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Incidence and Predictors of HBsAg Seroclearance in 10,614 Untreated Patients on Long-Term Follow-up: A Collaborative Study from North America and Asia Pacific

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Abstract Text

Background: Spontaneous HBsAg seroclearance is the functional cure of hepatitis B virus and is associated with a better prognosis. However, the reported rates of seroclearance have been limited by small sample size. In this study, we combined data from nine cohorts to investigate the incidence and determinants of HBsAg seroclearance.

Methods: Data were obtained from nine cohorts in North America (one cohort, n= 1,635) and Asia (eight cohorts, n=8979) totalling 10,614 CHB patients who never received treatment for hepatitis B infection. Serial laboratory data were collected to determine HBsAg seroclearance, defined as having two undetectable HBsAg results six months apart. Annual, and cumulative incidence rates of HBsAg seroclearance were estimated. Subgroup analyses and multivariable Cox proportional hazard regression were performed to assess the determinants of HBsAg seroclearance.

Results: A total of 1,273 spontaneous incident HBsAg seroclearance occurred during 95,886 person years of follow-up. The pooled annual seroclearance rate was 1.33% (95% CI: 1.26-1.40), while 5-, 10-, 15-, and 20-year cumulative incidence rate were 5.01%, 11.36%, 19.44%, and 25.49%, respectively. After adjusting for sex, age, baseline HBeAg status, cirrhosis at baseline, ALT level, clinical setting, and ethnicity, the hazard of spontaneous HBsAg seroclearance during follow-up was significantly higher in males (HR=1.17, 95%CI: 1.04-1.33 vs. female), older age group (age≥55: HR=1.79, 95%CI: 1.49-2.15; age 45-54: HR=1.52, 95%CI: 1.28-1.80; age 35-44: HR=1.25, 95%CI: 1.06-1.48 vs. age≤35), higher baseline ALT level (HR=1.01, 95%CI: 1.00-1.01 for every 10 unit increase) and lower in those with baseline HBeAg (+) (HR=0.25, 95%CI: 0.19-0.32 vs. HBeAg[-]), higher HBV DNA level (>20,000IU/mL: HR=0.35, 95%CI: 0.28-0.43; 2,000-20,000IU/mL: HR=0.43, 95%CI: 0.36-0.52 vs. HBV DNA<2,000IU/mL),and higher quantitative HBsAg (qHBsAg) level (>1,000IU/mL: HR=0.21, 95%CI: 0.18-0.25 vs qHBsAg≤1000IU/mL). Subgroup analysis showed that patients with genotype C had higher likelihood of achieving HBsAg seroclearance than those with genotype B.

Conclusion: The spontaneous annual HBsAg seroclearance rate in hepatitis B patients is 1.33%, with approximately 25% of patients achieving seroclearance after 20 years of follow-up. Being male, older, and HBeAg-negative and having higher ALT, lower HBV DNA level, and lower qHBsAg level were associated with a higher likelihood of attaining HBsAg seroclearance.

Table: Multivariable analysis to assess the determinants for spontaneous HBsAg seroclearance

Subgroups		aHR*	95% CI	*P*-value
Sex (n=9,607)	Female	1		
	Male	**1.17**	**1.04-1.33**	**0.012**
Age (n=9,607)	≤35	1		
	35-44	**1.25**	**1.06-1.48**	**0.009**
	45-54	**1.52**	**1.28-1.80**	**<0.001**
	≥55	**1.79**	**1.49-2.15**	**<0.001**
Baseline HBeAg (n=9,607)	HBeAg (-)	1		
	HBeAg (+)	**0.25**	**0.19-0.32**	**<0.001**
Baseline ALT (n=9,607)	every 10 U/L increase	**1.01**	**1.00-1.01**	**<0.001**
Baseline HBV DNA (n=7,895)	<2,000IU/mL	1		
	2,000-20,000IU/mL	**0.43**	**0.36-0.52**	**<0.001**
	>20,000IU/mL	**0.35**	**0.28-0.43**	**<0.001**
Baseline qHBsAg (n=6,929)	≤1000IU/mL	1		
	>1,000IU/mL	**0.21**	**0.18-0.25**	**<0.001**
Baseline cirrhosis (n=9,607)	Non-cirrhosis	1		
	Cirrhosis	0.89	0.62-1.28	0.523
Race (n=9,607)	Asian	1		
	Non-Asian	1.64	0.22-12.23	0.629
Clinical settings (n=9,607)	Population-based	1		
	Hospital-based	0.63	0.10-3.89	0.621

Abbreviation: aHR: adjusted hazard ratio, CI: confidence interval, HBeAg: hepatitis B e antigen, ALT: alanine transaminase, qHBsAg: quantitative hepatitis B surface antigen

*Adjusted for sex, age, baseline HBeAg status, cirrhosis at baseline, ALT level, clinical setting, and race

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