Original Article

Propranolol use in patients with cirrhosis and refractory ascites: A nationwide study

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Abstract

Background: The impact of propranolol on patients with cirrhosis and refractory ascites is controversial. We conducted a nationwide longitudinal cohort study to compare the survival between patients with cirrhosis and refractory ascites, with and without using propranolol.

Methods: Data of patients with cirrhosis and refractory ascites using propranolol, and controls matched by age and gender, were extracted from The National Health Insurance Research Database of Taiwan. The baseline demographic characteristics were compared between groups. Cox regression analysis was used to examine the predictors of mortality.

Results: In this study, 1788 patients were enrolled in each group; 1304 patients (72.9%) in the propranolol group and 1445 patients (80.8%) in the control group died ($P < 0.001$). The mean survival was 34.3 ± 31.2 months in the propranolol group and 20.8 ± 26.6 months in the control group ($P < 0.001$). Propranolol (hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.55–0.64, $P < 0.001$), statins (HR: 0.43, 95% CI: 0.34–0.56, $P < 0.001$), age (HR: 1.02, 95% CI: 1.01–1.02, $P < 0.001$), and diabetes mellitus (HR: 1.14, 95% CI: 1.05–1.24, $P = 0.002$) were the independent predictors for mortality.

Conclusions: Use of propanolol was associated with reduced mortality, compared with controls, in this nationwide cohort of patients with cirrhosis and refractory ascites.

Keywords: Cirrhosis, propranolol, refractory ascites, spontaneous bacterial peritonitis

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See accompanying Editorial

INTRODUCTION

Ascites is most frequently the first sign of hepatic decompensation in patients with cirrhosis.[1] Up to 50% of the patients with compensated cirrhosis develop ascites after a 10-year observation.[2] Refractory ascites was present in 11% of the patients with cirrhosis hospitalized for the management of ascites.[3] The presence of

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refractory ascites usually indicates a worsening prognosis including spontaneous bacterial peritonitis (SBP), variceal bleeding (VB), jaundice, and poor survival. Non-selective beta-blockers (NSBBs) are frequently used for the primary or secondary prophylaxis of VB.[4] Long-term NSBB treatment also reduces the frequency of rebleeding from portal hypertensive gastropathy.[5] In addition to prophylaxis of VB, the use of NSBBs is associated with a reduced risk of ascites development and SBP.[6,7]

Unfortunately, NSBBs are reported to be detrimental to the survival of patients with cirrhosis and refractory ascites.[8] Paracentesis-induced circulatory dysfunction caused by NSBBs was proposed as the mechanism for the deleterious effects on survival.[9] In a subsequent study, NSBBs were found to increase the risk for hepatorenal syndrome and death in patients with refractory ascites.[10] Several studies also found that NSBBs are harmful to the survival of cirrhotic patients with refractory ascites. Nevertheless, there are still other conflicting studies. NSBBs did not affect the survival in a post hoc analysis of patients with refractory ascites.[11] Furthermore, NSBBs were found to improve the survival of refractory ascites patients waiting for liver transplantation.[12]

Since, the impact of NSBBs, such as propranolol, for the survival of patients with cirrhosis and refractory ascites is controversial we conducted a nationwide study to compare the survival, the development of SBP, and the development of hepatocellular carcinoma (HCC) between patients with cirrhosis and refractory ascites, with and without using NSBBs.

PATIENTS AND METHODS

Study design

The National Health Insurance Research Database (NHIRD) of Taiwan provided detailed health care data of more than 23 million enrollees, covering more than 99% of the Taiwanese population. The accuracy of NHIRD has been validated in previous studies.[13] The Longitudinal Health Insurance Database 2000 (LHID2000), a subset of NHIRD containing one million unique individuals randomly sampled between January 2000 and December 2013, and the Registry for Catastrophic Illness Patients Database (RCIPD), another subset database of NHIRD, were used in this study. Refractory ascites is among the catastrophic illnesses that are formally approved by the Department of Health. We compared propranolol users with non-propranolol users matched by age, gender, and enrollment time in a 1:1 ratio. The diagnosis was based on an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code. The inclusion criteria were (1) patients with newly diagnosed refractory ascites (ICM-9 CM code: 571.2) between January 1, 2000, and December 31, 2012; (2) aged 20 years or older. The exclusion criteria were (1) malignancy, including HCC (ICD-9-CM codes: 145.9–199.1, 202.80, and 203.00); (2) uremia with catastrophic illness card (ICD-9-CM code: 585); (3) heart failure (ICD-9-CM code: 428); (4) chronic obstructive pulmonary disease (ICD-9-CM codes: 490–505 and 506.4); and liver transplantation during the study period.

Definitions

Comorbidities were defined as patients with an ICD-9-CM code once for hospitalizations, emergency room visits, or at least three times for outpatient visits before enrolment. The comorbidities included diabetes mellitus (ICD-9-CM codes: 250.xx), dyslipidemia (ICD-9-CM codes: 272.0, 272.01, 272.3, and 272.4), hypertension (ICD-9-CM codes: 401.xx–405.xx), coronary artery disease (ICD-9-CM codes: 411.xx–414.xx), ischemic stroke (ICD-9-CM codes: 433.xx and 434.xx), chronic kidney disease (CKD) (ICD-9-CM codes: 586, 588.8,588.9, 250.4, 274.1, 403.x1, 404.x2, 404.x3, and 440.1), peptic ulcer disease (ICD-9-CM codes: 531.30, 531.70, 531.90, 532.30, 532.70, 532.90, 533.30, 533.70, and 533.90), and peptic ulcer bleeding (ICD-9-CM codes: 531.0, 531.00, 531.01, 531.2x, 531.4x, 531.6x, 532.0, 532.00, 532.01, 532.2x, 532.4x, 532.6x, 533.00, 533.01, 533.2x, 533.4x, 533.6x, 534.0, 534.00, 534.01, 534.2x, 534.4x, and 534.6x). Patient follow-up arrangements were assessed using the prescription registries and the ICD-9 CM codes for hospitalizations, emergency room visits, and outpatient visits. Treatment adherence to propranolol was defined as redemption of the prescription with intervals of less than 2 weeks. Mortality was defined as withdrawal of the patient from the National Health Insurance program. Occurrence of SBP was defined as hospitalization with a primary diagnosis of SBP (ICD-9 CM code: 567) during the study period. Occurrence of HCC was defined as hospitalization with a primary diagnosis of HCC (ICD-9-CM code: 155.0).

Endpoints of the study

The primary endpoint of this study was mortality of the patients. The secondary endpoint was the occurrence of SBP and HCC.

Statistical analysis

The demographic data of propranolol users and controls were expressed as frequency or means with standard deviations. Categorical data were compared using Chi-square or Fisher's exact tests. Continuous variables with normal distributions were compared using independent

Student's *t* test. Continuous variables without normal distributions were compared using the Mann–Whitney U test. Kaplan–Meier estimator was used to estimate the time starting from the enrollment to the occurrence of the endpoints. A log-rank test was used to compare the distribution of the time until the occurrence of the endpoints between propranolol users and controls. Cox proportional-hazards models were constructed to assess the independent predictors for mortality and HCC in propranolol users and controls.

Ethical aspects

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The need for informed consent was waived off by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS15-EM4-01) in lieu of the retrospective nature of the study. Part of the results were presented as an abstract in the 46th annual meeting of The Gastroenterological Society of Taiwan.

RESULTS

Baseline characteristics of propranolol users and non-propranolol users

A total of 1788 propranolol users and 1788 non-propranolol users (controls) were included in this study [Figure 1]. The baseline characteristics of both groups are shown in Table 1. The demographic data were similar between both groups except that more patients in the propranolol group had more alcohol-induced cirrhosis (28.9% vs. 25.1%, $P = 0.009$), hypertension (29.6% vs. 25.8%, $P = 0.01$), peptic ulcer disease (63.8% vs. 57.9%, $P < 0.001$), banding ligation (25.6% vs. 13.2%, $P < 0.001$), sclerotherapy (4.0% vs. 2.5%, $P = 0.008$), tissue glue obturation (2.2% vs. 0.9%, $P = 0.005$), use of statins (3.9% vs. 2.1%, $P = 0.001$), and higher Charlson comorbidity index score (5.1 ± 2.3 vs. 4.8 ± 2.6, $P = 0.002$) than the control group. Fewer patients in the propranolol group had chronic kidney disease than in the control group (9.7% vs. 15.4%, $P < 0.001$).

Incidence and risk factors for mortality

One thousand three hundred and four patients (72.9%) in the propranolol group and 1445 patients (80.8%) in the control group died ($P < 0.001$) [Table 2 and Figure 2]. The follow-up period was 34.3 ± 31.2 months in the propranolol group and 20.8 ± 26.6 months in the control group ($P < 0.001$).

Univariate Cox regression analyses showed that age (hazard ratio (HR): 1.02, 95% confidence interval (CI): 1.01–1.02, $P < 0.001$), hepatitis C (HR: 1.19, 95% CI: 1.08–1.30, $P < 0.001$), diabetes mellitus (HR: 1.22, 95% CI: 1.12–1.32, $P < 0.001$), CKD (HR: 1.24, 95% CI: 1.11–1.39, $P < 0.001$), and cerebrovascular accident (HR: 1.27, 95% CI: 1.11–1.46, $P = 0.001$) were associated with mortality in patients with cirrhosis and refractory ascites. The protective factors for mortality were propranolol (HR: 0.59, 95% CI: 0.55–0.64, $P < 0.001$), statins (HR: 0.42, 95% CI: 0.33–0.55, $P < 0.001$), and endoscopic therapy (HR: 0.88, 95% CI: 0.80–0.97, $P = 0.008$) [Table 3]. Multivariate analyses showed that age (HR: 1.02, 95% CI: 1.01–1.02, $P < 0.001$) and diabetes mellitus (HR: 1.14, 95% CI: 1.05–1.24, $P = 0.002$) were associated with mortality. Use of propranolol (HR: 0.60, 95% CI: 0.55–0.64, $P < 0.001$) and statins (HR: 0.43, 95% CI: 0.34–0.56, $P < 0.001$) were protective factors of mortality.

Table 1: Demographic data of patients with cirrhosis and refractory ascites

Variables	Propranolol group (*n*=1788)	Control group (*n*=1788)	*P*
Age (years)	52.8±12.2	52.9±11.9	0.10
Male gender	1366 (76.4%)	1366 (76.4%)	1.00
Etiology of cirrhosis			
Hepatitis B	561 (31.4%)	574 (32.1%)	0.64
Hepatitis C	366 (20.5%)	350 (19.6%)	0.50
Alcohol	518 (28.9%)	449 (25.1%)	0.009
Hypertension	530 (29.6%)	462 (25.8%)	0.01
Cerebrovascular accident	120 (6.7%)	144 (8.0%)	0.13
Acute coronary syndrome	146 (8.2%)	127 (7.1%)	0.23
Myocardial infarction	9 (0.5%)	11 (0.6%)	0.65
Peripheral vascular disease	42 (2.3%)	37 (2.1%)	0.57
Dementia	8 (0.4%)	11 (0.6%)	0.49
Dyslipidemia	158 (8.8%)	142 (7.9%)	0.33
Diabetes mellitus	514 (28.7%)	527 (29.5%)	0.63
Peptic ulcer disease	1141 (63.8%)	1035 (57.9%)	<0.001
Chronic kidney disease	173 (9.7%)	275 (15.4%)	<0.001
Charlson comorbidity index score	5.1±2.3	4.8±2.6	0.002
Management before enrollment			
Banding ligation	457 (25.6%)	236 (13.2%)	<0.001
Sclerotherapy	72 (4.0%)	44 (2.5%)	0.008
Tissue glue obturation	39 (2.2%)	18 (0.9%)	0.005
Transjugular intrahepatic portosystemic shunt	0 (0%)	2 (0.1%)	0.56
Shunt surgery	2 (0.1%)	1 (0.1%)	1.00
Devascularization surgery	15 (0.8%)	11 (0.7%)	0.43
Propranolol (mg daily)			
<80	1532	NA	
80-160	159	NA	
>160	97	NA	
Use of statins	70 (3.9%)	37 (2.1%)	0.001

Incidence and risk factors for SBP

We further analyzed the risk factors of SBP in patients with cirrhosis and refractory ascites with and without

Table 2: The outcome of propranolol group versus control group in patients with cirrhosis and refractory ascites

Variables	Propranolol group (*n*=1788)	Control group (*n*=1788)	*P*
Variceal bleeding	169 (9.5%)	57 (3.2%)	<0.001
hepatocellular carcinoma	145 (8.1%)	79 (4.4%)	<0.001
Mortality	1304 (72.9%)	1445 (80.8%)	<0.001
Survival (months)	34.3±31.2	20.8±26.6	<0.001

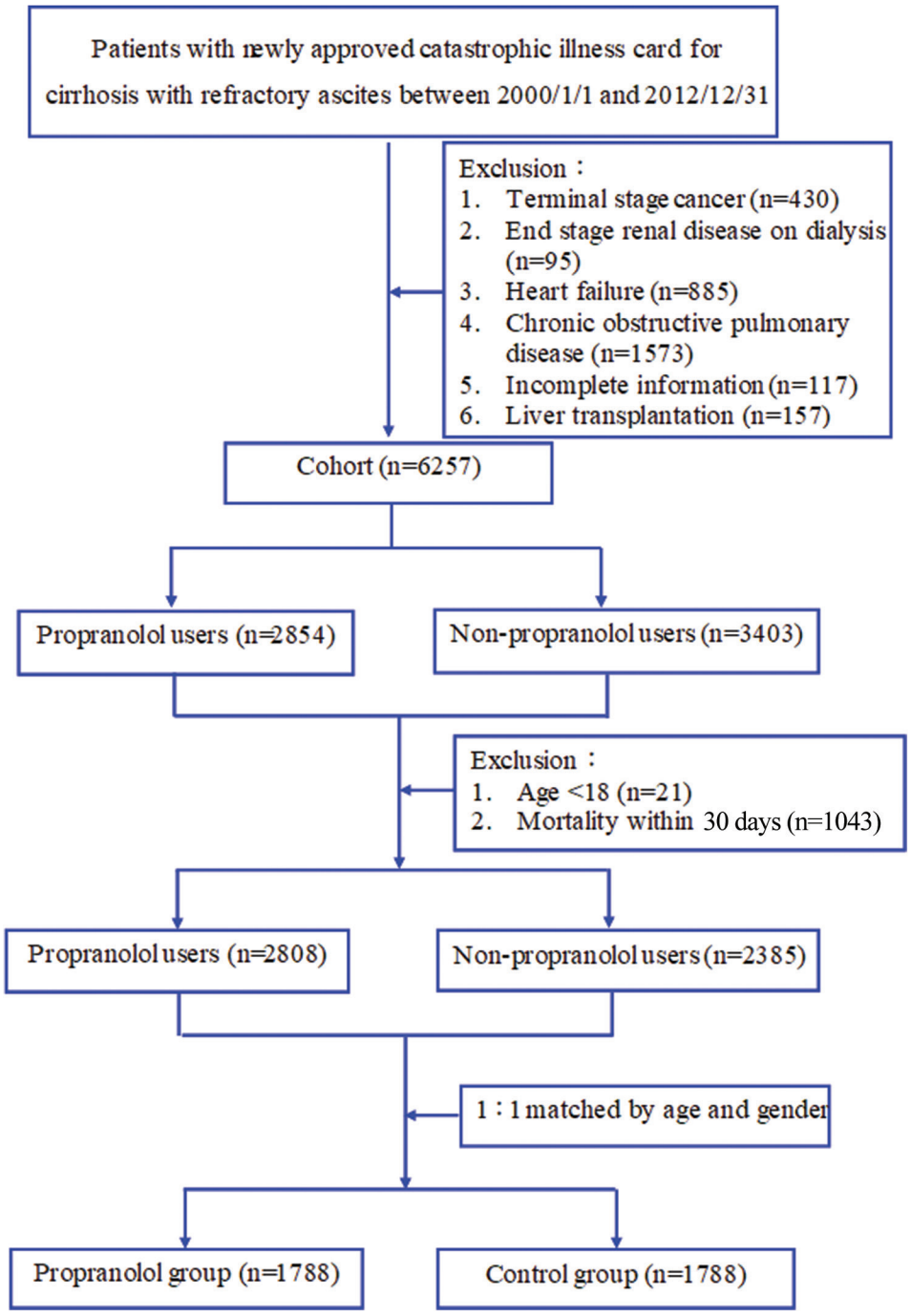

Figure 1: Flowchart of the study

propranolol usage. Univariate Cox regression analysis showed that propranolol use (HR: 0.81; 95% CI, 0.71–0.92; $P < 0.001$), statin use (HR: 0.49; 95% CI, 0.33–0.73; $P < 0.001$), hepatitis B (HR: 1.18, 95% CI: 1.04–1.34, $P = 0.013$), hepatitis C (HR: 1.24, 95% CI: 1.07–1.44, $P = 0.005$), and peptic ulcer disease (HR: 1.19; 95% CI: 1.04–1.35, $P = 0.009$) were associated with SBP development [Supplementary Table 1]. Multivariate Cox regression analysis showed that propranolol use (HR: 0.81; 95% CI, 0.71–0.91; $P < 0.001$), statin use (HR: 0.50; 95% CI, 0.34–0.75; $P = 0.001$), hepatitis B (HR: 1.17, 95% CI: 1.03–1.34, $P = 0.017$), hepatitis C (HR: 1.23, 95% CI: 1.06–1.43, $P = 0.007$), and peptic ulcer disease (HR: 1.20; 95% CI: 1.05–1.37, $P = 0.006$) were associated with SBP development [Supplementary Table 2].

Incidence and risk factors for HCC

One hundred and forty-five (8.1%) patients in the propranolol group and 79 patients (4.4%) in the

Table 3: Univariate analysis of the risk factors of mortality in patients with cirrhosis and refractory ascites

Variables	Hazard ratio	95% confidence interval	*P*
Age	1.02	1.01-1.02	<0.001
Male gender	0.92	0.85-1.01	0.07
Propranolol use	0.59	0.55-0.64	<0.001
Statin use	0.42	0.33-0.55	<0.001
Hepatitis B	1.05	0.97-1.13	0.27
Hepatitis C	1.19	1.08-1.30	<0.001
Alcohol	0.93	0.85-1.01	0.10
Hypertension	1.06	0.97-1.15	0.19
Peptic ulcer disease	1.01	0.93-1.09	0.86
Diabetes	1.22	1.12-1.32	<0.001
Myocardial infarction	0.91	0.52-1.61	0.75
Chronic kidney disease	1.24	1.11-1.39	<0.001
Peripheral vascular disease	1.21	0.95-1.54	0.12
Dementia	1.23	0.76-1.98	0.40
Cerebrovascular accident	1.27	1.11-1.46	0.001
Dyslipidemia	1.03	0.90-1.18	0.69
Connective tissue disease	1.08	0.98-1.20	0.12
Hemiplegia	1.09	0.80-1.50	0.59
Variceal bleeding	1.09	0.80-1.50	0.59
Hepatic encephalopathy	0.80	0.62-1.04	0.10
Endoscopic therapy	0.88	0.80-0.97	0.008

control group developed HCC during the follow-up period ($P < 0.001$) [Table 2]. Univariate Cox regression analysis showed that age (HR: 1.04; 95% CI, 1.03–1.05; $P < 0.001$), hepatitis B (HR: 1.72, 95% CI: 1.32–2.24, $P < 0.001$), hepatitis C (HR: 2.18, 95% CI: 1.65–2.89, $P < 0.001$), alcohol (HR: 0.61; 95% CI: 0.43–0.86, $P = 0.005$), diabetes (HR: 1.36; 95% CI: 1.03–1.81, $P = 0.03$), and cerebrovascular accident (HR: 1.57; 95% CI: 1.00–2.47, $P = 0.048$) were associated with HCC development [Supplementary Table 3]. Multivariate Cox regression analysis showed that age (HR: 1.04, 95% CI: 1.02–1.05, $P < 0.001$), hepatitis B (HR, 1.64: 95% CI: 1.26–2.14; $P < 0.001$), and hepatitis C (HR: 1.79, 95% CI: 1.34–2.38, $P < 0.001$) were associated with HCC development [Supplementary Table 4]. The incidence of HCC was similar between propranolol users and non-propranolol users after long-term follow-up [Figure 3].

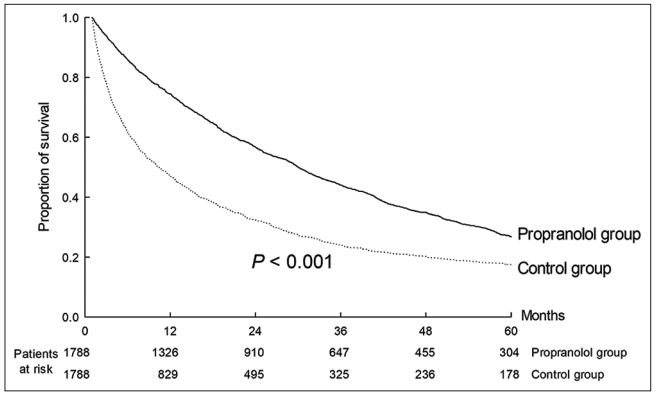

Figure 2: Survival curve of propranolol group versus control group

DISCUSSION

NSBBs are beneficial for the prevention of gastrointestinal bleeding associated with portal hypertension induced by cirrhosis.[4] However, the role of NSBBs in patients with cirrhosis and refractory ascites remains controversial. We found that propranolol use was associated with improved survival and reduced risk of SBP in a nationwide cohort of patients with cirrhosis and refractory ascites.

The unfavorable impact of NSBBs on the survival of patients with cirrhosis and refractory ascites was first proposed by a pilot study by Sersté *et al*.[8] However, in cirrhotic patients receiving NSBBs, a decrease in the hepatic venous pressure gradient of more than 20% or to less than 12 mm Hg was associated with a marked reduction in the long-term risk of developing complications of portal hypertension and improved survival.[14] Survival benefit was also observed in the NSBBs responders with ascites.[15] Moreover, mortality was significantly lower in cirrhotic patients using NSBBs than in those not using NSBBs.[16] Our nationwide study found that propranolol was associated with reduced mortality among patients with cirrhosis and refractory ascites. The possible underlying mechanisms can be as follows: (1) Systemic inflammation is harmful to patients with cirrhosis.[17] NSBBs might lower the systemic inflammatory response and therefore improve survival.[18] (2) Portal hypertension increases the permeability of intestinal mucosa, which further exacerbates bacterial translocation and subsequent infectious complications.[19] NSBBs probably decrease the severity of portal hypertension and lower the risk of mortality associated with bacterial infection.

Decreasing propranolol to a low dose (<80 mg per day) is recommended in patients with severe or refractory ascites.[20] However, propranolol use was associated with reduced mortality in decompensated cirrhosis patients receiving

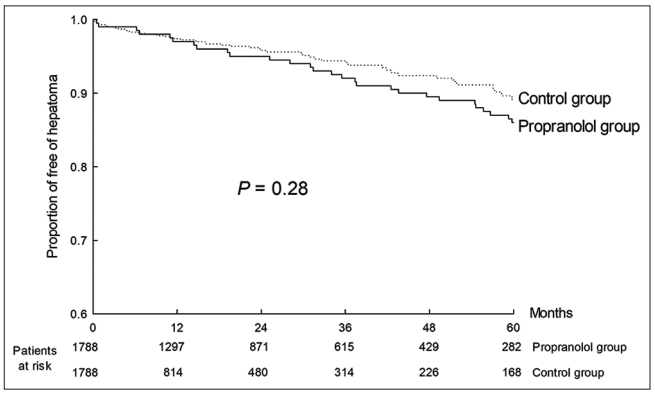

Figure 3: Occurrence of hepatocellular carcinoma in cirrhotic patients with refractory ascites

propranolol less than 80 mg and 80–160 mg daily but not in patients receiving propranolol more than 160 mg daily, as seen in a Danish nationwide study.[21] In another Korean nationwide cohort, low-dose propranolol (40–120 mg daily) decreased the overall mortality and recurrent VB in patients with tense ascites, but the beneficial effect was masked at doses greater than 120 mg daily.[22]

Statins were also found to be a protective factor of mortality and SBP in this study. Statins possess anti-oxidant, anti-fibrotic, and anti-inflammatory properties and improve endothelial dysfunction.[23] In patients with cirrhosis, statins reduce the risk of liver decompensation and mortality.[24] Statins improve survival in decompensated cirrhosis via the downstream mechanism.[25] Atorvastatin and fluvastatin were associated with more favorable outcomes compared with other statins, and the effect seemed to be dose-dependent.[26]

Portal hypertension, especially those with a hepatic venous pressure gradient higher than 10 mm Hg, has been identified as one of the risk factors for HCC development.[27] A previous study showed that NSBB use may reduce the development of HCC in patients with cirrhosis.[28] Nevertheless, our results revealed that the use of propranolol was not associated with the occurrence of HCC [Figure 3]. Instead, age, hepatitis B, and hepatitis C were found to be the predictors of HCC. Refractory ascites could generally indicate a shorter survival in patients with cirrhosis, which may be a competing risk of HCC occurrence.

We found that the rate of VB was higher in propranolol users than that in the controls. These results should not be interpreted as propranolol use itself resulting in a higher incidence of VB. Patients using NSBBs tend to have more advanced cirrhosis and a higher prevalence of high-risk varices than those not using NSBBs.[29] NSBBs are usually indicated for primary or secondary prophylaxis of VB. For primary prophylaxis, the varices are medium- or large-sized and the bleeding risk is higher than that for small varices.[30] For secondary prophylaxis, although NSBBs decreased the rate of rebleeding, portal hypertension can still be significant enough to develop new varices and further bleeding in some cases.[31]

In addition to NSBBs, comorbidities play an important role in the mortality of patients with cirrhosis because of the additional or synergistic effects.[32] Our multivariate analysis demonstrated that diabetes was associated with mortality in patients with cirrhosis and refractory ascites. Diabetes mellitus may aggravate the liver disease via associated complications. Chronic hepatitis B patients with diabetes have a higher incidence of cirrhosis and liver decompensation.[33] Moreover, diabetes negatively impacts the major outcomes of cirrhotic patients, including ascites, renal dysfunction, bacterial infection, and HCC development.[34]

It is to be noted that our study has obvious strengths. First, the study enrolled more patients with a longer observation period than most of the previous studies. Second, the effect of statins on survival was evaluated among the patients using and not using propranolol. However, our study also had some limitations. First, NHIRD could not provide detailed information such as the Child–Turcotte–Pugh score for each cirrhotic patient. Therefore, the risk by the severity of cirrhosis was not further analyzed. Moreover, other information such as family history could not be obtained from NHIRD. Second, although there was more alcohol consumption as cirrhosis etiology in the propranolol group, the survival may be similar between alcohol, hepatitis B, and hepatitis C etiology in patients with cirrhosis.[35-37] Thus, the different etiologies may not affect the primary endpoint of the NSBBs and the non-NSBBs group. Third, it was not possible to have information on the actual adherence to the study medications. Information on redemption of the prescription or the dispensed amount was usually used to evaluate the treatment adherence.[38] Fourth, patients receiving liver transplantation during the study period were excluded to minimize the competing risks of the study endpoints. Finally, ICD-9-CM was used in the NHIRD during the study period. Further studies using the 10th Revision of the International Classification of Diseases are required.

In conclusion, the use of propranolol was associated with reduced mortality but not HCC development in a nationwide cohort of patients with cirrhosis and refractory ascites. Future randomized controlled trials are necessary to investigate the effect of propranolol use in patients with cirrhosis and refractory ascites.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Univariate analysis of the risk factors of spontaneous bacterial peritonitis in patients with cirrhosis and refractory ascites

Variables	Hazard ratio	95% confidence interval	*P*
Age	1.00	0.99-1.01	0.46
Male gender	0.94	0.81-1.08	0.38
Propranolol use	0.81	0.71-0.92	<0.001
Statin use	0.49	0.33-0.73	<0.001
Hepatitis B	1.18	1.04-1.34	0.013
Hepatitis C	1.24	1.07-1.44	0.005
Alcohol	0.98	0.85-1.13	0.76
Hypertension	0.91	0.79-1.05	0.21
Peptic ulcer disease	1.19	1.04-1.35	0.009
Diabetes	0.95	0.82-1.09	0.48
Myocardial infarction	1.29	0.58-2.88	0.53
Chronic kidney disease	0.96	0.78-1.18	0.66
Peripheral vascular disease	0.66	0.39-1.11	0.12
Dementia	0.62	0.20-1.93	0.41
Cerebrovascular accident	0.97	0.75-1.25	0.81
Dyslipidemia	0.99	0.79-1.26	0.99
Connective tissue disease	1.04	0.88-1.24	0.65
Hemiplegia	0.59	0.30-1.19	0.14
Variceal bleeding	0.90	0.73-1.11	0.32
Hepatic encephalopathy	1.14	0.78-1.66	0.49
Endoscopic therapy	1.13	0.98-1.31	0.10

Supplementary Table 2: Multi-variate analysis of the risk factors of spontaneous bacterial peritonitis in patients with cirrhosis and refractory ascites

Variables	Hazard ratio	95% confidence interval	*P*
Propranolol use	0.81	0.71-0.91	<0.001
Statin use	0.50	0.34-0.75	0.001
Hepatitis B	1.17	1.03-1.34	0.017
Hepatitis C	1.23	1.06-1.43	0.007
Peptic ulcer disease	1.20	1.05-1.37	0.006

Supplementary Table 3: Univariate analysis of the risk factors of hepatocellular carcinoma in patients with cirrhosis and refractory ascites

Variables	Hazard ratio	95% confidence interval	*P*
Age	1.04	1.03-1.05	<0.001
Male gender	0.79	0.59-1.06	0.12
Propranolol use	1.16	0.88-1.53	0.28
Statin use	1.11	0.66-1.86	0.69
Hepatitis B	1.72	1.32-2.24	<0.001
Hepatitis C	2.18	1.65-2.89	<0.001
Alcohol	0.61	0.43-0.86	0.005
Hypertension	1.31	0.99-1.74	0.06
Peptic ulcer disease	0.80	0.62-1.05	0.11
Diabetes	1.36	1.03-1.81	0.03
Myocardial infarction	1.00	0.14-7.16	0.99
Chronic kidney disease	0.82	0.52-1.30	0.39
Peripheral vascular disease	1.16	0.48-2.82	0.74
Dementia	2.20	0.55-8.87	0.27
Cerebrovascular accident	1.57	1.00-2.47	0.048
Dyslipidemia	1.37	0.89-2.11	0.15
Connective tissue disease	1.26	0.89-1.78	0.19
Hemiplegia	1.62	0.67-3.94	0.29
Variceal bleeding	1.11	0.73-1.69	0.61
Hepatic encephalopathy	0.67	0.25-1.80	0.43
Endoscopic therapy	0.72	0.50-1.03	0.07

Supplementary Table 4: Multi-variate analysis of the risk factors of hepatocellular carcinoma in patients with cirrhosis and refractory ascites

Variables	Hazard ratio	95% confidence interval	*P*
Age	1.04	1.02-1.05	<0.001
Hepatitis B	1.64	1.26-2.14	<0.001
Hepatitis C	1.79	1.34-2.38	<0.001
Alcohol	0.94	0.65-1.36	0.76
Diabetes	1.13	0.85-1.51	0.40
Cerebrovascular accident	1.12	0.71-1.77	0.63