

Dear Editors:

Thank you very much for your attention and the reviewers' evaluation and comments on our manuscript (Manuscript NO.: 84658, Observational Study). We have revised the manuscript according to your kind advices and reviewers' detailed suggestions. Enclosed please find the responses to the reviewers. We sincerely hope this manuscript will be finally acceptable to be published on the World Journal of Gastrointestinal Surgery. Thank you very much for all your help and looking forward to hearing from you soon.

Please find the following Response to the comments of reviewers:

Reviewer #1:

Comment 1: Normally, PBC is classified as stages 1-4. In the present study, the vast majority of patients was in a rather progressed stage. Can the scores be applied to PBC patients in stages 1 or 2, also?

Response: These prognostic scores can be applied to all stages of PBC patients (stage 1-4), also can be applied to PBC patients in stages 1 or 2. But different scores may have different predictive effects on different stages. Because there are few studies on the prognostic effect of PBC patients in the advanced stage, this study mainly selects the study on the assessment of PBC patients in the advanced stage.

Comment 2: All patients included into this study were treated with UDCA. Did the authors consider patients treated with a combination of UDCA + obeticholic acid or UDCA + bezafibrate?

Response: First, These prognostic scoring systems were derived from large patient cohorts and use combinations of UDCA response parameters and features that show liver disease stage. (Am J Gastroenterol. 2019 Jul;114(7):1101-1108. Validation of Risk Scoring Systems in Ursodeoxycholic Acid-Treated Patients With Primary Biliary Cholangitis). secondly, The first-line drug for PBC is UDCA, management focuses on initiation of UDCA for all patients and risk stratification based on baseline and on-treatment factors, evaluating biochemical indicators after 1 year of UDCA treatment, a second-line treatment (UDCA + obeticholic acid or UDCA + bezafibrate) for patients with PBC who are unresponsive to UDCA was recommended. (Gut. 2018

Sep;67(9):1568-1594.The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines.). This study is about the prognostic effect of prognostic score, rather than the therapeutic effect of UDCA. Based on the support of the above views, All patients included into this study were treated with UDCA, Meet the research objectives and requirements.

Comment 3: In my impression, there are several typographical and grammatical errors that must be corrected.

Response: The typographical and grammatical errors have been carefully corrected according to the requirements of manuscript revision. If there is any discrepancy, it will be improved in time soon.

Reviewer #2:

Comment 1: The article must become shorter. It includes 44 double-spaced pages and 4672 words excluding References, Tables and Figures. The text should comply with the WJG publishing guidelines.

Response: The article has now been modified as required, and has been reduced to 3251 words. The revisions to this article had followed the WJG publishing guidelines.

Comment 2: English language needs major improvement. Many typing errors need correction.

Response: The English language has been carefully corrected and modified, and has been professionally polished

Comment 3: What proportion of end-stage cirrhosis patients are transplanted per year in Yunnan Province of China? Major Comments: 1. (Page 2, Lines 3-5): This statement does not hold true for Western World communities, where PBC is now diagnosed in earlier stages than before (J Hepatol 2019;71:357, Aliment Pharmacol Ther 2019;49:285).

Response: The proportion of end-stage cirrhosis patients receiving transplant surgery in Yunnan Province of China per year has not been studied. In this study, Of the 397 patients 82 patients had died, and four had undergone liver transplantation. We have carefully studied the two papers provided by reviewer. Clinically, due to the

development of diagnostic technology and the improvement of people's understanding of the disease, the number of patients diagnosed with PBC in the early stage is indeed more than before. However, as PBC is a chronic progressive liver disease, the number of old cases and total patients with PBC are still mostly in the middle and late stage. The PBC patients selected in this study were diagnosed during hospitalization. Since most of the patients were hospitalized due to obvious symptoms and need urgent treatment, the majority of patients diagnosed were in the middle and late stages. We have revised the statement to “patients with advanced PBC should not be ignored”, let the expression more objective and close to the true situation of the western world.

Comment 4: (Page 5, Line 6): How the authors ascertained the “middle and the late PBC stage” in their cohort? By liver biopsy? By other means? Please explain.

Response: The ascertained methods of staging in this cohort had been added in the corresponding position of the article.

Comment 5: (Page 6, Line 5): Please, give a reference.

Response: A references has been given comply with the requirement.

Comment 6: (Page 7, Line 20): Authors must give the references of these “few studies”.

Response: The references of these “few studies” have been given comply with the requirement.

Comment 7: (Page 8, Line 20): The actual criteria, which had been used to make the diagnosis of PBC in each one of the 9 cooperating Hospitals, must be mentioned explicitly here and not by simply referring to 2018 AASLD guidelines.

Response: The actual diagnosis criteria of PBC in each one of the 9 cooperating Hospitals has been mentioned explicitly in the corresponding position of the article.

Comment 8: (Page 9, Line 19): Authors should mention the actual means used for the diagnosis of cirrhosis. Besides those cases with a histological diagnosis of cirrhosis, was liver stiffness measured by Fibroscan or a SWE, or by other non-invasive tests? Please be more informative.

Response: The actual means used for the diagnosis of cirrhosis in this study have been mentioned explicitly in the corresponding position of the article.

Comment 9: (Page 12, Line 5): Please clarify how variables with missing values of more than 5% were handled.

Response: We have clarify the handled method in the corresponding position of the article.

Comment 10: (Page 13, Line 1): In Figure 1, Authors could possibly include also data of the transplant free survival (or death) of patients with baseline compensated or decompensated PBC cirrhosis.

Response: We have include the data of the transplant free survival of patients with baseline compensated or decompensated PBC cirrhosis in Figure 1.

Comment 11: (Page 13, Line 21): Figure 2 must be omitted. It is confusing. All the necessary information is included in Table 2.

Response: We have omitted Figure 2 from the manuscript and put it in the Supplementary materials.

Comment 12: (Page 14, Line 10): Table 3 must be omitted. The information in the text can be extended to include the non- significant values of C-scores between GLOBE, UK-PBC, Mayo and ALBI.

Response: We have omitted Table 3 from the manuscript and put it in the Supplementary materials.

Comment 13: (Page 15, Line 6): Table 5 must be omitted.

Response: We have omitted Table 5 from the manuscript and put it in the Supplementary materials.

Comment 14: (Page 15, Line 7,11,17): Please give the actual numbers of the C-Statistic.

Response: The actual numbers of the C-Statistic of all prognostic scores had showed in Table 1. We have added the statement” The C-statistics of all scores before adding are displayed in Table 1.” in the corresponding position of the manuscript.

Comment 15: (Page 35, Table 1): Serum alkaline phosphatase and GGT are missing. They should be added. The unit of measurement of all parameters should be also added. The upper normal limit of all biochemical values must appear in a footnote of the Table. The number and percentage of patients without cirrhosis and with compensated and decompensated cirrhosis at baseline and at the end of follow up, should be added in the

Table.

Response: The above requirements have been completed and added in Table 1.

Comment 16: (Page 35, Table 1): Male: No need to mention male patients. The number and percentage of female patients suffices.

Response: It has been corrected according to this requirement.

Comment 17: (Page 35, Table 1): Liver biopsy: Please mention whether you refer to Ludwig or Nakamura classification staging.

Response: We used Scheuer classification for liver biopsy staging, and it has been described in the appropriate places in Table 1.

Comment 18: (Page 35, Table 1): MELD: It appears that something is not correct with these numbers. If they are correct, then all the PBC patients seem to have been on the verge of death from the start of the study.

Response: We recalculated and carefully checked the data on MELD score, the result numbers still high, but the corresponding clinical data showed that most of them were not in the terminal stage. Considering the reason is that it was related to the characteristics of the samples of the sample patients, MELD score was not suitable to be used in this study. We have eliminated the analysis of MELD score in this study, and the relevant statistics have been recalculated. The main reanalysis involved the Multivariable Cox regression analyses, and We have rechecked all the statistical results. All final results still demonstrate that Mayo score had the best prediction efficacy.

Comment 19: (Page 10, line 10): ...was the optimal...

Response: It has been revised according to the prompt.

Comment 20: (Page 4, line 18): Please explain what is the exact meaning of the phrase "active personal participation" in the study. Its meaning is not clear.

Response: The exact meaning of the phrase is explained as follow: this study was conducted by retrospective collection of patients' clinical data from medical records and did not require patients' personal participation or effort. This sentence has been removed from the revised version for the worry of ambiguity or incomprehension.

Comment 21: (Page 13, lines 2-3): The verb of this sentence is missing.

Response: It has been revised according to requirement.

Comment 22: (Page 13, lines 21): ...that did or did not...

Response: It has been revised according to the prompt in the corresponding position.

Comment 23: (Page 15, lines 18): Do you mean “Mayo”?

Response: Yes, it has been revised according to the prompt.

Thank you very much for your review.

Sincerely yours,

Dr. Feng