Author’s response to reviews

Title: Identify the degree of liver fibrosis in CHB patients using an artificial neural network based on routine and serum markers

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Author’s response to reviews: see over
Identification of the risk for liver fibrosis on CHB patients using an artificial neural network based on routine and serum markers

Danan Wang, Qinghui Wang, Fengping Shan, Beixing Liu and Changlong Lu

Dear Editor-in-Chief,

Thank you for response to our submission (ref. MS1380188429335485). We are very grateful for the reviewers’ kindest help with not only science but also English. The authors really appreciated them.

Now, enclosed with a response to the reviewers, we would like to resubmit the paper to your journal for publication. After carefully studying the comments from the reviewers, we made a major revision to our manuscript and highlighted all the changes accordingly. From the revised manuscript, you can see that we have rewritten the whole paper on the previous manuscript from the abstract, background through the discussion. We also put a lot of efforts into English to improve the readability with concise English. Before the resubmission, we also asked an English native speaker to do proofediting in order to keep English mistakes as few as possible. In addition, all the changes made in the manuscript are marked in different color, which may help the reviewer to compare with the previous manuscript. Also, I approve the use of the data in this study. We have revised all detailed through the whole manuscript to conforms to the journal style.

Should you need further information about this submission, please contact us at your early convenience.

P.S. Enclosed with a response to the reviewers.

Yours sincerely,

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Response to reviewer 1

Dear Dr. Karine Lacombe,

Firstly, we would like to thank you for your kindest comments on our manuscript. Upon getting the comments back, we carefully studied your comments word by word and made major revisions on the previous manuscript.

The following are our responses to your comments accordingly:

1. “I do not see what new is brought by this study to the already very well explored field of liver non invasive scores.” Thank you very much for your comments. Although noninvasive biochemical markers of liver fibrosis had made considerable progression, most of them include nonroutine laboratory assays or use complex and patented models so that their regular use were limited. In our study, we constructed the artificial neural network model based on PLT, ALT, GGT, etc., which are routine test and easy to be measured with low cost in some laboratories. The artificial neural network(ANN) is a nonlinear statistical model in predicting clinical outcome, and has significant advantages over other traditional statistical model. We thought that this predictive model could provide more help to clinicians. In view of rationale and purpose of this study, we made a major revision to this part in Background: Second, third and fourth paragraphs.

2. “The paper particularly lacks of precision and English is poor, the paper needs very thorough English editing before publication.” Thank you for your comments. We put a lot of efforts into English to improve the readability with concise English. We also asked an English native speaker to do proofediting in order to keep English mistakes as few as possible.

3. “it is not clear whether informed consent has been collected from patients for participating in this study.” Thank you very much for your comments. In our study, all data including biopsy, routine and serum markers, didn’t involved in the secrets or
ethical problem of patients. Clinical chemistry tests (including routine and serum markers) should be measured among HBsAg-positive in-patients. According to patients’ demand, liver biopsy was required to test with patients’ permission. Therefore, we thought that informed consent was collected from patients.

Some major remarks

4. “It is difficult to see which biochemical markers and socio-demographical data have been introduced in the model.” Thank you for your comments. We wrote this question in **Results: Patients characteristics, first paragraph:** last line (Except for gender, HB, ALP and TP, other markers were found to be statistically significant factors associated with significant fibrosis, and were used to initially constructed the artificial neural network.). In second paragraph, we have rewritten this part as “The variables used to constructed the artificial neural network were compared in three sets (Table 2)”.

5. “In this case, abbreviations must be explained.” Thank you for your comments. In manuscript, all abbreviations had been listed in the back of Conclusions. We supplement the abbreviations of all words at its first appearance in manuscript.

6. “I am very surprised by the range of biochemical variables reported in table 1: ...” You are right. We examined the output of data analysis and locked data sets according to original records. We found that the analysis output of TP and Alb are right, but we made a mistake in recording them. Now, they had been rewritten in Table 1.

7. “It is well known that patients with acute hepatitis should not be included in validation scores as they artificially increase the global score and do not reflect the true level of fibrosis.” Thank you very much for your comments. You are right. Some markers of acute hepatitis patients couldn’t reflect the true level of fibrosis. We neglected the key problem. So, we checked original records of all patients, and found that 5 patients firstly went to hospital for their disease of the liver. They were diagnosed as acute hepatitis. We had excluded them in the revised manuscript. Therefore, all data were
analyzed over again. The new results without 5 patients with acute hepatitis were listed in tables and figures in the revised manuscript.

8. **“The conclusion lacks a paragraph on the comparison of this model with other simple published and widely used scores (APRI, FIB-4, fibrometer, fibrotest, etc.).”** Thank you for your comments. In our study, we used an model (ANN) to predict the risk for liver fibrosis. So we mainly compared with other models, eg a multivariate logistic regression model constructed by Hui AY, a scoring system with forward logistic regression constructed by Zeng MD, and Fibrotest and the Actitest.

9. **“It also lacks a paragraph on the limitations of such methodology.”** Thank you very much for your suggestions. We didn’t state the limitations of the work clearly. In this revision manuscript, we added **“Limitations of the study”** after Discussion. Please see the detailed in **Discussion: last paragraph**- Limitations of the study.
Response to reviewer 2

Dear Dr. Giada Sebastiani

Firstly, thank you for your kindest comments on our manuscript. We really appreciate your patient help with not only scientific critiques but also our some minor corrections including spelling and statistical descriptions. We carefully studied your comments word by word as soon as getting your comments back, and made major revisions on the previous manuscript accordingly.

The following are our responses to your comments accordingly:

Major compulsory revisions

1. “the authors reported a good performance, as indicated by AUROC. The prevalence of significant fibrosis was relatively low (27%). …” Thank you for your comments. The accuracy of a test could vary with the definition of the target condition. The definition of significant fibrosis or insignificant fibrosis could also affect the estimation of AUROC. In our study, the occurrence of F2, F3, or F4 was considered as significant fibrosis according to other studies’ criterion, and the prevalence of significant fibrosis was relatively low. Therefore, the prevalence of liver fibrosis stages should be taken into account. DANA (difference of prevalence of advanced and nonadvanced fibrosis stages) suggested by Poynard could be used to correct the AUROC. However, comparing with other studies, we didn’t correct the AUROC by DANA. But we considered it as a limitation to clarify in “Limitations of the study” after Discussion.

2. “the division of the population in three groups is really not clear in the abstract.” We agree with you. We have rewritten this part as “339 chronic hepatitis B patients with HBsAg-positive were investigated retrospectively, and divided at random into 2 subsets with twice as many patients in the training set as in the validation set; 116 additional patients were consequently enrolled in the study as the testing set.” in Abstract. All the
3. “Moreover, the authors state that NPV was 100% and all patients with significant fibrosis would be captured. This would be true for a PPV of 100%, while if the NPV is 100%, it should mean that all patients without significant fibrosis should be captured! Please clarify.” Thank you very much for your suggestions. The NPV is a negative predictive value. It refers to the percentage of actual negative individual diagnosed by gold standard among negative individual detected by our methods. If NPV was 100%, all negative patients detected by our methods were actual negative individual; all positive patients detected by our methods include all actual positive patients and a part of actual negative patients. So, in our study, when NPV was 100%, all patients with significant fibrosis could be detected by our methods, and couldn’t be missed diagnosis. To make this clear, we had rewritten this part in Discussion, last paragraph.

Some minor errors
We have made them revised. All the changes made in the manuscript are marked in different color.
Response to reviewer 3
Dear Dr. hongbo,

Firstly, we would like to thank you for your kindest comments on our manuscript. Upon getting the comments back, we carefully studied your comments word by word and made major revisions on the previous manuscript.

The following are our responses to your comments accordingly:

Major compulsory revisions

1. “It would provide very useful information to help reduce the number of liver biopsies of CHB patients.” is hard to understand. …” You are right. Liver biopsies is a gold standard of diagnosing liver fibrosis. It is not able to be replaced by any method of predictive models. The neural network designed in this study can predict the risk probability of liver fibrosis in CHB patients, and further identify and classify different levels of risk for liver fibrosis of CHB patients. In view of rationale and purpose of this study, we made a major revision to this part in Background: Second and fourth paragraphs.

2. “Sensitivity analysis: There are many different methods that one can use to determine the sensitivity of the different input features. …” Thank you for your comments. The sensitivity analysis used in our study is a common method which often were used by some researchers. The basic idea of this method is that the inputs to the network is varied within a reasonable interval(or between its mean plus (minus) a user-defined number of standard deviation), and the network output is recorded as a percentage deviation. The size of this interval certainly influence on the result of the output. But the order of the change in the output can not be changed.

3. “the rate of liver fibrosis” is calculated according to the number of patient with liver fibrosis, and non-invasive evaluation of liver fibrosis couldn’t be used to
diagnose liver fibrosis of patients. ...” You are right. Liver biopsies is a gold standard of diagnosing liver fibrosis. Non-invasive evaluation of liver fibrosis couldn’t be used to diagnose liver fibrosis of patients, and only could predict the risk probability of liver fibrosis in CHB patients. So, we have rewritten this part as “Due to the limitation of liver biopsy, non-invasive evaluation of liver fibrosis is thus of great clinical interests in order to assess the degree of liver fibrosis dynamically, or identify and monitor the patients who should be considered antiviral therapy or others.” in Discussion: First paragraph.

4. “Are the conclusions well balanced and adequately supported by the data? The question posed by the author didn’t be generalized in Conclusions section.” Thank you for your comments. For this issue, we not only rewrite this question in Discussion and Conclusion parts, but also made many major revisions about this issue through thewhole manuscript, including Background. Please see the detailed in Discussions: first and sixth paragraph, and Conclusions.

5. “Are limitations of the work clearly stated?” Thank you very much for your suggestions. We didn’t state the limitations of the work clearly. In this revision manuscript, we added “Limitations of the study” after Discussion. Please see the detailed in Discussion: last paragraph - Limitations of the study.

Minor essential revisions
We have made them revised. All the changes made in the manuscript are marked in different color.

Discretionary Revisions
“A very common approach when using neural networks is to use an ensemble approach to increase the performance of the network. ...” We agree with you. Ensemble learning methods is a popular approach in the machine learning and data processing of some researches. It can improve the generalization of single learning machine, and obtain better generalization performance with nonlinear models. In this
study, we didn’t take an account of this method, but used a Bayesian learning algorithm by introducing probabilistic treatment of the Bayesian inference technique. As a simple and feasible method, it can overcome some difficult problems, and also can improve the generalization better than other learning algorithm. You give us a kindly suggestion. We were going to use the ensemble approach to increase the performance of the network in a next study.