Prognostic value of chronic hepatitis B virus infection in patients with breast cancer in a hepatitis B virus endemic area

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Background: Except for hepatocellular carcinoma, chronic hepatitis B virus (HBV) infection has also been reported to be associated with increased morbidity and mortality of other cancers. However, the impact of chronic HBV infection on the prognosis of breast cancer (BC) remains unclear. Our study aimed to evaluate the prognostic value of HBV infection for BC in an endemic area of HBV in China.

Methods: There was a total of 1,904 patients with early BC who underwent mastectomy or breast-conserving surgery enrolled in our study. HBV infection on overall survival (OS) and hepatic metastasis-free survival (HMFS) was the main research indicator for this study.

Results: A total of 212 patients (11.1%) were identified with chronic HBV infection due to serum hepatitis B surface antigen (HBsAg) positive. HBsAg-positive patients had inferior OS (84.9% *vs.* 90.4%, P=0.005) and HMFS (92.5% *vs.* 97.1%, P=0.016) at 5 years than HBsAg-negative patients. Chronic HBV infection was an independent predictor of poor OS in patients with BC [multivariate analysis; hazard ratio (HR), 1.52; P=0.038], but not for HMFS. Subgroup analysis showed that chronic HBV infection was an unfavorable independent prognostic factor for OS in patients with stage II/III BC (HR, 1.59; P=0.025). The 5-year OS and HMFS rates of HBsAg-positive patients were 81.9% and 90.5% for patients with stage II/III BC, while those rates of HBsAg-negative patients were 88.5% and 96.3%, respectively. In stage I patients, there was no significant difference in 5-year OS (95.8% *vs.* 97.1%; P=0.629) and HMFS (100.0% *vs.* 99.0%; P=0.447).

Conclusions: In conclusion, chronic HBV infection predicts a worse prognosis in patients with stage II/III BC, but not stage I BC.

Keywords: Breast cancer (BC); hepatitis B virus infection (HBV infection); clinic-pathological features; survival; liver metastasis

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Introduction

Chronic hepatitis B virus (HBV) infection has been recognized as an urgent public health problem due to high infection rates, with more than 240 million chronic HBV carriers worldwide (1). China is one of the countries with a high incidence of hepatitis B infection in the world, while South China is one of the regions with the highest rate of chronic HBV infection in China. The seroprevalence of hepatitis B surface antigen (HBsAg) is 10% to 12% in the general population in South China (2). Chronic HBV infection has been widely confirmed as a causative factor in chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). However, in addition to HCC, it has also been reported that chronic HBV infection affects the progression of other tumors, including non-Hodgkin lymphoma (3,4), hepatic cholangiocarcinoma (5,6), leukemia (7), gastric cancer (8), nasopharyngeal cancer (9), and pancreatic cancer (10). For example, HBV-infected non-HCC cancer patients, such as nasopharyngeal (9) or pancreatic cancer (11), have significantly worse clinicopathological features and prognosis than uninfected patients.

However, the impact of chronic HBV infection on the clinicopathological features and prognosis of patients with breast cancer (BC) is unclear. Therefore, this study intends to investigate the impact of chronic HBV infection on the clinicopathological features and prognosis of patients with BC in an epidemic area of HBV.

Methods

Study population and data extraction

This study mainly retrospectively collected patients with BC who had undergone surgery at the Sun Yat-sen University Cancer Center (Guangzhou, China) from February 2008 to December 2010. A total of 1,904 patients with BC who were pathologically confirmed and had no distant metastasis were identified. Patients with missing basic information such as tumor staging and unknown follow-up were excluded. All patients signed the informed consent form, and the study was approved by the Ethics Committee of the Cancer Center of Sun Yat-sen University. The staging of the tumor was performed according to the 7th edition of the TNM staging system of the American Joint Committee on Cancer (AJCC).

Serological detection of HBV infection

Blood tests for HBV infection in this study were performed before surgery for BC. Briefly, HBV is detected by collecting blood samples, separating serum, and then measuring serum samples by enzyme-linked immunosorbent assay. To ensure the accuracy of the test, HBV testing is performed and quality controlled according to standard operating procedures.

Patient follow-up and statistical analysis

All patients were routinely followed up after surgery. Patients were followed up every 3 months for the first 2 years, and every 3 to 6 months for the 3rd to 5th years, and 1–2 times a year until the death after the 5th year. The duration of follow-up refers to the interval between the diagnosis of BC to death or the last follow-up. The median follow-up time for HBsAg-positive patients was 68.5 months, compared with 70 months for HBsAg-negative patients. The effect of chronic HBV infection on overall survival (OS) and hepatic metastasis-free survival (HMFS) was the main research indicator for this study. We calculated the interval from the first day of diagnosis to the death or the last follow-up as OS and calculated the interval from the first day of diagnosis to the clinical detection of liver metastases as HMFS.

SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA) was adopted to perform most of the statistical analysis. Chi-square test was used to compare statistical differences in clinical and pathological variables between HBsAg-positive and HBsAg-negative patients. When we analyzed the effect of chronic HBV infection on patient survival, we used Kaplan-Meier survival analysis to plot the survival curve and the difference was compared using a log-rank test. Statistically significant variables after univariate analysis were further used in the multivariate analysis of the Cox proportional hazard model to test the independent significance of the variables. The standard for statistical significance is set to 0.05, and all P values are based on two-sided testing. Kaplan-Meier curves for OS and HMFS were plotted by SAS software (SAS Institute Inc. version 9.4, USA).

Results

A total of 212 (11.1%) of the 1,904 patients were seropositive HBsAg. HBsAg-positive and HBsAg-negative patients are similar in most clinicopathological features. Besides, there was no significant difference in the surgical approach between the two groups. However, the proportion of younger patients (age ≤35 years) in the HBsAg-positive

group was higher (15.6% *vs.* 9.0%; P=0.003) compared with the HBsAg-negative group in patients with BC (*Table 1*). In addition, the premenopausal patients in the HBsAg-positive group also had a higher proportion than the HBsAg-negative group (70.8% *vs.* 61.2%; P=0.004) (*Table 1*). Finally, the percentage of patients with lymphovascular invasion in the HBsAg-positive group was significantly higher than that in the HBsAg-negative group (5.2% *vs.* 2.5%; P=0.042) (*Table 1*).

Effect of chronic HBV infection on the prognosis of patients with BC

The 5-year OS rate (84.9% *vs.* 90.4%, P=0.005) was significantly lower in HBsAg-positive BC patients than in HBsAg-negative patients (*Figure 1A*). Univariate analysis showed that the OS of HBsAg-positive BC patients was significantly worse than HBsAg-negative patients (*Table 2*). To adjust the influence of various confounding factors, Cox proportional hazards regression model is used for multivariate analysis. Multivariate analysis further determined that, chronic HBV infection is an independent risk factor for OS in patients with BC [hazard ratio (HR), 1.52; 95% confidence interval (CI), 1.02–2.26, P=0.038] (*Table 2*). Furthermore, the 5-year HMFS (92.5% *vs.* 97.1%, P=0.016) of patients with chronic HBV infection were significantly shorter compared with those without HBV infection (*Figure 1B*). In addition, later T and N staging were also independent risk factors for poor prognosis (*Table 2*).

Effect of chronic HBV infection on survival outcome in BC patients with luminal or non-luminal BC

In patients with luminal BC, HBsAg-positive patients had worse OS compared with HBsAg-negative patients (85.7% *vs.* 91.7%; P=0.016) (*Figure 2A*). Multivariate analysis further confirmed that chronic HBV infection was an independent prognostic factor for OS in patients with luminal BC (HR, 1.62; 95% CI, 1.03–2.55; P=0.038). However, there is no significant association between chronic HBV infection and HMFS in luminal BC patients (*Figure 2B*). In non-luminal BC patients, chronic HBV infection also appeared to be associated with worse OS, but no statistical difference was observed (79.0% *vs.* 84.9%; P=0.139) (*Figure 2C*). Moreover, chronic HBV infection was significantly associated with poor 5-year HMFS (82.9% *vs.* 95.8%; P=0.002) (*Figure 2D*) in patients with non-luminal BC.

Table 1 Baseline characteristics of HBsAg-positive and HBsAg-negative BC patients

Variable	$HBsAg^+$ (%) (N=212)	$HBsAg^-$ (%) (N=1,692)	P value
Age at diagnosis			0.003
≤35 years	33 (15.6)	153 (9.0)	
>35 years	179 (84.4)	1,539 (91.0)	
ER			0.211
Positive	143 (67.5)	1,191 (70.4)	
Negative	69 (32.5)	501 (29.6)	
PR			0.282
Positive	145 (68.4)	1,194 (70.6)	
Negative	67 (31.6)	498 (29.4)	
HER2			0.379
Positive	39 (19.3)	327 (20.6)	
Negative	163 (80.7)	1,264 (79.4)	
Lymphovascular invasion			0.042
Yes	11 (5.2)	42 (2.5)	
No	201 (94.8)	1,650 (97.5)	
Tumor size			0.291
T1	74 (34.9)	677 (40.0)	
T2	111 (52.4)	861 (50.9)	
T3	13 (6.1)	81 (4.8)	
T4	14 (6.6)	73 (4.3)	
Lymph node metastasis			0.286
N0	95 (44.8)	888 (52.5)	
N1	59 (27.8)	406 (24.0)	
N2	33 (15.6)	238 (14.1)	
N3	25 (11.8)	160 (9.5)	
Menopause at diagnosis			0.004
No	150 (70.8)	1,035 (61.2)	
Yes	62 (29.2)	657 (38.8)	
Histological grade			0.148
G1 or G2	151 (71.2)	1,266 (74.8)	
G3	61 (28.8)	426 (25.2)	
Surgery types			0.075
Mastectomy	190 (89.6)	1,569 (92.7)	
Breast-conserving	22 (10.4)	123 (7.3)	

HBsAg, hepatitis B surface antigen; BC, breast cancer; ER, estrogen receptor; PR, progesterone receptor.

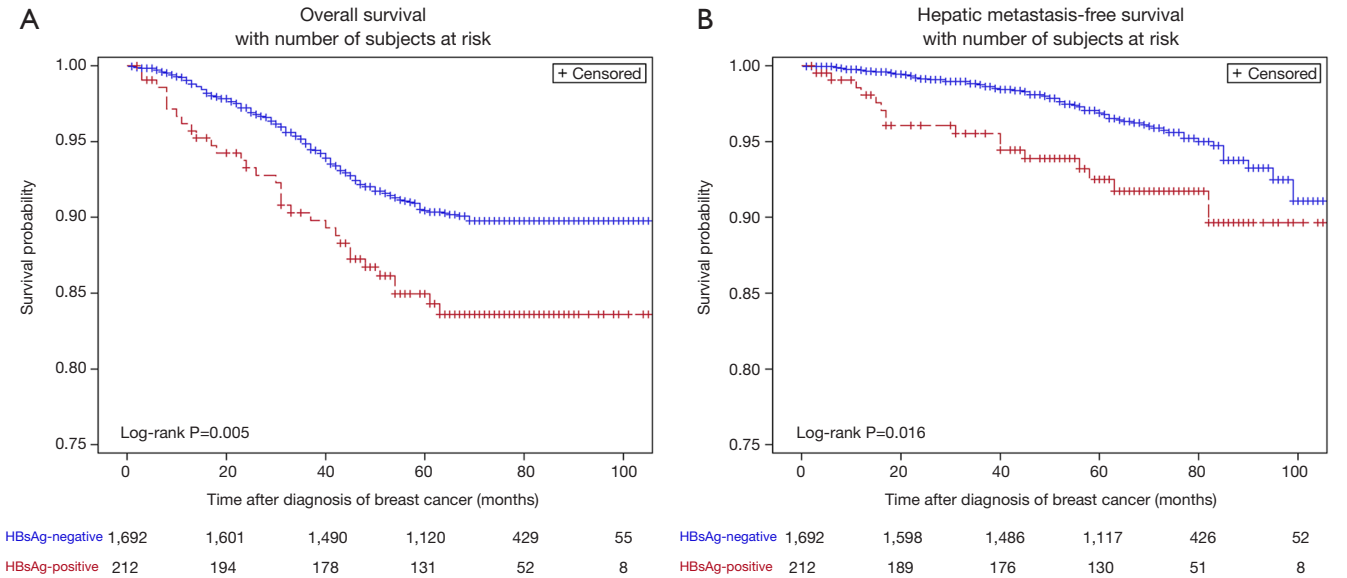

Figure 1 Kaplan-Meier survival curves showing overall survival (A) and liver metastasis-free survival (B) in patients with hepatitis B surface antigen (HBsAg) positive and HBsAg-negative breast cancer. P values were calculated using an unadjusted log-rank test. 95% CI, 95% confidence interval.

Effect of chronic HBV infection on survival outcome in BC patients with stage I or II/III

In stage I patients, no significant difference was observed in OS (95.8% *vs.* 97.1%; P=0.629) (*Figure 3A*) between HBsAg-positive patients and HBsAg-negative patients. In patients with stage II/III BC, HBsAg-positive patients had worse OS compared with HBsAg-negative patients (81.9% *vs.* 88.5%; P=0.006) (*Figure 3B*). Multivariate analysis further confirmed that chronic HBV infection was an independent prognostic factor for OS in patients with luminal BC (HR, 1.59; 95% CI, 1.06–2.39; P=0.025) (*Table 3*). Additionally, chronic HBV infection predicted a poor 5-year HMFS in stage II/III patients (90.5% *vs.* 96.3%; P=0.016) (*Figure 3C*), but not in patients with stage I BC (*Figure 3D*).

Discussion

To the best of our knowledge, the current study is the first large-scale study to determine the impact of chronic HBV infection in an endemic HBV region on the prognosis of patients with non-metastatic BC. The main finding of this study is that chronic HBV infection is an independent prognostic factor for stage II/III BC, but not stage I BC. In this cohort, the HBsAg positive rate of BC patients was 11.1%, and this infection rate was basically consistent with the general population in South China. We observed that young BC patients (less than or equal to 35 years old) accounted for a higher proportion of patients with chronic HBV infection than those older than 35 years. Furthermore, the proportion of premenopausal patients with chronic HBV infection is also higher in patients with BC than those without HBV infection. Another interesting finding is that patients with HBsAg-positive patients have a higher proportion of patients with lymphovascular invasion.

HBV mainly infects the liver and causes necrosis and inflammation of liver cells. In recent years, the impact of chronic HBV infection on cancer patients has received increasing attention. Previous studies have focused on the impact of HBV reactivation on cancer patients (12-15). In recent years, more and more studies have shown that chronic HBV infection can affect the prognosis of non-HCC cancer patients. Wang *et al.* found that compared with HBsAg-negative patients, diffuse large B-cell lymphoma patients with HBsAg-positive had a later clinical stage at the time of initial diagnosis (16). Liu *et al.* reported that chronic HBV infection was an independent risk factor for the survival of patients with locally advanced nasopharyngeal carcinoma (17). Wei *et al.* found that patients with HBV-infected pancreatic cancer had a worse prognosis and

Table 2 Multivariate analysis of prognostic factors in patients with BC (N=1,904)

Characteristics	N	Univariate analysis			Multivariate analysis		
		HR	95% CI	P value	HR	95% CI	P value
Age at diagnosis							
≤35 years	186	1.00	–	–	–	–	–
>35 years	1,718	0.71	0.46–1.10	0.125	–	–	–
ER							
Negative	570	1.00	–	–	1.00	–	–
Positive	1,334	0.53	0.39–0.70	<0.001	0.75	0.52–1.07	0.108
PR							
Negative	565	1.00	–	–	1.00	–	–
Positive	1,339	0.44	0.33–0.59	<0.001	0.68	0.48–0.96	0.028
HER2							
Negative	1,427	1.00	–	–	1.00	–	–
Positive	366	1.79	1.30–2.47	<0.001	1.15	0.82–1.63	0.42
Lymphovascular invasion							
No	1,851	1.00	–	–	1.00	–	–
Yes	53	3.99	2.39–6.66	<0.001	1.98	1.16–3.39	0.012
Tumor size							
T1	751	1.00	–	–	1.00	–	–
T2	972	1.56	1.09–2.22	0.015	1.12	0.77–1.63	0.511
T3	94	5.81	3.63–9.29	<0.001	2.74	1.64–4.56	<0.001
T4	87	5.95	3.65–9.68	<0.001	3.67	2.17–6.20	<0.001
Lymph node metastasis							
N0	983	1.00	–	–	1.00	–	–
N1	465	2.23	1.46–3.41	<0.001	2.07	1.33–3.22	0.001
N2	271	4.21	2.77–6.41	<0.001	2.75	1.75–4.33	<0.001
N3	185	9.09	6.10–13.5	<0.001	6.02	3.88–9.36	<0.001
Menopause at diagnosis							
No	719	1.00	–	–	1.00	–	–
Yes	1,185	1.54	1.16–2.05	0.003	1.44	1.06–1.96	0.018
Histological grade							
G1 or G2	1,417	1.00	–	–	1.00	–	–
G3	487	1.87	1.40–2.51	<0.001	1.43	1.04–1.95	0.027
HBsAg status							
Negative	1,692	1.00	–	–	1.00	–	–
Positive	212	1.71	1.17–2.50	0.006	1.52	1.02–2.26	0.038

BC, breast cancer; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HBsAg, hepatitis B surface antigen.

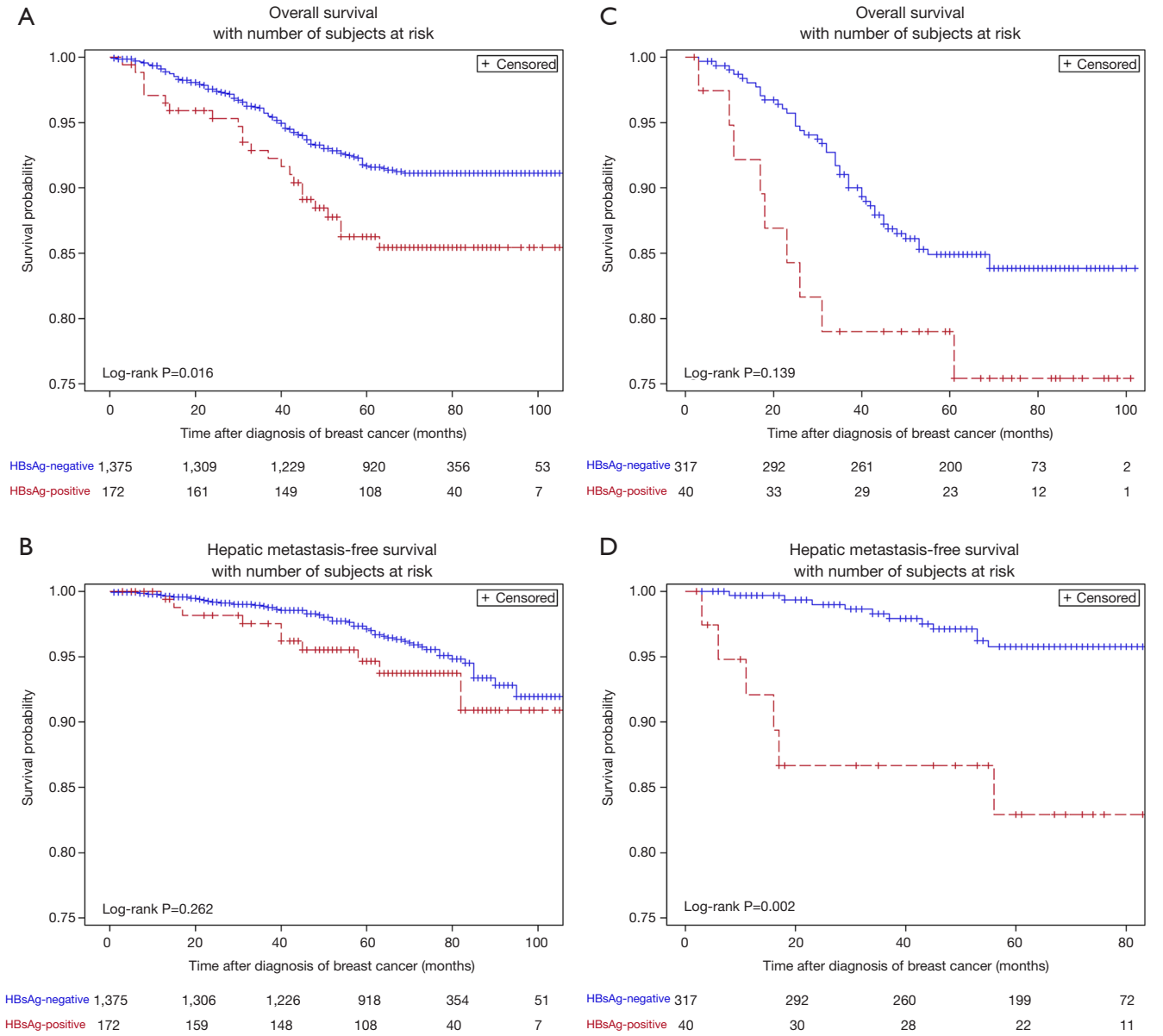

Figure 2 Kaplan-Meier survival curves showing overall survival (A,C) and hepatic metastasis-free survival (B,D) in hepatitis B surface antigen (HBsAg)-positive and -negative luminal breast cancer (A,B) or non-luminal breast cancer (C,D). P values were calculated using an unadjusted log-rank test.

was significantly associated with an increased rate of simultaneous liver metastases (11).

Because the liver is most affected by HBV infection, does persistent HBV infection cause a microenvironment that is prone to liver metastasis? For the effect of chronic HBV infection on liver metastasis, the inconsistent conclusions have been reported in different tumors. It has been reported that chronic HBV infection increased the rate of simultaneous liver metastases in patients with pancreatic cancer but decreases the risk of liver metastasis in colorectal cancer (11,18). Although we found that 5-year HMFS (93.2% *vs.* 97.3%, P=0.016) was significantly worse in patients with chronic HBV infection than in those without HBV infection, multivariate analysis failed to confirm

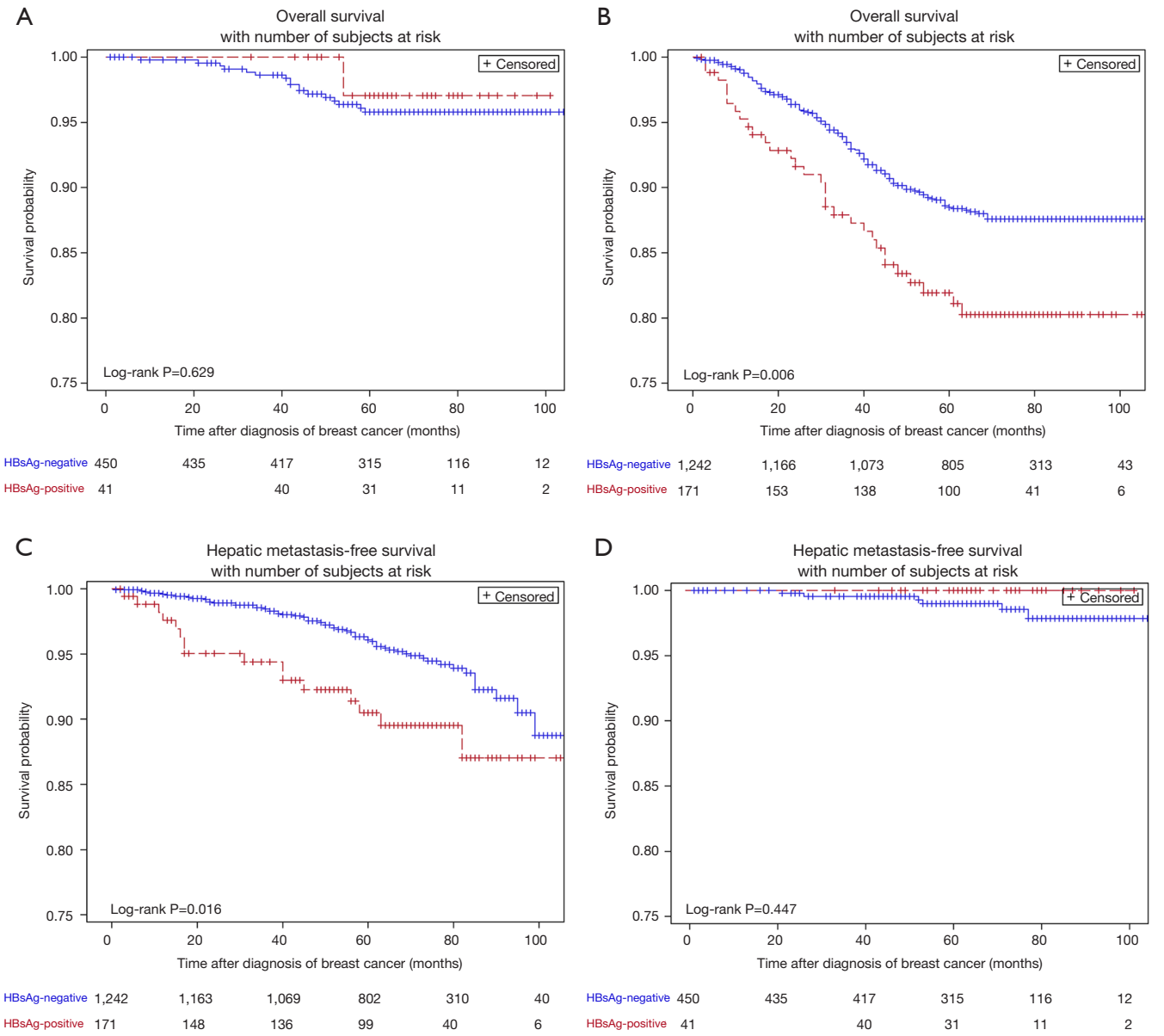

Figure 3 Kaplan-Meier survival curves showing overall survival (A,B) and hepatic metastasis-free survival (C,D) in hepatitis B surface antigen (HBsAg)-positive and -negative stage I breast cancer (A,D) or stage II/III breast cancer (B,C). P values were calculated using an unadjusted log-rank test.

that chronic HBV infection independently affects HMFS. Therefore, whether HBV infection affects the occurrence of BC liver metastasis needs further research to verify.

The biological mechanisms by which chronic HBV infections affect BC prognosis observed in this study are still elusive. First of all, chronic HBV infection can damage liver cells and impair the deactivation of estrogen by hepatocytes (8,19). Persistent and long-term HBV infection in the liver impairs the normal function of the liver, which leads to elevated estrogen levels as it is primarily inactivated in the liver (20). This may explain to some extent that the observation of chronic HBV infection in this study mainly affects the prognosis of luminal BC, rather than other subtypes. Secondly, HBV may also directly affect breast

Table 3 Multivariate analysis of prognostic factors in stage II/III breast cancer patients (N=1,413)

Characteristics	N	Univariate analysis			Multivariate analysis		
		HR	95% CI	P value	HR	95% CI	P value
Age at diagnosis							
≤35 years	136	1.00	–	–	–	–	–
>35 years	1,277	0.73	0.46–1.16	0.180	–	–	–
ER							
Negative	970	1.00	–	–	1.00	–	–
Positive	443	0.55	0.41–0.74	<0.001	0.71	0.48–1.03	0.074
PR							
Negative	448	1.00	–	–	1.00	–	–
Positive	965	0.48	0.36–0.65	<0.001	0.69	0.48–1.00	0.048
HER2							
Negative	1,025	1.00	–	–	1.00	–	–
Positive	300	1.52	1.08–2.14	0.017	1.06	0.74–1.53	0.741
Lymphovascular invasion							
No	1,363	1.00	–	–	1.00	–	–
Yes	50	3.45	2.06–5.78	<0.001	1.97	1.15–3.39	0.013
Tumor size							
T1	262	1.00	–	–	1.00	–	–
T2	971	0.85	0.56–1.29	0.448	1.17	0.74–1.84	0.511
T3	93	3.07	1.82–5.19	<0.001	2.69	1.53–4.74	<0.001
T4	87	3.22	1.87–5.50	<0.001	3.76	2.11–6.69	<0.001
Lymph node metastasis							
N0	493	1.00	–	–	1.00	–	–
N1	464	1.82	1.11–2.97	0.018	2.10	1.23–3.57	0.006
N2	271	3.49	2.14–5.70	<0.001	2.85	1.69–4.83	<0.001
N3	185	7.52	4.70–12.00	<0.001	6.34	3.78–10.60	<0.001
Menopause at diagnosis							
No	531	1.00	–	–	1.00	–	–
Yes	882	1.40	1.03–1.89	0.03	1.29	0.93–1.78	0.129
Histological grade							
G1 or G2	1,012	1.00	–	–	1.00	–	–
G3	401	1.72	1.26–2.34	0.001	1.41	1.01–1.95	0.043
HBsAg status							
Negative	1,242	1.00	–	–	1.00	–	–
Positive	171	1.72	1.17–2.54	0.006	1.59	1.06–2.39	0.025

HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HBsAg, hepatitis B surface antigen.

cells through the action of oncoprotein HBV X protein (HBX) (21-23). For example, several studies have found that BC tissue highly expresses the oncoprotein HBXIP, a protein that interacts with HBX (24). Besides, chronic HBV infection may affect the host's immune function, and it is reported that HBV is associated with immune dysfunction (25). The results of Li *et al.* revealed an HBV-induced immunosuppressive cascade in which HBV produces inhibitory monocytes that initiate regulatory NK cell differentiation leading to T cell suppression (26). Additionally, patients with chronic or regressive HBV infection are prone to complications of HBV reactivation during systemic therapy due to the immunosuppressive effects of administered chemotherapy. This may lead to liver damage, which may destroy the effect of anticancer treatment and affect the prognosis of patients (14,27). Most anti-cancer therapies, such as chemotherapy and radiation therapy, can cause immunosuppression, which can cause HBV reactivation and affect treatment (28,29). This may explain in part why the prognosis of patients with stage II/III complicated with chronic HBV infection is worse, as patients with stage II/III BC tend to receive chemotherapy, which may be harmful to the patient's immune function. Lei *et al.* found that postoperative HBV reactivation is associated with increased postoperative complications and reduced survival in intrahepatic cholangiocarcinoma (30).

The results of this study provide the first evidence to be known as the poor prognosis of chronic HBV infection in patients with BC. Especially in areas with endemic chronic HBV infection, we should consider the impact of chronic HBV infection on the prognosis of patients with BC. We recommend that every BC patient in the HBV endemic area should have a serological test for HBV at the time of first admission and during the response assessment, whereas patients with serological HBsAg-positive should pay special attention to their possible adverse clinical outcomes. Due to the retrospective nature of this study, we were unable to examine the effect of HBV-DNA levels and antiviral therapy on the prognosis of patients with BC with chronic HBV infection. This is a major shortcoming of current research, and therefore, whether BC patients with higher HBV infection burden have poor survival remains unknown. With the increasing use of chemotherapy, targeted therapy, and endocrine therapy for systemic treatment of BC, the occurrence of HBV reactivation may increase during this period. However, there is a lack of data on clinical management of HBV screening and reactivation as well as BC patients with HBV infection. The difference in the risk of HBV reactivation in BC patients during different treatments and how to manage BC in the HBV endemic area deserves further study.

Conclusions

This study proved that chronic HBV infection was an independent risk factor for prognosis in patients with stage II/III BC. It is necessary to further confirm these results through large prospective studies, including the impact of HBV DNA load on BC prognosis. In addition, there is a need to investigate the underlying mechanisms of chronic HBV infection affecting the survival outcome of stage II/III BC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of the Cancer Center of Sun Yat-sen University (No. GZR2016-076). All patients signed the informed consent form.

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