Author's response to reviews

Title: Serum S-100beta and NSE levels after off-pump versus on-pump coronary artery bypass graft surgery

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Response to Reviewers

Dear Editor-in-Chief,

Thank you very much for having our manuscript entitled “Serum S-100beta and NSE levels after off-pump versus on-pump coronary artery bypass graft surgery” reviewed in a timely and professional manner and for giving us an opportunity to revise the manuscript. We also deeply appreciate the reviewers for their critical review of the manuscript with thoughtful and constructive comments, based on which we have revised the manuscript and we hope our manuscript can be accepted by “BMC Cardiovascular Disorders” While the changes made in the revised manuscript are highlighted by colored (blue) text, our point-by-point responses to the reviewers’ comments are detailed below.

Responds to the reviewers’ comments:

**Reviewer 1**: Serum S-100beta and NSE levels after off-pump versus on-pump coronary artery bypass graft surgery Authors presented a meta-analysis of 10 retrospective studies on the impact of off and on pump cabg on Serum S-100beta and NSE levels as markers of neurological injury. They concluded that both the strategies increased S-100beta and NSE levels but on-pump CABG was associated with an higher increase. Overall the paper is well written and authors acknowledge limitation of such an analysis.

Major compulsory revisions

1. **Comment**: Authors need to better clarify that among several number of RCT comparing off-pump versus on-pump available none looked into this aspect and therefore a meta-analysis of retrospective cohort might get insights into this
Response: Thanks for your suggestion on our manuscript. Through searching the databases, only 5 RCT relevant to the topic were found (the other 6 studies were NON-RCT), which may cause bias due to the small sample size. Therefore, a meta-analysis of retrospective cohort was conducted. This problem has been better clarified in the Discussion section as “First, through searching the databases, only 5 randomized controlled trials relevant to the topic were found (the other 6 studies were non-randomized controlled trials), which may cause bias due to the small sample size.”

2. Comment: Authors should state that all RCT could not demonstrated any significant impairment of cognitive function after both on-pump and off-pump and therefore studies on bio-markers are more likely to provide “academic” rather than clinical evidence

Response: Greatly appreciate your reminding. We have added this explanation in the Discussion section as “Second, because all the included randomized controlled trials could not demonstrated any significant impairment of cognitive function after both on-pump and off-pump surgeries, these studies are more likely to provide “academic” rather than clinical evidence, therefore future clinical evidence are needed.” Thank you again.

3. Comment: As shown in table, few studies reported on groups not comparable for age (see Cao and Zhao) or gender (Bahram). No further information are provided on
other baselines which might have significantly influenced markers serum levels such as renal function. Authors should provide more information of baselines and conduct a subgroup (sensitivity) analysis including only studies which included comparable groups.

Response: Thanks for your valuable and constructive advice. We have carefully read the included studies again and extracted potential factors affecting cerebral function as comprehensive as possible, which has been added in Figure 1. In addition, we have examined the possible sources of heterogeneity via sensitivity analyses and meta-regression analyses, as stated in the Materials and Methods section “Using sensitivity analysis of variables, the impact on the overall results by removing one single study was evaluated. Moreover, Funnel plots as well as Egger’s linear regression test were applied for the investigation of publication bias [27]. Possible sources of heterogeneity were examined through univariate and multivariate meta-regression analyses and verified by Monte Carlo Simulation [28,29].”

4. Comment: Finally due to the small sample size of studies included, authors should propose the minimum sample size and effect size for future studies aiming to look into this aspect.

Response: We sincerely appreciate for your advice. Just as you mentioned, our study had the limitation of sample size, and we have presented the discussion and suggestions for future researchers in Discussion section. As for the minimum sample size and effect size, we should say that it is determined by the objectives and inclusion-exclusion criteria of future studies. Medical researchers are more associated
with patients, experiments and other uncontrollable elements. Future researchers could propose their own minimum sample size and effect size, but our study might be a reference for more accuracy.

**Reviewer 2:** In the manuscript Serum S100b and NSE levels after off-pump versus pump coronary artery bypass graft surgery, Zheng et al evaluated the S100 and NSE profile of patients undergoing either on or off-pump surgery. They found that these brain markers increased in both surgical strategies, but on pump CABG surgery was associated with higher NSE and S100b levels when compared with off pump surgery, especially in the first 24 hours. The manuscript is interesting and well written. However, there are several points which need to be addressed:

1. **Comment:** Half of your introduction does not say anything regarding your study as it refers to common phrases well known by our readers. Introduction should be a brief review of literature, introducing your study. This part should be removed.

   **Response:** Thanks for your kind instruction for introduction writing. We have reorganized the inner structure of **Introduction** to make it more focused. Redundant and “too general” information was removed, and directly-related literature was added as much as could. Please check it for use once again. Please tell us if it still needs revision. Thank you very much.

2. **Comment:** in the introduction section authors state the superiority of OPCAB vs on pump surgery, citing just 1 reference (11). There have been published important trials such as ROOBY trial and the BEST BYPASS trial which have reported
different conclusions. Please reformulate your sentences.

Response: We sincerely appreciate your comment. We have re-organized the Introduction section to make it more profound and pertinent. The sentence citing reference (11) has been deleted because we focused on the correlation between markers and surgeries. The superiority of OPCAB vs on pump surgery was mentioned in the Discussion part as “Huseyin Bayram et al. has showed that the postoperative serum S-100β levels in the off-pump group were significantly lower than that in the on-pump CABG group [22]. Similarly, Lee et al. have observed that off-pump CABG surgery may decrease neurological and clinical morbidity in comparison to on-pump CABG in a randomized group of 60 patients undergoing on-pump and off-pump procedures and complemented by neurocognitive testing before surgery and 2 week/1 year after surgery [47]. By contrast, Edwards compared on-pump and off-pump CABG with a year of follow-up study, reporting that on-pump CABG is superior to off-pump CABG, although off-pump CABG had advantages of time on mechanical ventilation, bleeding and need for reoperation etc [48]. Despite the contradictory results on whether off-pump CABG is superior to the on-pump CABG [49], our results are in accordance with several studies that demonstrated that the preoperative brain injury evaluated by the release of NSE and S-100β protein is significantly higher in patients undergoing off-pump CABG than patients receiving on-pump CABG.” Thanks again for your kind reminding.

3. Comment: the aim of your study was to evaluate brain markers after off pump vs on pump surgery. However, looking at your results section, you spend only 4 rows
to describe the potential differences. This should be the essence of your study. My suggestion is to describe your results at different times: 0, 6, 24, 48 and 72 hours. In addition, you might create a single graph using on Y axis the means at different times. This may help the readers to understand what happen during surgery.

Response: Thanks for your comments on our results, which make our manuscript more precise. According to your advice, we have checked the Results section and made corresponding corrections by describing the potential differences at different times: 0, 6, 24, 48 and 72 hours. In Figure 5, we have presented the difference of the serum S-100β levels between on-pump and off-pump groups at different times. At the same time, since our results did not reveal much significant difference on serum NSE levels, the comparison was not exhibited in the figure. Thanks again for your valuable suggestions.

4. Comment: which technique was used in on pump surgery? single or double cross clamp technique? How many patients underwent to the "no touch technique"? this is important bias your study.

Response: Much obliged for your valuable suggestion. Due to the limited information on the techniques used in the surgeries in the included studies, we could not extract data for the analysis of techniques and this is a common limitation for most meta-analyses. To clarify this limitation for future studies, we have explained it in the Discussion section as “Third, the meta-analysis could not acquire the original data and information on the techniques used in the surgeries was limitedly provided
in the studies included, which may restrict further evaluation of the plausible effect of off-pump and on-pump CABG on serum S-100β and NSE levels.”

5. Comment: If possible, a met regression would improve the quality of your results and evaluate whether off pump surgery really reduces the brain markers relapse.

Response: Thank you. We have conducted meta-regression analyses to figure out potential sources of heterogeneity and improve the quality of our results, which has been presented in the Materials and Methods section: “Possible sources of heterogeneity were examined through univariate and multivariate meta-regression analyses and verified by Monte Carlo Simulation.” The results were described in Results section and presented in Table 2.

6. Comment: what about neurological events? Are described in your selected studies. Please, if possible, try to identify a relationship between higher marker levels and neurological events

Response: Greatly appreciate your reminding. Due to the lack of data on neurological complications in the enrolled studies, we failed to identify a relationship between higher marker levels and neurological events. Thanks for your valuable suggestion, and we have explained this problem in the Discussion section. In the future, we will probe into this aspect with own experiments or observations in practice. The moment we obtain enough evidence of the association between higher marker levels and neurological events, we will write another manuscript to demonstrate that. Thank you for orienting us for a new research topic.
7. **Comment:** In the discussion section authors should give a perspective. What do author suggest to reduce brain markers release?

**Response:** Thank you. As what has been presented in this manuscript, we focused on evaluating serum S-100β and NSE levels in patients with CHD after off-pump versus on-pump CABG surgery, and the results demonstrated that the off-pump and on-pump CABG surgeries may increase serum S-100β and NSE levels in CHD patients. We have mentioned the information on brain markers release in the **Discussion** section as “*Interestingly, in previous studies the time of cardiopulmonary bypass has been proved strongly correlated with the release of S-100β and NSE, and the restrictive fluid management may reduce perioperative cerebral injury [23,30].*”

**Minor issues:**

1. **Comment:** Figure 2 is too chaotic and should be splitted in at least two or better figures.

**Response:** Thank you. We have divided the original Figure 2 into Figure 2 and Figure 3 according to your advice.

2. **Comment:** Please report the initial letter of authors who selected the studies

**Response:** Thanks for your reminding. The initial letters of authors who selected the studies are LZ and Z-Y W, which have been added in the **Authors’ contributions** section.
We tried our best to improve the manuscript and have made some changes in the manuscript. These changes will not influence the content and framework of the paper. Here we did not list all the specific changes but they are marked in red in the revised paper. We greatly appreciate your warm work and hope that the corrections can meet expectations.

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

Thank you and best regards.

Yours sincerely,

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