Author’s response to reviews

Title: Role of enteral nutrition in nonthyroidal illness syndrome: a retrospective observational study

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Author’s response to reviews:

Thank you for your comments and suggestions. We have revised the manuscript and would like to re-submit it for your consideration. All comments by the reviewers have been addressed, and the modified text is underlined in the revised version. Point-by-point responses to the reviewers’ comments are listed below.

We would like to express our sincere thanks to both the reviewers and the editors for the constructive and positive comments. We have made considerable modifications based on these comments.
Reviewer reports:

Reviewer #2: This is a retrospective chart review of 80 consecutive patients with nonthyroidal illness and enterocutaneous fistulas between 2013-2014 in China. The authors attempt to study the relationships between initiation of enteral nutrition (including the time from hospital admission) and resolution of nonthyroidal illness as measured by serum thyroid function tests. It is an interesting proposal to examine if this intervention may improve the course of nonthyroidal illness, and thus morbidity and mortality in an ICU setting. However, there are some significant limitations related to the design of the study that limit the rigor of the paper.

MAJOR

1. The various subgroups could be better clarified. It appears that there are two exposure groups: those with early enteral nutrition vs those with late enteral nutrition. Then there appears to be a single outcome (resolution of nonthyroidal illness), which is used to categorize subjects into those with the outcome vs those without the outcome. If this is the case, consider assessing the proportions of these four groups with a Chi-square statistical test instead. As the data in Table 2 are quite confusing and lack any statistical interpretation.

Answers: First of all, thank you for your constructive suggestion. We have revised our manuscript. The key finding of this study is that patients could resolve from NTIS after administration of EN therapy. However, not all patients with NTIS would resolve from the thyroid function alternation with EN therapy and the treatment success rate is 82.50% in our study. Thus, we did further analysis to explore the associations between baseline index (age, gender, primary disease, etc.) which involved in our study and the treatment success. We found that the initial time of EN therapy is significantly different between patients who resolved and who did not resolve from NTIS after EN therapy. The logistic regression analysis demonstrated that the initial time of EN therapy within 2 weeks is significantly associated with treatment success.

In the revised manuscript, we did not categorize our patients in early enteral nutrition group and late enteral nutrition group, which we thought may bring confusions to the readers. Thus, patient cohorts are only divided into two groups (those with the outcome vs those without the outcome) in the revised manuscript.

We admit that Table 2 is quite confusing and hard to read. In the revised manuscript, we use the line graph to demonstrate the change of thyroid function in our cohort instead of a table, which may make those data easy to read.

2. Why was 2 weeks chosen as the threshold timepoint for the initiation of enteral nutrition to result in the two groups. This timepoint appears arbitrary and seems to be chosen after the study was completed, rather than a priori. The authors’ previous study (reference #10) is cited, but that timepoint is also not clearly rationalized.
Answers: Two week is chosen as the threshold time point for initiation of enteral nutrition in our patients because the median initial time of EN therapy in our center are around 2 weeks. Established the route of EN therapy is not easy in fistula patients, although we invented several methods (e.g. PMID: 23511162). The median time for initial EN therapy might be longer than those in other surgical critical illness patients. In this study, the median initial time of EN therapy is 12 days.

In the revised manuscript, we did not categorize our patients in early enteral nutrition group and late enteral nutrition group. We just use logistic regression to explore associations between factors and treatment success. The reason why we chose 2 weeks as the threshold is mentioned in the revised manuscript.

3. Table 2: If Group A are those which recovered from their nonthyroidal illness, while Group B are those that did not, it is unclear what the differences in their serum TFTs are from these data. The TFTs look very similar. It may be clearer to predefine what you consider "recovery of nonthyroidal illness".

Answers: We have pre-defined the "recovery of nonthyroidal illness" in our manuscript. In detail, we defined in this study that patients whose FT3 level is above 3.8 pmol/L at week 4 are those who recovered from NTIS.

According to our data, FT3 and TT3 level at week 2, week 3 and week 4 are significantly higher than those at baseline in group A while no significant differences lie in group B (Figure 2 and supplementary material table 1, 2).

MINOR

1. Patients and study design: The reasons for excluding those with these specific major comorbidities is unclear.

Answers: Thyroid function could be easily influenced by many factors including disease (e.g. coronary artery disease, myocardial infarction, etc.) and drugs (e.g. thyroidal hormone, antithyroid drugs, etc.). In this study, we mainly focused on the alternation of thyroid function caused by critical illness (enterocutaneous fistula). Thus, we excluded patients who have comorbidities which have been demonstrated to have an impact on the thyroid functions according the published literatures. We admit the detailed exclusion criteria may limit our patient numbers and we have added this point to the limitation.

2. Results: Suggest clarifying that the TFT changes are expressed in mean +/- SD.

Answers: we have changed the expression according to your constructive suggestions.

3. Table 1: Usually only the baseline characteristics are shown, thus it is strange to see those for Groups A and B also shown here. Those data would be better in a separate table.
Answers: We have used another table to reveal data for group A and group B.

4. Table 2: Suggest re-presenting these data as a line graph.
   Answers: We have changed this table into a line graph.

5. Table 4 and Figure 1 can be deleted as they are irrelevant or already stated in the text.
   Answers: We have combined data from Figure 1 and table 4 with other tables and figures.

6. There are extensive English syntax and grammar problems throughout. Significant revisions are needed.
   Answers: We have invited a native speaker to help us for revising the manuscript.