Format for ANSWERING REVIEWERS

July 28, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4173.doc).

Title: Risk factors for hepatocellular carcinoma in patients with drug-resistant chronic hepatitis B

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4173

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1

(1) Title: the title appears to be appropriated;

→ Thank you

(2) Abstract: it needs a reevaluation for the English style. Moreover, AFP and CRP must be explained the first time they are reported in the abstract text.

→ We correct the manuscript as you point out. The manuscript was re-evaluated by an English native speaker (American Journal Expert)

(3) Introduction: the meaning of LAM is explained after the first time it is reported in the text. ETV is not explained in the text.

→ We correct the manuscript as you point out.

(4) Material and methods:

- Authors reported that the great majority of the investigated patients was composed by genotype C HBV cases. However, I think it could be more scientifically valid to report the effective percentages of the different genotypes.

→ We did not check genotype in all patients (n=90/432), but 92 patients (100%) who checked genotype were genotype C. In south Korea, It is well known that genotype of CHB patients are almost genotype C. We add the paragraph at manuscript

- AFP is explained in two different parts of the text.

→ We corrected them as you point out.

- statistical analysis section is not completely clear: for non-parametric data, Student's t-test is not correct to be used, so in these cases (easily detectable using the Kolmogorov-Smirnov test), it is better to use Mann-Whitney test. Please report it in this section and recalculate the p-value when it is opportune. Authors say that they used a logistic regression analysis with the intent to evaluate the development of HCC and other variables (?): I did not found any use of this statistical test in the text. Afterwards, Authors report the use of a multivariate analysis using the Cox proportional hazards model. Probably, Authors need to select one of these tests (possibly the time-dependent Cox regression model), using a stepwise approach with the intent to minimize the variables inserted in the model. Tests for the risk of multicolinearity must be reported. Kaplan–Meier test is correctly used with the intent to analyze survivals, and the log rank test with the intent to compare them.

→ We correct statistics such as medians + ranges or IQR, clearly underlying the variables with non-parametric distribution (U Mann-Whitney test).

(5) Results: CRP is not explained the first time it is reported in the text;

--> We corrected them as you point out.

(6) Discussion: clearly reported;

→ Thank you

(7) References: the references are relevant;

→ Thank you

(8) Table 1:

- it is better to use the term "gender" respect to "sex";
- the percentage of male and female patients is not reported;
- several variables clearly showing a non-parametric distribution (AST, ALT, AFP) are represented as means ± SD, despite in the statistical analysis section it is reported that in these cases it is better to report the median value + ranges. Please report these values as medians + ranges or IQR, clearly underlying the variables with non-parametric distribution. In these cases, Student's t-test is not correct to be used, so the Authors need to recalculate the p-value with adequate statistical tests (U Mann-Whitney test).

→ We corrected them as you point out.

(9) Table 2:

- the upper 95%CI of presence of rtM204I mutants is identical to its HR: please recalculate it.

(10) Table 3:

- it is better to use the term "gender" respect to "sex";
- the percentage of male and female patients is not reported;
- the percentage of UICC groups is not reported;
- several variables clearly show a non-parametric distribution (AST, ALT, AFP, CRP, duration of ant-virual tx): please report median value + ranges and recalculate p-values using the U Mann-Whitney test.

→ We corrected them as you point out.

(11) Table 4:

- it must be updated adopting the same statements used for the table 3.

→ We corrected them as you point out.

(12) presentation and readability of the manuscript: the paper needs to be reevaluated by an English native speaker.

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The manuscript was re-evaluated by an English native speaker (American Journal Expert)

Reviewer 2

1. There are many English grammar errors, please correct them and I would suggest find a native-English speaker who knows medicine to read through.

--> The manuscript was re-evaluated by an English native speaker (American Journal Expert)

2. Many abbreviations showed up in the text for the first time without giving full-names. Several abbreviations in the text never showed full name even not showing in the abbreviation list.

--> We corrected them as you point out.

3. This study involves many statistics. I would suggest the authors to find a statistician to help with the statistics and make sure they correctly used.

--> We correct statistics such as medians + ranges or IQR, clearly underlying the variables with non-parametric distribution (U Mann-Whitney test).

4. The authors mentioned majority of the patients are genotype C, do the authors see difference between type C and other types?

--> We did not check genotype in all patients (n=90/432), but 92 patients (100%) who checked genotype were genotype C. In south Korea, It is well known that genotype of CHB patients are almost genotype C.

5. There are different types of mutants which are associated with different anti-viral drugs, such as LMV, ETV or ADV. What kind of anti-viral drug used in this study?

--> Based on Guideline of Korean Association for the Study of the liver 2007, 2011

50% of the patients received LMV+ADV, 35.7% of the patients received ETV 1mg, 14.3% of the patients received ETV+ADV.

Tenofovir is not available in our institution at 01. July 2013.

6. The authors found the R group HCCs with lower CRP, lower AFP and lower stage. Do the authors have any explanation why these HCC patients with lower CRP or AFP? How many HCC patients with liver biopsy? Any difference of HCC differentiation (tumor grade) the authors observed? Any difference of background liver histopathology? More inflamed?

--> We mentioned the paragraph (14 page), "HCC arising from resistant CHB (R group) had lower serum CRP, AFP and earlier tumor stage than HCC arising from naïve CHB (N group). We think these differences may be attributed to more frequent tumor surveillance in the R group".

Only 2 patients had liver biopsy, so we did not find any difference of HCC differentiation.

7. The authors only briefly mentioned the relationship between CRP and poor prognosis of HCC. Any explanation for that? Who produced CRP? Background hepatocytes versus HCC cells versus

inflammatory cells? It is suggested the authors give some explanation in the discussion.

--> We added the paragraph in the discussion such as "serum CRP is associated with the poor prognosis (association of tumor recurrence after a surgical resection, association of large tumor size, poorly defined tumor type)"

It is explained that C-reactive protein (CRP) is an acute-phase reactant synthesized by hepatocytes. It is regulated by pro-inflammatory cytokines such as IL-6 in responding to acute inflammation, infection, tissue damage and cancer.

8. I don't see clear evidence to predict HCC arising from drug-resistant group have a poorer survival. Can the authors explain more in detail in the discussion?

--> we remove the paragraph

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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