

Dear editors and reviewers:

Thank you very much for giving us the opportunity to resubmit the revised manuscript. The comments are very important to improve the quality of our article. We have carefully modified the manuscript according to your comments.

Reviewer #1 (Reviewer's code: 03257023)

Comments: The manuscript provides useful information on the subject, but needs language rewriting. The flow of patients needs to be captured properly. The study started with 3119 patients, of whom 410 were chosen for study, but only 138 are included in the data. This needs to be expressed properly with regard to tally of the numbers. Table 3 shows Control 1 and Control 2, but does not show cases. The actual numbers of cases and the 2 control groups should be shown along with OR and CI. P value is not important if space is a constraint. Table 4 should also show the numbers for each group and should show the reference group in each horizontal category.

Answers: Thank you for your valuable comments. In this retrospective study, we identified 410 patients were fungal positive in ascitic fluid culture.

Majority patients (373 patients) were not met the diagnosis of SFP or fungiasictes (patients without cirrhosis or with recent abdominal surgical procedure or endoscopic biliary intervention were excluded). Finally, Only 22

patients with SFP and 13 patients with fungiasictes were identified. As you suggestion, the actual number of cases and control groups were showed in Table 3 and Tale 4. Additionally, the language was polished and rewrited.

Reviewer #2 (Reviewer's code: 03537089)

Comments: Abstract: needs shortage, and corrections as shown Introduction needs some shortage, and vigorous language correction Patients and methods need shortage, language correction, correction of statistical analysis Results need shortage, and rearrangement Discussion needs some shortage, language correction and reference correction as shown The manuscript needs major correction See the manuscript.

Answers: Thank you for your useful comments. The language was corrected as you suggested. The abstract, introduction, method, results and discussion were properly shorted.

Reviewer #3 (Reviewer's code: 02942549)

It is a retrospective study about spontaneous fungal peritonitis in patients with liver cirrhosis. The limited published data regarding this difficult medical field, make this study interesting and important enough I have some comments to make:

1) You described that you enrolled your sample from a database of 3119 patients with culture positive ascitic fluid. But during your analysis you

describe a group of patients (group 2) with diagnosis of SBP and PMN > 250 but culture negative ascitic fluid. How this can happen as your sample of patients derived from a pool of 3119 patients that all had culture positive ascitic fluid? Please explain

Answer: Thank you for your question. In this retrospective study, the culture positive patients, including bacteria and fungal, were selected from hospital's microbiology database. In other words, the case group and control-1 group were enrolled from 3119 patients with culture positive ascitic fluid. While, the patients in control-2 group were selected from in-hospital record and were negative ascitic fluid culture in microbiology database.

2) As you mentioned the vast majority of patients diagnosed with SFP had at the same time ascitic cultures positive for microbes (SBP). How can we know which of the two factors (fungi or microbe) played the most important role?

Answer: Thank you for your good question. It was hard to completely distinguish true SFP from polymicrobial secondary peritonitis and simple colonization of fungus. This is a limitation in current study, and was also put forward in previous studies (Reference: Spontaneous fungal peritonitis: a severe complication in patients with advanced liver cirrhosis).

3) The administration of antibiotics during the hospitalization was found as an important factor predisposing to the presence of SFP. I believe that you

must describe how many patients with SFP had a past history of SBP and how many of them had been taking prophylactic antibiotic treatment for the prevention of SBP before their hospitalization

Answer: We have to apologize this mistake and inaccurate describe. Actually, the patients with prophylactic antibiotic treatment for the prevention of SBP were also accumulated in the length of antibiotic administration. We have revised in the article. However, consideration of long retrospective period (more than 10 years), the past history of SBP in some patients with SFP was not recorded in detail.

4) The use of NSBB or PPI's was different among the 3 groups (SFP, SBP group 1 and SBP group 2)?

Answer: PPI administration was not showed statistically different among three groups. However, the results need further verified by large sample study. NSBB were not included in current study.

5) How many patients were finally analyzed and how many of them died?

You give the Kaplan-Meier analysis but you do not describe the number of patients that finally died

Answer: After 15-day follow-up, 10 of 35 patients in case group, 3 of 13 patients in fungiasictes group, 9 of 44 patients in control-1 group and 5 of 72 patients in control-2 group were died. The number was showed in Table 1

and Table 2.

6) In how many patients the prognostic scoring systems SOFA, CLIF-SOFA and APPACHE II were applied?

Answer: All patients in current study were calculated SOFA, CLIF-SOFA and APPACHE II

7) Your manuscript has a lot of grammatical problems that must be solved.

Answer: Thank you for your recommendation. The language was polished and the grammatical problems were revised.

Reviewer #4 (Reviewer's code: 02942549)

In this article, Chunhong Huang et al, compared the difference of clinical manifestation between spontaneous fungal peritonitis (SFP) and spontaneous bacterial peritonitis and evaluated risks factors for occurrence and short-term mortality of SFP. The design of the study is quite complex, since it is declared as a case-control study, but the authors also performed a survival analyses for one of the outcomes. Additionally, several scores are compared in terms of prediction of mortality in patients with SFP. Of note, in methods the authors only declare with sufficient detail how the case control study was designed. Very little information is given about the methodology used to perform the survival analyses and to compare the scores in patients with SFP. In the same

line, no sample size calculating is given for any of the objectives of the study.

The article would be very much improved if all these aspects are addressed in detail (an individual section to detail each methodology would be welcomed)

Answer: Thank you for your kind comments. We have added more information about methodology in survival analysis and scores comparison as you suggested.

Other suggestions: 1) In the introduction, when the mortality of the SBP is reported (second line) it should be declared in which time period (for example, 10-46% at 1 year?). I suggest to include as a reference a though recent review which has a table that clearly details the incidence of renal failure and death in patients with SBP ("Spontaneous bacterial peritonitis in patients with cirrhosis: incidence, outcomes, and treatment strategies", *Hepat Med.* 2019; 11: 13-22.)

Answer: Thank you for your suggestion. We have revised in the manuscript as you suggested.

2) Consider at the end of the introduction declaring your third objective: to evaluate the predictive ability of different prognostic scoring systems...."

Answer: Thank you for the suggestion. We added the information that you pointed out.

3) Please detail in methods or in the discussion how incorporating the variables “hepatorenal-syndrome” and “creatinine” in the model that evaluated factors associated with SFP mortality could affect its performance (both variables share very similar information)

Answer: Thank you for your comment. hepatorenal-syndrome and creatine are similar information. The collinearity between two parameters affects the result of multivariate regression analysis. Therefore, we deleted the creatine and recalculated multivariate cox regression model. The result showed hepatorenal syndrome (HR: 5.328, 95%CI: 1.050-18.900), total bilirubin ($\mu\text{mol/L}$, HR: 1.005, 95%CI: 1.002-1.008) represented independent predictors for SFP-related early mortality.

4) Please detail in the inclusion criteria that patients had to be cirrhotic, and how did you evaluate this from the medical records

Answer: Thank you for the suggestion. We have added the information that you pointed out. Cirrhosis was diagnosed by (1) liver biopsy, (2) radiological evidence of liver nodularity in patients with chronic liver diseases, (3) clinical evidence of signs of portal hypertension or hepatic decompensation.

5) Table 5 could be improved if confidence intervals are reported for sensibility, and specificity. Also, the HR could be incorporated in a column.

Answer: Thank you for the suggestion. We added the information that you

pointed out.

Sincerely yours

Zhi Chen