

Response to Review

I think that the major problem of this analysis is the lack of liver status. Non-cirrhotic liver with HCC has a different prognosis from a liver cirrhosis and HCV-related cirrhosis has a different survival rates in comparison to other etiologies. this aspect should be more stressed in the discussion.

We acknowledge on page 13 that our lack of knowledge of patients' viral infections and cirrhosis is a limitation, and we have added the following discussions of HCC in the setting of a non-cirrhotic liver and HCV-related cirrhosis on page 12.

HCC in the setting of a non-cirrhotic liver (NCL) is rare and has different etiologic, genetic, and pathologic characteristics from cirrhotic HCC, including a lower prevalence of HBV, HCV, and alcohol abuse, a lower rate of p53 mutation, and more advanced tumor stage at diagnosis^[39]. Risk factors for the development of HCC in NCL include metabolic syndrome and non-alcoholic fatty liver disease, which may co-exist with viral hepatitis or alcohol abuse^[40]. Hepatic resection is generally the best treatment choice for HCC patients with NCL, leading to better overall and disease-free survival than those of cirrhotic patients; in fact, survival after resection among NCL patients with non-advanced tumors is comparable to that of cirrhotic patients with early tumors who receive liver transplantation^[39].

Compared to other etiologies, HCV-related HCC has been associated with poorer overall and recurrence-free survival after surgery^[41]. Among patients with cirrhosis, those with chronic HCV experienced lower survival at 1, 3, and 5 years after liver transplantation compared to those without HCV. An accelerated progression to cirrhosis in HCV patients post-transplant may be responsible for this phenomenon seen in an era when treatment with interferon-based therapies was minimally effective in this population^[42]. These outcomes will need to be revisited in the era of highly effective direct acting antiviral medications^[41].

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40. **Schütte K**, Schulz C, Poranzke J, Antweiler K, Bornschein J, Bretschneider T, Arend J, Ricke J, Malfertheiner P. Characterization and prognosis of patients with hepatocellular carcinoma (HCC) in the non-cirrhotic liver. *BMC Gastroenterol* 2014;**14**:117. [PMID: 24990270 DOI: 10.1186/1471-230X-14-117]
41. **Shindoh J**, Hashimoto M, Watanabe G. Surgical approach for hepatitis C virus-related hepatocellular carcinoma. *World J Hepatol* 2015;**7**:70-7. [PMID: 25624998 DOI: 10.4254/wjh.v7.i1.70]
42. **Bozorgzadeh A**, Orloff M, Abt P, Tsoulfas G, Younan D, Kashyap R, Jain A, Mantry P, Maliakkal B, Khorana A, Schwartz S. Survival outcomes in liver transplantation for hepatocellular carcinoma, comparing impact of hepatitis C versus other etiology of cirrhosis. *Liver Transpl* 2007;**13**:807-13. [PMID: 17539001 DOI: 10.1002/lt.21054]