April 28, 2018

World Journal of Gastroenterology

Dear Editors:

First of all, we would like to thank all of the reviewers for their professional comments and suggestions. Our point-by-point responses to the reviewers' comments is listed below:

Reviewer1

Comment 1：The abstract does not clearly represent the study and in some parts is confusing. I think to better represent the study work, the abstract should be re-written.

Reply: The abstract has been rewritten now in the revised manuscript.

Comment 2：There is some overlap between decompensated cirrhosis and acute on chronic liver failure and sometimes we are not able to definitely differentiate the two entities from each other.

Reply: We thank the reviewer for rising this issue. At this current study,, ACLF was diagnosed according to the definition of APASL. DC patients are those patients with previously confirmed liver cirrhosis , was hospitalized due to a decompensated liver function but do not meet the ACLF criteria.. Some DC patients who were under the condition of liver failure was defined as chronic liver failure--CLF, not ACLF. However we do agree with the reviewer, in patients with HBV-ACLF, some patients did have evidence of cirrhosis.

Comment 3：There is question about excluding patients with proteinuria from the study. as they may represent CKD.

Reply: We thank the reviewer for this question. Patients who have been previously diagnosed with chronic kidney disease or massive proteinuria were excluded. In this study we mainly focused on AKI associated with

HBV-ACLF or HBV-DC.

Comment 4： Has any comparison being made for the mean of BP between the two studied groups?

Reply: Yes, we had compared the mean arterial pressure in this study and there was no significant difference in two studied groups. The results were shown in Table1.

Comment 5: Is there any data regarding the outcome of patients with AKI after liver transplant?

Reply： A total of 14 patients had received liver transplantation in this study. One of fourteen patients had AKI before transplantation and this patient survived until a 90 days follow-up. This information is now incorperated in the results section page 11 line 288-290.

Comment 6： What is the definition of response to treatment with terlipressin?

Reply: As stated in the material and method section, patient's response to terlipressin therapy was defined according to the recommendations in ICA criteria: No response, no regression of AKI; Partial response, regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 μmol/L) above the baseline value; Full response, return of sCr to a value within 0.3 mg/dl (26.5 μmol/L) of the baseline value.

Reviewer2

Comment 1： The study regarded only HBV patients and used the APASL definition for ACLF. Because of both these factors, more than half of patients with ACLF were not cirrhotics. Therefore, authors must address in Discussion the issue of the generalizability of their results. It is quite possible that results could be different in Western countries, where HBV is much less frequent and where ACLF is a condition associated mainly to cirrhosis.

Reply：Yes, we entirely agree with the reviewer. We have now discussed this issue in the discussion section (page 15 line 414-419). one should consider the definitions and etiology differences when interpret these results into western patients where alcoholism constitutes the major etiology of ACLF (type A non-cirrhosis, type B with compensated cirrhosis, type C with decompensated cirrhosis) and DC.

Comment 2： Authors must comment in Discussion that if the CLIF-C definition for ACLF had been used instead of the APASL definition, results would probably be completely different, since most of the patients with AKI would be classified as having ACLF just because of having AKI (at least those with creatinine >2mg/dL or with creatinine >1.5mg/dL and another organ failure). The fact that, according to CLIF-C definition, most patients with DC-AKI would actually have ACLF might even explain why the group with DC-AKI had greater mortality than the group with ACLF-non-AKI in the present study.

Reply：It is good idea to use CLIF-C for patients classifications simultaneously and compared the results for a better understanding of the similarity and difference between east and west. In this first set of observational study, a good number of patients was enrolled by APASL definition, however this was not sufficient to analyses by CLIF-C definition since more than half of these patients are excluded due to lack of cirrhosis. But this issue will be investigated and discussed in next study.

Comment 3: Probably, the greatest matter about this study is that authors did not clearly define which patients received terlipressin, so that readers could understand if they fulfilled the diagnostic criteria for hepatorenal syndrome (authors only mentioned that they were volume non-responsive). If they did not, terlipressin simply would not be expected to work (and should not be used). As the authors have demonstrated, many ACLF patients had evidence

of renal structural damage (which was actually expected in ACLF) and, therefore, would not be diagnosed with hepatorenal syndrome. I understand that the study does not allow the conclusion that ACLF patients are less responsive to terlipressin than DC patients (even if they really are), because we do not know if ACLF patients in this study really had hepatorenal syndrome.

Reply: We understand the reviewer's concern. Basically, the criteria for terlipressin treatment for both HBV-ACLF and HBV-DC was according to ICA recommendations. Patients with stage 2 or 3 AKI who do not respond to the diuretic withdrawal and plasma volume expansion with albumin and without apparent structural kidney injury were treated with terlipressin. We also agree with the reviewer, at this point it is difficult to diagnose patients only having hepatorenal syndrome.

Comment 4： Minor grammar review is needed (for example, lines 102, 180, 249, 379, 649). Authors should also be careful when they cite percentages in parethesis: the order should coincide with the preceding text (for example, in lines 62 and 63, it would probably be better to state "(49.3% vs. 17.9%, p=0.013)" – the same happens other times in the text)

Reply: We thank the reviewer for this suggestion. We have carefully checked and improved the manuscript. Editions were highlighted .

Reviewer3

Comment 1. The authors focused on HBV-induced cirrhoses and kidney injury. However, in Western countries, HBV-cirrhosis with AKI is a rare condition. This should be discussed in more detail.

Reply： Yes, we entirely agree with the reviewer. We have now discussed this issue in the discussion section (page 15 line 414-419). One should consider the definitions and etiology differences when interpret these results into western patients where alcoholism constitutes the major etiology of ACLF (type A

non-cirrhosis, type B with compensated cirrhosis, type C with decompensated cirrhosis) and DC.

Comment 2. Was genotype of HBV of relevance ?

Reply: This is an good point. However, due to Hepatitis B virus genotype is not a routine test in this set of patients we regret that there was no data available for analysis.

Comment 3. How many patients were HDV positive ?

Reply: Another good point from the review. However, due to Hepatitis D virus is neither a routine test in this set of patients, thus there was no data available for analysis.

Comment 4. Which of the patients received terlipressin ?

Reply: Basically, the criteria for terlipressin treatment for both HBV-ACLF and HBV-DC was according to ICA recommendations. Patients with stage 2 or 3 AKI who do not respond to the diuretic withdrawal and plasma volume expansion with albumin and without apparent structural kidney injury were treated with terlipressin.

Comment 5. How many patients were treated with albumin or octreotid ?

Reply: This is a good point. All patients were treated with intravenous albumin. For those who did not response to the diuretic withdrawal and plasma volume expansion with albumin, a terlipressin treatment was applied. A total of sixteen patients with gastrointestinal bleeding or acute pancreatitis received both terlipressin and Octreotide. Among them ten out of seventy one (10/71) were from ACLF-AKI and six out of twenty eight (6/28) from DC-AKI . However there were no significant difference in terms of patients proportion who received Octreotid between two treated groups. This information has now been incorporated into discussion part.

Comment 6. Was dialysis necessary?

Reply: Previous studies have indicated that patients who do not respond to vasoconstrictor drugs should be considered for timely dialysis treatment, especially when they have uremic syndrome, refractory fluid overload and acidosis, and severe electrolyte disturbances. In this set of patients, none of them received dialyses due to severe disorder of coagulation and there is no consensus for ACLF or DC patient to received dialyses. It is difficult to make a statement if a dialyses would be helpful in this setting of patients.

Reviewer 4

Comment 1: In this study, the APASL 2014 definition for ACLF, and ICA-criteria were used for the diagnosis of AKI. Please use AKIN criteria for the categorization of AKI as recommended by APASL ACLF consensus recommendations.

Reply : We thank the reviewer for this comment. The ICA criteria were modified from the RIFLE criteria, AKIN criteria and KIDGO criteria, mainly used for patients with cirrhosis and ascites, and has been adopted in many recent researches. In ICA criteria, the use of a reduction in urine output as part of the diagnostic criteria was eliminated because cirrhotic patients with ascites frequently have a low urine output as part of their sodium and water retention syndrome. Studies from Angeli P et al suggested that many of these patients have a daily urine output below the diagnostic criteria for the diagnosis of AKI, but their glomerular filtration is near normal. In addition, these patients may have an increased urine output because of diuretic treatment, urine collection is often inaccurate in clinical practice. Since most of the patients in our study were patients with cirrhosis and ascites, we believed that ICA criteria may be more suitable for this study.

Comment 2: Please indicate how many patients suffered from hepatorenal

syndrome (HRS-AKI), and report whether urinary markers and terlipressin – response were different from non HRS-AKI.

Reply：We thank the reviewer for this insightful question. At present, there is no unified non-invasive method to accurately distinguish different types of renal injury. Therefore, we cannot accurately estimate the number of patients with HRS-AKI. Recent studies have indicated that urine biomarkers such as N-GAL, L-FABP, KIM-1, CysC, IL18 may be used to distinguish types of renal injury, including prerenal azotemia, HRS, and structural renal injury. Therefore, in this study, we examined the levels of these biomarkers to assess the possible types of kidney injury in different groups of patients. However since there was no kidney biopsy pathological evidence to confirm, it is very unlikely to diagnose HRS-AKI.

Comment 3: Please go into detail about the actual categorial differences of ACLF and decompensated cirrhosis (introduction).

Reply：We thank the reviewer for this suggestion. In the introduction of the revised manuscript, we have supplemented the comparison between ACLF and DC patients (page 4, line 90-99).

Comment 4：Please include the CLIF-C ACLF score in your analysis and show us, whether there are differences in urinary marker profiles and terlipressin response if categorized according to CLIF-C-ACLF vs. APASL.

Reply：It is a good idea to use CLIF-C for patients classifications and compared the results set for a better understanding of the similarity and differrence between east and west. In this first set of observational study, a good number of patients was enrolled by APASL definition, however this was not sufficient to analyses by CLIF-C definition since more than half of these patients was excluded due to lack of cirrhosis. But this issue will be investigated and discussed in next study.

Comment 5: Please explain the patient collective in detail? Did you also include ICU-patients?

Reply： All participates were enrolled from our center, the Department of Infectious Diseases of Tongji hospital, from general wards as well as ICU wards of our center.

Comment 6: Did some patients receive renal replacement therapy/vasopressors additionally to terlipressin, mechanical ventilation etc. How did this impact on outcome?

Reply: Previous studies have indicated that patients who do not respond to vasoconstrictor drugs should be considered for timely dialysis treatment, especially when they have uremic syndrome, refractory fluid overload and acidosis, and severe electrolyte disturbances. However for patients in this current study, none of them received dialyses due to severe disorder of coagulation and there is no consensus for ACLF or DC patient to received dialyses. It is difficult to make a judgement if a dialyses would be helpful in this setting of patients.

A total of sixteen patients with gastrointestinal bleeding or acute pancreatitis received both terlipressin and Octreotide.Among them ten out of seventy one (10/71) were from ACLF-AKI and six out of twenty eight (6/28) from DC-AKI . However there were no significant difference interms of patients proportion who received Octreotid between two treated groups. this information has now been incorperated into discussion part.

No other vasoconstrictor drugs were administered and no patients had received mechanical ventilation.

Comment 7: Minor concerns: - The article, despite native speaker certificate needs major language polishing, especially concerning semantics

Reply: We have had our revised manuscript thoroughly reviewed for English

language by a biomedical editing company.

Sincerely,

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