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Letter: hepatocellular carcinoma risk in patients with non-selective beta blockers—authors' reply

Editors,

We read the letter by Drs. Huang and Nguyen with great interest.[1] We agree that it would be interesting to compare or adjust for severity of cirrhosis such as MELD-Na score or Child-Pugh score between the groups on and not on non-selective beta-blockers (NSBBs) in our study.[2] To address this, we have calculated the MELD-Na scores and compared them between groups.[3,4] MELD-Na scores of all three NSBB groups (i.e., carvedilol, nadolol and propranolol) were significantly higher than that of the no NSBB group (all *P*-values <0.001) (Table 1). After employing the same propensity score matching (PSM) with 2:1 ratio in our original paper,[2] MELD-Na scores in the carvedilol group remained significantly higher, while the nadolol and propranolol groups showed no significant difference with the no NSBB group (Table 1). The result confirmed that the NSBB groups had more advanced cirrhosis or severe hepatic dysfunction in the original cohort. After adjusting for several confounding factors using PSM, MELD-Na scores in the no NSBB group was still not higher than in the 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 performed subgroup analysis in cirrhosis without complications to see whether there was a significant difference in the incidence of HCC between cirrhotic patients who took NSBBs versus the no NSBB group since

TABLE 1 Comparison of MELD-Na scores in the most recent encounter between NSBBs groups and no NSBB group

Kruskal–Wallis test (before propensity score matching with ratio 2:1[†])					
	Number of patients[‡]		**(Mean ± std) of MELD-Na Score[§]**		
	No NSBB	**NSBB**	**No NSBB**	**NSBB**	***P*-value**
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**		
	No NSBB	**NSBB**	**No NSBB**	**NSBB**	***P*-value**
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 (ie, 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 (ie, 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.

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both groups had similar severity of cirrhosis (no decompensated cirrhosis).[5] Cirrhotic patients who took NSBBs had a significantly lower incidence of HCC than the no NSBB group.[5]

Cirrhotic patients who are compliant with NSBBs may be more compliant with 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 in the NSBBs group. However, there are some confounding factors that we could not control, such as health behaviours as discussed in the manuscript.[2]

We agree that use of NSBBs can lead to substantial harm such as hypotension and acute kidney injury; caution should be exercised before using NSBBs, as discussed in the current guidance.[6] However, a recent article emphasised that NSBBs are safe if used in the appropriate setting; future studies should focus on their role in the prevention of decompensation in patients with compensated cirrhosis, and death among patients with decompensated cirrhosis.[7] The current finding supports the early use of carvedilol and NSBBs in all patients with 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 large randomised controlled trials are warranted to validate the association of NSBBs use with the reduced risk of HCC.

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LINKED CONTENT

This article is linked to Wijarnpreecha et al and Huang & Nguyen papers. To view these articles, visit https://doi.org/10.1111/apt.16590 and https://doi.org/10.1111/apt.16576

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