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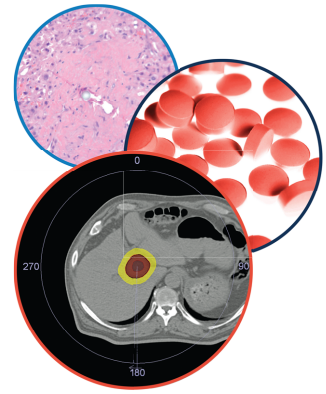

Hepatic Oncology

Impact of β-blockers on survival outcomes in patients with unresectable hepatocellular carcinoma

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Background: β-blockers (BBs) have shown promise in improving overall survival (OS) in patients with breast, ovarian, pancreatic and lung cancer. However, few studies have evaluated the impact of BBs on unresectable hepatocellular carcinoma (HCC). **Methods:** The authors compared clinical data and outcomes between unresectable HCC patients based on whether they were prescribed BBs. **Results:** There was significantly decreased disease progression in the BB group compared with the non-BB group (22.8 vs 28.0%; $p < 0.05$). No difference was seen in OS or progression-free survival between groups. Those specifically on selective BBs had improved OS (hazard ratio: 0.75; 95% CI: 0.61–0.94; $p = 0.01$) and progression-free survival (hazard ratio: 0.66; 95% CI: 0.45–0.96; $p = 0.03$) compared with non-BB patients. **Conclusion:** Although the authors' study did not demonstrate that BBs improve OS in HCC, it did show decreased disease progression among patients with HCC who were taking BBs compared with those who were not.

First draft submitted: 4 November 2021; Accepted for publication: 7 April 2022; Published online: 24 May 2022

Keywords: β-blockers • hepatocellular carcinoma • unresectable

ß-adrenergic receptors are commonly expressed in various cancer types, including hepatocellular carcinoma (HCC). In *in vitro* studies, β-blockers (BBs) have been shown to inhibit cancer cell proliferation, invasion and resistance to apoptosis through inhibition of ß-adrenergic receptors [1]. Clinically, BBs have shown promise in improving survival in patients with breast, ovarian, pancreatic and lung cancer. Propranolol is especially effective in liver cells; however, clinical data on the impact of BBs on HCC patients remain unclear [2].

HCC is a highly vascular malignancy. Common risk factors for HCC development include hepatitis B, hepatitis C, alcohol abuse and nonalcoholic steatohepatitis. Angiogenesis plays an important role in the development of HCC, with the VEGF and FGF pathways highlighted as major contributors. These pathways have been exploited in the treatment of HCC, with therapies, such as transarterial chemoembolization (TACE), bevacizumab and sorafenib, directly inhibiting these pathways. Patients with nonmetastatic disease can be treated with various modalities, including liver transplantation. Patients who are not candidates for these modalities invariably have progressive disease. Systemic therapies are largely limited by remaining liver function; patients with metastatic or refractory HCC have few options thereafter and ultimately succumb to their disease.

BBs are commonly prescribed in the United States. In patients with cirrhosis, they are primarily used for esophageal varices bleeding prophylaxis. *In vitro* studies have demonstrated that BBs are effective at suppressing VEGF and ultimately angiogenesis, likely through β-adrenergic receptor blockade [3]. However, the role of BBs in modifying HCC disease progression and its impact on survival remains unknown. In this study, the authors conducted a retrospective analysis in a single large tertiary liver transplantation center evaluating the effects of BBs

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on the outcomes of patients with unresectable HCC. The authors present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

Methods

Structure & patient population

The authors performed a retrospective chart review at the University of Florida Shands Hospital (FL, USA), a large tertiary medical center. The overall design and ethical structure of the study received approval from the institutional review board. The study included adult patients aged 18 years and older who carried an *International Classification of Diseases, Tenth Revision* HCC code (C22.0) between 2007 and 2017. Patients with resectable HCC, patients less than 18 years old and patients with incomplete records and records with a follow-up period of less than 24 months were excluded from the study. The entire dataset was stratified into two cohorts, BB users and non-BB users, based on the presence of an active BB prescription at the time of diagnosis.

Data collection

After initial screening, baseline patient characteristics, including age, sex and race, were collected. Past medical history, including hypertension, cardiovascular disease, diabetes mellitus and history of smoking and alcohol use, was also obtained. The authors collected the date of HCC diagnosis, size and stage of tumor upon initial diagnosis, treatment modality (TACE, ^{90}Y, systemic therapy) and date of cancer progression. The authors also collected relevant laboratory data at the time of HCC diagnosis, such as Model for End-Stage Liver Disease score, hepatic function panel, prothrombin time/international normalized ratio and platelet count. The etiology of cirrhosis and its complications, including hepatic encephalopathy, esophageal varices and spontaneous bacterial peritonitis, were also recorded. In addition, medication history and BB use at the time of HCC diagnosis were noted. Primary outcome variables included overall survival (OS) and disease progression. OS was defined as time to death, and disease progression was defined as radiological progression of HCC. Secondary variables collected included progression-free survival (PFS), which was defined as time to first disease progression, death or last follow-up.

Statistical analysis

Basic statistical comparisons were made between the non-BB and BB groups in terms of demographics, past medical history, labs at HCC diagnosis and other HCC-related data. Continuous variables were represented as mean ± standard deviation and compared using two-sample *t*-tests. Categorical variables were represented as frequency percentage and compared using chi-square and Fisher's exact tests. Proportional hazard models were fitted using all available data, and Kaplan–Meier survival curves were provided along with results of the log-rank test. PFS and OS were analyzed via Cox proportional hazard models and depicted with Kaplan–Meier survival curves. A $p < 0.05$ was deemed statistically significant. The data analysis for this article was generated using SAS software version 9.4 of the SAS System for PC (SAS Institute Inc., NC, USA).

Results

Baseline characteristics

The authors identified 1444 patients with unresectable HCC who were in the University of Florida Health system between 2007 and 2017 and had adequate records. Compared with 732 patients who did not have an active BB prescription at the time of diagnosis, a total of 712 patients had an active BB prescription at the time of diagnosis of HCC. A total of 85.2% of patients in the BB group had cirrhosis compared with 79.3% in the non-BB group. The most common cause of cirrhosis in the authors' patient population was hepatitis C (49.6%) followed by unknown etiology (16.9%), alcohol abuse (9.9%), multifactorial etiology (7.8%), other cause (5.7%), cryptogenic etiology (4.6%), nonalcoholic steatohepatitis (4.4%), autoimmune etiology (0.6%) and alpha-1 antitrypsin deficiency (0.5%).

Among those on BBs, the specific BB medications used by the BB group included metoprolol (31.4%), nadolol (25.0%), propranolol (18.7%), atenolol (9.2%), carvedilol (8.9%), labetalol (5.5%) and sotalol (1.2%). Common indications for BB use included esophageal varices prophylaxis (38.5%), hypertension (23.7%), heart failure or coronary artery disease (15.5%), atrial fibrillation (4.3%) and unknown indication (18.0%).

Table 1. Baseline demographics of patients with hepatocellular carcinoma in the β-blocker versus non-β-blocker group.

Variable	BB	Non-BB	p-value
Age at diagnosis, mean ± SD	63.4 ± 10.2	61.9 ± 10.8	0.008
Sex, n (%)			0.52
Male	543 (77.68)	544 (76.08)	
Female	156 (22.32)	171 (23.92)	
Race, n (%)			0.86
American–Indian/Alaska Native	0 (0.00)	1 (0.14)	
Asian	18 (2.61)	24 (3.42)	
Native Hawaiian/Other Pacific Islander	1 (0.14)	2 (0.29)	
Black or African–American	61 (8.84)	68 (9.70)	
White	545 (78.99)	540 (77.03)	
Hispanic/Latino	38 (5.51)	35 (4.99)	
Unknown/NR	27 (3.91)	31 (4.42)	
Smoking, n (%)			0.0001
Never	166 (24.20)	196 (27.64)	
Active	140 (20.41)	200 (28.21)	
Quit	380 (55.39)	313 (44.15)	
Type 2 diabetes mellitus, n (%)	291 (41.28)	184 (25.31)	< 0.0001
Metformin use, n (%)	110 (38.87)	69 (38.98)	1
Coronary artery disease, n (%)	199 (28.23)	90 (12.35)	< 0.0001
Hypertension, n (%)	447 (63.31)	317 (43.60)	< 0.0001
Cirrhosis, n (%)	606 (85.23)	578 (79.29)	0.004
Ascites, n (%)	341 (47.89)	289 (39.48)	0.002
Hepatic encephalopathy, n (%)	205 (28.79)	140 (19.13)	< 0.0001
Spontaneous bacterial peritonitis, n (%)	29 (4.07)	21 (2.87)	0.27
Esophageal varices, n (%)	338 (47.47)	161 (21.99)	< 0.0001
Hepatorenal syndrome, n (%)	25 (3.51)	12 (1.64)	0.04
Child–Pugh score, n (%)			0.001
A	346 (57.1)	250 (46.2)	
B	181 (29.9)	199 (36.8)	
C	79 (13.0)	92 (17.0)	

Continuous variables were compared via two-sample *t*-test and are presented as mean ± SD. Categorical variables were compared via chi-square test and are presented as frequency percentage. A $p < 0.05$ is considered statistically significant.
BB: β-blocker; NR: Not reported; SD: Standard deviation.

Group comparison

Patients who took BBs tended to be older at diagnosis and were more likely to have a history of cirrhosis, hepatic encephalopathy and esophageal varices ($p < 0.01$) (Table 1). Specifically, 47.5% of patients in the BB group had esophageal varices compared with 22.0% of patients in the non-BB group ($p < 0.0001$). BB users were also more likely to have diabetes mellitus, coronary artery disease and hypertension ($p < 0.01$). Mean follow-up duration was 33.5 months for the BB group and 30.3 months for the non-BB group ($p = 0.09$).

At the time of HCC diagnosis, patients who had been prescribed BBs were observed to have lower aspartate aminotransferase values ($p < 0.05$) and lower platelet counts ($p < 0.001$) than patients not taking BBs. Differences in alanine aminotransferase, BMI, albumin, prothrombin time and international normalized ratio were not statistically significant. Average Model for End-Stage Liver Disease score was 11.4 for the non-BB group and 11.7 for the BB group ($p = 0.35$). Largest tumor diameter at presentation averaged 5.65 cm in the BB group and 4.59 cm in the non-BB group ($p = 0.34$). Approximately 15.8% of patients in the BB group and 19.2% of patients in the non-BB group had distant metastatic disease at presentation ($p = 0.11$).

Disease progression

At a median follow-up period of 31.7 months, 22.8% of patients in the BB group were observed to have disease progression at some point during treatment compared with 28.0% of patients in the non-BB group ($p < 0.05$)

Table 2. Laboratory findings at hepatocellular carcinoma diagnosis in the β-blocker versus non-β-blocker group.

Variable, mean ± SD	BB	Non-BB	p-value
BMI	28.4 ± 5.9	29.6 ± 45.1	0.58
Albumin	3.5 ± 0.7	3.5 ± 0.7	0.30
PT	15.6 ± 8.1	14.9 ± 3.9	0.09
INR	1.3 ± 0.7	1.3 ± 0.4	0.26
AST	98.9 ± 107.6	112.8 ± 141.5	0.04
ALT	74.4 ± 90.7	82.6 ± 91.7	0.1
Platelets	142.3 ± 90.1	164.02 ± 107.3	0.0001
AFP	4618.8 ± 14,522.9	3619.6 ± 23,496.9	0.37
Largest tumor diameter, cm	5.65 ± 4.16	4.59 ± 4.05	0.34

Continuous variables were compared via two-sample *t*-test. A $p < 0.05$ is considered statistically significant.
AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BB: β-blocker; INR: International normalized ratio; PT: Prothrombin time; SD: Standard deviation.

Table 3. Hepatocellular carcinoma outcomes and treatment modalities in the β-blocker versus non-β-blocker group.

Variable, n (%)	BB	Non-BB	p-value
Disease progression	150 (22.80)	184 (28.01)	0.04
Systemic therapy	154 (22.42)	159 (22.65)	0.97
Distant metastasis	111 (15.81)	138 (19.22)	0.11
TACE	350 (51.17)	297 (42.25)	0.001
^{90}Y	144 (20.78)	134 (19.65)	0.65

Categorical variables were compared via chi-square test. A $p < 0.05$ is considered statistically significant.
BB: β-blocker; TACE: Transarterial chemoembolization.

(Table 3). There was no statistically significant difference in initial tumor size, systemic therapy, local therapy or stage of HCC between the two groups (Tables 2 & 3). A similar percentage of patients in each group were on systemic therapy, with 22.4% (154) in the BB group and 22.6% (159) in the non-BB group. The vast majority of patients (296 [93.6%]) who received systemic therapy received sorafenib, whereas two patients received lenvatinib, three received capecitabine, one received nivolumab, four received fluorouracil, two received doxorubicin and five received thalidomide. However, patients who took BBs were more likely to receive TACE ($p < 0.01$).

Overall & progression-free survival

There was no statistically significant difference in OS ($p = 0.25$) or PFS ($p = 0.09$) between patients who took BBs and those who did not (Figures 1 & 2). However, upon further subgroup analysis, the authors found that patients who were on selective BBs had improved OS (hazard ratio [HR]: 0.75; 95% CI: 0.61–0.94; $p = 0.01$) and PFS (HR: 0.66; 95% CI: 0.45–0.96; $p = 0.03$) compared with patients who were not on BBs. This survival benefit was not seen when comparing OS (HR: 1.05; 95% CI: 0.94–1.32; $p = 0.68$) and PFS (HR: 1.17; 95% CI: 0.76–1.78; $p = 0.48$) between the nonselective BB group and the group not taking BBs (Figures 3 & 4). Survival analysis was overall adjusted for age, sex, race, cirrhosis, pertinent laboratory values, initial tumor size, disease progression, presence of metastasis, TACE, ^{90}Y, comorbidities and cirrhosis complications (Table 4).

Additional survival analysis indicated that older age, higher aspartate aminotransferase level, presence of cirrhosis, disease progression and metastasis were associated with decreased OS. Higher albumin, increased alanine aminotransferase level and use of TACE were associated with improved OS. Moreover, Asian patients with HCC had improved OS compared with White patients, and African–American patients with HCC had decreased PFS compared with White patients (Table 4).

Discussion

Although BBs have long been known for their cardiovascular and airway effects, their effects on cancer have only recently come into focus [4]. Because carcinogenesis is recognized to be mediated in part by the cellular stress response, BBs are proposed to have a protective effect against carcinogenesis and cancer progression by limiting the impact of catecholamines [5]. Epinephrine and norepinephrine activate α- and β-cellular receptors that ultimately promote cellular survival, proliferation and motility [6].

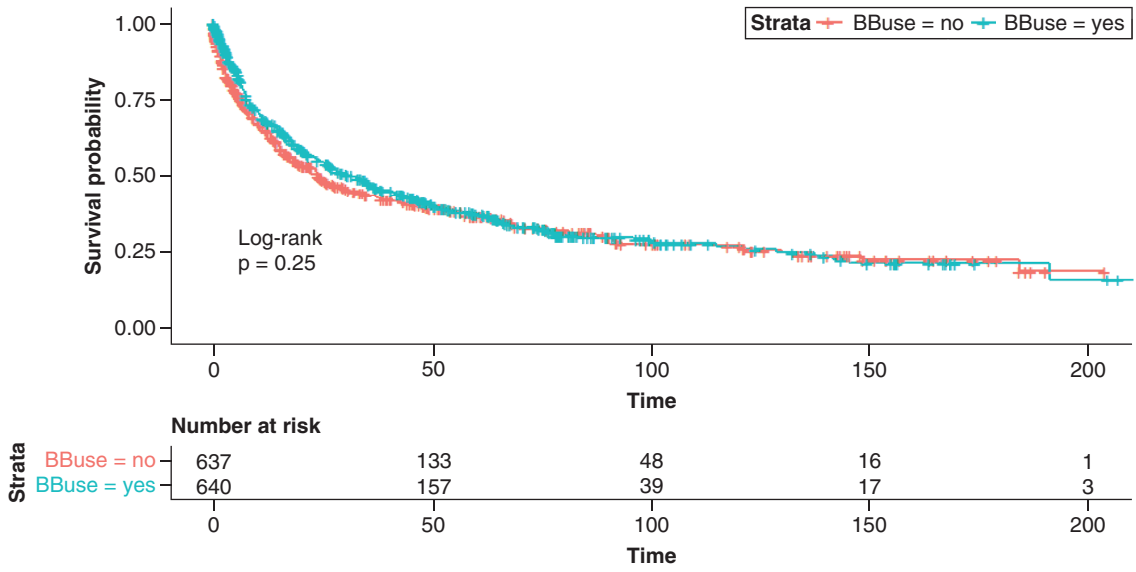

Figure 1. Kaplan–Meier curve comparing overall survival between patients in the β-blocker versus non-β-blocker group.
BB: β-blocker.

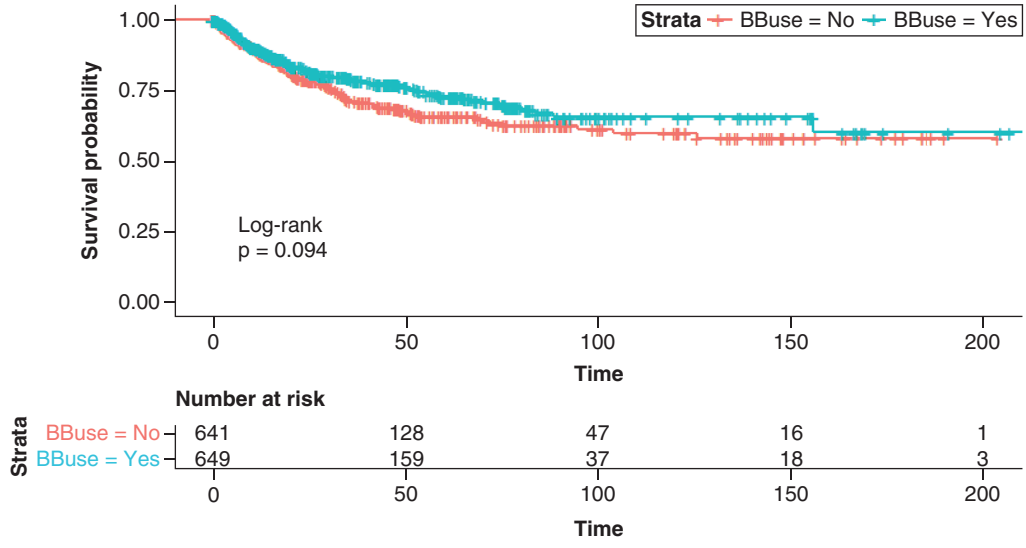

Figure 2. Kaplan–Meier curve comparing progression-free survival between patients in the β-blocker versus non-β-blocker group.
BB: β-blocker.

In vitro animal studies have demonstrated the importance of catecholamines for tumor angiogenesis and invasiveness [7]. Activation of β-2 receptors on human hepatocytes has been shown to stimulate cellular division [8]. In a 2018 study of human liver cells, Wang *et al.* demonstrated that β-adrenergic receptor expression was higher in malignant hepatocytes and that propranolol selectively inhibited cancer cells [9]. Chen *et al.* showed that the degree to which β-2 receptors are upregulated on cancer cells can be used as a marker of poor prognosis in HCC [10].

Although promising clinical data have emerged regarding the potential role of BBs in breast and pancreatic cancer, research on the role of BBs in the treatment of HCC is sparse [11,12,13]. Recent studies have focused more on the role of BBs in preventing HCC in cirrhotic patients, with both prospective and retrospective data showing overall decreased incidence of HCC in those taking BBs [14,15,16]. However, data are lacking on the role of BBs in

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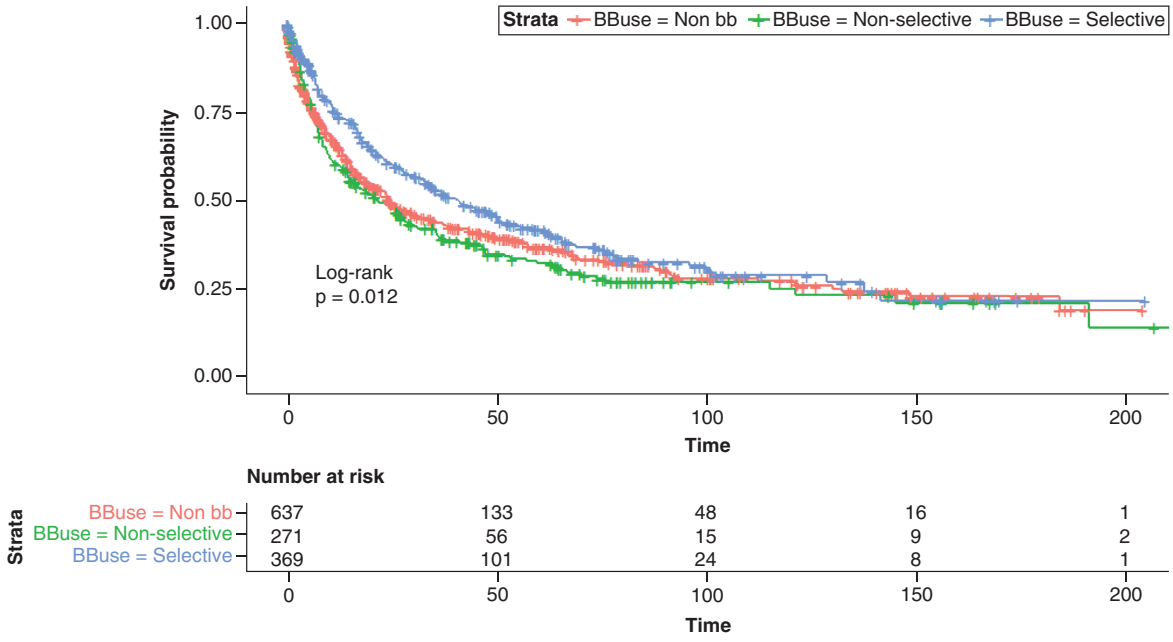

Figure 3. Subgroup analysis comparing overall survival between patients on selective β-blockers versus nonselective β-blockers versus no β-blockers.
BB: β-blocker.

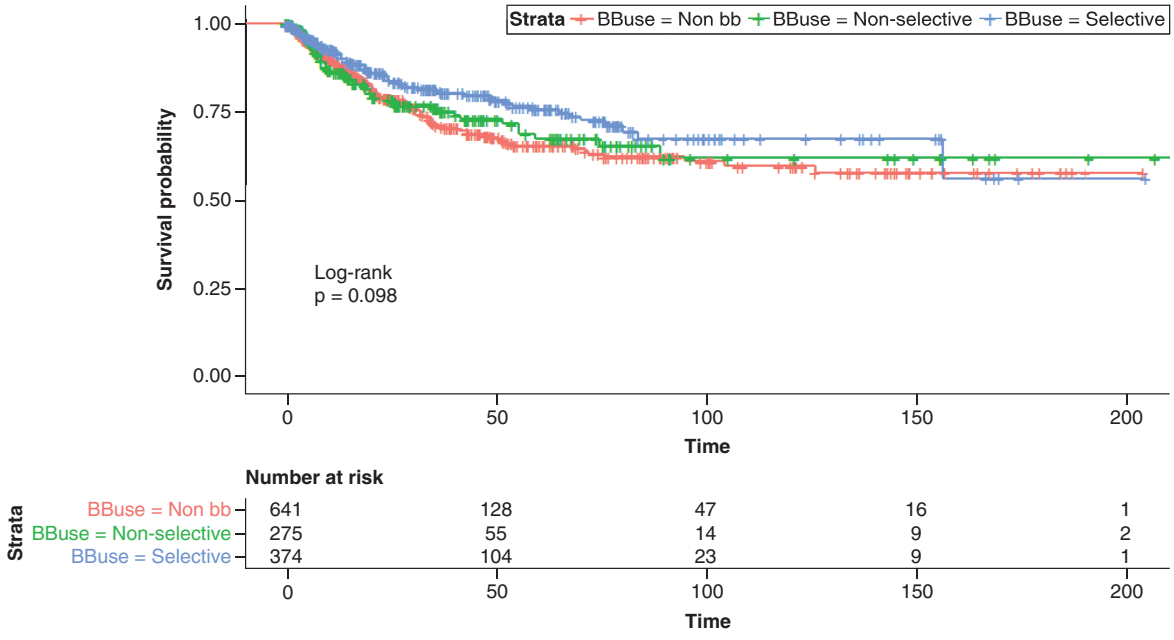

Figure 4. Subgroup analysis comparing progression-free survival between patients on selective β-blockers versus nonselective β-blockers versus no β-blockers.
BB: β-blocker.

the prevention of HCC in noncirrhotic patients, with Cheng *et al.* showing no impact on the incidence of HCC in those with chronic hepatitis B but without cirrhosis [17].

Data remain limited on the role of BBs in those with HCC. However, three large studies have aimed to characterize the association between BB use and mortality in patients diagnosed with HCC. In a 2015 meta-analysis that included a total of 2618 cirrhotic patients with randomized nonselective BB use, Thiele *et al.* found a

Table 4. Cox proportional hazard model demonstrating overall survival in months to death.

Variable	HR ± SD	p-value
BB usage	0.95 ± 0.17	0.52
Male	1.10 ± 0.24	0.36
Race		
American–Indian/Alaska Native	1.64 ± 10.18	0.63
Asian	0.40 ± 0.37	0.007
Native Hawaiian/Other Pacific Islander	0.50 ± 3.08	0.49
Black or African–American	0.99 ± 0.32	0.96
Hispanic/Latino	0.80 ± 0.37	0.25
Unknown/NR	1.15 ± 0.52	0.47
Cirrhosis	1.36 ± 0.43	0.03
Disease progression	2.37 ± 0.54	<0.0001
Metastasis	1.52 ± 0.38	<0.0001
TACE	0.58 ± 0.10	<0.0001
Albumin	0.60 ± 0.08	<0.0001
AST	1.00 ± 0.0012	<0.0001
ALT	0.99 ± 0.0016	<0.0001

Each race was compared relative to the White race. A $p < 0.05$ is considered statistically significant.
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BB: β-blocker; HR: Hazard ratio; NR: Not reported; SD: Standard deviation; TACE: Transarterial chemoembolization.

lower incidence of HCC among those taking BBs but did not find a difference in HCC-associated mortality [18]. In a 2019 retrospective population study in Taiwan involving over 4000 patients with unresectable metastatic HCC, those taking propranolol had a 22% lower mortality risk (HR: 0.78; 95% CI: 0.72–0.84; $p < 0.0001$) [19]. However, no statistically significant association was found for patients with resectable HCC. In addition, in a 2020 Swedish national population-based cohort study of over 2000 patients, Udumyan *et al.* found a statistically significant inverse association between BB use at time of diagnosis and overall HCC mortality [20]. The strength of the inverse association between BB use and mortality was more pronounced for nonselective BBs.

Although the authors' study did not demonstrate that BBs improved OS in HCC, it did show decreased disease progression among HCC patients taking BBs compared with those not taking BBs. Similarly, other studies have found associations between BBs and a lower incidence of HCC and mortality risk; however, to date, no studies have identified improved OS. Interestingly, after adjusting for comorbidities and tumor size and stage, the authors found in subgroup analysis that patients who were taking selective BBs had improved PFS and OS compared with those who were not on BBs. However, no difference in OS was observed in patients on nonselective BBs compared with those on no BBs. No prior study has compared the roles of selective versus nonselective BBs in survival outcomes in HCC, and future research is warranted to explain this finding.

One important aspect to note is that the group who received BBs had significantly more medical comorbidities, such as coronary artery disease, hypertension, diabetes, cirrhosis, esophageal varices and other complications of cirrhosis. It is interesting that although the authors expected patients with more medical comorbidities (in the BB group) to have worse outcomes, they in fact had less disease progression. The authors suspect that the driving factor behind selective BBs showing improved survival is their cardioprotective effect. Hence, although the authors may expect fewer deaths from cardiac complications, we cannot definitively say that selective BBs reduce death from HCC complications. Furthermore, the authors identified the effects of race on PFS and OS, with Asian patients with HCC having improved OS and African–American patients having worse PFS compared with White patients. Similar findings have been identified in prior studies [9, 21].

The authors' study adds to the current body of literature investigating the role of BBs in OS and disease progression in HCC. To date, the authors' project is the largest retrospective study based in the United States to assess the role of both selective and nonselective BBs in strictly unresectable HCC. The role of BBs in decreasing disease progression in these patients is a novel finding. Furthermore, the authors' study sheds light on the mortality benefits of selective BBs in unresectable HCC patients. Although the authors' study did not show a significant impact of BBs on OS, the results help reiterate that further studies are needed to better identify specific features among those with unresectable HCC who may clinically benefit from BBs.

One strength of the authors' study is the large sample size of 1444 patients treated at the same institution. The authors' study is overall limited in its retrospective approach and single-center design. Because of the retrospective nature of the study, a further limitation is that patients who received BBs did not match the non-BB group with regard to medical comorbidities, and more patients on BBs received TACE, which has been shown to improve OS in HCC. However, to counteract the effects of TACE, the authors adjusted for potential confounders such as treatment modality, race, medical comorbidities and laboratory tests at diagnosis when performing the Kaplan–Meier survival analyses. Despite using measures to control for these potential confounders, the authors' results are still limited by the impact these modalities may have had on disease progression, OS and PFS. In addition, because of the limitations of chart documentation, duration of treatment was not known or collected.

Conclusion

The role of BBs in overall outcomes in unresectable HCC remains under investigation. We present the largest United States-based study focusing on strictly unresectable HCC and the role of BBs in disease progression, OS and PFS. Our results indicate that BBs may be associated with a decrease in disease progression; however, no significant impact on OS or PFS was seen. Survival analysis did demonstrate a role of selective BBs in improved OS; however, further studies across multiple centers are needed to further add to our findings.

Future perspective

The impact of BBs on the prevention and treatment of cancer will likely be elucidated in the next 5–10 years. We suspect that there will be a role for β-blockade as adjunct treatment or prevention for at least some malignancies.

Summary points

- β-blockers (BBs) have been proposed to inhibit the growth of highly vascular malignancies such as hepatocellular carcinoma (HCC) through the inhibition of angiogenesis pathways; however, to date, studies have not defined their impact on survival outcomes in HCC.
- Although the authors' study did not identify a significant difference in overall survival among patients on BBs, this cohort was observed to have decreased HCC disease progression.
- Upon subgroup analysis, the authors noted improved overall and progression-free survival in patients on selective BBs.
- It is important to note that patients taking BBs have more medical comorbidities, such as heart failure, diabetes and cirrhosis, that increase their risk of mortality at baseline.
- In the setting of worse prognosis, decreased disease progression and lack of difference in overall survival among patients taking BBs may suggest protective mechanisms of BBs in HCC.

Author contributions

K Pan conceived the idea for the project and assisted with chart review and was principally in charge of writing the manuscript. E Altshuler and M Aryan assisted with writing the manuscript and performing chart review. G Kallumkal, J Wilson, E De Leo, A Ouni and W Hanayneh assisted with chart review and idea conception. H Gao assisted with statistical analysis.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all investigations.

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