*Article*

# Propranolol Treatment is Associated with Better Survival in Cirrhotic Patients with Hepatic Encephalopathy

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**Abstract:** Hepatic encephalopathy (HE) reduces survival in cirrhotic patients and correlates with systemic inflammation and gut-liver disequilibrium. We investigated the association between propranolol treatment and outcomes for cirrhotic patients with HE. Using data from the Taiwan National Health Insurance Research Database, we identified 4,754 cirrhotic patients newly diagnosed with HE. Among them, 519 patients received propranolol treatment and the other 519 patients without exposure to propranolol were enrolled into our study, both of which were matched by sex, age, and propensity score. The median overall survival (OS) was longer in the propranolol-treated cohort than in the untreated cohort (3.46 versus 1.88 years, p<0.001). A dose-dependent increase in survival was observed (median OS: 4.49, 3.29, and 2.46 years in patients treated with propranolol >30mg/day, 20–30mg/day, and <20mg/day, respectively [p<0.001, p=0.001, and p=0.079 versus the untreated group]). In addition to reduce the risk of mortality (adjusted hazard ratio, 0.58; p<0.001), propranolol also diminished the risk of sepsis-related death (adjusted hazard ratio, 0.31; p=0.006) according to the multivariate analysis. However, the risk of circulatory or hepatic failure was non-significantly altered by propranolol treatment. In conclusion, propranolol treatment was associated with a better OS in cirrhotic patients with HE and its effects were dose-dependent.

**Keywords: c**irrhosis; hepatic encephalopathy; propranolol; prognosis

## 1. Introduction

Non-selective beta blockers (NSBBs) have been the mainstay treatment for portal hypertension for more than three decades ever since Lebrec et al. demonstrated the beneficial effects of propranolol on reducing portal pressure and recurrent variceal bleeding in cirrhotic patients [1]. By acting on β-1 receptors (to reduced cardiac output and splanchnic blood flow) and blocking β-2 receptors (to cause splanchnic vasoconstriction), NSBBs can effectively decrease portal venous pressure [2]. Based on several studies [3-6], NSBBs are recommended by the Baveno VI consensus for primary and secondary prophylaxis of variceal bleeding in cirrhotic patients [7].

Despite these clinical benefits, a previous retrospective study from Sersté T et al. declared that treatment with NSBBs is associated with increased mortality in cirrhotic patients with refractory ascites [8]. Furthermore, another retrospective study also suggested the correlation between NSBB therapy and increased mortality in patients with spontaneous bacterial peritonitis (SBP) because of the development of hepato-renal syndrome [9]. However, other studies could not confirm these deleterious outcomes in NSBB users, even in those patients who went on to develop acute-on-chronic liver failure (ACLF) [10-13].

Hepatic encephalopathy (HE) is a neuropsychiatric complication associated with advanced liver disease or porto-systemic shunts. HE significantly impairs the quality of life and survival of cirrhotic patients [14]. This disease displays a wide spectrum of clinical manifestations including minor cognitive dysfunction, lethargy, and even coma [15]. In addition to hyperammonemia resulting from decreased detoxification in the liver or the presence of porto-systemic shunts [16], inflammation, immune dysfunction, leaky intestinal barriers, and alterations in gut microbiota and their by-products (such as endotoxins) play important roles in the development of HE [17]. Considering the beneficial effects of NSBBs on gut permeability [18,19] and systemic inflammation [11] which are closely related to HE [20-22], we investigated the influence of this drug on the health outcomes for cirrhotic patients with HE using a population-based cohort study.

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## 2. Materials and Methods

### 2.1. Study Design and Study Population

This population-based cohort study was conducted by retrieving data from the National Health Insurance Research Database (NHIRD) of Taiwan. Since National Health Insurance covers more than 99% of Taiwan's residents, the NHIRD is an excellent source of detailed health care data on more than 25 million enrollees. This dataset includes information for such services as outpatient, inpatient, emergency, dental, traditional Chinese medicine, and prescriptions. It also contains information about the extent of urbanization and enrollees' economic statuses that are reflected by the monthly insurance fee [23,24]. The accuracy of diagnoses for major diseases in the NHIRD has been validated, and details regarding the NHIRD have been described in previous studies [25,26].

The Longitudinal Health Insurance Database (LHID), a subset of NHIRD, is a representative database containing 1,000,000 patients randomly sampled from the registry of all enrollees [27]. In this study, we used the LHID to examine patients tracked from 2000 to 2011. Adult patients aged 20 years or older with a diagnosis of cirrhosis (ICD-9-CM codes, 571.2, 571.5, and 571.6) were initially selected. Among these patients, those without a history of HE at the time of enrollment and who subsequently developed HE (ICD-9-CM code, 572.2) between January 1, 2000 and December 31, 2010 were enrolled in our study cohort. Patients were excluded if they underwent liver transplantation or were followed-up for less than 90 days. This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (IRB number: 2017–10–002CC).

### 2.2. Definition of Study Cohorts

Adult cirrhotic patients, who had been newly diagnosed with HE during the study period, were divided into two cohorts, based on whether or not they had been treated with propranolol for at least 90 days. To avoid biases arising from treatment with other NSBBs, we excluded patients treated with nadolol or carvedilol. Furthermore, the treated and untreated cohorts were one-to-one matched by age, sex, and propensity score.

### 2.3. Main Outcomes and Measurements

The untreated and treated cohorts were followed-up after diagnosis of HE or initiation of propranolol. Both cohorts were followed until the date of death or the end of 2011. The main outcomes were the overall mortality and its correlation to propranolol dosage. Furthermore, detailed causes of death and risk factors for mortality were also identified.

### 2.4. Assessment of and Adjustment for Confounders

Because of different baseline characteristics between the propranolol-treated and untreated groups, we performed a propensity score-matched analysis after patient selection to reduce potential biases [28]. The propensity score was calculated to assess the likelihood of being treated with propranolol using multivariate logistic regression analysis, which was conditional on the baseline covariates listed in **Table 1** and other comorbidities involved in the Charlson Comorbidity Index. The Greedy 8 to 1 digit match algorithm was used to create propensity-score-matched pairs without replacement (1:1 match) [29].

**Table 1. Study Cohort Characteristics**

| | Before propensity score-matched | | | After propensity score-matched | | |
|---|---|---|---|---|---|---|
| | PPL user | Non-user | *p* | PPL user | Non-user | *p* |
| Characteristics | (*n* = 650) | (*n* = 1,177) | | (*n* = 519) | (*n* = 519) | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Age, mean (SD), yrs. | 53.1 (12.9) | 60.1 (14.8) | < 0.001 | 54.1 (13.0) | 54.0 (12.9) | 0.500 |
| Sex, no. (%) | | | | | | |
| Female | 163 (25.1) | 394 (33.5) | < 0.001 | 127 (24.5) | 127 (24.5) | 1.000 |
| Male | 487 (74.9) | 783 (66.5) | | 392 (75.5) | 392 (75.5) | |
| Follow-up, yrs. | | | | | | |
| Mean (SD) | 2.7 (1.7) | 1.8 (1.6) | < 0.001 | 2.7 (1.7) | 2.0 (1.6) | < 0.001 |
| Median (IQR) | 2.4 (1.2–4.5) | 1.2 (0.5–2.6) | | 2.3 (1.2–4.6) | 1.4 (0.6–3.1) | |
| Etiology of cirrhosis, no. (%) | | | | | | |
| Other | 31 (4.8) | 150 (12.7) | < 0.001 | 28 (5.4) | 34 (6.5) | 0.121 |
| Viral hepatitis | 375 (57.7) | 705 (59.9) | | 291 (56.1) | 293 (56.5) | |
| Alcohol | 244 (37.5) | 322 (27.4) | | 200 (38.5) | 192 (37.0) | |
| Cirrhosis related diseases, no. (%) | | | | | | |
| Ascites | 168 (25.8) | 303 (25.7) | 0.962 | 139 (26.8) | 126 (24.3) | 0.352 |
| Gastroesophageal varices | 245 (37.7) | 207 (17.6) | < 0.001 | 150 (28.9) | 139 (26.8) | 0.227 |
| SBP | 24 (3.7) | 69 (5.9) | 0.043 | 20 (3.9) | 20 (3.9) | 1.000 |
| Hepatocellular carcinoma | 90 (13.8) | 254 (21.6) | < 0.001 | 78 (15.0) | 86 (16.6) | 0.458 |
| Cirrhosis related medical service utilization, times [a] /yr. | | | | | | |
| Mean (SD) | 5.2 (6.9) | 4.1 (6.5) | < 0.001 | 4.5 (6.7) | 4.5 (6.7) | 0.989 |
| Median (IQR) | 2 (0–8) | 1 (0–6) | | 2 (0–6) | 1 (0–7) | |
| Lactulose prescription (%) | 588 (90.5) | 1087 (92.4) | 0.184 | 466 (89.8) | 481 (92.7) | 0.079 |
| Monthly insurance fee, no. (%) | | | | | | |
| > 21,899 NTD | 140 (21.5) | 198 (16.8) | 0.004 | 107 (20.6) | 112 (21.6) | 0.946 |
| 15,840 – 21,899 NTD | 232 (35.7) | 400 (34.0) | | 184 (35.5) | 182 (35.0) | |
| < 15,840 NTD | 154 (23.7) | 275 (23.4) | | 122 (23.5) | 112 (21.6) | |
| Dependent | 124 (19.1) | 304 (25.8) | | 106 (20.4) | 113 (21.8) | |
| Urbanization level [b], no. (%) | | | | | | |
| Level 1 | 322 (49.6) | 574 (48.8) | 0.135 | 261 (50.3) | 249 (48.0) | 0.933 |
| Level 2 | 236 (36.3) | 474 (40.3) | | 193 (37.2) | 194 (37.4) | |
| Level 3 | 82 (12.6) | 112 (9.5) | | 57 (11.0) | 66 (12.7) | |
| Level 4 (rural) | 10 (1.5) | 17 (1.4) | | 8 (1.5) | 10 (1.9) | |
| Major coexisting diseases, no. (%) | | | | | | |
| Congestive heart failure | 24 (3.7) | 64 (5.4) | 0.095 | 22 (4.2) | 15 (2.9) | 0.209 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Hypertension | 142 (21.8) | 352 (29.9) | < 0.001 | 121 (23.3) | 116 (22.4) | 0.697 |
| Arrhythmia | 23 (3.5) | 57 (4.8) | 0.192 | 19 (3.7) | 16 (3.1) | 0.590 |
| Coronary artery disease | 54 (8.3) | 107 (9.1) | 0.572 | 39 (7.5) | 44 (8.5) | 0.558 |
| Cerebral vascular disease | 37 (5.7) | 115 (9.8) | 0.003 | 36 (6.9) | 38 (7.3) | 0.808 |
| COPD | 50 (7.7) | 155 (13.2) | < 0.001 | 39 (7.5) | 54 (10.4) | 0.100 |
| Chronic kidney disease | 26 (4.0) | 115 (9.8) | < 0.001 | 23 (4.4) | 20 (3.9) | 0.631 |
| Diabetes mellitus | 172 (26.5) | 368 (31.3) | 0.031 | 143 (27.6) | 144 (27.7) | 0.942 |
| Dyslipidemia | 52 (8.0) | 75 (6.4) | 0.190 | 33 (6.4) | 42 (8.1) | 0.272 |
| Peptic ulcers | 295 (45.4) | 476 (40.4) | 0.041 | 222 (42.8) | 208 (40.1) | 0.378 |
| Malignancy | 100 (15.4) | 271 (23.0) | < 0.001 | 88 (17.0) | 91 (17.5) | 0.792 |
| Charlson comorbidity index | | | | | | |
| Mean (SD) | 4.51 (1.58) | 5.05 (1.94) | < 0.001 | 4.56 (1.63) | 4.63 (1.77) | 0.472 |
| Median (IQR) | 4 (3–5) | 5 (3–6) | | 4 (3–6) | 4 (3–5) | |
| | | | | | | |
| Propensity score | | | | | | |
| Mean (SD) | 0.45 (0.18) | 0.31 (0.16) | | 0.40 (0.15) | 0.40 (0.16) | |
| Median (IQR) | 0.43 (0.33–0.57) | 0.29 (0.18–0.42) | < 0.001 | 0.40 (0.29–0.49) | 0.40 (0.29–0.49) | 0.167 |

[a] Cirrhosis related medical service utilization: the sum of total emergency department visit, outpatient visits, hospitalization with the primary diagnosis of liver cirrhosis in one year before the index day.

[b] Urbanization level: Urbanization levels in Taiwan are divided into 4 strata according to the Taiwan National Health Research Institute. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.[23]

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PPL, propranolol; SBP, spontaneous bacterial peritonitis; SD, standard deviation; NTD, new Taiwan dollar.

### 2.5. Statistical Analysis

The Kaplan-Meier method was employed for survival analyses, and statistical significance was based on a log-rank test. Multivariate analyses and stratified analyses were carried out using a modified Cox proportional hazards models after adjusting for age, sex, and the other covariates listed in Table 1 to determine the independent risk factors for overall mortality or specific causes of death. All risk factors were treated as time-dependent variables to avoid the immortal time bias [30]. A lag time of one year was also used to avoid a detection bias and misclassification bias. The results were expressed with the estimated numbers, and the 95% confidence intervals (CIs). A two-tailed $p$ value < 0.05 was considered statistically significant for all analyses.

## 3. Results

### 3.1. Identification of the Study Cohort

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We identified 4,754 adult cirrhotic patients newly diagnosed with HE between January 1, 2000 and December 31, 2010. After excluding 1,984 patients who had a short follow-up period of less than 90 days and 34 patients who underwent liver transplantation, all remaining participants were divided into two cohorts according to whether or not they were treated with propranolol. As shown in **Figure 1**, 765 patients receiving propranolol for less than 90 days and 75 patients prescribed with nadolol or carvedilol were excluded from the treated cohort. Likewise, 69 patients treated with nadolol or carvedilol were excluded from the untreated cohort. Patients were one-to-one match by age, sex, and propensity score, resulting in 519 patients allocated to each cohort for analysis. The mean duration of propranolol therapy was 1.18 years (standard deviation [SD]: 1.22 years).

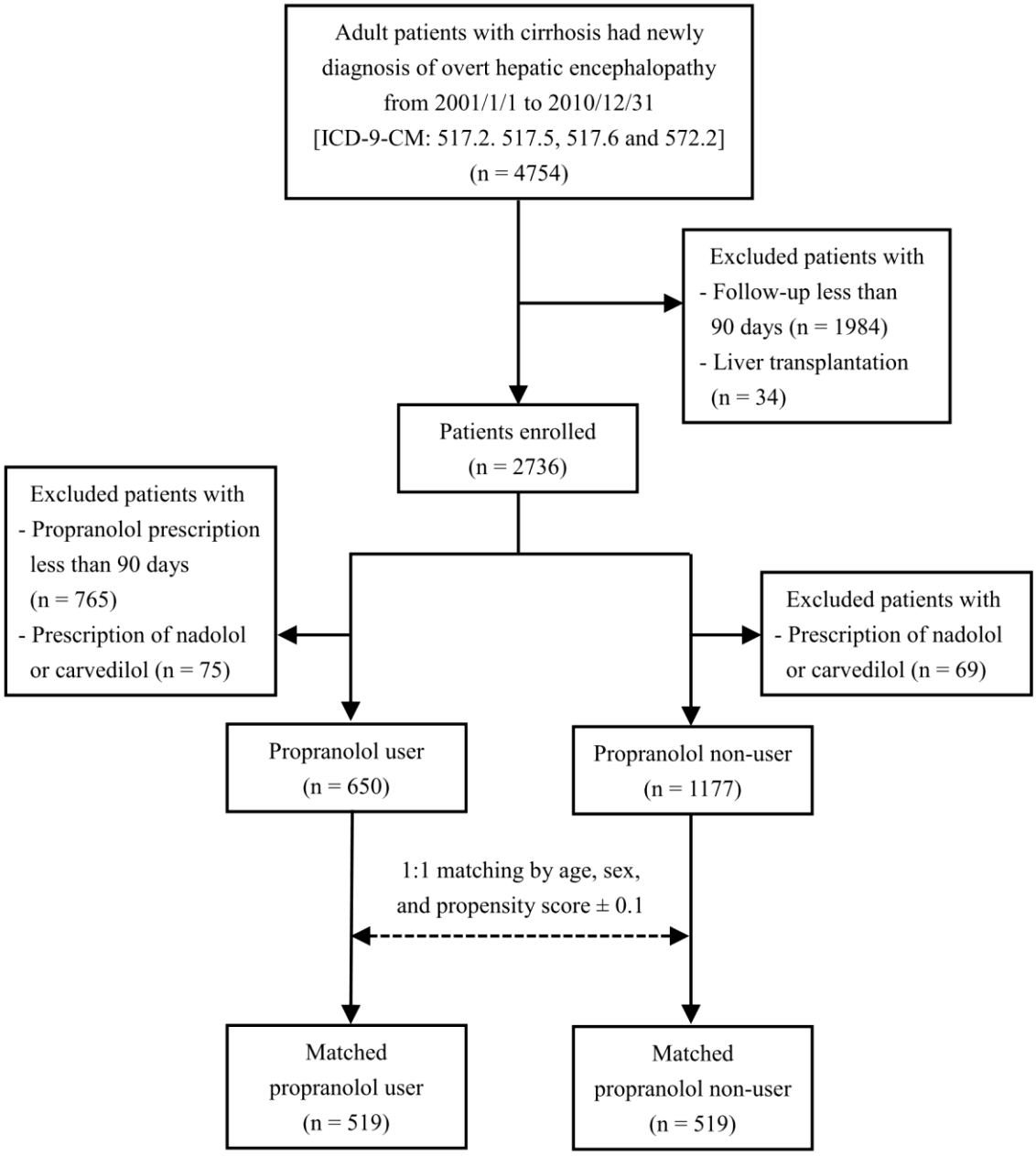


**Figure 1. Selection of Study Cohort.**

### 3.2. Demographic Characteristics of the Study Cohort

Demographic characteristics, comorbidities and socioeconomic statuses of the patients are presented in **Table 1.** Both cohorts were male-predominant; however, the propranolol users were significantly younger, and their average follow-up duration was longer than its counterpart. Viral hepatitis was the major cause of cirrhosis in both groups. The propranolol-treated cohort had more

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cases of gastroesophageal varices and received more medical care related to cirrhosis. In contrast, the untreated cohort presented with more cases of SBP and HCC. In addition, the treated cohort had a better personal income which was reflected by the monthly insurance fee, fewer underlying diseases, and a lower value on the Charlson Comorbidity Index. Moreover, the mean (and median) propensity score for the treated and untreated cohorts were 0.45 (0.43), and 0.31 (0.29), respectively ($p < 0.001$). After one-to-one matching, both cohorts had similar characteristics. However, the follow-up durations for the treated cohort (median 2.3, interquartile range [IQR] 1.2–4.6 years) were still significantly longer than the counterpart (median 1.4, IQR 0.6–3.1 years). Additionally, the mean duration of propranolol treatment in the treated cohort was 1.18±1.22 years after matching.

### 3.3. Overall Survival (OS) of the Study Cohort

As shown in Fig. 2A, significantly better OS was observed in patients received propranolol treatment (median OS: 3.46 years, 95% CI: 2.80–4.13) compared with the untreated ones (median OS: 1.88 years, 95% CI: 1.60–2.15). Besides, the survival rates increased with propranolol treatment in a dose-dependent manner. The median OS was 4.49, 3.29, and 2.46 years in patients treated with propranolol at the dosage of >30 mg/day, 20–30 mg/day, and <20 mg/day, respectively. ($p$<0.001, $p$=0.001, and $p$=0.079 versus the untreated group, respectively) (Fig. 2B).

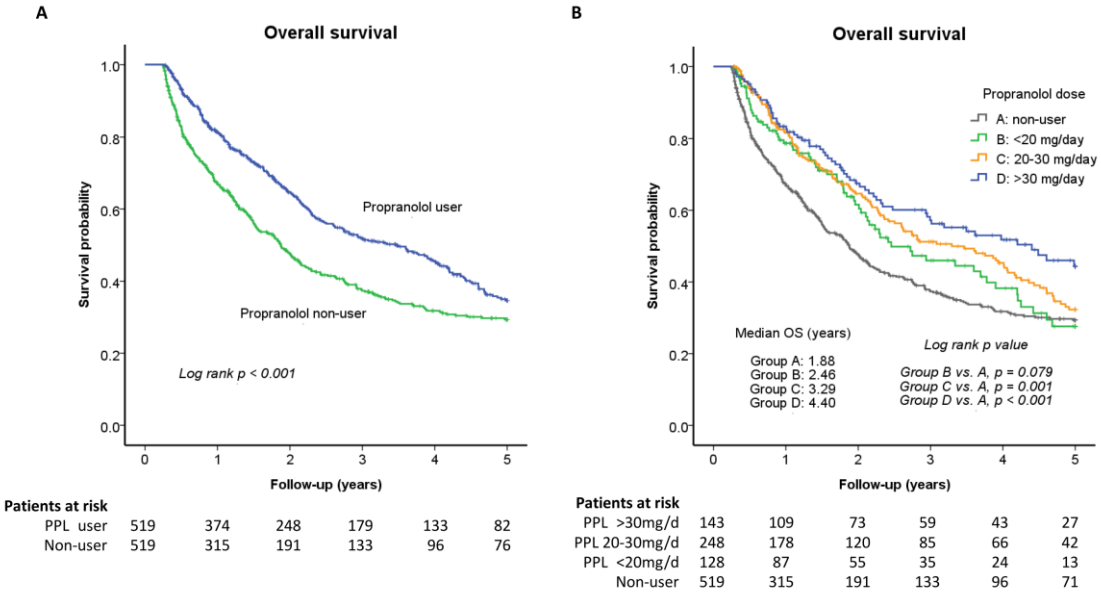


**Figure 2. Overall Survival of Patients with Hepatic Encephalopathy. The overall survival is dependent on (A) propranolol treatment and (B) different doses of propranolol. OS, overall survival.**

### 3.4. Multivariate Analysis

Compared to the untreated cohort, the propranolol-treated patients experienced a significantly lower risk for mortality (Hazard ratio [HR], 0.58; 95% CI, 0.46–0.72). On the other hand, patients aged 60 years or older and those with cirrhotic complications, such as ascites, gastroesophageal varices, SBP, and HCC, had a higher risk of mortality than their counterparts **(Table 2)**.

**Table 2. Risk factors predicting mortality**

| | No. of deaths | Exposure time, patient-years | HR (95% CI)[a] | *p* |
|---|---|---|---|---|
| Propranolol | | | | |
| Non-user | 489 | 1,925 | 1 [Reference] | |
| User | 94 | 571 | 0.58 (0.46-0.72) | <0.001 |

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| | | | | | |
|---|---|---|---|---|---|
| Age | | | | | |
| | < 50 yrs. | 199 | 1,131 | 1 [Reference] | |
| | 50–59 yrs. | 164 | 696 | 1.18 (0.95-1.48) | 0.140 |
| | ≥ 60 yrs. | 220 | 669 | 1.46 (1.13-1.88) | 0.004 |
| Sex | | | | | |
| | Female | 177 | 542 | 1 [Reference] | |
| | Male | 406 | 1,954 | 0.83 (0.66-1.04) | 0.103 |
| Viral hepatitis | | | | | |
| | No | 235 | 1,140 | 1 [Reference] | |
| | Yes | 348 | 1,356 | 0.91 (0.64-1.29) | 0.577 |
| ALD | | | | | |
| | No | 387 | 1,476 | 1 [Reference] | |
| | Yes | 196 | 1,020 | 0.86 (0.59-1.26) | 0.429 |
| Ascites | | | | | |
| | No | 411 | 1,951 | 1 [Reference] | |
| | Yes | 172 | 545 | 1.27 (1.04-1.55) | 0.021 |
| Gastroesophageal varices | | | | | |
| | No | 395 | 1,916 | 1 [Reference] | |
| | Yes | 188 | 580 | 1.25 (1.03-1.52) | 0.028 |
| SBP | | | | | |
| | No | 555 | 2,444 | 1 [Reference] | |
| | Yes | 28 | 52 | 1.91 (1.28-2.86) | 0.002 |
| Hepatocellular carcinoma | | | | | |
| | No | 455 | 2,210 | 1 [Reference] | |
| | Yes | 128 | 286 | 1.62 (1.26–2.09) | <0.001 |
| Hypertension | | | | | |
| | No | 436 | 2,007 | 1 [Reference] | |
| | Yes | 147 | 489 | 1.12 (0.90-1.38) | 0.315 |
| Diabetes mellitus | | | | | |
| | No | 405 | 1,865 | 1 [Reference] | |
| | Yes | 178 | 631 | 0.91 (0.73-1.14) | 0.396 |
| Chronic kidney disease | | | | | |
| | No | 554 | 2,423 | 1 [Reference] | |
| | Yes | 29 | 73 | 1.52 (1.03-2.24) | 0.036 |
| Coronary artery disease | | | | | |
| | No | 528 | 2,314 | 1 [Reference] | |
| | Yes | 55 | 182 | 1.02 (0.75-1.37) | 0.922 |
| Arrhythmia | | | | | |
| | No | 565 | 2,413 | 1 [Reference] | |
| | Yes | 18 | 83 | 0.84 (0.52-1.36) | 0.475 |
| Dyslipidemia | | | | | |
| | No | 547 | 2,338 | 1 [Reference] | |

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| | | | | |
|---|---|---|---|---|
| Yes | 36 | 158 | 0.98 (0.68-1.40) | 0.901 |
| Cirrhosis associated medical service utilization | | | | |
| 0–4 visits | 366 | 1,734 | 1 [Reference] | |
| 5–9 visits | 93 | 351 | 1.01 (0.79-1.29) | 0.928 |
| 10–14 visits | 63 | 234 | 1.08 (0.81-1.44) | 0.614 |
| ≧15 visits | 61 | 177 | 1.19 (0.88-1.59) | 0.262 |
| Charlson comorbidity index | | | | |
| 3 | 136 | 905 | 1 [Reference] | |
| 4 | 163 | 700 | 1.31 (1.02-1.66) | 0.031 |
| ≧5 | 284 | 891 | 1.33 (0.99-1.79) | 0.056 |
| Urbanization level | | | | |
| Level 1 | 286 | 1,235 | 1 [Reference] | |
| Level 2 | 221 | 928 | 1.00 (0.83-1.20) | 0.990 |
| Level 3 | 63 | 289 | 0.86 (0.65-1.14) | 0.294 |
| Level 4 (rural) | 13 | 44 | 1.30 (0.73-2.32) | 0.377 |
| Insurance fee | | | | |
| > 21,899 NTD | 104 | 477 | 1 [Reference] | |
| 15,840 – 21,899 NTD | 210 | 969 | 0.99 (0.77-1.26) | 0.914 |
| < 15,840 NTD | 134 | 539 | 1.25 (0.95-1.64) | 0.110 |
| Dependent | 135 | 511 | 0.93 (0.70-1.22) | 0.584 |

[a]Adjusted for covariates, including age, sex, and comorbidities.

Abbreviations: ALD, alcoholic liver disease; HR, hazard ratio; NTD, new Taiwan dollar; SBP, spontaneous bacterial peritonitis.

### 3.5. Multivariate Stratified Analysis

Propranolol therapy was associated with a lower risk of mortality in most stratified analyses, including in patients who developed HCC. However, the effect was less apparent in patients younger than 50 years old, those with chronic kidney disease or dyslipidemia, and in patients who received more cirrhosis-related medical services probably because of limited patient numbers in each subgroup (**Figure 3**).

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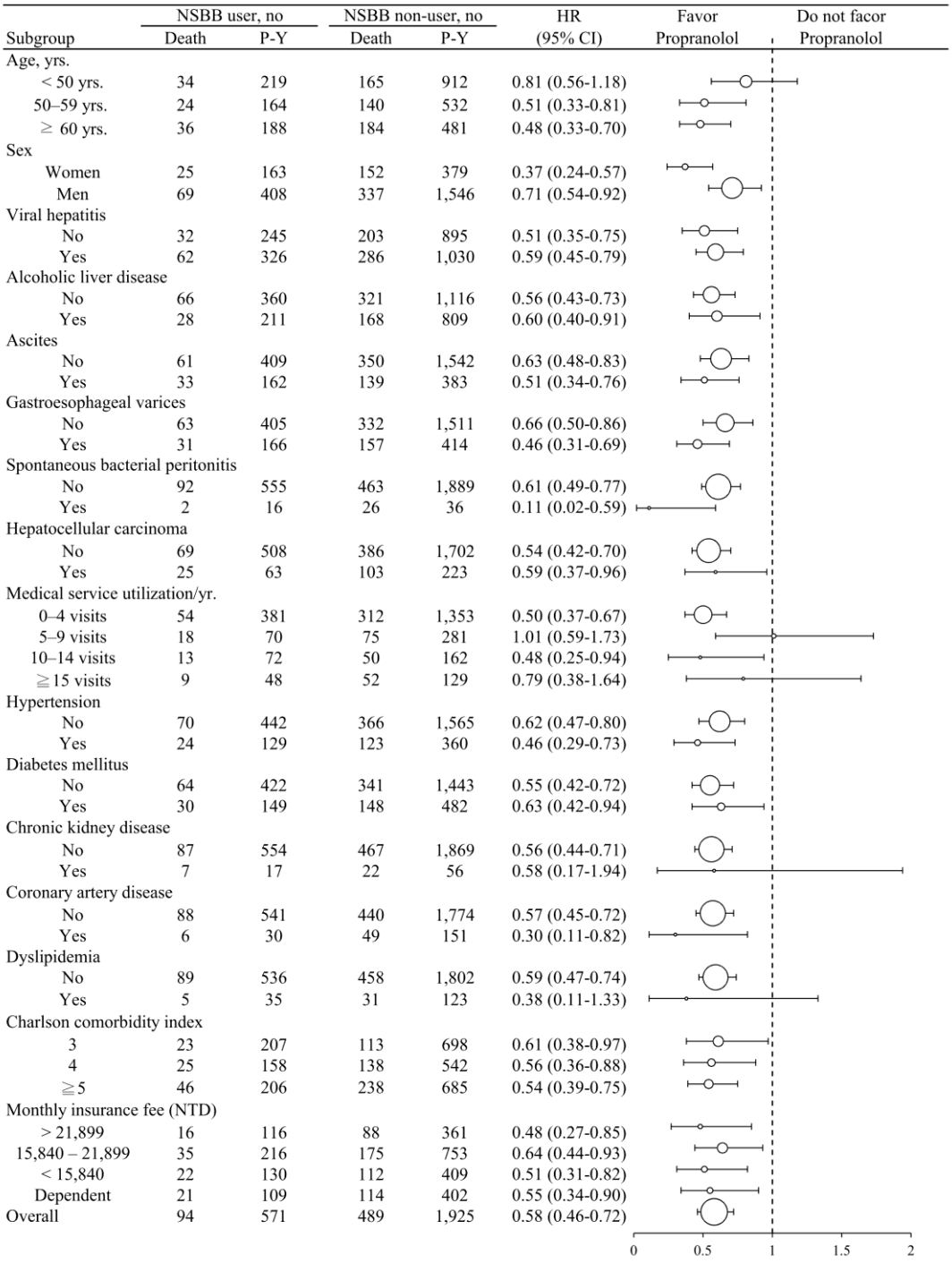


**Figure 3. Multivariate Stratified Analyses for the Association Between Propranolol Treatment and Mortality. All subgroup analyses are adjusted for confounders. CI, confidence interval; HR, hazard ratio; NTD, New Taiwan dollar; P-Y, person-years.**

### 3.6. Detailed Causes of Death

Propranolol treatment reduced the risk of overall mortality in cirrhotic patients with HE. With regard to the causes of death, the risk for sepsis-related death was significantly lower in propranolol treated patients (adjusted HR: 0.31; 95% CI: 0.13–0.71; $p$=0.006) compared to the untreated patients. On the other hand, the treated cohort also had a reduced risk for other causes of death but without statistical significance. This included mortality related to liver failure (adjusted HR: 0.77; 95% CI:

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0.53–1.11), variceal bleeding or upper gastrointestinal bleeding (adjusted HR: 0.83; 95% CI: 0.20–3.51), HCC (adjusted HR: 0.98; 95% CI: 0.56–1.71), and circulatory failure (adjusted HR: 0.24; 95% CI: 0.06–1.06).

## 4. Discussion

This nationwide population-based study examined for the first time about the prognostic effects of propranolol on cirrhotic patients with HE. Our study yielded two conclusions. First, we demonstrated the dose-dependent beneficial effects of propranolol on OS in cirrhotic patients with HE. Second, the use of propranolol was associated with a reduced risk of sepsis-related death in these patients.

HE is characterized by cognitive impairment commonly identified in patients with advanced liver disease or cirrhosis. It was shown to impair the survival of these patients remarkably [31,32]. Besides, HE may even provide additional prognostic information independent of the MELD score [32]. Hyperammonemia is crucial in developing HE by causing astrocyte swelling and cerebral edema [14,20,21]. However, recent evidence suggests that oxidative stress, systemic inflammation, gut dysbiosis, and intestinal barrier dysfunction also contribute to HE development [17,33]. Bacterial overgrowth and an impaired gut barrier result in endotoxemia and systemic inflammation. Many studies have demonstrated that systemic inflammation exacerbates encephalopathy and even plays a more important role than ammonia in cirrhotic patients across all grades of HE [22,34,35]. Thus, current treatments for HE, including lactulose and antibiotics [14], and recent clinical studies related to HE, such as researches on proton pump inhibitors [36,37], all focus on the mechanisms involved in the gut-brain axis. However, evidence for using beta blockers to treat HE is still lacking.

In this study, we demonstrated that propranolol would decrease the risk of sepsis-related death in cirrhotic patients with HE. Apart from attenuating portal hypertension by blocking beta adrenoreceptors, NSBBs was declared to reduce severity of systemic inflammation in ACLF patients based on the observation of significantly lower white blood cell counts [11]. Furthermore, a meta-analysis of randomized trials and observational studies also found that NSBB could reduce the risk of SBP independent of a portal pressure response [38]. These studies suggested that there are non-hemodynamic effects of NSBB in treating cirrhosis [39]. In a prospective human study, propranolol was shown to ameliorate gastroduodenal/intestinal permeability, reduce bacterial translocation, and decrease serum levels of interleukin-6 by 21% in cirrhotic patients [18]. Another human report even demonstrated a reduction in gastric permeability as early as 10 days following the initiation of propranolol treatment [40]. In addition, propranolol can accelerate intestinal transit, decrease bacterial overgrowth and reduce bacterial translocation in ascitic cirrhotic rats [41]. These beneficial effects of NSBB might explain the reduced sepsis-related death observed in our population-based analysis.

For several decades, NSBBs have been effectively used in the primary and secondary prophylaxis of variceal bleeding in cirrhotic patients with significant portal hypertension [7]. However, this treatment was challenged in patients with refractory ascites or SBP because of the theoretically detrimental effects of NSBBs on the cardiac compensatory reserves and renal perfusion [2,42]. In a retrospective study, NSBBs were first reported to have adverse survival outcomes in cirrhotic patients with refractory ascites [8]. However, this study was not well-controlled, and patients receiving NSBB had more advanced cirrhosis in addition to more deaths associated with hepatocellular carcinoma. Nevertheless, Mandorfer et al. demonstrated that NSBBs increased the risks for compromised hemodynamics, longer hospitalizations, acute kidney injury, hepatorenal syndrome, and reduced transplant-free survival among cirrhotic patients with SBP [9]. These clinical studies aroused intense discussion about whether or not to refine the therapeutic window for NSBBs in advanced cirrhosis [39,43,44], particularly because other studies showed beneficial effects of NSBBs on complications related to portal hypertension and mortality [45-47]. The benefits were even observed among patients with ACLF and those listed for liver transplantation [10,11]. In this study, we observed the survival benefit of propranolol in cirrhotic patients with HE. This effect was possibly mediated via the non-hemodynamic effects of propranolol on the gut-brain axis, which was suggested by the observed decrease in sepsis-related death.

On the other hand, the dosage of NSBBs may also affect the survival of cirrhotic patients. In the study by Sersté T et al. which identified the deleterious effects of NSBB, the mean dose of propranolol was 100 mg per day for patients with refractory ascites [8]. Among them, about half of patients received daily propranolol up to 160 mg. In contrast, the median dose of propranolol that provided benefits to patients with ACLF from the CANONIC study was only 40 mg per day [11]. In another retrospective study among patients with SBP, a high dose of NSBBs (160 mg daily) correlated with a higher risk of mortality than placebo group. However, a low dose of NSBBs (80 mg daily) correlated with increased survival after an episode of SBP [48]. Moreover, a recent nationwide Danish study in decompensated cirrhotic patients also found reduced mortality rates for those prescribed propranolol at a dose less than 160 mg per day [49]. In spite of the positive dose-dependent survival benefits of NSBBs, the highest dose of propranolol prescribed to patients in our treated cohort was only 80 mg per day. Therefore, our result is in line with previous studies, but could not be expanded to the HE patients receiving a higher dose of NSBBs.

A key strength of this study is that we examined information taken mainly from a computerized population-based cohort, which was highly representative and had a large sample size. However, there are several limitations to this study. First, information about several potential confounders was not included in this database, such as status of alcohol consumption and biochemical data. Additionally, important prognostic scores, such as the Child-Pugh score and MELD score, could not be calculated. To avoid possible biases arising from baseline discrepancies, the enrolled patients were matched by age, sex, and the propensity score to ensure the comparability of these two cohorts. Second, the dose obtained from the NHIRD was derived from the filled prescriptions, which might not reflect the actual dose taken by the patients. We assumed that all patients had good compliance with their prescriptions, but this could overestimate the actual ingested dosage. Conversely, some patients might have used self-paid propranolol, and thus been misclassified as non-users. Considering that no specific restrictions exist for prescribing propranolol to patients in the coverage of National health insurance in Taiwan, this misclassification might be minimal and could be ignored. Third, coding errors are possible in any database. We were unable to check the accuracy of either the diagnosis of HE or propranolol use in the NHIRD. However, previous studies using the NHIRD found that the accuracy of diagnoses for stroke (94%) and acute coronary syndrome (100%) were quite high, suggesting that the data provided by the NHIRD is highly reliable [25,26]. The enrollment of patients who received NSBB for more than 90 days was also designed to prevent drug-coding errors at each medical visit. Finally, the conclusions we drew cannot be extended to a higher propranolol dose because the maximal dose in our study cohort was only 80 mg per day. In addition, our observations cannot necessarily be extended to another NSBB, such as nadolol or carvedilol, because too few cases identified to be assessed that had been excluded from this study. (Before exclusion, the total nadolol and carvedilol users were 75 and 69 patients, respectively).

## 5. Conclusions

In conclusion, propranolol use is associated with a better OS in cirrhotic patients with HE in a dose-dependent manner. The risk of sepsis-related death was reduced by propranolol treatment, but circulatory or hepatic failure was not significantly affected. Therefore, the prescription of an optimal dose of propranolol should be considered for these patients. Additional prospective studies are needed to confirm these findings.

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