Author's response to reviews

Title: Multiple Intracranial Arterial Stenosis Influences the Long-term Prognosis of Symptomatic Middle Cerebral Artery Occlusion

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Author's response to reviews: see over
Dear editor,

Thank you for processing our manuscript timely. We would like to thank the reviewers for the positive and constructive comments. According to the comments, we have revised the manuscript and submitted it. We hope these changes will make the manuscript acceptable for publication.

A list of the changes made according to reviewers’ comments is attached.

Thank you very much for your help.

Xinfeng Liu
Comments to author

This study discussed a novel issue in stroke and could be of interest to the readers. However, some points need clarification which are listed below. The main problem should be the methodology and patient recruitment. Only with a sound and clear methodology, this manuscript could be of value to be published.

1. Line 104: occlusion in the M1 segment of MCA proven by magnetic resonance angiography (MRA). It is known that the MRA is difficult to differentiate tight stenosis and occlusion because the detection of artery depends on the flow volume. Both tight stenosis and occlusion may cause reduced flow and may probably cause the same image findings.

   Responding: DSA remains the gold standard of diagnosis of luminal stenosis for intracranial arterial disease. MRA is flow-sensitive, but not as accurate as DSA. However, DSA is expensive, invasive, and not readily available in most community hospitals, and thus is not well-suited for a large scale cohort study that more closely reflects common clinical practice. However, MRA is noninvasive and more easily accessible compared with DSA. So, in this study, a DSA was performed in patients in whom MCA occlusion was suspected from the MRA. Some patients were only performed MRA. This is a limitation in the study, which has been description in the discussion section.

2. Line 114: sever liver, should be severe liver disease.

   Responding: “sever liver” has been changed as “severe liver disease”.

3. Line 119: How many patients received MRA and how many patients received further DSA study should be presented.

   Responding: In this study, all patients were performed MRA. One hundred twenty-eight patients were performed DSA.

4. Line 139: About the definition of hypertension, if the patients were taking antihypertensive agents, will they be defined having hypertension?
Responding: Hypertension was defined as use of antihypertensive agents, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.

5. Line 143: Why both cholesterol and LDL levels are not included for defining hyperlipidemia?

Responding: Hyperlipidemia was defined as use of antihyperlipidemic medication, or a total serum cholesterol level > 6.0 mmol/L or LDL cholesterol concentration 3.63 mmol/l.

6. Line 144: About cigarette smoking, at least 10 cigarettes during the past 5 years or more, which means probably 2 cigarettes in one year?

Responding: Cigarette smoking was defined as at least 10 cigarettes per day during the past 5 years or more.

7. Line 145: What is the definition of alcohol intake?

Responding: Alcohol intake was defined as consumed regularly more than 300 g alcohol/week.

8. In Line 91, the author mentioned “We therefore conducted this retrospective analysis…….” However, in Line 150-154, the author mentioned they will follow the patients who survived from the acute phase of stroke by interview or telephone and if stroke is suspected, a study neurologist will evaluate the patients. This kind of description is more like conducting a prospective study. The author needs to define clearly whether this is a prospective or retrospective study.

Responding: In this study, the patients’ data were recruited from Nanjing Stroke Registry Program. Nanjing Stroke Registry Program is an ongoing, prospective observational project aimed at consecutively assembling demographic, clinical, neuroimaging and laboratory data of registered patients (Reference: Liu X, Xu G, Wu W, Zhang R, Yin Q, Zhu W. Subtypes and one-year survival of first-ever stroke in Chinese patients: The Nanjing Stroke Registry. Cerebrovasc Dis. 2006;22(2-3):130-6.). The recruited data were analyzed retrospectively in this study.

9. Line 166: Chicago, □, USA. Any mistake?

Responding: “Chicago, □, USA” is “Chicago, Illinois, USA”, which had been
changed.

10. Line 180: 306 acute stroke or TIA patients were recruited from the databank. How many patients in the databank? What is the percentage of 306 in all patients? And 306 are all first-ever stroke?

Responding: During the study, 3460 patients were enrolled from the databank. 306 patients (8.8%) were recruited, all of them were first-ever stroke.

11. Line 187: If this is a retrospective study, how can the author be sure that “All patients were continuously treated with both antiplatelet agents and statin”? Line 319 mentioned that this study had lower annual rate of cerebrovascular event and one of the reasons is that nearly all the inclusion subjects used antiplatelet therapy and statins. What is the percentage of patients receiving antiplatelet and statin? Did these patients have well control of their lipid level?

Responding: In this study, the patients’ data were recruited from Nanjing Stroke Registry Program. Nanjing Stroke Registry Program is an ongoing, prospective observational project aimed at consecutively assembling demographic, clinical, neuroimaging and laboratory data of registered patients (Reference: Liu X, Xu G, Wu W, Zhang R, Yin Q, Zhu W. Subtypes and one-year survival of first-ever stroke in Chinese patients: The Nanjing Stroke Registry. Cerebrovasc Dis. 2006;22(2-3):130-6.). “All of the patients were continuously treated with both antiplatelet agents and statins if the patients had not any adverse events” had been described in the result section. Eighty-four patients have well control of their lipid level (total cholesterol (TC) <3.6 mmol/L, LDL-C<1.8 mmol/l).


Responding: The revised version had been revised by Elsevier Language Editing.

13. The writing format needs to follow the general regulations, such as 95%CI (should be space between 95% and CI).

Responding: “95%CI” has been revised as “95% CI”

14. Tables are not well presented. Each table should be independent and the abbreviations should be explained.
Responding: The abbreviations had been explained in each tables.

15. In Figure 1, it is confusing how many groups are presented, 2 or 4 groups? The title said MCAO and MCAO+ICAD, but the figure showed besides the two groups, MCAO-censored and MCAO+ICAD-censored?

Responding: Two groups (MCAO and MCAO-AIS) were presented in Figure 1. MCAO-censored and MCAO+ICAD-censored (MCAO-AIS censored) were described as censored data in each group.

Reviewer: Bernard Yan

Minor essential revisions

1. In the abstract and introduction, please state clearly the hypothesis.

Responding: In the abstract and introduction, the hypothesis of “Coexisting AIS may reflect the extent of the atherosclerotic intracranial disease, we hypothesize that coexisting AIS influenced the prognosis of MCAO.” have been stated.

2. Methods section:

   a. How was MCAO defined? E.g. was it determined by degree of stenosis exceeding 50%? If so, please confirm if stenosis 40% on DSA was categorized as non-MCAO?


Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Responding: The revised version had been revised by Elsevier Language Editing. We hope our revised work is acceptable for publication.
Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer: Tsong-Hai Lee

Reviewer's report:
Major Compulsory Revisions
Responding: According to the reviewers’ and editors’ comments, we have revised the manuscript and submitted it.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being Published
Responding: The revised version had been revised by Elsevier Language Editing. We hope our revised work is acceptable for publication.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.
Reviewer: neal rao

Reviewer's report:
The authors present a large case series comparing patients who have middle cerebral artery occlusion (MCAO) with patients who have a combination of MCAO and diffuse asymptomatic intracranial stenosis (AIS). This is an important topic given the high prevalence of intracranial atherosclerosis world wide and particularly in Asia.

- Major Compulsory Revisions

It is unfortunate that the poor sentence structure detracts from the science of the paper.

I would highly recommend that a proficient English speaker edit the paper, with particular attention to the abstract.

Responding: The revised version had been revised by Elsevier Language Editing.

In the group of patients with isolated M1 occlusion, there may be a high incidence of paroxysmal atrial fibrillation as the etiology of the infarction. As the goal of the study is to contrast two types of atherosclerotic occlusive disease, an imbalance in the incidence of paroxysmal atrial fibrillation in one group may color the analysis. Please expand on how paroxysmal atrial fibrillation was evaluated, as it is an important exclusion criterion for this study.

Responding: Two excluded the atrial fibrillation as the etiology of the infarction, the patients with atrial fibrillation (AF) were excluded. AF included chronic or paroxysmal AF. Paroxysmal atrial fibrillation was defined as episodic AF on an electrocardiogram, or transient AF (< 24 hours) on a 24-hour ambulatory electrocardiographic recording. The definition of paroxysmal AF had been added in the exclusion criterion.

Please expand on the follow-up section in “methods.” How often was a follow up interview performed? Were the interviewers blinded to the patient’s clinical history or group allocation? How was the interview standardized? As responses to
telephone interviews may be highly subjective, potential sources of bias should be addressed.

Responding: We followed the patients discharged after 1, 3, 6, 12 months. Asymptomatic patients had subsequent yearly follow-up visits. The interviewers were blinded to the patient’s group allocation. The patients were asked whether they had experienced any sudden episode of weakness, blindness, numbness, speech difficulty and any other new symptoms and documented in Nanjing Stroke Registry Program. If a stroke was suspected, the patients were invited to our Neurology Clinic and were evaluated by study neurologists. The follow-up section had been expanded in the revised edition.

- Minor Essential Revisions:
  I would like to suggest renaming the category “MCAO concomitant intracranial arteries disease” to “MCAO with concomitant intracranial arterial disease (MCAO-AIS)” and uniformly using MCAO-AIS subsequently throughout the paper to avoid confusion.

Responding: Thanks your good advice. “MCAO concomitant intracranial arteries disease” has revised as “MCAO with concomitant intracranial arterial disease (MCAO-AIS)” and uniformly using MCAO-AIS subsequently throughout the revised paper.

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, but I do not feel adequately qualified to assess