

17 September, 2017

Dear Professor Damian Garcia-Olmo,

Title: Epidemiology and natural history of Wilson's disease in the Chinese: A territory-based study in Hong Kong between 2000 and 2016

Thank you for your letter concerning the revision of our manuscript. The manuscript has been revised according to the reviewers' comments. The changes have been highlighted in the manuscript for your reference. The followings are the point-by-point responses to the reviewers' comments.

Concerning the similarity of our manuscript with other articles, we have followed your advice to revise the manuscript by iThenticate offered by the CrossCheck.

The similarity of this manuscript has reduced from 22% to 18%, which is now well less than the 30% threshold as suggested.

Regrettably, there is still overlapping of words with the current literature (>200). We have figured out several reasons:

First, as we have presented the PBC epidemiology article (similar research method was used in this Wilson epidemiology manuscript) in international conference, it is unavoidable there will be certain overlapping of the words.

In addition, a lot of terminology, statistical terms and methods, definitions of diseases, statistical statement (e.g. 5-year, 10-year, 15-year rates of survival; HR 1.23, 95% CI 0.90 - 1.50, AUROC, median age at diagnosis, interquartile range) are erroneously regarded as overlapping.

We have tried our best to reduce similarity. We do sincerely hope that it can be understood there is no any evidence of plagiarism if the aforementioned reasons can be taken into account.

Yours sincerely,

Man-Fung Yuen

Language

Concerning the language of the manuscript, we have asked for advice from our colleague who is a native English speaker.

Reviewers' Comments to Author

Reviewer 01047326

Dr. Cheung et al. have made a territory-based study in Hong Kong with a population of 7.3 million to address the epidemiology and natural history of Wilson's disease in the Chinese population. A retrospective study was undertaken between 2000 and 2016. Data were retrieved from the Clinical Data Analysis and Reporting System (CDARS) and Clinical Management System (CMS) of the Hong Kong Hospital Authority and were identified by the International Classification of Diseases (ICD)-9 code. This is a well written article with the strengths of a large assessed sample during long time. The conclusion drawn from the analysis is reasonable and well considered. I have only minor considerations to make in order to improve the clarity. I believe that this paper adds new insights into evolution of Wilson Disease patients.

Minor remarks

1. Page 14. The number of patients identified as Wilson Disease does not appear until "Patient characteristics". It would be necessary an introductory sentence before it

Our response:

We thank you for your comments. An introductory sentence "Two hundred and eleven patients with Wilson's disease were identified" was added on page 13 line 3.

2. Page 19, line 16. Please specify the abbreviation PBC

Our response:

We thank you for your comments. We actually referred to Wilson's disease instead (page 19 line 3).

3. It could be meaningful a specific comment about the low incidence of Wilson Disease in Asian population.

Our response:

We thank you for your comments. A Taiwanese study was quoted illustrating the low incidence and prevalence of Wilson's disease in the Asian population on page 7 lines 16-19.

Reviewer 01047326

The Cheung's work, is one of the few epidemiological studies of Wilson's disease in Asian population. While it has some shortcomings, as the authors themselves acknowledge. But I think that some aspect would be clarify.

1.-With regard to obesity, what clinical criteria was used? Dyslipidemia of what type?, Were they being treated, and what medications?

Our response:

We thank you for your comments. Obesity was defined as having a body mass index ≥ 25 kg/m² in the Asian population (page 11 lines 5-6). Dyslipidemias are defined as disorders of lipoprotein metabolism with high levels of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, or low level of high-density lipoprotein cholesterol. The cutoff value depends on the individual patient's cardiovascular risk profile (page 11 lines 6-10).

2.- Neurological / neuropsychiatric disorders; Were the patients treated with neurological and / or psychiatric diseases? What drugs? This clinical manifestation was before or after the diagnosis of Wilson's disease and then how could these drugs affect the liver?

Our response:

We thank you for your comments. Patients were treated for the neurological and/or psychiatric diseases. The use of various medications were listed in the newly added Table 2, with a paragraph added on page 14 lines 5-8 to direct readers to the table.

Forty-nine patients had neurological and/or psychiatric involvement (with the symptoms manifested in 28 patients at the time of Wilson's disease diagnosis).

The remaining 21 patients had both neurological/psychiatric and liver involvement. Some of the drugs (e.g. anticonvulsants) could potentially lead to

deranged liver function, however it is difficult to differentiate drug-induced hepatotoxicity from liver involvement due to Wilson's disease by using this electronic healthcare database system. This limitation was addressed on page 24 lines 15-18.