Author's response to reviews

Title: Regional disparities in interferon therapy for chronic hepatitis C in Japan: A nationwide, retrospective cohort study

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Author's response to reviews: see over
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Prof. Carl Latkin
Editor
*BMC Public Health*

Re: Submission of the revised manuscript (MS: 1684795701394958) entitled, “Regional disparities in interferon therapy for chronic hepatitis C in Japan: A nationwide retrospective cohort study”

Dear Prof. Latkin,

Please find attached the above revised manuscript submitted for publication as an original research article in *BMC Public Health*. We believe that the findings reported in this study are relevant to the scope of your journal and will be of interest to its readership.

We would like to respond point by point to the Reviewers’ comments;

To Reviewer 1:

1) According to the suggestion of the Journal Editorial Office, we asked Edanz Editing to edit our revised manuscript.

2) Rather than focusing on the treatment outcome etc (facts that are not new and well known) describe more the public health facts eg in Figure 8-10 you show that the relative number of hepatologists does not correlate with treatment outcome, but the population density did.

   In relation to your suggestion to shorten the manuscript, I discussed this with my co-authors. Because this is our first manuscript to report the findings concerning regional disparities, and another Reviewer suggested publishing this aspect of our study in the revised manuscript, we decided not to change much this time. However, to shorten the revised manuscript, we deleted the Additional Tables 1 and 2, by adding the results of the univariate analysis to Tables 2 and 3. Furthermore, the Additional Figures 1 and 2 were also deleted, because the contents for the unified format of the report were precisely described in the Method section.

3) Apparently, all parameters were added to the multivariate analysis, regardless of the results of the univariate analysis, this is statistically not sound!

   For the parameters applied to the multivariate analysis, we adopted only the parameters that had a $P$-value $<0.10$ by univariate analysis, with your instructive advice. The details are shown in Tables 2 and 3.

4) At least 2/3 of the patients were genotype 1 patients, u describe that the SVR rate gradually increased after 2008 = were any of the patients treated with boceprevir/Telaprevir?

   Although the virological response rates were significantly different according to year of starting treatment in the univariate analysis, they were not so strongly correlated in the multivariate analysis (Table 3). In this retrospective cohort until May 2013, no patients treated with directly acting antiviral agents such as telaprevir or simeprevir were included. Boceprevir is not approved by the Japanese government.
To Reviewer 2:
We have made clear our principal research question at the end of the Background section, as follows, “The substantial amount of public money allocated for the subsidy policy urged us to perform a nationwide retrospective study to evaluate whether the performance and outcome of IFN therapy have been standardized throughout Japan.”, at lines 77-80 on page 5.

Major comments:
1) Abstract, conclusions: ‘regional disparities ... may affect treatment performance and outcome’. This is an observational study; a causal relationship cannot be inferred.
Thanks for your comments. We agreed completely and changed the descriptions as follows: “are strongly associated with”, at line 43 on page 3, and “were independently associated with”, at lines 253-254 on page 12.
2) Abstract, conclusions, final sentence: Which measures and how exactly should they be formulated to match the regional characteristics? This is too vague... treatment regimes are designed for individual patients, so it is not clear what was meant here.
Thanks for your comments. To avoid confusion, we changed the descriptions in the Abstract and in the Conclusions as follows: “The policies for treatment of hepatitis of the Japanese government”, at lines 44-45 on page 3, and at lines 344-345 on page 15, instead of “measures”.
3) Results, Treatment performance section and further throughout manuscript: sub-group analyses within strata formed by genotype and viral load appear to have been conducted without adjusting the family-wise error rate. If this has been done, by the Bonferroni method or another method, please clearly state so.
According to your advice, $P$-values were adjusted with the Bonferroni method for the number of strata, as shown in Figure 4. Hence, the descriptions in the Results were slightly changed, as shown from line 199 on page 9 to line 202 on page 10, and at lines 236-237 on page 11. In addition, the descriptions in the legend to Figure 4 were changed, at lines 488-492 on page 21.
4) Results, Predictive factors for performance section: again the wording ‘factors that might affect...’ implies causality; ‘factors associated with..’ is better. Adjust further uses of ‘affect’ and ‘cause’ similarly.
Thanks for your instructive comments again. We changed the descriptions in the Results, as follows: “factors associated with”, at line 205 on page 10 and at 226 on page 11.
5) Concl.: This study does not suggest how to solve the ‘problem’ of across-region heterogeneity, perhaps because data on relevant factors has not not been collected.
As already commented above, please explain further exactly what measures would be considered and how they could be implemented. ·······I’d reword ‘equally receive’ to something like ‘all receive the highest standard’.
Thanks for your comments. We added some comments on further measures to solve regional disparities, as follows: “Taken together, additional policies should be formulated by the Japanese government, to build up closer cooperation between base hospitals and local clinics”, at lines 281-283 on page 13 We also reworded “equally receive” to “receive
the highest standard", at line 347 on page 16.

Minor comments:

1) Background last paragraph: Final sentence is not grammatical/understandable.
   Thanks for your advice. Final sentence of Background was corrected: “The substantial amount of public money allocated for the subsidy policy urged us to perform a nationwide retrospective study to evaluate whether the performance and outcome of IFN therapy have been standardized throughout Japan.”, at lines 77-80 on page 5.

2) Results, Predictive factors for outcome section: ‘tentatively’ is not the right word here.
   According to your advice, we deleted the word: “tentatively” from the Results section.

3) Table 2: the ORs for 2008, 2009 and 2010+ are extremely lower, indicating that a better reference category should be chosen.
   Thanks for your comments on this issue. Since the numbers of the patients who initiated treatment before 2007 were relatively small, the ORs for 2008, 2009 and 2010+ seemed to become strange. We combined the patients who initiated treatment before 2007 and in 2008, and adopted them as a new reference category in the revised manuscript (Tables 2 and 3). Hence, the descriptions in the Results were changed at lines 212-214 on page 10, at lines 232-234 on page 11, and at lines 244-245 on page 11.

4) Indicate in Tables 2 and 3 the number of patients in each category (n). I would delete the p-value column as the same information is present in the 95% CI.
   According to your advice, we indicated the numbers of patients in each category in the univariate analysis in Tables 2 and 3. The P-values in multivariate analysis were deleted.

We hope that our responses to the reviewers’ comments are sufficient to allow publication of our paper in BMC Public Health.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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