# Association between HBsAg loss and long-term clinical outcome in chronic hepatitis B: a systematic review and meta-analysis

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# ILC Late-Breaker Poster LBP-02

- Abstract was accepted as a Late-Breaker Poster
  - Reference number: LBP-02
- Please respect that the data presented here is confidential
- Will be on display during all three poster sessions at ILC

# Background

- Studies have shown an association between hepatitis B surface antigen (HBsAg) loss and improved long-term clinical outcomes in chronic hepatitis B (CHB) patients
- Evaluation of HBsAg seroclearance as a ‘functional cure’ on a larger scale is crucial for drug development and regulatory decision making

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# Objectives

- To perform a systematic literature review and meta-analysis describing the association between functional cure (defined as HBsAg seroclearance with or without anti-HBs seroconversion) of CHB infection and long-term clinical outcome.

# Methods

- Literature search in PubMed, EMBASE and Cochrane Library databases
- Full-text articles published in English between January 1990 – November 2018

# Methods

- Inclusion criteria:
  - >50 CHB patients
  - ≥2 years of follow-up
  - HBsAg serostatus measured at baseline & during follow-up
  - Reported data on 1 or more long-term clinical outcomes (decompensation, HCC, liver transplantation (LT), and/or all-cause mortality)

# Methods

- Exclusion criteria:
  - Study duplication
  - HBV reactivation studies
  - Studies on LT patients
  - Co-infection with HCV, HIV, and/or delta*
    - Included 4 studies with minority subpopulations of co-infected individuals
  - Clinical events reported prior to HBsAg loss
  - No HBsAg-persistent comparison cohort
  - Zero clinical events reported for both cohorts

# Methods

- Two investigators independently extracted and reviewed study data
- Comprehensive Meta-analysis Software was used to perform statistical analysis
  - Clinical events rates (number of clinical events in cohort/person-years follow-up in cohort) were used to calculate the rate ratio (RR) using a random effects model
    - Reciprocal continuity correction factors used for studies reporting zero-events for the HBsAg-loss cohort[1]
  - Patient population demographic characteristics were categorized and analyzed in sub-group (Q-test for heterogeneity) and sensitivity analyses
  - General study information was used as covariates in a meta-regression analysis



[1]Sweeting et al. *Statist. Med.* 2004; 23:1351-1375

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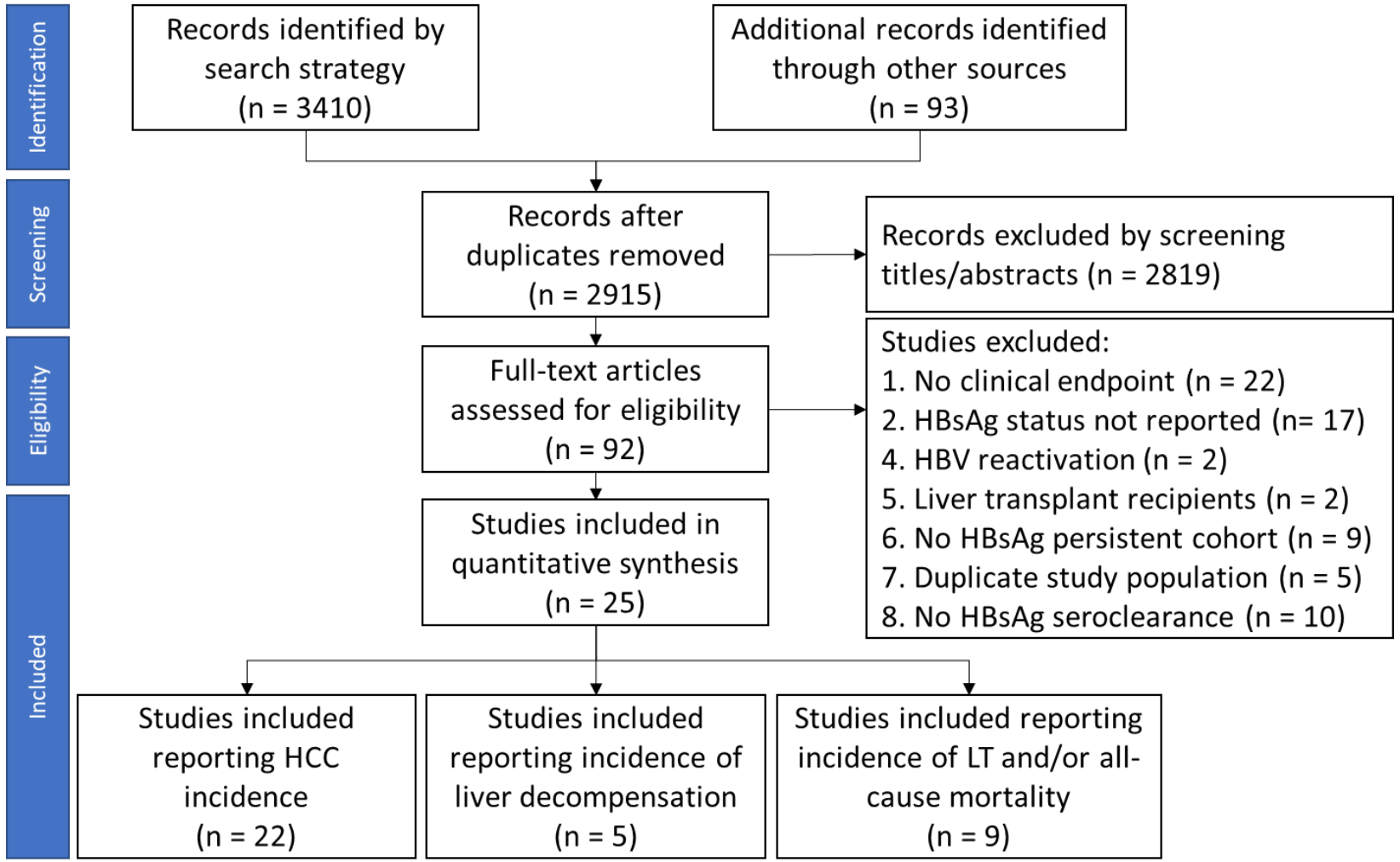
# Study Selection Flow Chart



# "First Clinical Event" Endpoint

- Composite endpoint of the first reported adverse clinical event
  - Decompensation, HCC, liver transplant, or death

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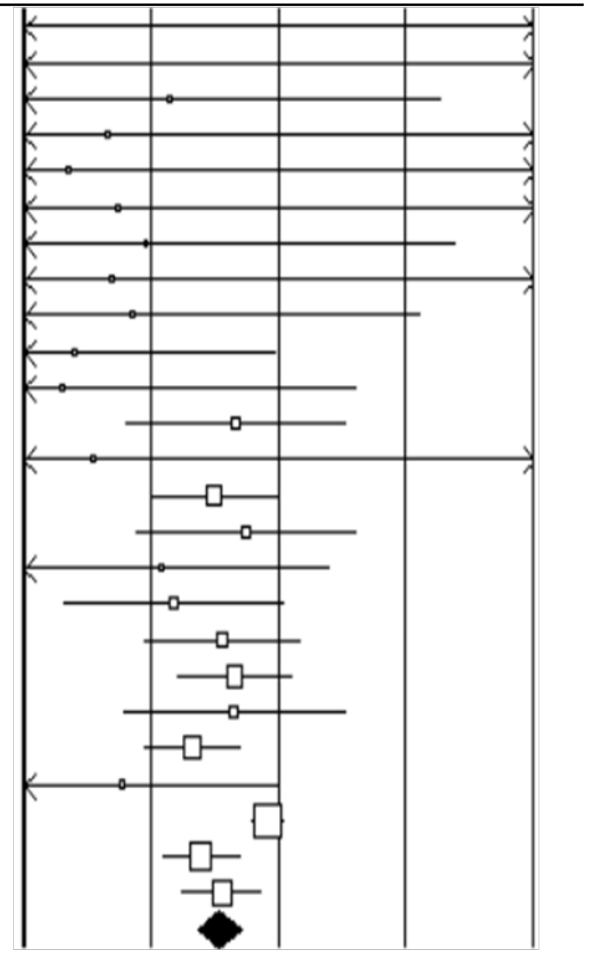
# First Clinical Event: Meta-Analysis

| Study | RR | Lower limit | Upper limit | p-value |
|---|---|---|---|---|
| Liang et al., 2015 | 0.008 | 0.000 | 1.7E+07 | 0.661 |
| Sun et al., 2014 | 0.007 | 0.000 | 1.6E+08 | 0.681 |
| Takkenberg et al., 2013 | 0.141 | 0.001 | 18.739 | 0.433 |
| Yang et al., 2013 | 0.045 | 0.000 | 242.785 | 0.480 |
| Kim et al.,2008 | 0.022 | 0.000 | 104.488 | 0.378 |
| Marcellin et al., 2009 | 0.054 | 0.000 | 153.848 | 0.473 |
| Buster et al., 2008 | 0.090 | 0.000 | 24.296 | 0.400 |
| Idilman et al., 2012 | 0.049 | 0.000 | 172.968 | 0.470 |
| Chan et al., 2011 | 0.071 | 0.000 | 13.176 | 0.321 |
| Orito et al., 2015 | 0.025 | 0.001 | 0.971 | 0.048 |
| Silva et al., 1996 | 0.020 | 0.000 | 4.044 | 0.149 |
| Psvedos et al., 2010 | 0.465 | 0.063 | 3.456 | 0.454 |
| Tseng et al., 2011 | 0.035 | 0.000 | 260.315 | 0.461 |
| Fattovich et al., 1998 | 0.309 | 0.098 | 0.978 | 0.046 |
| Arai et al., 2012 | 0.553 | 0.074 | 4.119 | 0.563 |
| Moucari et al., 2009 | 0.121 | 0.006 | 2.527 | 0.173 |
| Yang et al., 2016 | 0.152 | 0.021 | 1.123 | 0.065 |
| Lauret et al., 2015 | 0.360 | 0.087 | 1.494 | 0.159 |
| Yuen et al., 2004 | 0.452 | 0.157 | 1.300 | 0.141 |
| Tseng et al., 2012 | 0.451 | 0.060 | 3.412 | 0.440 |
| Yip et al., 2018 | 0.213 | 0.089 | 0.514 | 0.001 |
| Lim et al., 2016 | 0.059 | 0.003 | 0.992 | 0.049 |
| Gounder et al., 2016 | 0.821 | 0.614 | 1.097 | 0.182 |
| Liu et al., 2014 | 0.245 | 0.120 | 0.500 | 0.000 |
| Fwu et al., 2009 | 0.358 | 0.173 | 0.738 | 0.005 |
| **Overall** | **0.341** | **0.233** | **0.499** | **0.000** |



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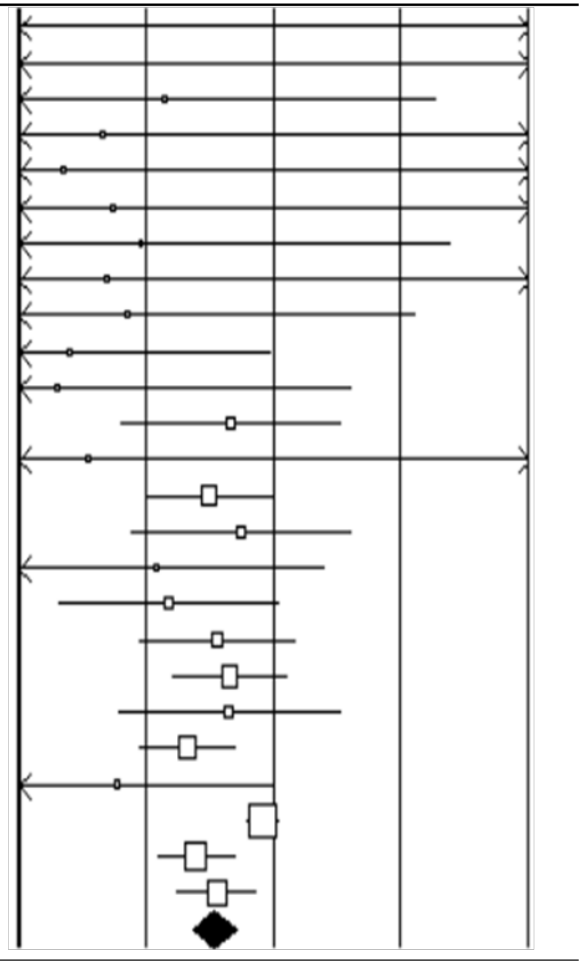



| | RR | Lower limit | Upper limit | p-value |
|---|---|---|---|---|
| **Overall** | 0.341 | 0.233 | 0.499 | 0.000 |

# Primary Clinical Endpoints: Independent Meta-analyses

| Endpoint | RR | Lower limit | Upper limit | p-value | RR and 95% CI 0.0 0.5 1.0 |
|---|---|---|---|---|---|
| Decompensation (n=5) | 0.313 | 0.150 | 0.654 | 0.002 | |
| HCC (n = 22) | 0.307 | 0.214 | 0.440 | 0.000 | .31 |
| LT/All-cause Mortality (n = 9) | 0.751 | 0.569 | 0.991 | 0.043 | .31 .75 |
| First Clinical Event (N = 25) | 0.341 | 0.233 | 0.499 | 0.000 | .34 |

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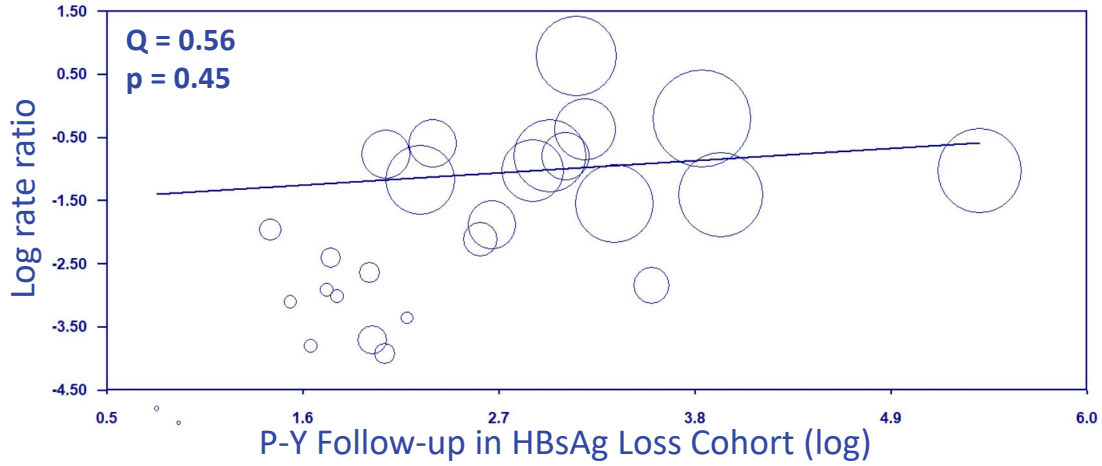
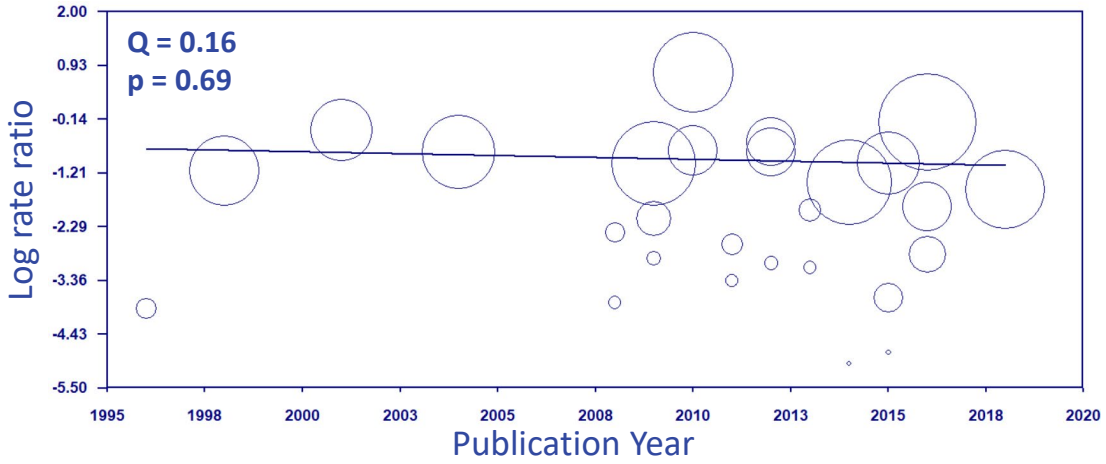
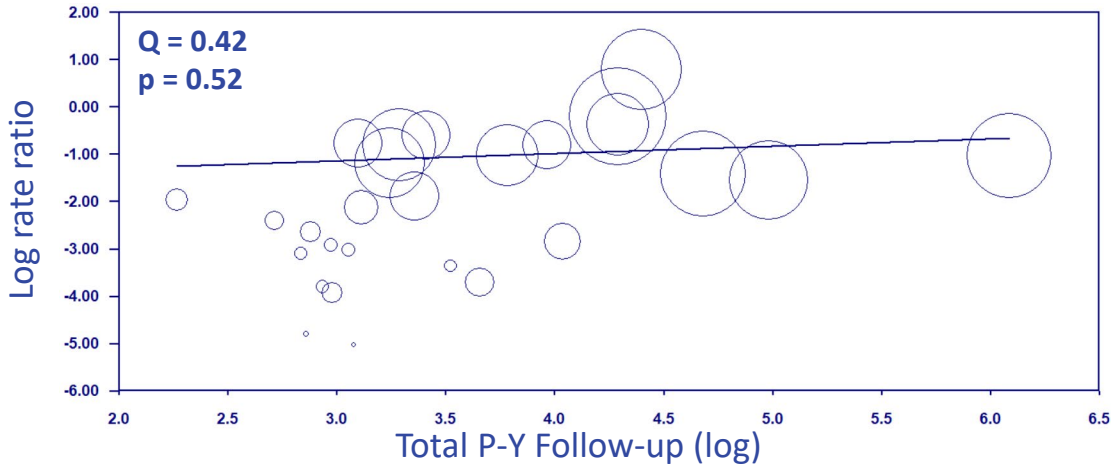
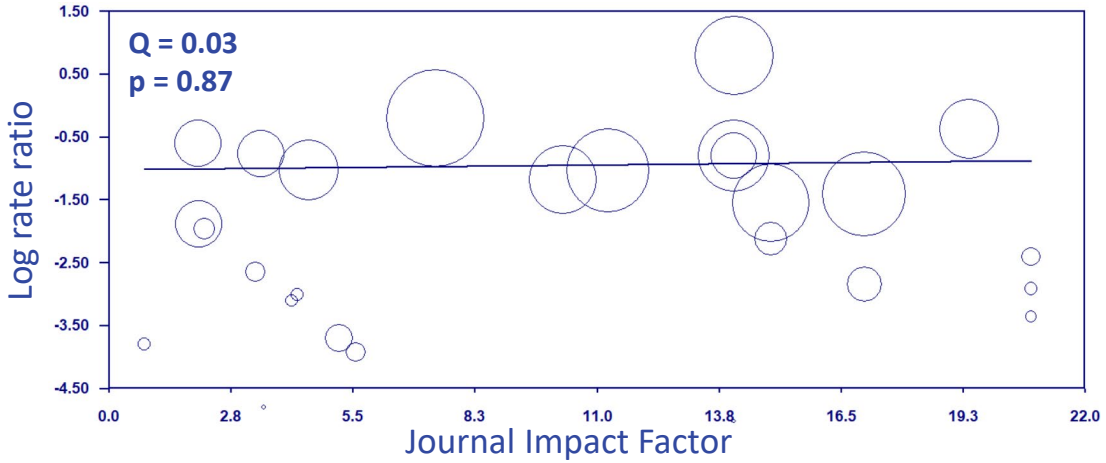
# First Clinical Event: Regression Analysis



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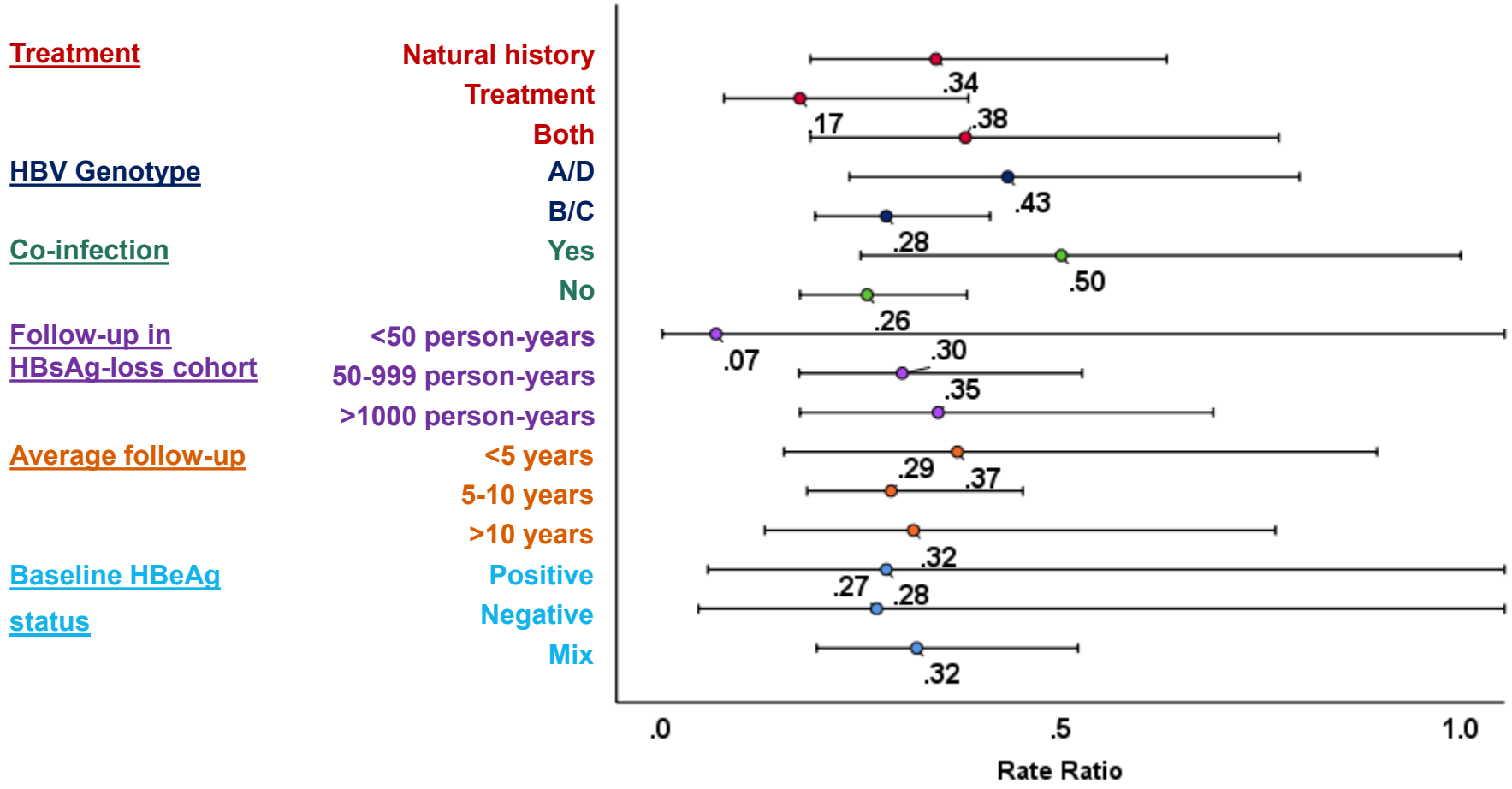
# First Clinical Event: Subgroup/Sensitivity Analysis



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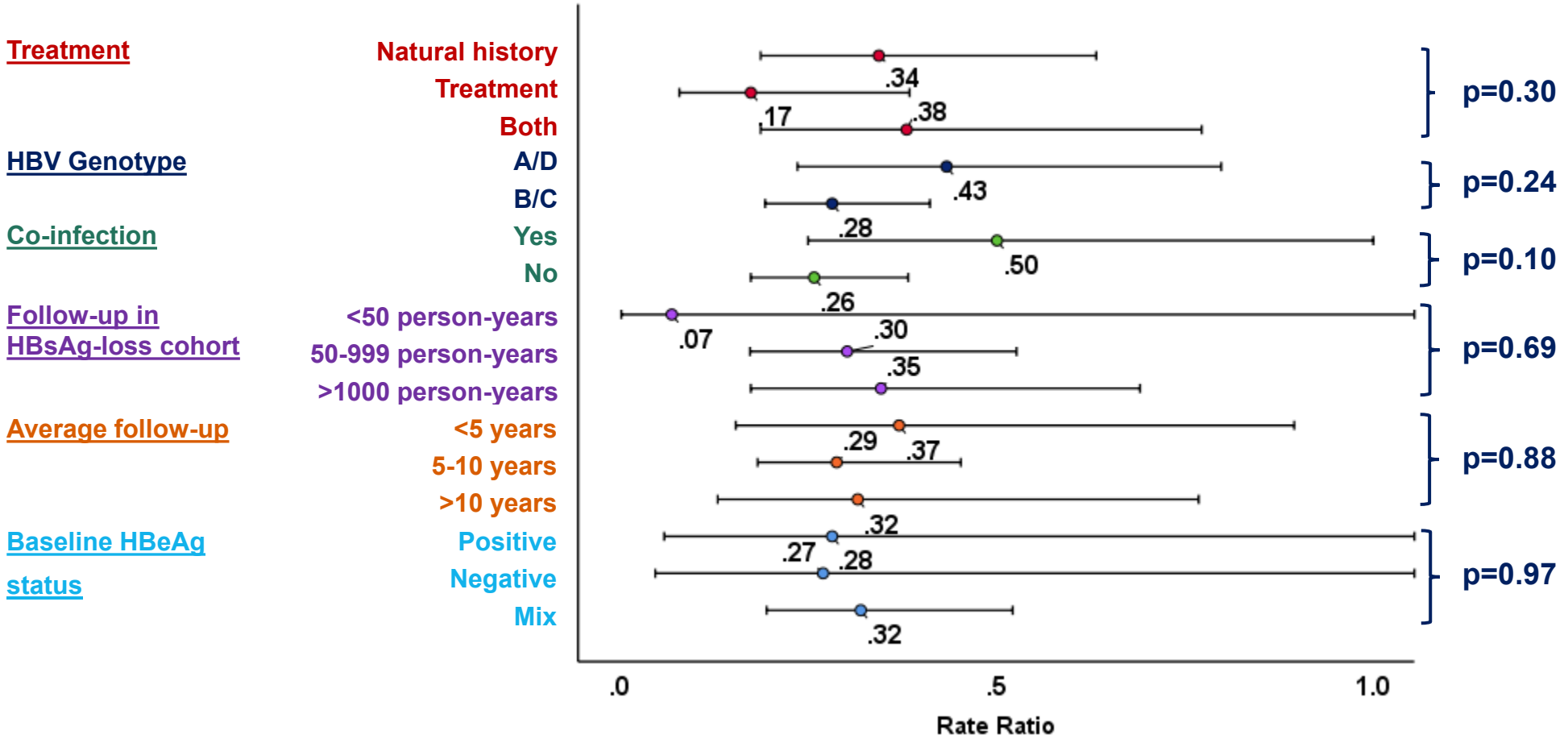
# First Clinical Event: Subgroup Analysis



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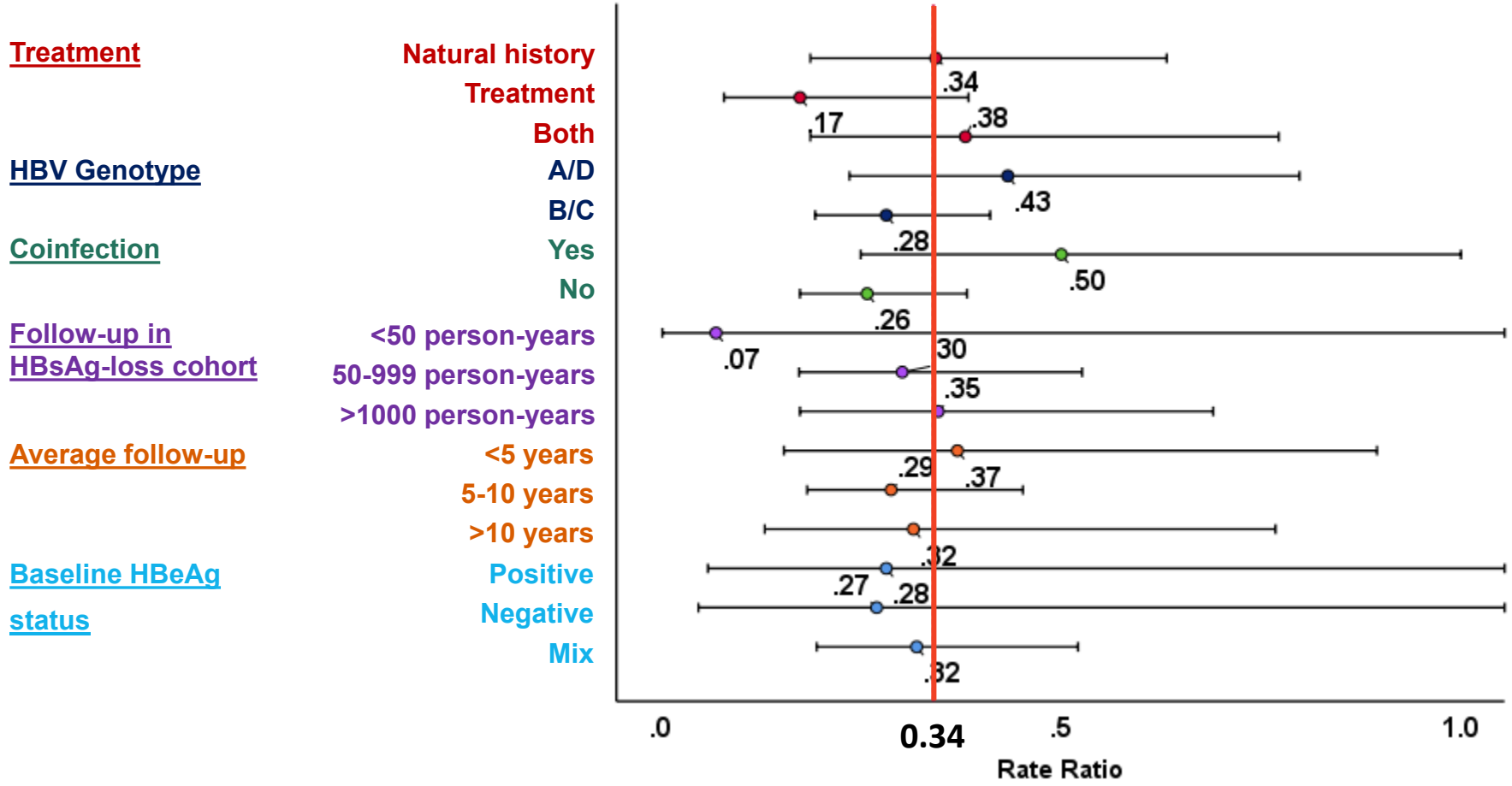
# First Clinical Event: Sensitivity Analysis



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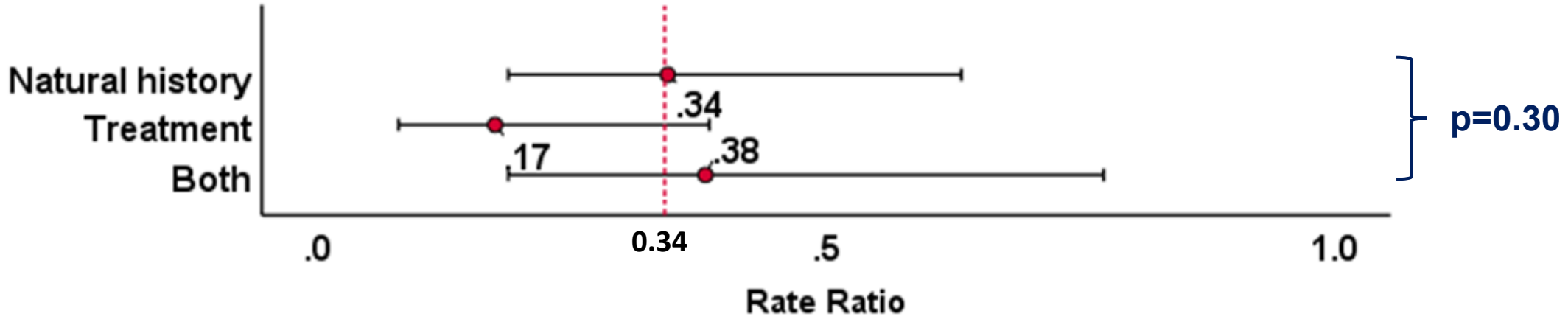
# First Clinical Event: Treatment Subgroups



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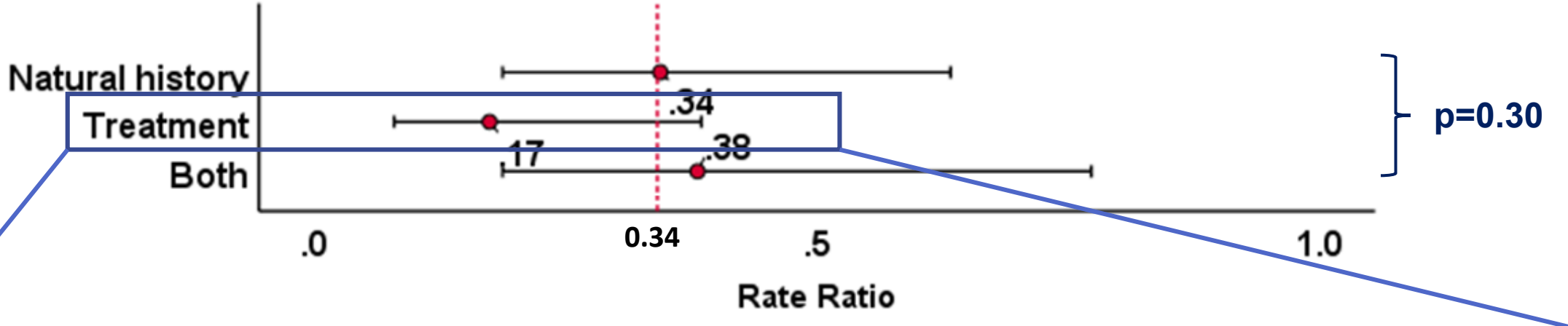
# First Clinical Event: Treatment Studies Sub-analysis




| Endpoint | RR | Lower limit | Upper limit | p-value | RR and 95% CI (0.0 – 0.5 – 1.0 – 1.5) |
|---|---|---|---|---|---|
| IFN (n = 1) | 0.121 | 0.006 | 2.527 | 0.173 | |
| Nuc (n = 5) | 0.185 | 0.079 | 0.433 | 0.000 | |
| Nuc+IFN (n = 3) | 0.102 | 0.004 | 2.873 | 0.180 | |
| **Overall (n = 9)** | **0.174** | **0.079** | **0.385** | **0.000** | |

# Conclusion

- The results of our analysis support the use of HBsAg seroclearance as a surrogate marker for improved clinical outcome in CHB patients
  - Significantly reduced risk of adverse clinical events in patients who achieved HBsAg loss
  - No difference in incidence of long-term clinical outcome between patients who cleared HBsAg on-treatment and those who cleared HBsAg spontaneously

# Next Steps

- We have reached out to corresponding authors for additional 15 articles that fulfilled our inclusion criteria, but did not differentiate endpoints based on HBsAg status
- Manuscript for peer review publication in preparation

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# Thank you!

- Study Co-authors
  - Hannah Choi, MS, *Toronto Centre for Liver Disease, University Heath Network*
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  - Brian McMahon, MD, *Alska Native Medical Center*
  - Poonam Mishra, MD, *US FDA*
  - Charu Mullick, MD, *US FDA*
  - Jeffrey Murray, MD, MPH, *US FDA*
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  - Daniela Paulson, *AiCuris*
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  - Hwai-I Yang, PhD, *Academia Sinica*
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