

Dear professors:

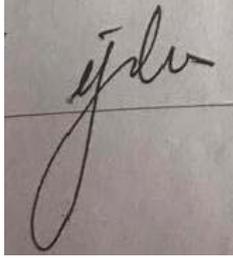
Thanks for your reviews to this paper. We will give the detailed answers to related problems as follows.

1. About the inducing factors of NAS, we accept that the deficient hepatic arterial blood flow plays an important role in its pathological process. While in this study, we can see, under the similar operative conditions as uncomplicated patients after OLT, patients suffered from NAS showed a significant different fecal microbial structure. While dysbacteriosis associated inflammation or microcirculation disorder had been reported correlated with ischemia reperfusion injury, and biliary epithelium was really sensitive to hypoxic-ischemic. So there had every reason to believe that factors of hepatic portal occlusion etc. may directly affect the structure of microbiota. Meanwhile those shifts of microbiota may induce or aggravate the pathological process and finally lead to NAS. As for the use of antibiotics, all patients enrolled in had no history of systemic antibiotics within previous 3 months, so the influences of antibiotics on microbiota can be negligible.
2. In this study, we excluded those patients with abnormal blood flow in hepatic artery, in other words, doppler ultrasound results showed all post-LT patients in this study were with no alterations of the arterial inflow. In the method part of this article, we specified all subjects in this study had no history of systemic antibiotics within previous 3 months. We absolutely agreed the essential role of alteration of intestinal permeability in this pathogenic process. While it's is a pity that we did not carry out related experiments due to the limitations of clinical research. In the future studies, we will focus on the assessment of intestinal permeability to explore the related mechanisms. But for these, revises of discussions and other sentences have been finished according to reviewer's suggestions.

3. (1)As reported, patients with biliary strictures but no liver transplantation or anastomotic strictures were commonly caused by iatrogenic injury or calculus, of which the pathological processes were different from NAS. Account for this factors, we didn't enroll this two groups at that time. (2) Normally, biliary systems were relatively sterile, while biliary injury or impaired barrier function may increase the risk of bacterial translocation, and pathogenic bacterium often were the culprit. So they were strictly not the same. (3) We can see, under the similar operation conditions as uncomplicated patients after OLT, patients suffered from NAS showed a significant different fecal microbial structure. While dysbiosis associated Inflammation or Microcirculation disorder had been reported may correlated with Ischemia reperfusion injury, and biliary epithelium was sensitive to Hypoxic-ischemic. So There is reason to believe that biliary stricture or hepatic portal occlusion etc. may directly affect the structure of microbiota, meanwhile those shifts of microbiota may promote the pathological process and finally led to NAS. As for the use of antibiotics. (4) For patients undergone OLT, all donors were DCDs, which to some degree an important inducing factor in pathogenesis of NAS. But patients with no complications after OTL also shared the same Organic source , and the factors of ischemic time were balanced between two groups.(5)All patients diagnosed with subacute liver failure were caused by HBV(6) all patients with HCC have cirrhosis(7)the discussion regarding the potential role of endotoxins and TLRs regarding the microbial population was proposed based on the current researches, no firm data available in this experimental setting, we will carried out related experiments to figure it out.(8)due to the limitations of Organ transplant ethics and hospital policy, more information form the donors themselves were unavailable at the present stage

Thanks very much,

Yours sincerely,

A square image showing a handwritten signature in black ink on a light-colored background. The signature is stylized and appears to be 'Yi Lv'.

Yi Lv, MD, PhD, Doctor

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