Higher Titer Hepatitis B Core Antibody Predicts a Higher Risk of Liver Metastasis and Worse Survival in Patients With Colorectal Cancer

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Research Article

Keywords: Hepatitis B virus, hepatitis B core antibody, colorectal cancer, colorectal liver metastasis

Posted Date: March 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-335277/v1

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Short title: Anti-HBc Predicts Prognosis of CRC

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Abstract

Purpose: This study aims to the find the association between HBV infection and postoperative survival and the risk of liver metastasis in colorectal cancer patients.

Methods: Patients who underwent curative surgical resection for colorectal cancer (CRC) between January 2011 and December 2012 were included. Patients were grouped according to anti-HBc. Differences in overall survival (OS), time to progress (TTP) and hepatic metastasis-free survival (HMFS) between groups and significant predictors were analyzed.

Results: 327 colorectal cancer patients are comprised of 202 anti-HBc negative cases and 125 anti-HBc positive cases, and anti-HBc positive cases are further divided into high-titer anti-HBc group (39) and low-titer anti-HBc group (86). High-titer anti-HBc group had significantly worse overall survival (5-Yr, 65.45% vs. 80.06%; $P < .001$), time to progress (5-Yr, 44.26% vs. 84.73%; $P < .001$) and hepatic metastasis-free survival (5-Yr, 82.44% vs. 94.58%; $P = .029$) than low-titer group. Multivariate model showed anti-HBc $\geq$ 8.8 S/CO was correlated with poor overall survival (HR, 3.510; 95% CI, 1.718-7.17; $P < .001$), time to progress (HR, 5.747; 95% CI, 2.789-11.842; $P < .001$) and hepatic metastasis-free survival (HR, 3.754; 95% CI, 1.054-13.369; $P = .041$) in the anti-HBc positive cases.

Conclusion: Higher titer anti-HBc predicts a higher risk of liver metastasis and a worse survival in anti-HBc positive colorectal cancer patients.

Keywords: Hepatitis B virus; hepatitis B core antibody; colorectal cancer; colorectal

liver metastasis.

Introduction

Colorectal cancer (CRC) is the third most common carcinoma in the world(Siegel et al. 2019). Distant metastasis is major cause of death and liver is the most common metastatic site(Fernandez et al. 2017).

Since the German doctor Rudolf Virchow(Virchow 1881) discovered the infiltration of leukocytes in tumor tissues in the 19th century, many studies have shown that inflammation is closely related to the occurrence and development of tumors(Hanahan and Weinberg 2011; Mantovani et al. 2008; Trinchieri 2015). Chronic inflammation could be sustained by the long-term activity of harmful microorganisms in the human body(Peinado et al. 2017; Psaila and Lyden 2009), which may promote tumor formation and development.

HBV is the virus that lead to inflammation and necrosis of hepatocytes during infection, and it is one of the leading public health problems in China(Ott et al. 2012). As a consequence, there are a large number of CRC patients accompanied by HBV. However, whether HBV infection affects the incidence of colorectal liver metastasis (CRLM) remains unclear. So, we sought to figure it out in this study.

As almost all of the patients generate hepatitis B core antibody (anti-HBc) after HBV infection, hepatitis B core antibody (anti-HBc) is recognized as the most sensitive serum marker(Song et al. 2015) in the course of HBV infection. Therefore, anti-HBc was used as a marker of recent or previously infection of HBV. Furthermore, as the titer of anti-HBc showed positive correlation with the activity of HBV replication(Caviglia

et al. 2018; Hoofnagle et al. 1974), the relationship between HBV replication and outcomes of the crowd in the study was also analyzed.

Materials & Methods

Patients

A retrospective analysis was conducted by reviewing the clinicopathological data of CRC patients who underwent curative resection from January 2011 to December 2012 at the Tianjin Union Medical Center. Patients who met the following criteria were enrolled: 1) histologically confirmed colorectal malignancy, 2) TNM stage II or III, 3) no evidence of distant metastases was found before the operation, 4) R0 resection for primary lesion, 5) aged between 40 and 75 years. All clinicopathological data, including clinicopathological features, tumor characteristics, and laboratory examinations, were obtained from medical records and follow-up system of Tianjin Union Medical Center. All the patients included were staged according to AJCC Cancer Staging Manual, 7th edition.

Treatment

The primary colorectal malignancy was radically resected from all eligible patients according to the principle of total mesorectal excision (TME) or complete mesocolic excision (CME). Depending on patients' conditions, neoadjuvant therapy and adjuvant therapy comprised of standardized, 5-fluorouracil-based chemotherapy and radiation therapy was administrated by the medical group according to the national comprehensive cancer network (NCCN) clinical practice guidelines in oncology.

Group

All of the cases were grouped based on the outcomes of anti-HBc. Firstly, all cases

were grouped into anti-HBc positive group and anti-HBc negative group. Moreover, the anti-HBc positive group was grouped into the high-titer anti-HBc group and the low-titer anti-HBc group by the cut-off point of 8.8 S/CO according to the titer of anti-HBc.

Serologic assay for CRC patients

All laboratory results, including biochemical tests, serum tumor markers, and HBV infection tests, were obtained within 1 week before the operation. Hepatitis B surface antigen (HBsAg), antibodies to hepatitis B surface antigen (anti-HBs), and anti-HBc were detected by electrochemical luminescence. Carcinoembryonic antigen (CEA) levels above 5 ng/ml, carbohydrate antigen 19-9 (CA19-9) levels above 37U/ml and anti-HBc levels above 1S/CO were considered to be elevated.

Follow-up of patients

All patients were followed up after hospital discharge. The patients were followed up every 3 months in the first two years after surgery and then semi-annually during the third to the fifth year. The follow-up evaluation included a routine blood test, tests for the tumor markers CEA and CA19-9, abdominal ultrasonography, and chest X-ray. Thoracic, abdominal and pelvic computed tomography (CT) and colonoscopy were performed annually. Magnetic resonance imaging (MRI) was performed when necessary. The follow-up period was terminated in July 2019.

Non-invasive Prediction Methods Calculation Formulae

The following fibrosis 4 score (FIB-4) equations was used to evaluate the

extent of fibrosis(Chen et al. 2013; Vallet-Pichard et al. 2007). Calculation formulae of FIB-4: $FIB-4=\frac{Age(years)\times AST(U/L)}{Platelets(10^9/L)\times\sqrt{ALT(U/L)}}$(Vallet-Pichard et al. 2007); Neutrophil to lymphocyte ratio (NLR) was used to indicate the extent of inflammatory response. $NLR=\frac{Neutrophil(10^9/L)}{Lymphocyte(10^9/L)}$(Xiao et al. 2014). The cut-off points for FIB-4 and NLR are 1.45 and 3.4, respectively.

Statistical methods

Continuous variables are presented as means ± standard deviation (SD). Categorical variables are shown as the number of cases and percentages. Comparisons for continuous variables were performed using the Student's t-test or Mann-Whitney U-test. Chi-square test and Fisher`s exact test was performed for the categorical variables. Overall survival (OS), Time to progress (TTP) and Hepatic metastasis-free survival (HMFS) outcomes were compared using Kaplan-Meier curves. Log-rank test was used to determine statistical differences between curves. Univariate and multivariate analyses were performed by Cox proportional hazards regression models to determine the hazard ratio of each factor. Variables that were showed a significant univariate relationship with outcome were entered into the multivariate analysis. OS was defined from the date of surgery to the date of death or last follow-up. TTP was defined from the date of surgery to the date of disease progression. HMFS was defined from the date of surgery to the date of occurrence of hepatic metastasis. The optimal cut-off point of NLR and anti-HBc are determined by X-tile 3.6.1 software (Yale University, New Haven, CT, USA) based on TTP. All statistical analyses were

performed using SPSS 22.0 statistical software (IBM, NY, USA) and GraphPad Prism version 8.01 (GraphPad Software, Inc, La Jolla, CA, USA). A two-tailed *P* value < .05 was interpreted as statistically significant.

Results

Baseline characteristics of patients

A total of 327 cases were qualified for the analyses. Among them, 202 (61.8%) cases were anti-HBc negative and 125 (38.2%) cases were anti-HBc positive including 8 (2.4%) HBsAg positive cases. The 125 anti-HBc positive cases were divided into two groups according to optimal cut-off point of anti-HBc titer (8.8 S/CO): 39 (31.2%) cases were classified into the high-titer anti-HBc group, while the remaining 86 (68.8%) cases were classified into the low-titer anti-HBc group. The comparisons of baseline characteristics were shown in Table 1. No statistical difference between the anti-HBc positive and negative group was identified except for the gender proportion in which the proportion of male was significantly higher in the anti-HBc positive group than the anti-HBc negative group (68% vs. 55.4%， $P = .027$). Besides, no significant difference was identified between the high-titer and low-titer anti-HBc group.

Overall survival, time to progress and hepatic metastasis-free survival difference according to anti-HBc status

The mean follow-up period was 61.2 ± 28.8 months. Recurrence was observed in 84 (25.7%) of 327 patients until the last follow-up. There were 30 (9.2%) hepatic recurrences, 37 (11.3%) lung recurrences, 11 (3.36%) bone recurrences, 11 (3.36%) pelvic recurrences and 5 (1.5%) instances of brain recurrences. The OS, TTP and HMFS curves for the anti-HBc positive and negative groups are shown in Figure 1. The 3-, 5-year OS (3-Yr, 87.72% vs. 89.96%; 5-Yr, 75.51% vs. 80.43%; $P = .395$; Figure 1A),

TTP (3-Yr, 79.97% vs. 77.85%; 5-Yr, 71.66% vs. 74.20%; *P* = .524; Figure 1B), and HMFS (3-Yr, 93.43% vs. 90.21%; 5-Yr, 91.09% vs. 88.85%; *P* = .739; Figure 1C) didn't differ between the two groups. In contrast, there are significant differences identified between the high-titer and low-titer anti-HBc groups (Figure 2). Patients in the high-titer anti-HBc group had worse OS (3-Yr, 78.74% vs. 91.80%; 5-Yr, 65.45% vs. 80.06%; *P* < 0.001; Figure 2A), TTP (3-Yr, 60.88% vs. 89.21%; 5-Yr, 44.26% vs. 84.73%; *P* < 0.001; Figure 2B) and HMFS (3-Yr, 87.29% vs. 96.11%; 5-Yr, 82.44% vs. 94.58%; *P* = .029; Figure 2C) than those in the low-titer anti-HBc group.

Prognostic factors for OS, TTP, and HMFS

Univariate and multivariate analyses of the prognostic factors for OS, TTP, HMFS are presented in the Table 2 and 3. For the CRC patients undergoing curative surgical resection, NLR ≥ 3.4 (HR, 1.838; 95% CI, 1.119-3.02; *P* = .016), CA19-9 > 37 U/ml (HR, 2.111; 95% CI, 1.229-3.624; *P* = .007) and stage III (HR, 3.511; 95% CI, 2.162-5.702; *P* < 0.001) were associated with worse OS; NLR ≥ 3.4 (HR, 1.783; 95% CI, 1.094-2.906; *P* = .02) and stage III (HR, 3.579; 95% CI, 2.247-5.699; *P* < .001) were associated with worse TTP; NLR ≥ 3.4 (HR, 2.231; 95% CI, 1.043-4.773; *P* = .039) and stage III (HR, 2.985; 95% CI, 1.394-6.391; *P* = .005) were associated with worse HMFS (Table 2). However, univariate and multivariate analyses for the anti-HBc positive CRC patients undergoing curative surgical resection revealed that anti-HBc ≥ 8.8 (HR, 3.510; 95% CI, 1.718-7.17; *P* = .001) and stage III (HR, 3.038; 95% CI, 1.423-6.484; *P* = .004) were associated with worse OS; anti-HBc ≥ 8.8 (HR, 5.747; 95% CI,

2.789-11.842; $P < 0.001$) and stage III (HR, 3.722; 95% CI, 1.752-7.908; $P < .001$) were associated with worse TTP; only anti-HBc ≥ 8.8 (HR, 3.754; 95% CI, 1.054-13.369; $P = .041$) was associated with worse HMFS (Table 3).

Discussion

Different from previous studies in which HBsAg was adopted as a marker of HBV infection(Au et al. 2018; Huo et al. 2018), we used anti-HBc as the marker of HBV infection in this study. Because using HBsAg as the criteria of grouping may lead to the grouping mistake by deeming occult hepatitis B infection as non-infected and generate significant deviation. After people get infected by HBV, a covalently closed circular DNA form (cccDNA) is deposited to serve as a template for the transcription of all HBV RNAs , the production of progeny virus(Lucifora and Protzer 2016) and conduct consistent inflammation of human body(Dong et al. 2018). The cccDNA can be detected frequently in the liver of the HBsAg negative phase patients(European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu and European Association for the Study of the Liver 2017). HBV can be hardly cured by available antivirals, because neither cccDNA nor relax circular DNA (rcDNA) is affected during the anti-viral process(Lucifora and Protzer 2016). For this reason, European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) termed the therapeutic goal of Chronic Hepatitis B (CHB) “functional cure”, while the true cure is the elimination of cccDNA(European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu and European Association for the Study of the Liver 2017; Terrault et al. 2018). Several studies have proved even HBV related hepatocellular carcinoma and complications of cirrhosis(Yip et al. 2017a, 2019, 2017b) can still occur in the resolved HBV patients

when they are receiving immunosuppressive therapy.

Anti-HBc, generated by humoral immunity, is highly stable. After acute HBV infection, IgM class antibodies are firstly observed in the host's organism, and then anti-HBc IgG begins to appear. Over time, IgM levels gradually decline until they can't be detected, and IgG can persist for 10 or even more than 20 years(Song et al. 2015). Anti-HBc also has a relatively high specificity, it is produced in the presence of HBV infection rather than a serological response to HBV vaccination, while anti-HBs can appear in both situations. Therefore, anti-HBc was chosen to use as a serum marker for HBV infection in our study.

Our data showed no statistical difference between the anti-HBc positive group and anti-HBc negative group about the incidence of CRLM. Prior to this, Utsunomiya T et al analyzed the association of hepatitis virus infection and the incidence of CRLM in 1999. He found that the incidence of CRLM of the infected group was significantly lower than non-infected group (8.1% vs. 21.2%, $P < .05$) (Utsunomiya et al. 1999). However, the study didn't analyze HBV and HCV separately. In 2001, Song E et al. found that the incidence of CRLM in patients with HBV infection was significantly lower than that in patients who are not infected (13.5% vs. 27.1, $P < .05$), and the prognosis of infected patients was better(Song et al. 2001).

Some studies reached the opposite conclusion. Huo T et al. performed a cross-sectional study about CRC patients and reported that chronic HBV infection increased the risk of CRLM. Also, the study found that the incidence of CRLM of the HBeAg-positive patients was higher than it of the HBeAg-negative patients (Huo et al. 2018).

It indicated that activated replication of HBV could increase the risk of CRLM, although there aren't any significant differences identified. A similar phenomenon was found in Wei XL's study where the pancreatic cancer was included as the object of the study instead of CRC, and the phenomenon that the rate of liver metastasis in CHB patients was higher than both uninfected patients and patients with resolved HBV infection (61.1% vs. 33.9%, $P < 0.05$, and 61.1% vs. 28.7%, $P < 0.05$, respectively)(Wei et al. 2013) was observed.

Our outcome differs from previous studies. The probably reason is the recognition of HBV infection in our study differs from other studies in which "HBV infection" was characterized by positive HBsAg. Therefore, the composition of "HBV-infected patients" in this study varies from other studies. Also, HBV replication activity of anti-HBc positive cases varies from the "HBV-infected" cases in previous studies. Additionally, both Wei XL and Huo T have observed a likely correlation between the activity of HBV replication and liver metastasis of malignant tumors.

In 1974, Hoofnagle et al.(Hoofnagle et al. 1974) proposed that anti-HBc, particularly in high titers, would reflect active replication of HBV. In 1992, Hisao Iizuka et al.(Iizuka et al. 1992) observed that the detection rate of HBV DNA in blood units with high-titer anti-HBc was higher than that with low-titer anti-HBc, which conforms with Hoofnagle's conclusion. In general, the cccDNA which serves as the template for HBV replication and transcription can directly reflect the intrahepatic activity of HBV replication. Unfortunately, the liver biopsy, which is indispensable for the quantitative analysis of cccDNA, cannot be carried out in this study.

It is worth mentioning that Caviglia GP et al. (Caviglia et al. 2018) reported the correlation between anti-HBc and cccDNA. They found that high-titer anti-HBc was associated with the finding of intrahepatic HBV cccDNA, while low-titer anti-HBc could exclude the presence of cccDNA. So, we conducted a subset analysis concerning the titer of anti-HBc, in which anti-HBc positive group was divided into the high-titer anti-HBc group and low-titer anti-HBc group. We found that higher titer anti-HBc predicts a higher risk of CRLM and worse survival. The possible explanations for this phenomenon are listed below. 1) HBV may promote the development of CRC by HBx-mediated miR-34a downregulation which was observed in the research about the HBV-related HCC(Rana et al. 2019), and the miR-34 family was found to have antitumor activity, especially miR-34a, which was reported to promote CRC when it was downregulated(Öner et al. 2018). 2) HBV may promote CRC by altering the human gut microbiome which plays an important role in the development of CRC(Coker et al. 2019; Kang and Martin 2017; Wu et al. 2018). Due to the existence of the hepato-intestinal axis, studies have shown that HBV affects the development of HCC by changing the intestinal flora(Liu et al. 2019), but whether this mechanism can be applied to CRLM needs to be further studied. However, Qin N et al(Qin et al. 2014). reported that in the patients with liver cirrhosis, the abundance of Lachnospiraceae which could inhibit the development of CRC by producing butyric acid was decreased(Louis et al. 2014; Wu et al. 2018), while there was an increase in the Fusobacterium which could promote CRC by upregulating tumor-associated macrophages (TAMs) (Kostic et al. 2013).

Some previous studies suggest that cirrhosis could inhibit CRLM. As early as 1975, Hamaya K et al. (Hamaya et al. 1975) conducted several autopsies and observed the incidence of liver metastasis in cirrhotics was lower than non-cirrhotics (26.3% vs. 43.2%). A series of subsequent studies have reached similar conclusions(Cai et al. 2014; Ramia et al. 2011). This is probably because under the stimulation of pathogenic factors such as inflammation, the liver gradually get fibrotic until pseudo lobules are formed, which leads to the tortuous deformation of intrahepatic small vessels, afterward hemodynamics changes of liver occur. Moreover, the sinusiod capillarization causes transformations of adhesion factors and extracellular matrix, which is not conducive to the growth of tumor cells in the liver. Furthermore, the expression level of MMP inhibitors in the cirrhotic liver is also higher, which may be another component that inhibits the formation of CRLM in cirrhotic cases. However, there is no more convincing explanation for this phenomenon so far(Ramia et al. 2011).

In this study, we used FIB-4 as predictors of fibrosis to evaluate its impact on CRLM. But no statistical difference was identified. This is probably because In spite of 81 cases with FIB-4 > 1.45 was identified, 77 cases of them were in the 1.45-3.25 interval which was not clearly defined so far(Gounder et al. 2018), and only 4 cases were in the FIB-4 > 3.25 interval which corresponds to F3 and F4 (also known as advanced fibrosis) in the Metavir stage classification system. Besides, as an indirect indicator of liver fibrosis(Chen et al. 2013; Vallet-Pichard et al. 2007), the accuracy of FIB-4 is not as good as the liver biopsy. It is worth mentioning that the liver biopsy, an invasive inspection, was not routinely performed before the colorectomy, except that

cirrhosis-related symptoms occurred.

We found that NLR ≥ 3.4, CA19-9 > 37 U/ml and stage III were the predictors of adverse outcomes, which strongly support previous reports(Dexiang et al. 2012; Ying et al. 2014; Zhang et al. 2017) and clinical experience.

There are several limitations in our approach. First, this is a retrospective single-institution study with relatively small sample size and a multi-center, prospective, large-scale trials are needed in the future. Second, some clinical data such as serum HBV DNA, intrahepatic HBV DNA and cccDNA weren't available in the study. As a retrospective study, we are unable to obtain these data. Finally, we didn't analyze the usage of antivirals which may affect the outcomes.

Of note, we developed a basis for understanding the relationship between HBV infection, prognosis and liver metastasis in CRC patients using anti-HBc as the criterion for distinguishing HBV infection, avoiding errors generated by using HBsAg as the criterion for grouping. Moreover, we first established a link between the anti-HBc titer and the prognosis and liver metastasis of CRC patients. Notably, we excluded patients who were infected with HAV, HCV, and HEV and patients with liver metastases before surgery to ensure the uniformity of baseline data to the greatest extent.

Conclusion

Our data demonstrated that higher titer anti-HBc predicts a higher risk of liver metastasis and worse survival in anti-HBc positive patients with colorectal cancer undergoing curative surgical resection, which implies the close relationship between highly active replication of HBV and occurrence of CRLM. This gives us some enlightenment on the management of CRC patients. For the management of CRC, we should pay more attention to the status of HBV, especially those whose serum anti-HBc are above 8.8 S/CO. Because this may pose great impact to improving the prognosis of such patients. Moreover, we can draw up more personalized follow-up plans for patients based on their anti-HBc titers.

Figure Legends:

Figure 1 Kaplan–Meier curves of overall survival (OS), time to progress (TTP) and hepatic metastasis-free survival (HMFS) between the anti-HBc positive group and anti-HBc negative group. (A) Overall survival curve. (B) Time to progress curve. (C) Hepatic metastasis-free survival curve. The light blue and red area represent 95% confidence intervals of each group. There is no significant difference between the two groups.

Figure 2 Kaplan–Meier curves of overall survival (OS), time to progress (TTP) and hepatic metastasis-free survival (HMFS) between the high-titer anti-HBc group and low-titer anti-HBc group. The light blue and red area represent 95% confidence intervals of each group. Patients in the high-titer anti-HBc group had shorter OS, TTP and HMFS than those in the low-titer anti-HBc group.

Supplementary Figure 1. Flow diagram of the retrospective analysis with adequate data.

Supplementary Figure 2. X-tile plots of the anti-HBc.

Notes: X-tile plots showing $\chi 2$ values with cut-off points to generate the low-titer and high-titer anti-HBc subgroups. (A) The optimal cutoff value of the anti-HBc was 8.8 at the maximum $\chi 2$ value of 18.44. (B) Histogram of the entire cohort divided into low-titer anti-HBc and high-titer anti-HBc subgroups according to the optimal cutoff value of 8.8. Blue bars represent the low-titer anti-HBc group, and gray bars represent the high-titer anti-HBc group.

Declarations：

Funding: The study was funded by The National Natural Science Foundation of China (grant number 81970469).

Conflicts of interest/Competing interests: The authors declare no competing interests.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable

Authors' contributions: Ziyao Li: study concept and design, data acquisition, analysis, and interpretation of data, drafting of the manuscript, manuscript review; Guoxun Li: study concept and design, data acquisition, analysis, and interpretation of the data, drafting of the manuscript, manuscript review. Shaofei Li, Hangbo Tao, Yixiang Zhan, Kemin Ni: Data acquisition, study conception, and manuscript review. Jianfeng Gong, study supervision. All authors approved the final version of the article, including the authorship list.

Additional declarations: Not applicable

Ethics approval: This study was approved by the Hospital Review Board of Tianjin Union Medicine Center, and study was conducted following the ethical standards of The Declaration of Helsinki. The follow-up data was obtained from the follow-up system of Tianjin Union Medicine Center which didn’t involve any identification data, and the confidentiality of patient information was maintained. So, Review Board of

Tianjin Union Medicine Center waived the need for informed patient consent.

Consent to participate: Not applicable

Consent for publication: Written informed consent for publication was obtained from all participants.

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Figures

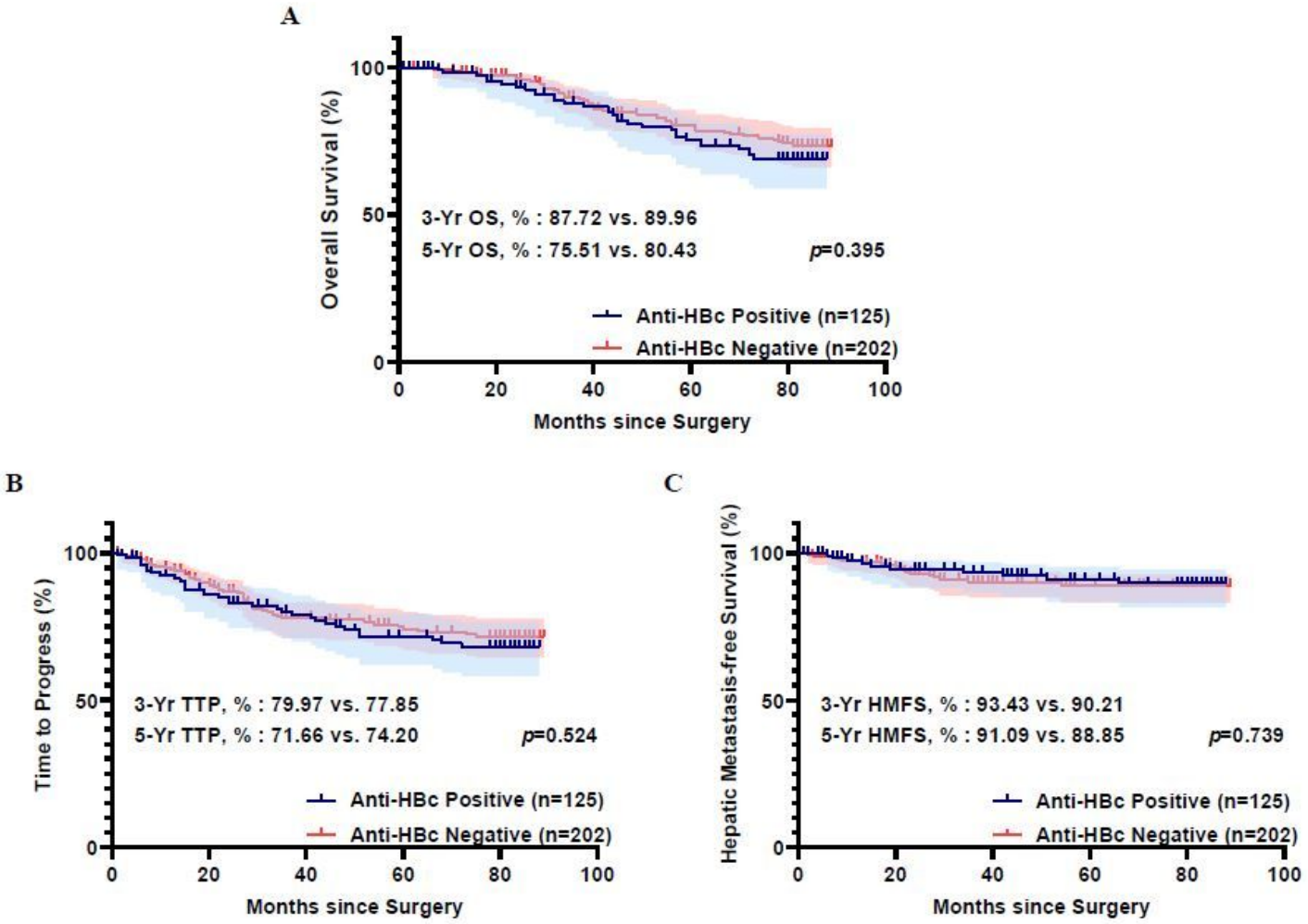

Figure 1

Kaplan–Meier curves of overall survival (OS), time to progress (TTP) and hepatic metastasis-free survival (HMFS) between the anti-HBc positive group and anti-HBc negative group. (A) Overall survival curve. (B) Time to progress curve. (C) Hepatic metastasis-free survival curve. The light blue and red area represent 95% confidence intervals of each group. There is no significant difference between the two groups.

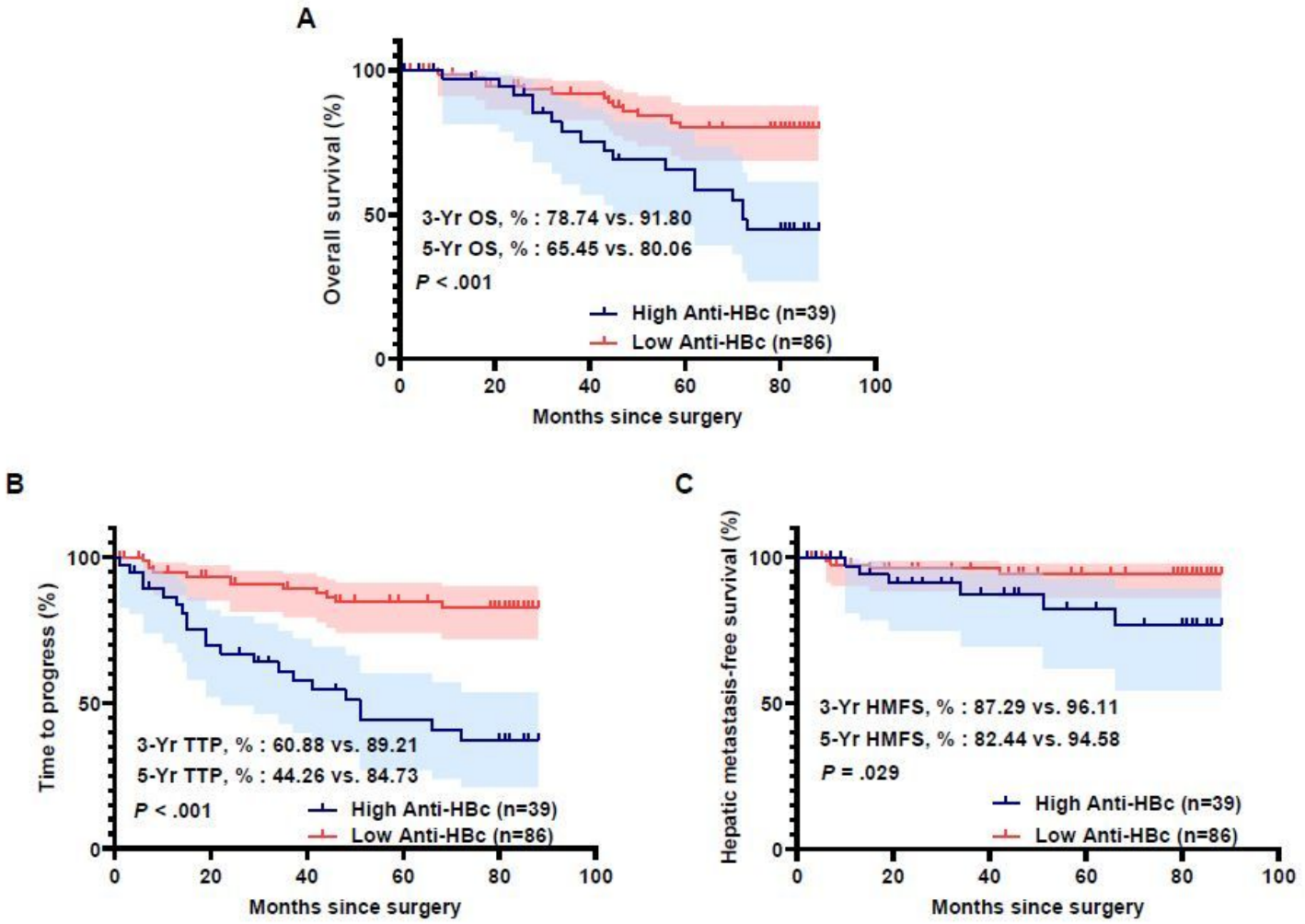

Figure 2

Kaplan–Meier curves of overall survival (OS), time to progress (TTP) and hepatic metastasis-free survival (HMFS) between the high-titer anti-HBc group and low-titer anti-HBc group. The light blue and red area represent 95% confidence intervals of each group. Patients in the high-titer anti-HBc group had shorter OS, TTP and HMFS than those in the low-titer anti-HBc group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigure1.pdf
- Supplementaryfigure2.pdf