ORIGINAL RESEARCH

Selection of β-Blocker in Patients With Cirrhosis and Acute Myocardial Infarction: A 13-Year Nationwide Population-Based Study in Asia

Victor Chien-Chia Wu, MD;* Shao-Wei Chen, MD;* Pei-Chi Ting, MD; Chih-Hsiang Chang, MD; Michael Wu, MD; Ming-Shyan Lin, MD; Ming-Jer Hsieh, MD; Chao-Yung Wang, MD; Shang-Hung Chang, MD; Kuo-Chun Hung, MD; I.-Chang Hsieh, MD; Pao-Hsien Chu, MD; Cheng-Shyong Wu, MD; Yu-Sheng Lin, MD

***Background*—**It is not clear whether β_1-selective or nonselective β-blockers should be used in patients with cirrhosis and acute myocardial infarction.

***Methods and Results*—**Medical records were retrieved from Taiwan NHIRD (National Health Insurance Research Database) during 2001-2013. Patients were excluded for age <20, previous acute myocardial infarction, contraindication to β-blockers, chronic obstructive pulmonary disease, asthma, or atrioventricular conduction disease. Patients who died during index admission, had a follow-up <6 months, had a medication ratio of either β_1-selective or nonselective β-blocker <80%, or who switched between β-blockers were also excluded. Patients on β_1-selective blockers and nonselective β-blockers were propensity score matched and compared for outcome. Primary outcomes were 1- and 2-year cardiovascular events, liver adverse outcomes, and all-cause mortality. A total of 203 595 patients with acute myocardial infarction were enrolled, of whom 6355 had cirrhosis. After screening for exclusion criteria, 1769 patients (655 patients on β-blockers and 1114 patients not on β-blockers) were eligible for analysis. Among patients on β-blockers, propensity score matching was performed, and 218 patients on β_1-selective blockers and 218 patients on nonselective β-blockers were studied. During a 2-year follow-up, patients on β_1-selective blockers had significantly fewer major cardiac and cerebrovascular events (hazard ratio=0.62; 95% confidence interval=0.42-0.91; *P*=0.014), a trend toward lower all-cause mortality (hazard ratio=0.66; 95% confidence interval=0.38-1.14; *P*=0.135), and nonworsening liver outcome (hazard ratio=0.66; 95% confidence interval=0.38-1.14; *P*=0.354).

***Conclusions*—**In patients with cirrhosis and acute myocardial infarction, selecting a β-blocker is a clinical dilemma. Our study showed that the use of β_1-selective blockers is associated with lower risks of major cardiac and cerebrovascular events. **(*J Am Heart Assoc*. 2018;7:e008982. DOI: 10.1161/JAHA.118.008982.)**

Key Words: acute myocardial infarction • cirrhosis • outcome

Cirrhosis is end-stage liver disease with many debilitating complications and a high risk for mortality. In patients with cirrhosis, portal hypertension inevitably leads to ascites and esophageal varices. The most feared conditions that follow are varicose vein rupture and hematemesis.[1] Approximately half of patients with cirrhosis develop esophageal varices, and one third of these patients may develop a variceal bleed.[2] The reported mortality is up to 50% for the initial bleed and 30% for subsequent bleeds.[3] Few medications were useful in treating variceal bleeding; however introduction of a nonselective β-blocker by Lebrec and colleagues in the 1980s was found to be effective for secondary prevention and later

From the Division of Cardiology (V.C.-C.W., M.-J.H., C.-Y.W., S.-H.C., K.-C.H., I.-C.H., P.-H.C.), Cardiothoracic and Vascular Surgery (S.-W.C.), and Departments of Anesthesiology (P.-C.T.) and Nephrology (C.-H.C.), Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan; Divison of Cardiovascular Medicine, Rhode Island Hospital, Warren Alpert School of Medicine, Brown University, Providence, RI (M.W.); Departments of Cardiology (M.-S.L., Y.-S.L.) and Gastroenterology and Hepatology (C.-S.W.), Chang Gung Memorial Hospital, Chiayi, Taiwan.

Accompanying Tables S1 through S5 and Figures S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008982

*Dr Victor Chien-Chia Wu and Dr Chen contributed equally to this work.

Correspondence to: Yu-Sheng Lin, MD, Department of Cardiology, Chang Gung Memorial Hospital, No. 6 Section West, Jiapu Rd, Chiayi County 613, Taiwan. E-mail: dissertlin@yahoo.com.tw

Received February 26, 2018; accepted August 6, 2018.

Clinical Perspective

What Is New?

- In patients with cirrhosis and incident acute myocardial infarction, choosing an appropriate β-blocker can be complicated.
- Previous studies have not fully explored this topic; therefore, we aimed to investigate which β-blockers could be beneficial for the treatment of concomitant high-risk diseases.

What Are the Clinical Implications?

- In patients with cirrhosis and acute myocardial infarction, our studies showed that the use of β_1-selective blockers is associated with lower risks of major adverse cardiac and cerebrovascular events, a trend toward lower all-cause mortality, and nonworsening liver outcome.
- Accordingly, it is appropriate to use β_1-selective blockers in patients with cirrhosis and acute myocardial infarction.

primary prevention.[4,5] Nonselective β-blockers have theoretical therapeutics on 2 ends: 1 is to halt the rising heart rate, and the other is to decrease blood flow through splanchnic vessels to relieve portal vein hypertension.[6] β_1-Selective blockers were shown to be less effective than nonselective β-blockers in portal hypertension in cirrhotic patients.[7,8]

Although myocardial infarction has been shown to have low incidence in patients with liver cirrhosis,[9] the coexistence of the 2 diseases presents clinical challenges to the physicians who are required to give appropriate and effective treatment in these patients, who have a high risk for mortality.[10] Previous cardiovascular literature has shown that β_1-selective blockers have proven their role in a number of diseases, including coronary artery disease, acute myocardial infarction (AMI), and heart failure, producing fewer side effects while controlling the heart rate.[11] In the event of AMI occurring in patients with cirrhosis, the conflicting nature in the choice between the 2 β-blockers becomes unavoidable. In this study, therefore, we aimed to determine which β-blocker should be recommended and used in patients with both cirrhosis and AMI.

Methods

Data Source

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Taiwan's NHI (National Health Institute) Program started in 1995 and provides 99.5% coverage for the 23 million residents in Taiwan. NHIRD (the NHI Research Database) provides all dates of inpatient and outpatient services, diagnosis, prescriptions, examinations, operations, and expenditures, and data are updated biannually. With over 95% of Taiwan's population being Han Chinese, our study is considered to have a uniform ethnic background. The NHI system offers detailed follow-up information on medication, intervention, admission, outpatient clinic, and emergency visits of patients. In addition, accurate records of health reimbursement are ensured by having prescription of medications and arrangement of interventions be followed by appropriate examinations and by having false reimbursement claims result in magnified penalties. Medications for chronic illnesses were refilled at an outpatient clinic for a maximum period of 3 months per the Taiwan NHI reimbursement policy. Informed consent from study subjects was waived because of the nature of this database study. The Institutional Review Board of Chang Gung Memorial Hospital Linkou Branch approved this study (No. 201800177B1).

Study Patients

By searching electronic medical records from the NHIRD between January 1, 2001 and December 31, 2013, we retrieved patients with a principal diagnosis of AMI admission. We further identified patients with a diagnosis of cirrhosis (2 consecutive outpatient diagnoses or 1 inpatient diagnosis). The diagnoses of AMI and liver cirrhosis in NHIRD have both been validated against hospital electronic medical records in previous studies, with AMI and liver cirrhosis having positive predictive values of 88% and 100%, respectively.[12,13] The date of discharge from the index admission was defined as the index date. Patients who were <20 years old, had experienced previous AMI, or had a contraindication to the use of a β-blocker such as chronic obstructive pulmonary disease, asthma, or atrioventricular conduction disease without pacemaker implantation were excluded. In addition, patients who died during the index admission, follow-up <6 months, medication possession ratio of either β_1-selective blocker or nonselective β-blocker <80% (β_1-selective blockers include bisoprolol, metoprolol, atenolol; nonselective β-blockers include carvedilolol, propranolol) and switching between the 2 kinds of β-blockers were excluded (Figure 1). The remaining patients using β_1-selective blockers and nonselective β-blockers were propensity score matched in the categories of age, sex, comorbidity, hospital level, coronary intervention at the index admission, post-AMI medication, and the index date (Table 1). In addition, liver cirrhosis–related clinical characteristics of the patients were also propensity score matched in the variables of disease leading to cirrhosis (alcohol, hepatitis B virus, and hepatitis C virus), gastrointestinal bleeding, hepatocellular carcinoma, complication of cirrhosis, severity of cirrhosis, and catastrophic illness certificate (Table 2).

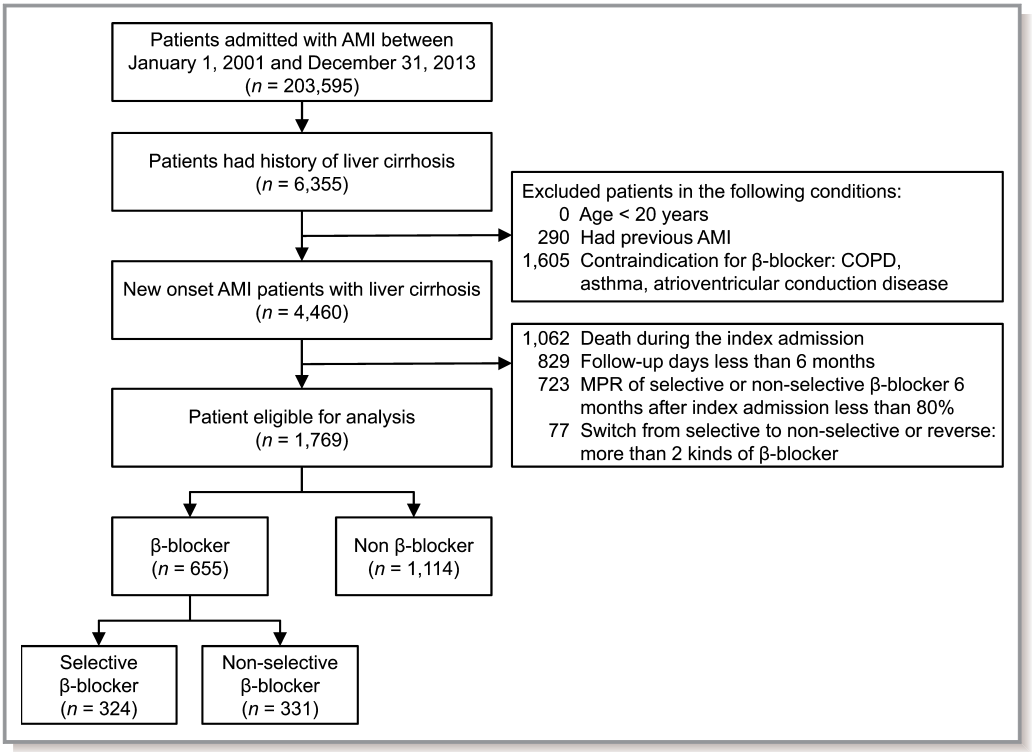


Figure 1. Flow chart for the inclusion of study patients. AMI indicates acute myocardial infarction; COPD, chronic obstructive pulmonary disease; MPR, medication possession ratio.

Covariate and Study Outcomes

Disease was detected using *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* codes. Covariates included sex, age, and clinical medical history of diabetes mellitus, hypertension, hyperlipidemia, heart failure, peripheral arterial disease, atrial fibrillation, history of stroke, chronic kidney disease, end-stage renal disease, malignancy, Charlson comorbidity index, and medications at baseline. One point and 3 points were assigned to mild liver disease and severe liver disease in the Charlson comorbidity index, respectively.[14] The comorbidity was defined as having 2 outpatient diagnoses or 1 inpatient diagnosis in the previous year and also some liver cirrhosis– or AMI-related complications, which were also defined according to the diagnosis of *ICD-9-CM* or related therapies as listed in Table S1. Similarly, use of medication was retrieved based on claim data within 6 months after the index enrollment date.

Outcomes of primary interest included major cardiac and cerebrovascular events (MACCE; which includes all-cause mortality, AMI, heart failure, and stroke), all-cause mortality, cardiovascular death, recurrent myocardial infarction, any revascularization, coronary stenting, heart failure, stroke, new-onset dialysis, liver outcomes (any liver outcome, hepatic encephalopathy, ascites tapping, spontaneous peritonitis, or bleeding from esophageal varices), major bleeding, or any cause of readmission. The detection of new-onset dialysis was verified via catastrophic illness certificate. All time-to-event outcomes (except for death) had to meet an in admission setting. All-cause mortality was defined by withdrawal from the national health insurance.[15] Each patient was followed until the day of outcome occurrence or December 31, 2013, whichever came first. The disease codes and Anatomical/Therapeutic/Chemical codes of medication are provided in Tables S1 and S2.

Statistical Analysis

There might be a nonbalanced distribution in the clinical characteristics between the study patients (ie, β-blocker versus non–β-blocker and selective versus nonselective β-blockers), which can seriously confound the results; therefore, we performed propensity score matching to make the 2 groups comparable. We performed 2 propensity score matchings: the first to match β-blocker users with non–β-blocker users, and the second to match β_1-selective blocker users with nonselective β-blocker users. The propensity score was the predicted probability of being in the β-blocker group (or the β_1-selective blocker group) derived from logistic regression. The covariates included in the propensity score should be variables theoretically and clinically related to outcomes, including demographics (age and sex), 10 comorbidities and Charlson comorbidity index, hospital level, coronary intervention at the index admission, and 8 medications at baseline (listed in Table 1). The index date was also

Table 1. Clinical Characteristics of Study Population Before and After Propensity Score Matching

Variable	Before Matching			After Matching		
	β_1-Selective (n=324)	Nonselective (n=331)	*P* Value	β_1-Selective (n=218)	Nonselective (n=218)	*P* Value
Characteristics						
Age, y	64.1±11.7	64.1±12.4	0.937	64.0±12.1	64.0±12.0	0.963
Age ≥65 y	150 (46.3)	160 (48.3)	0.601	102 (46.8)	102 (46.8)	1.000
Male sex	258 (79.6)	245 (74.0)	0.089	171 (78.4)	167 (76.6)	0.646
Comorbidity						
Hypertension	256 (79.0)	226 (68.3)	0.002	161 (73.9)	162 (74.3)	0.913
Diabetes mellitus	161 (49.7)	168 (50.8)	0.785	108 (49.5)	108 (49.5)	1.000
Hyperlipidemia	127 (39.2)	104 (31.4)	0.037	76 (34.9)	76 (34.9)	1.000
Heart failure	30 (9.3)	39 (11.8)	0.293	22 (10.1)	22 (10.1)	1.000
Peripheral arterial disease	14 (4.3)	22 (6.6)	0.192	12 (5.5)	14 (6.4)	0.686
Atrial fibrillation	22 (6.8)	25 (7.6)	0.705	17 (7.8)	17 (7.8)	1.000
Old stroke	58 (17.9)	49 (14.8)	0.284	34 (15.6)	33 (15.1)	0.894
Chronic kidney disease	86 (26.5)	102 (30.8)	0.227	63 (28.9)	62 (28.4)	0.916
ESRD (dialysis)	25 (7.7)	37 (11.2)	0.130	21 (9.6)	25 (11.5)	0.533
Malignancy	39 (12.0)	46 (13.9)	0.479	29 (13.3)	29 (13.3)	1.000
CCI total score	4.0±2.1	4.4±2.3	0.006	4.1±2.2	4.2±2.2	0.861
Hospital level			0.621			0.923
Medical center (teaching hospital)	167 (51.5)	177 (53.5)		118 (54.1)	119 (54.6)	
Regional/district hospital	157 (48.5)	154 (46.5)		100 (45.9)	99 (45.4)	
Coronary intervention at the index admission	200 (61.7)	183 (55.3)	0.094	132 (60.6)	133 (61.0)	0.922
Post-MI medication						
ACEI or ARB	245 (75.6)	253 (76.4)	0.806	166 (76.1)	171 (78.4)	0.568
CCB	122 (37.7)	100 (30.2)	0.044	73 (33.5)	76 (34.9)	0.762
α-Blocker	31 (9.6)	24 (7.3)	0.285	21 (9.6)	16 (7.3)	0.390
Nitrates	102 (31.5)	90 (27.2)	0.228	68 (31.2)	67 (30.7)	0.917
Diuretics	99 (30.6)	130 (39.3)	0.019	68 (31.2)	66 (30.3)	0.836
Antiplatelet	310 (95.7)	291 (87.9)	<0.001	204 (93.6)	206 (94.5)	0.686
Anticoagulant	17 (5.2)	16 (4.8)	0.809	13 (6.0)	11 (5.0)	0.675
Statin	191 (59.0)	153 (46.2)	0.001	108 (49.5)	116 (53.2)	0.443
Follow-up, y	3.7±2.7	4.2±3.0	0.035	4.2±2.9	4.1±3.1	0.800
Propensity score	0.582±0.181	0.409±0.196	<0.001	0.500±0.160	0.500±0.162	0.979

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CCI, Charlson comorbidity index; ESRD, end-stage renal disease; MI, myocardial infarction.

included in the propensity score to ensure equal potential follow-up duration between groups. In addition, liver cirrhosis–related clinical characteristics were also used to calculate propensity score (listed in Table 2). The matching ratio was 1 to 1. The matching was processed using a greedy nearest-neighbor algorithm with a caliper of 0.2.

We compared the baseline characteristics, comorbidities, and medication between the study groups (β_1-selective blockers versus nonselective β-blockers) using t test for continuous variables or chi-squared test for categorical variables. We compared the risk of all-cause mortality between groups using a Cox proportional hazard model. The risk of other time-to-event outcomes (those not directly related to death, listed in Table 3) was compared between groups using a subdistribution hazard model that considered death during the follow-up as a competing risk.[16] We generated the plot of cumulative incidence rate using subdistribution hazard function for time to event outcomes

Table 2. Liver Cirrhosis–Related Clinical Characteristics of the Patients

Variable	Before Matching			After Matching		
	Selective (n=324)	Nonselective (n=331)	*P* Value	Selective (n=218)	Nonselective (n=218)	*P* Value
Alcoholic cirrhosis	45 (13.9)	43 (13.0)	0.736	24 (11.0)	26 (11.9)	0.764
Viral hepatitis, HBV	77 (23.8)	71 (21.5)	0.479	50 (22.9)	46 (21.1)	0.644
Viral hepatitis, HCV	68 (21.0)	57 (17.2)	0.220	35 (16.1)	40 (18.3)	0.526
Old GI bleeding	108 (33.3)	108 (32.6)	0.848	69 (31.7)	70 (32.1)	0.918
Hepatocellular carcinoma	21 (6.5)	30 (9.1)	0.218	19 (8.7)	16 (7.3)	0.597
Complication of cirrhosis						
Hepatic encephalopathy	7 (2.2)	17 (5.1)	0.043	7 (3.2)	5 (2.3)	0.558
Ascites (diagnosis or treatment)	33 (10.2)	38 (11.5)	0.594	25 (11.5)	21 (9.6)	0.533
EV bleeding (diagnosis or treatment)	6 (1.9)	31 (9.4)	<0.001	6 (2.8)	6 (2.8)	1.000
Admission for FFP (coagulopathy)	44 (13.6)	63 (19.0)	0.059	35 (16.1)	35 (16.1)	1.000
Admission for albumin infusion (hypoalbuminemia)	22 (6.8)	28 (8.5)	0.421	16 (7.3)	19 (8.7)	0.597
Severity of cirrhosis			0.013			0.913
Early cirrhosis	252 (77.8)	229 (69.2)		161 (73.9)	162 (74.3)	
Advanced cirrhosis	72 (22.2)	102 (30.8)		57 (26.1)	56 (25.7)	
Catastrophic illness certificate			0.001			0.703
No	320 (98.8)	311 (94.0)		215 (98.6)	214 (98.2)	
Yes	4 (1.2)	20 (6.0)		3 (1.4)	4 (1.8)	

EV indicates esophageal varices; FFP, fresh frozen plasma; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus.

(ie, major composite liver outcome). In regard to all-cause mortality, we plotted Kaplan-Meier survival curves. Two sensitivity analyses were done. First, the result of comparing risks of MACCE was further adjusted for propensity score. Second, propensity score stratification analysis was done in comparing risks of MACCE. Finally, prespecified subgroup analysis was done on the 2-year MACCE to explore whether the beneficial effect of selective β-blockers was inconsistent across different levels of some subgroups. $P<0.05$ was considered to be statistically significant. No adjustment for multiple testing (multiplicity) was made in this study. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC).

Results

Study Population

There were 203 595 patients admitted with a principal diagnosis of AMI during 2001, and 2013 were identified in the NHIRD. A total of 6355 patients were identified with a history of cirrhosis. After excluding patients <20 years old or with any of the aforementioned clinical exclusion criteria, there were 4460 patients with new-onset AMI and liver cirrhosis. Additionally, patients with death occurring during index admission, follow up <6 months, medication possession ratio of either β-blocker <80% (prescribed within 144 days), or switch of β-blockers were excluded, and there remained 1769 patients eligible for analysis. Among these patients, 655 were on β-blockers, and 1114 were not on β-blockers. The 655 patients were further separated into 324 patients who were on β_1-selective blockers, and 331 patients who were on nonselective β-blockers (Figure 1). A substantial overlap of estimated propensity score between the 2 groups indicated that propensity score matching can be effectively and validly performed (Figure S1A).[17] After matching, the distributions of baseline characteristics, comorbidity, hospital level, coronary intervention, medication, follow-up duration, and liver cirrhosis–related clinical characteristics were similar between selective and nonselective β-blocker groups (right panel in Tables 1 and 2). An overlap of estimated propensity scores between the 2 groups after matching has been noted (Figure S1B).

β-Blocker Versus Non–β-Blocker

We first compared the risk of all-cause mortality in patients with and without β-blockers. After propensity score matching, there were 481 patients in each group. The baseline and

Table 3. Time to Event Outcome During the 1- and 2-Year Follow-Up

Variable	Selective (n=218)	Nonselective (n=218)	Selective vs Nonselective	
			HR (95% CI)*	*P* Value
1-y follow-up				
MACCE†	28 (12.8)	40 (18.3)	0.68 (0.42, 1.10)	0.114
All-cause mortality	9 (4.1)	11 (5.0)	0.81 (0.34, 1.96)	0.646
Cardiovascular death	3 (1.4)	0 (0.0)	NA	NA
Recurrent MI	12 (5.5)	15 (6.9)	0.78 (0.37, 1.67)	0.525
Any revascularization	52 (23.9)	52 (23.9)	0.99 (0.68, 1.46)	0.972
Coronary stenting	28 (12.8)	29 (13.3)	0.96 (0.57, 1.62)	0.889
Heart failure	8 (3.7)	8 (3.7)	1.00 (0.38, 2.66)	1.000
Stroke	7 (3.2)	10 (4.6)	0.70 (0.27, 1.84)	0.469
New-onset dialysis	6 (2.8)	8 (3.7)	0.75 (0.26, 2.17)	0.599
Liver outcomes				
Any liver outcome	11 (5.0)	21 (9.6)	0.50 (0.24, 1.04)	0.064
Hepatic encephalopathy	2 (0.9)	4 (1.8)	0.50 (0.09, 2.69)	0.415
Ascites tapping	6 (2.8)	12 (5.5)	0.49 (0.19, 1.30)	0.150
Spontaneous peritonitis	3 (1.4)	2 (0.9)	1.50 (0.25, 8.95)	0.655
EV bleeding	5 (2.3)	10 (4.6)	0.49 (0.17, 1.43)	0.191
Major bleeding	1 (0.5)	2 (0.9)	0.50 (0.05, 5.45)	0.568
Any cause of readmission	129 (59.2)	122 (56.0)	1.03 (0.81, 1.32)	0.793
2-y follow-up				
MACCE†	43 (19.7)	65 (29.8)	0.62 (0.42, 0.91)	0.015
All-cause mortality	21 (9.6)	31 (14.2)	0.66 (0.38, 1.14)	0.138
Cardiovascular death	7 (3.2)	4 (1.8)	1.69 (0.50, 5.78)	0.402
Recurrent MI	15 (6.9)	21 (9.6)	0.69 (0.36, 1.34)	0.279
Any revascularization	61 (28.0)	66 (30.3)	0.92 (0.65, 1.30)	0.629
Coronary stenting	33 (15.1)	36 (16.5)	0.91 (0.57, 1.46)	0.705
Heart failure	12 (5.5)	15 (6.9)	0.79 (0.37, 1.69)	0.542
Stroke	9 (4.1)	15 (6.9)	0.59 (0.26, 1.36)	0.217
New-onset dialysis	6 (2.8)	10 (4.6)	0.60 (0.22, 1.65)	0.323
Liver outcomes				
Any liver outcome	18 (8.3)	23 (10.6)	0.75 (0.41, 1.38)	0.354
Hepatic encephalopathy	4 (1.8)	4 (1.8)	0.98 (0.25, 3.90)	0.982
Ascites tapping	10 (4.6)	16 (7.3)	0.61 (0.28, 1.33)	0.210
Spontaneous peritonitis	5 (2.3)	4 (1.8)	1.24 (0.33, 4.63)	0.750
EV bleeding	6 (2.8)	10 (4.6)	0.59 (0.22, 1.60)	0.299
Major bleeding	2 (0.9)	3 (1.4)	0.66 (0.11, 3.87)	0.640
Any cause of readmission	153 (70.2)	150 (68.8)	1.00 (0.80, 1.25)	0.992

CI indicates confidence interval; EV, esophageal varices; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.
*Estimated using the Fine and Gray[16] subdistribution hazard model, which considered all-cause mortality as a competing risk. The results of MACCE, all-cause mortality, and cardiovascular death were derived from the Cox proportional hazard model.
†Any 1 of all-cause mortality, MI, heart failure, or stroke.

cirrhosis-related characteristics were well balanced between the 2 groups (Tables S3 and S4). During the study duration, all-cause mortality was assessed in cirrhosis patients with AMI who were on β-blockers or non–β-blockers. As shown in Figure 2, survival curves derived the from Kaplan-Meier estimator showed that patients on β-blockers had

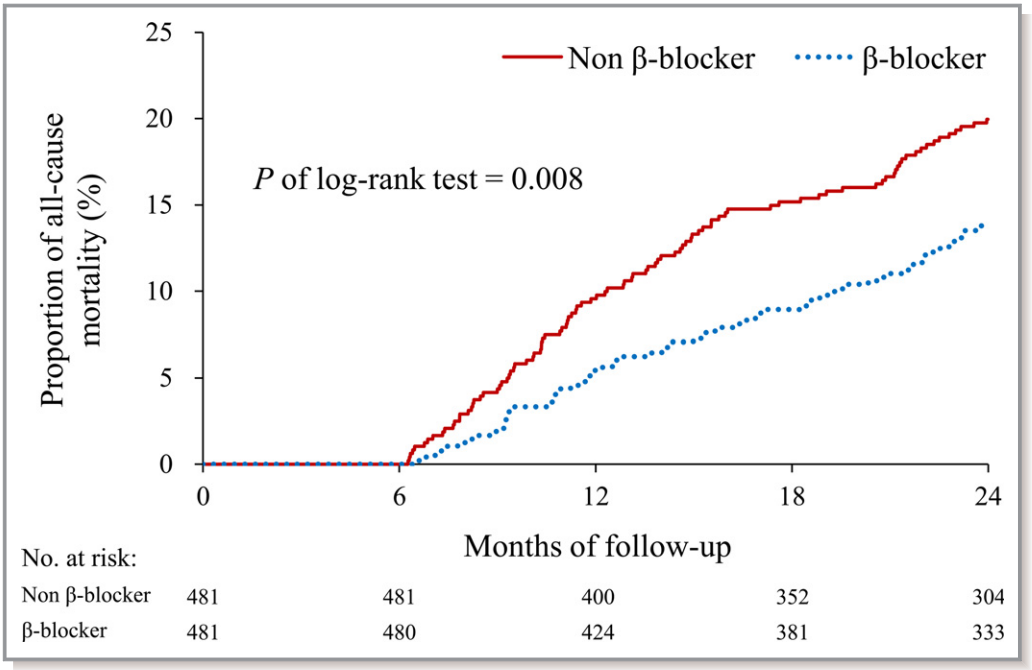


Figure 2. Kaplan-Meier survival curves of all-cause mortality in the β-blocker and non–β-blocker users during a 2-year follow-up.

significantly less risk of mortality compared with patients not on β-blockers throughout the 2-year follow-up (*P* of log-rank test=0.008).

β_1-Selective Blocker Versus Nonselective β-Blocker

As shown in Table 3, there was no difference in the cardiovascular, liver, or mortality outcomes between the groups of patients who were on β_1-selective blockers versus nonselective β-blockers in the 1-year follow-up. Within a 2-year follow-up, MACCE reached statistical significance between β_1-selective blockers and nonselective β-blockers (hazard ratio 0.62; 95% confidence interval 0.42-0.91; *P*=0.015).

In terms of all-cause mortality, the Kaplan-Meier survival curves showed fewer events in patients who were on β_1-selective blockers, but the difference did not reach statistical significance (hazard ratio 0.66; 95% confidence interval 0.38-1.14; *P*=0.135) (Figure 3A). In terms of MACCE, the results showed significantly fewer events in patients who were on β_1-selective blockers throughout the follow-up (hazard ratio 0.62; 95% confidence interval 0.42-0.91; *P*=0.014) (Figure 3B). Sensitivity analyses done by using either adjustment of propensity score (Figure S2) or propensity score stratification analysis (Table S5) showed results similar to those of the primary analysis. In terms of liver outcome, the cumulative incidence plots derived from the competing risk survival model showed fewer events in patients who were on β_1-selective blockers, although the difference did not reach statistical significance (hazard ratio 0.66; 95% confidence interval 0.38-1.14; *P*=0.354) (Figure 3C).

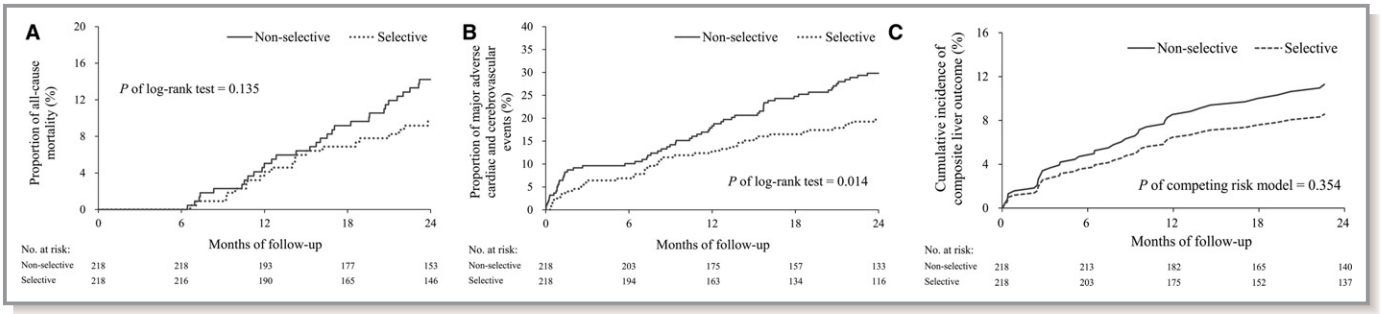


Figure 3. Kaplan-Meier survival curves of all-cause mortality (A) and MACCE (B), and cumulative incidence of major composite liver outcome (C) in the selective β-blocker and nonselective β-blocker users during a 2-year follow-up. MACCE indicates major adverse cardiac and cerebrovascular events.

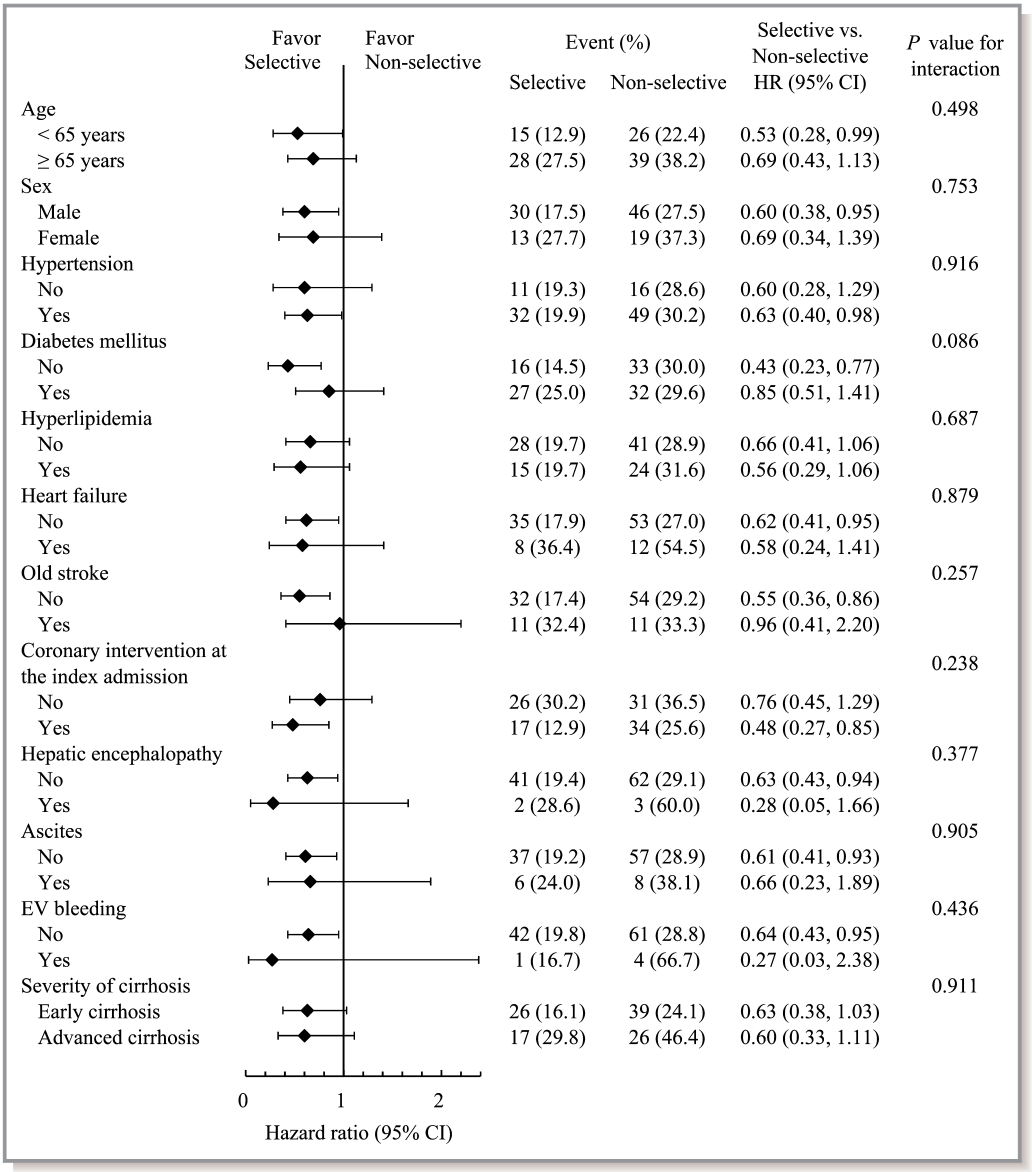


Figure 4. Subgroup analysis of MACCE. CI indicates confidence interval; EV, esophageal varices; HR, hazard ratio.

Figure 4 presents the subgroup analysis in MACCE. The selected subgroups included age group, sex, hypertension, diabetes mellitus, hyperlipidemia, heart failure, stroke, coronary intervention during the index admission, hepatic encephalopathy, ascites, bleeding from esophageal varices, and severity of cirrhosis. Result showed that the observed beneficial effect of β_1-selective blockers on MACCE was comparable across sex, age, comorbidities, coronary intervention, and liver events (*P* for interaction >0.05).

Discussion

Our study had several findings. (1) This is the first study to directly compare the clinical outcome of β_1-selective blockers versus nonselective β-blockers in patients with liver cirrhosis and new-onset AMI using extensive propensity score matching. (2) Use of β_1-selective blockers provided clinical benefits with significantly decreased MACCE with trends toward less all-cause mortality and liver outcomes compared with the use of nonselective β-blockers in the patients with combined cirrhosis and AMI.

In patients with liver cirrhosis, nonselective β-blockers remain the cornerstone of medical treatment of portal hypertension due to the evidence derived from prospective trials of their efficacy in preventing variceal bleeding. However, with increasing knowledge of portal hypertension–induced changes in systemic hemodynamics, cardiac function, and renal perfusion, emerging studies have raised

concerns about the harmful effects of nonselective β-blockers. Clinicians are facing an ongoing controversy about the use of nonselective β-blockers in patients with advanced cirrhosis.[18]

A literature search for patients with liver cirrhosis and concurrent AMI showed a small number of studies that specifically addressed the selection of β-blocking agents for the treatment of coincident high-risk diseases.[9,10] Although there was a possible class effect distinguishing the β_1-selective blocker bisoprolol from the nonselective β-blockers carvedilol and propranolol in the treatment of AMI,[19] the same cannot be extrapolated to β-blocking agents used in the treatment of liver cirrhosis,[18] and currently no data exist regarding the appropriate selection of β-blockers in these patients. Because of the difference in the management strategies in the 2 diseases, we investigated the use of nonselective β-blockers in patients with cirrhosis versus β_1-selective blockers recommended in patients with coexistent AMI and cirrhosis. Propensity score matching was performed in the baseline cardiovascular and liver parameters for 2 groups of patients to study the outcome.

During the 2-year study duration, MACCE was significantly decreased, and there was a trend toward lowered risk of cirrhotic complications and all-cause mortality in patients who were on β_1-selective blockers compared with patients on nonselective β-blockers. Contrary to previous beliefs that only nonselective β-blockers are beneficial in patients with cirrhosis, this is the first study to report evidence that β_1-selective blockers also offer protection in patients with cirrhosis. In this cohort the patients had 2 combined high-risk diseases, and our study end point assessed both cardiovascular outcome and liver outcome as well as all-cause mortality. Our study showed that β_1-selective blockers given to patients with cirrhosis and AMI provided better protection and benefits in terms of MACCE than did nonselective β-blockers at 2-year follow-up. On the other hand, the use of β_1-selective blockers had no significant difference for liver outcome compared with nonselective β-blockers at 1- and 2-year follow-up. In addition, both all-cause mortality and cardiovascular death were not significantly different between the 2 groups. One hypothesis is that patients with AMI had higher risk for MACCE within the 2-year follow-up, and thus, the difference in the use of β-blockers could result in a better outcome with a β_1-selective blocker. However, fewer cases of liver outcome were observed; therefore, the difference in the β-blockers could not result in a discernable liver outcome difference.

In previous studies β-blockers have been shown to be effective in the clinical therapy of patients with heart failure, but only bisoprolol, metoprolol, and carvedilol had evidence from large randomized trials.[20-22] Some reports have noted that β_1-selective blockers are slightly more effective in terms of antihypertensive action than the nonselective blockers. There were data from an early investigation with the β_2-selective blocker ICI 188 551 that blocking of β_2 receptors does not offer the antihypertensive effect of β-blockade[23]; in fact, there was a greater rise in blood pressure due to blocking its β_2 vasodilating effect.[24] Blocking of β_2 receptors by use of nonselective β-blockers may antagonize the slightly vasodilating effect of 2- to 3–mm Hg greater fall in blood pressure observed with blocking at β_1 receptors.[25] β-Blockers with intrinsic sympathomimetic activity are observed to show reduced clinical benefits in patients after AMI; therefore, these drugs should be avoided in this situation.[26] And in this study, our findings supported the pharmacological characteristics of these β-blockers.

In summary, this is the first study to directly compare β_1-selective blockers and nonselective β-blockers in patients with cirrhosis and AMI. Our study suggested lower risks of MACCE in patients at 2-year follow-up on selective β_1-blockers compared with nonselective β-blockers. However, there was no difference of all-cause mortality between these 2 groups.

Limitations

There are several limitations in epidemiologic data from NHIRD. First, the generalizability of the current findings was limited because almost 60% of patients were excluded. The conclusion might apply to patients with AMI and cirrhosis who had relatively low disease severity because patients who died within 6 months were excluded from the analysis. Second, using *ICD-9-CM* codes for patient screening may miss some cases for conditions not coded correctly. However, when *ICD-9-CM* codes have been matched with hospital electronic medical records in validation studies for NHIRD, the *ICD* codes showed a sensitivity of up to 99% for positive predictive value against the gold standard electronic medical records. Third, because of the limitations of NHIRD where laboratory results and clinical evaluations were unavailable, the traditional risk stratification using Child-Pugh criteria in patients with liver cirrhosis could not be performed. However, we used surrogate markers such as the requirement for fresh frozen plasma and albumin transfusion to indicate the patients' coagulopathy and hypoalbuminemia. In addition, due to the nonrandomized assignment of the study patients, differential or nondifferential selection bias may exist in our study even if rigorous exclusion criteria and propensity score matching were applied. Fourth, it is noted that only 1 test (MACCE at 2-years) reached statistical significance among the 32 tests of time to event outcome and may result from type I error inflation (chance). Therefore, further work is warranted to confirm our findings. Last, because our study consisted of people with a uniform ethnic background, application of the results to other populations requires interpretation in the proper context.

Conclusions

In patients with cirrhosis and AMI, selecting a β-blocker to use can be difficult. Our study showed that the use of β_1-selective blockers is associated with lower risks of MACCE.

Acknowledgments

We would like to thank Alfred Hsing-Fen Lin and Zoe Ya-Jhu Syu for their statistical assistance during the completion of this manuscript.

Disclosures

None.

References

1. Rahimi RS, Rockey DC. Complications of cirrhosis. *Curr Opin Gastroenterol*. 2012;28:223–229.
2. Krige JEJ, Kotze UK, Cornman PC, Shaw JM, Klipin M. Variceal recurrence, rebleeding, and survival after endoscopic injection sclerotherapy in 287 alcoholic cirrhotic patients with bleeding esophageal varices. *Ann Surg*. 2006;244:764–770.
3. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Am J Gastroenterol*. 2007;102:2086–2102.
4. Lebrec D, Nouel O, Corbic M, Benhamou JP. Propranolol-a medical treatment for portal hypertension?. *Lancet*. 1980;26:180–182.
5. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. *N Engl J Med*. 1981;305:1371–1374.
6. Ge PS, Runyon BA. The changing role of beta-blocker therapy in patients with cirrhosis. *J Hepatol*. 2014;60:643–653.
7. Hillon P, Lebrec D, Munoz C, Jungers M, Goldfarb G, Benhamou JP. Comparison of the effects of a cardioselective and a nonselective β-blocker on portal hypertension in patients with cirrhosis. *Hepatology*. 1982;2:528–531.
8. Westaby D, Melia WM, Macdougall BR, Hegarty JE, Gimson AE, Williams R. B1 selective adrenoreceptor blockade for the long term management of variceal bleeding. A prospective randomised trial to compare oral metoprolol with injection sclerotherapy in cirrhosis. *Gut*. 1985;26:421–425.
9. Howell WL, Manion WC. The low incidence of myocardial infarction in patients with portal cirrhosis of the liver: a review of 639 cases of cirrhosis of the liver from 17,731 autopsies. *Am Heart J*. 1960;60:341–344.
10. Abougergi MS, Karagozian R, Grace ND, Saltzman JR, Qamar AA. ST elevation myocardial infarction mortality among patients with liver cirrhosis: a nationwide analysis across a decade. *J Clin Gastroenterol*. 2015;49:778–783.
11. DiNicolantonio JJ, Fares H, Niazi AK, Chatterjee S, D'Ascenzo F, Cerrato E, Biondi-Zoccai G, Lavie CJ, Bell DS, O'Keefe JH. β-Blockers in hypertension, diabetes mellitus, heart failure and acute myocardial infarction: a review of the literature. *Open Heart*. 2015;2:e000230.
12. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. *J Epidemiol*. 2014;24:500–507.
13. Lin YT, Wu PH, Lin CY, Lin MY, Chuang HY, Huang JF, Yu ML, Chuang WL. Cirrhosis as a risk factor for tuberculosis infection—a nationwide longitudinal study in Taiwan. *Am J Epidemiol*. 2014;180:103–110.
14. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in *ICD-9-CM* and *ICD-10* administrative data. *Med Care*. 2005;43:1130–1139.
15. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, Lin JT. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA*. 2012;308:1906–1914.
16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
17. Brookhart MA, Wyss R, Layton JB, Stürmer T. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes*. 2013;6:604–611.
18. Reiberger T, Mandorfer M. Beta adrenergic blockade and decompensated cirrhosis. *J Hepatol*. 2017;66:849–859.
19. Lin TT, Chan KA, Chen HM, Lai MS. Class effect of beta-blockers in survivors of ST-elevation myocardial infarction: a nationwide cohort study using an insurance claims database. *Sci Rep*. 2015;5:13692.
20. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, Ponikowski P, Skene A, van de Ven L, Verkenne P, Lechat P; CIBIS III Investigators. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation*. 2005;112:2426–2435.
21. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001–2007.
22. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334:1349–1355.
23. Robb OJ, Webster J, Petrie JC, Harry JD, Young J. Effects of the beta 2-adrenoceptor antagonist ICI 118,551 on blood pressure in hypertensive patients known to respond to beta 1-adrenoceptor antagonists. *Br J Clin Pharmacol*. 1988;25:433–438.
24. Prichard BN, Ross EJ. Use of propranolol in conjunction with alpha receptor blocking drugs in pheochromocytoma. *Am J Cardiol*. 1966;18:394–398.
25. Cruickshank JM. Beta-blockers continue to surprise us. *Eur Heart J*. 2000;21:354–364.
26. Freemantle N, Cleland J, Young P, Mason J, Harrison J. β Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318:1730–1737.

Supplemental Material

Table S1. ICD-9-CM code used for diagnosis in the current study.

Variable	ICD-9-CM code
Acute myocardial infarction	410.xx
Old myocardial infarction	410.xx, 412.xx
Chronic obstructive pulmonary disease	491.xx, 492.xx, 496.xx
Asthma	493.xx
Atrioventricular conduction disease	426.0 (complete AV block), 426.12 (Mobitz type II)
Liver cirrhosis	571.2x, 571.5x, 571.6x
Hypertension	401.xx–405.xx
Diabetes mellitus	250.xx
Hyperlipidemia	272.xx
Heart failure	428.xx
Peripheral arterial disease	440.0x, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x, 444.22, 444.8x, 447.8x, 447.9x
Atrial fibrillation	427.31
Old stroke	430.xx–437.xx
Chronic kidney disease	580.xx–589.xx, 403.xx–404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
ESRD (dialysis)	585.xx (Catastrophic illness card)
Malignancy	140.xx–208.xx (Catastrophic illness card)
Alcoholic cirrhosis	571.2
Virus hepatitis, HBV	070.20, 070.22, 070.30, 070.32, V02.61
Virus hepatitis, HCV	070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V02.62
Gastrointestinal bleeding	530.21, 530.7, 530.82, 531.xx–534.xx, 535.xx, 537.83, 537.84, 578.xx
Hepatocellular carcinoma	155.xx (Catastrophic illness card)
Hepatic encephalopathy	572.2
Ascites	789.5x
Esophageal varices bleeding	456.0, 456.20
Spontaneous peritonitis	567.2x, 567.8x, 567.9x

Table S2. ATC code used for medication in the current study.

Variable	ATC code
Angiotensin-converting enzyme inhibitors / angiotensin receptor blockers	C09
Calcium channel blockers	C08
α blocker	C02
Nitrates	C01
Diuretics	C03
Antiplatelet	B01AC
Anticoagulant	B01AA
Statin	C10AA
Beta-blocker	C07
Selective beta-blocker	C07AB07, C07AB02, C07BB02, C07AB03, C07BB03
Non-selective beta-blocker	C07AG02, C07AA05
Bisoprolol	C07AB07
Carvediolol	C07AG02

Table S3. Clinical characteristics of study population before and after propensity score matching.

	Before matching			After matching		
Variable	β1-blocker (*n* = 655)	Non β-blocker (*n* = 1,114)	*P*	β1-blocker (*n* = 481)	Non β-blocker (*n* = 481)	*P*
Characteristics						
Age, years	64.1±12.0	66.0±14.1	0.003	65.0±12.1	65.4±12.9	0.617
Age ≥ 65 years	310 (47.3)	615 (55.2)	0.001	246 (51.1)	249 (51.8)	0.847
Male sex	503 (76.8)	775 (69.6)	0.001	361 (75.1)	355 (73.8)	0.657
Comorbidity						
Hypertension	482 (73.6)	668 (60.0)	<0.001	343 (71.3)	357 (74.2)	0.311
Diabetes mellitus	329 (50.2)	495 (44.4)	0.018	239 (49.7)	237 (49.3)	0.897
Hyperlipidemia	231 (35.3)	238 (21.4)	<0.001	152 (31.6)	144 (29.9)	0.576
Heart failure	69 (10.5)	165 (14.8)	0.010	52 (10.8)	59 (12.3)	0.480
Coronary artery disease	211 (32.2)	286 (25.7)	0.003	143 (29.7)	154 (32.0)	0.443
Peripheral arterial disease	36 (5.5)	53 (4.8)	0.493	24 (5.0)	20 (4.2)	0.537
Atrial fibrillation	47 (7.2)	108 (9.7)	0.070	41 (8.5)	42 (8.7)	0.909
Old stroke	107 (16.3)	222 (19.9)	0.061	77 (16.0)	79 (16.4)	0.861
Chronic kidney disease	188 (28.7)	330 (29.6)	0.681	135 (28.1)	139 (28.9)	0.775
ESRD (dialysis)	62 (9.5)	104 (9.3)	0.928	43 (8.9)	43 (8.9)	1.000
Malignancy	85 (13.0)	137 (12.3)	0.677	61 (12.7)	60 (12.5)	0.923
CCI total score	4.2±2.2	4.6±2.6	0.001	4.3±2.2	4.4±2.6	0.790
Hospital level			<0.001			0.332
Medical center (teaching hospital)	344 (52.5)	389 (34.9)		231 (48.0)	216 (44.9)	
Regional / district hospital	311 (47.5)	725 (65.1)		250 (52.0)	265 (55.1)	
Coronary intervention at index admission (CABG or PCI)	383 (58.5)	353 (31.7)	<0.001	254 (52.8)	250 (52.0)	0.796
Post MI medication						
ACEI or ARB	498 (76.0)	541 (48.6)	<0.001	345 (71.7)	348 (72.3)	0.829
CCB	222 (33.9)	311 (27.9)	0.008	165 (34.3)	160 (33.3)	0.733
α blocker	55 (8.4)	70 (6.3)	0.094	43 (8.9)	40 (8.3)	0.730
Nitrates	192 (29.3)	240 (21.5)	<0.001	143 (29.7)	152 (31.6)	0.529
Diuretics (include spironolactone)	229 (35.0)	386 (34.6)	0.894	185 (38.5)	173 (36.0)	0.423

Antiplatelet (aspirin or clopidogrel)	601 (91.8)	663 (59.5)	<0.001	427 (88.8)	432 (89.8)	0.602
Anticoagulant (Warfarin or NOAC)	33 (5.0)	58 (5.2)	0.877	25 (5.2)	25 (5.2)	1.000
Statin	344 (52.5)	256 (23.0)	<0.001	199 (41.4)	204 (42.4)	0.744
Follow-up (years)	3.9±2.9	3.8±3.1	0.346	4.0±2.9	3.8±2.9	0.166
Propensity score	0.514±0.190	0.286±0.210	<0.001	0.539±0.185	0.541±0.182	0.871

ESRD, end stage renal disease; CCI, Charlson Comorbidity Index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitors, ARB, angiotensin receptor blockers; CCB, calcium channel blockers; NOAC, novel oral anticoagulant.

Table S4. Liver cirrhosis related clinical characteristics of the patients before and after propensity score matching.

	Before matching			After matching		
Variable	β-blocker (*n* = 655)	Non β-blocker (*n* = 1,114)	*P*	β-blocker (*n* = 481)	Non β-blocker (*n* = 481)	*P*
Alcoholic cirrhosis	88 (13.4)	216 (19.4)	0.001	73 (15.2)	67 (13.9)	0.583
Virus hepatitis, HBV	148 (22.6)	204 (18.3)	0.029	104 (21.6)	93 (19.3)	0.379
Virus hepatitis, HCV	125 (19.1)	231 (20.7)	0.403	103 (21.4)	93 (19.3)	0.423
Old GI bleeding	216 (33.0)	505 (45.3)	<0.001	166 (34.5)	168 (34.9)	0.892
Hepatocellular carcinoma	51 (7.8)	72 (6.5)	0.291	35 (7.3)	32 (6.7)	0.704
Complication of cirrhosis						
Hepatic encephalopathy	24 (3.7)	94 (8.4)	<0.001	22 (4.6)	24 (5.0)	0.763
Ascites (diagnosis or treatment)	71 (10.8)	182 (16.3)	0.001	58 (12.1)	55 (11.4)	0.764
EV bleeding (diagnosis or treatment)	37 (5.6)	86 (7.7)	0.098	29 (6.0)	19 (4.0)	0.139
Admission for FFP (coagulopathy)	107 (16.3)	227 (20.4)	0.036	80 (16.6)	79 (16.4)	0.931
Admission for albumin infusion (hypoalbuminemia)	50 (7.6)	157 (14.1)	<0.001	42 (8.7)	40 (8.3)	0.817
Severity of cirrhosis			<0.001			0.563
Early cirrhosis	481 (73.4)	718 (64.5)		345 (71.7)	353 (73.4)	
Advanced cirrhosis	174 (26.6)	396 (35.5)		136 (28.3)	128 (26.6)	
Catastrophic illness certificate			0.061			0.624
No	631 (96.3)	1,051 (94.3)		460 (95.6)	463 (96.3)	
Yes	24 (3.7)	63 (5.7)		21 (4.4)	18 (3.7)	

GI, Gastrointestinal; EV, esophageal varices; FFP, fresh frozen plasma.

Table S5. Sensitivity analysis of comparing risks of MACCE between selective and non-selective groups by using propensity score stratification analysis.

	Selective		Non-selective		Selective *vs*. Non-selective	
Quintile	No.	Event (%)	No.	Event (%)	Hazard ratio (95% CI)	*P* value
First	11	25.6	16	36.4	0.71 (0.33, 1.54)	0.388
Second	10	23.3	14	31.8	0.72 (0.32, 1.62)	0.427
Third	8	18.2	11	25.0	0.64 (0.26, 1.60)	0.341
Fourth	8	18.2	15	34.9	0.45 (0.19, 1.06)	0.068
Fifth	6	13.6	9	20.9	0.64 (0.23, 1.81)	0.403
Combined	**43**	**19.7**	**65**	**29.8**	**0.63 (0.43, 0.92)**	**0.018**

MACCE, major adverse cardiac and cerebrovascular events; CI, confidence interval.

Figure S1. The distribution of the estimated propensity score stratified by treatment status before matching (A) and after matching (B).

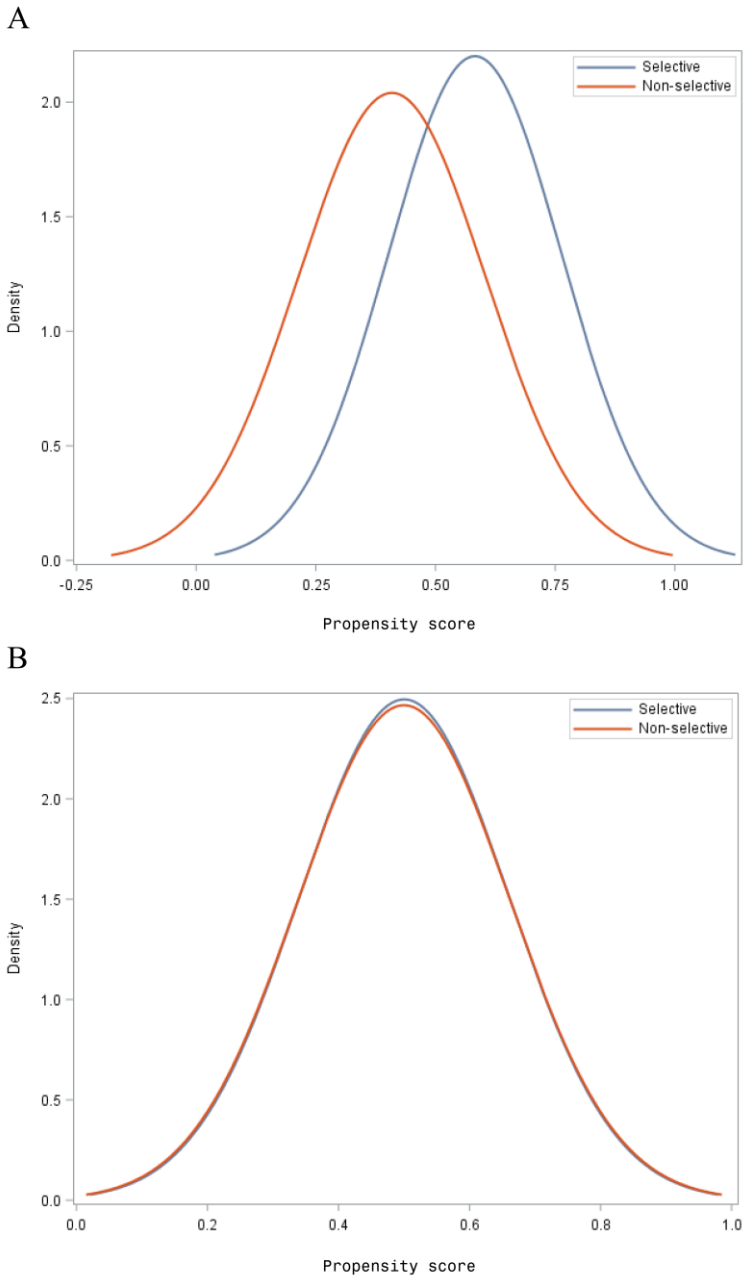
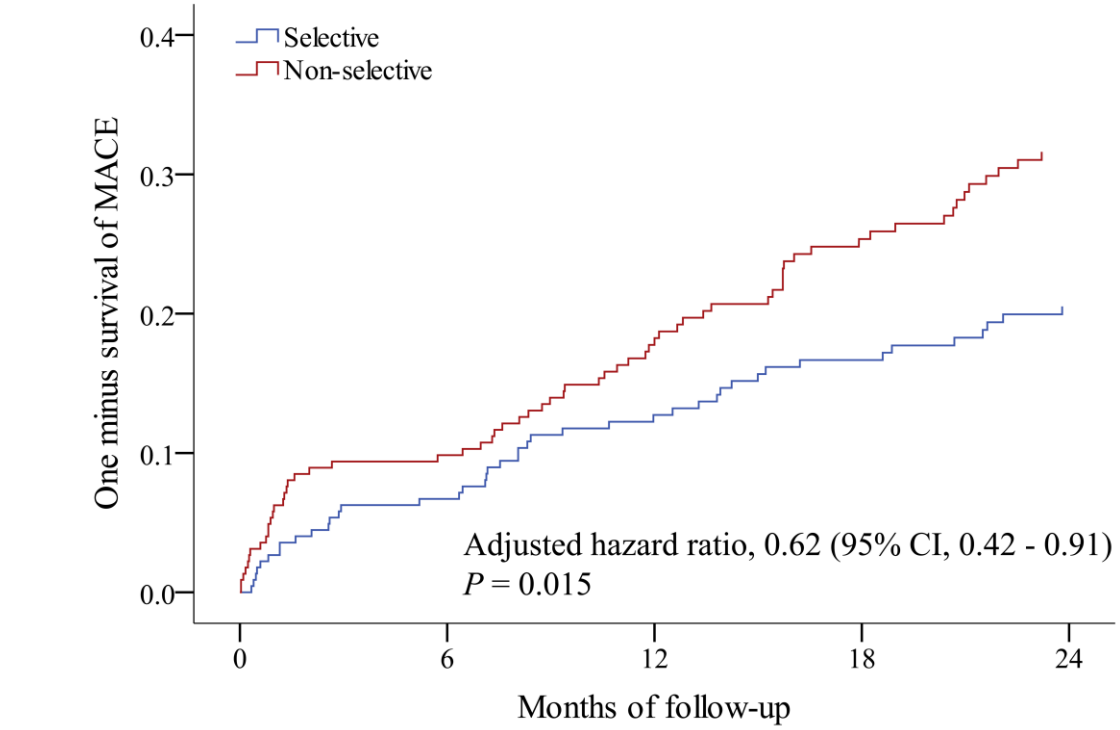


Figure S2. Sensitivity analysis on comparing risks of MACCE in the selective β-blocker and non- selective-β blocker users during a 2-year follow up by additional adjusting propensity score.



No. at risk:

Non-selective	218	203	175	157	133
Selective	218	194	163	134	116