Author’s response to reviews

Title: Self-motivated medical care-seeking behaviors and disease progression in a community-based cohort of chronic hepatitis B virus-infected patients in China

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RE: Manuscript PUBH-D-18-03470R1: Self-motivated Medical Care and Disease Progress among Community Chronic HBV Infections in China

Dear Dr. Faham Khamesipour:

Thank you for allowing us to revise our manuscript according to the suggestions from you and your reviewers. These have helped us to substantially improve our manuscript. We have completed the suggested revisions as indicated in the attached pages.

Sincerely yours,

Cui Fuqiang, Ph.D

We thank all of the reviewers for their very useful and constructive comments.
Reviewer reports:

Responses to Comments by Dr. Gautam Ray (Reviewer 1):

[1] There are multiple grammatical mistakes of English language [syntax, punctuations, sentence construction etc.]. Some of the initial mistakes edited for example, others are highlighted. Needs editing from an English language resource before any further consideration. [A semi edited version of the script in enclosed]

We have modified the text.

[2] No statistical method of sampling for establishing the cohort from different regions mentioned. Cohort number appear too small for 31 provinces. What is the population number in each district? From diagram it appears that sampling was not uniform from all provinces.

(in line 114-116)

We used convenient sampling method to recruit the HBV infected people. Our cohort recommendations are based on convenience sampling to observe medical behavior in previously known HBV infected individuals.

[3] Statistical methods need detailed elaboration

(in line 162-173)

We have done so. We rewrite the “Statistical analysis” section as:

All the data were double-entered using EPI Data 3.1 and checked for consistency. We used SPSS software (version 23, IBM, United States) and SAS software (version 9.4, SAS Institute, Inc., Cary, NC, USA) for statistical analyses. Descriptive statistic method was used to analyze the demographic characteristics and the proportion of disease status among HBV infections. Chi-square test and multivariate regression analyses [presented in relative risk (RR) with 95% confidence intervals (CI)] were used to compare the risk factors related to HBV infected person’s active medical seeking behaviors and antiviral treatments. The estimation on the rate of disease progression or HBsAg sero-clearance were calculated by a person year. The statistical significance was considered for those results with a two-tailed p<0.05.

[4] What were the antivirals used?
In our questionnaire, the antivirals including oral nucleotide drugs and intramuscular injection of interferon, we provide a list for investigation staff, and the investigators judge whether the patient and antivirals according to their medical records.

(in line 376-381)

We rephrased this part as “The policies of the reimbursement of hepatitis B antiviral drug varied across the different insurance types and also varied from province to province, ranging from 2000 nearly $300 to $3000 for URBMI (mainly covered the urban people, normally with higher reimbursement than NRCMS) or CHI (applicant purchases commercial insurance from an insurance company at his own expense according to his personal economic ability and willing). For the NRCMS covered people who were mostly in rural areas, the reimbursement rate was the lowest among these three types of insurance”

[6] Only 370 cases of those [1579] not receiving any antivirals followed up for disease progression. Number too small to make definite comment on community level disease status. What was their initial disease status?
(in line 554)

We have revised table 1, and all the initial disease status of the follow-ups and lost to follow-ups had been shown in table 1

[7] In bibliography, format is improper [punctuations, pubmed names of journal]

(in reference)

Done, we have already revised the reference format

[8] Table 1. Age group not properly written.

(in line 554)

Done, we have already revised it in table 1
Responses to Comments by Dr. Rong-Nan Chien (Reviewer 2): Dr. Zheng et al. reported their report entitled "self-motivated medical care and disease progress among community chronic HBV infections in China". Several drawbacks of this manuscript are found.

The major comment is that the definition of terminology is incorrect.

1. Inactive HBsAg carrier should be HBsAg(+), anti-HBe(+), normal ALT, HBV DNA<2000 IU/mL plus HBsAg level<1000 IU.
2. Chronic hepatitis B: HBsAg(+), either HBeAg(+) or anti-HBe(+), HBV DNA>2000 IU/mL plus abnormal ALT>6 months
3. Liver cirrhosis diagnosed by ultrasonography, the accuracy is only 70-75%
4. HCC diagnosed by ultrasonography is not correct enough.

(in line 123-144)

Done, we have revised the diagnosis section in Method, as following:

Each participant was clinically examined for signs and symptoms of liver disease after which routine blood tests including alanine transaminase (ALT) and abdominal ultrasound was done. According to the definitions of national guidelines [20, 21], hepatitis B case-patients should be classified as: (1) Carrier: HBsAg positive cases with no symptoms of liver diseases (e.g. nausea, vomiting, diarrhea, anorexia, abdominal pain, and jaundice), and normal ALT levels (≤40 IU/ml). (2) CHB: HBsAg positive cases, with at least one of the following items including HBV infection ≥6 months prior, chronic inflammatory changes reported on abdominal ultrasound, or anti-HBc IgM negative. (3) liver cirrhosis (LC): Cases with cirrhosis of the liver as reported on abdominal ultrasound. (4) HCC: Cases with liver lesion(s) suggestive of hepatocellular carcinoma reported on abdominal ultrasound were classified as HCC.

5. HIV or HDV coinfection is not excluded.
6. Alcoholic or nonalcoholic fatty liver disease or steatohepatitis are not excluded.

(in line 120-122)

In our study, with the participants inclusion criteria, we had excluded the other possible liver diseases besides HBV infection, so we rewrote this sentence to make it more accurate as “(4) has no other chronic liver diseases such as co-infection with HCV or HDV, alcoholic or nonalcoholic fatty liver disease or steatohepatitis”
7. The community study is too diverse and not well defined.

8. The cases numbers are too small to make a conclusion and high drop out rate

(in line 388-392)

In this study, we conducted a community-based study which meant the participants were recruited not from hospitals. And the cohort size and high drop rate are real limitation and these two points are also described in the discussion as study limitations.

Responses to Comments by Dr. Kwenti Emmanuel Tebit (Reviewer 3):

Title:

* Rephrase the title for clarity. What do you mean by "community chronic HBV infections"? This phrase has been used throughout the manuscript. "Community-based" should be reserved to the study design to indicate that participants were recruited from the community as opposed to the hospital. Furthermore, "chronic hepatitis B virus infections" as presented in the title is referring to the disease and not the patients (persons) with chronic hepatitis B. It is better to just use "Chronic hepatitis B virus-infected persons (or patients)". This should also be corrected throughout the manuscript. I suggest you use the title "Self-motivated medical care seeking behaviours and disease progression in a community-based cohort of chronic hepatitis B virus-infected patients in China".

Thanks! Done.

Abstract:

* Pg. 3, lines 14 - 16: What do you mean by "clinical diagnosis of the latest active seeking medical care…"?

(in line 39)

We have rephrased this sentence as “clinical diagnosis at last visit provided by hospital”.

* Pg. 3, lines 28 - 30: Complete the sentence.

(in line 44-62)
We have rewritten the results in abstract section, as following:

Results: Among the 2422 chronic hepatitis B infected patients recruited in 2009, 1784 (73.7%) were followed up to 2014, and 638 (35.8%) HBV infected persons had initiatively seeking medical care in hospitals and among them only 140 (21.9%) received antiviral treatments. We found active seeking medical cares were more likely to be in HBV infected participants with living in urban (aRR=1.3, 95% CI:1.0-1.6), those in 0-19 years old (aRR=1.5, 95% CI:1.1-2.1), 20-39 years old (aRR=2.2, 95% CI:1.7-3.0) and 40-49 years old (aRR=1.5, 95% CI:1.1-2.0), and persons with insurance of URBMI or CHI (aRR=2.5, 95% CI:1.7-3.6) and NRCMS (aRR=1.9, 95% CI:1.4-2.6). For the antiviral treatment, it was more likely to be in patients in 20-39 years old (aRR=0.4, 95% CI:0.3-0.7), persons with insurance of URBMI or CHI (aRR=2.6, 95% CI:1.1-6.3) and NRCMS (aRR=3.0, 95% CI:1.3-6.9) and patients from prefecture and above level hospitals (aRR=2.0, 95% CI:1.4-3.0).

Background:

* Pg. 4, lines 56 - 62: Rephrase the sentence. Do you mean HBV infected patients who were not on anti-viral treatment?

(in line 105-110)

We have rewritten this paragraph, as “We designed and conducted a prospective study on community-based HBV infected persons to analyze their initiative medical seeking behaviors and the antiviral treatment situation, as well as the related impact factors; for those HBV infected case but without anti-viral treatment, we observed their disease progress after 5 years follow-up.”

Methods:

* Pg. 5, lines 17 - 18: What do you mean by “living in a community”? Are there some HBV infected patients living in the hospital?

(in line 119)

All the participants came from community, so we cancelled this item.

* How was the sample size of 2422 obtained? Describe the sampling technique.

(in line 114-117)

We used the convenience sampling method in this study, so we made it clear in method part as
“In 2009, using convenience sampling method, we recruited the chronic HBV infected persons from communities based on previously available database obtained from 2006 national sero-survey.”

* Pg. 5, lines 58 - 61: What do you mean by "the clinical diagnosis of the latest actively sought medical care"? Change "anti-virus" to "anti-viral" throughout the manuscript.

(in line 150-151)

Done, we rephrased the writing of this as “the clinical diagnosis at last visit provided by hospital”, and changed the "anti-virus" to "anti-viral" throughout the manuscript.

* Pg. 6, lines 7 - 10: Can you provide a reference for the unified questionnaire used in this study?

We designed a questionnaire for this survey, so we have no reference here.

* Pg. 6, lines 18 - 23: I suggest you include multiple logistic regression analysis adjusting for confounding as one of your analysis for risk factors of treatment-seeking behavior of the study population.

(in line589)

Done, we have already added the multiple regression in table 3

* Can you describe clearly how self-motivated medical care behavior was assessed? What were the criteria for classifying one as having self-motivated medical care behavior?

(in line 152-155)

We added this criteria in method section “3. Follow-up investigation and data collection”, as following:

“The patients could be admitted as having self-motivated medical care behavior for HBV related disease by providing relative evidences during the study period, such as hospital diagnostic records, doctors' prescription or hospital testing results”
Results:

* Pg. 6, 48 - 52: Table 1 already contains the data, no need to spell it out all over. Specify which Figure 1 (A or B) when citing figure 1.

(in line 182-192)

We revised the results section as a whole to simplify the unimportant and repetitive content.

* Pg. 6, line 55: Table 1 does not contain information on the number of participants that were followed up.

(in line 155)

We have updated table 1 to make it more detailed with information on followed-up cases and lost to follow-up cases.

* Pg. 6, lines 58 - 60: The sentence is incomplete. What about the rural area?

We revised the results section as a whole to simplify the unimportant and repetitive content. So this sentence has been cancelled.

* Pg. 7, lines 56 - 60: The sentence is not clear. What were the national criteria used for? Can you elaborate more in the methods section, providing a reference for it?

We revised the results section as a whole to simplify the unimportant and repetitive content. So this sentence has been cancelled.

* Pg. 8, lines 12 - 16: These factors may be interrelated. As earlier mentioned, perform multiple logistic regression adjusting for confounding. Include your model in Table 3.

(in line 245-258)

Done, we have already added the multiple regression in table 3, and changed the results section accordingly. Now this part in results section is revised as following:

In our bivariate analysis, we found significant differences in age-groups and insurance types in both of chronic HBV infected persons’ active medical seeking behaviors and antiviral treatments, and significant differences were seen in regions and living in rural/urban on chronic HBV infected persons’ active medical seeking behaviors (all p-values < 0.05) (Table 3). In the multivariable analysis, active seeking medical cares were more likely to be in urban participants
(aRR=1.3, 95% CI:1.0-1.6), cases in 0-19 years old (aRR=1.5, 95% CI:1.1-2.1), 20-39 years old (aRR=2.2, 95% CI:1.7-3.0) and 40-49 years old (aRR=1.5, 95% CI:1.1-2.0), and persons with insurance of URBMI or CHI (aRR=2.5, 95% CI:1.7-3.6) and NRCMS (aRR=1.9, 95% CI:1.4-2.6). And the antiviral treatments were more likely to be in patients in 20-39 (aRR=0.4, 95% CI:0.3-0.7), persons with insurance of URBMI or CHI (aRR=2.6, 95% CI:1.1-6.3) and NRCMS (aRR=3.0, 95% CI:1.3-6.9) and patients from prefecture and above level hospitals (aRR=2.0, 95% CI:1.4-3.0) (Table 3).

* Add a footnote to Table 1, 2 and 4 defining the abbreviations.

(in line 558-560, 565-567, 580-582.)

Done

* Complete the class boundary for age in Table 1.

(in line 39)

Done, have revised Table 1.

* Rephrase the titles of all the tables for clarity.

Done

Discussion:

* Pg. 9, lines 28 - 33: The sentence is not clear, rephrase.

(in line 302-305)

We have revised this sentence as “As our results suggested, with the age increasing, the proportions of CHB (from 23% to 40%), LC (from 0.5% to 2.3%) and HCC (from 0% to 0.5%) increased respectively.”

* Pg. 9, lines 37 - 38. "It might be due to the differences among diagnosis criteria". Can you elaborate further to clarify your point?

(in line 305-310)
Since the diagnostic criteria for CHB were not detailed in Yang SG’s study, we only suspected that the difference with our results might be caused by this reason, because they identified 95% of HBV infected people as carriers, which much higher than general understanding. We also make a brief explanation in the text, as following:

While Yang SG found the proportion of CHB among HBsAg positive persons were only 3.98% in a community-based study in Zhejiang province., which was much lower than our findings. It might be due to the differences among diagnosis criteria, because they classified 95% of HBsAg positive person as HBV carrier in their study, which was much higher than general understanding.

* Pg. 10, lines 5 - 10: The sentence is not clear. There are two treatment rates in the sentence. What is the difference between the two?

(in line 330-331)

We have revised this sentence as “In addition, there were 6% of the lost to follow-ups (LTFUs) from the fear of their HBV infection being known by others”

* Pg. 8, lines 12 - 21: "Our findings demonstrated that the age groups and insurance circumstances were the two main factors that dictated the patients' self-motivated medical behaviors and antiviral therapy reception (Table 3). The 20-29-yrs group had the highest health care visiting rate (44.4%), but the lowest antiviral treatment rate (15.3%), however, the 50-62-yrs group had lower health care visiting rate (26.0%) and the highest antiviral treatment rate (30.3%)". Can you discuss the reason(s) behind this observation?

(in line 352-356)

We added the reasons analysis for this phenomenon in discuss section, as “However, we also found that although the proportion of young people seeking medical treatment was higher, the proportion of antiviral treatment was very low which partly because some of young HBV infected cases not meeting antiviral indications, it was largely because young patients, especially those under the age of 30, felt asymptomatic and did not take medication.”

* Pg. 10, line 53 - 54: The antiviral treatment rate was not significantly different between chronic hepatitis B virus-infected patients residing in rural and urban areas. Why bring it up here?

(in line 357-359)
We have revised this sentence as “In addition, we found rural population had lower active seeking medical behavior rate than those living in urban areas, which might explain why we found rural persons more vulnerable, having serious consequences with 60% of LC and 100% of HCC diagnosed in rural areas at the beginning of this study”

* Pg. 11, lines 10 - 16: The sentence is not clear, rephrase.
Because we have changed the results section, the data for this sentence was not analyzed as key point, so we removed this sentence in discussion section.

* Pg. 11, lines 17 - 31: Also present the equivalents of the amounts in US dollars. This will easily be understood by the international audience.

(in line 372-379)
Done, we have changed the costs in US dollar.

Minor revision

Abstract:

* Pg. 3, lines 2 - 4: "…treatment behaviours among a community-based cohort of chronic hepatitis B virus-infected persons…"

(in line 28)
done

* Pg. 3, lines 9 - 11: We conducted a community-based prospective study on people with chronic hepatitis B infection in…

(in line 33-34)
done

* Pg. 3, We recruited chronic hepatitis B virus-infected persons

(in line 35-38)
We have revised this sentence as “we recruited the participants who were identified HBV infected in national sero-survey in 2006 to set up cohort”

* Pg. 3 lines 20 - 22: Among the 2422 chronic hepatitis B infected patients recruited in 2009…
  
(in line 44-45)

done

* Pg. 3 lines 24 - 25: Of the 2422 participants, 1784 (73.7%) were followed up to 2014,
  
(in line 44-50)

done

* Pg. 3 lines 40: …medical treatment-seeking behaviour…
  
(in line 63)

done

* Pg. 3, line 42: change "locating" to "residing"
  
(in line 63-70)

Done. We have rephrased this conclusion in abstract.

Methods:

* Pg. 6, lines 4 - 6: …lost to follow-up rate
  
(in line 158-159)

We have revised this sentence as “Regular communications were conducted to reduce loss of follow up”

Results:

* Pg.6, line 42: In all, 2422 hepatitis B virus-infected patients were enrolled…

Done, in line 182.
Discussion:

* Pg. 9, line 35: …community-based study in Zhejiang province…

Done, in line 307.

* Pg. 9, lines 58 - 59: …to slow down the progression when necessary.

Done, in line 323.

* Pg. 10, line 40: Compared to…

Done, in line 346.

Conclusion:

* Pg. 12, line 1: What is LA?

Have been corrected as HBV carriers, in line 396.

* Pg. 12, line 9: Change "locating" to "residing"

Done, in line 401.