(2)-39591 Answering Reviewers

Reviewer 03317257

1. **Authors suggest that liver transplantation is reasonable for some HLH cases, but they did not give any evidence for those suggestions,**

Author's response:

The theme is changed throughout the paper from the reasonability of liver transplantation for some HLH cases, to the lack of adequate data on liver transplantation for HLH.

Abstract CHANGED TO:

Patient was judged not to be a liver transplant candidate despite MELD score=33 because liver failure was secondary to severe systemic disease from HLH, including septic shock, focal centrilobular hepatocyte necrosis from hypotension, bone marrow failure, and explosive immune activation from HLH. The patient eventually succumbed to overwhelming sepsis, progressive liver failure, and disseminated intravascular coagulopathy. Systematic review reveals liver injury is very common in HLH, and liver failure can sometimes occur. Data on liver transplantation for patients with HLH are very limited, and so far the results have shown a generally much worse prognosis than for other liver transplant indications. Liver transplantation should not be guided solely by MELD score, but should include liver biopsy results and determination whether liver failure is from intrinsic liver injury versus multisystem (extrahepatic) organ failure from HLH.

CONCLUSION: This case report illustrates that liver transplantation may not be warranted when liver failure associated with HLH is primarily from multisystem failure from HLH. Liver biopsy may be very helpful in determining the severity and pathophysiology of the liver disease.

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activation from HLH. The patient eventually succumbed to overwhelming sepsis, progressive liver failure, and disseminated intravascular coagulopathy. Systematic review reveals liver injury is very common in HLH, and liver failure is sometimes associated with HLH. However, liver transplantation should not be guided solely by MELD score, but whether liver failure is from is from intrinsic liver injury versus multisystem (extrahepatic) organ failure from HLH.

CONCLUSION: This case report illustrates that liver transplantation may not be warranted when liver failure associated with HLH is primarily from multisystem failure from HLH.

Introduction. CHANGED TO:

2.1: Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of aggressive immune hyperactivation from hypercytokinemia that frequently causes liver injury and sometimes causes acute liver failure (ALF) which can contribute to the high syndromic mortality. Systematic literature review revealed hundreds of reported cases of HLH in adults, but provides insufficient data on indications and contraindications for liver transplantation for ALF associated with HLH[1]. Liver transplantation for ALF associated with HLH is currently controversial due to prominent systemic morbidities from HLH, the generally poor condition of patients suffering from both ALF and HLH, potential curability of ALF from HLH with HLH-specific therapy alone, and risk of recurrent HLH after liver transplantation[2,3]. A case is reported of fatal HLH in an adult presenting prominently with ALF, with the liver injury primarily due to severe systemic disease from HLH, as documented by liver biopsy and clinical evaluation, and liver transplantation refused on this basis. This case report is important in illustrating potential pitfalls in liver transplantation for ALF associated with HLH,

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immune hyperactivation from hypercytokinemia that frequently causes liver injury and sometimes causes acute liver failure which can contribute to the high syndromic mortality. Systematic literature review revealed hundreds of reported cases of HLH in adults, but provides insufficient data on the patterns and pathophysiology of liver injury. It is particularly important clinically to determine whether acute liver failure associated with HLH is due primarily to intrinsic liver injury versus secondary to extrahepatic injury from HLH to help determine whether liver transplantation is warranted. A case is reported of fatal HLH in an adult presenting prominently with acute liver failure, with the liver injury primarily due to severe systemic disease from HLH, as documented by liver biopsy and clinical evaluation, and liver transplantation refused on this basis.

2. **Furthermore, they report interesting study of small clinical series of 6 liver transplantation for HLH; but we do not have any details of indications of transplantation.**
Author's response: The details on this interesting study of a small series of liver transplantation is added to the discussion, as follows:

Page 12. CHANGED TO:

Liver transplantation has been offered to patients who present predominantly with ALF, from severe hepatic inflammation and necrosis, in association with potentially reversible HLH[1,2,3]. In a literature review of 7 individual case reports, only 2 (28%) of 7 patients undergoing liver transplantation for ALF with HLH survived $\geq$6 months[3,29] . In a small clinical series, 9 pediatric patients underwent liver transplantation for life-threatening ALF associated with secondary HLH[3]. These patients typically had extremely abnormal liver function tests: ALT=2512 $\pm$ 1158 U/L, (range: 1135-4113 U/L), AST=3165 $\pm$ 2276 U/L (range: 779-8789 U/L), conjugated bilirubin=257 $\pm$ 108 micromol/L (range: 141-448 micromol/L, normal 0-2 micromol/L), and INR=7.7 $\pm$ 1.7 units (range: 3.9->9 units). Liver biopsy in these patients

generally revealed severe-to-massive (25%-95%) hepatocyte necrosis, lymphocytic infiltrates, numerous macrophages, and intrahepatic erythrophagocytosis[3]. These patients had extremely frequent medical and surgical complications after transplantation, including: severe or opportunistic infections-6, acute liver rejection-5, recurrent HLH-5, bile duct strictures-3, post-transplant lymphoproliferative disease of liver-2, bowel obstruction-1, and wound dehiscence-1. Three patients died at 1.5, 8, and 14 months after liver transplantation. The other 6 pediatric patients were alive and well at a median of 24 months after liver transplantation[3].

In contradistinction, the currently reported patient had much less evident liver injury, but severe clinical manifestations of HLH. The current work may suggest that liver transplantation is not indicated for HLH when: 1)-ALF is not present or imminent (MELD score <20-22); 2)-the patient has a poor prognosis due to the combined effects of ALF and HLH; 3)-the liver injury by itself does not underlie this poor patient prognosis; or 4)-the HLH is advanced and highly likely irreversible. This case illustrates three of these factors that militated against liver transplantation, in the current case the ALF was most likely from septic shock with focal centrilobular ischemia from hypotension, bone marrow failure, and explosive immune activation from HLH.

Page 12. CHANGED FROM:

When patients present with imminent or confirmed liver failure from predominantly liver involvement from HLH, liver transplant may be indicated, and appears to prolong patient survival in the appropriate clinical setting. In such cases, the liver failure may be documented by a MELD score>24-26, and the liver failure should contribute significantly to the poor patient prognosis. However, the current case illustrates that patients may be poor candidates for liver transplantation from liver failure secondary to HLH, if the HLH is likely irreversible, or if the

patient has major comorbidities (systemic complications) from the HLH that are highly lethal. For example, the currently reported patient had highly lethal comorbidities of overwhelming sepsis, shock, and disseminated intravascular coagulopathy, that precluded liver transplantation despite having a MELD score of 33 that would normally qualify the patient for liver transplantation. This work illustrates that decisions on liver transplantation in patients with HLH depend upon the presence of imminent or present liver failure, the potential reversibility of the HLH, and the absence of severe complications associated with HLH that are most likely fatal. The patient with a high MELD score in the setting of HLH should be evaluated for liver transplantation before these highly lethal complications supervene.

3. **In my opinion, no suggestions for liver transplantation can be done according to available data. We can only suggest to have at least liver biopsy before to decide for liver transplantation all HLH cases.**

Author's response:

CONCLUSION OF ABSTRACT.
CHANGED TO:
CONCLUSION: This case report illustrates that liver transplantation may not be warranted when liver failure associated with HLH is primarily from multisystem failure from HLH. Liver biopsy may be very helpful in determining the severity and pathophysiology of the liver disease.

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Page 13. ADDED PARAGRAPH:

This prior clinical data suggest caution in liver transplantation for HLH. The data are limited. Reported outcomes for liver transplantation with HLH are much worse than that for

liver transplantation without HLH[3]. The current work suggests that high mortality from advanced and likely irreversible HLH may limit the benefits of liver transplantation. Liver biopsy may be very helpful to assess the liver injury and to determine whether acute liver failure associated with HLH is due primarily to intrinsic liver injury versus secondary to extrahepatic injury from HLH to help determine whether liver transplantation is warranted.

I thank this reviewer for his excellent and insightful criticisms. The authors are prepared to further revise the manuscript as requested by this reviewer.

Reviewer 00054048

No responses required for this manuscript World J Hepatol # 39591.

Reviewer 02860897

No responses.