

Dear Reviewer and Editor:

Thank you for giving us the opportunity to submit a revised version of the manuscript NO: 68043 entitled “Analysis of the incidence and influencing factors of hyponatremia before the 131I treatment of differentiated thyroid carcinoma” for consideration at the Journal of "World Journal of clinical cases". Our responses to the comments by the reviewers are outlined below. Please also see the revised manuscript for details. For easily reading, we use the TRACK function of MICROSOFT WORD. Please simply select “Accept changes” to get rid of the TRACK markers if you do not like the tracks.

Responds to the reviewer’s comments:

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors aimed to assess the incidence and to find the potential factors that may play a role in hyponatremia in patient on thyroxine withdrawal before radioactive iodine treatment in a large cohort of patients. The subject is under debate and worth investigating. There are a few issues to be clarified.

1. Please provide a more concise and informative abstract which contains the main points.

Response: As suggested, we have extensively revised the abstract to be more concise and informative. Please check the revised abstract for details.

2. The introduction section is presented too briefly. There should be more details about the problem and the available knowledge and the unknown or the gaps. Then, justify the need for further investigation.

Response: As suggested, we have further expanded the introduction section. More details about the problem and the available knowledge and the unknown or the gaps have been added to justify the need for further investigation. Please check the revised Introduction for details.

3. Study design and methodology: the authors classified the patient into two group based on hyponatremia (as an outcome) and then intended to find the association of several variable with this outcome. So, the study is a case control one, not a retrospective cohort. Clarify this mislabeling.

Response: Yes, this study is a case control one. Thank you for pointing this out. The reviewer is correct, and we have clarified this mislabeling in the revised manuscript. Please check!

4. Present more details about the lab tests for measuring hyponatremia. The time before and after surgery and before iodine therapy and the method and whether they are performed in one laboratory.

Response: As suggested, we have presented more details about the lab tests for measuring hyponatremia. For example, the morning urine and fasting blood samples

were collected for laboratory examination on the day of ^{131}I administration. The data before and after operation and before ^{131}I treatment were examined in the same laboratory. The tests were performed in one laboratory on the VISTA 1500 systems (Siemens Diagnostics). Please check the revised manuscript for details.

5. No need to report the values of t or z statistics. P value is enough but mention the test used to compare. For example, the test used for comparing Na before surgery and just before iodine therapy.

Response: Thank you for this suggestion. We have removed t and Z values from the revised manuscript. Please check the revised manuscript for details.

6. For number of patients in each context, present the percentages.

Response: Thank you for this suggestion. We have added the percentages of patients to the Results section. Please check the revised manuscript for details.

7. Clarify and explain that why distant metastasis can be regarded as an influencing factor (statistically significant difference between the proportion in two groups). Is it related to presence of confounding factor? Is it related to presence of other comorbidities?

Response: This influence factor has been mentioned in the discussion section. Please check the following and the revised manuscript for details.

We found distant metastasis was an independent influencing factor for the occurrence of hyponatremia. Patients with distant metastasis can lead to the syndrome of dysregulation of ADH secretion, which leads to hyponatremia[15]. The main mechanism may be that the increase in ADH secretion phosphorylates aquaporin-2 on the cell membrane and promotes water reabsorption [3].

Reference:

[3] Pantalone KM, Hatipoglu BA. Hyponatremia and the Thyroid: Causality or Association? *J Clin Med* 2014;4:32-6 [PMID: 26237016 DOI: 10.3390/jcm4010032]

[15] Lee JE, Kim SK, Han KH, Cho MO, Yun GY, Kim KH, Choi HY, Ryu YH, Ha SK, Park HC. Risk factors for developing hyponatremia in thyroid cancer patients undergoing radioactive iodine therapy. *PLoS One* 2014;9:e106840 [PMID: 25170831 DOI: 10.1371/journal.pone.0106840]

8. Since the study is a case control one please provide the odds ratio for each variable.

Response: As suggested, we have supplemented OR values for each variable in the manuscript (Table 4). Please check!

9. In logistic regression, one of the assumptions is that there should not be a collinearity between independent variables. use correlation matrix for this purpose. Use fewer number of independent variables and then, present the formula or model for regression as well as the plots.

Response: Thank you for this suggestion. We have performed correlation analysis and showed the correlation results in the revised Table 2. We show in the article that the

fit of the model. Hosmer and Lemeshow test ($\chi^2 = 2.841$, $P = 0.944$) suggests a high fit of the model.

10. Do not conclude causality in discussion section. For example, the hyponatremia caused by iodine treatment. There is only an association.

Response: As suggested, we modified the conclusions. For example, the sentence “the occurrence of hyponatremia could not be simply attributed to hypothyroidism” was deleted. We have given a relatively solid conclusion: “Preparation for radioactive iodine therapy was not a risk factor for the development of hyponatremia in thyroid cancer patients.”

11. To examine the gender predisposition, first consider other factors including the use of diuretics and other medical conditions. Make some refinement or exclude some and then make a comparison.

Response: Thank you for this suggestion. We have examined the gender predisposition. After re-performing multivariate regression analysis, we found that gender was not an independent influencing factor.

12. Format the references according to the journal style.

Response: Thank you for this suggestion. The references have been revised according to the format. The “PMDI and DOI” numbers have been added.

6 EDITORIAL OFFICE’S COMMENTS

Authors must revise the manuscript according to the Editorial Office’s comments and suggestions, which are listed below:

1 Scientific quality: The manuscript is a retrospective study investigating incidence and influencing factors of hyponatremia in patients with differentiated thyroid cancer (DTC) before ^{131}I treatment. The topic is within the scope of the WJCC.

(1) Classification: Grade D;

(2) Summary of the Peer-Review Report: aimed to assess the incidence and to find the potential factors that may play a role in hyponatremia in patient on thyroxine withdrawal before radioactive iodine treatment in a large cohort of patients. Please improve the overall writing of the paper, abstract should summarize key finds, introductions should define the problem and knowledge gap. Technical part of the study should be further improved, including clarify the study type as retrospective or case control, provide the odds ratio for each variable. Please address all 12 points raised by the reviewer.

(3) Format: There is 1 figures and 2 tables

(4) References: A total of 16 references are cited, with 2 references published in the last 3 years

(5) Self-cited references: There is no self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper

self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated;

(6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately

2 Language evaluation: Classification: Grade B. A certificate from Beijing Chunfenglv Biomedical Technologies was issued. The company website-<http://www.chunfenglv.com> of the language certificate that was issued cannot be opened, the certificate cannot be verified. Please clarify.

3 Academic norms and rules: No academic misconduct was found in the Google/Bing search

4 Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJCC.

5 Issues raised:

(1)The "Author Contributions" section is missing

Response: "Author Contributions" section has been added in title page. Please check!

(2)Core-tip and audio is missing

Response: The core-tip has been added after the Abstract and as a separate file.

(3) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)

Response: This study did not receive any funding.

(4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout

Response: We have added PubMed numbers and DOI citation numbers to the reference list and listed all authors of the references.

(5) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text

Response: We have added the "Article Highlights" as suggested.

(6) Figure legends should be written per journal standard

Response: We have revised the figure legends per journal standard.

(7) Manuscript format should be updated per journal standard

Response: Yes, we have formatted the revised manuscript.

(8) Copyright License Agreement and Conflict-of-Interest Disclosure Form are missing

Response: We have provided Copyright License Agreement and Conflict-of-Interest Disclosure Form.

(9) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

Response: We have provided original pictures in PPT.

(10)The company website-<http://www.chunfenglv.com> of the language certificate that was issued cannot be opened, the certificate can not be verified. Please clarify

Response: The correct company website should be <http://www.chunfenglv.net>. We have provided the language certificate with the correct company website.

6 Re-Review: Required

7 Recommendation: Conditional acceptance