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Original Article

Predictors of long-term recurrence and survival after resection of HBV-related hepatocellular carcinoma: the role of HBsAg

I-Cheng Lee[1,2], Hao-Jan Lei[3], Gar-Yang Chau[3], Yi-Chen Yeh[4], Chi-Jung Wu[1], Chien-Wei Su[1,2], Teh-Ia Huo[1,5,6], Yee Chao[7], Han-Chieh Lin[1,2], Ming-Chih Hou[1,2], Yi-Hsiang Huang[1,2,8]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [2]Faculty of Medicine, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan; [3]Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [5]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan; [6]Institute of Pharmacology, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan; [7]Cancer Center, Taipei Veterans General Hospital, Taipei, Taiwan; [8]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

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Abstract: The recurrence rate remains high even under nucleos(t)ide analogues (NUCs) therapy in patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) after resection. The aim of this study is to evaluate the prognostic role of HBsAg in patients undergoing surgical resection for HBV-related HCC in NUCs era. Consecutive 522 patients undergoing surgical resection for HBV-related HCC were retrospectively enrolled. Factors associated with early (within 2 years), late (year 2 to 5), very late (beyond 5 years) recurrence and early or late mortality (within or beyond 5 years) were evaluated. During a median follow-up period of 59 months, 308 (59%), and 146 (28%) patients developed recurrence and mortality, respectively. HBsAg level did not correlate with early recurrence and mortality. By multivariate analyses, HBsAg >200 IU/mL (hazard ratio (HR)=1.778, P=0.037) and presence of cirrhosis (HR=2.157, P=0.001) were independent predictors of late recurrence, while HBsAg >50 IU/mL (HR=4.658, P=0.038), body mass index >25 kg/m^2 (HR=2.720, P=0.013) and significant hepatic fibrosis (HR=2.509, P=0.039) were independent predictors of very late recurrence. HBsAg >50 IU/mL (HR=11.427, P=0.017), age >60 years (HR=2.688, P=0.006), albumin ≤3.5 g/dL (HR=4.739, P<0.001) and presence of cirrhosis (HR=2.781, P=0.006) were independent predictors of late mortality beyond 5 years. Combining these factors could well predict patients with minimal risk of long-term recurrence and mortality. In conclusion, tumor factors, liver function surrogate markers, metabolic factors and serum HBsAg levels play distinct roles in recurrence and survival at different time intervals after surgical resection for HBV-related HCC. Pre-operative HBsAg level is an important predictor of long-term recurrence and survival in patients with HBV-related HCC undergoing surgical resection.

Keywords: Hepatitis B virus, hepatocellular carcinoma, recurrence, survival, resection

Introduction

Hepatocellular carcinoma (HCC) remains the fourth leading cause of cancer-related deaths in the world, and chronic hepatitis B (CHB) accounts for more than half of the global HCC cases [1]. Surgery leads to a higher probability of long-term cure in well-selected candidates [2], but nearly 70% of patients may develop HCC recurrence after resection [2-4]. Early and late recurrences, within and beyond two years of surgery, are associated with different prognostic factors [5, 6]. Higher tumor burden, microvascular invasion and poorer liver function reserve has been shown to be predictors of early recurrence of HCC, whereas greater degree of hepatic necro-inflammation and fibrosis has been shown to be predictors of late recurrence of HCC [5-8].

In patients with hepatitis B virus (HBV)-related HCC, high HBV viral load is an important risk factor of late recurrence after surgery [7, 9, 10]. Previous studies have demonstrated that effec-

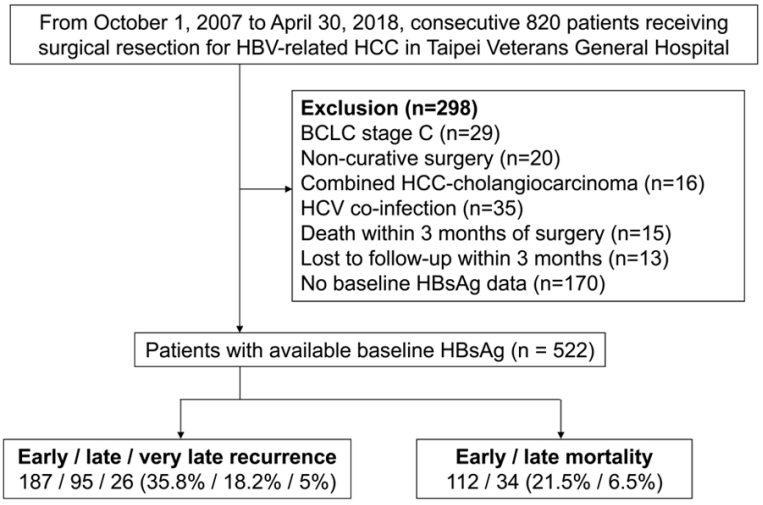

Figure 1. Screening, enrollment and grouping of patients.

tive viral suppression with nucleos(t)ide analogues (NUCs) could decrease the risk of postoperative HCC recurrence [10, 11]. Recent randomized controlled trials further confirmed that NUCs significantly decreased the risk of HCC recurrence [12, 13]. Therefore, NUCs therapy is generally prescribed for HCC patients with high viral load after surgery.

HBV viral load may lose the predictive value of HCC occurrence or recurrence in CHB patients with low level viremia or under NUCs therapy [14-17]. In patients with low HBV viral load, HBsAg levels could further differentiate the risk of HCC development [18]. Apart from HBV viral load, HBsAg levels were reported to correlate with HCC recurrence in CHB patients without NUCs treatment [19, 20]. Currently, majority of HCC patients with high HBV DNA received NUCs therapy after surgical resection, and long-term outcomes are generally improved under NUC therapy [21]. Currently, most patients with high HBV viremia were under NUCs therapy, and the virological factors associated with recurrence and survival after resection for HBV-related HCC would be different. The aim of this study is to evaluate the prognostic role of HBsAg levels in recurrence and survival of patients with HBV-related HCC undergoing curative surgical resection.

Material and methods

Patients

We retrospectively screened patients who received surgical resection for HBV-related HCC during October 1, 2007 to April 30, 2018 in Taipei Veterans General Hospital (**Figure 1**). Inclusion criteria included age older than 20 years, curative resection, and HBsAg-positive with available baseline quantitative level. Exclusion criteria included BCLC stage C, presence of other malignancy, and lost to follow-up or death within 3 months after surgery. HCC was diagnosed prior to surgical resection by contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) [22], and was further confirmed by pathology after surgery. After confirmation of the curative resection by CECT or MRI after surgery, patients were followed every 3 months with alpha-fetoprotein (AFP) measurement, ultrasound, CECT or MRI. HCC recurrence was confirmed by CECT or MRI.

This study complied with current ethical guidelines and standards of the Declaration of Helsinki, and has been approved by the Institutional Review Board, Taipei Veterans General Hospital (IRB number: 2019-10-001BC).

Endpoint

The primary endpoints were early, late and very late recurrence, defined as tumor recurrence within 2 years, between year 2 to 5, and beyond 5 years, respectively, after the surgery (**Figure 2A**). The secondary endpoints were early and late mortality, defined as death within or beyond 5 years, respectively, after surgery (**Figure 3A**).

Laboratory tests and pathology

The clinical parameters including age, sex, Barcelona Clinic Liver Cancer (BCLC) stage, body mass index (BMI), Child-Pugh score and class, serum ALT, AST, total bilirubin, albumin, creatinine, AFP levels and complete blood counts were collected. Serum HBV DNA level was measured by Roche Cobas Taqman HBV DNA assay (Roche Diagnostics, Switzerland) with detection limit of 20 IU/mL. Quantitative HBsAg level was measured by the Elecsys HBsAg II assay (Roche Diagnostics, Mannheim,

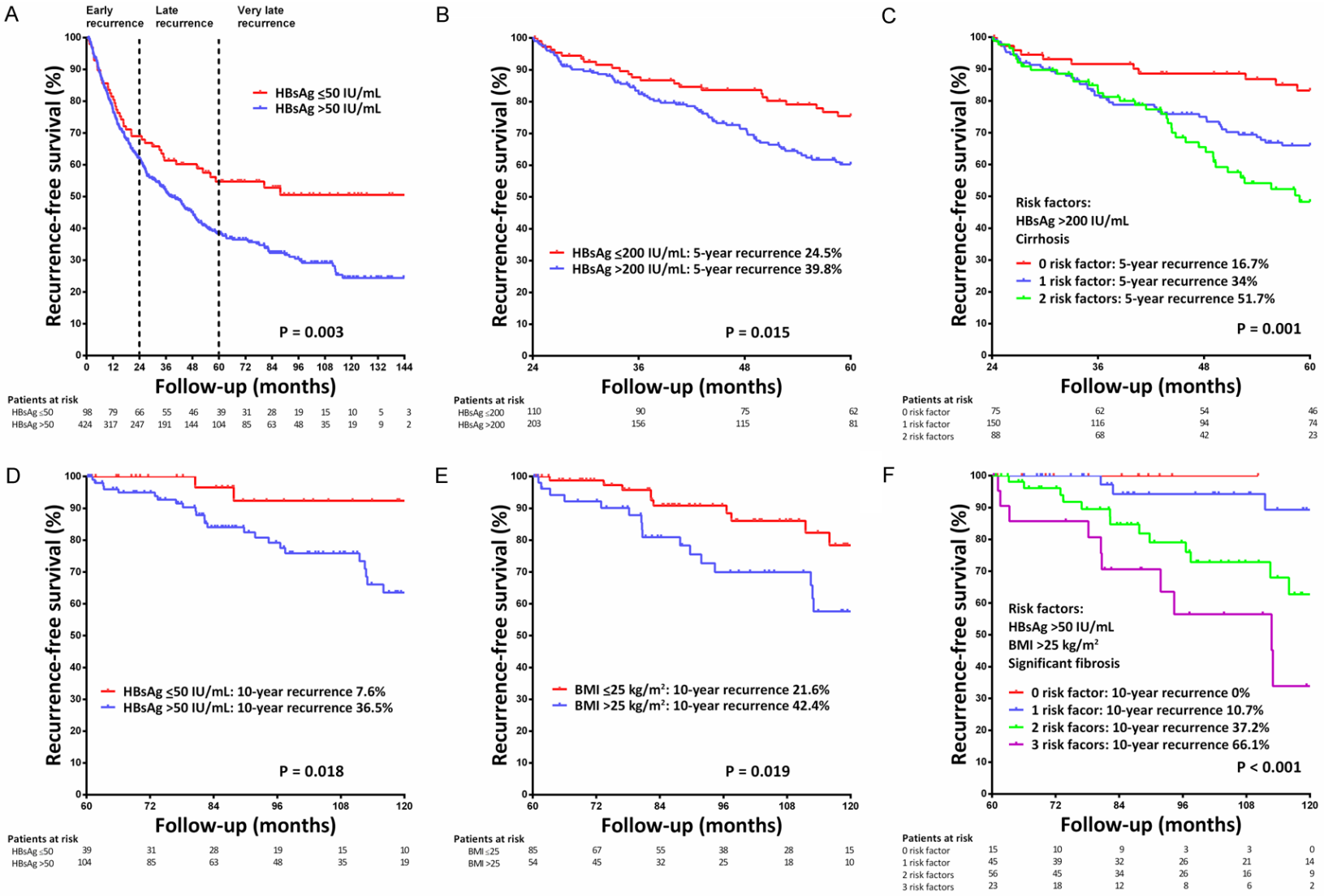

Figure 2. Kaplan-Meier curves of early, late and very late recurrence-free survival (RFS) in patients with HBV-related HCC receiving surgical resection. A. Overall RFS stratified by baseline HBsAg level. B. Late RFS stratified by baseline HBsAg level. C. Late RFS stratified by HBsAg level and cirrhosis status. D. Very late RFS stratified by baseline HBsAg level. E. Very late RFS stratified by body mass index (BMI). F. Very late RFS stratified by baseline HBsAg level, BMI and significant fibrosis.

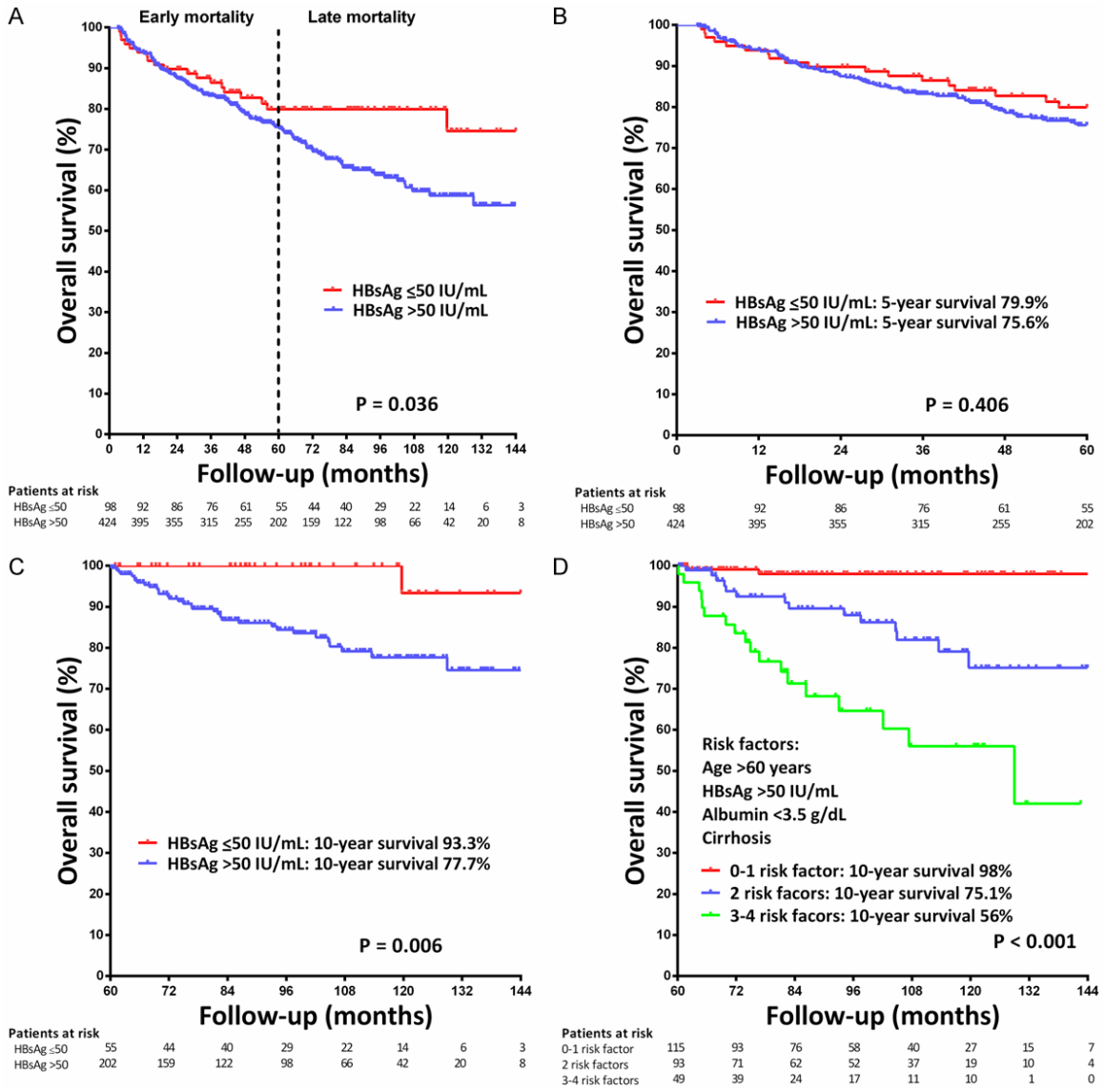

Figure 3. Kaplan-Meier curves of early and late mortality in patients with HBV-related HCC receiving surgical resection. A. Overall survival stratified by baseline HBsAg level. B. Early mortality stratified by baseline HBsAg level. C. Late mortality stratified by baseline HBsAg level. D. Late mortality stratified by the number of risk factors.

Germany) or Abbott Architect HBsAg assay (Abbott Diagnostics, Abbott Park, IL) with detection limit of 0.05 IU/mL.

Albumin-Bilirubin (ALBI) score and ALBI grade were calculated as previously described [23]. Histological features including tumor size and number, Edmonson histological grade, microvascular invasion, surgical cut margin, hepatic steatosis, and Ishak hepatic inflammation and fibrosis scores [24, 25] were recorded. Significant hepatic fibrosis and cirrhosis were defined as Ishak hepatic fibrosis scores greater than 2 and 4, respectively.

Statistical analysis

Descriptive statistic values were shown as mean ± standard deviation (SD) or as median (ranges) when appropriate. Continuous variable was compared by Mann-Whitney *U* test. Categorical variable was compared by Pearson chi-square analysis or the Fisher exact test. We used the Kaplan-Meier method to estimate survival rates, and log-rank test to compare survival curves between different groups. Cox proportional-hazards model was used to analyze the prognostic factors. Factors with $P<0.1$ by univariate analysis were included in the multi-

Table 1. Characteristics of the 522 patients with HBV-related HCC receiving curative surgical resection

Characteristics	
Age (years)	59.2 ± 11.9
Sex (male), n (%)	438 (83.9)
BMI (kg/m^2)	24.5 ± 3.5
Child-Pugh score 5/6/7, n (%)	458/60/4 (87.7/11.5/0.8)
HBsAg (Log IU/mL)	2.35 ± 1.08
HBV DNA (Log IU/mL)*	4.10 ± 2.01
Undetectable HBV DNA, n (%)	47 (11.4)
HBV DNA <2000 IU/mL	139 (33.6)
HBeAg-positive, n (%)*	40 (12.3)
Nucleos(t)ide analog treatment, n (%)	353 (67.6)
BCLC stage 0/A/B, n (%)	45/413/64 (8.6/79.1/12.3)
Tumor size (cm)	4.65 ± 3.58
Multiple tumors, n (%)	109 (20.9)
AFP (ng/mL)	22.1 (1-399976.4)
Albumin (g/dL)	4.09 ± 0.44
Total bilirubin (mg/dL)	0.84 ± 0.46
Albumin-Bilirubin (ALBI) score	-2.74 ± 0.39
ALBI grade 1/2/3, n (%)	359/162/1 (68.8/31.0/0.2)
Platelet count (10^9/L)	172 ± 77
ALT (U/L)	52.0 ± 61.3
AST (U/L)	47.4 ± 41.8
Creatinine (mg/dL)	0.96 ± 0.64
MELD score	6.40 ± 2.71
Tumor characteristics and histological features, n (%)	
Edmonson histological grade >1	200 (38.3)
Microvascular invasion	350 (67.0)
Surgical cut margin >1 cm*	118 (37.2)
Presence of steatosis*	188 (41.0)
Ishak hepatic inflammation scores >6	49 (9.4)
Ishak hepatic fibrosis score 5-6 (cirrhosis)	217 (41.6)
Outcomes	
Early/late/very late recurrence, n (%)	187/95/26 (35.8/18.2/5)
Early/late mortality, n (%)	112/34 (21.5/6.5)

*Available baseline HBV DNA data: n=414; available HBeAg data: n=324; available cut margin data: n=317; available steatosis data: n=459.

variate analysis by forward stepwise Cox proportional-hazards model. A two-tailed $P<0.05$ was considered statistically significant. The statistical analysis was performed using the IBM SPSS Statistics V22 (IBM, Armonk, NY).

Results

A total of 522 HCC patients were finally enrolled (**Figure 1**). The baseline characteristics of the 522 patients were shown in **Table 1**. About one-third (33.6%) of patients had baseline HBV DNA <2,000 IU/mL, while about two-third (67.6%) of patients received NUCs therapy after surgical resection. In patients with NUC therapy, 20 (5.6%), 296 (83.9%) and 37 (10.5%) patients received lamivudine, entecavir and tenofovir, respectively. In patients without NUCs therapy, 62.6% and 26.6% of them had HBV DNA <2000 IU/mL and cirrhosis, respectively.

Table 2. Different cutoff levels of HBsAg in predicting early, late, very late recurrence and mortality before or after 5 years of surgery

	HBsAg	HR	95% CI	*P*
Early recurrence	>50 vs ≤50	1.261	0.853-1.864	0.245
	>100 vs ≤100	1.214	0.853-1.728	0.280
	>200 vs ≤200	1.338	0.970-1.846	0.076
	>500 vs ≤500	1.290	0.936-1.779	0.120
	>750 vs ≤750	1.278	0.918-1.778	0.146
	>1000 vs ≤1000	1.231	0.867-1.746	0.245
Late recurrence	>50 vs ≤50	2.074	1.132-3.800	0.018
	>100 vs ≤100	1.732	1.024-2.927	0.040
	>200 vs ≤200	1.765	1.111-2.805	0.016
	>500 vs ≤500	1.263	0.817-1.951	0.294
	>750 vs ≤750	1.398	0.894-2.188	0.142
	>1000 vs ≤1000	1.374	0.858-2.201	0.187
Very late recurrence	>50 vs ≤50	4.815	1.138-20.376	0.033
	>100 vs ≤100	2.615	0.901-7.589	0.077
	>200 vs ≤200	2.075	0.872-4.938	0.099
	>500 vs ≤500	0.937	0.384-2.284	0.886
	>750 vs ≤750	0.805	0.273-2.370	0.693
	>1000 vs ≤1000	0.447	0.105-1.905	0.276
Early mortality	>50 vs ≤50	1.238	0.747-2.049	0.407
	>100 vs ≤100	1.141	0.726-1.791	0.568
	>200 vs ≤200	1.160	0.773-1.742	0.474
	>500 vs ≤500	1.124	0.707-1.785	0.622
	>750 vs ≤750	1.039	0.640-1.688	0.877
	>1000 vs ≤1000	1.031	0.615-1.727	0.908
Late mortality	>50 vs ≤50	9.587	1.311-70.110	0.026
	>100 vs ≤100	2.123	0.822-5.486	0.120
	>200 vs ≤200	1.655	0.772-3.548	0.195
	>500 vs ≤500	0.712	0.311-1.629	0.421
	>750 vs ≤750	0.739	0.298-1.833	0.515
	>1000 vs ≤1000	0.902	0.364-2.235	0.823

HR, hazard ratio; CI, confidence interval.

During a median follow-up period of 59 months (range 3.1-155 months), 308 (59%) patients developed recurrence of HCC after resection, including 187 (35.8%), 95 (18.2%) and 26 (5%) patients with early, late and late recurrence, respectively. The estimated 1-, 2-, 3-, 4-, 5- and 10-year RFS rates were 77.7%, 63.3%, 53.3%, 48%, 41.6% and 29.5%, respectively. One hundred and forty-six patients (28%) died during the follow-up period, including 112 (21.5%) and 34 (6.5%) cases with early and late mortality, respectively. The estimated 1-, 2-, 3-, 4-, 5- and 10-year OS rates were 94%, 88%, 83.9%, 79.6%, 76.4% and 61.8%, respectively.

Association of serum HBsAg levels and HCC recurrence or mortality

We compared different cutoffs of HBsAg levels and their associations with recurrence and mortality at different time intervals after resection (**Table 2**). Serum HBsAg at different cutoff levels were not associated with early recurrence and early morality. Serum HBsAg at cutoff levels of 50, 100 or 200 IU/mL were significantly associated with late recurrence, while 50 IU/mL was the only cutoff associated with very late recurrence and late mortality. Therefore, these cutoff levels were further used in the following analyses.

Factors associated with early, late and very late recurrence

In univariate analysis, BCLC stage, ALBI grade, AFP, albumin, AST levels, tumor size, tumor number, and microvascular invasion were factors associated with early recurrence (**Table 3**). Baseline HBsAg level was not associated with early recurrence. In multivariate analysis, ALBI grade 2-3 (hazard ratio (HR) =1.580, P=0.003), tumor size >5 cm (HR=1.991, P<0.001), AFP >20 ng/mL (HR=1.473, P=0.021), and microvascular invasion (HR= 1.571, P=0.018) were independent predictors of early recurrence.

In univariate analysis, factors associated with late recurrence include ALBI grade, tumor number, serum HBsAg levels, platelet counts, presence of significant hepatic fibrosis and cirrhosis (**Table 4**). By multivariate analysis, HBsAg >200 IU/mL (HR=1.778, P=0.037, **Figure 2B**) and cirrhosis (HR=2.157, P=0.001) were independent predictors of late recurrence. Combining HBsAg level and cirrhosis status could stratify patients into low, medium and high risk of late recur-

Table 3. Univariate and multivariate analyses of factors associated with early recurrence

		Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	>60 vs ≤60	0.951	0.714-1.267	0.732			
Sex	Female vs male	0.792	0.548-1.143	0.213			
BMI (kg/m^2)	>25 vs ≤25	0.780	0.579-1.050	0.102			
BCLC stage	B vs 0-A	2.345	1.635-3.363	<0.001			NS
Child-Pugh class	6-7 vs 5	1.351	0.898-2.031	0.149			
ALBI grade	2-3 vs 1	1.706	1.272-2.288	<0.001	1.580	1.173-2.129	0.003
HBV DNA (IU/mL)	>20 vs ≤20	1.591	0.881-2.871	0.123			
	>2000 vs ≤2000	1.084	0.768-1.531	0.645			
HBsAg (IU/mL)	>50 vs ≤50	1.261	0.853-1.864	0.245			
	>200 vs ≤200	1.338	0.970-1.846	0.076			NS
HBeAg	Positive vs negative	0.905	0.517-1.583	0.725			
NUC therapy	Yes vs no	1.209	0.881-1.658	0.240			
Tumor size (cm)	>3 vs ≤3	2.034	1.492-2.773	<0.001			NS
	>5 vs ≤5	2.226	1.664-2.978	<0.001	1.991	1.458-2.717	<0.001
Tumor number	Multiple vs single	1.783	1.299-2.446	<0.001	1.779	1.291-2.451	<0.001
AFP (ng/mL)	>20 vs ≤20	1.546	1.118-2.138	0.008	1.473	1.061-2.045	0.021
Bilirubin (mg/dL)	>1.2 vs ≤1.2	1.054	0.705-1.575	0.798			
Albumin (g/dL)	>3.5 vs ≤3.5	0.578	0.384-0.869	0.008			NS
Creatinine (mg/dL)	>1.2 vs ≤1.2	1.349	0.864-2.104	0.188			
MELD score	>6 vs ≤6	1.317	0.980-1.769	0.068			NS
Platelet count (10^9/L)	>150 vs ≤150	0.895	0.671-1.193	0.449			
ALT (U/L)	>40 vs ≤40	1.061	0.796-1.416	0.685			
AST (U/L)	>40 vs ≤40	1.541	1.153-2.059	0.003			NS
Histological grade	>1 vs 1	1.165	0.868-1.562	0.309			
Microvascular invasion	Presence vs absence	2.043	1.440-2.898	<0.001	1.571	1.081-2.284	0.018
Surgical margin (cm)	>0.5 vs ≤0.5	0.699	0.476-1.026	0.068			NS
	>1 vs ≤1	0.739	0.489-1.116	0.150			
Steatosis	Presence vs absence	0.851	0.622-1.165	0.314			
Ishak hepatic inflammation score	>6 vs ≤6	1.274	0.801-2.028	0.307			
Ishak hepatic fibrosis score (significant fibrosis)	3-6 vs ≤2	1.153	0.851-15.62	0.357			
Cirrhosis	Presence vs absence	1.099	0.823-1.468	0.521			

HR, hazard ratio; CI, confidence interval; NS, not significant.

rence, with 5-year recurrence rate of 16.7%, 34% and 51.7%, respectively (P=0.001, **Figure 2C**).

Among 143 patients without recurrence before year 5, 26 (18.2%) developed very late recurrence. In univariate analysis, factors associated with very late recurrence include HBsAg level, BMI, presence of significant hepatic fibrosis and cirrhosis (**Table 5**). By multivariate analyses, independent predictors of vey late recurrence were HBsAg >50 IU/mL (HR=4.658, P=0.038, **Figure 2D**), BMI >25 kg/m^2 (HR=2.720, P=0.013, **Figure 2E**) and significant hepatic fibrosis (HR=2.509, P=0.039). Combining the 3 risk factors HBsAg levels, BMI and significant fibrosis could stratify patients into very low, low, medium and high risk of very late recurrence, with 10-year recurrence rate of 0%, 10.7%, 37.2% and 66.1%, respectively (P<0.001, **Figure 2F**). Notably, none of the patients with low baseline HBsAg, BMI and liver fibrosis had tumor recurrence after 5 years.

Factors associated with early and late mortality

By multivariate analyses, ALBI grade 2-3 (1.917, P=0.011), tumor size >5 cm (HR=2.100, P=0.004), histological grade >1 (HR=2.851, P<0.001) and surgical cut margin >0.5 cm (HR=0.449, P=0.004) were independent predictors of early mortality (**Table 6**). Baseline HBsAg level had no association with early mortality (**Figure 3B**).

Among 257 patients without mortality before year 5, 34 (13.2%) developed late mortality

Table 4. Univariate and multivariate analyses of factors associated with late recurrence

		Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	>60 vs ≤60	1.250	0.836-1.870	0.278			
Sex	Female vs male	1.092	0.619-1.926	0.760			
BMI (kg/m^2)	>25 vs ≤25	1.212	0.810-1.814	0.350			
BCLC stage	B vs 0-A	1.450	0.753-2.792	0.267			
Child-Pugh class	6-7 vs 5	1.366	0.761-2.452	0.297			
ALBI grade	2-3 vs 1	1.572	1.019-2.425	0.041			NS
HBV DNA (IU/mL)	>20 vs ≤20	2.166	0.940-4.992	0.070			NS
	>2000 vs ≤2000	1.155	0.715-1.865	0.556			
HBsAg (IU/mL)	>50 vs ≤50	2.074	1.132-3.800	0.018			NS
	>200 vs ≤200	1.765	1.111-2.805	0.016	1.778	1.034-3.055	0.037
HBeAg	Positive vs negative	1.359	0.688-2.682	0.377			
NUC therapy	Yes vs no	1.208	0.777-1.878	0.402			
Tumor size (cm)	>3 vs ≤3	0.673	0.447-1.011	0.056			NS
	>5 vs ≤5	0.515	0.292-0.909	0.022			NS
Tumor number	Multiple vs single	1.736	1.077-2.801	0.024			NS
AFP (ng/mL)	>20 vs ≤20	1.268	0.832-1.932	0.269			
Bilirubin (mg/dL)	>1.2 vs ≤1.2	0.959	0.534-1.722	0.889			
Albumin (g/dL)	>3.5 vs ≤3.5	0.535	0.285-1.004	0.052			NS
Creatinine (mg/dL)	>1.2 vs ≤1.2	0.790	0.366-1.705	0.547			
MELD score	>6 vs ≤6	1.543	1.022-2.330	0.039			NS
Platelet count (10^9/L)	>150 vs ≤150	0.636	0.425-0.952	0.028			NS
ALT (U/L)	>40 vs ≤40	1.010	0.674-1.512	0.963			
AST (U/L)	>40 vs ≤40	0.798	0.516-1.236	0.312			
Histological grade	>1 vs 1	1.140	0.755-1.722	0.533			
Microvascular invasion	Presence vs absence	0.899	0.594-1.362	0.615			
Surgical margin (cm)	>0.5 vs ≤0.5	1.006	0.599-1.688	0.983			
	>1 vs ≤1	0.735	0.428-1.263	0.265			
Steatosis	Presence vs absence	1.167	0.747-1.821	0.497			
Ishak hepatic inflammation score	>6 vs ≤6	1.763	0.962-3.231	0.066			NS
Ishak hepatic fibrosis score (significant fibrosis)	3-6 vs ≤2	2.259	1.411-3.618	0.001			NS
Cirrhosis	Presence vs absence	1.934	1.291-2.898	0.001	2.157	1.361-3.416	0.001

HR, hazard ratio; CI, confidence interval; NS, not significant.

after year 5. By multivariate analyses, HBsAg >50 IU/mL (HR=11.427, P=0.017, **Figure 3C**), age >60 years (HR=2.688, P=0.006), albumin ≤3.5 g/dL (HR=4.739, P<0.001) and cirrhosis (HR=2.781, P=0.006) were independent predictors of late mortality beyond 5 years (**Table 7**). By calculating the number of risk factors of late mortality, we could also stratify patients into low, medium and high risk of late mortality, with 10-year survival rate of 98%, 75.1% and 56%, respectively (P<0.001, **Figure 3D**).

The role of HBsAg in subgroup patients with NUC therapy

We further evaluated the predictive value of HBsAg in late recurrence, very late recurrence and late mortality in subgroup patients with NUC therapy. In patients with NUC therapy, those with HBsAg ≤200 IU/L had a trend of lower late recurrence rate (P=0.098, **Figure 4A**), while none of the patients with HBsAg ≤50 IU/L developed very late recurrence or late mortality during the follow-up period (**Figure 4B**, **4C**). Combining HBsAg and the corresponding risk factors could still stratify the risk of late recurrence, very late recurrence and late mortality (**Figure 4D-F**).

Discussion

In this long-term follow-up study, we evaluated the predictors of recurrence and mortality at different time intervals after resection of HBV-related HCC. Our results showed that baseline HBsAg levels was not associated early recur-

Table 5. Univariate and multivariate analyses of factors associated with very late recurrence

		Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	>60 vs ≤60	1.658	0.768-3.578	0.198			
Sex	Female vs male	2.293	0.542-9.709	0.260			
BMI (kg/m^2)	>25 vs ≤25	2.487	1.128-5.482	0.024	2.720	1.230-6.013	0.013
BCLC stage	B vs 0-A	2.257	0.677-7.526	0.185			
Child-Pugh score	6-7 vs 5	1.276	0.382-4.261	0.691			
ALBI grade	2-3 vs 1	1.615	0.646-4.037	0.305			
HBV DNA (IU/mL)	>20 vs ≤20	1.177	0.394-3.523	0.770			
	>2000 vs ≤2000	1.634	0.639-4.181	0.306			
HBsAg (IU/mL)	>50 vs ≤50	4.815	1.138-20.376	0.033	4.658	1.092-19.874	0.038
	>200 vs ≤200	2.075	0.872-4.938	0.099			NS
HBeAg	Positive vs negative	1.157	0.339-3.952	0.816			
NUC therapy	Yes vs no	2.187	0.825-5.803	0.116			
Tumor size (cm)	>3 vs ≤3	0.672	0.311-1.452	0.312			
	>5 vs ≤5	0.628	0.236-1.667	0.350			
Tumor number	Multiple vs single	1.221	0.366-4.070	0.745			
AFP (ng/mL)	>20 vs ≤20	1.115	0.516-2.407	0.782			
Bilirubin (mg/dL)	>1.2 vs ≤1.2	0.828	0.248-2.762	0.759			
Albumin (g/dL)	>3.5 vs ≤3.5	0.606	0.143-2.569	0.497			
Creatinine (mg/dL)	>1.2 vs ≤1.2	1.692	0.507-5.644	0.393			
MELD score	>6 vs ≤6	1.706	0.782-3.722	0.179			
Platelet count (10^9/L)	>150 vs ≤150	0.582	0.267-1.269	0.173			
ALT (U/L)	>40 vs ≤40	1.542	0.699-3.402	0.284			
AST (U/L)	>40 vs ≤40	1.198	0.550-2.609	0.650			
Histological grade	>1 vs 1	0.607	0.244-1.514	0.285			
Microvascular invasion	Presence vs absence	0.975	0.428-2.220	0.951			
Surgical margin (cm)	>0.5 vs ≤0.5	0.914	0.360-2.319	0.850			
	>1 vs ≤1	0.751	0.282-2.003	0.568			
Steatosis	Presence vs absence	2.270	0.798-6.461	0.124			
Ishak hepatic inflammation score	>6 vs ≤6	2.209	0.827-5.899	0.114			
Ishak hepatic fibrosis score (significant fibrosis)	3-6 vs ≤2	3.171	1.332-7.551	0.009	2.509	1.050-6.000	0.039
Cirrhosis	Presence vs absence	2.298	1.062-4.969	0.035			NS

HR, hazard ratio; CI, confidence interval; NS, not significant.

rence or mortality after surgical resection, but play major prognostic roles in long-term recurrence and mortality after surgery.

In this cohort, more than two-third of patients received NUCs therapy after surgery, while about two-third of the patients without NUCs therapy had low HBV DNA level, suggesting that NUCs therapy is now generally prescribed for HCC patients with high viral loads. The 5-year RFS rate of 41.6% in this study was comparable to other studies of CHB patients with NUCs treatment after resection of HCC [10]. Baseline ALBI grade, AFP level, tumor size, tumor number, and status of microvascular invasion were independent predictors of early recurrence. Tumor size, tumor number, AFP level and microvascular invasion were well known tumor factors associated with early recurrence after resection [6-8]. The ALBI grade has been reported to be an important prognostic factor for patients with different stages of HCC [23, 26]. A recent report also revealed that ALBI grade was an independent predictor of early recurrence [8]. A study showed that baseline HBsAg >1,000 IU/mL might predict a higher risk of early recurrence after resection [19]; nevertheless, in the study, antiviral therapy was not prescribed. In our study, we found that HBsAg levels with cutoff levels from 50 to 1000 U/L were all not associated with early recurrence.

Previous studies showed that tumor recurrence beyond two years of resection (late recurrence) had clonal origins different from the primary

Table 6. Univariate and multivariate analyses of factors associated with early mortality

		Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	>60 vs ≤60	0.996	0.687-1.444	0.984			
Sex	Female vs male	1.347	0.769-2.358	0.297			
BMI (kg/m^2)	>25 vs ≤25	0.968	0.663-1.412	0.866			
BCLC stage	B vs 0-A	2.692	1.745-4.154	<0.001			NS
Child-Pugh class	6-7 vs 5	1.510	0.912-2.501	0.110			
ALBI grade	2-3 vs 1	1.686	1.153-2.465	0.007	1.917	1.162-3.162	0.011
HBV DNA (IU/mL)	>20 vs ≤20	1.601	0.738-3.471	0.233			
	>2000 vs ≤2000	1.059	0.677-1.657	0.801			
HBsAg (IU/mL)	>50 vs ≤50	1.238	0.747-2.049	0.407			
	>200 vs ≤200	1.160	0.773-1.742	0.474			
HBeAg	Positive vs negative	0.481	0.193-1.194	0.114			
NUC therapy	Yes vs no	0.941	0.633-1.399	0.765			
Tumor size (cm)	>3 vs ≤3	2.690	1.744-4.148	<0.001			NS
	>5 vs ≤5	3.444	2.374-4.998	<0.001	2.100	1.261-3.499	0.004
Tumor number	Multiple vs single	1.673	1.114-2.512	0.013			NS
AFP (ng/mL)	>20 vs ≤20	1.837	1.190-2.836	0.006			NS
Bilirubin (mg/dL)	>1.2 vs ≤1.2	0.923	0.536-1.590	0.773			
Albumin (g/dL)	>3.5 vs ≤3.5	0.598	0.352-1.016	0.057			NS
Creatinine (mg/dL)	>1.2 vs ≤1.2	1.744	1.027-2.962	0.039			NS
MELD score	>6 vs ≤6	1.473	1.002-2.165	0.049			
Platelet count (10^9/L)	>150 vs ≤150	1.068	0.733-1.556	0.732			
ALT (U/L)	>40 vs ≤40	1.085	0.749-1.572	0.666			
AST (U/L)	>40 vs ≤40	1.490	1.025-2.164	0.036			NS
Histological grade	>1 vs 1	1.991	1.374-2.886	<0.001	2.851	1.722-4.718	<0.001
Microvascular invasion	Presence vs absence	2.483	1.516-4.068	<0.001			NS
Surgical margin (cm)	>0.5 vs ≤0.5	0.403	0.240-0.678	0.001	0.449	0.261-0.771	0.004
	>1 vs ≤1	0.542	0.308-0.953	0.033			NS
Steatosis	Presence vs absence	0.685	0.447-1.049	0.082			NS
Ishak hepatic inflammation score	>6 vs ≤6	0.733	0.357-1.506	0.398			
Ishak hepatic fibrosis score (significant fibrosis)	3-6 vs ≤2	1.043	0.709-1.536	0.830			
Cirrhosis	Presence vs absence	1.010	0.693-1.472	0.959			

HR, hazard ratio; CI, confidence interval; NS, not significant.

tumors [27]. In this study, baseline serum HBsAg level and cirrhosis are identified as independent predictors of late recurrence between year 2 to 5. Cirrhosis is a well-known factor associated with de novo HCC occurrence and has been shown to be a predictor of late recurrence after curative resection [5-7]. A study showed that baseline HBsAg level >4,000 IU/mL might predict a higher risk of late recurrence [20]. However, in that study, antiviral therapy was only prescribed to 19% of patients. Furthermore, only 3% of patients had baseline HBsAg >4,000 IU/mL in our study. Another study reported that HBsAg >1,000 IU/mL was associated with late recurrence, but patients under antiviral therapy was excluded in the study [28]. Our analysis showed that the cutoff value of HBsAg 50 IU/mL was most discriminative for the risk of late recurrence in patients mainly with NUC therapy or low-level viremia. Combining HBsAg and cirrhosis status could well discriminate patients to 3 risk groups of late recurrence (**Figure 2C**).

Complete remission for 5 years or more after surgical resection for HCC is often considered as cure of the disease. Nevertheless, some CHB patients still develop HCC recurrence beyond 5 years of surgery, and predictors of recurrence after 5 years have not been reported. In this study, we showed that among the 143 patients without recurrence within 5 years, 26 (18.2%) developed very late recurrence after year 5. Serum HBsAg level, BMI and significant liver fibrosis are identified as independent predictors of very late recurrence. Our pre-

Table 7. Univariate and multivariate analyses of factors associated with late mortality

		Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	>60 vs ≤60	2.678	1.325-5.414	0.006	2.688	1.323-5.462	0.006
Sex	Female vs male	0.674	0.293-1.550	0.353			
BMI (kg/m^2)	>25 vs ≤25	1.289	0.657-2.528	0.460			
BCLC stage	B vs 0-A	1.926	0.744-4.982	0.177			
Child-Pugh class	6-7 vs 5	2.592	1.127-5.963	0.025			NS
ALBI grade	2-3 vs 1	2.302	1.151-4.607	0.018			NS
HBV DNA (IU/mL)	>20 vs ≤20	1.223	0.421-3.553	0.711			
	>2000 vs ≤2000	0.787	0.357-1.738	0.554			
HBsAg (IU/mL)	>50 vs ≤50	9.587	1.311-70.110	0.026	11.427	1.549-84.300	0.017
	>200 vs ≤200	1.655	0.772-3.548	0.195			
HBeAg	Positive vs negative	2.339	0.895-6.112	0.083			NS
NUC therapy	Yes vs no	1.691	0.700-4.088	0.243			
Tumor size (cm)	>3 vs ≤3	0.903	0.460-1.773	0.766			
	>5 vs ≤5	1.017	0.474-2.178	0.966			
Tumor number	Multiple vs single	1.332	0.580-3.062	0.499			
AFP (ng/mL)	>20 vs ≤20	0.732	0.369-1.449	0.370			
Bilirubin (mg/dL)	>1.2 vs ≤1.2	1.212	0.469-3.134	0.691			
Albumin (g/dL)	>3.5 vs ≤3.5	0.252	0.110-0.580	0.001	0.211	0.091-0.489	<0.001
Creatinine (mg/dL)	>1.2 vs ≤1.2	1.471	0.449-4.820	0.524			
MELD score	>6 vs ≤6	1.398	0.705-2.770	0.338			
Platelet count (10^9/L)	>150 vs ≤150	0.311	0.154-0.629	0.001			NS
ALT (U/L)	>40 vs ≤40	0.649	0.327-1.289	0.217			
AST (U/L)	>40 vs ≤40	1.873	0.955-3.677	0.068			NS
Histological grade	>1 vs 1	0.966	0.462-2.022	0.927			
Microvascular invasion	Presence vs absence	1.675	0.754-3.720	0.205			
Surgical margin (cm)	>0.5 vs ≤0.5	1.882	0.757-4.683	0.174			
	>1 vs ≤1	1.447	0.614-3.412	0.399			
Steatosis	Presence vs absence	0.821	0.400-1.685	0.591			
Ishak hepatic inflammation score	>6 vs ≤6	1.423	0.545-3.715	0.471			
Ishak hepatic fibrosis score (significant fibrosis)	3-6 vs ≤2	3.173	1.310-7.686	0.011			NS
Cirrhosis	Presence vs absence	3.381	1.647-6.941	0.001	2.781	1.351-5.727	0.006

HR, hazard ratio; CI, confidence interval; NS, not significant.

vious study showed that higher BMI level contribute to hepatic necro-inflammation and fibrosis in CHB patients [29]. Obesity has also been shown to increase the risk of HCC development [30]. These data suggest that liver fibrosis, virological and metabolic factors constantly contribute to de novo HCC occurrence in patients with prior HCC with complete remission 5 years after surgery. Combining HBsAg, BMI level and significant liver fibrosis could also well discriminate patients to 4 risk groups of very late recurrence (**Figure 2F**), and patients with low baseline HBsAg, BMI and no significant fibrosis had minimal risk of tumor recurrence after 5 years.

In this study, the 5- and 10-year OS rates were 76.4% and 61.8%, respectively, indicating a much better long-term survival rate as compared to HCC patients without NUC treatment after resection [7, 31]. ALBI grade, AFP, creatinine levels, tumor size, number and histological grade were independent predictors of mortality within 5 years of surgery, suggesting that tumor factors and baseline liver or renal function play important roles in the early outcomes after surgery. There was no reported predictors of mortality after 5 years of surgery. In this long-term follow-up study, we showed that among 257 patients survived over 5 years, 34 (13.2%) developed late mortality after year 5. Age, HBsAg, albumin levels and significant liver fibrosis were independent predictors of late mortality after year 5. Lower albumin levels and significant liver fibrosis represent poorer liver function reserve, while older age represents a shorter residual life expectancy, which lead to a

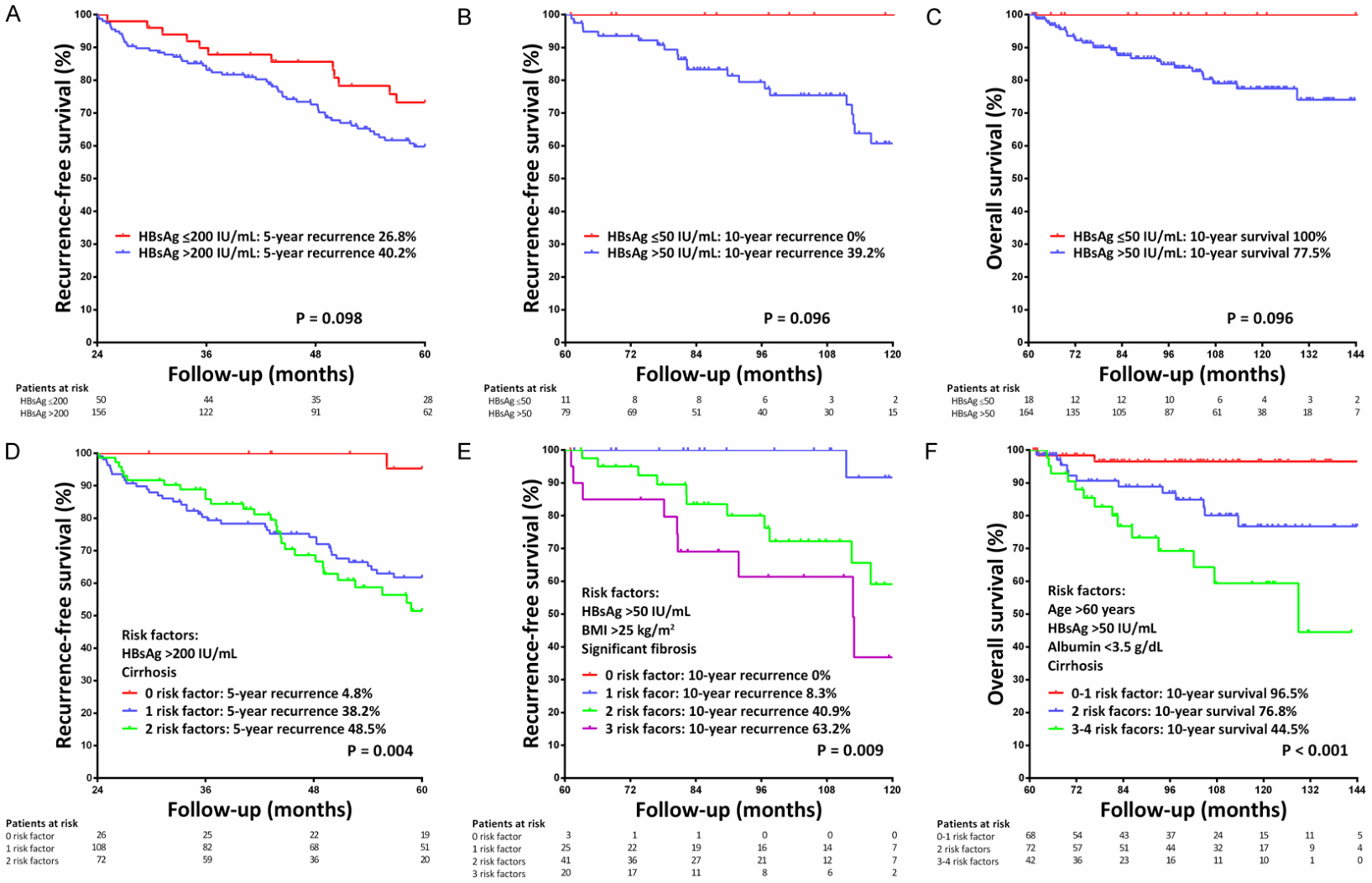

Figure 4. Kaplan-Meier curves of late, very late recurrence-free survival (RFS) and late mortality in subgroup patients with NUC therapy. A. Late RFS stratified by baseline HBsAg level. B. Late RFS stratified by HBsAg level and cirrhosis status. C. Very late RFS stratified by baseline HBsAg level. D. Very late RFS stratified by baseline HBsAg level, BMI and significant fibrosis. E. Late mortality stratified by baseline HBsAg level. F. Late mortality stratified by the number of risk factors.

poorer long-term survival rate. Patients with lower HBsAg levels had lower late and very late recurrence rates, and may have a lower hepatic fibrosis progression, leading to a better long-term survival. By calculating risk factors including HBsAg, albumin, age and significant liver fibrosis we could also discriminate patients to 3 risk groups of late mortality, and patients with 0-1 risk factor had the minimal risk of late mortality, with 10-year survival rate of 98% (**Figure 3D**).

Although NUCs therapy could achieve complete suppression of HBV replication in most CHB patients, declines in serum HBsAg levels were generally not significant [32]. Serum HBsAg level might reflect the intrahepatic HBV covalently closed circular DNA level and the transcriptional activity inside the hepatocytes, thus may have further impact on hepatocarcinogenesis even in patients with low viral load or under NUCs therapy [33]. Our results confirmed the major prognostic value of HBsAg levels on long-term outcomes including late recurrence, very late recurrence and late mortality in a cohort of patients with mainly under NUCs therapy or with low HBV viral load. Several ongoing clinical trials (Checkmate 9DX, Keynote 937, Emerald-2) select intermediate to high risk patients based on tumor factors only (tumor size, number, differentiation, microvascular invasion) for adjuvant immunotherapy after curative treatment of HCC to prevent recurrence [34]. Our findings can provide more comprehensive outcome predictors to select patients who need adjuvant therapy for clinical trials design.

This study has some limitations. Firstly, this was a single-center study. Further external validation of the prognostic role of HBsAg needs to be conducted. Secondly, the impact of HBV genotype was not assessed in this study. However, most CHB patients were infected with HBV genotype B or C in Taiwan [7]. Whether the prognostic value of HBsAg could be applied to patients with other HBV genotypes needs further study.

In conclusion, tumor factors, liver function surrogate markers, virological factors and metabolic factors play distinct roles in recurrence and survival at different time intervals after surgical resection for HBV-related HCC. Preoperative serum HBsAg level is an important predictor of late and very late recurrence as well as late mortality in patients with HBV-related HCC undergoing surgical resection.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yi-Hsiang Huang, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; Institute of Clinical Medicine, National Yang Ming Chiao Tung University, 201 Shih-Pai Road, Sec. 2, Taipei 112, Taiwan. Tel: +886-2-28712121 Ext. 7506; Fax: +886-2-28739318; E-mail: yhhuang@vghtpe.gov.tw

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