Dec 10, 2017

Prof. Lian-Sheng Ma

President and Company Editor-in-Chief

World Journal of Gastroenterology

Re: WJG 37011

Dear Prof. Lian-Sheng Ma,

Thanks for your letter on Nov 27, 2017 regarding our article titled as: **Nucleos(t)ide analogues decreases dialysis risk in chronic kidney disease patients acquiring HBV infection: A nationwide cohort study**. We've learned a lot from your valuable advice. According to your suggestion, we make some revisions marked as red words in the manuscript. More clear details are described as the follows.

Reply to Reviewer 1 (03647881)

1. Response to "...But, interesting, the incidence of ESRD in uninfected group (7.3%) was high than treated group (2.2%), too. The authors should try to explain this result....But, is NA improving renal function in general population? Or the overall incidence of ESRD in this study (which is better in treated group than uninfected group) is not so exactly and causes by the bias due to the study design."

Fig 2A showed the cumulative ESRD incidence of the untreated, uninfected, and treated groups before propensity matching, and Fig 2B and Fig 2C showed the cumulative ESRD incidence of the propensity-matched untreated and uninfected cohorts as well as the propensity-matched untreated and treated cohorts, respectively. We ever tried to match treated patients with the other untreated and uninfected

patients in a propensity score in order to compare the cumulative ESRD incidence of the propensity-matched three cohorts, however, the propensity score matching cannot fit well in all three groups. Thus, we cannot exactly compare the cumulative ESRD incidence of the propensity-matched three treated, uninfected, and untreated cohorts. We list this as a limitation (page 18, lines 15-17). The cumulative ESRD incidence of the unmatched three groups (Fig 2A) appears to draw a misleading conclusion. To address the reviewer's concern, we delete Fig 2A and make some changes in the revised abstract (page 4, lines 15-20), text (page 11, lines 18, 20, 23), and figure 2 (Fig 2B labeled as 2A, Fig 2C labeled as 2B).

Reply to Reviewer 2 (02888410)

1. Response to "Overall, manuscript is too long. Tables 1, 2 ,3 and 4 would be better placed on a supplementary file. Table S1 is unneeded, data are shown in Results."

To address the reviewer's concern, we do our best to shorten this manuscript (abstract: 241 words, text: 3266 words at present). We also delete Table S1 and placed Tables 1, 2 ,3 and 4 on a supplementary file, which was labeled as Tables S1, S2 ,S3 and S4. The original Table S2 was changed to Table S5. We made some changes in the revised text (page 11, lines 12, 14; page 12, lines 3, 10-11, 17, 19).

2. Response to "...Why treated patients have lower incidence rates than those uninfected? The conclusion could be that antiviral drugs are nephroprotective, but the current evidence is that antiviral therapy may be nephrotoxic. How can this effect be explained."

Fig 2A showed the cumulative ESRD incidence of the untreated, uninfected, and treated groups before propensity matching, and Fig 2B and Fig 2C showed the cumulative ESRD incidence of the propensity-matched untreated and uninfected

cohorts as well as the propensity-matched untreated and treated cohorts, respectively. We ever tried to match treated patients with the other untreated and uninfected patients in a propensity score in order to compare the cumulative ESRD incidence of the propensity-matched three cohorts, however, the propensity score matching cannot fit well in all three groups. Thus, we cannot exactly compare the cumulative ESRD incidence of the propensity-matched three treated, uninfected, and untreated cohorts. We list this as a limitation (page 18, lines 15-17). The cumulative ESRD incidence of the unmatched three groups (Fig 2A) appears to draw a misleading conclusion. To address the reviewer's concern, we delete Fig 2A and make some changes in the revised abstract (page 4, lines 15-20), text (page 11, lines 18, 20, 23), and figure 2 (Fig 2B labeled as 2A, Fig 2C labeled as 2B).

3. Response to "...Discussion, abstract and conclusions should be modified. Discussion is extremely long. In the third paragraph the statement: "None of the above studies evaluated NNT. Our present study showed that the NNT for one fewer ESRD at 12 years was 12" has been used previously in the first paragraph and should be erased. The fifth paragraph does not add information, it should be excluded. The other paragraphs should be shortened."

To address the reviewer's concern, we modify discussion, abstract and conclusions, and shorten the discussion. We do our best to shorten this manuscript (abstract: 241 words, text: 3266 words at present).

Reply to Reviewer 3 (00503207)

1. Response to "1. Authors conclude, that HBV serological evaluation should be considered especially in areas of high HBV endemicity. Was this Taiwanese population such a cohort?"

This study is a Taiwanese cohort.

2. Response to "2. Relatively low proportion of HBV infected CKD patients did get the proper NA therapy. What was the reason of it?"

One possible cause may be that gastroenterologists may be afraid of NA therapy in HBV-infected CKD patients, and the other possible cause may be that nephrologists do not recognize untreated HBV infection as a progression factor of CKD to ESRD and then do not transfer to gastroenterologists for proper NA therapy.

3. Response to "3. From the results, as the lowest progression of CKD to ESRD was in the NA treated group and it seems to be significantly lower (was it?) compared with the uninfected CKD cohort, one could suppose, that NA treatment might be useful also in CKD patients without HBV infection to slow down CKD progression to ESRD. Is this idea absurd? It should be also discussed."

Fig 2A showed the cumulative ESRD incidence of the untreated, uninfected, and treated groups before propensity matching, and Fig 2B and Fig 2C showed the cumulative ESRD incidence of the propensity-matched untreated and uninfected cohorts as well as the propensity-matched untreated and treated cohorts, respectively. We ever tried to match treated patients with the other untreated and uninfected patients in a propensity score in order to compare the cumulative ESRD incidence of the propensity-matched three cohorts, however, the propensity score matching cannot fit well in all three groups. Thus, we cannot exactly compare the cumulative ESRD incidence of the propensity-matched three treated, uninfected, and untreated cohorts. We list this as a limitation (page 18, lines 15-17). The cumulative ESRD incidence of the unmatched three groups (Fig 2A) appears to draw a misleading conclusion. To address the reviewer's concern, we delete Fig 2A and make some changes in the

revised abstract (page 4, lines 15-20), text (page 11, lines 18, 20, 23), and figure 2 (Fig 2B labeled as 2A, Fig 2C labeled as 2B).

4. Response to "Some typos in the manuscript: page 6, line 8- "glomerular filtration rate" page 7, line 2- "HBV-DNA". page 8, line 15- >18 years page 9, line 15- 442+1326 is not 1120."

To address the reviewer's concern, we make some changes in the revised text (page 6, line 8; page 7, line 2; page 8, line 15; page 9, line 15).

Reply to Reviewer 4 (02844701)

1. Response to "Please add study limitations and recent references".

We list study limitations in the 6th paragraph of discussion section (page 17, lines 20-25; page 18, lines 1-17). There are only five research (Ref 7, 16, 17, 30, 31) studying on HBV-related GN and HBV in DM nephropathy in 2005-2015. At present, there is no study focusing on both treated and untreated HBV infection in CKD patients regardless of etiology.

Thank you heartily for your invaluable opinions on this paper. We are deeply honored by the time and efforts that you had spent in reviewing and revising this manuscript. By incessantly reviewing and revising our texts, we are spurred to read more and learn more from your comments.

Yours sincerely,

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