Regression of liver fibrosis after seroclearance of hepatitis B surface antigen: a prospective matched case-control study using transient elastography and serum Enhanced Liver Fibrosis test (abridged secondary publication)

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KEY MESSAGES

1. Chronic hepatitis B infection is usually lifelong. Only 0.5% to 2.0% of patients per year achieve functional cure, defined as seroclearance of hepatitis B surface antigen (HBsAg), which is associated with a lower risk of liver cancer.
2. It remains unclear whether HBsAg loss is associated with regression in liver fibrosis.
3. Assessments via imaging (transient elastography) and a serum-based biomarker (Enhanced Liver Fibrosis test score) showed that HBsAg loss was not associated with a higher rate of liver fibrosis regression at 3 years.
4. Age at HBsAg loss has prognostic implications for advanced fibrosis and cirrhosis risks. Patients achieving HBsAg seroclearance after age 50 years should receive ongoing surveillance for liver-related complications.

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Introduction

Patients with chronic hepatitis B infection (CHB) are at risk for cirrhosis and liver cancer. Only 0.5% to 2.0% of patients per year achieve functional cure, defined as seroclearance of hepatitis B surface antigen (HBsAg). This seroclearance, also known as HBsAg loss, is associated with a lower risk of hepatocellular carcinoma (HCC), especially when it occurs before age 50 years.[1] Risks of liver decompensation, transplantation, and death are also reduced. Nonetheless, it remains uncertain whether HBsAg loss produces similar beneficial effects on cirrhosis.

The use of non-invasive methods, such as the Enhanced Liver Fibrosis (ELF) test and transient elastography, to quantify liver fibrosis is standard care for patients with CHB. The ELF test measures three serum markers of advanced liver fibrosis and cirrhosis, including tissue inhibitor of metalloproteinase 1, amino-terminal pro-peptide of type III pro-collagen, and hyaluronic acid. It has been validated by histology-based studies in patients with CHB. Transient elastography exhibits good performance characteristics for assessing liver fibrosis. It is safe, fast, and reproducible; therefore, it has been widely adopted as a surrogate marker for liver fibrosis.[2] A combination of tests for fibrosis assessment is recommended. The use of both a serum-based test and an imaging-based test (rather than either test alone) may improve diagnostic accuracy and reduce the need for liver biopsies.[3]

We aimed to compare the percentages of patients with fibrosis regression between CHB patients with and without HBsAg loss. We hypothesised that HBsAg loss is associated with ongoing favourable effects on liver fibrosis and increased odds of fibrosis regression.

Methods

Patients with CHB (ie, HBsAg positivity for >6 months) aged 18 to 75 years with spontaneous HBsAg loss (defined as sustained HBsAg negativity for >6 months) were prospectively recruited from the Liver Clinic, Department of Medicine, Queen Mary Hospital, Hong Kong. Matched controls were CHB patients without HBsAg loss who were not receiving antiviral treatment; these controls were recruited at a 1:1 ratio after matching for age and sex. We specifically excluded antiviral-treated patients because such treatment is known to influence fibrosis regression. Patients were also excluded if they had abnormal alanine aminotransferase (ALT) on two occasions separated by >6 months (because elevated ALT confounds liver stiffness [LS] measurement), concomitant liver disease, a prior history of HCC or liver transplantation, or other serious medical conditions. All recruited patients underwent liver assessment by transient elastography and serum

ELF measurement at baseline and 3 years. The age at HBsAg loss and the time since HBsAg loss were recorded.

The controlled attenuation parameter (CAP) for liver steatosis estimation was recorded in decibels per meter (dB/m). Liver fibrosis stages were classified in accordance with European Association for Study of Liver guidelines, as follows: minimal fibrosis (F1) with LS of <6 kPa, grey zone (F2) [6-9 kPa], advanced fibrosis (F3) [9-12 kPa], and cirrhosis (F4) [>12 kPa]. Steatosis was categorised as mild (CAP: 248-267 dB/m), moderate (CAP: 268-279 dB/m), and severe (CAP: ≥280 dB/m). ELF scores of ≥8.5, ≥9.4, and ≥10.1 were defined as F2, F3, and F4, respectively.

The primary outcome was the percentage of patients with fibrosis regression at 3 years between those with and without HBsAg loss. The time interval was chosen based on observations that clinically significant fibrosis regression occurred after disease quiescence was achieved by nucleoside analogue therapy or HBsAg loss for a minimum of 3 years.[4] Fibrosis regression was arbitrarily defined as an LS reduction of ≥30% from baseline. No data were available regarding longitudinal changes in ELF score or a standardised definition of 'significant change'.[5] Therefore, a significant change in ELF score was arbitrarily defined as downstaging (ie, >10.1 to <9.4, >9.4 to <8.5, or >8.5 to <8.5). Analysis was performed according to the intention-to-treat principle; all patients who completed the 3-year follow-up were included in the endpoint analysis.

TABLE. Baseline characteristics of patients with and without hepatitis B surface antigen (HBsAg) loss

Variable	HBsAg loss (n=142)*	No HBsAg loss (n=142)*	P value
Age, y	60 (53.3-66.9)	55.7 (49.5-61.4)	<0.001
Male sex	51.4	51.4	1.000
Overweight	56.3	66.9	0.087
Body mass index, kg/m^2	23.8	24.3	0.185
Controlled attenuation parameter (CAP), dB/m	234 (207-294)	251 (208-297)	0.208
Type 2 diabetes	17.6	18.3	1.000
Alanine aminotransferase, U/L	21 (16-29)	24 (19-31)	0.012
Aspartate aminotransferase, U/L	24 (21-28)	24 (21-31)	0.364
Platelets, ×10^9/L	214 (183-254)	216 (183-250)	0.837
Hepatitis B virus DNA, IU/mL	-	267 (69-887)	-
Age at HBsAg loss, y	57.4 (50.5-63.2)	-	-
Time since HBsAg loss, y	5.5 (4.9-6.2)	-	-
Steatosis (CAP ≥248 dB/m)	43.7	52.1	0.191
Liver stiffness, kPa	5.1 (4.1-6.2)	5.2 (4.3-6.8)	0.420
Advanced fibrosis/cirrhosis (F3/F4)	4.9	3.5	0.770
Enhanced Liver Fibrosis test score	9.3 (8.8-9.9)	8.4 (7.9-9.3)	<0.001
Advanced fibrosis/cirrhosis (F3/F4)	41.1	14.1	<0.001

* Data are presented as median (interquartile range) or % of patients.

Results

In total, 284 patients (142 with HBsAg loss and 142 without HBsAg loss), matched for sex (51.4% male), were included in the analysis (Table). Despite efforts to match for age, the baseline age was higher in patients with HBsAg loss than in patients without HBsAg loss (60 vs 55.7 years, P<0.001). A higher percentage of patients with HBsAg loss had ELF-defined advanced fibrosis or cirrhosis (F3/F4) [41.1% vs 14.1%, P<0.001]. However, LS-defined F3/F4 was present in <5% of patients in both groups.

Overall, 1.8% of patients with CHB demonstrated fibrosis regression at 3 years when both ELF and LS criteria were applied (1.4% in patients with HBsAg loss vs 2.1% in patients without HBsAg loss, P=1.000). When only the ELF criteria were applied, 14.5% of patients with HBsAg loss and 16.9% of patients without HBsAg loss showed fibrosis regression at 3 years (Fig).

Compared with the age at HBsAg loss of >50 years, the age at HBsAg loss of <50 years was associated with lower prevalences of ELF-defined F3/F4 at baseline (5.9% vs 52.3%, P<0.001) and 3 years (20.6% vs 63.8%, P<0.001), as well as lower prevalences of LS-defined F3/F4 at baseline (2.9% vs 5.6%, P=1.000) and 3 years (3.0% vs 13.9%, P=0.118).

Discussion

HBsAg loss is considered a clinical endpoint of functional cure in CHB, associated with lower risks of HCC and decompensated liver disease. In our study, only 1.4% of patients with HBsAg loss showed fibrosis regression at 3 years when both ELF and LS criteria were applied. Using only the ELF criteria, 14.5% of patients with HBsAg loss exhibited fibrosis regression at 3 years. Outcomes were similar between patients with and without HBsAg loss. Our hypothesis that HBsAg loss would be associated with fibrosis regression was not supported, possibly due to the higher mean age among patients with HBsAg loss. Despite the finding of HBsAg loss, these patients remain at risk for advanced fibrosis and cirrhosis-related complications.

The low percentage of patients with fibrosis regression may be related to the protocol-defined endpoint of fibrosis regression, which required meeting both LS and ELF criteria. At baseline, 95.8% of patients had LS values indicative of F0/F1 or grey zone. The ELF criteria are more sensitive than LS criteria in patients with an apparently low risk of liver complications (normal ALT, treatment-naïve); half of our patients had already achieved functional cure.

Age at HBsAg loss of <50 years was associated with a lower prevalence of ELF-defined F3/F4 at baseline, compared with the age at HBsAg loss of >50 years (5.9% vs. 52.3%, P<0.001). These findings confirm that the benefits of HBsAg seroclearance are most prominent when it occurs before age 50 years.[1] Nonetheless, patients can exhibit F3/F4 despite achieving HBsAg seroclearance, especially if the seroclearance occurs after age 50 years. Ongoing surveillance for liver-related complications is recommended for these patients.

Metabolic factors, including overweight and type 2 diabetes, were present in a high percentage of patients with HBsAg loss (56.3% and 17.6%, respectively) and may have contributed to the high prevalence (41.1%) of ELF-defined F3/F4 at baseline.

Limitations of the present study included its lack of liver biopsy for histological assessment of liver fibrosis and its short follow-up period. Strengths of the study included its prospective design, the use of a combination of non-invasive assessments for liver fibrosis, and the inclusion of a homogenous population.

Conclusion

Although a longer duration of HBsAg loss was associated with a higher likelihood of fibrosis regression, the effects were influenced by age. Age at HBsAg loss has prognostic implications for advanced fibrosis and cirrhosis risks. Patients achieving HBsAg seroclearance after age 50 years should receive ongoing surveillance for liver-related complications. Novel treatments to induce functional cure in CHB patients should target younger populations, who have greater potential for clinical improvement.

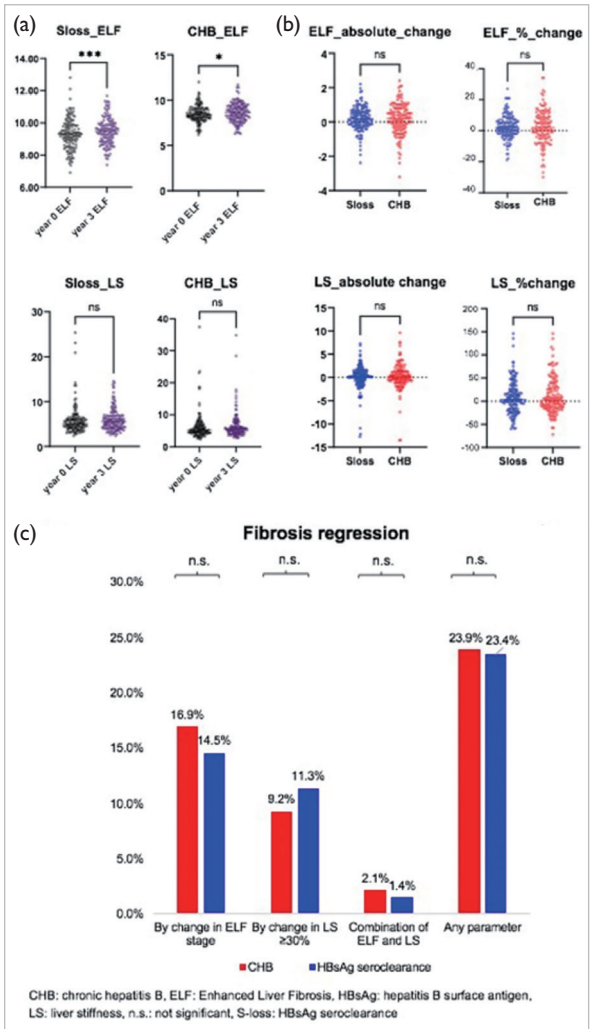

FIG. Comparisons between patients with and without hepatitis B surface antigen (HBsAg) loss in terms of (a) median Enhanced Liver Fibrosis (ELF) test and liver stiffness (LS) values at baseline and 3 years, (b) median absolute and percentage changes in ELF and LS values at 3 years, and (c) percentages of patients achieving fibrosis regression at 3 years based on various criteria.

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Disclosure

The results of this research have been previously published in:

1. Mak LY, Hui RW, Chung MSH, et al. Regression of liver fibrosis after HBsAg loss: a prospective matched case-control evaluation using transient elastography and serum enhanced liver fibrosis test. J Gastroenterol Hepatol 2024. doi:10.1111/jgh.16728

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