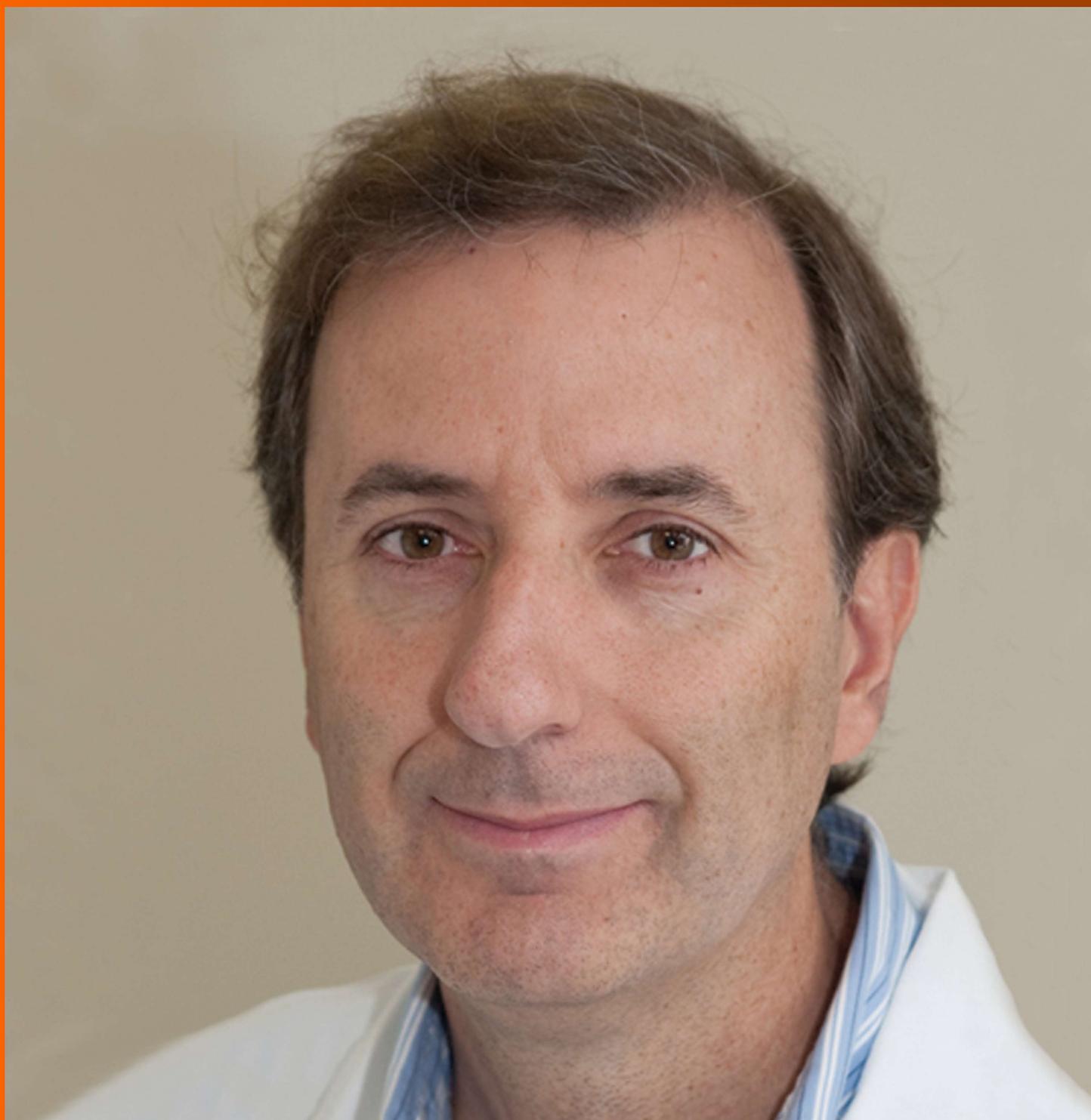


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World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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World Journal of Clinical Cases (*WJCC*) is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2018 Edition of Journal Citation Reports cites the 2017 impact factor for *WJCC* as 1.931 (5-year impact factor: N/A), ranking *WJCC* as 60 among 154 journals in Medicine, General and Internal (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
 ISSN 2307-8960 (online)

LAUNCH DATE
 April 16, 2013

FREQUENCY
 Monthly

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World Journal of Clinical Cases
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 7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
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 E-mail: editorialoffice@wjgnet.com
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PUBLISHER
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
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 Help Desk: <http://www.f6publishing.com/helpdesk>
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PUBLICATION DATE
 August 16, 2018

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Case Control Study

Negative impact of hepatitis B surface seroclearance on prognosis of hepatitis B-related primary liver cancer

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Author contributions: Lou C and Du Z designed research; Lou C, Du Z, Bai T and Bi LW treated patients and collected material and clinical data; Gao YT collected and sorted material and clinical data; Lou C and Bi LW performed the assays and analyzed data; Lou C wrote the paper.

Supported by Tianjin Health Industry Key Project, No. 15KG113; Tianjin Science Foundation of China, No. 17JCYBJC26100.

Institutional review board statement: This study was approved by the Institutional Review Board of Third Central Hospital of Tianjin (Shu-ye Liu, China).

Informed consent statement: Informed consent was obtained.

Conflict-of-interest statement: There are no conflicts of interest to report.

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Manuscript source: Unsolicited manuscript

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Received: May 15, 2018

Peer-review started: May 15, 2018

First decision: June 4, 2018

Revised: June 6, 2018

Accepted: June 30, 2018

Article in press: June 30, 2018

Published online: August 16, 2018

Abstract**AIM**

To assess the impact of hepatitis B surface (HBsAg) seroclearance on survival outcomes in hepatitis B-related primary liver cancer.

METHODS

Information from patients with hepatitis B-related liver cancer admitted in our hospital from 2008-2017 was retrieved. Cases diagnosed with HBsAg (-) and HBcAb (+) liver cancer were included in the HBsAg seroclearance (SC) group. HBsAg (+) liver cancer patients strictly matched for liver cancer stage (AJCC staging system, 8th edition), Child-Pugh score, and first diagnosis/treatment method (surgery, ablation and TACE) were assigned to the HBsAg non-seroclearance (NSC) group. Then, clinical, pathological and survival data in both groups were assessed.

RESULTS

The SC and NSC groups comprised of 72 and 216 patients, respectively. Patient age ($P < 0.001$) and platelet count ($P = 0.001$) in the SC group were significantly higher than those of the NSC group. SC group patients who underwent surgery had more intrahepatic cholangiocarcinoma (ICC) and combined HCC-CC (CHC) cases than the NSC group, but no significant differences in tumor cell differentiation and history of liver cirrhosis were found between the two groups. The numbers of interventional treatments were similar in both groups (4.57 *vs* 5.07, $P > 0.05$). Overall survival was lower in the SC group than the NSC group ($P = 0.019$), with 1-, 3-, and 5-year survival rates of 82.1% *vs* 85.1%, 43.2% *vs* 56.8%, and 27.0% *vs* 45.2%, respectively. Survival of patients with AJCC stage I disease in the SC group was lower than that of the NSC group ($P = 0.029$).

CONCLUSION

Seroclearance in patients with hepatitis B-related primary liver cancer has protective effects with respect to tumorigenesis, cirrhosis, and portal hypertension but confers worse prognosis, which may be due to the frequent occurrence of highly malignant ICC and CHC.

Key words: Primary liver cancer; Hepatitis B surface; Hepatitis B surface seroclearance; Prognosis; Chronic hepatitis B

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Core tip: Through strict case-control, we eliminated prognostic confounding factors, such as tumor stage, Child-Pugh score, and therapeutic mode, to determine the impact of hepatitis B surface (HBsAg) seroclearance (SC) on the prognosis of HBV related liver cancer. Statistical analysis shows that although HBsAg SC is protective in tumorigenesis, liver cirrhosis, and portal hypertension, the prognosis of HBsAg SC patients with primary liver cancer is worse than that of controls.

Lou C, Bai T, Bi LW, Gao YT, Du Z. Negative impact of hepatitis B surface seroclearance on prognosis of hepatitis B-related primary liver cancer. *World J Clin Cases* 2018; 6(8): 192-199 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v6/i8/192.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v6.i8.192>

INTRODUCTION

Chronic infection with hepatitis B virus (HBV) is the most common cause of liver cancer in Asia, especially in China. In Asia, about 60% of liver cancer cases are associated with HBV infection^[1]. Hepatitis B surface antigen (HBsAg) seroclearance is considered the gold standard for hepatitis B viral clearance and chronic hepatitis B cure, and is now regarded as the end point of antiviral therapy^[2,3]. Approximately 0.1%-0.8% of

adult patients with chronic HBV infection achieve HBsAg seroclearance in the course of natural development^[4,5]. Antiviral therapy could also lead to HBsAg seroclearance in some patients, improving the clinical outcome of individuals with chronic hepatitis B infection^[6,7].

After HBsAg seroclearance in these patients, the liver retains very low HBVDNA levels. Compared with chronic hepatitis B patients with positive HBsAg, a further decrease of HBVDNA *in vivo* results in significantly improved liver histology and biochemistry. However, the incidence of liver cancer remains in patients with seroclearance^[5,6,8,9]. A history of cirrhosis and age above 50 years at HBsAg seroclearance are high risk factors for liver cancer^[10,11]. Existing studies have confirmed that HBV seroclearance could effectively improve the prognosis of liver cancer patients with positive HBsAg^[12,13]. However, whether HBsAg seroclearance, which indicates a further decrease in viral load, affects the prognosis of patients with liver cancer remains unclear. Because of the small number of such cases, it is currently difficult to have an effective patient control group, leading to few studies in this field. Moreover, inconclusive findings have been reported by the small amount of studies available^[14].

In this study, the clinicopathological characteristics of liver cancer patients with HBsAg seroclearance were assessed with strict case control and elimination of confounding factors. The correlation between HBsAg seroclearance and the prognosis of patients with liver cancer was established.

MATERIALS AND METHODS

Patients with primary liver cancer admitted to our hospital from 2008 to 2017 were included. Hepatitis markers, auto-antibodies in liver disease, drinking history, and other etiological data were recorded. Patients with underlying liver diseases (hepatitis C virus, autoimmune liver disease, alcoholic liver disease, cryptogenic cirrhosis and hepatolithiasis) were excluded. Serum HBV DNA levels are routinely detected in HCC patients with HBsAg (-) and HBcAb (+) except for occult hepatitis B (OHB). Then liver cancer patients characterized by HBsAg (-) and HBcAb (+) were selected as the HBsAg seroclearance (SC) group. Those with HBsAg (+) constituted the HBsAg non-seroclearance (NSC) group. According to the consistent principles of the Child-Pugh scoring system for liver function and the 8th edition of the AJCC/UICC staging system for liver cancer and treatment methods, patients in the SC group were strictly matched with those of the NSC group at a proportion of 1:3. According to Child-Pugh scores, the patients were divided into three grades, including A, B, and C. Based on the initial treatment after diagnosis, the patients were divided into surgical resection, ablation, and TACE groups. According to the 8th edition of the AJCC/UICC staging system for liver cancer, the patients were divided into stages I, II, III, and IV. To accurately reflect treatment responses and the prognosis of patients with liver cancer, AJCC stage

IV cases were excluded. Meanwhile, in the TACE group, only the patients who received at least two intervention treatments were selected, which fully reflected TACE efficacy.

The hepatitis B status in all patients was determined at diagnosis. HBsAg status was re-examined after the initial treatment and during follow-up. Serum HBsAg was tested quantitatively [Architect assay, Abbott Laboratories, Chicago, Illinois, United States; lower limit of detection (LLOD), 0.05 IU/mL]. Serum HBV DNA levels were measured by using a real-time PCR assay (Roche Laboratories; Basel, Switzerland; LLOD, 100 IU/mL). Before the initial treatment, routine examinations, including routine blood tests, liver function, coagulation function tests, serum-alpha fetoprotein assessment, abdominal ultrasound, contrast ultrasound, enhanced CT, and/or enhanced MRI were performed to determine the diagnosis of liver cancer, tumor size and number, the status of macrovascular invasion, and distant metastasis, as well as liver cancer stage (8th edition of the AJCC/UICC staging system for liver cancer). Patients treated by surgery were routinely examined by ICG. According to liver cancer stage, Child-Pugh score, liver volume obtained from CT scan, ICG findings, and patient willingness, the subjects were respectively selected to undergo surgical excision, ablation therapy, or TACE after the initial diagnosis. Tumor pathology, cell differentiation, underlying liver disease, and other parameters were recorded after surgery. The numbers of interventional treatments in the TACE group were recorded.

All patients were followed up after treatment, and overall survival (OS) was the only main evaluation index. The initial diagnostic time of liver cancer was used as the starting time. The deadline for follow up was December 31, 2017, and survival time was recorded.

Statistical analysis

Continuous data were expressed as mean \pm standard deviation (SD). Tumor size and follow-up time were represented by median. *T*-test was used for comparison. Count data were expressed as frequency and proportion, and assessed by the χ^2 test. The Kaplan-Meier method was used for survival analysis, and the log-rank test for comparison.

RESULTS

The clinical data of liver cancer patients in a single center for ten years were retrieved. Of the 4745 patients with liver cancer, there were 1772 cases of hepatitis B-related liver cancer. Among them, 91 cases were diagnosed as liver cancer patients with HBsAg seroclearance, accounting for 5.14% (91/1772), of which five patients were excluded from the analysis due to incomplete data or loss to follow-up. Considering the short life span of patients with advanced liver cancer and poor therapeutic responses, six AJCC stage IV liver cancer

patients were excluded, and eight additional patients were excluded for only receiving a single TACE treatment, which was not suitable for evaluating treatment efficacy. Finally, the clinical data of 72 patients with liver cancer in the SC group were collected. The serum HBVDNA levels of patients in the SC group were all negative and OHC were excluded. Meanwhile, 216 matched patients in the NSC group were enrolled according to a proportion of 1:3.

The baseline characteristics of these patients are shown in Table 1. Median patient age in the SC group was significantly higher than that of the NSC group (63.5 \pm 8.9 years vs 57.0 \pm 9.0 years, $P < 0.001$). Due to Child-Pugh score matching, there were no significant differences in coagulation, albumin, and bilirubin between the two groups, but platelet levels in the SC group were significantly higher than those of the NSC group (163.2 \pm 87.5 vs 126.7 \pm 76.2, $P = 0.001$).

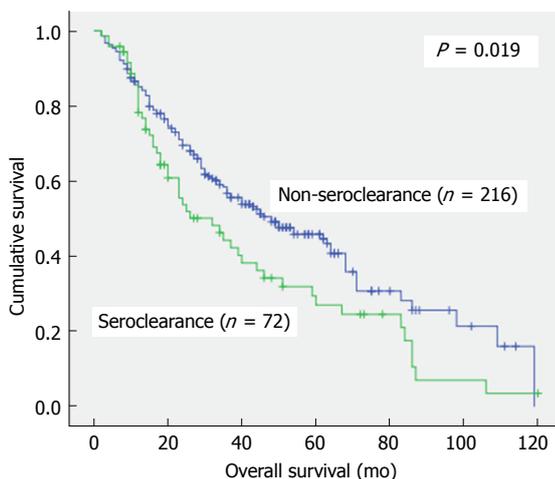
Stratification was carried out according to the treatment method, with 26 patients and 78 patients treated by surgery in the SC and NSC groups, respectively. The clinical data of the above patients are shown in Table 2. Consistent with the overall data, patient age and platelet levels in the SC group were significantly higher than those of the NSC group. A significant difference was found in pathological types of liver cancer between the two groups ($P = 0.002$). The SC group had more ICC and CHC cases compared to the NSC group, but there were no significant differences in tumor cell differentiation and history of cirrhosis between the two groups. A total of 23 patients in the SC group were administered interventional therapy, versus 69 patients in the NSC group. Based on this stratification, patients in the SC group also showed differences in age and platelet levels, which was consistent with the overall data. There was no statistical difference in the number of interventional treatments between the two groups (4.57 vs 5.07, $P > 0.05$), indicating the consistency of intervention intensity.

All patients in the SC and NSC groups were followed up, with median follow-up times of 20 mo and 33 mo, respectively, indicating no significant difference between the two groups ($P > 0.05$). As shown in Figure 1, overall survival in the SC group was lower than that of the NSC group ($P = 0.019$). The 1-, 3- and 5-year survival rates were 82.1%, 43.2% and 27.0% in the SC group, respectively, which were significantly lower than those of the NSC group (85.1%, 56.8%, and 45.2%, respectively). Stratification analysis was further carried out according to tumor stage (Figure 2); overall survival in patients with AJCC stage I disease in the SC group was significantly lower than that of the NSC group ($P = 0.029$). Meanwhile, the 1-, 3- and 5-year survival rates were 84.6%, 53.6% and 33.8% in the SC group, respectively, which were significantly lower than those of the NSC group (93.7%, 79.3%, and 66.1%, respectively). Although AJCC stage II and III patients in the SC group also showed trends of lower survival rates, statistical significance was not achieved.

Table 1 Baseline clinicopathological characteristics

Variables	Seroclearance (n = 72)	Non-seroclearance (n = 216)	P value
Ages [median (range)]	63.5 ± 8.9	57.0 ± 9.0	< 0.001
Sex (male:female)	59:17	171:45	0.871
Hemoglobin (mg/dL)	130.6 ± 28.0	135.3 ± 21.7	0.144
Platelet count (× 10 ⁹ /μL)	163.2 ± 87.5	126.7 ± 76.2	0.001
PTA (%)	90.5 ± 20.7	87.7 ± 18.5	0.282
Albumin (g/L)	40.5 ± 5.6	40.1 ± 5.9	0.675
AST (IU/L)	33.3 ± 28.6	39.9 ± 36.7	0.163
ALT (IU/L)	36.9 ± 40.7	42.4 ± 41.7	0.327
TBil (μmol/L)	21.2 ± 20.9	19.8 ± 17.5	0.567
AFP (ng/mL)			
≤ 15	36	100	0.456
15-200	19	54	
≥ 200	17	62	
Size of tumor (cm) [median (range)]	5.4 (1-15.4)	4.35 (1-15)	0.064
Number of tumor nodules			
Solitary	51	138	0.318
Multiple	21	78	
Treatment			
Resection	26	78	-
Ablation Tx	23	69	
TACE	26	78	
AJCC 8 th edition			
Stage I	41	123	-
Stage II	9	27	
Stage III	22	66	
Child-Pugh grade			
A	67	171	-
B	14	42	
C	1	3	

PTA: Prothrombin time activity; AST: Aspartate aminotransferase (Normal range 15-40 U/L); ALT: Alanine aminotransferase (Normal range 9-50 U/L); TBil: Total bilirubin (Normal range 5.1-19.0 μmol/L); AFP: Alpha fetoprotein (Normal range < 15 ng/mL); TACE: Transhepatic arterial chemotherapy and embolization.



	Seroclearance (n = 72)	Non-seroclearance (n = 216)
Follow-up duration (mo)[median (range)]	20 (2-120)	33 (2-119)
Overall survival rate		
1-yr	82.1%	85.1%
3-yr	43.2%	56.8%
5-yr	27.0%	45.2%

Figure 1 Overall survival of all hepatocarcinoma patients.

DISCUSSION

In the present study, through strict design matching, important confounding factors closely related to survival in patients with liver cancer (such as tumor stage, Child-Pugh score, and treatment method) were eliminated. Then, the effects of HBsAg seroclearance on the clinical

characteristics and survival outcome of patients with hepatitis B-related liver cancer were determined. Patients with HBsAg seroclearance accounted for 5.14% (91/1772) of all cases of hepatitis B-related liver cancer in this study. Compared with the NSC group, the patients in the SC group were older and had higher platelet counts, but the overall prognosis of these patients was

Table 2 Baseline clinicopathological characteristics for the resection group

Variables	Seroclearance (n = 26)	Non-seroclearance (n = 78)	P value
Ages (median)	61.6 ± 10.1	56.4 ± 8.4	0.010
Sex (male:female)	22:6	69:9	0.216
Hemoglobin (mg/dL)	138.3 ± 21.0	142.1 ± 18.7	0.385
Platelet count (× 10 ⁹ /μL)	197.7 ± 91.6	154.8 ± 81.7	0.026
PTA (%)	96.9 ± 16.2	94.5 ± 17.8	0.538
Albumin (g/L)	41.8 ± 4.3	42.2 ± 4.8	0.716
AST (IU/L)	37.7 ± 39.5	42.7 ± 33.9	0.529
ALT (IU/L)	41.4 ± 41.6	41.2 ± 46.7	0.985
TBil (μmol/L)	19.7 ± 23.2	17.4 ± 14.8	0.570
AFP (ng/mL)			
≤ 15	12	30	0.581
15-200	5	23	
≥ 200	9	25	
Size of tumor (cm) [median (range)]	7.2 (2.3-15.4)	6.1 (2.3-15)	0.140
Number of tumor nodules			
Solitary	20	49	0.235
Multiple	6	29	
Pathological type			
HCC	18	74	0.002
ICC	3	2	
CHC	5	2	
Cell differentiated degree			
Highly differentiated	5	13	0.180
Moderately differentiated	11	48	
Poorly differentiated	10	17	
Liver cirrhosis			
Yes	20	68	0.221
No	6	10	
AJCC 8 th edition			
Stage I	14	42	-
Stage II	2	6	
Stage III	10	30	
Child-Pugh grade			
A	25	75	-
B	1	3	
C	0	0	

PTA: Prothrombin time activity; AST: Aspartate aminotransferase (Normal range 15-40 U/L); ALT: Alanine aminotransferase (Normal range 9-50 U/L); TBil: Total bilirubin (Normal range 5.1-19.0 μmol/L); AFP: Alpha fetoprotein (Normal range < 15 ng/mL); HCC: Hepatocellular carcinoma; ICC: Intrahepatic cholangiocarcinoma; CHC: Combined hepatocellular carcinoma and cholangiocarcinoma.

worse.

Previous studies have shown that the older the liver cancer patient with HBsAg seroclearance, the better the liver function reserve^[6,9,14,15]. In the present study, this notion was confirmed by both holistic and subgroup analysis, and patients in the SC group were significantly older. These results indicated a delay in the occurrence of liver cancer, suggesting the protective effects of HBsAg seroclearance. As both groups were matched for Child-Pugh scores, we could not compare liver function between the two groups. However, a significant difference in platelet levels was found between the two groups. Platelet count is a sensitive index of hypersplenism, which indirectly reflects the severity of portal hypertension in cirrhosis. Our results showed that the higher the platelet count, the better the liver function reserve as in previous studies. This also suggests a potential protective effect of HBsAg seroclearance in the liver.

Although the above results confirmed liver protection by HBsAg seroclearance in patients with chronic hepati-

tis B, the final survival analysis yielded opposite data. Indeed, the prognosis of patients in the SC group was worse than that of the NSC group. Further analysis showed that for liver cancer patients with AJCC stage I disease, the SC group showed worse overall survival compared with the NSC group. Generally, tumors at the early stage are more likely to be curatively treated with better therapeutic efficacy. Therefore, prognosis of these patients could better reflect the biological behavior of the tumor. Based on this common knowledge, the survival results in stage I patients indicated the higher malignancy of tumors in the SC group. Although subsequent survival analysis of AJCC stage II and III patients showed no statistical significance, the SC group still showed a worse survival trend.

Comparing the pathological types of liver cancer treated with surgery, the two patient groups showed different distributions. The SC group showed more ICC and CHC cases, and malignancy in these two pathological types is obviously higher than that of HCC^[16]. Unfortunately, the ablation group was limited by the rate of biopsy in addition

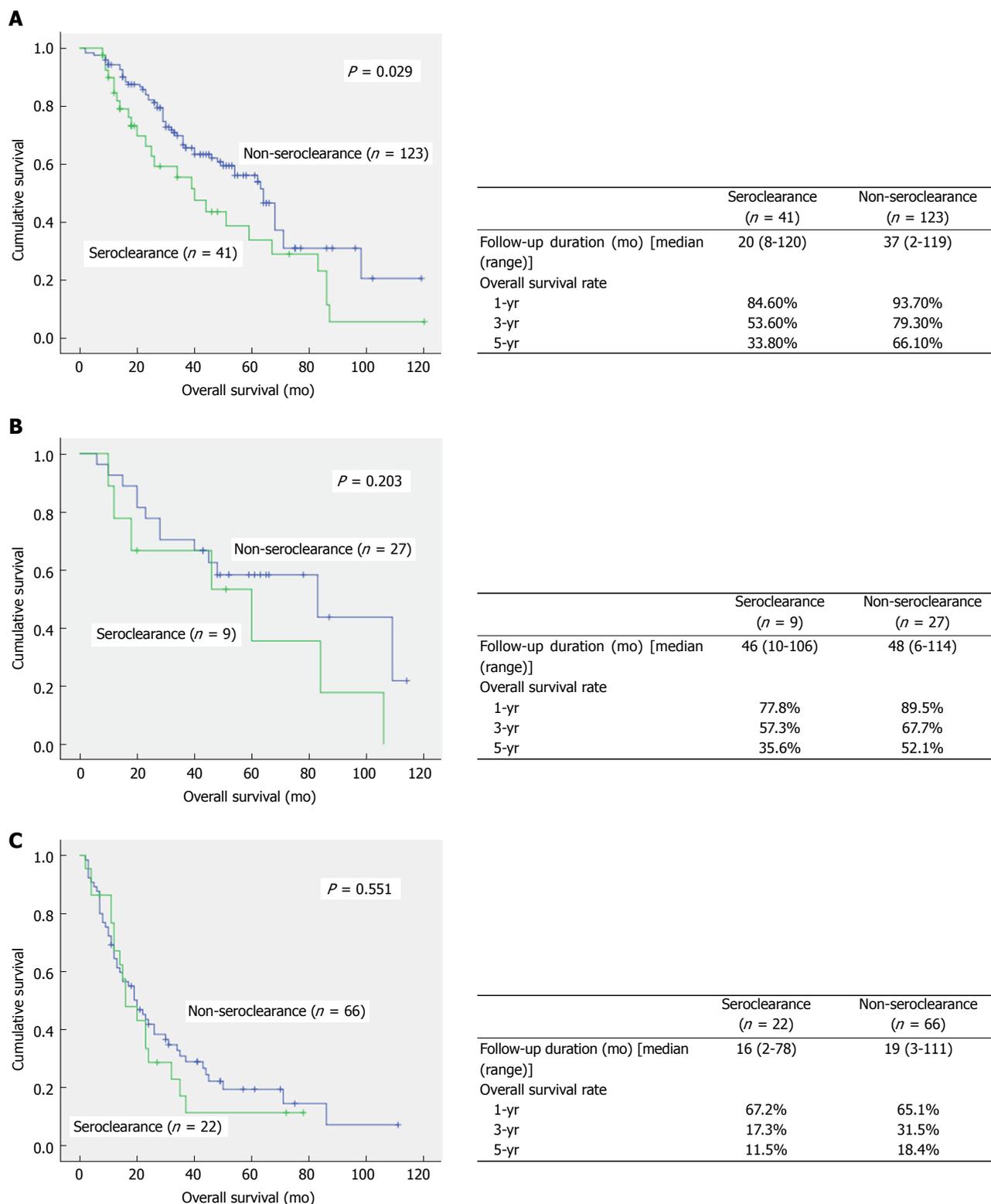


Figure 2 Stratification analysis was carried out according to tumor stage. A: Overall survival of stage I hepatocarcinoma (HCC) patients. B: Overall survival of stage II HCC patients. C: Overall survival of stage III HCC patients.

to the limitations of puncture pathology itself. Therefore, insufficient data could not be effectively analyzed. Results of the sole operation group could not represent the tumor type characteristics of the whole cohort. However, due to the highly significant difference observed

in pathological types for the surgery group, the results were representative. More importantly, these findings corroborated survival data, which could partly explain the worse prognosis of patients with liver cancer in the SC group.

Studies have confirmed that HBV infection is closely related not only to HCC, but also to the incidence and prognosis of ICC^[17-19]. In addition, a recent meta-analysis assessing the correlation between the HBV infection status and the risk of cholangiocellular carcinoma showed that consistent with positive HBsAg, HBsAg seroclearance is also a high risk factor for ICC^[20]. This was confirmed by the above pathological findings. In another report, 928 patients with hepatitis B-associated ICC were assessed, including 24.7% with chronic hepatitis B and HBsAg seroclearance, and a high incidence of ICC in the SC group was also obtained^[21]. Another important surgical and pathological finding in this study was the frequent occurrence of CHC in the SC group. Among twenty-six patients that underwent surgical excision in the SC group, five CHC cases were found, including two also diagnosed with cirrhosis. This pathological type is infrequently represented among all liver cancer cases, accounting for only 1.0%-4.7%. However, its malignancy exceeds that of ICC and HCC^[16,22,23]. Zhou *et al.*^[24] found that HBV infection is an independent risk factor for CHC, with 64.3% of cases also diagnosed with cirrhosis. Multiple studies have shown that this mixed hepatocarcinoma might be largely derived from hepatic precursor cells (HPCs). Indeed, carcinogenic factors affect the multi-differentiation potential of HPCs, leading to the formation of a mixed source of hepatocytes and cholangiocytes^[25-27]. Although previous studies have confirmed the associations of HBV infection with ICC and CHC incidence rates, it is very challenging to understand why these two highly malignant tumors were more likely to occur in the SC group. These findings still require confirmation in large sample trials.

The limitations of the present study should be mentioned. First, this was a single center retrospective case control study, with a possibility of selection bias in the control group. Second, since liver cancer incidence in patients with HBsAg seroclearance is low, the sample size was limited, and the number of cases after stratification was even more reduced, which resulted in wide confidence intervals. Third, because of difficulties in tracing the disease history, the current study lacked key data such as time of antiviral treatment, time of HBsAg seroclearance, and time of cirrhosis diagnosis. The correlation of HBsAg seroclearance with cirrhosis and liver cancer occurrence could not be well explained. Multicenter prospective studies are needed to solve the above problems.

In conclusion, patients with HBsAg seroclearance still have a risk of developing liver cancer. Although HBsAg seroclearance has some protective effects in respect to tumorigenesis, cirrhosis, and portal hypertension, prognosis in these patients is worse, likely because of the frequent occurrence of highly malignant ICC and CHC.

ARTICLE HIGHLIGHTS

Research background

Hepatitis B surface antigen (HBsAg) seroclearance is considered the gold

standard for hepatitis B virus (HBV) clearance and chronic hepatitis B cure. Existing studies have confirmed that HBsAg seroclearance could result in significantly improved liver histology and biochemistry in patients with chronic HBV, but a certain incidence of liver cancer still exists. The current question is whether HBsAg seroclearance plays a role in the prognosis of liver cancer patients. Due to the small number of such patients, there is currently no reliable research and conclusion.

Research motivation

The effect of HBsAg seroclearance on prognosis in hepatitis B-related primary liver cancer remains unclear. The solution to this problem would improve the understanding of the etiology and pathogenesis of HBV-related liver cancer and to guide clinical treatment.

Research objectives

Our objective was to assess the impact of HBsAg seroclearance on survival outcomes in hepatitis B-related primary liver cancer.

Research methods

We designed a case-control study. Information from patients with hepatitis B-related liver cancer admitted to our hospital in 2008-2017 was retrieved. Cases diagnosed with HBsAg (-) and HBcAb (+) liver cancer were included in the HBsAg seroclearance (SC) group. HBsAg (+) liver cancer patients were strictly matched for liver cancer stage (AJCC staging system, 8th edition), Child-Pugh score, and first diagnosis/treatment method (surgery, ablation and TACE) and were assigned to the HBsAg non-seroclearance (NSC) group. Then, clinical, pathological, and survival data in both groups were assessed.

Research results

The SC and NSC groups comprised of 72 and 216 patients, respectively. Patient age ($P < 0.001$) and platelet count ($P = 0.001$) in the SC group were significantly higher than those of the NSC group. SC group patients who underwent surgery had more intrahepatic cholangiocarcinoma (ICC) and combined HCC-CC (CHC) cases than the NSC group, but no significant differences in tumor cell differentiation and history of liver cirrhosis were found between the two groups. Overall survival was lower in the SC group than the NSC group ($P = 0.019$). Survival of patients with AJCC stage I disease in the SC group was lower than that of the NSC group ($P = 0.029$).

Research conclusions

Seroclearance in patients with hepatitis B-related primary liver cancer has protective effects with respect to tumorigenesis, cirrhosis, and portal hypertension but confers worse prognosis, likely due to the frequent occurrence of highly malignant ICC and CHC.

Research perspectives

This is the first reliable study about the effect of HBsAg seroclearance on the prognosis of hepatitis B-related liver cancer. In the future, more SC patients should be accumulated, and it is necessary to further verify this result by propensity score matching.

ACKNOWLEDGEMENTS

The authors thank Dr. Qi Xin for assistance with data analysis and Mrs. Xu-xia Li for assistance with data collection.

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P- Reviewer: Aghakhani A, Ahmed Said ZN, Kanda T, Sazci A

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