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Reviewer's code: 02521807

COMMENTS TO AUTHORS

The review from is well written and involves updated references. Major comments: 1. The references and analysis appears to be more strongly focussed on data collected from Asia and in a substantial low incumbence from Europe and US. Only three references are mentioned from these countries. Likewise, from South America a single study from Brazil is mentioned. The Table 1 is eloquent. It is difficult to find countries other from Asia included. These data could be misinterpreted from non-specialist reader. 2. The incumbence of genomic recombination on HBV is not mentioned nor analysed at all. This phenomenon could be involved among countries where such genomic variants are predominant. This topic should be discussed. 3. The coinfection with HIV is ignored and may impact on prevalence of HBV resistance. Only two references are included but this hot topic is essentially ignored. Minor comments The authors should polish throughout the manuscript some typing errors (i.e. line 129, page 6: "patients"; line 282, page 13:"negative"

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Major comments:

1. The references and analysis appears to be more strongly focussed on data collected from Asia and in a substantial low incumbence from Europe and US. Only three references are mentioned from these countries. Likewise, from South America a single study from Brazil is mentioned. The Table 1 is eloquent. It is difficult to find countries other from Asia included. These data could be misinterpreted from non-specialist reader.

Reply:

When we originally reviewed 40 articles and estimated the pooled incidence of preexisting RT mutations, 10 articles published from institutions in Europe and US (Salpini et al(2011, Italy), Pollicino et al(2009, Italy), Mirandola et al(2011, Italy), Lampertico et al(2008, Italy), Solmone et al(2009, Italy), Zollner et al(2005, Germany), Jardi et al(2006, Spain), Margeridon-Thermet et al(2009, US), Nguyen et al(2009, US), Vutien et al(2014, US)), and one each from Canada(Fung (2008, Canada)) and Brazil(Pacheco (2017, Brazil)) were included. However, as reviewer mentioned, table 1 didn't reflect the diversity of countries, it rather seemed too

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biased toward Asia because we marked just some typical countries in Table 1, rather than all counties associated with each RT mutation. To avoid confusion, we marked all countries in Table 1 (line 1052, page 40) and added a supplementary table (line 1088, page 52), which provides the details of 50 articles from which the pooled incidence of preexisting RT mutations was calculated. In addition, we supplemented 10 more studies, thus, a total of 50 articles were included; 32 articles published from institutions based in Asia (12 published from China, four from Iran, four from Turkey, four from India, three from Japan, two from Taiwan, and one each from Korea, Jordan, and Indonesia), 11 articles published from institutions based in Europe (six from Italy, two from Germany, and one each from Austria, Ireland, and Spain), four articles published from institutions based in North America (three from USA and one from Canada), two articles published from institutions based in South America (both from Brazil), and one article published from an institution in South Africa (Table S1). **(line 121-127, page 6), (Figure 1 and 2) (line 1086, page 49-50).**

2. The incumbence of genomic recombination on HBV is not mentioned nor analysed at all. This phenomenon could be involved among countries where such genomic variants are predominant. This topic should be discussed. 3. The coinfection with HIV is ignored and may impact on prevalence of HBV resistance. Only two references are included but this hot topic is essentially ignored.

Reply:

These are good points involved with the preexisting mutations in HBV RT region. To reflect reviewer's opinion, we created a new category (line 357-395, page 16-18) and described HBV intergenotypic recombination and coinfection with HIV, which can affect the incidence of preexisting RT mutations, in details (reference 12, 95-111). As stated in the body contents, the high prevalence of vertical infection in HBV endemic areas could lead to a chronic infection, which may result in a high probability of coinfection and a high risk for virus recombination. These two factors associated with preexisting RT mutations were also

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included in the schematic representation (Figure 3, line 1087, page 51).

Minor comments: The authors should polish throughout the manuscript some typing errors (i.e. line 129, page 6: "patients"; line 282, page 13:"negative"

Reply:

We corrected the spelling errors the reviewer pointed out.

(line 131, page6: “patients”; line 285, page 13: “negative”)

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Reviewer's code: 00032020

COMMENTS TO AUTHORS

Manuscript NO: 38992 Title: Naturally occurring hepatitis B virus reverse transcriptase mutations related to potential antiviral drug resistance and liver disease progression Manuscript Type: Review Dr. Choi YM et al. This is an interesting and informative review. However, it is too complicated to understand it. One of the reasons was the duplication statement. Authors should revise the duplicated categories and statement in manuscript. For example, 'disease progression' and 'clinical severity of liver disease' was the same category. Next, association between the detection rate and the method was important issue for consideration of mutations in RT. This issue is not related to pathology of mutation of HBV infection, is a technical problem. So, the difference of detection rate by method should be written as the limitation. Minor; In line 127, page 6, 'demonst58ted' should be revised.

This is an interesting and informative review. However, it is too complicated to understand it. One of the reasons was the duplication statement. Authors should revise the duplicated categories and statement in manuscript. For example, 'disease progression' and 'clinical severity of liver disease' was the same category.

Reply:

According to reviewer's opinion, we revised the duplicated categories and statements and arranged them in one category (line 420-481, page 19-22). For example, regarding 'disease progression' and 'clinical severity of liver disease' (those used to be in two different sections), we organized the categories as follows; '***Clinical factors (HBeAg serostatus and HBV viral loads) affecting incidence of preexisting RT mutations in treatment-native patients'*** (line 276-277, page 13) ***'Preexisting RT mutations are related to the progression of liver diseases'*** (line 420, page 19)**.** We described the progression of liver disease or clinical severity only in the latter category. Also, we deleted duplicated statements (for example, one of these two statements was deleted and integrated into a section (currently described in line

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420-481, page 19-22):

Kim *et al*[33] reported that there was a significant difference in the overall frequency of preexisting NAr mutations between chronic hepatitis patients (2.09%) and HCC patients (3.17%; p = 0.003), suggesting that emergence of preexisting NAr mutations may be related to disease severity. (Previously, line 306-310, page 14)

Kim *et al*[33] compared types and frequencies of pre-existing RT mutations between CHB and HCC treatment-naïve patients. As described in the previous section, these authors found a significantly higher rate of RT mutations in HCC patients than in those with chronic hepatitis (3.17% vs. 2.09%, p=0.003) (Previously, line 385-388, page 18).

Next, association between the detection rate and the method was important issue for consideration of mutations in RT. This issue is not related to pathology of mutation of HBV infection, is a technical problem. So, the difference of detection rate by method should be written as the limitation.

Reply:

This is a valid point which can reduce the potential for misunderstanding and clarify the characteristics of each factor. We made a new category (line 397-418, page 18-19) and described the different sensitivity of detection methodology as a limitation factor which can affect the reported prevalence of preexisting RT mutations or may cause the discrepancy among the studies.

Minor; In line 127, page 6, 'demonst58ted' should be revised.

Reply:

We corrected the misspelled word the reviewer had mentioned.

(Line 135, page 7: "demonstrated")