correlation with intranuclear covalently closed circular DNA, which in turn gauges the immune control of the virus. However, HBsAg loss is a rare event in HBeAg-negative patients during NA therapy and is not realistic as a national policy in countries with prevalent CHB (Lim et al., 2015). The present meta-analysis from the current evidence showed that higher levels of HBsAg at baseline and EOT were associated with a higher probability of relapse after the cessation of NA treatment. These results are consistent with those of a recent systematic review, which concluded that HBsAg levels <100 IU/ml at EOT were a useful marker for the discontinuation of NA therapy for both HBeAg-positive and HBeAg-negative CHB patients (Liu et al., 2018a, b). Moreover, patients with lower EOT HBsAg levels were found to be

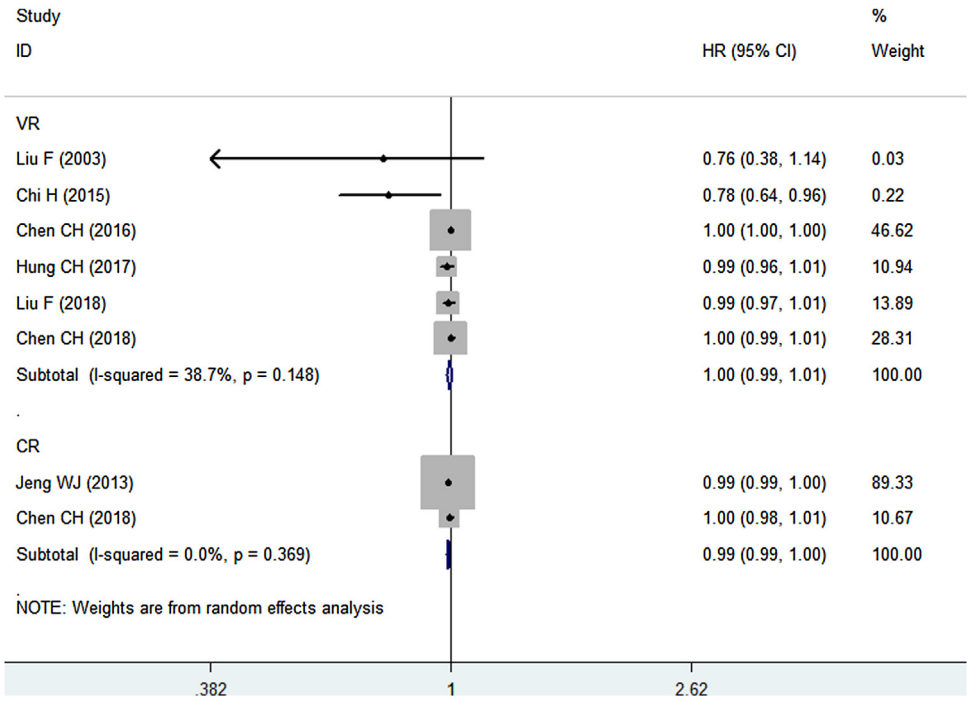

Figure 5. Forest plots for the association of the duration of consolidation therapy (per month) with virological relapse (VR) and clinical relapse (CR).

Table 2
Meta-analysis of predictors for relapse after discontinuation of nucleos(t)ide analog therapy in the Asian population.

Predictors	Virological relapse			Clinical relapse		
	No. Study	HR (95% CI)	*p*-Value	No. Study	HR (95% CI)	*p*-Value
Age (per year)	9	1.026 (1.005, 1.048)	0.017*	2	1.007 (0.989, 1.026)	0.454
Sex (male vs. female)	11	1.059 (0.804, 1.395)	0.682	4	1.097 (0.644, 1.867)	0.734
Liver cirrhosis (yes vs. no)	3	1.117 (0.735, 1.699)	0.604	–	–	–
Antiviral agents (ETV/TDF vs. LAM/ADV/TBV)	3	0.842 (0.524, 1.351)	0.475	2	0.897 (0.556, 1.446)	0.655
Baseline ALT (per IU/l)	7	1.000 (1.000, 1.000)	0.991	2	1.000 (1.000, 1.000)	1.000
Baseline HBV DNA (per log copies/ml)	7	1.010 (0.849, 1.202)	0.912	2	1.065 (0.873, 1.301)	0.534
Total treatment time (per month)	8	1.007 (0.993, 1.020)	0.324	2	1.006 (0.972, 1.041)	0.736
Consolidation therapy duration (per month)	5	0.999 (0.995, 1.003)	0.555	–	–	–
EOT HBsAg (per log IU/l)	5	2.189 (1.759, 2.723)	<0.001*	–	–	–

HR, hazard ratio; CI, confidence interval; ETV, entecavir; TDF, tenofovir; LAM, lamivudine; ADV, adefovir; TBV, telbivudine; ALT, alanine aminotransferase; HBV, hepatitis B virus; EOT, end of treatment; HBsAg, hepatitis B surface antigen.
*Significant association with relapse.

more likely to lose HBsAg after discontinuing NA therapy, which results in stable remission of the disease (Hung et al., 2017).

Currently, there is no clear consensus on the optimal duration of oral antiviral therapy with NAs for patients with HBeAg-negative CHB. The results of the meta-analysis demonstrated that neither total treatment duration nor additional treatment was associated with post-treatment relapse, although a shorter duration of consolidation therapy seems to be associated with higher clinical relapse. In general, longer treatment durations contribute to suppression of viral replication and clearance of infected hepatocytes (Zeuzem et al., 1997). However, HBV cannot be completely eradicated without an effective immune response from the host. The immune responses to replicating HBV are much stronger in the absence of HBeAg than in its presence. In addition, lamivudine was used in most of the studies included in the current meta-analysis, which has been associated with progressively increasing rates of viral resistance due to mutations within the YMDD motif of the HBV polymerase gene after long-term monotherapy (Papatheodoridis et al., 2002). Chi et al. reported that prolonged consolidation therapy beyond 3 years resulted in a reduction in virological relapse and additional HBsAg loss (Chi et al., 2015). More prospective studies are warranted to confirm the effects of long-term NA consolidation therapy (≥3 years) on off-treatment responses.

The baseline levels of HBV DNA, ALT, and AST were not significantly associated with off-therapy relapse. Moreover, the time to HBV DNA suppression (undetectable) or ALT normalization (within 3 months) during treatment was not a predictive factor for post-treatment relapse. Although patients with a low viral load before treatment (i.e., DNA $\leq 2 \times 10^5$ copies/ml) or stronger endogenous antiviral defenses (i.e., ALT more than five times the upper limit of normal (ULN)) were similar in their achievement of a sustained off-treatment response, further studies are needed to draw definitive conclusions.

One factor that has not been sufficiently addressed is the effect of NA combined with IFN treatment on the rate of relapse. A recent meta-analysis showed that NA combined with IFN therapy was more effective than NA monotherapy for HBeAg-positive CHB (Wei et al., 2015). Unfortunately, only two studies on this issue were included in the present meta-analysis, and no significant

association was detected. These findings should be validated in a multicenter randomized trial.

The results of this study should be interpreted in view of certain limitations. First, most studies included in this meta-analysis were retrospective; such studies may be limited by historical accuracy due to recall bias, imperfect information within medical records, and loss to follow-up. Second, definitions of cessation criteria were adopted in these studies and varied widely. Unfortunately, we were unable to pursue any further analysis of the risk factors for relapse due to the limited number of related studies. Finally, various NAs were used among the studies, although the type of NA was not a predictor of the relapse rate in the current meta-analysis.

In conclusion, although the interpretation of the study findings may be restrained by the heterogeneity and other methodological limitations of the available evidence, the findings suggest that age, the level of HBsAg at baseline and EOT, and a shorter duration of consolidation therapy are useful predictors of relapse after NA cessation. Longer follow-up of a larger number of patients is needed to confirm the findings and to further refine the criteria for NA withdrawal in patients with HBeAg-negative CHB.

Author contributions

Wei Jiang and Yifan Feng were responsible for the study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and obtaining funding. Yun Liu, Minglei Jia, and Wei Jiang performed the literature search. Yun Liu, Minglei Jia, and Wei Jiang carried out the data extraction and statistical analysis. Yun Liu, Minglei Jia, and Shengdi Wu performed the quality assessment. Yun Liu and Minglei Jia wrote the manuscript. All authors read and approved the final manuscript.

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Ethical approval

All analyses were based on previously published studies, thus no ethical approval or patient consent was required.

Conflict of interest

All authors declare no conflict of interest, including financial and/or material support for the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.07.036.

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