Author’s response to reviews

Title: Late Presentation of Hepatitis B among Patients with Newly Diagnosed Hepatocellular Carcinoma: A National Cohort Study

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Author’s response to reviews:

Dear Drs. Gummlich and Hodges:

We thank the editors and the reviewers for their interest in our paper and for their comments, which have helped us improve the manuscript substantially. We have revised the paper in response to these comments and we provide a point-by-point response to the concerns raised by the reviewers. All changes have been marked in the revised manuscript, and we also provide a clean copy of the paper. Please do not hesitate to contact us if you have any questions related to this paper.

Sincerely,

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Reviewer 1 (Akinobu Takaki)

1. Given that the younger and lower income was the characteristics for late presentation, the academic background should be included in the analysis.

As the reviewer notes, patients’ knowledge and involvement in decision-making (J Clin Gastroenterol 2011;45:727-32) and education level (J Hepatol, 2016:65:653) were associated with higher HCC surveillance rates. Unfortunately, these variables were not available in the dataset and we could not include them in the analysis. Now we include this as a limitation of the study (lines 278-280):

“We also were not able to include some information that might be associated with late presentation such as knowledge or education level.”

2. The general hepatitis B carrier frequency in Korea should be added in Introduction or Discussion. The hepatitis B carrier status is affected by neonatal vaccine administration system. The universal vaccine system in Korea should be mentioned as well.

Thank you for this comment. We now include information on the hepatitis B carrier frequency and the universal vaccine system in Korea in the Background (lines 103-111).

“In 1990s, the prevalence of HBsAg positivity was 8-10% in Korea. Because of high endemicity of HBV infection, several population wide-programs were implemented to reduce the burden of HBV infection and its consequences since the 1990s. The programs included universal HBV vaccination for newborns (started in 1995), a vertical transmission prevention program (started in 2002), free liver cancer screenings for individuals aged 40 years and older with HBV, HCV or cirrhosis (started in 2003), and a mandatory surveillance system for acute hepatitis B cases (started in 2010). Due to these programs, the prevalence of HBsAg positivity had been decreased to 2.9% in 2013. However, Korea is still classified as an area of intermediate endemicity for HBV.”

3. Given that the health coverage systems are different in different countries, the standard individual payment responsibility for regular hepatitis B management in Korea should be stated.

In response to this comment, now we include this information in the Discussion section (lines 244-250).

“We observed an income differential in the risk of late presentation in spite of a national health insurance system. Korea has a single-payer national health insurance system and it covers most costs associated with medical care, including treatments, for all citizens. Accordingly, costs for hepatitis B management are covered by the national health insurance and individual payment responsibility is the same for all citizens. Our findings may not generalize to countries with
different health coverage or different individual payment responsibility for hepatitis B management."

4. The reason for late presentation must be grouped to some types such as forgotten once, ignored every year for more than 10 years, or the primary care physician did not indicate the right was for the patients. There needs these analysis.

In this study, we defined ‘late presentation of hepatitis B’ when a patient who had never been to clinic visit for hepatitis B prior to the index date of HCC diagnosis. Patients who had 1 or less clinic visit for hepatitis B in the 1 year period prior to the index date were categorized into the irregular visits group. Thus, patients who had forgotten once belonged to the irregular visits group while patients who ignored every year belonged to the late presentation group. Unfortunately, we did not have information on specific reason for late presentation such as physician’s recommendation. We now discuss about this limitation in the Discussion section (lines 280-282).

“Moreover, we did not have information on specific reason for late presentation (e.g., unawareness of HBV infection, lack of knowledge about the need for HCC surveillance, or misguidance by primary care physician, etc.).”

Reviewer 2

1. In the survival analysis, endpoints such as death and date of closure of the database are defined but authors gave no information on how lost to follow-up were managed.

In this study we used the national health insurance service (NHIS) data. Because Korea has a single-payer national health insurance system, and the NHIS maintains records of medical information including inpatient and outpatient visits, procedures, and prescriptions of virtually all citizens, losses to follow-up are negligible. Now we clarified this in the Methods section (lines 121-123).

“Korea has a single-payer national health system. The NHIS maintains national records of all covered inpatient and outpatient visits, procedures, and prescriptions as well as mortality data, and NHIS-NSC follow-up information is considered virtually complete.”

2. The use of three different models is confusing: what support the use of these three models? why not using a more usual procedure to select a final multivariate model such as step-wise ascending or descending procedure to select the final model.

Thank you for this comment. We used three models with increasing degrees of adjustment to account for potential confounding factors at the time of HCC diagnosis. In this way, the reader can appreciate how the estimates change with progressive degrees of adjustment. Our approach
is consistent with the current practice of identifying potential confounders a priori based on biological and subject matter knowledge, rather than based on data-driven statistical methods (such as step-wise methods).

In response, we have revised the Methods section to better describe and to justify the use of the three models (lines 178-183).

“We used three models with increasing degrees of adjustment to account for potential confounding factors at the time of HCC diagnosis. These models were determined a priori based on biological and subject matter considerations. Model 1 was adjusted for sex, age group, and year of HCC diagnosis. Model 2 was further adjusted for income level category and residential area. Finally, model 3 was further adjusted for initial treatment.”

3. In the result section, Table 1 should be completed with absolute numbers of participants (overall, included in the model and according to each variable category: are there any missing values?).

Now we include absolute numbers of participants in Table 1. There were no missing values.

4. Table 3: I don't see the added value of presenting three models, authors should identify and present the multivariate model that best predict all-cause mortality.

Please see the response to comment #2 of the Reviewer 2.

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Done. Please see below for the declarations.

**Declarations**

**Ethics approval and consent to participate**

The Institutional Review Board of the Samsung Medical Center approved this study and waived the requirement for informed consent as we used only de-identified data.

**Consent to publish**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

**Competing interests**

The authors declare that they have no competing interests.

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The authors received no financial support for this article.

**Authors' Contributions**

DHS: Study design and drafting of the manuscript.

DK: Data collection, statistical analysis, and drafting of the manuscript.

MK: Data collection and statistical analysis.

SWP: Critical revision of the manuscript.
EG: Statistical analysis, critical revision of the manuscript, and study supervision.

JC: Statistical analysis, critical revision of the manuscript, and study supervision.

GYG: Study design, drafting of the manuscript, and study supervision.

All authors approved the final submission.