HBsAg Loss Meta-Analysis

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Association between HBsAg loss and risk of hepatocellular carcinoma in chronic hepatitis B: a systematic review and meta-analysis

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Background

- Loss of hepatitis B surface antigen (HBsAg): desired treatment endpoint for chronic hepatitis B (CHB)
- Studies have shown an association between HBsAg loss and improved long-term clinical outcomes in CHB patients
- Its utility as a surrogate endpoint needs to be well-described for development of novel therapies and regulatory decision making
Objectives

- To describe the association between HBsAg loss and HCC development
- To evaluate HBsAg loss as a surrogate endpoint for improved long-term clinical outcome in CHB
Methods

- Systematic literature review conducted in PubMed, EMBASE, and Cochrane Library databases for articles published between Jan 1990-Nov 2018

- Inclusion criteria:
  - >50 CHB patients
  - ≥2 years of follow-up
  - Measured for serum HBsAg status at baseline and during follow-up
  - Reported data on HCC
Methods

- Exclusion criteria:
  - Duplicate study population
  - HBV reactivation
  - Liver transplant recipients
  - No clinical endpoint studied
  - No HBsAg loss/HBsAg-persistent cohort for comparison
  - HCC prior to HBsAg loss
  - HCV/HDV/HIV coinfected population
  - Case-control studies
Methods

- Incidence rates of HCC from HBsAg loss and HBsAg-persistent groups used to calculate rate ratios (RR)
  - HCC incidence rate = number of HCC in cohort/total person-years of follow-up in cohort
  - Reciprocal continuity correction factors used for studies reporting zero events in the HBsAg loss cohort

- Meta-analysis of RRs using a random effects model performed

- Subgroup and sensitivity analyses conducted to test robustness of results

1Sweeting, Statistics in Medicine (2014)
Study selection flow chart

Records identified by search strategy (n = 3410)

Additional records identified through other sources (n = 94)

Records after duplicates removed (n = 2916)

Records excluded by screening titles/abstracts (n = 2822)

Studies excluded:
1. Duplicate study population (n = 8)
2. Case-control studies (n = 3)
3. <2 years average follow-up (n = 3)
4. HBV reactivation (n = 6)
5. Liver transplant recipients (n = 5)
6. Co-infected population (n = 1)
7. No clinical endpoints studied (n = 9)
8. No HBsAg persistent cohort (n = 9)
9. No HBsAg seroclearance (n = 14)
10. HBsAg status not reported (n = 8)*

Full-text articles assessed for eligibility (n = 94)

Studies included in quantitative synthesis (n = 28)

Studies included reporting HCC incidence (n = 26)

Studies included reporting incidence of liver decompensation (n = 7)

Studies included reporting incidence of LT and/or all-cause mortality (n = 13)

*Investigators reached out to the corresponding authors of these articles and either did not receive a response or the response did not include the needed clarifications.
## HCC Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>n[\text{no.}]</th>
<th>p-\text{Y[\text{no.}]}</th>
<th>n[\text{met}]</th>
<th>RR and 95% CI</th>
<th>RR</th>
<th>Lower limit</th>
<th>Upper limit</th>
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**OVERALL**

| Overall            | 33264          | 273032.3                 | 154519        | 1211810.9     | 0.30 | 0.20        | 0.43        | <0.001 | 100.00% |
## Subgroup analysis

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<tr>
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<th>Subgroup</th>
<th>K</th>
<th>N</th>
<th>P-Y</th>
<th>RR</th>
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<th>p-value</th>
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### Sub-analysis of treatment studies

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<th>Number of studies</th>
<th>Number of patients</th>
<th>Total person-years of follow-up</th>
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<th>Upper limit</th>
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<td>0.06</td>
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<td>0.006</td>
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Meta-regression sensitivity analysis

A. $p=0.74$

B. $p=0.94$

C. $p=0.67$

D. $p=0.51$

E. $p=0.98$

F. $p=0.91$

G. $p=0.95$

H. $p=0.01$

I. $p=0.52$
Sensitivity analysis: Average follow-up

- Average follow-up duration was the only factor that had a significant influence on the rate ratio.
- Magnitude of HCC risk reduction associated with HBsAg loss increased with increasing follow-up duration.
- Excluding studies with <5 or >10 years of follow-up mitigated this effect; however, the trend persisted.
Conclusion

- HBsAg loss was strongly associated with a significantly reduced risk of HCC
- Both spontaneous and treatment-induced HBsAg loss were associated with reduced risk of HCC, regardless of treatment type
- Although the degree of risk reduction may differ, the positive effect associated with HBsAg loss persisted through all patient subpopulations
- Achieving HBsAg loss is a reliable measure of tangible clinical benefit
- Our results provide validation for the use of HBsAg loss as a surrogate endpoint for HCC risk reduction and improved clinical outcome in CHB patients
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  - Poonam Mishra, MD, US FDA
  - Charu Mullick, MD, US FDA
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  - Daniela Paulson, AiCuris
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  - Ross Leland Pierce, MD, US FDA
  - Sybil Tasker, MD, MPH, Altimmune
  - Andrew Vaillant, PhD, Replicor
  - Hwai-I Yang, PhD, Academia Sinica

- **Surrogate Endpoints WG Members**
  - Ibronke Addy, MBBS, MSc, AiCuris
  - Nat Brown, MD, Hepatitis B Foundation
  - Henry Chan, MD, The Chinese University of Hong Kong

- **HBV Forum Sponsors**
  - Abbott Molecular
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  - Assembly Biosciences
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  - DDL Diagnostics
  - Gilead Sciences
  - GlaxoSmithKline, Hepatitis B Foundation
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  - PPD
  - Quest Diagnostics
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