Dear Editor and Reviewers:

Thank you very much for your constructive and insightful comments on our manuscript. In the new version of our manuscript, many changes have been made according to the suggestions of editor and reviewers.

We wish that the quality of revised manuscript will meet the requirements of World Journal of Gastroenterology.

Yours sincerely

Hai Li

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

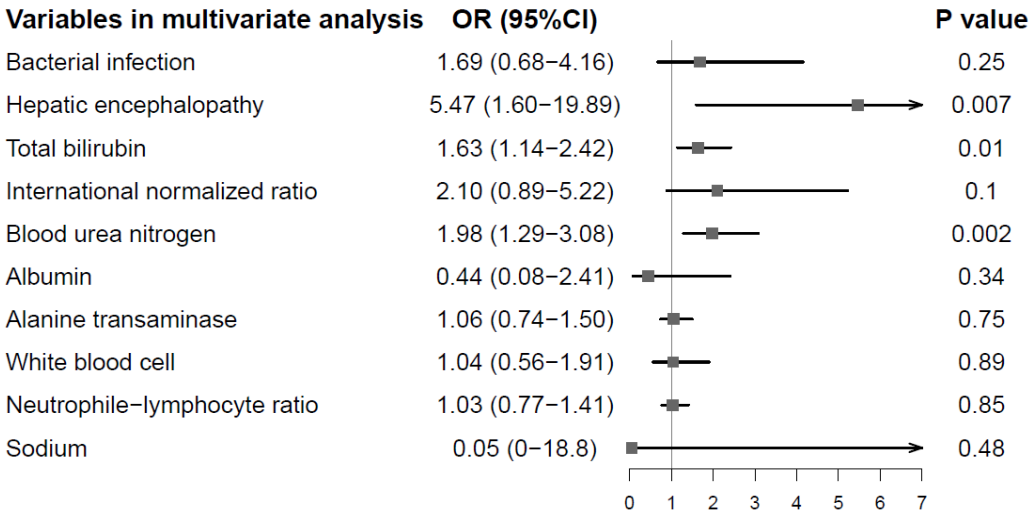
Conclusion: Major revision

Specific Comments to Authors: Thank you for inviting me to review a manuscript entitled "Prevalence and clinical characteristics of autoimmune liver disease in hospitalized patients with cirrhosis and acute decomposition in China". I have some comments that a manuscript may benefit from. Methods The authors should state the reason for using p-value 0.05 as the cut-off point to select variables for multivariable logistic regression analysis. Results The authors should calculate the ACLF by using all CLD patients with cirrhosis as the denominator, unless it's overestimated. The authors should minimize the text and write only the pertinent sentences. It might confuse the readers. The authors should report the incidence rate rather than the prevalence. The authors should state variables adjusted in Adjusted I and adjusted II. Discussion Why did the authors discuss the results that were not statistically significant? What is the relevance to it? What would be the recommendation? The authors failed to write the implication of the findings in the discussion

section.

1. Methods The authors should state the reason for using p-value 0.05 as the cut-off point to select variables for multivariable logistic regression analysis.

   Thank you very much for this helpful suggestion. We reviewed relevant literature[1-2] to determine the optimal p-value cutoff to select variables and changed our p-value threshold to the most common 0.1. Eventually, 10 variables in univariate analysis were eligible to enter multivariate logistic regression model (see figure below or Figure 4). The final results were consistent with previous conclusion: HE, TB and BUN were independent risk factors of 90-day LT-free mortality in AILD patients with cirrhosis and AD in multivariate analysis. And we have quoted the relevant literature in the last paragraph of method section.



Reference:

(1) Jalan R, Stadlbauer V, Sen S, Cheshire L. Role of predisposition, injury, response and organ failure in the prognosis of patients with acute-on-chronic liver failure: a prospective cohort study. Crit Care. 2012 Nov 27;16(6): R227. PMID: 23186071.

(2) Montalvo M, Mistry E, Chang AD, Yakhkind A. Predicting symptomatic intracranial haemorrhage after mechanical thrombectomy: the TAG score. J Neurol Neurosurg Psychiatry. 2019 Dec;90(12):1370-1374. PMID: 31427365.

2. Results The authors should calculate the ACLF by using all CLD patients with cirrhosis as the denominator, unless it's overestimated.

   Many thanks for your suggestions. We calculated the prevalence of ACLF according to your suggestion. Among 2597 patients with cirrhosis and AD, the overall prevalence of ACLF was 22.8%, which was significantly higher than those in AILD cases (14%) ($p<0.001$). This result has been added to the first part of result section. In addition, in the second paragraph of discussion section, we compared the prevalence of ACLF in AILD cases with those in other etiology types (Alcohol-related cirrhosis, HBV-related cirrhosis) reported in other studies.

3. Results The authors should minimize the text and write only the pertinent sentences. It might confuse the readers.

   Many thanks for this suggestion. We completely agree with the reviewers' comment and have revised and simplified our expression throughout the results section (see below).

   RESULTS

   Prevalence of AILD and ACLF in patients with cirrhosis and AD

   A total of 3970 patients from CATCH-LIFE study were screened, 2597 of whom had cirrhosis and AD. Eventually, 242 patients conforming the diagnostic criteria of AILD were finally enrolled (Figure 1).

   In patients with cirrhosis and AD, the overall prevalence of AILD was 9.3% (242/2597). Prevalence of ACLF was significantly lower in AILD cases (14%) than those with all etiology groups with cirrhosis and AD (22.8%) ($p<0.001$).

Distribution of participating centers in this study and number of AILD patients enrolled from each center were displayed in Figure 2A and Figure 2B, respectively. Among the 242 enrolled AILD patients, 234 (96.6%) are from eastern China, where 94% of Chinese population resides; 8 (3.4%) are from western China, where 6% of Chinese population resides. Due to Renji Hospital accounted for 60.3% (146/242) of the total enrolled patients, we further analyzed district distribution of patients enrolled from Renji Hospital. Actually, these patients were from 20 different district all over the country (Figure 2C), the number of patients from each district was shown in Figure 2D. Distribution of patients enrolled from Renji Hospital were also consistent with population density distribution (divided by Hu Line) in China.

Baseline characteristics and outcomes among different etiologies in AILD patients

Baseline characteristics of 242 AILD patients with cirrhosis and AD categorized by etiology are depicted in Table 1. 123 (50.8%) patients showed PBC, 69 (28.5%) displayed AIH, 29 (12.0%) had AIH-PBC overlap syndrome and 21 (8.7%) patients manifested other uncommon etiologies of AILD. Most patients were female (81.0%) and their mean age was 56.04 years. Patients with PBC/AIH had higher white blood cell ($p<0.001$) and neutrophil-lymphocyte ratio (NL ratio) ($p<0.001$) levels than patients with PBC, AIH or others. ALT ($p<0.001$) and AST ($p=0.04$) levels were higher in the AIH/PBC group. In addition, the PBC group tended to have lower hemoglobin ($p=0.003$) and higher alkaline phosphatase ($p<0.001$) levels than other AILD etiologies.

Baseline characteristics of 34 ACLF patients categorized by etiology are shown in Table 2. PBC (41.2%) was still the most common etiology among ACLF patients with AILD, followed by AIH (29.4%) and AIH-PBC overlap syndrome (20.6%).

At the end of 28-day and 90-day, no patients were lost to follow up. At the

end of 365-day, 3 (1.2%) patients were lost to follow-up. Short-term (28-day, 90-day and 365-day) LT-free mortality of AILD patients with cirrhosis and AD are presented in Figure 3. Generally, among AILD patients with cirrhosis and AD, 90-day LT-free mortality were 17%. AIH/PBC had higher 28-day, 90-day and 365-day mortality, although the results were not statistically significant. Among patients with AILD-related ACLF, 28-day and 90-day mortality were 43.8% and 80.0%, respectively.

The impact of etiology on mortality

To investigate the effect of etiology on short-term (28-day, 90-day and 365-day) LT-free mortality in AILD patients with cirrhosis and AD, we constructed 3 models to gradually control other potential confounding factors (Table 3). Both univariate (Unadjusted) and multivariate (Adjusted I and Adjusted II) analyses showed that compared to PBC, AIH patients were at lower risk for death at 90-day and 365-day, whereas PBC/AIH patients were at higher risk for death at all time periods. However, none of the associations were statistically significant.

Subgroup analysis were conducted according to Child Turcotte Pugh class and MELD score, there was no heterogeneity in the impact of etiology types on 90-day LT-free mortality between different subgroups, as was shown in supplementary Figure 1.

Risk factors of short-term mortality in AILD patients with cirrhosis and AD

Logistic regression model was conducted to assess the risk factors for 90-day LT-free mortality. Univariable analysis identified 10 variables on admission correlated with 90-day prognosis: bacterial infection, hepatic encephalopathy (HE), TB, INR, blood urea nitrogen (BUN), albumin, ALT, white blood cell, NL-ratio and sodium (Supplementary Table 1). Variables with P<0.1 were selected into multivariable model for further analysis. Only HE, TB and BUN were found to be independently associated with 90-day mortality in AILD patients with cirrhosis and AD (Figure 4). We also

investigated risk factors for ACLF development during hospitalization (Table 4). 21 ACLF patients diagnosed on admission were excluded from analysis. Multivariable analysis revealed that only TB (p=0.046) and INR (p=0.048) independently correlated with ACLF development.

4. Results The authors should report the incidence rate rather than the prevalence.

   Thanks for this suggestion, we acknowledge that reporting the incidence for a rare disease would be very helpful. However, as our multi-center study was a cross-sectional study, clinical data were collected on admission, it was difficult to collect dynamic data on the number of new AILD cases in 1 year. Thus, in our paper, we reported only the prevalence. We will take your valuable advice in our future prospective study designed specifically for AILD.

   The prevalence of a disease is the proportion of people who have it at one point in time.

   The incidence rate is the number of new cases in 1 year divided by the number at risk.

   Reference

   (1) An introduction to Medical Statistics. Fourth Edition. Martin Bland. Oxford University Press.

5. The authors should state variables adjusted in Adjusted I and adjusted II.

   Thank you for your suggestion. The adjusted confounders are presented underneath Table 3. In In adjusted I, we adjusted for age and gender; In adjusted II, we adjusted age, gender, ascites, the presence of hepatic encephalopathy, gastrointestinal bleeding and infection.

6. Discussion Why did the authors discuss the results that were not

statistically significant? What is the relevance to it?

Thank you so much for your insightful comments. We greatly benefitted a lot from your suggestion and carefully revised our discussion part.

Although the impact of etiology on 90-day prognosis was not statistically significant, this result could provide some clues for clinical management of AILD.

Previous studies showed that worse clinical consequences (death and LT) were observed in patients with PBC-AIH overlap syndrome than patients with pure PBC or AIH[3-4]. Based on these results, some experts suggested that PBC/AIH should be given a more aggressive treatment. Notably, these studies evaluate only the univariate prognostic value of etiology and did not take confounders into consideration. It is, therefore, likely that they fail to objectively reveal the independent impact of etiology on the prognosis of AILD. PBC, AIH and PBC/AIH are all complex disorders but result in significant morbidity and mortality. Once the patients progressed to end-stage liver disease, no effective treatment is clinically available. Herein, our results clearly showed that presence of HE, higher TB and BUN levels, rather than liver disease etiologies, were independently associated with short-term mortality in AILD patients with cirrhosis and AD. Therefore, in clinical management of AILD, physicians are supposed to pay more attention to the presence of HE and closely monitor the changes of liver and renal function.

And we have added this in our discussion section.

Reference:

(3). Neuhauser M, Bjornsson E, Treeprasertsuk S, Enders F. Autoimmune hepatitis-PBC overlap syndrome: a simplified scoring system may assist in the diagnosis. Am J Gastroenterol. 2010 Feb;105(2):345-53. PMID: 19888204.

(4). Yang F, Wang Q, Wang Z, Miao Q. The Natural History and Prognosis of Primary Biliary Cirrhosis with Clinical Features of Autoimmune

Hepatitis. Clin Rev Allergy Immunol. 2016 Feb;50(1):114-23. doi: 10.1007/s12016-015-8516-5. PMID: 26411425.

7. Discussion What would be the recommendation? The authors failed to write the implication of the findings in the discussion section.

Many thanks for this important question. As was shown in question 6, we compared our results with previous findings. Our studies revealed that HE, higher TB and BUN levels, rather than liver disease etiologies, were independently associated with short-term mortality in AILD patients with cirrhosis and AD. In clinical management, physicians should pay more attention to the presence of HE and closely monitor the changes of liver and renal function.

According to your suggestion, we have added the recommendation in our discussion section.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: 1- It is a pleasure to review this article. The data analysis part is incomplete. I do not see any list of other confounders such as gender, BMI etc. Please explain. They might have some impact on the outcomes. 2- Did you classify the cirrhotic patients as a Child Pugh classification? Subclassification and reporting the results in different child classification might create interesting results if analysis considered to be done. Please include the information. 3- There is a risk of selection bias in this study. The patients have been selected from a small population area. Although it was explained in the study limitations section, there is still needed to address. Because the generalization of these results would not be valid. 4- Please mention what the population size was at the end of study when that follow up of outcomes

happened for different durations.

1. It is a pleasure to review this article. The data analysis part is incomplete. I do not see any list of other confounders such as gender, BMI etc. Please explain. They might have some impact on the outcomes.

   Thank you for your recognition of our research. The adjusted confounders have been presented underneath Table 3. In In adjusted I, we adjusted age and gender; In adjusted II, we adjusted age, gender, ascites, hepatic encephalopathy, gastrointestinal bleeding and infection.

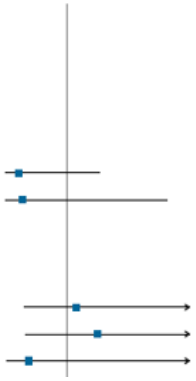
2. Did you classify the cirrhotic patients as a Child Pugh classification? Subclassification and reporting the results in different child classification might create interesting results if analysis considered to be done. Please include the information.

   We greatly appreciate the helpful question.

   We have added the subgroup analysis according to Child-Turcott-Pugh class (see below or supplementary Figure 1). There was no heterogeneity in the impact of etiology on 90-day LT-free mortality in AILD patients with cirrhosis and AD between different Child classes (P=0.98). However, due to the reduced sample size in some subgroups, these results need to be verified in a larger population.

   Adjusted confounders: age, gender, hepatic encephalopathy, ascites, infection, gastrointestinal bleeding.

Subgroup	Number	Num of death (mortality)	Odds Ratio (95%CI)	P value for interaction
CHILD PUGH				0.98
A				
PBC	5	1 (20)	1	
AIH	3	0 (0)		
PBC/AIH	0	0 (0)		
Others	1	0 (0)		
B				
PBC	60	7 (11.7)	1	
AIH	34	1 (2.9)	0.22(0.01−1.53)	
PBC/AIH	14	1 (7.1)	0.28(0.01−2.64)	
Others	10	0 (0)		
C				
PBC	33	10 (30.3)	1	
AIH	26	7 (26.9)	1.16(0.32−4.20)	
PBC/AIH	12	6 (50)	1.51(0.33−6.96)	
Others	7	2 (28.6)	0.38(0.03−3.32)	



3. There is a risk of selection bias in this study. The patients have been selected from a small population area. Although it was explained in the study limitations section, there is still needed to address. Because the generalization of these results would not be valid.

Many thanks for the helpful suggestion. Your rigorous attitude has benefited us a lot. We have added the distribution and number of patients enrolled from each center and Renji Hospital in Figure 2 (see below) as you suggested.

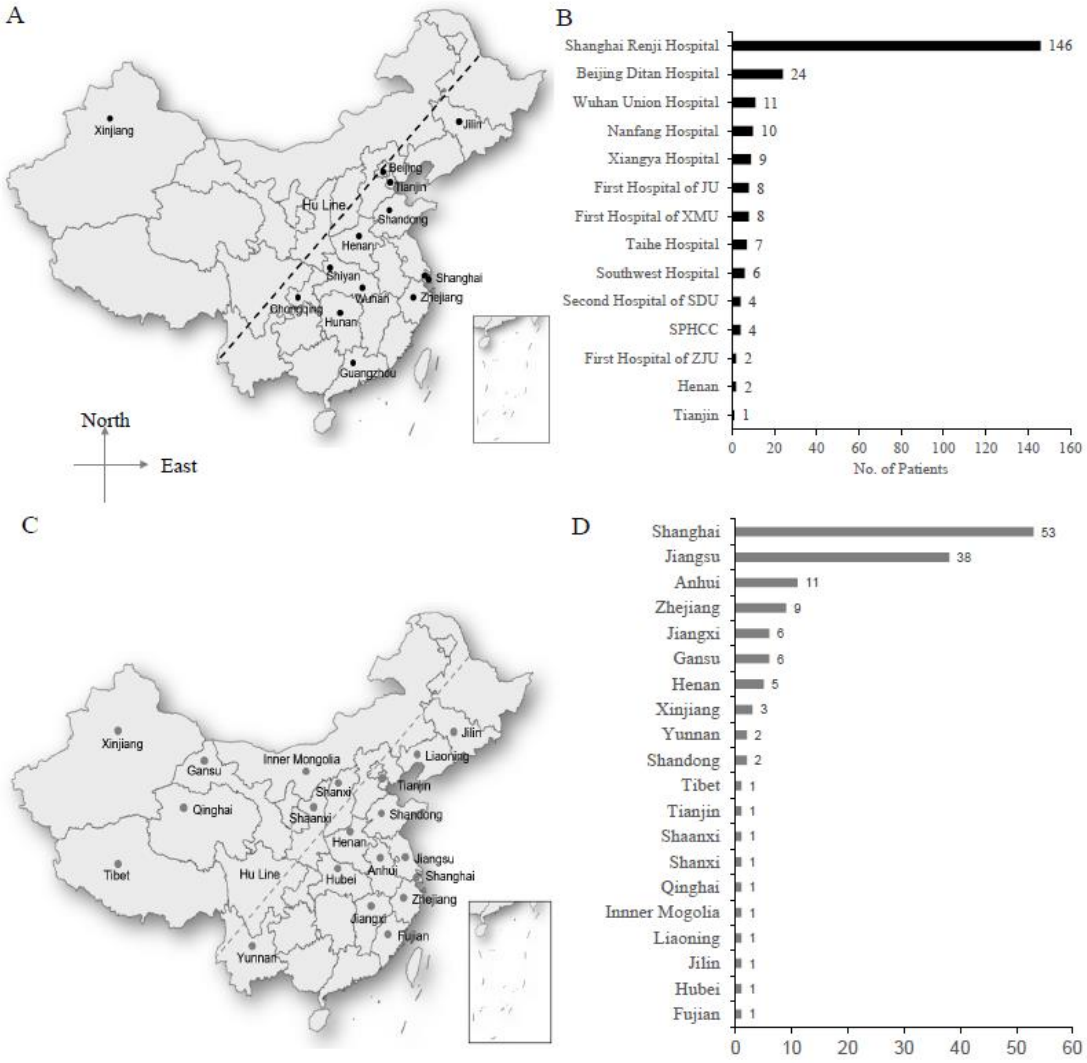
Due to the low prevalence and complexity of diagnosis in China, the vast majority of AILD patients are diagnosed at top hepatology centers. The participating center in this study were all tertiary hospitals in China. Among the 242 enrolled AILD patients, 234 (96.6%) are from eastern China, where 94% of Chinese population resides. 8 (3.4%) are from western China, where 6% of Chinese population resides (Figure 2A and Figure 2B).

Division of Gastroenterology and Hepatology in Renji Hospital is the largest and most prestigious specialized AILD center in China. Due to Renji Hospital accounted for 60.3% (146/242) of the total enrolled patients, we further analyzed district distribution of patients enrolled from Renji Hospital Actually, patients enrolled from Renji hospital are from 20 different districts all over the country (Figure 2C). Among 146 patients enrolled from Renji hospital, 131 (90%) are from eastern China, 14 (10%) are from western China. The distribution was also consistent with population distribution in China

Figure 2. Distribution and the number of AILD patients enrolled from each of center and from Renji Hospital. (A) District distribution of each enrolled center. (B) The number of patients enrolled from center. (C) Population

distribution of patients enrolled from Renji Hospital. (D) The number of patients enrolled from each of the 20 districts.

Approximately 94% of the total Chinse population resides east of the dividing line (Hu Line) in the figure, and 6% resides west of the line; 13 centers lie in eastern China, and 1 lies in western China.



4. Please mention what the population size was at the end of study when that follow up of outcomes happened for different durations.

Many thanks for this question. In this study, among 242 AILD patients with cirrhosis and AD, no patients were lost to follow-up at the end of 28-day

and 90-day, and 3 (1.2%) at the end of 365-day. This part has been added to the second paragraph of result section.

Re-reviewer:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors have adressed all comments.

Many thanks for your comments.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

This is a very interesting paper on autoimmune liver diseases and ACLF. The authors use the current definitions of the EASL-CLIF consortium, and they come to relevant conclusions. This is a very important topic of research, as we need to better understand how to diagnose, prognosticate and treat ACLF. I recommend publication after a minor revision, as appointed by the reviewers.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide decomposable Figures (in which all components are movable and editable), organize them

into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Thank you for your recognition and encouragement of our research. Your comments are significant for us. We will strive to improve the shortcomings of the manuscript according to the reviewers' suggestions.