Answers to reviewer,

Thank you very much for your valuable comments. We improved the manuscript based on your comments.

Comment 1: Newly proposed prognostic biomarker in assessment of ACLF should be added.

Answers: We discussed prognostic biomarkers. Biomarkers section was added in the manuscript.

BIOMARKERS

Treatment strategies in ACLF are mainly supportive. Biomarkers have been the subject of research in predicting the prognosis of the disease. These biomarkers aim to predict organ dysfunctions early. Oxidative stress factors such as S100A12 and sRAGE, markers of cell death such as caspase pathway proteins (reflect death of hepatocytes) and immune function studies have been performed in adult patients with ACLF. Unfortunately validity of such markers unknown (26). Due to the role of infections in the etiopathogenesis of adult ACLF, the use of some biomarkers such as galactomanan or B – D Glucan for invasive fungal infections and C-reactive protein and procalcitonin for bacterial infections have been recommended for early diagnosis by APASL (15). Renal complications are common in ACLF. While hepatorenal syndrome improve with LT, acute tubular necrosis or structural acute kidney injury, which may causes permanent renal damage, requires both LT and kidney transplantation. Therefore, the use of new biomarkers of acute tubular necrosis such as N-GAL, Kim-1, IL-18 and 1-FABP in ACLF may be beneficial for appropriate

treatment (15,27). Finally, non-invasive tools and biomarkers that will be developed to measure liver fibrosis may provide useful information in predicting the prognosis of ACLF.

Comment 2: Authors should add pathophysiology of ACLF.

Answers: We added pathophysiology section in the manuscript.

PATHOPHYSIOLOGY

The knowledge about the pathophysiology of ACLF is insufficient. It is stated that the main trigger of ACLF in adults is increased severe systemic inflammation. How systemic inflammation causes ACLF is explained by several mechanisms; i) immune mediated tissue damage, ii) mitochondrial dysfunction caused by oxidative stres, iii) development of renal hypoperfusion and multiple organ failure due to effective arteriolar volume decrement caused by vasoactive substances (21,22). The main causes of systemic inflammation have been reported as bacterial infections and sepsis originating from the gastrointestinal tract, gastrointestinal bleeding, and severe alcoholic hepatitis (21,23). It is suggested that gastrointestinal hemorrhage causes systemic inflammation by causing ischemia reperfusion injury secondary to liver ischemia and intestinal bacterial translocation (24). Excessive alcohol consumption stimulates systemic inflammation by causing intestinal dysbiosis and bacterial translocation in severe alcoholic hepatitis (23). The differences of triggering factors, underlying diseases and comorbidities in children from adults suggest that factors other than these mechanisms also play role in the pathophysiology of pediaric ACLF.

Comment 3: In “Clinical features of ACLF” section, “Prognosis” should be placed after “Scoring system”.

Answers: Prognosis section placed after Scoring system section.

Comment 4: Some grammar errors should be revised.

Answers: The manuscript was edited by a native English speaker. Language was improved.

Thank you very much for all your comments again.

Best regards