

Answering review

Reviewer #1: Minor Comment: • The editing of the manuscript needs careful revision. • Author No. (4)- Ying- Tang Gao- contribution is missing and has to be added. • Language level: B

Ying-Tang Gao collected and sorted out material and clinical data

Comments to Authors:

TITLE Reflect the major content of the article; however, HBsAg sero-clearance is better to be replaced by HBsAg-negativity.

Although HBsAg seroclearance and HBsAg negativity look similar, there is a obviously different in the meaning between the two. HBsAg seroclearance is the result of the natural history of chronic hepatitis B or changes after antivirus drug treatment. The chronic infection of hepatitis B virus is the basic prerequisite for HBsAg seroclearance. HBcAb (+) is a serological marker of hepatitis B infection in the past. We set HBsAg (-) and HBcAb (+) patients as HBsAg seroclearance group, which is defined as patients with chronic hepatitis B who undergo HBsAg seroclearance.

Although not all patients can provide the history of chronic hepatitis B in our SC group, but it is not hard to see that pathological result in SC surgical group show 77% (20/26) of patients has liver cirrhosis, suggesting the existence of chronic hepatitis B. HBsAg negativity is not enough to explain the background of chronic hepatitis B.

In view of this, we insist on the use of 'HBsAg seroclearance'

ABSTRACT It partially fulfills the journal requirements; the aim of the work is not clearly identified.

AIM: To assess the impact of hepatitis B surface (HBsAg) seroclearance on survival outcomes in hepatitis B-related primary liver cancer
"background "has been replaced by" aim "in abstract.

INTRODUCTION It provides insufficient background regarding the studied topic because of the following:

- o The authors need to address quantitative HBsAg as a useful tool to predict seroclearance.

We do apply quantitative assay to determine the status of HBsAg. It will be described in the part of material and method.

o Also, occult HBV infection, where HBVsAg is not present, but still the patient has HBV infection has to be emphasized.

Occult hepatitis B (OHB) was defined as detectable serum HBV DNA in the absence of HBsAg. Being regarded as one of the general clinical examination, we detected serum HBVDNA levels in all liver cancer patients with HBsAg (-) and HBcAb (+). The serum HBVDNA levels of patients in SC group were all negative and there were no OHB patients in my study.

Serum HBV DNA levels are routinely detected in HCC patients with HBsAg (-) and HBcAb (+) except for occult hepatitis B (OHB).

Serum HBV DNA levels were measured by using a real-time PCR assay (Roche Laboratories; Basel, Switzerland; LLOD, 100 IU/mL).

The above-mentioned content will be added to “materials and methods” and “results”

o Last paragraph: It was mentioned that “correlation between HBsAg seroclearance and the prognosis of patients with liver cancer was demonstrated” . This has to be revised, because no correlation was presented.

The sentence is revised to be “correlation between HBsAg seroclearance and the prognosis of patients with liver cancer was established”.

MATERIALS AND METHODS: It was nearly covered, but some important issues have to be considered.

o HBsAg status: patient selection based on quantitative/qualitative HBsAg is not clarified.

Serum HBsAg was tested quantitatively (Architect assay, Abbott Laboratories, Chicago, Illinois, USA; lower limit of detection (LLOD), 0.05 IU/mL).

o HBsAg clearance is not clarified if it is in the course of natural development or in response to antiviral therapy.

The medical history showed that in all 72 SC patients, only 5 patients had a history of antiviral therapy. HBsAg seroclearance of the 5 patients were considered as the response to antiviral therapy, and that of the other 67 patients as the result of the natural development of HBV.

However, because of difficulties in tracing the disease history, the current study lacked key data such as time of antiviral treatment, time of HBsAg seroclearance. (This point has been emphasized in the limitation of my manuscript.) In addition, the clarification of the reason for HBsAg seroclearance is not the key point of our research. So we are not ready to add these data in my manuscript.

o SC group were strictly matched with those of the NSC group at a proportion of 1:3. The reason for the chosen ratio is better to be explained.

We strictly matched the tumor staging, Child-pugh score and treatment methods in two groups of patients. Due to the strict matching, the patients in group NSC were severely restricted, and 1:3 was the largest proportion we could obtain based on existing data. We chose the largest proportion to get more reliable statistical results.

RESULTS: Are well presented and informative, however, the following remarks are better to be considered:

o The average age is better to be expressed as mean age \pm SD.

According to the suggestion, we have revised the expression of age.

o Tables were informative, but p value is missing> Also, normal values for AST, ALT, TBiL & AFP have to be mentioned.

According to reviewer suggestion, we have add p value in each group of comparisons and normal values for AST, ALT, TBIL and AFP in the description of the two tables

o % is always has to be associated with any presented number of patients; e.g.: 26/72 (%).

Patients with HBsAgseroclearance accounted for 5.14%(91/1772) of all cases of hepatitis B-related liver cancer in this study.

o Figures 2- 4 are better to be figure 2(A, B, C).

Have been amended according to the suggestion

Discussion: An overall theoretical analysis of the study results is nearly covered.

None

REFERENCES:

- Relevant updated references are cited.
- PMID is maintained for all included references.
- The journal style for writing this section is maintained.

None

Reviewer #2: This paper investigated the "impact of HBsAg seroclearance on prognosis of hepatitis B-related primary liver cancer". The authors found that 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. The manuscript is well presented and of interest and can contribute to increase the knowledge of this topic. Only some grammatical errors were seen in the manuscript which should be corrected.

Some grammatical errors have been corrected.

Reviewer #3: The manuscript entitled “ Negative impact of HBsAg seroclearance on prognosis of hepatitis B-related primary liver cancer” has been evaluated as follows; The effect of HBsAg seroclearance on prognosis in hepatitis B-related primary liver cancer has been studied in the HBsAg seroclearance (SC) group and the HBsAg non-seroclearance (NSC) group. The SC and NSC groups consist of 72 and 216 patients, respectively. The authors demonstrated that 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. It is an interesting paper with statistically significant data but needs language polishing.

Some language polishing have been made.

Reviewer #4: Authors concluded "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." However, authors excluded the patients with underlying liver diseases (hepatitis C virus, autoimmune liver disease, alcoholic liver disease, cryptogenic cirrhosis and hepatolithiasis). Authors should included these patients in the present study and show the HBV status and compare these patients.

We do not agree to the opinion of the reviewer. Our aim is to assess the impact of HBsAg seroclearance on survival outcomes in hepatitis B-related primary liver cancer. Excluding the other underlying liver diseases is the first step for eliminating the interference factors in this study. To ensure that all patients are liver cancer secondary to chronic hepatitis B is the basic elements of this study. We suspect that the reviewer does not really understand the intention of our manuscript.