STROBE statement- case control study

Title:

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

Abstract

AIM

To explore the impact of hepatitis B surface (HBsAg) seroclearance on survival outcomes for primary liver cancer with chronic hepatitis B

METHODS

All patients with hepatitis B-related HCC were identified between 2008 and 2017 in our hospital. Of these patients, hepatitis marker with HBsAg(-) and HBcAb(+) were identified as HBsAg seroclearance (SC) group and HBsAg(+) as non-seroclearance (NSC) group. Each patient in SC group were strictly matched in the ratio of 1 to 3 with patients in NSC group according to the 8th AJCC stage, Child-pugh score and the initial treatment method including surgery, ablation and intervention. Considering the limited therapeutic effect, we excluded patients who only had single intervention and patients in stage Ⅳ. Baseline clinical demographics and survival outcome were collected and compared between the two groups.

RESULTS

Finally, seventy-two HCC patients with HBsAg SC were identified as SC group, including 41 patients in stage I, 9 patients in stage II and 22 patients in stage III. Of these, there were 26 patients in surgical group, 23 patients in ablation group, and 26 patients in transhepatic arterial chemotherapy and embolization (TACE) group. 216 HCC patients with HBsAg(+) were strictly matched with SC patients and identified as NSC group. Statistical analysis showed that age of patients in SC group was higher than that in NSC group (63 year-old vs 57 year-old, P<0.001). Platelet number in SC group was higher than that in group NSC (163.2±87.5×10^9/μL vs 126.7±76.2×10^9/μL, P=0.001). There was significant different in the pathological type of liver cancer in patients treated with surgery (P=0.002), patients in SC group had more intrahepatic cholangiocarcinoma (ICC) and combined hepatocellular carcinoma and cholangiocarcinoma (CHC), but there was no significant different in the differentiation of tumor cells and the background of liver cirrhosis between two groups. The patients with intervention treatment underwent similar times of TACE in two groups (4.57 vs 5.07, P>0.05), which indicated a consistent intensity of intervention. Survival analysis showed a worse overall survival (OS) of SC group compared to NSC. The 1-, 3-, 5-year survival rates in SC group was lower than that in NSC (82.1% vs 85.1%, 43.2% vs 56.8% and 27% vs 45.2%, P=0.019, respectively). In hierarchical comparison, each stage of SC group revealed a worsen survival trend than that of NSC group. The trend in stage I patients showed statistical

different. Of the patients in stage I, the 1, 3, 5 year survival rate in SC group was lower than that in NSC group(84.6% vs 93.7%, 53.6% vs 79.3% and 33.8% vs 66.1%, *P*=0.029 respectively).
CONCLUSION:
The prognosis of HBsAg SC patients with primary liver cancer is worse than that of NSC. Among them, the frequent occurrence of highly malignant ICC and CHC was a possible cause.

Introduction

Background:

Studies found that patients with surface antigen seroclearance still had a very low level of HBVDNA in liver. Compared with chronic hepatitis B patients with positive surface antigen, the further decrease of HBVDNA in vivo could result in significant improvement in liver histology and biochemistry. But there were still a certain incidence of liver cancer in these patients. The existed cirrhosis background and over 50 years of age to achieve surface antigen seroclearance were high risk factors for liver cancer in these patients. Existing studies have confirmed that the seroclearance of serum HBV could effectively improve the prognosis of liver cancer patients with positive surface antigen, so did surface antigen seroclearance that indicated a further decrease in viral load had an effect on the prognosis of patients with liver cancer? At present, there are few studies in this field. Because of the small number of cases of such patients, it was difficult to generate effective clinical control, only a small number of research results were not sure.

Objectives:

The purpose of this study was to investigate the clinicopathological characteristics of liver cancer patients with surface antigen seroclearance, and to demonstrate the correlation between hepatitis B surface antigen seroclearance and the prognosis of patients with liver cancer through strict case control on the premise of trying to eliminate confounding factors.

Methods

Study design:

Case- control study

Setting:

Patients with primary liver cancer admitted in Tianjin third central hospital from 2008 to 2017 were retrieved. Patients in this study were followed up after treatment, and the overall survival (OS) was used as the only evaluation index. The initial diagnosis time of liver cancer was used as starting time; deadline was on 31st December, 2017; survival time was recorded.

Participants:

Patients with underlying liver diseases of hepatitis C virus, autoimmune liver disease, alcoholic liver disease, cryptogenic cirrhosis and hepatolithiasis were excluded. Liver cancer patients with hepatitis B markers HBsAg (-) and HBcAb (+) were selected as HBsAg seroclearance (SC) group; liver cancer patients

with hepatitis B markers HBsAg (+) were selected as HBsAg non-seroclearance (NSC) group.

Variables:

According to the Child-phgh score of liver function, patients were divided into three grades which were grades A, B and C. According to the initial treatment after diagnosis, patients were divided into surgical resection group, ablation group and TACE group. According to the 8th edition of AJCC/UICC staging system for liver cancer, patients were divided into stage I, II, III and IV,

Data sources and measurement:

The hepatitis B status in all patients was determined when it was diagnosed, and the surface antigen was re-examined after the first treatment and during follow-up period. Before the initial treatment, routine examinations including routine blood test, liver function, coagulation function, serum-alpha fetoprotein, abdominal ultrasound, ultrasound contrast, enhanced CT and/or MRI enhancement were performed to determine the diagnosis of liver cancer, the size and number of tumor, whether macrovascular invasion or not, distant metastasis and so on, as well as to determine the stage of liver cancer (the 8th edition of AJCC/UICC staging system for liver cancer). Patients treated with surgery were routinely examined by ICG. According to the stage of liver cancer, Child-Pugh score of liver function, the calculation of liver volume from CT scan, the value of ICG and the willingness of patients, all the patients were treated with surgical excision, ablation therapy and TACE respectively after the initial diagnosis. Pathological type of tumor, cell differentiation, background of liver diseases and so on were recorded after surgery. The number of interventional treatment in TACE group was recorded.

Bias:

According to the consistent principle of the Child-pugh score of liver function, the 8th edition of AJCC/UICC staging system for liver cancer and treatment method, patients in SC group were accurately matched with patients in NSC group based on the proportion of 1:3.

Study size:

The clinical data of liver cancer in a single center for 10 years were retrieved. Among a total of 4745 patients with liver cancer, there were 1772 cases of hepatitis B-related liver cancer.

Quantitative variables:

Statistical methods:

Continuous data were expressed as mean±standard deviation. Among them, age, tumor size, follow-up time and so on were represented by median. T-test was used for proofreading. Classification data were expressed as frequency and proportion. Chi square test was used for proofreading. Kaplan-Meier method was used for survival analysis, and long-rank test was used for the comparison of survival difference.

Results

Participants:
Ninty-one cases were diagnosed and determined as liver cancer patients with surface antigen seroclearance, accounting for 5.14%; of which, 5 patients were absent due to undocumented case record or lose to follow-up. Considering the short life of patients with advanced liver cancer and poor therapeutic reaction, 6 liver cancer patients with AJCC stage IV were excluded, and another 8 patients were also excluded because they only received single TACE treatment and it was not good to evaluate the efficacy of treatment. Finally, the clinical data of 72 patients with liver cancer in SC group were collected. According to the consistent principle of liver cancer stage, Child-Pugh score of liver function and treatment method, a total of 216 patients in NSC group were enrolled according to the proportion of 1:3.

Descriptive data:
See table 1 and 2.
Outcome data:
See table 1 and 2.
Main results:
Statistical analysis showed that age of patients in SC group was higher than that in NSC group (63 year-old vs 57 year-old, P<0.001). Platelet number in SC group was higher than that in group NSC (163.2±87.5×10^9/μL vs 126.7±76.2×10^9/μL, P=0.001). There was significant different in the pathological type of liver cancer in patients treated with surgery (P=0.002), patients in SC group had more intrahepatic cholangiocarcinoma (ICC) and combined hepatocellular carcinoma and cholangiocarcinoma (CHC), but there was no significant different in the differentiation of tumor cells and the background of liver cirrhosis between two groups. Survival analysis showed a worse overall survival (OS) of SC group compared to NSC. The 1-, 3-, 5-year survival rates in SC group was lower than that in NSC (82.1% vs 85.1%, 43.2% vs 56.8% and 27% vs 45.2%, P=0.019, respectively). In hierarchical comparison, each stage of SC group revealed a worsen survival trend than that of NSC group. The trend in stage I patients showed statistical different. Of the patients in stage I, the 1, 3, 5 year survival rate in SC group was lower than that in NSC group(84.6% vs 93.7%, 53.6% vs 79.3% and 33.8% vs 66.1%, P=0.029 respectively).

Other analyses:
The patients with intervention treatment underwent similar times of TACE in two groups (4.57 vs 5.07, P>0.05), which indicated a consistent intensity of intervention.

Discussion

Key results:
Age of patients in SC group was higher than that in NSC group. Platelet number in SC group was higher than that in group NSC. There was significant

different in the pathological type of liver cancer in patients treated with surgery, patients in SC group had more intrahepatic cholangiocarcinoma (ICC) and combined hepatocellular carcinoma and cholangiocarcinoma (CHC). Survival analysis also showed a worse overall survival (OS) of SC group compared to NSC. The 1-, 3-, 5-year survival rates in SC group was lower than that in NSC.
Limitations:
There were still some limitations in the present study. Firstly, this was a single center retrospective case-control study, there was a possibility of selection bias in control group. Secondly, since the incidence of liver cancer in patients with surface antigen seroclearance was lower, the number of cases in our study group was not much, the number of cases after further stratification was less, and it was easy to have a statistically wider confidence interval. Thirdly, because of the difficulties in tracing the history of disease, the study lacked key data such as the time of antiviral treatment, the time of surface antigen seroclearance and the time of diagnosis of cirrhosis, which could not well explain the correlation of surface antigen seroclearance with the occurence of cirrhosis and liver cancer.
Interpretation:
This conclusion still needs to be confirmed by accumulating more cases. Multicenter prospective studies were needed to solve above-mentioned problems in the future.

Generalisability:
This study is representative and has universal reference value for clinicians.

Other information

Funding:
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Table1 Baseline clinicopathological characteritics

Variables	Seroconversion (n=72)	Non-seroconversion (n=216)	P value
Ages[median(range)]	63(36～83)	57(23～86)	<0.001
Sex(male:female)	59:17	171:45	0.871
Haemoglobin(mg/dL)	130.6±28.0	135.3±21.7	0.144
Platelet count ($\times 10^9/\mu L$)	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
No. of tumor nodules			
Solitory	51	138	0.318
Multiple	21	78	
Treatment			
Resection	26	78	-
Ablation Tx	23	69	
TACE	26	78	
AJCC 8th 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	

Table2 Baseline clinicopathological characteritics for resected group

Variables	Seroconversion (n=26)	Non-seroconversion (n=78)	P value
Ages[median(range)]	61(36～82)	57(29～74)	0.010
Sex(male:female)	22:6	69:9	0.216
Haemoglobin(mg/dL)	138.3±21.0	142.1±18.7	0.385
Platelet count ($\times 10^9/\mu L$)	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
No. of tumor nodules			
Solitory	20	49	0.235
Multiple	6	29	
Pathological type			
HCC	18	74	0.002
ICC	3	2	
CHC	5	2	
Cell differentiated degree			
Hige differentiatiated	5	13	0.180
moderately differentiated	11	48	
Poorly differentiated	10	17	
liver cirrhosis			
Yes	20	68	0.221
No	6	10	
AJCC 8th 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	