Dear Jia-Ping Yan,

Thank you very much for your letter and advice.

We have revised the manuscript, which we would like to submit for your consideration for publication. The reviewers have no questions about our manuscript.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

We look forward to hearing from you soon.

Yours sincerely,

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Answers to the Reviewer 1

Q-1: The abstract should have all abbreviations spelled out.
A-1: All abbreviations have been spelled out in abstract.

Q-2: Introduction: “especially in China”. Perhaps this statement should be re-worded to express the specific problem (I’m guessing quality and access to health care) rather than stating that the entire country of China has this problem. I imagine China has a spectrum of quality health care.
A-2: We deleted “especially in China” on the advice of reviewer.

Q-3: Results: check spelling on “Billirubin” in several locations.
A-3: We corrected the spelling of “Bilirubin”.

Q-4: P-values listed as 0.000 should be listed as <0.01, or some appropriate value.
A-4: P-values listed as 0.000 have been corrected as <0.01.

Q-5: ‘Sex’ is the appropriate word in regards to biological males and females. ‘Gender’ is not the correct word.
A-5: “Gender” has been changed to “Sex” in result and table 1.

Q-6: Spelling ‘gruops’ in Table 2.
A-6: We corrected the spelling mistake of “groups” in table 1 and table 2.

Q-7: Discussion: “lackness” is not a word. Use ‘lack of’
A-7: Discussion: “lackness” changed to “lack of”.

Q-8: Discussion: The authors need to provide references in regards to the sex-based differences in enzyme levels that are discussed. For instance the following statement needs to be substantiated: “While males have a higher basal metabolic rate than females, a higher activity rate of liver cells can lead to more ALT, AST and genomic DNA released from apoptotic liver cells into the blood.” Studies have reported differences based on sex and various liver enzymes.
A-8: We added references in regards to the sex-based differences in enzyme levels that are discussed in the sentence “While males have a higher basal metabolic rate than females, a higher activity rate of liver cells can lead to more ALT, AST and genomic DNA released from apoptotic liver cells into the blood.”

Q-9: Including fibrosis stages in Fig. 4 would be informative.

A-9: The pathological changes of liver in chronic hepatitis B patients are mainly inflammation and fibrosis, which are accompanied by each other at the same time and cannot be strictly distinguished. According to the classification standard of lesions in China, when the two are inconsistent, the grade of inflammation shall prevail. Therefore, fibrosis stages were not indicated in figure 4.

Answers to the Reviewer 2

Q-1: In particular, the primers and probes as well as the conditions used for the duplex real-time PCR and the quantification of the serum HBV DNA by real-time PCR should be included.
A-1: We added a few more experiments of duplex real-time PCR and marked "Specific probes and primers were described in our previous report [8]". We added the information of extract kit of HBV DNA. But we can't provide primers and probes because it's a manufacturer's secret.

Q-2: In addition, a brief description of the experiments carried out to measure the ALT, AST, bilirubin and albumin should be included.
A-2: The detection methods of ALT, AST, bilirubin and albumin have been added.

Q-3: Minor comments Lack instead of lackness
A-3: Discussion: "lackness" changed to "lack of".

Q-4: "The similar results were found in serum AST." Delete the word The.
A-4: "The similar results were found in serum AST." We deleted the word "The".

Q-5: The sentence "This suggests that nearly half of the patients with severe liver injury that was diagnosed only based on serum ALT or AST levels may have a missed diagnosis" is grammatically incorrect.
A-5: "This suggests that nearly half of the patients with severe liver injury that was diagnosed only based on serum ALT or AST levels may have a missed diagnosis" changed to "This suggests that nearly half of patients, which were diagnosed with severe liver injury based solely on serum ALT or AST levels, may be misdiagnosed".

Q-6: In the Tables 1 and 2 correct the spelling of the word "Groups"
A-6: We corrected the spelling mistake of "groups" in table 1 and table 2.

Answers to the Reviewer3

Q-1: 1 – Statistical analysis: the statistical methods used and described in the manuscript are the Spearman's rank correlation test and the AUC of the ROC. However, a logistic regression model (binary or ordinal if several liver inflammation categories are considered) is the best and more specific method to build a predictive model. Why the authors have excluded the logistic regression model in their methods? The authors must build a logistic regression model using as independent variables ALT, bilirubin, plasma DNA, HBV DNA, AST, albumin and controlling by variables such as age, drinking, and gender (since they show significant differences in table 1) and then fit the best and harmonic model. The model's AUC can be used to measure the predictive information provided by the model.

A-1: In our study, Spearman's rank correlation was used to analyze the correlation between blood markers and the severity of liver injury. If we choose logistic regression model according to the reviewer's opinion, because the liver injury degree is divided into four grades, we will adopt ordinal logistic regression, which is barely possible to achieve. In this study, the grade of liver injury is based on the number and proportion of cells after immunohistochemical staining of liver biopsy, which can also be used as a linear primary index. Therefore, correlation analysis is feasible in our study.

In addition, we did not analyze whether age, sex and drinking were risk factors for high blood markers, so we did not need to do a logistic regression model.

Q-2: 2 – Statistical analysis: multiple comparisons are made in data analysis (table 1). A correction for multiple comparisons must be done and new p values should be indicated on the table.

A-2: There are no multiple comparisons in table 1, only comparisons between two groups.

Q-3: 3 – healthy controls with a history of drinking alcohol had higher ALT, AST, bilirubin, and plasma DNA levels. Were these patients true healthy controls? How the authors discharged an alcoholic liver disease?

A-3: All healthy controls were clinically diagnosed without alcoholic liver disease according to clinical signs and imaging examination. Higher serum levels of ALT, AST, bilirubin, and plasma DNA in healthy controls with a history of alcohol consumption were compared with controls without alcohol consumption. Most are still in the normal range.

Q-4: 4 – How the authors combine serum ALT, bilirubin and plasma DNA to calculate AUC of ROC? Authors must explain the followed method in the statistical methods section.

A-4: The serum ALT, bilirubin and plasma DNA results, as well as the liver injury information of the patients were input into stata software. After specific instructions were executed, the single-indicator roc curve and multi-indicator combined roc curve could be generated.