Author’s response to reviews

Title: Clinical prediction and diagnosis of neurosyphilis in HIV-negative patients: a case-control study

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Author’s response to reviews:
Reply to the Reviewer

Reviewers’ Comments to Author:

Reviewer: 1

Reviewer Name: Weiming Tang

Competing Interests: None declared.

1. Line 170: please explain why only dilute the serum TPPA titer to 1:1280? Does those results affect the diagnosis of neurosyphilis?

Response: Thank you for your comments. According to sexually transmitted diseases treatment guidelines 2015[1], most syphilis patients will have reactive treponemal antibody test and the titers of treponemal antibody do not predict the treatment response. Therefore, as a diagnostic indicator of syphilis, some hospitals only dilute the serum TPPA titer to 1:1280. As the results of previous study showed, when cerebrospinal fluid indicators are not available, serum TPPA can be used as an alternative indicator of neurosyphilis [2]. However, in our study, we added some cerebrospinal fluid indicators. When considering cerebrospinal fluid indicators, the diagnostic efficacy of serum TPPA can be replaced.

2. Line 200: please define separately "one common unit" of CSF TPPA titer, CSF protein and CSF WBC.

Response: Thank you for your suggestion. We have defined separately "one common unit" of CSF TPPA titer, CSF protein and CSF WBC on Page 12, Lines 214-217 in the revised manuscript. When CSF TPPA titer doubled, patients were 1.004-fold more likely to be diagnosed as neurosyphilis. When CSF protein increased 1 mg/L, patients were 1.005-fold more likely to be diagnosed as neurosyphilis. When CSF WBC increased 1 cells/μL, patients were 1.120-fold more likely to be diagnosed as neurosyphilis.

3. Line 242: please write clearly what is the titer of CSF TPPA to diagnose neurosyphilis is 100%?

Response: Thank you for your suggestion. In reference 17 of manuscript [3], the study mentioned that in the 16 patients of neurosyphilis, they all had reactive CSF TPPA tests. So positive CSF TPPA could be considered as a diagnostic indicator of neurosyphilis. It did not mention the titer of CSF TPPA. We have added a description on Page 15 lines 266-267 in the revised manuscript.

4. Line 245: please write clearly what is the titer of CSF TPPA to diagnose neurosyphilis is 100%?
Response: Thank you for your suggestion. In reference 4 of manuscript [4], the study mentioned that among 1132 syphilis patients, 210 were neurosyphilis. They all had reactive CSF TPPA tests. So positive CSF TPPA could be considered as a diagnostic indicator of neurosyphilis. It did not mention the titer of CSF TPPA. We have added a description on Page 15 lines 266-267 in the revised manuscript.

5. Line 252-253: whether these indicators include CSF TPPA? If so, remove the CSF TPPA results and do a sensitivity analysis again.

Response: Thank you for your suggestion. In Lines 252-253, the combinational indicator included CSF TPPA. As you suggested, we removed CSF TPPA, and combined neurological symptoms, CSF protein, and CSF WBC as a diagnostic indicator of neurosyphilis. The AUC was 0.793, and 95% CI was 0.700-0.887; sensitivity was 92.00%, while specificity was 33.30%. We have added the results in Table 4 and description on Page 13 lines 238-239 in the revised manuscript.

6. Line 258: was there any standard threshold of CSF WBC used to diagnose neurosyphilis?

Response: Thank you for your comments. According to previous literature reviewer and case definitions of American CDC [5, 6], a cutoff value of >5 cells/μL usually be used as a standard threshold of CSF WBC to diagnosis neurosyphilis in HIV negative patients. We have added a description on Page 16 lines 287-288 in the revised manuscript.

7. In the discussion part, please indicate what the value of this study added into the existing literature.

Response: Thank you for your comments. In HIV negative patients, a cutoff value of >5 cells/μL is usually used as a standard threshold of CSF WBC to diagnose neurosyphilis [5, 6]. However, previous study conducted in China indicated that 10 cells/μL should be considered as threshold of CSF WBC [7]. Chinese CDC Guidelines also suggested ≥10 cells/μL as threshold of diagnosis of neurosyphilis [8]. And the results of our study showed the cutoff of CSF WBC should be >3cells/μL. There was no standard threshold of CSF protein used to diagnose neurosyphilis because of the different laboratory conditions [5]. The results of our study showed the cutoff of CSF protein should be >497mg/L which was close to the threshold proposed by the U.S. CDC [6]. More and large population studies should be conducted to confirm the standard threshold of CSF WBC and CSF protein. Compared with previous studies, the results of our study confirmed that neurological symptoms, CSF protein, CSF WBC, and CSF TPPA can be used alone or in combination as indicator for the diagnosis of neurosyphilis. More and large population studies should be conducted to confirm the standard threshold of CSF WBC, CSF protein and CSF TPPA. We have added this part in the Discussion section on Page 16.

8. How the multivariable analysis model was built? Which variables were adjusted? As a matched case-control study, the authors need to control for the variables that were used for matching, but the author did not control this in the multivariable model.
Response: Thank you for your comments. We conducted a univariable analysis firstly. The variables which P value < 0.1 were retained. The multivariate models were created through stepwise elimination of variables from univariable analysis. In the multivariate analysis, odds ratios were adjusted for age and gender. We have added a description in the Methods section on Page 9 and Table 3.

9. The author needs to mention the potential bias for the case-control designing.

Response: Thank you for your suggestion. The data for this study were collected from patients who underwent lumbar puncture examination, which may lead to potential bias in patient selection. Potential selection bias may exist since patients of control group were included based on matched age and gender. There was a possibility that some cases were misclassified because of the lack of gold standard for the diagnosis of neurosyphilis. We have added a description in the Discussion section on Page 16 lines 299-303.

10. "Early diagnosis and treatment of neurosyphilis is of great significance." The result cannot support this conclusion.

Response: Thank you for your comments. We have deleted this sentence in the conclusion section.

Reviewer: 2

Reviewer Name: Junjie Xu

Competing Interests: None declared.

1. Abstract section, the selection criteria of the study control group was not described in the method section.

Response: Thank you for your comments. Fifty patients who were clinically diagnosed with neurosyphilis were selected as case group. Control group consisted of 50 general syphilis patients who were matched with age and gender. We have added the selection criteria in Methods section of Abstract.

2. Method section,

1) the sample size is essential to ensure the quality of the study results, the study sample size of this study is relatively small, it is only 100 subjects. It is necessary to add related process of sample size calculation.

Response: Thank you for your suggestion. Before we started our study, we have calculated the sample size. According to previous studies, we assumed that CSF WBC and CSF protein could be used as diagnostic indicators [7]. We selected the formula for calculating sample size for a
case-control study with exposure variable as continuous variable. The formula is as follows: 

\[ n = \frac{1}{r} \left( \frac{\sigma^2 (Z\beta + Z\alpha/2)^2}{\text{Difference}^2} \right) \] 

[9]. In this formula, \( r \) is ratio of controls to cases, \( \sigma \) is the standard deviation of the variable which were compared, difference is the difference between the means of the case group and the control group, \( \alpha \) is significance level, \( \beta \) is desired power. We used CSF WBC and CSF protein to calculate the sample size separately, and chose the larger one which was calculated with parameters of CSF protein as the sample size of our study. In the calculation process, \( \alpha = 0.05 \), \( Z\alpha/2 = 1.96 \), \( \beta = 0.8 \), \( Z\beta = 0.84 \), \( r = 1 \), Difference = 150 mg/L, \( \sigma = 350 \) mg/L. The values of Difference and \( \sigma \) were derived from previous research [7]. The sample size was calculated as 86. We have added process of sample size calculation in Methods section of the revised manuscript.

2). This study miss used the term of multivariable analysis and multivariable analysis, it should be multivariable analysis in this study, after all there is only one dependent/outcome variable with many independent variable.

Response: Thank you for your comments. We have corrected this error in the revised manuscript.

3. Result section, there is lack of unit measurement of age is table 1.

Response: Thank you for your comments. We have added the unit of age in the revised manuscript.

4. Discussion section,

1). There are no discussion contents about the study results of influencing factors of neurosyphilis.

Response: Thank you for your comments. The purpose of our study was aimed to explore the factors associated with the clinical diagnosis of neurosyphilis rather than risk factors of neurosyphilis. We have reworded accordingly in the manuscript.

We have added explanation about diagnostic indicators of neurosyphilis in the discussion section. The contents were as follows: Sensitivity of neurological symptoms, CSF protein, CSF WBC changed from 46% to 54%. These predictors were insensitive and nonspecific. A literature review indicated that part of early neurosyphilis patients presented neurological symptoms of typical aseptic meningitis, including headache, stiff neck, nausea, vomiting. The most common symptoms included papilledema, convulsions, confusion, and focal and cranial nerve abnormalities. In the advanced stage of neurosyphilis, the neurological symptoms of patients were usually dementia and tabes dorsalis. Meanwhile, there were still some asymptomatic neurosyphilis patients. So the indicator of neurological symptoms showed a high specificity and low sensitivity [10].
In HIV negative patients, a cutoff value of $>5$ cells/$\mu$L is usually used as a standard threshold of CSF WBC to diagnose neurosyphilis. However, previous study conducted in China indicated that 10 cells/$\mu$L should be considered as threshold of CSF WBC [7]. Chinese CDC Guidelines also suggested $\geq$10 cells/$\mu$L as threshold of diagnosis of neurosyphilis [8]. And the results of our study showed the cutoff of CSF WBC should be $>3$cells/$\mu$L. There was no standard threshold of CSF protein used to diagnose neurosyphilis because of the different laboratory conditions [5]. The results of our study showed the cutoff of CSF protein should be $>497$mg/L which was close to the threshold of American CDC[6]. Compared with previous studies, the results of our study confirmed that neurological symptoms, CSF protein, CSF WBC, and CSF TPPA can be used alone or in combination as indicator for the diagnosis of neurosyphilis. More and large population studies should be conducted to confirm the standard threshold of CSF WBC, CSF protein and CSF TPPA.

2). It is suggested that the discussion contents of practical significance or theoretical value of the results of this study be added.

Response: Thank you for your comments. The practice significance was that the results of our study confirmed that neurological symptoms, CSF protein, CSF WBC, and CSF TPPA can be used alone or in combination as indicator for the diagnosis of neurosyphilis. More and large population studies should be conducted to confirm the standard threshold of CSF WBC, CSF protein and CSF TPPA. We have added this part in the Discussion section on Page 16.

Reviewer: 3

Reviewer Name: Xiaojun Meng

Competing Interests: None declared.

1. Line 122: In fact, the purpose of your study was aimed to explore the associated factors to clinical diagnosis of neurosyphilis other than risk factors of neurosyphilis.

Response: Thank you for your comments. The purpose of our study was aimed to explore the factors associated with the clinical diagnosis of neurosyphilis rather than risk factors of neurosyphilis. We have reworded accordingly in the manuscript.

2. Line 129: The abbreviation of "NS" should be given full name.

Response: Thank you for your suggestion. We have revised in Line 131.

3. Line 129: Whether 50 patients in control group were general syphilis patients should be declared.

Response: Thank you for your suggestion. We have revised in Line 131.
4. In the first paragraph in page 9, diagnosis details of 50 patients with neurosyphilis should be given. For example, how many patients were given confirmed neurosyphilis diagnosis using diagnosis criteria 1 and how many patients were diagnosed with neurosyphilis using diagnosis criteria 2 and 3.

Response: Thank you for your suggestion. In the 50 neurosyphilis patients, 32 patients were diagnosed by criteria 1, and 18 patients were diagnosed by criteria 2. We have added the description in Lines 161-163.

5. Line 178-179: These explanatory notes were redundant because these abbreviations were described in Background and Methods parts.

Response: Thank you for your comment. We have read two articles recently published in the BMC Infectious Disease [11, 12]. In these two articles, the abbreviations and full name appeared in the body part, meanwhile they were also placed in the notes of the tables. The possible reason is to make the readers understand the tables better. We think these explanatory notes should be kept.

6. Line 180-183, Line 191-192: These explanatory notes were also given in Statistical Analysis part.

Response: Thank you for your comment.

Lines 191-192

We have read two articles recently published on the BMC infectious disease [11, 12]. In these two articles, the abbreviations and full name appeared in the body part, meanwhile they were also placed in the notes of the tables. The possible reason is to make the readers understand the tables better. We think these explanatory notes should be kept.

Lines 180-183

The explanatory notes were given in the body part of this article. We have deleted these notes in revised manuscript.

7. In page 12, maybe ROC curve should be provided, which was more intuitive to describe the sensitivity and specificity.

Response: Thank you for your comments. We have added a figure in the Results section.

8. Line 262-263: Sensitivity and specificity have been analyzed in your paper, why did you mention that sensitivity analysis can not be performed in your study?

Response: Thank you for your comments. In the results section, we have showed the results of ROC analysis. Sensitivity and specificity were also listed. This sentence was a statement error, and we have deleted this sentence in the revised manuscript.
9. Line 265: "Early diagnosis and treatment of neurosyphilis is of great significance." was a fact, which was not a conclusion due to your study.

Response: Thank you for your comments. We have deleted this sentence in the Conclusion section.

Reference


12 Atalabi TE, Adubi TO. The epidemiology and chemotherapeutic approaches to the control of urinary schistosomiasis in school-age children (SAC): a systematic review. BMC Infectious Diseases, 2019, 19:73.