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Spontaneous Loss of Surface Antigen among Adults Living with Chronic Hepatitis B Virus Infection: A Systematic Review and Pooled Meta-Analyses

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Abstract

Background—Spontaneous loss of hepatitis B surface antigen (HBsAg), or functional cure, in patients with chronic hepatitis B (CHB) significantly reduces liver-related complications. Differential rates have been suggested by individual studies performed in non-endemic and endemic regions, potentially related to likelihood of spontaneous clearance if CHB was acquired as an adult versus child. We systematically determined a pooled annual rate of HBsAg loss in untreated CHB-infected adults and examined impact of regional endemicity.

Methods—Pubmed/EMBASE were searched for observational cohort studies and non-treatment arms of randomized controlled trials (RCTs) reporting proportion of patients with CHB achieving spontaneous HBsAg loss. RCTs were excluded from meta-analyses due to substantial cohort differences. Results were stratified on whether the underlying cohort primarily arose from an endemic, defined as CHB prevalence >2%, or non-endemic region. We explored sources of heterogeneity through univariate meta-regression.

Results—Of 4771 screened, 66 studies (11 RCTs, 38 prospective and 17 retrospective cohort studies) met inclusion criteria and 55 were included in meta-analyses with exclusion of RCTs. Spontaneous HBsAg loss occurred in 3489 (7.6%) of 45,975 patients with 341,862 person-years of follow-up. The pooled annual incidence rate of HBsAg loss was 1.13% (0.92–1.36%, I^2=96%). Rates did not differ by endemicity: 1.13% (0.85–1.45%) in endemic vs 1.29% (0.99–1.62%) in non-endemic cohorts. Meta-regression showed proportion of cohort HBeAg-negative and cohort age were primary contributors to substantial heterogeneity.

Conclusion—Globally, spontaneous HBsAg loss occurs infrequently (~1% per year) in treatment-naïve adults with CHB infection. The low and homogeneous rate of HBsAg loss

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Contributors

KZ, CC, and NT were responsible for the study design. KZ, CC, EW and NT performed the literature search. KZ, CC, and NT did the data collection. KZ and NT did the data analysis, interpretation and creation of figures. KZ, CC and NT wrote the manuscript.

Declaration of interests

KZ, CC and EW have no conflicts to report. NT reports grant support from Gilead Sciences and BMS.

highlights the need for new therapeutics aimed at achieving functional cure across different patient profiles and geographic regions.

Keywords

hepatitis B virus (HBV) infection; meta-analysis; hepatitis B surface antigen loss or seroclearance

Introduction

Chronic hepatitis B (CHB) virus infection impacts an estimated 240 million individuals worldwide and is a leading cause of cirrhosis and hepatocellular carcinoma (HCC), the fifth most common cancer globally(1, 2). Burden of CHB infection, despite introduction of effective hepatitis B virus (HBV) vaccine three decades ago, endures as a pressing public health concern, particularly in endemic regions of Asia and sub-Saharan Africa(3).

Seroclearance or loss of circulating hepatitis B surface antigen (HBsAg), with or without development of antibodies to surface antigen, signifies profound suppression of viral replication and is an important, if infrequent, achievement in the natural history of CHB infection. Mechanism of spontaneous loss of HBsAg is poorly understood but likely relates to a gradual decline out of HBsAg transcription, disruption of transcription from integrated viral genomes, and the slow process of cccDNA loss(4). Spontaneous HBsAg loss typically occurs after a long period of sustained inactive disease, characterized by hepatitis B e-antigen negativity, low levels of viremia, and minimal if any progression of fibrosis(5). The term “functional cure” has been ascribed to loss of HBsAg, either spontaneous or with treatment, as risk of cirrhosis, if not already present, becomes negligible and development of HCC is reduced by over 60%(6). It is not, however, considered a true cure since viral covalently closed circular DNA (cccDNA) can persist within hepatocytes despite clearance of both viral DNA and antigen from serum, and reactivation with reversion to positive HBsAg can occur if host immunity is disrupted(7).

Early reports on CHB-infected cohorts indirectly suggested geographical disparities in the frequency of HBsAg loss, with higher rates of loss in non-endemic(8) than endemic regions(9) (>1% vs. <1%, respectively) reported in individual studies. One proposed explanation was age at CHB acquisition, with infections occurring predominantly in neonates/infancy in endemic regions compared to adults in non-endemic regions. Age-dependent immunity to HBV is well-established, with 95% of acutely infected adults clearing infection compared to only 10% of neonates(10). Natural history also differs as the decades long immune-tolerant period in those infected as neonates is short or non-existent in adults(10). Maturity as well as the diversity of the immune response in adults, therefore, could plausibly lead to higher rates of HBsAg loss in non-endemic regions(11). However, more recent studies from Asia demonstrating comparatively equivalent rates of HBsAg loss suggest duration of follow-up and underlying distribution of cohort characteristics may play a larger role in previously identified regional differences(12).

As we move towards loss of HBsAg rather than viral suppression as the therapeutic endpoint for novel CHB therapeutics, establishing a baseline rate of spontaneous HBsAg loss, for the large population of patients with inactive and indeterminant CHB who do not meet current

treatment criteria, as a point of comparison is crucial(13). As yet, a systematic effort to pool rates of spontaneous HBsAg loss has not been undertaken. In this systematic review of published literature, we performed pooled meta-analyses of annual rates of HBsAg loss in CHB cohorts with longitudinal follow-up. In addition, we examined potential drivers of variation in rate estimates, with a focus on impact of regional endemicity.

Methods

Search strategy and selection criteria

A systematic review and meta-analysis was carried out to estimate a pooled annual rate of HBsAg loss among treatment-naïve adults with CHB infection (PROSPERO #CRD42018074086). A literature search was completed on September 9th, 2017 within PubMed and EMBASE. A combination of search terms relating to “chronic hepatitis B,” “surface antigen,” and “seroclearance or loss” was used and is detailed in Appendix p1. Additional citations were identified via manual search of references from included articles. If necessary, authors were contacted directly for additional details.

We searched for observational cohort studies and non-treatment arms of randomized controlled trials that reported outcome of HBsAg loss. Abstracts were included if sufficient data were presented. Case-control and cross-sectional studies, reviews, and dissertations/theses were excluded. All studies had cohorts with confirmed chronic infection. Often multiple studies reported HBsAg loss using the same cohort; we selected the study with the longest duration of follow-up for inclusion. Furthermore, studies that reported on a subgroup (i.e. HBeAg-negative only or inactive carriers) of an already included cohort were accepted for subgroup analysis only, but excluded from overall analysis to avoid duplication.

The following exclusion criteria were applied to reduce heterogeneity and allow for pooling of comparable studies: 1) studies with greater than 10% of cohort undergoing either oral nucleot(s)ide or interferon treatment during follow-up to limit influence of on-treatment rates of HBsAg loss; 2) studies with sample size less than 20 individuals; 3) studies with duration of follow-up less than one year; 4) CHB subpopulations including acute infection, post-liver transplant, hepatocellular carcinoma, decompensated cirrhosis, and hemodialysis; 5) pediatric cohorts, although we did include cohorts with an age range lower limit of 12 years; 6) non-English publications; and 7) insufficient reporting of outcome data for extraction. Cohorts comprised exclusively of co-infected patients with human immunodeficiency virus (HIV), hepatitis D virus (HDV) and/or hepatitis C virus (HCV) were excluded, but otherwise included. Cohorts derived from pregnant women and compensated cirrhotics were permitted.

Data extraction

Titles, abstracts and full-texts were sequentially screened by two reviewers (KZ, CC) and disagreements resolved by a third reviewer (NT). Two reviewers (KZ, CC) independently extracted data from accepted full-text studies, with discrepancies discussed with the third reviewer (NT). The following study variables were extracted: authors, journal of publication, publication year, study design, study country and region, population, inclusion and exclusion

criteria, type and timing of HBsAg testing, and definition of HBsAg loss. Cohort variables included mean age, sex, race, proportion HBeAg-negative, and proportion with co-infection. Outcome measures included annual incidence rate, total cohort sample size, number with HBsAg loss, and duration of follow-up (mean or person-years when provided). When an annual incidence rate was not reported, this outcome was calculated using number with HBsAg loss as the numerator, and either total cohort size*mean duration of follow-up or reported person-years of follow-up as denominator. Additionally, we extracted number with positive HBV DNA at time of HBsAg loss and number with positive surface antibody (anti-HBs) when reported.

Data analysis

We calculated a pooled annual rate of HBsAg loss using a random-effects meta-analysis with the Freeman-Tukey double-arcsine transformation to allow for studies with zero events and to stabilize variances(14). Due to substantial qualitative differences in cohorts arising from RCTs, with primarily immune-active patients and short duration of follow-up, and lack of overlap when results were stratified by study design (see Appendix p2), an overall pooled rate was reported with exclusion of RCTs, and RCTs were also excluded from subsequent subgroup meta-analyses. We reported pooled estimates for the following subgroups: HBeAg-negative cohorts, HBeAg-positive cohorts, and inactive carriers. Inactive carriers were defined as cohort inclusion criteria of HBV DNA<2000 IU/mL and normal ALT. Pooled estimates were also stratified by World Health Organization (WHO) region and by endemicity of the underlying study cohort. A study cohort was considered endemic by default if the CHB seroprevalence of the country in which the study was performed was greater than 2% based on a published systematic review of country-level estimates of CHB prevalence(2) or if a prevalence rate >2% was stated by the study for the specific region studied. In addition, a study was categorized as endemic (regardless of study country endemicity) if the underlying cohort was comprised of immigrants from an endemic region, and vice versa. Studies that did not report race or were of mixed endemicity (included individuals from both endemic and non-endemic regions) were excluded from this subgroup meta-analysis.

Statistical heterogeneity was assessed using I^2 test(15). We performed univariate meta-regression to examine the influence of study and cohort level factors on heterogeneity. Study level factors included study design, region, type of HBsAg test, and definition of HBsAg loss. Cohort level factors included endemicity, proportion HBeAg-negative, mean cohort age, proportion male, duration of follow-up, and cohort inclusion of co-infected or treated individuals. We also examined impact of cohorts that did not report co-infection testing or treatment status. Publication bias was assessed using a funnel plot and Egger's test(16). We also plotted log of outcome against study size with Peter's test as a secondary test for publication bias, as standard tests may not be reliable in pooled incidence meta-analyses(17). Methodologic quality of included studies was assessed using a tool adapted from Hoy et al (available in Appendix p3) (18). All analyses were conducted in STATA version 14.0 (College Station, TX).

Results

A total of 4771 studies were screened for inclusion, with 73 (1.5%) studies meeting eligibility criteria. Of the 73 studies, 7 were subgroup analyses of an already included cohort, resulting in 66 primary studies that met eligibility criteria(8, 12, 19–81). Characteristics of these 66 studies are summarized in Appendix p4–5. With exclusion of the 11 RCTs, there were a total of 55 cohort studies, 38 being prospective and 17 retrospective, that were further included in meta-analyses (Figure 1). Studies originated from 22 individual countries representing five WHO regions (see Appendix p6–7). The represented WHO regions included Western Pacific (n=30, 45%), European (n=23, 35%), Americas (n=9, 14%), South East Asian (n=2, 3%) and Eastern Mediterranean (n=2, 3%).

Of 55 cohort studies included in meta-analyses, 34 (62%) studies described HBsAg loss in cohorts with both HBeAg-negative and HBeAg-positive individuals compared to 17 (31%) with HBeAg-negative individuals only, 2 (4%) with HBeAg-positive only, and HBeAg status was not reported in 2 (4%) studies. Most studies (n=41, 75%) defined HBsAg loss as a one-time negative measurement of HBsAg. The other 14 studies used an outcome of sustained HBsAg loss, defined as at least two consecutive negative measurements, typically at least 6 months apart, and remaining negative until the end of follow-up. Ten studies included treated patients (although less than 10% of the cohort per inclusion criteria) and treatment status was unclear in 17 studies. In studies with treated patients, 4 included oral antivirals(35, 56, 62, 81), 3 interferon therapy(20, 35, 38) and 4 either did not specify(26, 65, 72) or included older non-standard drugs(77). Co-infected patients were not excluded in 17 studies and either not reported or not tested in 7 studies. Three studies evaluated HBsAg loss in compensated cirrhotics(34, 51, 61), and one study included only pregnant women(42). Ten studies provided baseline quantitative HBsAg (qHBsAg) levels, with 9 studies reporting an independent negative association between baseline qHBsAg and subsequent HBsAg loss(20, 23, 26, 40, 42, 47, 65, 74, 75).

Annual rates of spontaneous HBsAg loss

Of 45,975 patients with 341,862 person-years of follow-up, 3489 (7.6%) experienced spontaneous HBsAg loss. The pooled annual incidence rate (n=55 studies) was 1.13% (95% CI 0.92–1.36%, I^2=96%) (see Figure 2). Subgroup analysis by HBeAg status and inactive carrier cohorts are presented in Figure 3. The pooled annual incidence rate was 1.36% (95% CI 1.09–1.67%, I^2=95%) in HBeAg-negative cohorts (n=25) and 0.74% (95% CI 0.11–1.80%, I^2=92%) in HBeAg-positive cohorts (n=5). Eight studies used a strict definition for inactive carriers (HBV DNA<2000 IU/mL and normal ALT) for cohort inclusion, resulting in a pooled rate of 1.25% (95% CI 0.98–1.54%, I^2=22%).

Rates were similar when stratified by either WHO region or regional endemicity of study cohort (Figure 4). The annual rate was 1.13% (95% CI 0.83–1.47%), 1.01% (95% CI 0.80–1.25%) and 1.11% (95% CI 0.63–1.73%) for WHO Western Pacific, European, and Americas regions, respectively. Summary measures from South East Asian and Mediterranean regions were not presented due to insufficient number of studies for pooling. No statistical difference was observed by regional endemicity: endemic cohorts had an annual rate of 1.13% (95% CI 0.85–1.45%) compared to 1.29% (95% CI 0.99–1.62%) in

non-endemic cohorts. The annual incidence of HBsAg loss ranged 0.8–1.4% among three studies performed in treatment-naive compensated cirrhotics(34, 51, 61).

Twenty-six studies(8, 19, 21, 24, 27–29, 32, 33, 36, 37, 40, 42, 44, 46, 50, 51, 57, 58, 61, 62, 68, 73, 74, 77, 80) reported the proportion of individuals with anti-HBs concurrent with or after loss of HBsAg and 9 studies(19, 28, 37, 38, 43, 45, 58, 72, 73) tested HBV DNA at time of HBsAg loss. From those studies, a pooled 50.3% (95% CI 40.7–60%) with HBsAg loss developed anti-HBs and 5% (95% CI 0.5–12.5%) had detectable HBV DNA at time of HBsAg loss.

Sources of heterogeneity (meta-regression)

Results of meta-regression are available in Appendix p8. The primary sources of heterogeneity were proportion of cohort HBeAg-negative and cohort age. There was a positive association between both proportion of cohort HBeAg-negative and mean cohort age with rate of HBsAg loss (see Appendix p9). When categorized, cohorts with greater than 50% of individuals HBeAg-negative at start of follow-up had higher rates than cohorts with less than 50% (p=0.04). Similarly, studies with mean cohort age older than 40 years had a 1.7-fold higher rate of HBsAg loss than studies with cohorts younger than 40 (p=0.03), corresponding to an annual rate of 1.6% vs 1.1% in cohorts older than 40 and younger than 40, respectively. There were also higher rates of HBsAg loss reported in observational cohort studies compared to RCTs, although this did not reach statistical significance (p=0.06). Study-level factors that were not statistically significant in meta regression included type of HBsAg test (Abbott vs other), definition of HBsAg loss (one time versus multiple negative), and study region; cohort-level factors included proportion male, endemicity, follow-up time, inclusion of co-infection and inclusion of studies with treated individuals.

Quality assessment and bias

Overall quality of studies was limited by observational nature, which are at higher risk for bias from incomplete data or follow-up. However, prospective studies were more frequent than retrospective studies. For the majority of studies, consecutive recruitment was employed with clear descriptions of inclusion and exclusion criteria, diminishing the potential for selection bias. Instead of HBsAg testing at specified intervals, a few studies performed a one-time test in all patients that followed up and only included patients that received the test in their cohort, with time-of-follow-up spanning from entry into cohort to date of one-time testing. This method prevented potential competing risks such as liver transplant, loss to follow-up and death from influencing estimates. Full quality assessment of included studies is available in Appendix p10–11. Ten studies were found to be at high-risk of bias, 22 moderate-risk and 23 low-risk. There was no strong evidence of publication bias as visualized on the funnel plot and by statistical testing (see Appendix p12).

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Discussion

For adults living with CHB infection, loss of HBsAg, or functional cure, is a highly desired outcome as functional cure carries an excellent prognosis, with few developing cirrhosis, decompensation or HCC with long-term follow-up(82, 83). To our knowledge, this is the first systematic effort to characterize the frequency of spontaneous HBsAg loss. Data from over 45,000 individuals and across a diverse range of studies yielded a pooled seroclearance rate of 1.13% per year. Regional and cohort endemicity did not influence this rate. Even in inactive carrier cohorts, with the highest likelihood of achieving spontaneous HBsAg loss, the pooled annual rate was low at 1.25%. Notably, heterogeneity in underlying cohort distributions and outcome assessment was substantial and findings need to be interpreted within this context. Unfortunately, achieving functional cure remains a hard-to-reach endpoint even for CHB patients on treatment. Studies of on-treatment rates of HBsAg loss in immune-active patients have shown even lower rates than spontaneous loss with oral nucleos(t)ides, the largest study of over 5000 patients reporting only a 0.3% annual rate of loss(84), with up to 9% reported on combination therapy with pegylated-interferon, an uncommonly used drug in clinical practice(85). New highly effective and safe antivirals are urgently needed to augment functional cure rates for all patients living with CHB.

We did not find a higher rate of HBsAg loss in non-endemic regions, as previously proposed. Results of our meta-regression show some of the variation in reported rates of HBsAg loss can be attributed to cohort characteristics that have maximal impact on likelihood of loss. As expected, rate of HBsAg loss is a function of the percentage of the cohort that starts off HBeAg-negative. In our pooled meta-analyses, annual rate of HBsAg loss was 1.35% vs 0.74% in HBeAg-negative and HBeAg-positive cohorts, respectively. In East Asia where vertical transmission dominates, HBeAg seroconversion commonly occurs in the 2nd to 3rd decade and rates of HBsAg loss peak in the 5th decade, which suggests at least 10–20 years of disease inactivity typically precedes loss(12). Follow-up time in predominantly HBeAg-positive cohorts would therefore need to be much longer to achieve similar rates of HBsAg loss as HBeAg-negative cohorts. At a macro-level, we also corroborate findings from individual studies that HBsAg loss correlates with age(12, 36, 45, 46). However, it is unclear whether the relationship of age to seroclearance is related to the duration of inactive disease or the changes in viral immunogenicity and host immune responses accompanying that phase of infection. In a study of 483 individuals with CHB in Taiwan, younger age (by decade) at time of HBeAg seroconversion was associated with decreased risk of cirrhosis and HCC, but interestingly 15-year cumulative incidence of HBsAg loss was similar across age categories(86), providing support for length of time with inactive disease being more important than age. A deeper understanding of the viral and immunologic changes that occur with age and with phase transitions of CHB infection will be important for future therapeutic interventions that target HBsAg loss.

We found a paucity of data on HBsAg loss from highly endemic regions with low-to-middle income countries such as Southeast Asia and sub-Saharan Africa. A single study from Africa was identified during full-text selection, but unfortunately excluded from meta-analyses as over 50% of the cohort was less than 14 years old. This study performed in The Gambia, a West African country with an HBV seroprevalence of 12%, included 405 CHB-

infected participants followed for a median of 28 years and reported a consistent 1% HBsAg loss per year(87). Route and timing of transmission, either neonatal or in childhood, is difficult to accurately ascertain and is usually presumed based on geographic location and underlying prevalence. In Africa, horizontal transmission in childhood is predominant; the 1% annual rate of HBsAg loss reported in Gambia suggests similar rates between vertical and horizontal transmission. Possible reasons for the lack of published studies on HBsAg loss in these key regions include limited infrastructure for clinical research and more limited capacity for frequent serologic testing. Data from these regions on frequency and predictors of HBsAg loss are still important. For example, the contribution of aflatoxin to liver fibrosis progression and natural history of genotype E, not present in East Asia, including rates of seroclearance can only be clarified in these regions(88).

Three studies examined annual incidence of HBsAg loss in cirrhotics, reporting a range of 0.8–1.4%, similar to the 1.1% overall rate. In the majority of included studies with assessments of cirrhosis (either US, elastography, or histology), few with HBsAg loss had evidence of cirrhosis at baseline or at time of seroclearance. However, a high proportion with cirrhosis at time of seroclearance, ranging 15–35%, has been reported(19, 28, 50, 70). Incident cirrhosis after seroclearance was rare(43, 61), and cirrhotics with seroclearance had improved prognosis compared to those without(50). Cirrhosis as a predictor of HBsAg loss remains controversial, considering the long duration of infection prior to loss in most patients. Some included studies reported liver cirrhosis as a factor associated with HBsAg loss(27, 47), whereas many others showed no association(62, 65, 71, 73). In addition, while the risk of HCC is clearly ameliorated with HBsAg loss, it is much less so among cirrhotics and patients older than 50(7). Thus, younger patients who incur the most benefit from HBsAg loss unfortunately have the lowest potential to achieve it spontaneously.

While the rigorous and comprehensive approach of our study delivers the best estimates of spontaneous loss of HBsAg in CHB infection to date, a few limitations exist, primarily related to available data. First, there was a lack of diversity in represented countries, particularly in Asia. China and Taiwan alone accounted for over one-third of all included studies and two-thirds of studies from Asia. We had to exclude a number of large studies from unrepresented populations because they met extensive exclusion criteria(87, 89, 90), which were primarily instituted to limit heterogeneity that would threaten the validity of pooled estimates. Secondly, inherent bias exists in observational studies and may have affected the quality of included studies, particularly as details such as number of missing data or the mean number of measurements per patient were often not mentioned. However, we attempted to limit influential confounders (i.e. CHB treatment, subpopulations, and co-infection) as much as possible, without compromising the number of studies for pooling. Furthermore, as examined in our meta-regression, inclusion of studies with <10% on-treatment and co-infected patients did not impact our results.

There was wide variability in the definition, measurement and timing of outcome assessment across included studies, which may impact accuracy of our estimates. Regarding outcome definition and timing, no difference was found in meta-regression comparing a single to multiple negative HBsAg measurements. This suggests that HBsAg loss is generally durable and that repeat measures may not be necessary. However, there is a need for standardization

of reporting in future studies and clinical trials. Lastly, due to small number of qualifying studies and heterogeneity, we could not pool data to explore the relationship between HBV genotype, HBV DNA and quantitative HBsAg (qHBsAg) levels with HBsAg loss. HBV genotype A in western countries(91) and genotype B in Asian countries(82) have been associated with higher rates of HBsAg loss, but ultimately genotype testing is not useful in homogenous populations. On the other hand, one-time qHBsAg testing might be a more efficient, accurate, and cost-effective modality to implement broadly for predicting HBsAg loss in inactive CHB patients. A simple model incorporating age, HBV DNA and qHBsAg has been developed using existing data and may be valuable in resource-constrained settings to identify individuals who would benefit most from HBsAg monitoring(92). Further validation of these models as well as development of novel biomarkers to predict HBsAg loss in diverse populations is needed.

The WHO has set an ambitious target for HBV elimination by 2030(93). While enhancing delivery of HBV vaccine to high prevalence regions is a key strategy, parallel development of and access to effective and safe antivirals is essential. Key stakeholders have recognized HBsAg loss as the primary endpoint for clinical trials of emerging CHB therapeutics, as current drugs are highly efficacious at achieving viral suppression and complete eradication of virus is not presently feasible(13). Currently approved therapies are not recommended for persons with inactive or indeterminate CHB, but these patients may still benefit from functional cure, particularly at younger ages. Our pooled estimate of spontaneous HBsAg loss at 1.13% per year provides a reference point for future trials that may include CHB-infected outside of current treatment paradigms. The overall low rate of spontaneous functional cure underscores the urgency of developing novel CHB drugs with substantially improved efficacy to widen treatment candidacy and support the goal of HBV elimination worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Contesssxt

Evidence before this study

Chronic hepatitis B (CHB) infection is a leading contributor worldwide to morbidity and mortality from cirrhosis and hepatocellular carcinoma. Spontaneous loss of hepatitis B surface antigen (HBsAg), also called functional cure, occurs late in the natural history of the disease and portends a much better long-term prognosis. Previous to this review, studies on spontaneous HBsAg loss have come from individual countries or regions and have suggested differential rates of HBsAg loss in endemic and non-endemic regions. However, cohort level factors such as hepatitis B e-antigen status, age, and definition of HBsAg loss varied across these individual studies, and predictors of HBsAg loss arising from these cohorts cannot be generalized across populations.

Added value of this study

This large and comprehensive pooled meta-analysis provides a baseline annual rate of spontaneous HBsAg loss to support clinical trials with functional cure as primary endpoint. We demonstrate that CHB endemicity does not impact rates. Our use of meta-regression techniques contributes to our understanding of cohort level factors that may influence estimates.

Implications of all the available evidence

HBsAg testing is indicated in HBeAg-negative patients with a long duration of inactive disease. The low rate of HBsAg loss across geographic regions highlights need for novel therapeutics aimed at increasing treatment pool and achieving functional cure.

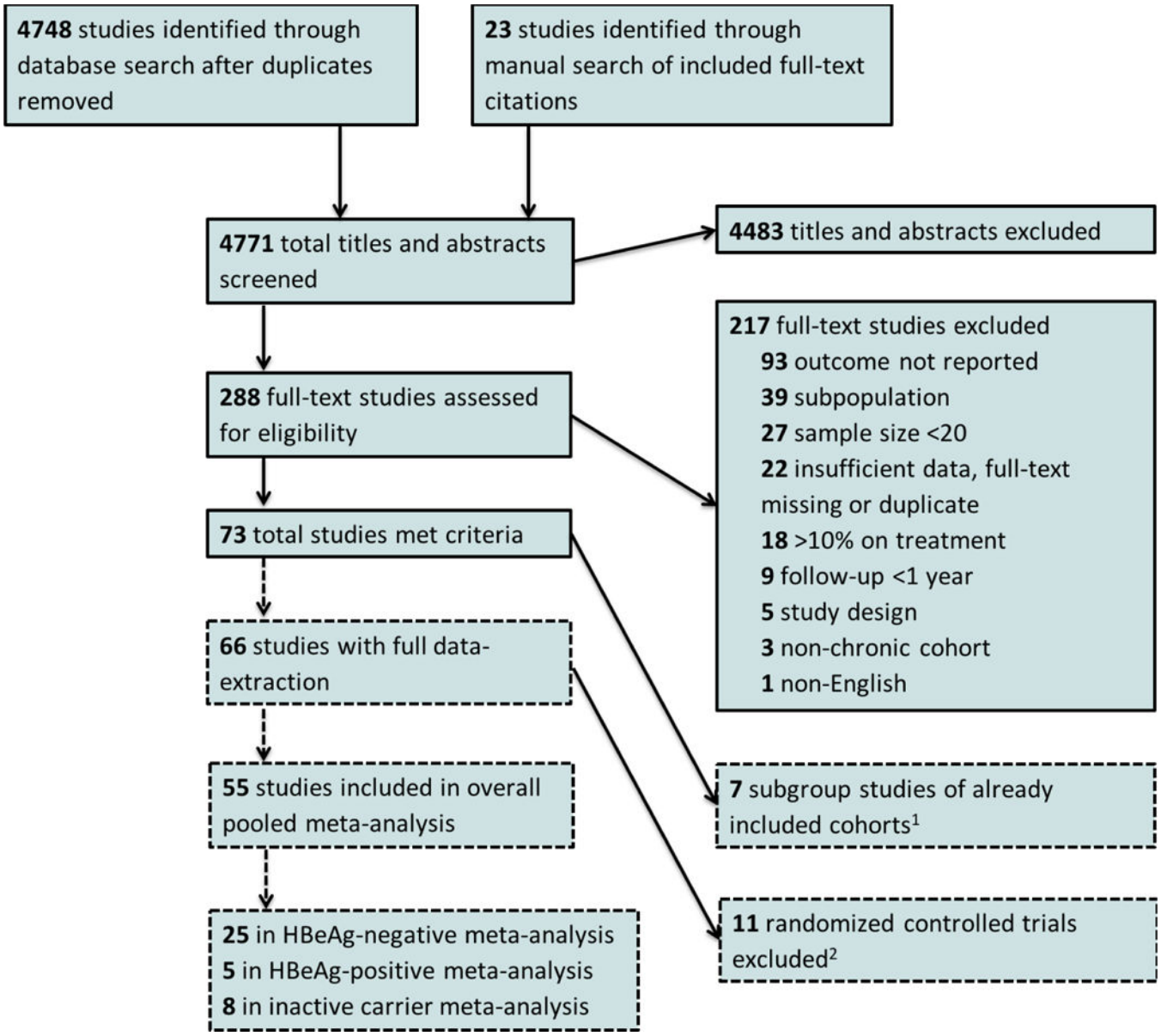


Figure 1.
Study selection
[1]Subgroup studies were used in subgroup meta-analyses
[2]Randomized controlled trials excluded from meta-analyses to limit heterogeneity

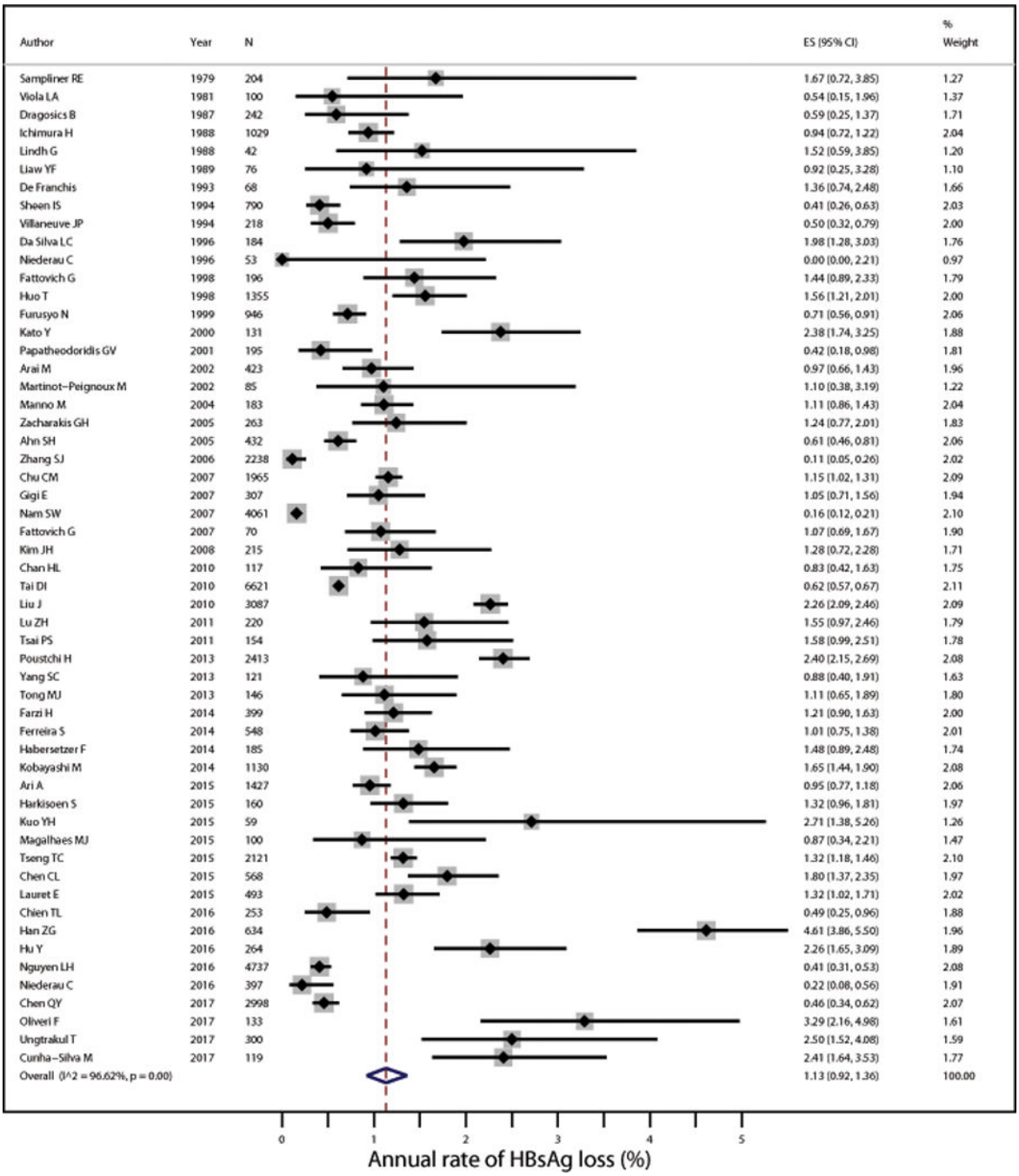
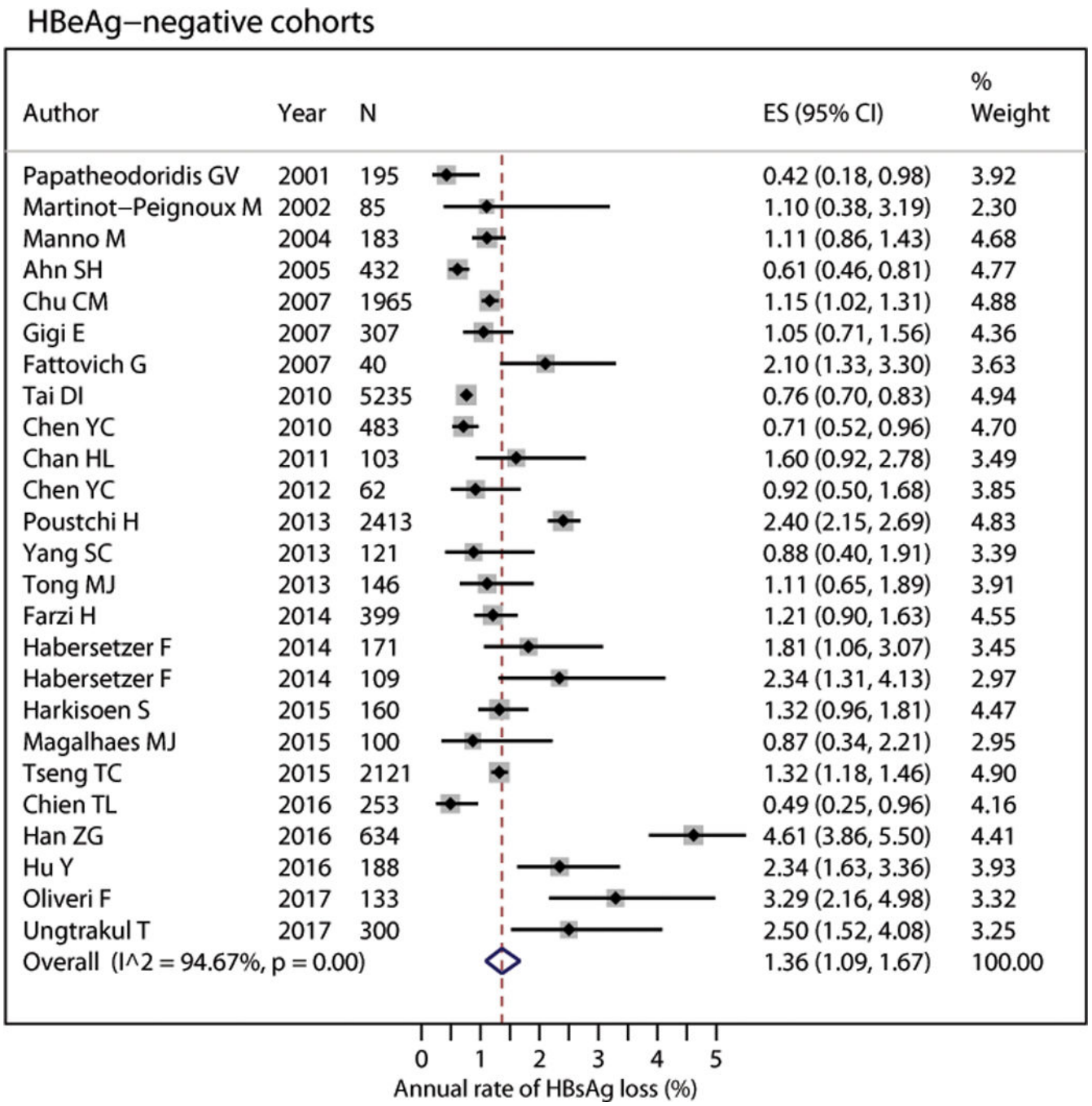
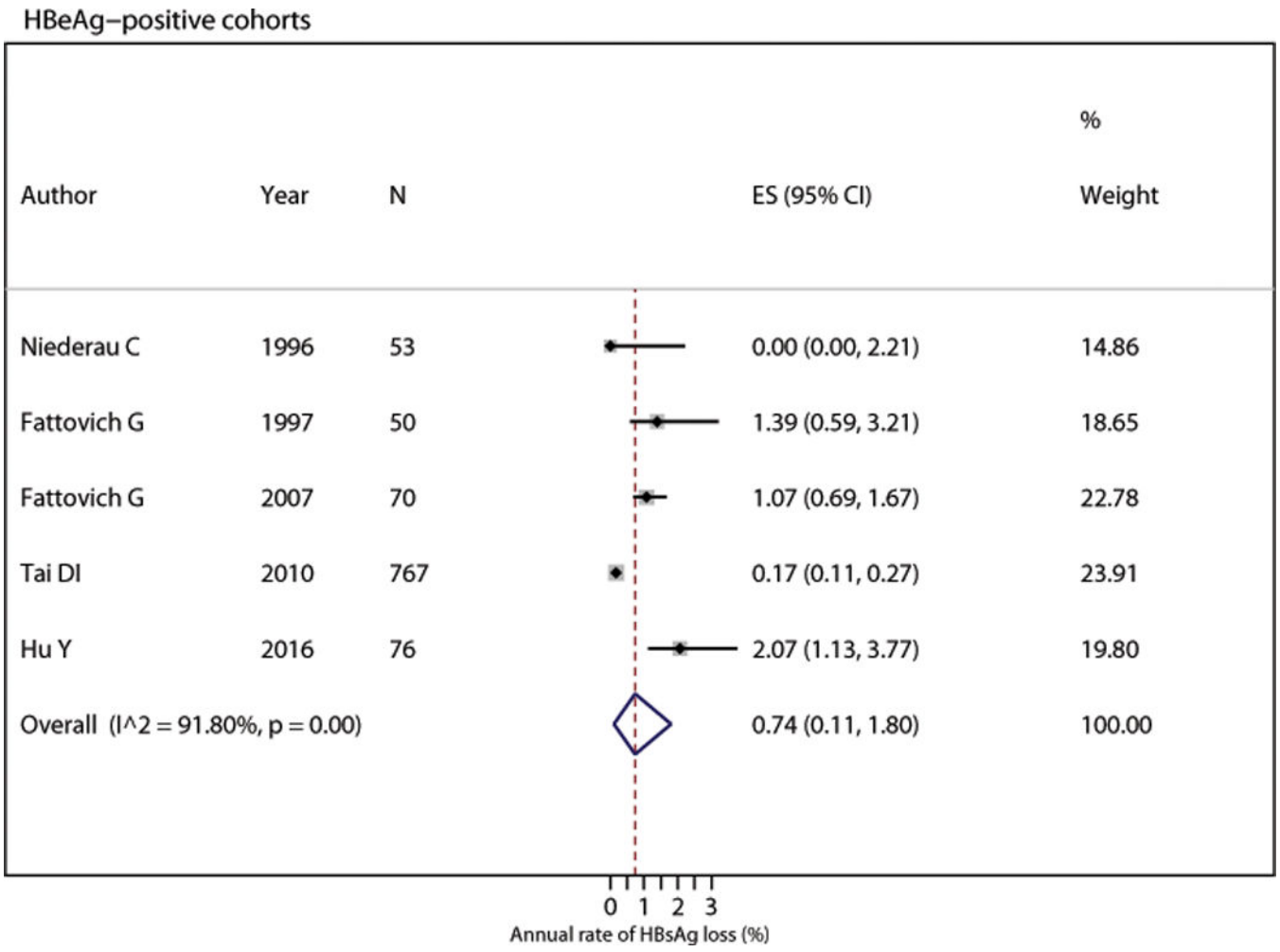


Figure 2.

Pooled annual rate of HBsAg loss among all observational studies (n=55)

Black diamonds represent point estimates of outcome for each study. Size of light gray box is determined by the weight attributed to the study in our random-effects model. Black line represents upper and lower bounds of 95% confidence intervals. Dotted red line marks point estimate of pooled outcome.





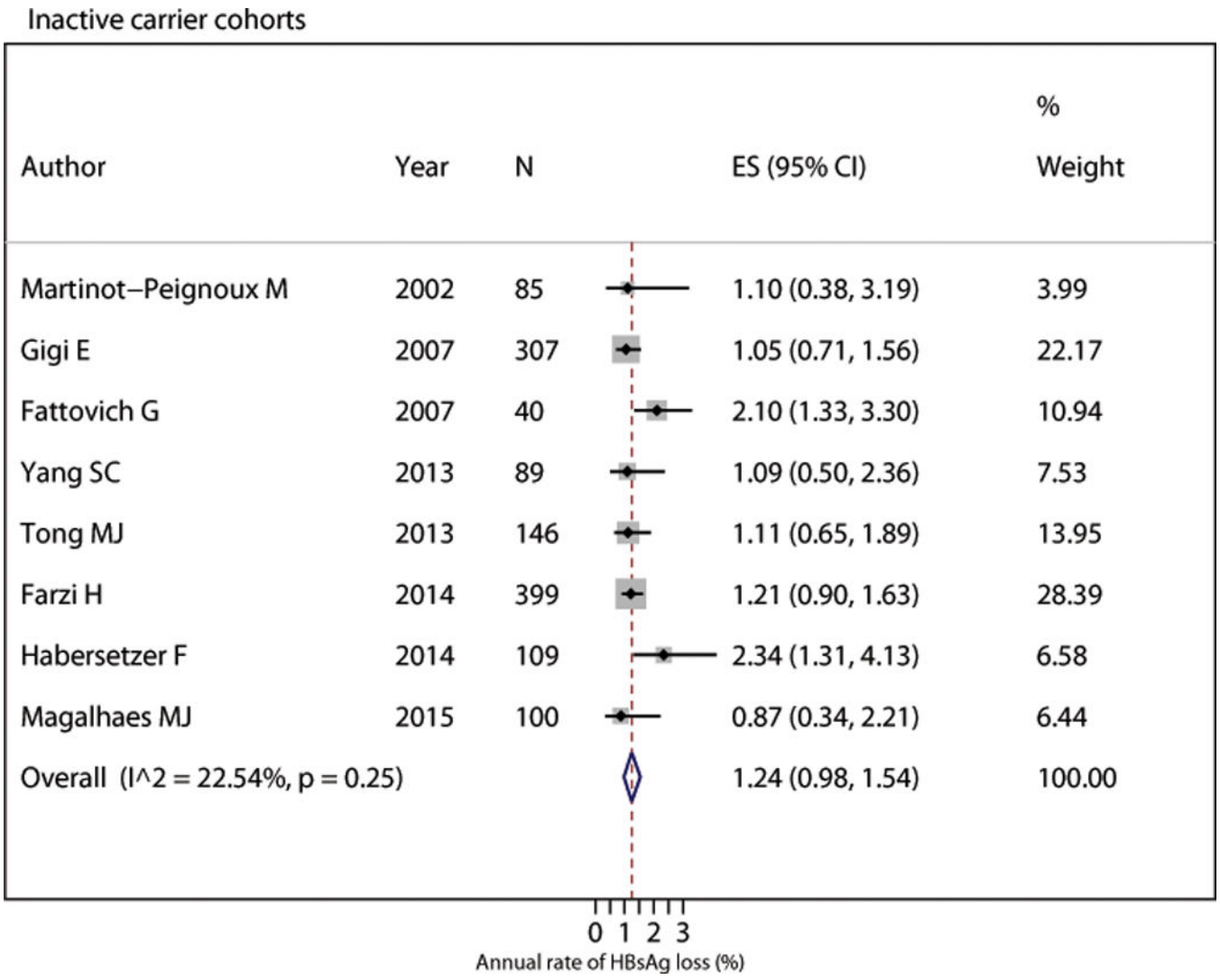
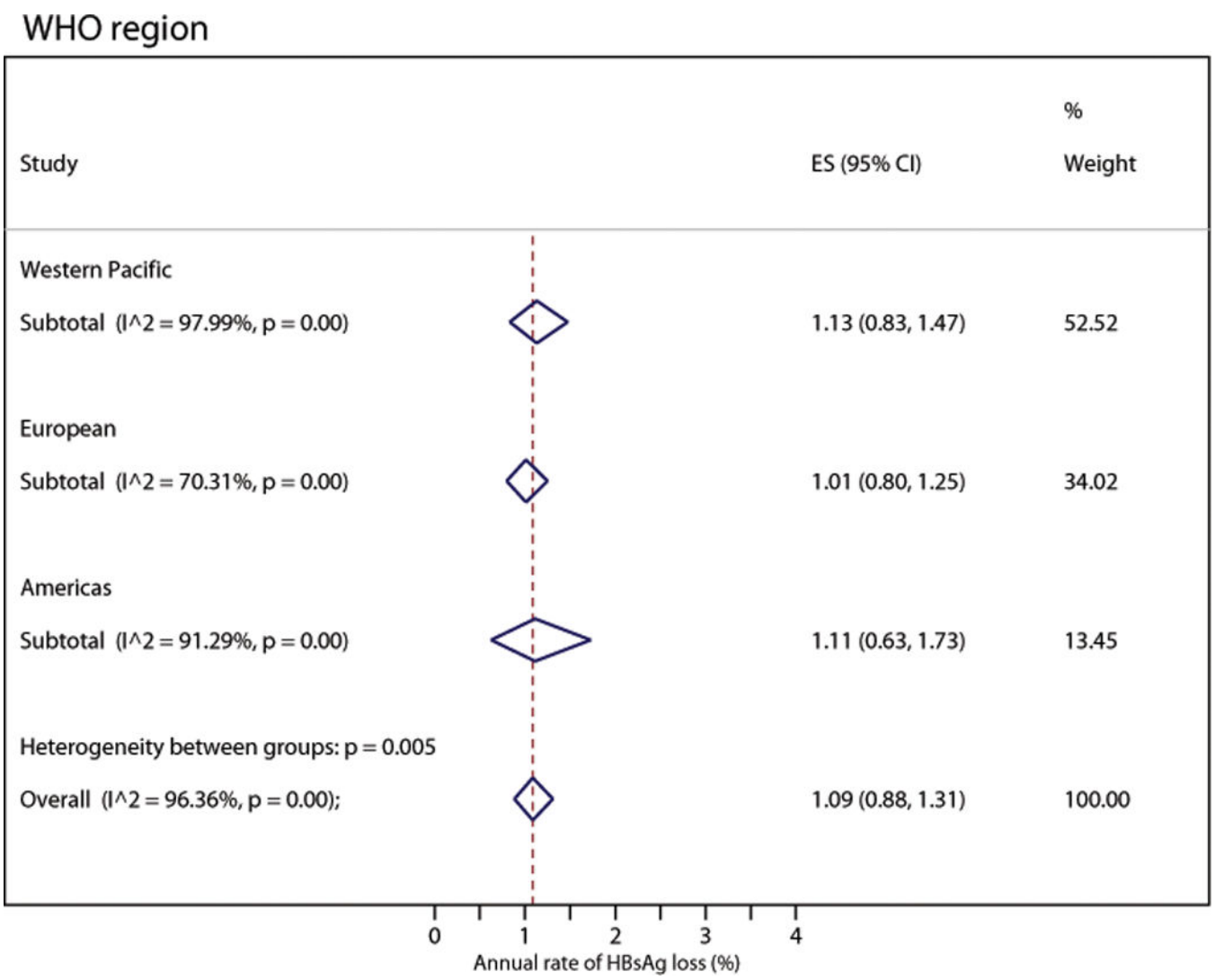


Figure 3.

Subgroup pooled meta-analysis of annual rate of HBsAg loss among HBeAg-negative (n=25), HBeAg-positive (n=5), and inactive carrier (n=8) cohorts



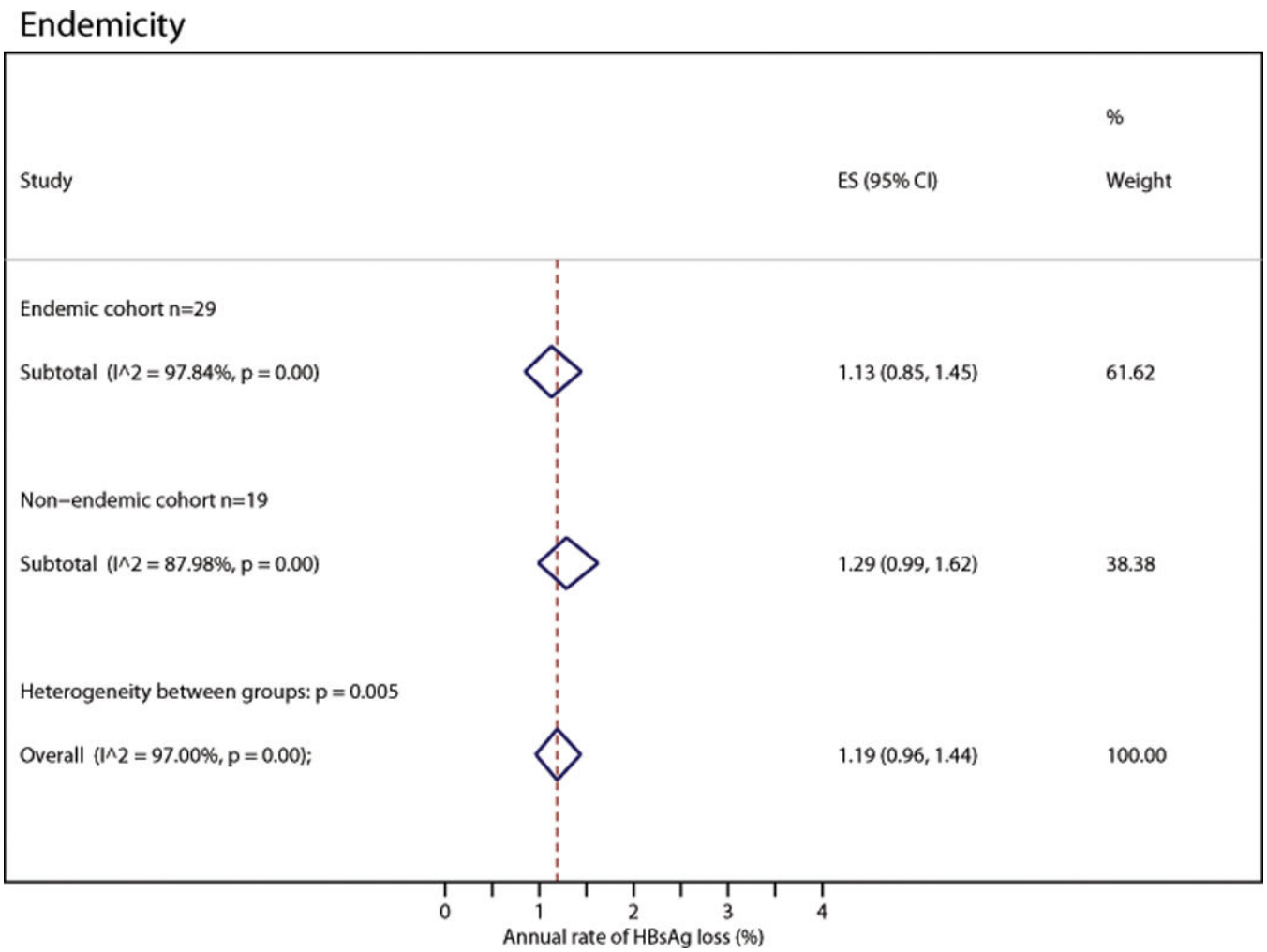


Figure 4.
Pooled annual rate of HBsAg loss stratified by WHO region and endemicity