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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

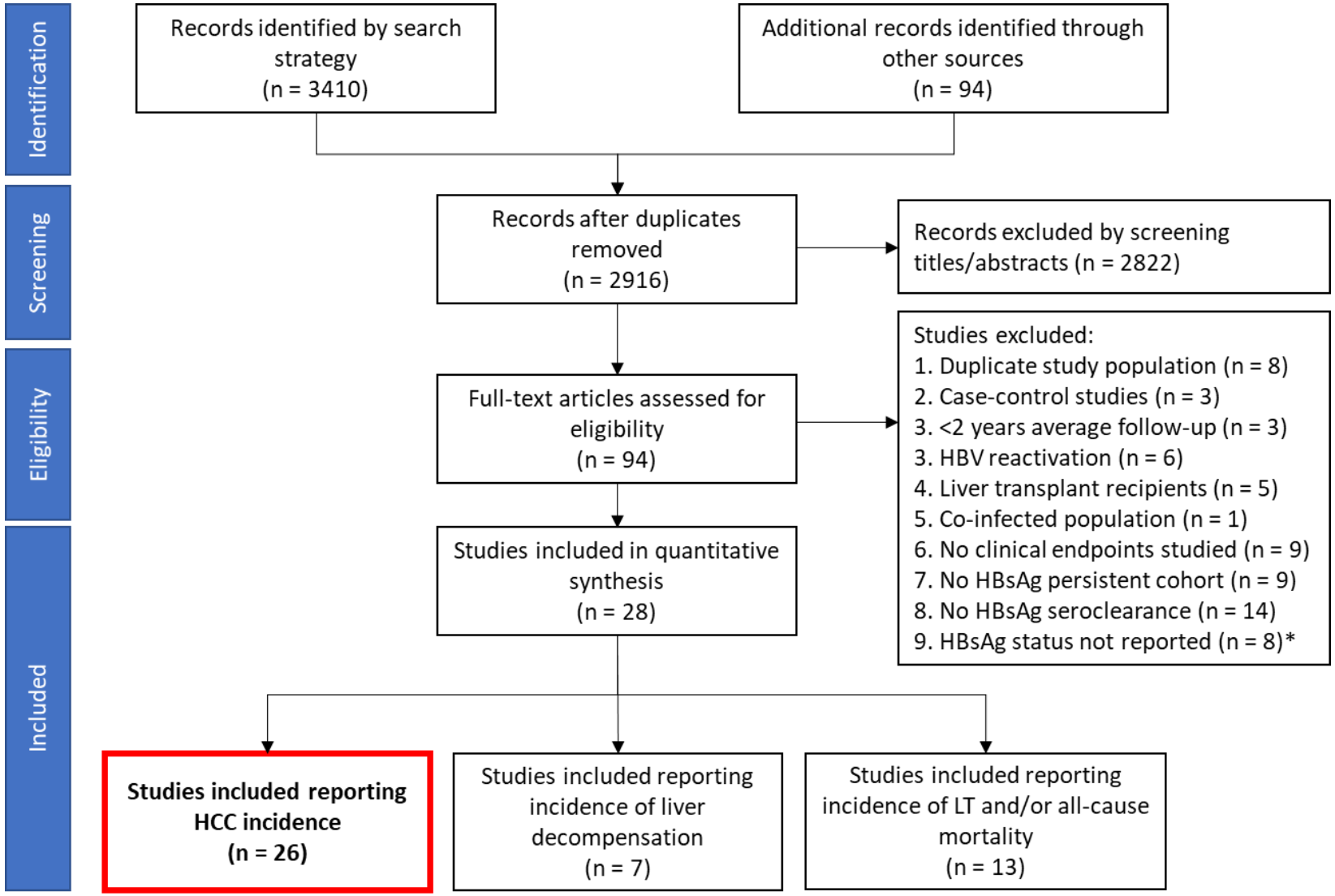
- Exclusion criteria:
  - Duplicate study population
  - HBV reactivation
  - Liver transplant recipients
  - No clinical endpoint studied
  - No HBsAg loss/HBsAg-persistent cohort for comparison
  - HCC prior to HBsAg loss
  - HCV/HDV/HIV coinfected population
  - Case-control studies

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[1]
- Meta-analysis of RRs using a random effects model performed
- Subgroup and sensitivity analyses conducted to test robustness of results

[1]Sweeting, *Statistics in Medicine* (2014)

Study selection flow chart



*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

Study	n^{srclr}	P-Y^{srclr}	n^{prstnt}	P-Y^{prstnt}	RR and 95% CI (0.01 0.1 1.0 10.0 100.0)	RR	Lower limit	Upper limit	p-value	Weight
Sun et al., 2014	4	8.0	595	1190.0		0.01	<0.01	1.6E+08	0.681	0.03%
Takkenberg et al., 2013	13	26.0	79	158.0		0.14	<0.01	18.74	0.433	0.62%
Yang et al., 2013	6	33.8	115	646.9		0.05	<0.01	242.78	0.480	0.20%
Kim et al.,2008	11	44.0	204	816.0		0.02	<0.01	104.49	0.378	0.21%
Marcellin et al., 2009	18	54.0	295	885.0		0.05	<0.01	153.85	0.473	0.24%
Idilman et al., 2012	10	61.8	173	1069.7		0.05	<0.01	172.97	0.470	0.22%
Chan et al., 2011	12	94.0	91	659.8		0.07	<0.01	13.18	0.321	0.54%
Orito et al., 2015	13	97.5	589	4417.5		0.01	<0.01	6.5E+03	0.512	0.09%
da Silva et al., 1996	20	114.0	164	836.4		0.05	<0.01	10.12	0.268	0.52%
Tseng et al., 2011	18	153.0	372	3162.0		0.03	<0.01	260.31	0.461	0.19%
Fattovich et al., 1998	32	181.3	277	1569.7		0.29	0.04	2.12	0.221	3.46%
Arai et al., 2012	25	212.9	398	2354.2		0.55	0.07	4.12	0.563	3.41%
Buti et al., 2015	62	310.0	634	3170.0		0.04	<0.01	24.05	0.333	0.38%
Brouwer et al., 2016	43	335.4	249	1942.2		0.13	<0.01	15.11	0.399	0.65%
Moucari et al., 2009	28	392.0	69	897.0		0.12	0.01	2.53	0.173	1.56%
Zonneveld et al., 2004	38	429.4	115	977.5		0.33	0.04	2.64	0.293	3.15%
Yang et al., 2016	37	456.8	181	1810.0		0.15	0.02	1.12	0.065	3.44%
Cho et al., 2014	165	566.5	1981	6801.8		1.12	0.59	2.15	0.728	18.99%
Fung et al., 2014	45	645.0	730	13930.8		0.01	<0.01	128.34	0.360	0.18%
Lauret et al., 2015	78	772.2	534	5286.6		0.53	0.07	4.03	0.537	3.33%
Kim et al., 2014	110	1078.0	5299	31794.0		0.04	0.01	0.29	0.001	3.56%
Yip et al., 2018	376	2218.4	19887	93568.3		0.12	0.03	0.47	0.002	6.54%
Lim et al., 2016	145	3591.6	293	7257.4		0.06	<0.01	0.99	0.049	1.80%
Tseng et al., 2015	338	4155.1	1783	21918.5		0.22	0.09	0.55	0.001	12.82%
Liu et al., 2014	529	8759.5	2417	38939.6		0.25	0.12	0.50	0.000	17.11%
Fwu et al., 2009	31088	248242.0	116995	965752.0		0.36	0.17	0.74	0.005	16.77%
OVERALL	**33264**	**273032.3**	**154519**	**1211810.9**		**0.30**	**0.20**	**0.43**	**<0.001**	**100.00%**

Subgroup analysis

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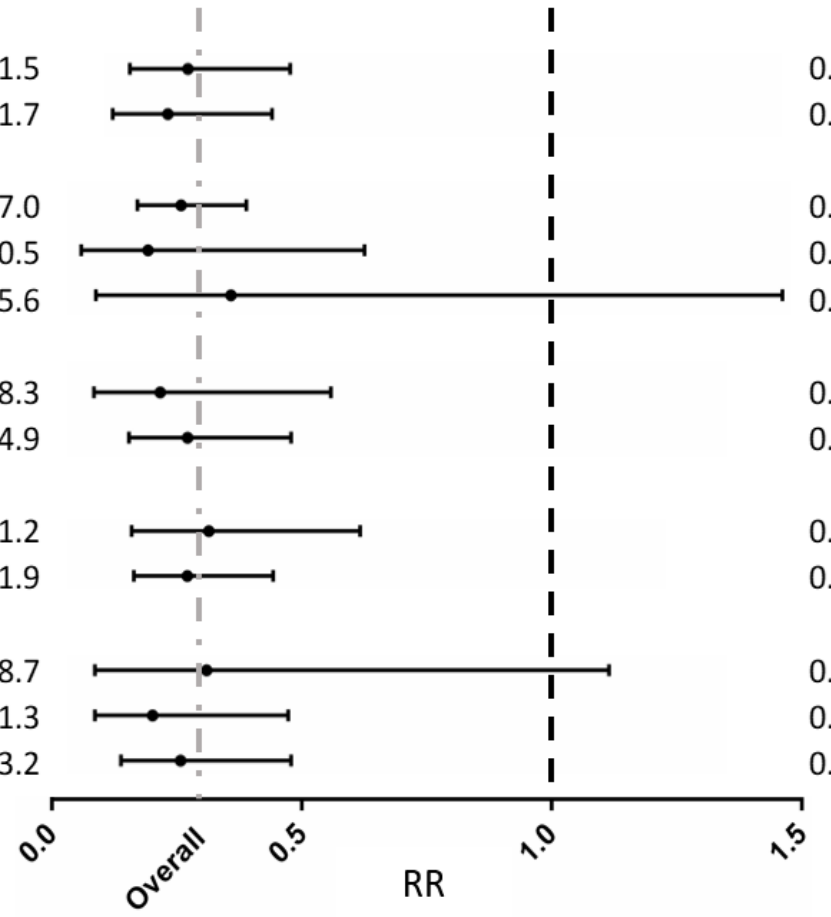
Number of studies

Number of patients

Total person-years of follow-up

Rate ratio

Variable	Subgroup	K	N	P-Y	RR	Lower limit	Upper limit	p-value
Study Design								
	Retrospective	18	182465	1416301.5	0.27	0.16	0.48	<0.001
	Prospective	8	5318	68541.7	0.23	0.12	0.44	<0.001
Cohort type								
	Untreated	12	155534	1312287.0	0.26	0.17	0.39	<0.001
	Treated	11	30553	150170.5	0.19	0.06	0.63	0.006
	Both	3	1696	22385.6	0.36	0.09	1.46	0.152
Genotype								
	A/D	10	3056	29378.3	0.22	0.08	0.56	0.002
	B/C	16	184727	1455464.9	0.27	0.15	0.48	<0.001
Co-infected subpopulation								
	Yes	3	148485	1217211.2	0.31	0.16	0.62	0.001
	No	23	39298	267631.9	0.27	0.16	0.44	<0.001
HBeAg Status at Baseline								
	(+)	5	1184	9258.7	0.31	0.09	1.11	0.073
	(-)	6	3787	45751.3	0.20	0.09	0.47	<0.001
	Mix	15	182812	1429833.2	0.26	0.14	0.48	<0.001



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Sub-analysis of treatment studies

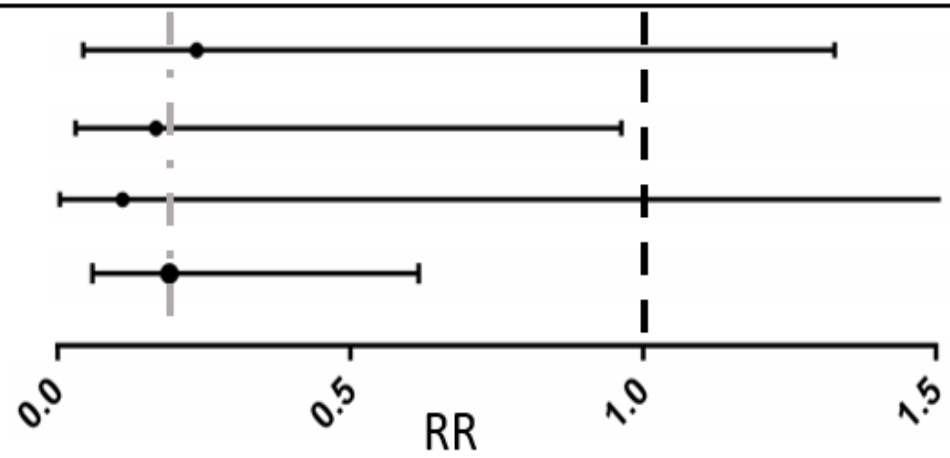
Number of studies

Number of patients

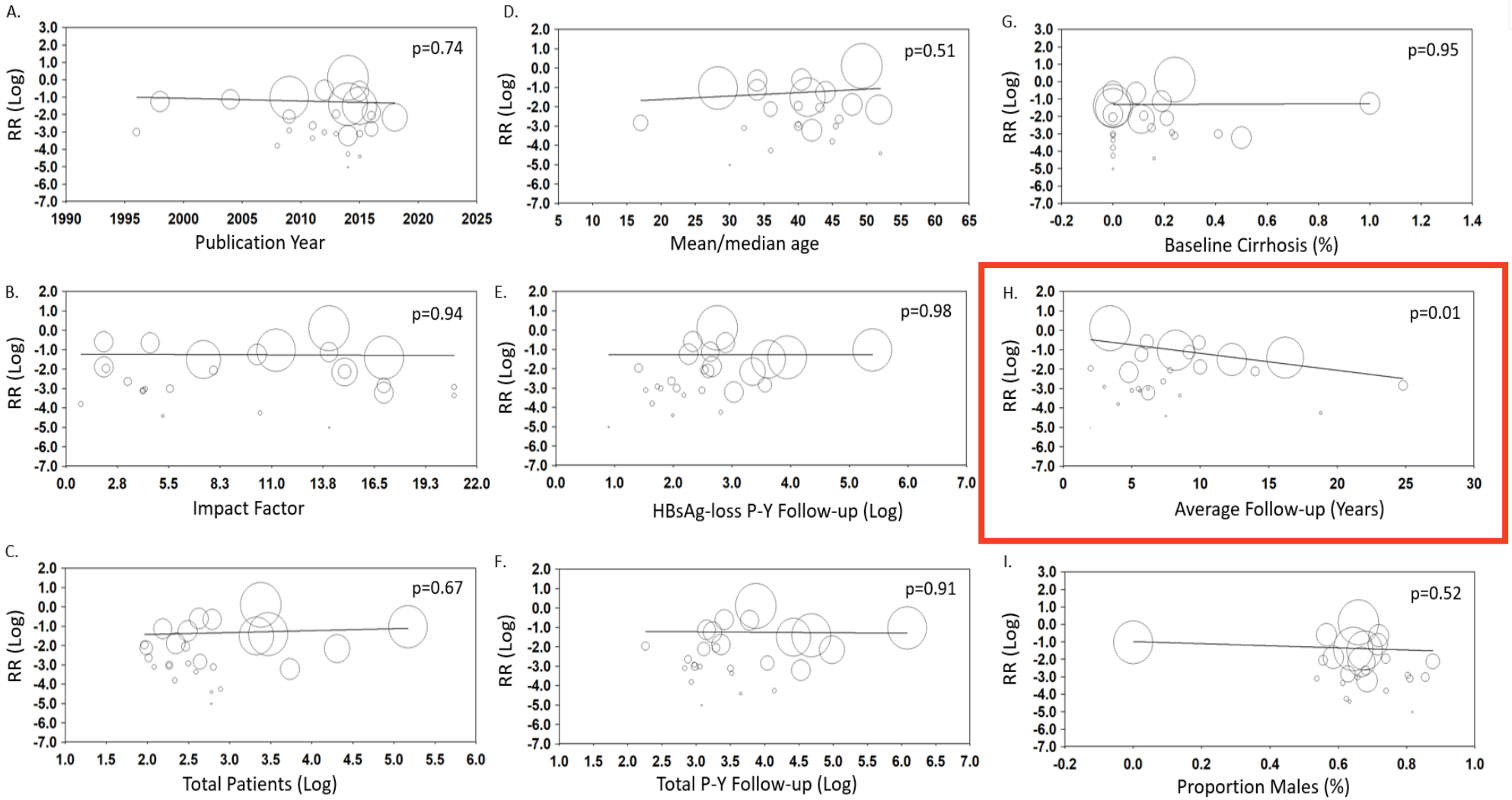
Total person-years of follow-up

Rate ratio

Drug Class	K	N	P-Y	RR	Lower limit	Upper limit	p-value
IFN	2	250	2695.9	0.24	0.04	1.33	0.101
NrtI	7	29898	146351.6	0.17	0.03	0.96	0.045
NrtI+IFN	2	405	1123.0	0.11	<0.01	6.99	0.296
Overall	**11**	**30553**	**150171**	**0.19**	**0.06**	**0.62**	**0.006**



Meta-regression sensitivity analysis



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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