

Review

Manuscript ID: 54703

Reviewer 1:

A multivariate predictive model for asymptomatic spontaneous bacterial peritonitis in patients with liver cirrhosis

Tu et al. defined a predictive model for SBP based on the analysis of clinical features and routine laboratory determinations by a multiple linear stepwise regression model. Despite the small size of the cohort, this study has particular innovative aspects. Several groups have already tried to describe a similar model. However, Tu et al. selected a comparable group of patients to establish a balanced distribution of case and control patients. Some clarifications could improve the quality of the manuscript.

Major comments

- According to the inclusion criteria, selected patients should have <250 neutrophils/mm³ in ascitis and no signs of infection. However in line 101, authors indicated “patients presented with disease deterioration signs (such as: ascites PMN > 250 /mm³, physical signs of infection....)”⁰.

Response: Thanks for the comments. The purpose of the current study was to construct a multivariate predictive model for asymptomatic SBP diagnosis in patients with liver cirrhosis. According to the diagnostic standards of SBP, without typical infection signs, the patients with PMN <250 mm³ in ascitis and positive culture results could not be diagnosed with SBP. Although they did not present typical SBP symptoms at initial diagnosis, they could present disease deterioration signs, and antibiotic treatments were necessary for them. In our study, the individuals in case group were asymptomatic SBP cases. With disease development they could present disease deterioration signs, and antibiotic treatments were in need. Therefore, an effective diagnostic model which could identify asymptomatic SBP at early stages could significantly improve the treatments and outcomes of asymptomatic SBP.

- Please clarify why the number of patients in the case group is 98 but the microbial examination revealed 111 positive patients

Response: Thanks for the comments. Among the 111 liver cirrhosis patients whose culture results were positive, 13 cases recovered without antibiotic treatments. They

were only confirmed with bacterial ascites , without inflammation. In our study, the individuals in case group were asymptomatic SBP, thus the 13 cases were not included in our analysis.

- According to the model, N in blood was selected as one of the variables. However, N is not statistically different between case and control groups. In addition, it is not clear how N is calculated. If it is the % of neutrophils(X100) in WBC, then in Table 2, case group has 1.48 and it could be a mistake

Response: We are really sorry for the typing mistake. In this version, the wrong data of N% in case group was corrected in Table 2.

- The application of a statistical model requires that variables were not correlated. Authors do not show if this is the case in the manuscript.

Response: Thanks for the professional suggestions. In our study, the multivariate predictive model was constructed using the multiple linear stepwise regression method of Logistic regression model. During the statistical process, the variables which were correlated could be compared, and the variables whose impacts on the final results were strong could be retained, while the variables with small impact on final results were eliminated. The statistical methods were explained in detail in the revised manuscript.

- Why other variables that are specifically sensitive to an inflammatory environment were not included in the analysis. Some of them, they have already been demonstrated as relevant in models to predict early SBT and are included in routine analysis (levels of bilirubin, heparin binding protein, CRP, IL-6,...)

Response: Thanks for the kind advice. The present study was a retrospective investigation, some indicators that might be significant for early diagnosis of SBP cannot be obtained. Thus, some potential biomarkers were not taken into consideration in our study, such as the inflammation factors. The well designed prospective studies are required to improve and verify our study. The issue was explained in the third paragraph of Discussion section.

- According to the rationale of this work, this model will allow determine patients at early stages of SBP and that could benefit from an early antibiotic treatment. However, it is also possible that despite the presence of pathogens, the lower presence of

neutrophils in ascitis could indicate that there is a competent immunological microenvironment and it is not going to progress into a severe SBP. Adding antibiotics could be unnecessary. Please, discuss.

Response: Thanks for the professional suggestions. All the individuals in case group could present disease deterioration signs, such as ascites PMN > 250/mm³, fever, and other physical signs of infection, or liver and kidney function deterioration, antibiotic treatments were necessary for the patients. The issue was stated in the subtitle of “Grouping” section of Materials and methods part.

- Please, discuss why MELD scores is included but according to recent publications MELD Score Is Not Related to Spontaneous Bacterial Peritonitis (Gastroenterol Res Pract. 2015; 2015: 270456)

Response: Thanks for the comments. MELD is an indicator for disease severity of end-stage liver disease. High MELD scores predict advanced disease stages, and the patients with high MELD scores are at high risk of infections. Although MELD had no direct association with SBP, MELD might be employed as a predictive biomarker for SBP. The issue was stated in the second paragraph of Discussion section.

Minor

- Please, clarify “no active infection signs” criteria

Response: Thanks for spending time on our paper. The no active infection signs referred to the infections of respiratory tract, digestive tract, urinary tract and central nervous system, etc. The information was supplemented in the revised paper.

Answers to review criteria:

Title. Does the title reflect the main subject/hypothesis of the manuscript? yes

Response: Thanks for the comment.

2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? yes

Response: Thanks for the comment.

3 Key words. Do the key words reflect the focus of the manuscript?yes

Response: Thanks for the comment.

4 Background. Does the manuscript adequately describe the background, present status and significance of the study? They do not mention other few works that have described comparable models in early SBP

Response: Thanks for the comments. SBP is regulated by a variety of risk factors, including decreased activity of the reticuloendothelial system, advanced liver dysfunction, medications, and genetic factors. To date, effective multivariate prediction models for asymptomatic SBP are not available. Therefore, few comparable models were mentioned in Background.

5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? yes

Response: Thanks for the comment.

6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? Yes, a model to predict early SBP

Response: Thanks for the comment.

7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? Some points need further clarification (as stated in my major comments)

Response: Thanks for the comment.

8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? OK

Response: Thanks for the comment.

9 Biostatistics. Does the manuscript meet the requirements of biostatistics? Yes, further analysis are required (as stated in major comments)

Response: Thanks for the comment.

10 Units. Does the manuscript meet the requirements of use of SI units? yes

Response: Thanks for the comment.

11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? ok

Response: Thanks for the comment.

12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? yes

Response: Thanks for the comment.

13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? yes

Response: Thanks for the comment.

14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? yes

Response: Thanks for the comment.

Reviewer 2:

Reviewer Name: **Reviewer 2:**

Review Date: 2020-03-10 18:16

Specific Comments To Authors: To: Editorial Board World Journal of Gastroenterology Title: “A multivariate predictive model for asymptomatic spontaneous bacterial peritonitis in patients with liver cirrhosis” Dear Editor, I read this manuscript and I think that: - The sample size is a limitation of the study design. This is a limitation and should be discussed in a dedicated limitation section. - A post-hoc sample size calculation should be provided. - Results section of the abstract should be implemented by including more numerical data. Please provide. - Furthermore, the authors should consider a healthy control group in order to compare the data and the productiveness of the model. - Once more, in order to evaluate the model, a validation cohort should be considered. - The role of care manager should also be considered in this context. Please discuss such a point in relation to the paper from Ciccone MM et al. Vasc Health Risk Manag. 2010 May 6;6:297-305.

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments To Authors (File):

Reviewer 2:

1.The sample size is a limitation of the study design. This is a limitation and should be discussed in a dedicated limitation section.

Response: Thank you for spending time on our paper. The SBP patients might not admit to hospital without obvious clinical symptoms, moreover, the positive rate of ascites culture was relatively low. Thus, the sample size was relatively small in our study. The limitation was stated in the third paragraph of Discussion section.

2.A post-hoc sample size calculation should be provided.

Response: Thanks for your professional suggestion. The present study was a retrospective and exploratory study. Due to the lack of basis for sample size estimation, we did not carry out sample size estimation before the study. We try to collect as much data as possible according to the research program. However, the SBP patients might not admit to hospital without obvious clinical symptoms, moreover, the positive rate of ascites culture was relatively low. Thus, only 98 cases meet the case conditions. After consulting the experts of diagnosis statistics, 98 samples of each group can meet the general requirements of the diagnosis test.

3.Results section of the abstract should be implemented by including more numerical data.

Response: Thanks for your professional suggestion. The information you mentioned has been supplemented in Abstract section in the revised paper.

4.The authors should consider a healthy control group in order to compare the data and the productiveness of the model.

Response: Thanks for your comments. There is no ascites in normal people, and SBP is impossible, so this model is not suitable for normal people.

5.Once more, in order to evaluate the model, a validation cohort should be considered.

Response: Thanks for your professional comments. The present study was a retrospective and exploratory study, and the sample size was relatively small. Only 98 cases meet the case conditions, basically can not be divided into a modeling group and a validation group. Thus, the validation group was not adopted to verify our model. We will further collect more study subjects to verify the model. The issue was stated in the third paragraph of Discussion section.

6.The role of care manager should also be considered in this context.

Response: Thanks for the kind advice. According to Project Leonardo, a health follow-up file may be established for patients with liver cirrhosis, especially those who have ascites. The special care manager will follow up the patients on a regular basis to gain the trust and cooperation of the patients, so as to discover the changes of the condition in time. Based on our diagnostic model, the time treatments could be supplied for the patients to improve the long-term prognosis. The issue was stated in the second paragraph of Discussion section, and the article you mentioned has also cited in our paper (Reference 28)..