Author's response to reviews

Title: Comparative-Effectiveness Research on Patients with Acute Ischemic Stroke Using Markov Decision Processes

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Author's response to reviews: see over
Dear Editors of BMC Medical Research Methodology,

We appreciate very much to the comments and suggestions of you and the reviewers, and thank you for providing us a chance to improve our paper. In this revision,

1. We have very carefully revised the paper, and addressed all the concerns raised by the editors and reviewers point-by-point in an attached document “Responses to Reviewer’s Comments”.

2. We have added a Background section including context information in addition to the objectives of the study within the Abstract.

3. All typos, grammatical errors, and inaccurate statements and notation in the previous version have been corrected. Moreover, we have language in our manuscript edited by a professional language editor who has seventeen years’ experience in this field.

4. This is a study based on electronic health records (EHR); it’s not an experimental research. We explained the ethic issues point-by-point in the attached document.

   We hope that you, the editor, and the reviewers would find this revision acceptable. Should you have further comments and suggestions, we would be more than happy to incorporate them into the final version of our paper.

Yours sincerely,

Darong Wu and Xianping Guo, on behalf of all the authors
Responses to Reviewer’s Comments
Reviewer 1: ATHANASSIOS VOZHIS

COMMENT (point 1): There are several substantial limitations in the paper. First of all, the model of applying a treatment and conducting it without any change through the whole course of acute stroke could not adequately consistent with Evidence Based Medicine (EMB).

RESPONSE: We agree with the reviewer’s comment. As we have stated in the manuscript “Multi-component structure of treatments is closer to real world practice especially in health care of stroke with complex dynamics from onset to progression [43]. Moreover, the model of applying a treatment and conducting it without any change through the whole course of acute stroke could not adequately consistent with the basic TCM theory known as altering treatment according to syndrome differentiation [15, 44]” (on page 22), if the treatment was conducted without any change through the whole course of acute stroke, it could not adequately consistent with the complex dynamics of acute stroke, nor could it coordinate with the theory of Traditional Chinese Medicine (TCM) or with Evidence-Based Medicine (EBM).

And that’s one of the reasons why we carry out this study, i.e. to apply MDPs as a thoughtful solution for uncertainties in relation with patient’s individually response to certain combination of treatments as well as the uncertainties concerning dynamic change of treatments for certain patients during the process of disease. We thought that the results of our study might be helpful in providing new reliable evidences which are originally generated from everyday clinical practice.

COMMENT (point 2): Moreover, the effectiveness between different prescriptions of TCM was not comparable.

RESPONSE: Thank the reviewer for pointing out this limitation. We did compare the different prescriptions of several patents of TCM, such as action 2(a2): used treatments of TCM on replenishing qi and wen yang (Yi Qi Wen Yang) or not, action 3(a3): used treatments of TCM on clearing heat and extinguishing wind (Qing Re Xi Feng) or not), action 4(a4: used treatments of TCM to relax the bowels or not); but due to practical reasons, we did not compare the different prescriptions of herbal medicine. And we have stated this as one of the limitations in the Discussion section (on page 23).

COMMENT (point 3): Finally, the optimal interventions obtained by MDPs in the paper, still need further validation in clinical practice.

RESPONSE: We understand the reviewer’s concern. In this study, all the data were collected from electronic health records (EHR) and the optimal interventions were obtained by MDPs, further validation studies are needed. We agree with this comment. As a result, in the conclusion section, we have stated “However, the optimal interventions obtained by the MDPs in this study require further validation in clinical practice. The results from the MDPs modeling should be interpreted with caution both due to the property of the MDPs themselves, and because of possible bias that may have been generated either from the data collection or the data management.” (on page 24)

COMMENT (point 4): But, as an option of new methods which might be useful in comparative effectiveness researches, the application of MDPs in dynamically comparing the effectiveness of variety combinations of complex treatments could be a thoughtful solution for uncertainties
related with patient’s individually response to certain combination of treatments as well as the uncertainties concerning dynamic change of treatments for certain patients during the process of disease.

RESPONSE: We sincerely thank the reviewer for your suggestions and valuable comments on our paper. We agree that the MDPs could be a useful option in comparative effectiveness researches.
Reviewer 2:

COMMENT (point 1): The article needs minor essential revision in order to be ready for publication. It is a good article.
RESPONSE: We sincerely thank the reviewer for reviewing our manuscript and providing the comments.

COMMENT (point 2): I recommend accepting the article with minor changes. Is a good article that shows how can be applied the methodology of Markov decision processes (MDPs) in biomedical research. In this article the MDPs are used to compare the effectiveness between different combinations of Traditional Chinese Medicine (TCM) and/or Western Medicine for patients with Acute Ischemic Stroke (AIS).
RESPONSE: We agree the reviewer’s comment on that the methodology of MDPs might be applied in clinical research.

COMMENT (point 3): I ask to do an English and typewritten review: Page 1, a coma is lacking after Jianxiong Cai.
RESPONSE: Thank the reviewer for pointing out this mistake. We have revised it by adding a coma.

COMMENT (point 4): Page 6, at the end of second paragraph. What are CT or MR.
RESPONSE: Thank you for your careful review. We have revised it as “Computerized X-ray tomography or magnetic resonance imaging”.

COMMENT (point 4): Page 9, first paragraph, write the meaning of IM (Integrate medicine).
RESPONSE: We added a sentence, “(i.e. the combination of practices and methods of alternative medicine with conventional medicine)”, to explain this term.

COMMENT (point 4):
Page 10, second paragraph, □(j,I,a) must be #(j,I,a).
Equation (Eq) must be Equation (1).
RESPONSE: We think that some errors may have occurred when we transferred the WORD version into the PDF one, as the □(j,I,a) was #(j,I,a) in our former WORD version. We sincerely appreciate the reviewer for pointing it out. We have revised both points as the reviewer suggested (see page 13).

COMMENT (point 4):
Page 11, Eq (4), π-1 must be N-1.
RESPONSE: Thank the reviewer for this comment. We have revised it (see page 14).

COMMENT (point 5):
Page 12, Eq (5), a right parenthesis is lacking after a(t).
After equation 9, f^t must be f_t^*.
A space is lacking in StepIII.
RESPONSE: We appreciate for your careful review. We have revised all these points accordingly (see page 15).

COMMENT (point 6): Page 13, first paragraph, would be used must be were used.
RESPONSE: Yes, thank you for this comment. We revised it as “were used” (see page 16).

COMMENT (point 7): Page 15, first paragraph, a phrase cannot start with a number as 68%.
RESPONSE: We revised it as “Sixty-eight percent of” (see page 18).

COMMENT (point 8): Page 18, third paragraph, write the meaning of RCT (Randomized Control Trials).
RESPONSE: Thank you for pointing it out. We revised it as “Randomized controlled trials (RCTs)” (see page 22). As RCTs is a commonly recognized term, we prefer not to put any more explanations here.

COMMENT (point 9): Page 27, reference 44, without parenthesis.
RESPONSE: Thank you for the comment. We added parenthesis on the title of this article (see page 30).

COMMENT (point 10):
Page 28, timepoint 1 (t1) must be timepoint 1 (t1).
timepoint 1 (t2) must be timepoint 1 (t2).
RESPONSE: From point 10 to point 12, we have revised all the t# into t4 accordingly (see page 31-32, page 36-37). We thank the reviewer very much for this valuable comment.

COMMENT (point 11):
Page 29, timepoint 1 (t2) must be timepoint 1 (t2).
timepoint 1 (t3) must be timepoint 1 (t3).
RESPONSE: See point 10.

COMMENT (point 12):
Page 33, timepoint 1 (t1) must be timepoint 1 (t1).
Rewards at t2 must be Rewards at t2
Page 33, timepoint 1 (t2) must be timepoint 1 (t2).
Rewards at t3 must be Rewards at t3
RESPONSE: See point 10.
Editorial comments:

COMMENT (point 1): Please provide a Background section within the Abstract. This section must include context information in addition to the objectives of the study.

RESPONSE: Thank you very much for your careful review and much effort on our paper. Indeed, your suggestions and comments have helped a lot to improve this paper. We have added a Background section including context information in addition to the objectives of the study within the Abstract (see the Abstract on page 3).

COMMENT (point 2): We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/info/authors/authorfaqs#12.

RESPONSE: All typos, grammatical errors, and inaccurate statements and notation in the previous version have been corrected. Some equations have been corrected (see from Note 2 to Note 8). Moreover, we have language in our manuscript edited by a professional language editor who has seventeen years’ experience in this field, and all the changes can be tracked in this revised version.

COMMENT (point 3): Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

RESPONSE: We understand the editor’s concern. However, this study was carried out only based on electronic health record (EHR). It is not an experimental research. All the data were obtained by a retrospective survey on existed EHR. In addition, we got an approval from the ethic committee before complementing the study. And we have added a statement to declare this (see page 8).

COMMENT (point 4): Informed consent must also be documented. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

RESPONSE: We thank the editor for this comment. As data in this study were from electronic health records, all the records were independently coded without mentioning any private information (such as name, working unit, etc) of any of the patients. According to the ethic committee’s suggestion, no informed consent would be needed in this study.