Author’s response to reviews

Title: A model to predict unstable carotid plaques in population with high risk of stroke

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Author’s response to reviews:

Dear Editor,

We thank the reviewers for their thoughtful comments and suggestions, which helped to improve our study. We have completely revised the manuscript according to the reviewers’ comments and suggestions. The reviewers’ comments are in italics and our point-by-point responses are in bold below.

Erkan Cüre, Assoc Prof (Reviewer 1):
1. The authors should reduce the background by at least 50%.
   Thank you for your suggestion. We reduced the background by at least 50%.
   Revisions have also been made to the abstract section of the manuscript (Abstract section, line 14-20, page 1).

2. delete the sentences in method section "Univariate and multivariable logistic regression were taken for risk factors. A predictive model scoring system were established by the coefficient. The Area under curve (AUC) value of both derivation and validation set group were used to verify the effectiveness of the model."
Thank you for your advice. We deleted that sentence in method section. Revisions have also been made to the abstract section of the manuscript (Abstract section, line 7, page 2).

3. Authors should move the sentence from the result section to the beginning of the method section. "A total of 2841 high-risk stroke patients were enrolled in this study, 266 (9.4%) patients were found instability plaque." Thank you for your suggestion. We moved the sentence to the beginning of the method section. Revisions have also been made to the abstract section of the manuscript (Abstract section, line 1-3, page 2).

Aldo Bonaventura, M.D. (Reviewer 2):
1. Methods
- Controls have not been included. Why didn't you include age- and gender-matched controls? Please explain.
Thank you for your suggestion. This study was a cross-sectional research, screening for risk factors of carotid unstable plaque, without any intervention. No control group was set up in previous similar studies. According to the previous study and cost-effective, there is no control group in this study.

- How was the CNSSPP structured? If possible, include the questionnaire as well as Supplementary Material: it may be of help to readers to better understand the paper.
Thank you for your advice. The CNSSPP questionnaire includes the following contents: demographic information, preliminary screening information, and re-screening information. After preliminary screening, it was suggested that the high-risk population (including previous stroke and TIA individuals) should be re-screened, otherwise the screening would be terminated. We will provide the questionnaire form as Supplementary Materials for readers.

- Why was hs-CRP not collected? This represents a flaw. It is now considered the most important indicator of CV disease.
Thank you for your very important suggestion. Hs-CRP is very important in CV diseases. Since 2012, this indicator has not been considered in the research design at that time. Thank you for your valuable advice, we will improve it in the future research.

2. Statistics
- Did you first check for normality since you chose to express continuous variables as mean and SD? Please explain.
Thank you for your advice. We have checked the normality of all continuous variables, and the results are shown in the figure below:

- No sample size is provided. This is welcome to improve the manuscript.
Thank you for your suggestion. In this study, 19 risk factors of unstable carotid plaque were analyzed. Empirical formula of sample estimation based on multi factor analysis: sample size (n) = number of research factors * (5-10). Increase 20% of the sample size calculated by empirical
formula to control the impact of lost visit. At least 228 cases are needed in this study. There are 2841 cases were finally included in this study, greatly exceeding the minimum sample size.
- All in all, this section needs to be re-phrase as it is confusing in the present form.
Thank you for your advice. We've rewritten the statistics section, especially on normality check and sample estimation.
Revisions have also been made to the methods section of the manuscript (Methods section, line 15-19, page 8).

3. Results
- Please provide a diagram summarizing the total number of enrolled patients and those excluded with the reasons of the exclusion. This will make the reading of the results easier.
Thank you for your very useful suggestion. We drew a diagram summarizing, including the total number of enrolled patients and those excluded with the reasons of the exclusion, which is shown in the figure below:
Revisions have also been made to the results section of the manuscript (Results section, line 6, page 9).

- What about obesity that was not considered? Take a look to this paper: Cardiovasc Diabetol. 2018 Mar 29;17(1):46.
Thank you for your reference. I have read it carefully. Obesity is considered in this study. The standard for overweight is BMI greater than 26 kg/m², it includes being overweight and obesity. In the questionnaire form, the original expression was overweight or obesity. For the convenience of writing, we simplify it to overweight. We apologize for the unclear statements. We revised all overweight to "overweight or obesity".

- Which were the covariates considered for analyses in Table 3?
Thanks for your question. Sex, age and marriage were the covariates in Table 3.

- Table 3: the CI for the different ages are very wide, maybe it is worth considering age as a continuous variable rather than to categorize it. Please try to perform again the analysis following this indication.
Thank you for your suggestion. We did use age as a continuous variable for statistical analysis. The results are roughly the same as before, the ROC is 0.743, which is shown in the following figure.

There are two reasons that we change it to categorical variable: 1. as a continuous variable, age does not well reflect that the older the age, the greater the risk; 2. as a continuous variable, age cannot be used to develop a practical and convenient risk scoring system based on statistical results. Previous studies on multiple risk factors have used similar methods to convert age into categorical variables for evaluation.
4. Discussion
- This section is too long and poorly focused on the results presented by the authors. Please change it accordingly.

Thank you for your advice. We revised the discussion section, deleted the part about whether to screen and what kind of personnel to screen, so that the discussion part is more suitable for the results of this paper.

Revisions have also been made to the discussion section of the manuscript (Discussion section, line 1, page 14).

5. General comments
- A wide English editing is needed. Please consider to have the manuscript read and corrected by an English native speaker.

Thank you for your advice. We have invited a native English speaker to edit the manuscript.

Suziane Ungari Cayres-Santos, PhD (Reviewer 3):
1. Background
Line 34, page 3 - Please add a reference after this sentence to sustain that information "[...] It is well-known that atherosclerosis is the main risk factor of cardiovascular and cerebral vascular disease".

Thank you for your suggestion. We added a reference after that sentence.

Revisions have also been made to the background section of the manuscript (Background section, line 9, page 3).

2. Methods
Line 59, page 5 - Please add a reference used to classify dyslipidemia in this study.

Thank you for your advice. We added the reference to classify dyslipidemia.

Revisions have also been made to the methods section of the manuscript (Methods section, line 16, page 5).

Line 42, page 7 - Carotid duplex examinations were performed by four experienced registered vascular technicians. Did you perform reproducibility test for this variable? If not, could you please add this information using a sub sample in the paper?

Thank you for your very important suggestion. The four experienced registered vascular technicians were all trained by the National Project Office of Stroke Prevention and Control, and passed the examination and certification.

Indeed, there may be inconsistencies in the examination results of the four doctors. However, since the screening work has been completed, the results of each doctor's screening were not marked separately at the time of design, so it is impossible to conduct subgroup analysis. Thank you again for your valuable comments. The above deficiencies will be avoided and improved in the future work.

3. Discussion
Line 51, page 13 - Please add some references after this sentence "The mechanism of stroke is various, thromboembolism is only part of it, which is focus on carotid plaque or stenosis, especially carotid instability plaque."

Thank you for your suggestion. We added a reference after that sentence.
Revisions have also been made to the discussion section of the manuscript (Discussion section, line 10, page 13).

We hope that these revisions are satisfactory and that the revision will be acceptable for publication in “BMC Cardiovascular Disorders”.

Thank you very much for your work concerning our paper.

Wish you all the best!

Sincerely yours,
Xiaoshan Wang