Author’s response to reviews

Title: The prognostic value of total T3 after acute cerebral infarction is age-dependent: a retrospective study on 768 patients

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Author’s response to reviews:

Dear editorial board of BMC Neurology and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “The prognostic value of total T3 after acute cerebral infarction is age-dependent: a retrospective study on 768 patients” (NURL-D-18-00818). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are indicated in the text using track changes.

The main corrections in the paper and the point-by-point response to the comments are as following:
Adomas Bunevicius, M.D., Ph.D. (Reviewer 1):

1. * My major concern is that it remains unclear reading the manuscript why the age cut-off of 65 years was selected. Authors should justify why age cut-off score of 65 years was selected?

   ● We selected the age cut-off of 65 years was referred to the following references and had cited them in the revised article.


2. * Did authors explore prognostic value of thyroid hormones in the total sample of patients adjusting for age as covariant?

   ● We have explored prognostic value of thyroid hormones in the total sample of patients according to the Reviewer’ suggestion, and we found the prognostic value of lower T3 remained after adjusting for age. However, the data was not shown in this article at last. Because we think it is of little significance in the present article.

3. * Did any of the study patients die? It would be interesting to see

   ● There were 6 patients enrolled as poor functional outcome dying at the study end, and all of them died in hospital.
4.* It would be also interesting to see if prognostic value thyroid hormones as function of stroke severity upon admission.

●We have made correction according to the Reviewer’s comments, and the related content has been added in “discussion” (line 236-248).

5.* What was the association between thyroid hormone concentrations with stroke severity (NIHSS score)? It was previously shown that greater stroke severity is associated with lower T3 concentrations independently of other parameters in independent cohort studies and in recent meta-analysis (for example, doi: 10.1016/j.clineuro.2018.03.025). I would recommend including and discussing these results because T3 can potentially serve as an indicator of stroke severity thus helping to risk-stratify patients.

●We have made correction according to the Reviewer’s comments, and the related content has been added in “results”(line 166-172) and “discussion”(line 236-248).

6.* More information is needed how the ischemic stroke was diagnosed. For example, do all patient undergo non-contrast head CT? What is the standard treatment protocol of ischemic stroke patients (thrombolysis etc), since some of the blood drawn might have happened after ischemic stroke treatments.

●The diagnosis of ischemic stroke has been revised in line 81-82 and the standard treatment protocol of ischemic stroke patients has been added in line 87-89 according to the Reviewer’s comments.

7.* Is assessment of thyroid hormone concentrations in patients presenting with ischemic stroke a standard practice at the authors' institution?

●Yes
8.* Do authors have information about cerebral arteries involved in the ischemic stroke?

- It is a study limitation that we just simply grouped the cerebral arteries involved into three subgroups: anterior circulation group, posterior circulation group, and both anterior and posterior circulation group. And this grouping method has been added in the revised manuscript (line 106-108).

9.* It would be interesting to see area under the ROC curve analyses exploring prognostic value of thyroid hormones vs. NIHSS score for stroke prognosis.

- The related content has been added in “results” (line 188-189) according to the Reviewer’s comments.

10.* T3 to T4 ratio is sometimes used as biomarker of peripheral T4 to T3 conversion representing peripheral deiodinase activity. Did authors explore the association of T3/T4 ratio with stroke outcomes?

- We had explored the association of T3/T4 ratio with stroke outcomes in our previous study (doi: 10.1155/2016/3470490), therefore, we did not include this content in the present manuscript.

11.* The authors should also discuss that patient-centered outcomes and cognitive outcomes were not evaluated in the study because these complications are common in stroke patients. One previous study has shown that reduced T3 concentrations can serve as a independent biomarker of worse cognitive outcomes of ischemic stroke (doi: 10.1007/s12020-013-9958-2).

- It is a very good suggestion and of meaningfulness. It is a pity that cognitive evaluation was not a routine examination in our hospital before 2016. We had mentioned it in the study limitations in revised manuscript (line 261-264). However, further study about cognitive and thyroid hormones is of necessary.
12.* Minor corrections; Line 169, please correct TT3 to total T3.

• I am sorry for our carelessness. TT3 in previous line 169 has been corrected to total T3 (line 187).

Special thanks to you for your good comments.

Wenjun Tu (Reviewer 2):

Although the study determined Total triiodothyronine (T3), total thyroxine (T4), free T3, free T4, and thyroid-stimulating hormone (TSH), disappointingly, total T3 is not a new biomarker and not a specific protein for brain tissues. Moreover, total T3 has been reported widely in the previous studies.

• Total T3 is really not a new biomarker and not a specific protein for brain tissues, and it has been reported in the previous studies. However, our study was designed to investigate the effect of age on the prognostic value of thyroid-related hormones after acute ischemic stroke. To the best of our knowledge, there has no such study reported previously. Therefore, we think it is original. Special thanks to you for your good comments.

Radoslaw Kazmierski (Reviewer 3):

1. Please explain the abbreviations on line 131: TFT (?), and line 188: TT3 (probably should be: serum total triiodothyronine)

• I am sorry for our carelessness. TFT is the abbreviation of thyroid function tests, and we have replaced it with the latter (line 142). Thank you.

• TT3 in previous line 188 has been revised as total T3 (line 207).
2. Did authors have any data about ischemic stroke etiology? It could be helpful to assigned obtained results to the stroke etiology, for example: according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria: large-vessel atherosclerosis, cardioembolic, small vessel disease (lacunar) etc... [see Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, et al. Stroke 1993; 24: 35 - 41 and Goldstein LB, et al. Stroke. 2001;32:1091-1097.]

If it is impossible authors should mention it in the study limitations. (In fact, there were no any mention of stroke subtypes in a recent meta-analysis, as well (see Jiang X. et al.

- Thank you for good suggestion. It is really the limitation of our study, and we had included it in the study limitations (line 266-267). Special thanks to you for your good comments.

We tried our best to improve the manuscript; and we appreciate for Editors/ Reviewers’ warm work earnestly. We hope our corrections will meet with approval.

Once again, thank you very much for your comments and suggestion.

Sincerely yours,

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