Predictors of HBsAg loss, including baseline quantitative HBsAg, in adults with chronic hepatitis B: A regional cohort study in China

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Plain language summary: This study looked at people with chronic hepatitis B in China to find out what factors are linked with loss of hepatitis B surface antigen (HBsAg), a sign of better long-term health. Patients with lower levels of HBsAg at the start were much more likely to lose HBsAg over time. These findings suggest that regular testing for HBsAg levels could help identify patients who are most likely to benefit from new treatments

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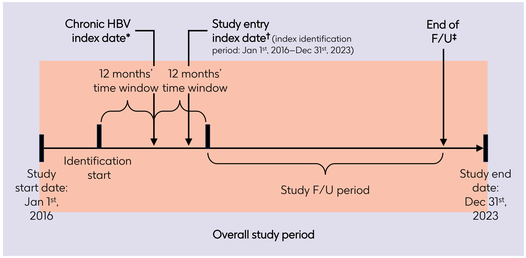
Background

- Chronic HBV infection is a major global public health problem and a leading cause of liver-related morbidity/mortality[1]
- In China, 75 million people are estimated to be chronically HBsAg-positive[2,3]
- The goal of current anti-HBV therapy is to improve quality of life and prevent disease progression to cirrhosis, decompensated liver disease, HCC, or death[4]
- Compared to suppression of HBV replication alone, HBsAg loss may be associated with a lower risk of HCC[5]
- Novel anti-HBV therapies aim to achieve FC[6,7]
- BL qHBsAg levels impact treatment response, with low levels predicting better outcomes[8], but routine qHBsAg testing is limited and population-level data are sparse
- This study characterised demographic, clinical and virological predictors–including BL qHBsAg–of HBsAg loss among patients with chronic HBV infection in China

Methods

- This retrospective cohort study used EMR data from the Tianjin regional database from 82 hospitals (identification period: 2016–2023)
- Eligible patients were adults (≥18 years of age) with chronic HBV infection, ≥1 qHBsAg measurement (first positive test = study entry index date), no coinfection (HCV, HDV and HIV) and no major adverse liver outcomes (compensated/decompensated cirrhosis, HCC or liver transplant) before study entry index (**Figure 1**)
- Demographic and clinical variables were recorded in the 12 months before study entry index
- A multivariate Cox proportional hazards model evaluated predictors of HBsAg loss

Figure 1: **Study design**



**Defined as the first evidence of chronic HBV infection within the identification period; †defined as the date when the first laboratory parameters of qHBsAg with a positive result have been recorded within 12 months before or after the chronic HBV index date; ‡defined as the last clinical encounter date or death*

Results

- In total, 28,659 individuals (**Table 1**) were included, with a median duration of F/U of 4.6 year; of these, 656 (2.3%) experienced HBsAg loss
- Among individuals with BL qHBsAg ≤3000 IU/mL, HBsAg loss occurred in 454/15,529 (2.9%)
- 5369 individuals were treated with NAs (18.7%), 387 (1.4%) with Peg-IFN and 22,903 (79.9%) remained untreated
- Of NA-treated individuals, 3039 (56.6%) had BL qHBsAg ≤3000 IU/mL and 1653 (30.8%) had ≤1000 IU/mL
- HBsAg loss was observed in 102/3039 (3.4%) of NA-treated individuals with BL qHBsAg ≤3000 IU/mL and 79/1653 (4.8%) of NA-treated individuals with BL qHBsAg ≤1000 IU/mL

Table 1: **Demographic and clinical characteristics of participating individuals**

	HBsAg loss (N=656)	No HBsAg loss (N=28,003)
Age, mean (SD)	42.3 (14.1)	41.6 (13.1)
Male, n (%)	365 (55.6)	15,667 (55.9)
Age (years) group distribution, n (%)		
18–<50	442 (67.4)	19,925 (71.1)
50–<70	192 (29.2)	7463 (26.6)
≥70	22 (3.4)	615 (2.2)
BL qHBsAg distribution (IU/mL), n (%)		
≤100	262 (39.9)	3670 (13.1)
>100–≤1000	113 (17.2)	5792 (20.7)
>1000–≤3000	79 (12.0)	5613 (20.0)
>3000	202 (30.8)	12,928 (46.2)
BL treatment,* n (%)		
NAs	122 (18.6)	5247 (18.7)
Peg-IFN	7 (1.1)	380 (1.4)
No treatment	527 (80.3)	22,376 (79.9)
BL qHBsAg (IU/mL) by treatment,† n (%)		
NAs, n (%, HBsAg loss vs no HBsAg loss)	122 (2.3)	5247 (97.7)
≤100	47 (38.5)	408 (7.8)
>100–≤1000	32 (26.2)	1166 (22.2)
>1000–≤3000	23 (18.9)	1363 (26.0)
>3000	20 (16.4)	2310 (44.0)
Peg-IFN, n (%, HBsAg loss vs no HBsAg loss)	7 (1.8)	380 (98.2)
≤100	4 (57.1)	45 (11.8)
>100–≤1000	0 (0.0)	81 (21.3)
>1000–≤3000	1 (14.3)	68 (17.9)
>3000	2 (28.6)	186 (48.9)
No treatment, n (%, HBsAg loss vs no HBsAg loss)	527 (2.3)	22,376 (97.7)
≤100	211 (40.0)	3217 (14.4)
>100–≤1000	81 (15.4)	4545 (20.3)
>1000–≤3000	55 (10.4)	4182 (18.7)
>3000	180 (34.2)	10,432 (46.6)

**105 (16.0%) and 4488 (16.0%) of individuals in the HBsAg loss and No HBsAg loss groups, respectively, were receiving NA monotherapy; 2 (0.3%) and 265 (0.9%) of individuals in the HBsAg loss and No HBsAg loss groups, respectively, were receiving Peg-IFN monotherapy; and 5 (0.8%) and 115 (0.4%) of individuals in the HBsAg loss and No HBsAg loss groups, respectively, were receiving Peg-IFN and NA combination therapy; †percentages in orange are calculated out of the total number of individuals within that treatment group regardless of whether they had HBsAg loss; for each treatment group, individual percentage breakdowns by BL qHBsAg levels are exhibited in black*

- Cox regression showed lower BL qHBsAg was strongly associated with HBsAg loss (**Figure 2**). Moreover, age and high ALT (1–2x vs 1× ULN) were associated with reduced likelihood of HBsAg loss, while higher ALT (>5× vs 1× ULN), BL HBeAg positivity, non-ALD and T2D were associated with increased likelihood of HBsAg loss. In particular, ALT elevation (>5× vs 1× ULN) was associated with a 3.05 increase in the odds of HBsAg loss (**Figure 3**)

Figure 2: **Association between BL qHBsAg and likelihood of HBsAg loss**

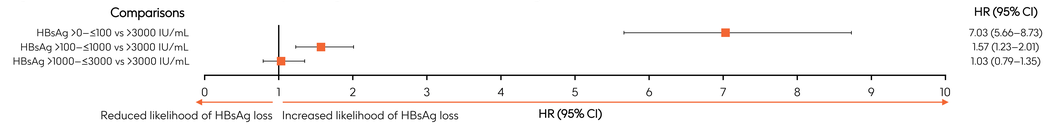
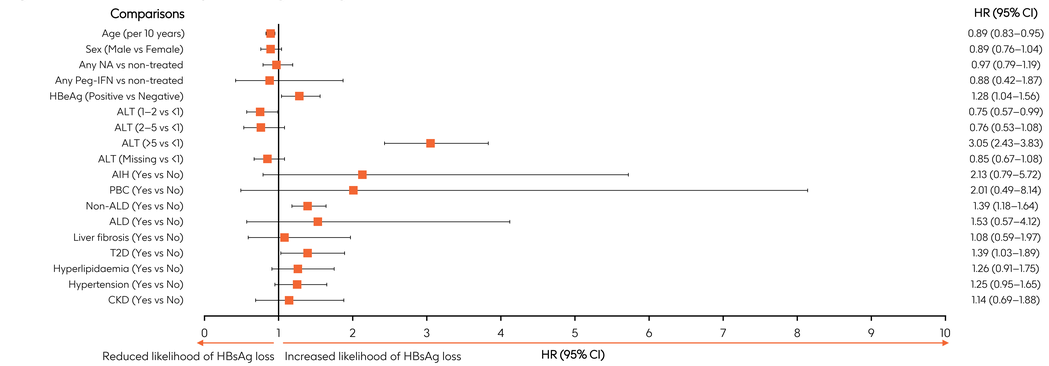
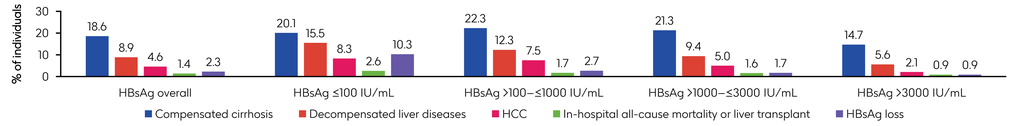


Figure 3: **Predictors of experiencing HBsAg loss**



- In the sub-cohort of patients treated only with NAs, HBsAg loss was more frequent in those individuals presenting lower BL HBsAg (**Figure 4**)

Figure 4: **Long-term clinical and virological outcomes by BL HBsAg in non-cirrhotic chronic HBV patients treated with NAs**



Conclusions

The results from this retrospective study reflect a strong association between very low (>0–≤100 IU/mL) and low (>100–≤1000 IU/mL) BL qHBsAg and HBsAg loss in patients with chronic HBV infection in China

This highlights the need for routine qHBsAg testing to identify patients with chronic HBV infection who are most likely to achieve FC with emerging therapies

Abbreviations

AIH, autoimmune hepatitis; ALD, alcoholic liver disease; ALT, alanine aminotransferase; BL, baseline; CI, confidence interval; CKD, chronic kidney disease; EMR, electronic medical records; F/U, follow-up; FC, functional cure (defined as ≥24 weeks of sustained HBV DNA <lower limit of quantification [LLOQ] and HBsAg loss after finite therapy, with or without hepatitis B surface antibody [anti-HBs]); HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; HR, hazard ratio; IU, international unit; NA, nucleot(s)ide analogue; PBC, primary biliary cholangitis; Peg-IFN, pegylated interferon; qHBsAg, quantitative HBsAg; SD, standard deviation; T2D, type 2 diabetes; ULN, upper limit of normal

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