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Title: Letter: hepatocellular carcinoma risk in patients with nonselective beta-blockers - authors' reply

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Editors,

We read the letter comments by Drs. Huang and Nguyen with great interest.[1] We agree that it would be interesting to compare or adjust for severity of liver cirrhosis such as MELD-Na score or Child-Pugh score between the non-selective beta-blockers (NSBBs) group versus no-NSBBs group in our study.[2] To address this constructive comment, we calculated the MELD-Na scores and compared them between the NSBBs group versus no-NSBBs.[3,4] Interestingly, we found the MELD-Na scores of all three NSBB groups (carvedilol, nadolol and propranolol) were significantly higher than no beta-blocker group (all p-values < 0.001) (Table 1). After employing the same propensity score matching (PSM) with ratio 2:1 in our original paper[2], MELD-Na scores in carvedilol group remained significantly higher, while the nadolol and propranolol groups showed no statistical difference with no beta-blocker (Table 1). The result confirmed that: 1) the NSBB groups had more advanced cirrhosis or severe hepatic dysfunction in the original cohort; 2) after adjusting for several confounding factors using PSM, MELD-Na scores in no beta-blocker group was still not higher than NSBB groups. Thus, we proved that the lower incidence of HCC was not attributable to the possible lower severity of cirrhosis in the NSBB groups. In addition, we did subgroup analysis in cirrhosis without complications to see whether there is a significant difference in the incidence of HCC between cirrhotic patients who took NSBBs versus no beta-blocker group given that both groups had similar severity of liver cirrhosis (no decompensated cirrhosis).[5] We found that cirrhotic patients who took NSBBs had significantly less incidence of HCC compared with no NSBB group.[5]

We agree that cirrhotic patients who are compliant with NSBB may be more compliant to anti-viral therapy, which may reduce HCC risk among those with viral hepatitis-related cirrhosis.[1] However, given that the HCC protective effect from NSBBs was also demonstrated in non-viral hepatitis-related cirrhosis, the compliance to anti-viral therapy might not be the only explanation for the decreased incidence of HCC in cirrhosis with NSBBs group. However, we acknowledge that there are some confounding factors that we could not control, such as health behaviors as discussed in the manuscript.[2]

Lastly, we entirely agree that NSBBs use can lead to substantial harm such as hypotension and acute kidney injury, and needs to be cautious before using it as discussed in the current guidance.[6] However, a recent article emphasized that NSBBs are safe if used in the appropriate setting, and future studies should focus on the role of NSBBs for the prevention of decompensated cirrhosis in compensated cirrhosis or mortality in decompensated cirrhosis.[7] The current finding supports the idea of considering early use of carvedilol and NSBBs in all cirrhosis, given the potential benefit of the HCC protective effect. However, we agree with Drs. Huang and Nguyen[1] that strong evidence is required when considering a therapy that is associated with a significant side effect profile. Future prospective large randomized controlled trials are warranted to validate the association of NSBBs use with the reduced risk of HCC.

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The authors' declarations of personal and financial interests are unchanged from those in the original article.[2]

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Table 1 Comparison of MELD-Na scores in the most recent encounter between NSBBs groups and no beta-blocker group

Kruskal-Wallis test (before propensity score matching with ratio 2:1[†])					
	Number of patients[‡]		(Mean ± std) of MELD-Na Score[§]		p-value
	No beta-blocker	**Beta-blocker**	**No beta-blocker**	**Beta-blocker**	
Carvedilol	7,111	594	18.1 ± 9.5	20.4 ± 8.0	< 0.001*
Nadolol	7,111	593	18.1 ± 9.5	21.2 ± 8.9	< 0.001*
Propranolol	7,111	611	18.1 ± 9.5	21.1 ± 8.6	< 0.001*
Kruskal-Wallis test (after propensity score matching with ratio 2:1)					
	Number of patients		(Mean ± std) of MELD-Na Score		p-value
	No beta-blocker	**Beta-blocker**	**No beta-blocker**	**Beta-blocker**	
Carvedilol	1,188	594	18.3 ± 8.6	20.4 ± 8.0	< 0.001*
Nadolol	1,186	593	20.7 ± 9.7	21.2 ± 8.9	0.129
Propranolol	1,222	611	20.7 ± 9.6	21.1 ± 8.6	0.145

[†]Propensity score matching (PSM): the matching factors included age, sex, complications (ascites, hepatic encephalopathy, hepatorenal syndrome, portal hypertension, SBP, and varices), risk factors (diabetes, NAFLD, viral hepatitis B, and viral hepatitis C), as well as comorbidities and comedications (essential hypertension, cerebrovascular diseases, heart disease, vitamin D deficiency, aspirin use, and statin use).

[‡]The qualified patients were the ones that had the four lab test results (i.e., serum total bilirubin, serum creatinine, INR and serum sodium) needed for the MELD-Na score calculation in their last encounter.

[§]MELD-Na score = MELD score + 1.32 × (137 - Na) - 0.033 × MELD score × (137 - Na), while MELD score = 9.57 × ln(creatinine) + 3.78 × ln(bilirubin) + 11.2 × ln(INR) + 6.43. Specifically, the serum sodium (i.e., Na) value was corrected for the range of 125-137 mmol/L, and for serum total bilirubin, serum creatinine, INR and serum sodium, if any value was less than 1, assigned a value of 1 to prevent a negative result in the natural logarithm calculation.

* $p<0.05$ is regarded as significance