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ORIGINAL ARTICLE

Beta-adrenergic receptor blockers and liver cancer mortality in a national cohort of hepatocellular carcinoma patients

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ABSTRACT

Background: β-adrenergic signaling has been implicated in the pathology of hepatocellular carcinoma (HCC), but the evidence from clinical studies is limited. In this national population-based cohort study, we investigated the possible association of β-adrenergic receptor blockers and cancer-specific mortality among patients with primary HCC diagnosed in Sweden between 2006 and 2014.

Methods: Patients were identified from the Swedish Cancer Register ($n = 2104$) and followed until 31 December 2015. We used Cox regression to evaluate the association of β-blockers dispensed within 90 days prior to cancer diagnosis, ascertained from the national Prescribed Drug Register, with liver cancer mortality identified from the Cause of Death Register, while controlling for socio-demographic factors, tumor characteristics, comorbidity, other medications and treatment procedures.

Results: Over a median follow-up of 9.9 months, 1601 patients died (of whom 1309 from liver cancer). Compared with non-use, β-blocker use at cancer diagnosis [$n = 714$ (predominantly prevalent use, 93%)] was associated with lower liver cancer mortality [0.82 (0.72–0.94); $p = .005$]. Statistically significant associations were observed for non-selective [0.71 (0.55–0.91); $p = .006$], β1-receptor selective [0.86 [0.75–1.00); $p = .049$] and lipophilic [0.78 (0.67–0.90); $p = .001$] β-blockers. No association was observed for hydrophilic β-blockers [1.01 (0.80–1.28); $p = .906$] or other antihypertensive medications. Further analysis suggested that the observed lower liver cancer mortality rate was limited to patients with localized disease at diagnosis [0.82 (0.67–1.01); $p = .062$].

Conclusion: β-blocker use was associated with lower liver cancer mortality rate in this national cohort of patients with HCC. A higher-magnitude inverse association was observed in relation to non-selective β-blocker use.

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Introduction

Liver cancer is one of the leading causes of cancer-related mortality worldwide [1]. Despite improving survival trends [2], the prognosis of liver cancer is poor with worldwide 5-year net survival estimates ranging from 5 to 30% [2].

A growing body of evidence suggests a role of β-adrenergic signaling in tumor biology, and links β-adrenergic-receptor blockers with reduced cancer progression, especially in early-stage disease [3], via inhibition of various cancer-related cellular and molecular processes involved in sympathetic nervous system (SNS) activation [4]. However, associations with mortality vary by tumor site [5,6] and subtype [7,8].

The predominant adrenoreceptors expressed in the human liver are of the α1- and β2-subtypes [9,10]. β2-adrenoreceptors have been shown to mediate noradrenaline/adrenaline-induced cell invasion and anoikis inhibition in hepatocellular carcinoma (HCC) [11], the most common type of primary liver cancer, and β2-adrenergic receptor signaling has been linked to sustained HCC cell proliferation and survival [12]. A higher density of β2-adrenoreceptors has further been detected in HCC tissue than in the nonadjacent non-tumor liver tissue [13,14]. The β2-adrenoreceptor upregulation has in turn been associated with clinico-pathological factors including large tumor size, vascular invasion, poor differentiation, and poor prognosis [15]. Further, the most frequently investigated β-blocker, propranolol, has been shown to inhibit proliferation, promote apoptosis, induce S-phase arrest [16], and reduce invasion and migration [17] in liver cancer cells. A meta-analysis of randomized trials on non-selective β-blockers for prevention of variceal bleeding in patients with liver cirrhosis has linked non-selective

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β-blockers with reduced risk of HCC but not HCC mortality [18]. However, the meta-analysis was limited by a small number of patients and events, mainly because the majority of eligible trials did not register HCC incidence or HCC mortality [18]. The evidence from studies designed to study the association of β-blocker use with liver cancer survival is still scarce. In a small ($n = 36$) retrospective study of adults with non-metastatic HCC, β-blocker use has been associated with improved overall survival [19]. In a population-based study using the National Health Insurance Research Database of Taiwan, propranolol was associated with improved overall survival in unresectable/metastatic HCC [20].

In this large population-based cohort of patients with primary HCC, we therefore tested the hypothesis that β-blocker use at cancer diagnosis may reduce liver cancer mortality rate.

Patients and methods

Study population and data sources

We used prospectively collected data available through national Swedish registers to conduct this retrospective cohort study. The unique personal identification number assigned to all Swedish residents was used to perform individual record linkage.

From the Swedish Cancer Register [21], we identified patients (aged 18 years or older) diagnosed with first primary liver cancer between 1 January 2006, and 31 December 2014, using the International Classification of Diseases (ICD) 7th revision code 155.0, and obtained information on tumor stage and histology, year of diagnosis, and age at diagnosis.

Prescriptions of β-blockers, as well as other relevant medications dispensed during the 90-day period before liver cancer diagnosis were identified from the Prescribed Drug Register [22] using the Anatomic Therapeutic Chemical (ATC) classification system. The number of distinct medication classes (medications with the same initial five characters of the ATC classification) was used to derive a medication-based comorbidity score to account for overall disease burden [23,24]. Post-diagnostic collection of a prescription for sorafenib, a kinase inhibitor used in advanced-stage liver cancer, was also identified.

The Patient Register [25] provided data on specific comorbidity, liver resection, liver transplantation and loco-regional therapies such as ablation and transarterial chemoembolization (TACE) (Supplementary Table S1). The Total Population Register provided migration data, while the LISA (Swedish acronym for Longitudinal Database of Education, Income and Occupation) [26] was used to ascertain the level of attained education, marital status and region of residence. The Cause of Death Register [27] provided information on the underlying cause of death.

We excluded patients with liver cancer other than HCC identified through the ICD-O-3 morphological code 81703 (Supplementary Figure S1).

β-Blocker exposure assessment

Patients were classified as exposed at the time of cancer diagnosis if they had collected β-blockers from the pharmacy any time during the 90 days preceding their cancer diagnosis, as prescriptions normally cover a period of 30 to 90 days (maximum 1 year) in Sweden. β-blocker exposure was further defined by receptor selectivity [nonselective (ATC codes: C07AA and C07AG), selective (C07AB and C07FB02)], and solubility (lipophilic, hydrophilic). Patients using both selective and non-selective β-blockers were placed in the non-selective subgroup, while users of both lipophilic and hydrophilic types were included in the lipophilic subgroup. Where possible, associations with individual β-blockers were investigated.

β-blocker use was also classified as incident or prevalent in a sensitivity analysis performed in 1965 patients diagnosed on or after 1 October 2006, where use was defined as incident if patients collected their β-blockers from the pharmacy within 90 days before cancer diagnosis date, but had no recorded collection in the previous year.

Outcome assessment

Cancer-specific mortality (CSM) was identified from the Causes of Death Register using ICD-10 code C22 capturing cancer of the liver including intrahepatic cholangiocarcinoma. Patients were followed from the date of cancer diagnosis until date of emigration, death, or 31 December 2015, whichever came first.

Statistical analysis

Patient characteristics were tabulated by β-blocker use and compared using the χ^2, ANOVA or median tests as appropriate. The observed 6-month, 1-year, and 5-year overall survival proportions were estimated using the actuarial method. Flexible parametric survival analysis (baseline hazards were modeled using splines with five degrees of freedom) [28] was applied to estimate age-adjusted median survival and liver cancer survival curves by β-blocker use. The multivariable fractional polynomials method [29] assessed the functional form of continuous variables in the log-hazard function. Cox regression models with time since diagnosis in months as the underlying time scale were fitted to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the β-blocker-CSM association. Test and plots of Schoenfeld residuals evaluated the proportional hazards assumption, which was satisfied for β-blockers.

Multivariable Cox regression models included age at cancer diagnosis, the medication-based comorbidity score, and year of diagnosis modeled as linear measures; sex; attained education [categories by duration: compulsory (up to 9 years), secondary (10–12 years), and postsecondary (more than 12 years); marital status [categories: unmarried, married/cohabiting, divorced/separated, or widowed]; region of residence; tumor–node–metastasis (TNM) stage [classified into stages 1–4B (Supplementary Table S2)]; specific comorbid diseases at liver cancer diagnosis [portal vein thrombosis, diabetes, gastro-esophageal varices with and without bleeding, viral hepatitis C and other types, diseases of liver under ICD-10: K70-K77 capturing fibrosis/cirrhosis of the liver and

other conditions] and specific medications [loop diuretics, other antihypertensive medications, NSAIDs, aspirin and statins]. To identify presence of liver decompensation not identifiable through ICD codes in the data, we included use of spironolactone and lactulose as indicators of cirrhotic ascites and hepatic encephalopathy, respectively. A further adjusted model (referred to as fully adjusted) included some other indicators of liver function such as alcohol abuse-related morbidity at diagnosis (more relevant in the Nordic countries [30], as well as ablation, TACE, liver resection, liver transplantation and sorafenib use. Ablation, TACE, liver resection, liver transplantation, sorafenib use as well as portal vein thrombosis were modeled as time-varying covariates in the fully adjusted model using time dependent Cox regression. Multiplicative interaction terms were added to the fully adjusted model to test whether associations differ by sex. In a sensitivity analysis, we further adjusted for cardiovascular diseases. Besides analyses in all HCC patients, analyses stratified by known distant metastases at diagnosis (M stage at diagnosis recorded as M0 or M1) were conducted.

Since patients with cirrhosis who have developed hepatorenal syndrome have been recommended to discontinue or avoid β-blocker use [31], we performed a sensitivity analysis where patients with likely hepatorenal morbidity [identified through ICD codes for moderate-to-severe renal disease and diseases under ICD-10 K76 code, which captures hepatorenal syndrome (K76.7)] were excluded. As it has been suggested that non-selective β-blockers may be associated with reduced survival in patients with hepatic decompensation/refractory ascites [31], we performed an exploratory analysis among patients likely to have decompensated liver disease. This subgroup of patients was identified based on diagnoses of hepatic failure (ICD-10: K72) or bleeding varices, or dispensed prescriptions of lactulose or spironolactone. In another sensitivity analysis among 1479 patients diagnosed on or after 1 July 2006, we compared with non-use the use of selective β-blockers and other antihypertensive medications dispensed for no other indication but hypertension (as specified in the Prescribed Drug Register). Prior prescriptions dispensed during 1 year before cancer diagnosis also had to be for no other indication but hypertension.

All analyses were performed using Stata version 14/SE for Windows (StataCorp) software. The study was approved by an ethical review board in Uppsala (DNR: 2012-361).

Results

Study population and overall survival estimates

The analytic cohort included 2104 patients with primary HCC. The median age at diagnosis was 68 years (range: 30–94 years). The cancer diagnosis was based on histopathology (73.4%); X-ray, scintigraphy, ultrasound, magnetic resonance imaging, computed tomography, or equivalent (3.0%); cytology (6.3%); or other laboratory tests (17.2%). About half (51.4%) of the patients had no known distant metastases at diagnosis. Patients with pre-existing liver morbidity ($n = 984$) were more likely to be diagnosed at early stages.

Over a total observation period of about 3316 person-years, 1601 (76.1%) patients died, another 7 (0.3%) emigrated, and 496 (23.6%) were followed to the end of the study. The causes of death were liver cancer ($n = 1309$), other tumors ($n = 84$), cardiovascular disease ($n = 55$), or other causes ($n = 153$) including chronic viral hepatitis ($n = 38$) and diseases of liver ($n = 46$)]. The median survival was 9.9 months.

The estimated 6-month, 1-year, and 5-year overall survival proportions were 59, 46, and 19%, respectively. The corresponding estimates were 59, 45, 19% for non-users; 55, 42, 13% for selective β-blocker users and 74, 62, 35% for non-selective β-blocker users.

β-Blocker use

Overall, 714 (34%) patients used β-blockers at the time of liver cancer diagnosis. Most commonly prescribed β-blockers belonged to the β1-cardio-selective type (68.1%), consisting predominantly of lipophilic metoprolol, while non-selective β-blockers comprised 33.9% and consisted mainly of lipophilic propranolol (Supplementary Table S3). Only 15 (2.1%) users received agents belonging to different β-blocker classes (for example, both selective and non-selective). β-Blockers with partial agonist activity were very rare.

The majority (about 93% of users) had received β-blockers also before the 90-day exposure window used by the study. Only a few (38 users of non-selective and 24 users of selective types) met the incident user definition for a sensitivity analysis performed in patients diagnosed on or after 1 October 2006.

In general, β-blocker users were more likely to be married/cohabiting and had a higher comorbidity score. Compared with users of selective β-blockers or non-users, users of non-selective types tended to be younger and more likely to be diagnosed with portal vein thrombosis, gastroesophageal varices, viral hepatitis, and various liver diseases [particularly, alcoholic liver disease (ICD-10: K70), hepatic failure (K72), fibrosis/cirrhosis of liver (K74), and other diseases of liver (K76)] as well as to be diagnosed at early stages of cancer (Table 1). Medications associated with cirrhotic ascites and hepatic encephalopathy were also more common among non-selective β-blocker users. Users of selective β-blockers had fewer years of education and were more likely to be diagnosed with diabetes, moderate-to-severe renal disease and cardiovascular diseases other than varices and portal vein thrombosis (for example, coronary artery disease, chronic heart failure and cerebrovascular disease). Other antihypertensive medications were also more common among users of selective β-blockers.

β-Blocker use and liver cancer specific mortality

The CSM rates (per 100 person-months) were lower among β-blocker users than non-users [2.85 (2.59–3.14) and 3.54 (3.32–3.78), respectively] with a corresponding statistically significant HR of 0.85 (0.76–0.96; $p = .007$). Further analysis suggested that the lower CSM rates among users were

Table 1. Baseline characteristics of patients diagnosed with primary hepatocellular carcinoma in Sweden in 2006 to 2014 by β-blocker use at cancer diagnosis.

	Non-selective β–blocker ($N = 242$)		Selective β–blocker ($N = 472$)		No β–blocker ($N = 1390$)		
	N	Col%	*N*	Col %	*N*	Col%	*p*[a]
Age at diagnosis, years (mean, SD)	63.3	9.2	72.3	8.8	66.6	11.4	<.001[b]
Male	197	81.4	346	73.3	1041	74.9	.050
Attained education							.023
Compulsory	91	37.6	233	49.4	619	44.5	
Secondary	120	49.6	178	37.7	570	41.0	
Post-secondary	31	12.8	61	12.9	201	14.5	
Marital status at diagnosis							<.001
Unmarried	39	16.1	54	11.4	244	17.6	
Married/cohabiting	125	51.7	253	53.6	655	47.1	
Divorced/separated	61	25.2	83	17.6	337	24.2	
Widowed	17	7.0	82	17.4	154	11.1	
TNM stage							<.001
Stage 1	55	22.7	61	12.9	190	13.7	
Stage 2	51	21.1	56	11.9	160	11.5	
Stage 3A	13	5.4	47	10.0	149	10.7	
Stage 3B	2	0.8	10	2.1	20	1.4	
Stage 4A	10	4.1	23	4.9	55	4.0	
Stage 4B	18	7.4	79	16.7	215	15.5	
Recorded incompletely[d]	57	23.6	82	17.4	351	25.3	
Missing[e]	36	14.9	114	24.2	250	18.0	
No distant metastases (M stage = M0)	146	60.3	224	47.5	711	51.2	.002
Comorbidity score (median, IQR)[f]	7	4–10	8	5-11	4	2-7	<.001[c]
Comorbidity before HCC diagnosis							
Varices without bleeding	176	72.7	16	3.4	138	9.9	<.001
Varices with bleeding	63	26.0	5	1.1	43	3.1	<.001
Viral hepatitis C	99	40.9	48	10.2	362	26.0	<.001
Viral hepatitis B, D	43	17.8	16	3.4	145	10.4	<.001
Various diseases of liver[g]	203	83.9	94	19.9	466	33.5	<.001
Portal vein thrombosis	13	5.4	8	1.7	19	1.4	<.001
Diabetes	99	40.9	242	51.3	429	30.9	<.001
Cardiovascular disease[h]	136	56.2	409	86.7	662	47.6	<.001
Moderate-severe renal disease	13	5.4	48	10.2	46	3.3	<.001
Other medications[i]							
Other anti-hypertensive medications[j]	61	25.2	334	70.8	402	28.9	<.001
Lactulose[k]	53	21.9	19	4.0	90	6.5	<.001
Spironolactone[l]	94	38.8	47	10.0	109	7.8	<.001
Loop diuretics[m]	88	36.4	140	29.7	176	12.7	<.001
NSAIDs	14	5.8	46	9.7	159	11.4	0.025
Aspirin	25	10.3	201	42.6	177	12.7	<.001
Statins	27	11.2	174	36.9	145	10.4	<.001

Patients were considered exposed to β-blocker use at cancer diagnosis if they collected at least one prescription during the 90-day period before cancer diagnosis, and unexposed otherwise. Patients using both selective and non-selective β-blockers ($n = 14$) are in the non-selective subgroup. TNM recording in the Cancer Register was introduced in 2004 and has improved over time. Diabetes and chronic lower respiratory diseases were defined using ICD codes from the Patient Register and medications (ATC: A10 and R03, respectively) from the Prescribed Drug Register; other comorbidities were defined using ICD codes in the Patient Register. Moderate-severe renal disease includes end stage renal disease.

ATC: Anatomic Therapeutic Chemical classification system; ICD: International Classification of Diseases; IQR: interquartile range; SD: standard deviation.

[a] *p* Values are from a χ^2 test.

[b] Robust one-way ANOVA.

[c] Median test.

[d] Either T, N or M stage was not specified.

[e] Captured patients with either all T, N, M stages missing or recorded as TxNxMx.

[f] Number of distinct medication classes (medications with the same initial five characters of ATC classification) within 90 days before cancer diagnosis were used to derive a comorbidity score.

[g] Includes alcoholic liver disease (ICD-10: K70), toxic liver disease (K71), hepatic failure (K72), chronic hepatitis (K73), fibrosis and cirrhosis of liver (K74), other inflammatory liver diseases (K75), other diseases of liver (K76).

[h] Other than varices and portal vein thrombosis.

[i] Medications (yes/no variables) are dispensed within 90 days before cancer diagnosis and are not mutually exclusive.

[j] Include angiotensin-converting enzyme inhibitors (ATC: C09: A, BA, BB), angiotensin receptor blockers (C09: C, DA, DB), calcium channel blockers (C08) and thiazide diuretics (C03A).

[k] Lactulose (ATC: A06AD11) is used for hepatic encephalopathy and as a laxative.

[l] Spironolactone (ATC: C03DA01) is the drug of choice for *cirrhotic ascites* if there is no renal failure. Other indications include hypokalemia, idiopathic edema, and nephrotic syndrome.

[m] Loop diuretics (ATC: C03CA): mainly (99%) furosemide (C03CA01), which complements the effect of spironolactone for edema caused by hepatic cirrhosis. Also indicated for the diuretic treatment of chronic heart failure and acute pulmonary edema.

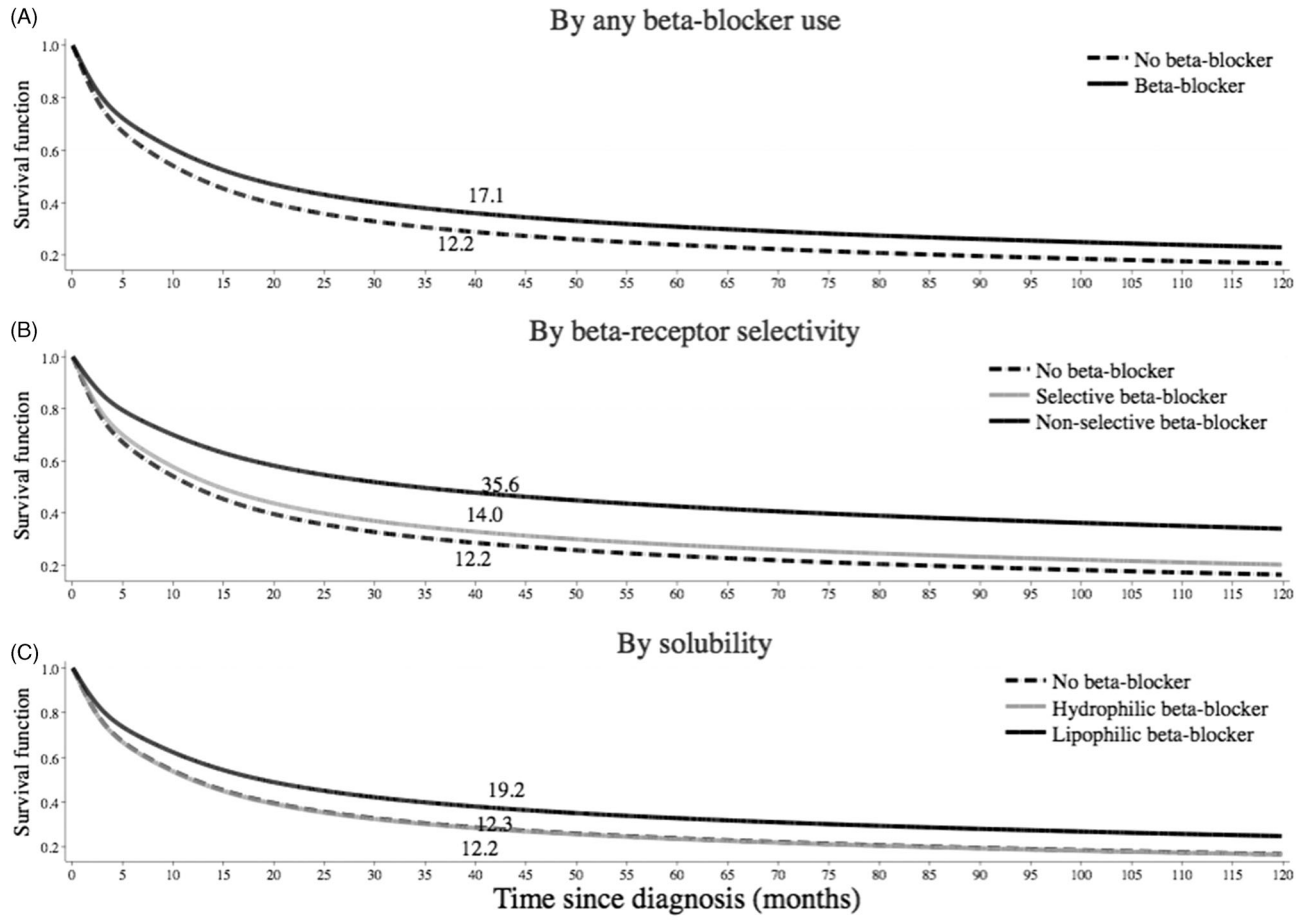

Figure 1. Age-adjusted liver cancer survival curves by β-blocker use among patients with primary hepatocellular carcinoma diagnosed in 2006 to 2014 in Sweden. Survival curves were estimated using flexible parametric survival analysis. The adjusted curves show the survival we would expect to see in exposure groups if each had the age distribution of the study population as a whole (to compare like with like). Values on the plot are age-adjusted median survival estimates by β-blocker use.

Table 2. Cox proportional hazards regression analyses for the association between β-blocker use and liver cancer mortality in patients diagnosed with primary hepatocellular carcinoma ($N = 2104$) in Sweden in 2006–2014.

β-blockers[a]	No. of events	HR[b] (95% CI)	*p*	HR[c] (95% CI)	*p*	HR[d] (95% CI)	*p*
Any β-blocker	414	0.81 [0.72, 0.91]	<.001	0.84 [0.73,0.95]	.008	0.82 [0.72, 0.94]	.005
Non-selective[e]	106	0.58 [0.48, 0.72]	<.001	0.74 [0.58, 0.95]	.017	0.71 [0.55, 0.91]	.006
β1-receptor selective[f]	308	0.94 [0.82, 1.07]	.362	0.87 [0.75, 1.00]	.053	0.86 [0.75, 1.00]	.049
Lipophilic[g]	327	0.76 [0.67, 0.86]	<.001	0.80 [0.69, 0.92]	.002	0.78 [0.67, 0.90]	.001
Hydrophilic[h]	87	1.09 [0.88, 1.37]	.422	1.00 [0.80, 1.26]	.974	1.01 [0.80, 1.28]	.906

ATC: Anatomic therapeutic chemical classification system; CI: confidence interval; HR: hazard ratio; TNM: tumor–node–metastasis.

[a]Exposed if collected at least one prescription during the 90-day period before liver cancer diagnosis, unexposed otherwise. Patients using both selective and non-selective β-blockers ($n = 14$) are in the non-selective subgroup, and patients using both lipophilic and hydrophilic β-blockers ($n = 2$) are in the lipophilic subgroup.

[b]β-blocker use compared with non-use adjusting for age at diagnosis.

[c]β-blocker use compared with non-use adjusting for age at diagnosis, sex, TNM stage, diagnosis year, healthcare/residence region, attained education, marital status, comorbidity score (number of distinct ATC classes prescribed during 90 days prior to diagnosis), diabetes, gastroesophageal varices with and without bleeding, viral hepatitis C and other, various liver diseases, portal vein thrombosis, other anti-hypertensive medications, NSAIDs, aspirin, statin, loop diuretics, lactulose, spironolactone.

[d]Further adjusted for alcohol abuse related morbidity at diagnosis, as well as ablation, transarterial chemoembolization (TACE), liver transplantation, liver resection, and sorafenib use modeled as time-varying covariates. Portal vein thrombosis is also modeled as time-updated covariate in this model.

[e]Includes pindolol, propranolol, sotalol, labetalol, carvedilol.

[f]Includes metoprolol, atenolol, bisoprolol, metoprolol + felodipine.

[g]Includes bisoprolol, carvedilol, labetalol, metoprolol, pindolol, propranolol, metoprolol + felodipine.

[h]Includes: sotalol, atenolol.

driven by rates among users of non-selective [1.51 (1.25–1.83)] rather than selective [4.09 (3.66–4.57)] β-blockers.

In age-adjusted analyses, any β-blocker use was associated with a 19% lower CSM (Figure 1, Table 2). The estimates remained largely unchanged and statistically significant after further multivariable adjustments (Table 2). Additional adjustment for cardiovascular diseases (main indications for β-blocker use, particularly selective types) did not affect the results.

Table 3. Cox proportional hazards regression analyses for the association between selected β-blockers and liver cancer mortality in patients diagnosed with primary hepatocellular carcinoma ($N = 2104$) in Sweden in 2006–2014.

β-blockers[a]	β-receptor selectivity ratio	Solubility	No. of events	HR[b] (95% CI)	*p*	HR[c] (95% CI)	*p*
Non-selective	β2 vs. β1						
Propranolol	8.3	Highly lipophilic	88	0.74 [0.56, 0.97]	.032	0.72 [0.55, 0.95]	.021
Carvedilol	4.5	Moderately lipophilic	12	0.63 [0.35, 1.13]	.120	0.52 [0.29, 0.94]	.031
Selective	β1 vs. β2						
Metoprolol	2.3	Highly lipophilic	177	0.84 [0.70, 1.00]	.053	0.81 [0.68, 0.97]	.021
Atenolol	4.7	Hydrophilic	84	1.00 [0.79, 1.27]	.973	1.01 [0.80, 1.28]	.928
Bisoprolol	13.5	Moderately lipophilic	49	0.82 [0.61, 1.11]	.195	0.90 [0.67, 1.22]	.513

Note: Selectivity ratio means, e.g., that the affinity of bisoprolol is 13.5-fold more at the β1- than β2-receptor, while the affinity of propranolol is 8.3-fold more at the β2- than β1-receptor. Carvedilol is a non-selective β-blocker that blocks β1 and β2 adrenergic receptors as well as α1 adrenergic receptors.
ATC: Anatomic therapeutic chemical classification system; CI: confidence interval; HR: hazard ratio.
[a]Exposed if collected at least one prescription during the 90-day period before liver cancer diagnosis, unexposed otherwise.
[b]β-blocker use compared with non-use adjusting for age at diagnosis, sex, TNM stage, diagnosis year, healthcare/residence region, attained education, marital status, comorbidity score (number of distinct ATC classes prescribed during 90 days prior to diagnosis), diabetes, gastroesophageal varices with and without bleeding, viral hepatitis C and other, various liver diseases, portal vein thrombosis, other anti-hypertensive medications, NSAIDs, aspirin, statin, loop diuretics, lactulose, spironolactone.
[c]Further adjusted for alcohol abuse related morbidity at diagnosis, as well as ablation, transarterial chemoembolization (TACE), liver transplantation, liver resection, and sorafenib use modeled as time-varying covariates. Portal vein thrombosis is also modeled as time-updated covariate in this model.

Analyses differentiating β-blockers by receptor selectivity suggested higher-magnitude associations for non-selective β-blockers, although the difference between the estimates was not statistically significant ($p = .143$) (Table 2). The hazard ratio for the association between non-selective β-blocker use and CSM was not significantly altered after adjustment for diagnosis of gastroesophageal varices, the most common indication for non-selective β-blocker treatment, although some attenuation of the inverse association was observed.

Analyses by solubility further indicated lower CSM for lipophilic but not hydrophilic β-blocker use (difference between the estimates: $p = .036$) (Table 2). There were no notable differences between men and women.

Results for selected individual β-blockers were consistent with results for β-blocker types evaluated in aggregate (Table 3). Non-selective and highly lipophilic propranolol was associated with a statistically significant 28% lower mortality rate, and commonly prescribed β1-selective and highly lipophilic metoprolol was associated with a 19% lower mortality rate. A higher magnitude association (48% lower mortality rate) was observed for the less often prescribed carvedilol, a moderately lipophilic and non-selective β-blocker with anti-α1 adrenergic activity. Use of moderately lipophilic bisoprolol or hydrophilic atenolol, both with higher (compared with metoprolol) β1-selectivity, did not show associations with CSM.

In our sensitivity analysis we observed similar magnitude associations for incident and prevalent use of non-selective β-blockers [0.71 (0.44–1.14) vs. 0.70 (0.53–0.93)] as well as for incident and prevalent use of selective β-blockers [0.87 (0.52–1.46) vs. 0.83 (0.71–0.97)].

Stratified analyses suggested a lower CSM among patients without known distant metastases at diagnosis [0.82 (0.67–1.01), $p = .062$], whereas the magnitude of association was close to null in patients with distant metastases [0.98 (0.71–1.36), $p = .910$].

In exploratory analyses among 655 patients with indications of decompensated liver disease, non-selective β-blockers were still associated with lower CSM [0.73 (0.50–1.05), $p = 0.089$)] although statistical significance was not achieved. Further analysis suggested an inverse association for propranolol [$n = 155$; HR: 0.67 (0.46, 0.98)] but not for the rarely used carvedilol [$n = 5$; HR: 1.33 (0.39, 4.55)]. The magnitude of association was close to null for selective β-blockers [0.98 (0.72–1.33)].

Non-selective β-blockers were associated with lower CSM [0.68 (0.51–0.90), $p = .007$] also in a sensitivity analysis excluding 363 patients with hepatorenal morbidity. A lower magnitude association was observed in relation to selective types [0.85 (0.73–1.00), $p = .055$].

In a sensitivity analysis excluding patients who used β-blockers and/or other antihypertensive medications dispensed for indications other than hypertension, selective β-blockers were associated with lower CSM, while other antihypertensive medications were not (Table 4).

Discussion

In this large population-based cohort of patients with primary HCC, β-blocker use at cancer diagnosis was associated with lower liver cancer specific mortality. The reduced liver cancer mortality rate was limited to patients without known distant metastases at diagnosis. Higher-magnitude inverse associations were suggested for non-selective than selective β-blockers, and the association was apparent for lipophilic but not hydrophilic β-blockers.

HCC typically arises in the background of cirrhosis and only about 20% of HCCs have been reported to develop in non-cirrhotic livers [32]. While tumor recurrence is the major cause of death in non-cirrhotic HCC [32], patients with HCC in cirrhotic liver often die from complications of liver cirrhosis and portal hypertension rather than from clearly tumor-related causes. Non-selective β-blockers are recommended for patients with cirrhosis and esophageal varices to prevent variceal hemorrhage [33,34]; and have been shown to lower the risk of spontaneous bacterial peritonitis in patients with cirrhosis and ascites [35] and risk of developing ascitic decompensation, refractory ascites and hepatorenal syndrome in patients with compensated cirrhosis [36]. Improved survival associated with non-selective β-blockers may thus be partly explained by reduced risk of hepatic decompensation-related mortality. Unlike non-selective β-blockers, selective

Table 4. Cox proportional hazards regression analyses for the association between antihypertensive medications and liver cancer mortality in patients diagnosed with primary hepatocellular carcinoma in Sweden between 1 July 2006 and 31 December 2014 ($N = 1479$).

Antihypertensive medications dispensed for hypertension[a]	No. of events	HR[b] (95% CI)	*p*
Selective β-blockers	178	0.82 [0.68, 0.98]	.030
ACEi	155	0.96 [0.79, 1.17]	.703
ARBs	122	1.16 [0.94, 1.43]	.162
CCB	160	0.95 [0.79, 1.15]	.589
Thiazide diuretics	36	0.91 [0.65, 1.30]	.615

ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; ATC: Anatomic therapeutic chemical classification system; CCB: calcium channel blockers; CI: confidence interval; HR: hazard ratio.

[a]Exposed if collected at least one prescription during the 90-day period before liver cancer diagnosis dispensed for no other indication but hypertension. Prior prescriptions dispensed during 1 year before cancer diagnosis also had to be for no other indication but hypertension.

[b]Antihypertensive medication use compared with non-use adjusting for age at diagnosis, sex, TNM stage, diagnosis year, healthcare/residence region, attained education, marital status, comorbidity score (number of distinct ATC classes prescribed during 90 days prior to diagnosis), diabetes, gastroesophageal varices with and without bleeding, viral hepatitis C and other, various liver diseases, NSAIDs, aspirin, statin, loop diuretics, lactulose, spironolactone, alcohol abuse related morbidity, as well as ablation, transarterial chemoembolization (TACE), liver transplantation, liver resection, sorafenib use, and portal vein thrombosis modeled as time-updated covariates.

β-blockers are more likely prescribed to patients with compensated liver who thus have a better liver function related prognosis irrespective of β-blocker use.

Increased surveillance of patients with cirrhosis leading to earlier cancer detection [37] may offer another potential explanation. This is less likely among patients with non-cirrhotic HCC as they are often diagnosed at an advanced stage due to lack of surveillance [32].

A growing body of evidence has suggested a role of β-adrenergic signaling in the pathobiology of various tumor types [4], including liver cancer [11,12,15–17,19,38], and the observed lower CSM rates among β-blocker users could also be related to reduced cancer progression linked to inhibited β-adrenergic signaling. The observed inverse association between CSM and use of selective β-blockers but not other antihypertensive medications dispensed for hypertension may add some additional suggestive evidence for the role of β-adrenergic signaling in HCC pathology.

A lower mortality rate among patients without distant metastases is consistent with the concept of greater influence of biobehavioral factors in early stage cancer when the metastatic capacity is physiologically modifiable [3], although some benefit even for late-stage disease may exist due to treatment-sensitizing effects of β-blockers [39].

It has been suggested that the β2-adrenoreceptor is the adrenoreceptor most involved in cancer related processes [40], including for liver-cancer [11,12,15,38]; and that propranolol, shown to have antiproliferative, antimigratory, and cytotoxic properties [16,17], may be more cytotoxic for liver cancer cells than atenolol [17]. This could potentially partially explain the higher-magnitude associations with non-selective β-blockers (comprised mainly of propranolol in this cohort). However, β1- and β2-receptors are in general very similar, and the majority of β-blockers used in clinical practice (including metoprolol and atenolol) show little selectivity for the β1- over the β2-adrenoreceptor [41]. Our results further suggested an association of lipophilic β-blockers with reduced CSM, while no association was observed for hydrophilic β-blockers. As lipophilic agents have greater penetrance of the blood-brain barrier, this finding may suggest that some of the hypothesized anti-tumor effects of β-blockers may be mediated through central β-adrenergic signaling [4]. Carvedilol, a non-selective β-blocker with anti-α1 adrenergic activity, which demonstrated higher magnitude associations in our study overall, has been studied as a promising β-blocker in liver pathology [31,34], but perhaps not among patients with severe or refractory ascites [31].

Strengths of this study include use of high-quality prospectively collected data from national registers in the setting of a tax-supported universal health care system, minimizing the risk of selection bias, and substantially reducing the likelihood of the findings being confounded by socioeconomic characteristics.

Defining exposure to medications through dispensed prescriptions prevents problems such as recall bias or failure to fill prescribed medication (a key component of non-adherence). However, exposure misclassification is still possible, and a prescription filled does not guarantee that the dispensed medication has been used. Although the information on medication compliance is unavailable, the requirement for patients to pay a component of the dispensed price should increase the probability of actual use. Our definition of exposure does not account for potential changes in use during follow-up, but resembles the intention-to-treat analysis in randomized studies and eliminates the possibility of immortal time bias. Besides studying β-blockers in aggregate, we studied some individual β-blockers with varying β-receptor ligand selectivity and lipophilicity/hydrophilicity. However, these analyses are limited by low prevalence of some β-blockers. For example, the low prevalence of hydrophilic sotalol and lack of lipophilic timolol, both with higher β2-selectivity compared to propranolol [41], limits the possibility to make inferences regarding relative importance of β2-selectivity level and solubility of non-selective types. As the medication data are only available since the start of the register in July 2005, we were unable to evaluate the role of duration of β-blocker use [42], the significance of which is largely unknown [43]. Since comparison of prevalent users

with non-users could be subject to selection bias [44], we examined associations for incident and prevalent β-blocker use compared with non-use. This analysis, although limited by a small number of incident users, did not reveal any clear differences between estimates for incident and prevalent use.

Due to the observational nature of the study, the possibility of residual confounding cannot be excluded, and confounding by indication [45] or by liver functional status is possible. Although the national register data allowed us to account for a number of important potential confounding and prognostic factors, the data was limited by the absence of stage information according to Barcelona-Liver Cancer (BCLC) staging system, one of the most widely used classifications for HCC in cirrhotic liver that accounts not only for tumor extent but also for other determinants of prognosis such as liver function and performance status [46]. The nature of the registry data limited our ability to accurately identify all patients with and without underlying cirrhosis and to adjust for severity of cirrhosis through Child-Pugh score or other specific measures of the underlying liver function [46]. Nevertheless, the inability to efficiently adjust for performance status and cirrhosis severity could explain the observed inverse associations if patients with poor performance status and more advanced liver impairment, who tend to have worse prognosis, were less likely to take β-blockers, for example, patients with cirrhosis who have developed hepatorenal syndrome [31,47]. However, excluding patients with hepatorenal morbidity did not affect the results. As β-blocker users tended to be older and with higher disease burden, the observed inverse association with CSM is less likely to be explained by selective avoidance of prescribing β-blockers to frail patients. Furthermore, patients on non-selective β-blockers generally have more advanced portal hypertension with large gastroesophageal varices [47].

In conclusion, β-adrenergic receptor blockers, particularly non-selective types, are associated with lower liver cancer mortality in patients with primary HCC. Various potential mechanisms could explain the observed inverse association, including an influence on hepatic decompensation-related mortality as well as early detection of cancer due to active surveillance (particularly among patients with HCC in cirrhotic liver). Reduced cancer progression due to β-adrenergic signaling inhibition could be another potential explanation. Further clinicopathological investigations are necessary to disentangle potential mechanisms. Thus, the role of β-blockers, particularly propranolol, in HCC progression could be an area for further investigation, but the findings from preclinical and observational studies need to be verified by prospective clinical trials.

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Ethical approval

Ethical review board in Uppsala (DNR: 2012-361).

Disclosure statement

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