



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 55430

Title: Serum ceruloplasmin can predict liver fibrosis in hepatitis B virus-infected patients

Reviewer’s code: 03721496

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer’s Country/Territory: Japan

Author’s Country/Territory: China

Manuscript submission date: 2020-03-17

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-03-17 23:44

Reviewer performed review: 2020-03-19 04:05

Review time: 1 Day and 4 Hours

| | |
|---------------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS



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The authors focused on a diagnostic ability of serum ceruloplasmin for liver fibrosis staging in HBV infection with PNALT, and established a diagnostic score combining ceruloplasmin with platelet count and HBs antigen titer. I want to make some questions. Major points:

1. In Methods, in Quantification of liver fibrosis, which classification did the authors adopted to evaluate inflammatory activity of liver tissues? Metavir scoring system classify activity grade A0, A1, A2 and A3. Metavir score does not assume A4.
2. In Methods, the authors evaluated statistical significance of data using parametric or non-parametric tests depending the data distribution. How did the authors test whether the data distributed normally or not?
3. In Methods, the authors compared AUCs using Z-test. As you know, Z- test should be applied on data with normal distribution. The authors should present evidences that AUCs in the current study distributed normally.
4. In Results, the authors established an equation; $37.122 - 10.072 * \text{Log CP (mg/L)} - 4.291 * \text{Log PLT (10}^9\text{/L)} - 0.958 * \text{Log HBsAg (IU/mL)}$. The authors should describe how to generate the equation.
5. In Results, the authors should present the median value of CPHBV with interquartile range.
6. In Results, the authors compare the diagnostic ability of CPHBV with ceruloplasmin alone, platelet count alone and HBsAg alone.
7. In Discussion, the authors should add other limitation of the study. The study lacks data of liver elastography, ELF score or WFA-M2BP.
8. In Tables 4-6, the authors should revise the data of Youden Index. Youden index means a representative value of ROC curve, which miximize the value= $1 - (\text{sensitivity} + \text{specificity})$. Usually, a cut-off value based on Youden index is similar to a cut-off value determined by selecting a point nearest to sensitivity =1 and specificity = 1. However, in tables 4-6, Cut-off were quite different from Youden index. I guess the authors should revise how to use Youden index in ROC curve analysis.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 55430

Title: Serum ceruloplasmin can predict liver fibrosis in hepatitis B virus-infected patients

Reviewer's code: 02441021

Position: Editorial Board

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2020-03-17

Reviewer chosen by: Jin-Zhou Tang (Quit in 2020)

Reviewer accepted review: 2020-04-12 10:01

Reviewer performed review: 2020-04-14 07:29

Review time: 1 Day and 21 Hours

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|---------------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS



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• MATERIALS AND METHODS Study population =All individuals were randomly stratified into a training and a validation group....what do you mean??? • REFERENCES Very reluctantly written, almost all of them need to be re-written and reformatted as in the Instructions to Authors e.g.: = Reference 2 needs correction (missing the Journal name) = Reference 4 needs correction (missing the Journal name) = Reference 12 needs correction (missing the Journal name) and why is there % mark??? = Reference 18 needs correction (missing the Journal name) =Reference 24 needs correction (Book or Journal???) =Reference 33 needs correction (missing the Journal name)



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 55430

Title: Serum ceruloplasmin can predict liver fibrosis in hepatitis B virus-infected patients

Reviewer’s code: 03536939

Position: Peer Reviewer

Academic degree: PhD

Professional title: Research Fellow

Reviewer’s Country/Territory: Hungary

Author’s Country/Territory: China

Manuscript submission date: 2020-03-17

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|---------------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
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| Re-review | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

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This study established a new test (a combination of three serum parameters, called CPHBV) in order to determine the progression of fibrosis in HBV-positive patients, in such cases when the usual parameters for fibrosis do not seem to indicate presence of fibrosis. This new test showed higher accuracy in finding the positive cases. Nevertheless, the data suggest that this new combination test (CPHBV) tends to identify 70-80% of F2 cases correctly and it eliminates negative cases with increasing precision in F3 and F4 but at the same time, the rate of false positivity seems to increase in F3 and F4. Regarding HBeAg status, the test did not perform well indeed, as it has a relative high false negativity rate in F2 and a relative high false positivity in F4. CPHBV performed better in comparison to 5 other fibrosis models. The comments are as follows: 1. Were the patients from the two mentioned previous studies included in both the training and validation groups? 2. Please specify what does the Abott Architect assay detect, HBsAg or HBeAg 3. Was the HBV DNA test performed by PG Co, including DNA isolation and PCR? Why is the unit for DNA content Log IU/ml and not original copy number? 4. Was not HAI (Knodell score) considered for determining fibrosis, if biopsies were available? 5. The purpose why CPHBV analysis in HBeAg+ and HBeAg- groups was performed is not clear. Please explain it, why it is needed, since HBsAg was determined and I assume that all of the 275 patients were HBsAg positive. There is indication in the Discussion, but still a few more sentence would be good to be included, I think. Is perhaps HBeAg less sensitive than HBsAg? 6. Please check the numbers in Table 1 - under gender, the number for female is not 71, and under HBsAg, check the numbers, because what shown is not the average. 7. In Table 2, cut-off values of CP seem to be very close between F2-F3-F4 8. Regarding CPHBV, for weighing the parameters, how did the calculation come from on top of page 10? 9. Regarding Table 3, the SD values are relative high for CP, HBsAg and PLT. Could this be a reason behind the false positivity in F3-F4 cases? 10. Regarding Table 4, it would be good to provide the



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original table for each column indicating the number of positive, false positive, total positive, false negative, negative, total negative, total F2/F3/F4 positive and total F2/F3/F4 negative cases. 11. Correlation between CP and fibrosis is not shown, only p value is provided. 12. The false positivity and negativity cases phenomenon is not discussed. 13. Check reference number 6.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 55430

Title: Serum ceruloplasmin can predict liver fibrosis in hepatitis B virus-infected patients

Reviewer's code: 03536939

Position: Peer Reviewer

Academic degree: PhD

Professional title: Research Fellow

Reviewer's Country/Territory: Hungary

Author's Country/Territory: China

Manuscript submission date: 2020-03-17

Reviewer chosen by: Ying Dou

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Reviewer performed review: 2020-05-28 13:49

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

No issue to be listed



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 02441021

Position: Editorial Board

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
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| Peer-reviewer statements | Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

Thanks for correcting what was required in the manuscript