Is there any vindication for low dose nonselective β-blocker medication in patients with liver cirrhosis?

Tae Wan Kim, Hong Joo Kim, Chang Uk Chon, Hyun Sun Won, Jung Ho Park, Dong Il Park, Yong Kyun Cho, Chong Il Sohn, Woo Kyu Jeon, and Byung Ik Kim

Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Background/Aims: Nonselective β-blockers (NSBBs), such as propranolol, reportedly exert a pleiotropic effect in liver cirrhosis. A previous report suggested that survival was higher in patients receiving adjusted doses of NSBBs than in ligation patients. This study investigated whether low-dose NSBB medication has beneficial effects in patients with liver cirrhosis, especially in terms of overall survival.

Methods: We retrospectively studied 273 cirrhotic patients (199 males; age 53.6±10.2 years, mean±SD) who visited our institution between March 2003 and December 2007; follow-up data were collected until June 2011. Among them, 138 patients were given a low-dose NSBB (BB group: propranolol, 20-60 mg/day), and the remaining 135 patients were not given an NSBB (NBB group). Both groups were stratified randomly according to Child-Turcotte-Pugh (CTP) classification and age.

Results: The causes of liver cirrhosis were alcohol (n=109, 39.9%), hepatitis B virus (n=125, 45.8%), hepatitis C virus (n=20, 7.3%), and cryptogenic (n=19, 7.0%). The CTP classes were distributed as follows: A, n=116, 42.5%; B, n=126, 46.2%; and C, n=31, 11.4%. Neither the overall survival (P=0.133) nor the hepatocellular carcinoma (HCC)-free survival (P=0.910) differed significantly between the BB and NBB groups [probability of overall survival at 4 years: 75.1% (95% CI=67.7-82.5%) and 81.2% (95% CI=74.4–88.0%), respectively; P=0.236]. In addition, the delta CTP score did not differ significantly between the two groups.

Conclusions: Use of low-dose NSBB medication in patients with liver cirrhosis is not indicated in terms of overall and HCC-free survival. **(Clin Mol Hepatol 2012;18:203-212)**

Keywords: Nonselective β-blockers; Liver cirrhosis; Overall survival; Child-Turcotte-Pugh

INTRODUCTION

Non-selective beta-blockers (NSBBs), such as propranolol, have a preventive effect on variceal bleeding in patients with liver cirrhosis. The effect of NSBBs is due to reduction of portal hyperten- sion which is caused by change of hemodynamics and vascular structure in chronic liver disease.[1-4] In addition, some beneficial effects of NSBBs, other than prevention of variceal bleeding, are reported in several studies.[5-8] For example, NSBBs can reduce complications of cirrhosis such as spontaneous bacterial peritoni-

Corresponding author : Hong Joo Kim

Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 110-746, Korea
Tel. +82-2-2001-2060, Fax. +82-2-2001-2049
E-mail; hongjoo3.kim@samsung.com

tis and other infections. In a study comparing band ligation with NSBBs, the ligation group showed a better preventive effect on varix re-bleeding than the NSBBs group, whereas the NSBBs group had a better survival than the ligation group.[9] These results imply that NSBBs may have additional effects for survival improvement that are not entirely explained by a marked reduction of portal hypertension. Recently, there is an opinion that NSBBs could be used as general preventive drugs for cirrhotic patients, irrespective of reduction of portal hypertension.[10] There are increasing needs for general preventive drugs of cirrhosis, similar to aspirin for cardiovascular disease,[10-12] because there is an increased number of patients with early stage cirrhosis due to early detection by advanced diagnostic tools.[13] Our institution has used a low dose (20-60 mg/day) of NSBBs for cirrhotic patients instead of using the maximally tolerated dose of NSBBs that is recommended in the American Association for the Study of Liver Disease guidelines.[3] Low-dose NSBBs would not significantly decrease the hepatic vein pressure gradient (HVPG), the surrogate marker for the severity of portal hypertension. Thus, by using a low dose of NSBBs, we could evaluate the possibility of other beneficial effects of NSBBs regardless of marked reduction of portal hypertension. In this study, we investigated whether low-dose NSBBs have beneficial effects in patients with cirrhosis, especially in terms of overall survival.

MATERIALS AND METHODS

Study population

All 683 consecutive cirrhosis patients who visited Sungkyunkwan University Kangbuk Samsung Hospital from March 2003 to December 2007 were collected, and follow-up data until June 2011 were measured retrospectively. The diagnosis of liver cirrhosis was based on unequivocal clinical data (physical examination, laboratory findings, and upper gastrointestinal endoscopy) and compatible findings on imaging technique and/or liver biopsy. The exclusion criteria were follow-up loss within 1 year, transfer within 1 year, coexistence of hepatocellular carcinoma (HCC) at enrollment, coexistence of other malignancy at enrollment or during follow-ups, and severe disease such as acute myocardial infarction and end-stage renal disease at enrollment or during follow-up. However, we included patients who died within 1 year. After exclusion, 349 patients were collected, and they were divided into the no beta-blocker group and the beta-blocker group. Stratified random selection according to Child-Turcotte-Pugh (CTP) clas-

sification and age was performed. Finally, 135 patients in the no beta-blocker (NBB) group and 138 patients in the beta-blocker (BB) group were enrolled in this study (Fig. 1).

Every enrolled patient in the beta-blocker group was given low-dose (20-60 mg/day) NSBBs (propranolol) continuously. Low dose of NSBBs is defined as a sub-optimal dose which is not titrated until resting heart rate is 55 beats per minute, or decreased by 25% from the baseline heart rate. Temporary discontinuation of NSBBs not exceeding one-fifth of the total follow-up period was still regarded as the beta-blocker group.

Data collection

Data regarding overall survival time and HCC-free survival time until June 2011 were measured using retrospective chart review. HCC-free survival was defined as the time interval between the date of enrollment and the date of HCC diagnosis. The diagnosis of HCC was defined as either histologically proven tumor or established tumor by noninvasive method according to the European Association for the Study of the Liver.[14] Enrollment of patients in the BB group occurred when NSBBs were first administered during the enrollment period (from March 2003 to December 2007). In the NBB group, the time of enrollment was the first visit for the care of cirrhosis during the enrollment period. Data at enrollment, including age, sex, CTP score, Model for End-stage Liver Disease (MELD) score, cause of cirrhosis, presence of esophageal varix, use of antiviral treatment, coexistence of diabetes, coexistence of hypertension, prothrombin time, international normalized ratio, albumin, total bilirubin, creatinine, aspartate aminotransferase, and alanine aminotransferase, were collected. CTP score at 3 years after enrollment, dose of NSBBs, duration of NSBBs administration, and cause of death were also obtained. The dose of NSBBs was determined by the highest dose of NSBBs during the follow-up period if the dose was changed.

Study design

The primary end point was the comparison of overall survival and HCC-free survival between NBB group and BB group. In addition, subgroup analysis of survival according to dose of NSBBs was performed. In BB group (138 patients), we divided into two subgroups (20-30 mg group: 83 patients, 40-60 mg group: 55 patients). 20-30 mg group (83 patients) was compared with 83 patients who are stratified random-selected according to CTP score and age from NBB group. 40-60 mg group (55 patients) was also
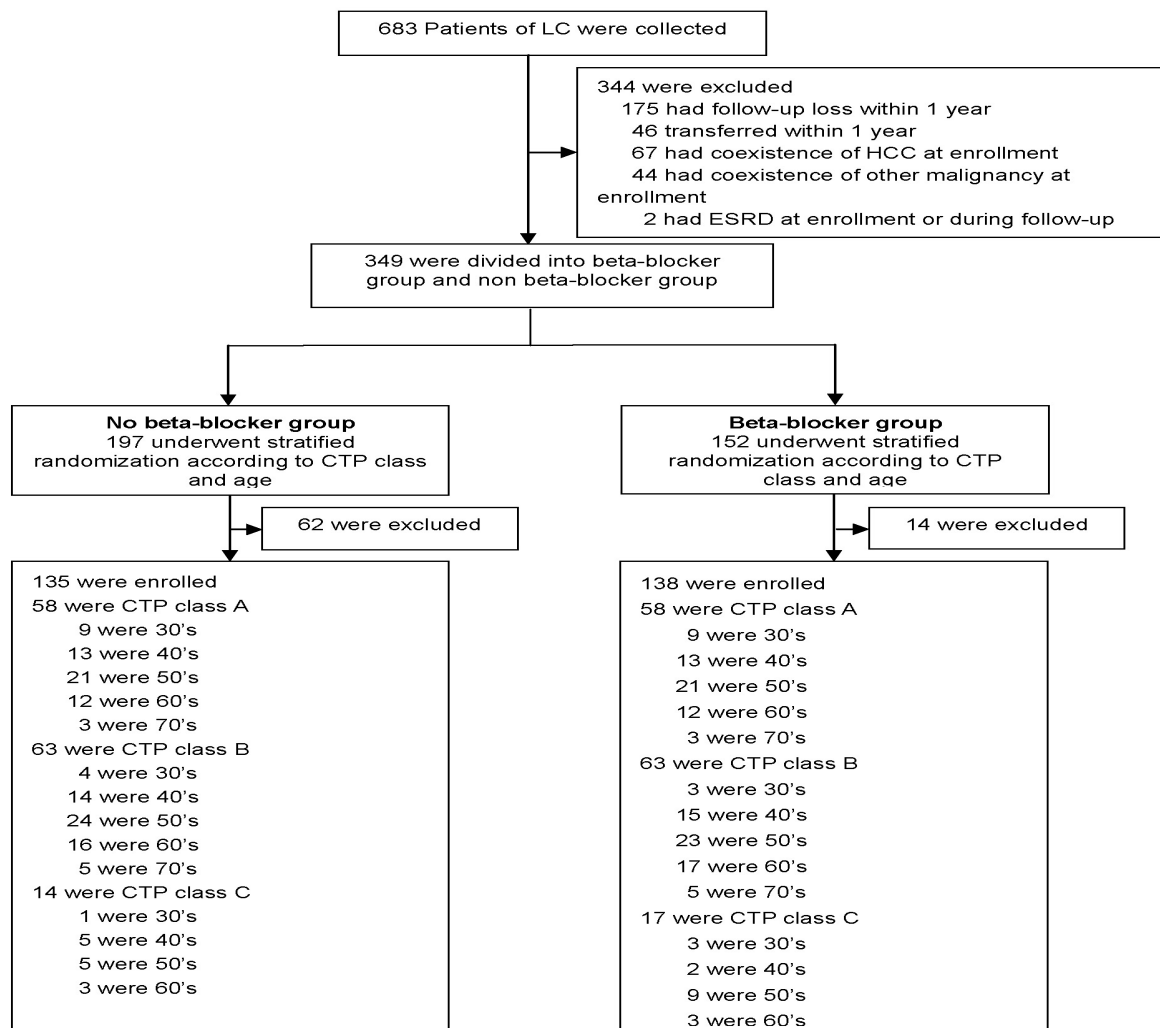
Figure 1. Enrollment. LC, liver cirrhosis; HCC, hepatocellular carcinoma; ESRD, end-stage renal disease; CTP, Child-Turcotte-Pugh.

compared with 55 patients who are stratified random-selected according to CTP score and age from NBB group. The secondary end point was the comparison of delta CTP scores (CTP score at baseline−CTP score at 3 years after enrollment) between NBB and BB groups. Independent predictors of mortality were analyzed as well.

Statistical analysis

Continuous data showing normal distribution are reported as mean±standard deviation, and group comparisons were made with t-test. Continuous data that were not normally distributed are presented as median and interquartile ranges, and group comparisons were made with Mann-Whitney U test. Categorical variables are reported as numbers and percentage, and group comparisons

were made with chi-square test. Overall survival and HCC-free survival were calculated by Kaplan-Meier method, and group comparisons were made with log-rank test. Comparisons of survival at a specific point in time (at 4 years, 8 years) were performed by Z-test using survival rate at the specific point in time in each group and standard error (SE). P-values of subgroup analysis of survival according to dose of NSBBs are adjusted by Bonferroni method. Predictors of mortality were calculated by univariate and multivariate Cox regression analyses. The results were reported as crude hazard ratios with 95% confidence intervals in univariate analysis and as adjusted hazard ratios with 95% confidence intervals in multivariate analysis. A P-value <0.05 was considered significant. Analyses were performed with the use of PASW statistical package (SPSS version 18.0, SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics

A total of 273 patients were enrolled. The mean age was 53.6±10 years. The composition of CTP class was as follows: A (n=116, 42.5%), B (n=126, 46.2%), and C (n=31, 11.4%). The etiologies of cirrhosis were alcohol (n=109, 39.9%), hepatitis B virus (n=125, 45.8%), hepatitis C virus (n=20, 7.3%), and cryptogenic (n=19, 7.0%). Due to stratified random selection at enrollment, there was no difference in age and distribution of CTP class between the NBB group and BB group. There were no significant differences between the two groups in the etiology of cirrhosis,

MELD score, proportion of antiviral treatment, and comorbidity of diabetes or hypertension. However, there was a significant difference between the two groups in terms of the presence of esophageal varix: NBB group (n=11, 8.1%), and BB group (n=138, 100%). Laboratory findings at enrollment showed no significant differences between the two groups, except albumin and pro-thrombin time, which showed very small differences (Table 1).

Dose and duration of NSBBs

In the BB group, the mean dose of NSBBs was 29.6±11.0 mg/day (range 20-60 mg/day): 20 mg/day (n=71, 51.4%), 30 mg/day (n=12, 8.7%), 40 mg/day (n=50, 36.2%), and 60 mg/day

Table 1. Baseline characteristics at enrollment

	No beta-blocker (n=135)	Beta-blocker (n=138)	*P* value
Age	53.6±10.2	53.6±10.1	0.962
Gender (male)	94 (69.6%)	105 (76.1%)	0.230
Etiology of cirrhosis			0.408
Alcoholic	60 (44.4%)	49 (35.5%)	
Hepatitis B virus	57 (42.2%)	68 (49.3%)	
Hepatitis C virus	8 (5.9%)	12 (8.7%)	
Cryptogenic	10 (7.4%)	9 (6.5%)	
Child-Turcotte-Pugh class			0.879
A	58 (43.0%)	58 (42.0%)	
B	63 (46.7%)	63 (45.7%)	
C	14 (10.4%)	17 (12.3%)	
Child-Turcotte-Pugh score	7.0 (5.0-8.0)	7.0 (6.0-8.2)	0.318
MELD score	11.0 (8.0-14.0)	12.0 (9.0-15.0)	0.134
Presence of esophageal varix	11 (8.1%)	138 (100%)	<0.001
Antiviral treatment in LC-B	18 (31.6%)	26 (38.2%)	0.438
Antiviral treatment in LC-C	0 (0%)	1 (8.3%)	1.000
Diabetes	36 (26.7%)	38 (27.5%)	0.872
Hypertension	10 (7.4%)	9 (6.5)	0.774
Prothrombin time (sec)	14.1 (12.6-15.9)	14.9 (14.0-16.1)	0.008
International normalized ratio	1.24 (1.06-1.48)	1.34 (1.23-1.49)	0.008
Total bilirubin (mg/dL)	1.60 (1.10-2.80)	1.60 (1.07-2.51)	0.653
Albumin (g/dL)	3.48±0.74	3.31±0.53	0.037
Creatinine (mg/dL)	0.90 (0.80-1.10)	1.00 (0.80-1.10)	0.200
Aspartate aminotransferase (IU/L)	56.0 (40.0-90.0)	55.0 (39.0-78.2)	0.431
Alanine aminotransferase (IU/L)	32.0 (19.0-48.0)	28.0 (18.0-43.0)	0.131

Data are presented as n (%), mean ± standard deviation, or median (range).
MELD, Model for End-stage Liver Disease; LC-B, liver cirrhosis due to hepatitis B virus; LC-C, liver cirrhosis due to hepatitis C virus.

(n=5, 3.6%). The mean duration of NSBBs therapy was 41.2±25.0 months (range 1-97 months). Almost all patients in the BB group took NSBBs constantly until the end of follow-up or until they had unstable vital signs.

Overall survival and HCC-free survival of both groups

During the follow-up period, 82 (30.0%) patients died, and 47 (17.2%) patients developed HCC. Overall survival and HCC-free survival of both groups are shown in Figure 2. The median follow-up time was 45 months (1-97 months). The probability of survival in both groups was 72.9% at 4 years (95% CI=67.3-78.4%) and 58.2% at 8 years (95% CI=47.4-68.9%). Causes of death were hepatic failure (40 patients), such as hepatic encephalopathy,

hepatorenal syndrome, and HCC progression; variceal bleeding (18 patients); sepsis (14 patients); death on arrival (4 patients); brain hemorrhage (4 patients); and acute ulcer bleeding (2 patients).

The probability of HCC-free survival in both groups was 79.5% at 4 years (95% CI=74.0-85.0%) and 77% at 8 years (95% CI=70.6-83.3%).

Comparison of overall survival and HCC-free survival between NBB group and BB group

The median follow-up time was 47 months (range 1-96 months) in the NBB group and 43.5 months (range 1-97 months) in the BB group. There was no significant difference in the overall survival between the NBB group and BB group (*P*=0.133) (Fig. 3A). There was no significant difference in the probability of survival at 4
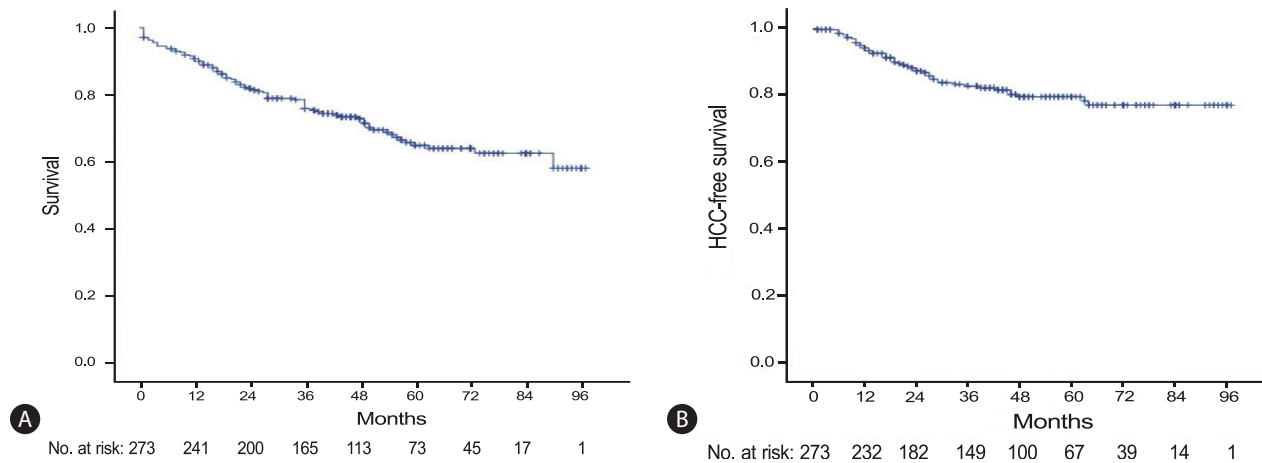

Figure 2. Kaplan-Meier curves for overall survival (A) and HCC-free survival (B) of both groups.
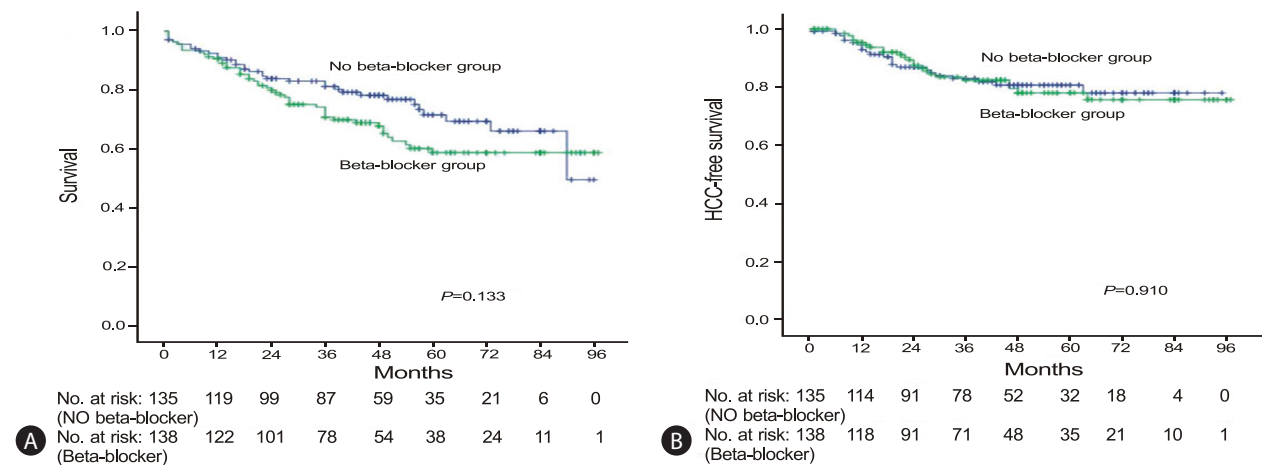

Figure 3. Kaplan-Meier curves for overall survival (A) and HCC-free survival (B) between the no-β-blocker (NBB) group and the β-blocker (BB) group.

years (*P*=0.236) and 8 years (*P*=0.088) between the two groups. In the NBB group, the probability of survival was 81.2% at 4 years (95% CI=74.4-88.0%) and 71.5% at 8 years (95% CI=62.3-80.8%). In the BB group, the probability of survival was 75.1% at 4 years (95% CI=67.7-82.5%) and 60.1% at 8 years (95% CI=50.8-69.5%).

There was no significant difference in the HCC incidence between the two groups (*P*=0.938); the HCC incidence of the NBB group was 23 (17.0%) during the follow-up period, and the HCC incidence of the BB group was 24 (17.4%). There was no significant difference in the HCC-free survival between the two groups (*P*=0.910) (Fig. 3B). In addition, there was no significant difference in the probability of HCC-free survival at 4 years (*P*=0.659) and 8 years (*P*=0.703) between the two groups. In the NBB group,

the probability of HCC-free survival was 80.6% at 4 years (95% CI=73.3-88.0%) and 78.0% at 8 years (95% CI=69.1-86.8%). In the BB group, the probability of HCC-free survival was 78.0% at 4 years (95% CI=69.7-86.3%) and 75.6% at 8 years (95% CI=66.4-84.8%).

Among the causes of death, the number of varix bleeding was different between the two groups. But, other causes of death were similar between the two groups. In detail, causes of death in BB group (48 patients) were hepatic failure (23), death on arrival (2), sepsis (8), varix bleeding (12), ulcer bleeding (1), brain hemorrhage (2). The causes of death in NBB group (34 patients) were hepatic failure (17), death on arrival (2), sepsis (6), varix bleeding (6), ulcer bleeding (1), brain hemorrhage (2).

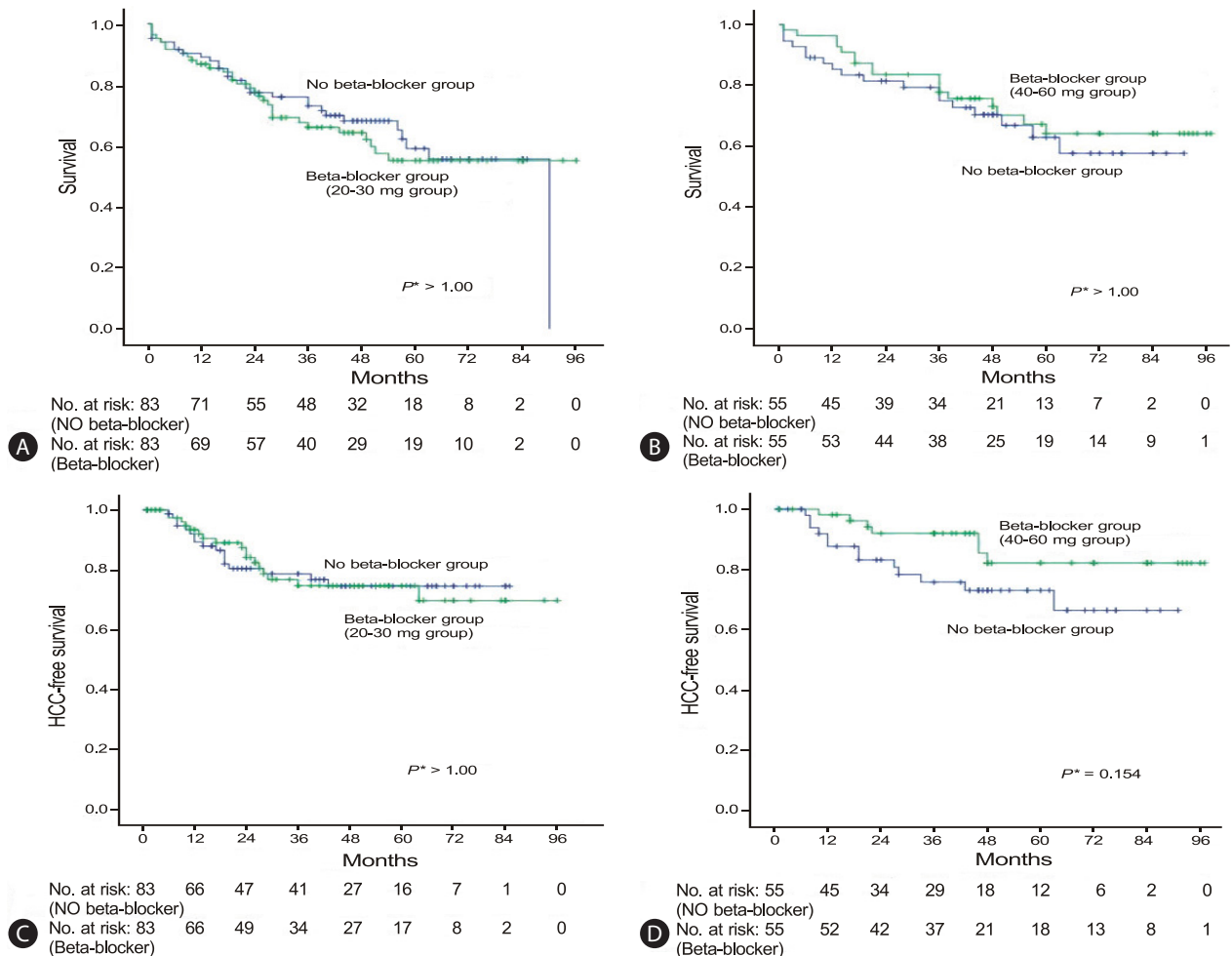**Figure 4.** Subgroup analysis of survival according to dose of NSBB. Kaplan-Meier curves for overall survival between the BB group (20+30 mg) and NBB group (A), overall survival between the BB group (40+60 mg) and the NBB group (B), HCC-free survival between the BB group (20+30 mg) and the NBB group (C), and HCC-free survival between the BB group (40+60 mg) and the NBB group (D). *Adjusted P value by the Bonferroni method.

Subgroup analysis of survival according to dose of NSBBs

In overall survival, there was no significant difference between BB (20-30 mg group, 83 patients) and NBB groups (83 patients) (*P*>1.00) (Fig. 4A). There was no significant difference between BB (40-60 mg group, 55 patients) and NBB groups (55 patients) (*P*>1.00) (Fig. 4B). In HCC-free survival, there was no significant difference between BB (20-30 mg group, 83 patients) and NBB groups (83 patients) (*P*>1.00) (Fig. 4C). There was no significant difference between BB (40-60 mg group, 55 patients) and NBB groups (55 patients) (*P*=0.154) (Fig. 4D). In summary, subgroup analysis according to dose of NSBBs showed no significant difference between BB and NBB group in both 20-30 mg and 40-60 mg groups.

Comparison of delta Child-Turcotte-Pugh score between NBB group and BB group

Delta CTP class (the change from CTP class at enrollment to CTP class after 3 years) could be evaluated from 178 patients (NBB group [n=92] and BB group [n=86]), because 95 of the enrolled patients were lost during follow-up, transferred, or died. More than half the patients (n=105, 59.0%) had no change of CTP class at 3 years after enrollment. Some patients (n=38, 21.3%) showed improved change of CTP class, and the others (n=35, 19.7%) had deteriorated CTP class after 3 years. There was no significant difference in the delta CTP class between the NBB group and BB group (*P*=0.703).

Delta CTP score (CTP score at baseline−CTP score at 3 years after enrollment) was also calculated from 178 patients. There was no significant difference in the delta CTP score between the two groups (*P*=0.898) (Table 2).

Predictors of mortality

The univariate cox regression analysis of predicting mortality is presented in Table 3. Significant univariate predictors of death were age, CTP score, MELD score, prothrombin time, international normalized ratio, total bilirubin, albumin, and aspartate aminotransferase. The significant univariate mortality predictors except prothrombin time, international normalized ratio, total bilirubin, and albumin which are dependent variables for CTP and MELD

Table 3. Univariate Cox regression predicting mortality (Crude HRs with 95% CIs)

Variable	HR (95% CI)	*P*-value
Age	1.038 (1.016-1.061)	0.001
Gender	0.967 (0.601-1.558)	0.891
CTP score	1.513 (1.340-1.708)	<0.001
CTP class B	2.983 (1.750-5.084)	<0.001
CTP class C	5.602 (2.833-11.077)	<0.001
MELD score	1.151 (1.102-1.201)	<0.001
Presence of esophageal varix	1.477 (0.942-2.316)	0.089
Use of beta-blocker	1.397 (0.900-2.170)	0.136
Cause of cirrhosis		
Alcoholic	1.445 (0.933-2.236)	0.099
Hepatitis B virus	0.792 (0.510-1.230)	0.299
Hepatitis C virus	1.028 (0.474-2.231)	0.945
Cryptogenic	0.577 (0.211-1.578)	0.284
Prothrombin time (sec)	1.153 (1.062-1.252)	0.001
International normalized ratio	3.102 (1.676-5.742)	<0.001
Total bilirubin (mg/dL)	1.186 (1.139-1.236)	<0.001
Albumin (g/dL)	0.383 (0.270-0.544)	<0.001
Creatinine (mg/dL)	1.943 (0.976-3.868)	0.059
Aspartate aminotransferase (IU/L)	1.005 (1.002-1.007)	0.002
Alanine aminotransferase (IU/L)	1.003 (0.996-1.009)	0.436

CTP, Child-Turcotte-Pugh; MELD, Model for End-stage Liver Disease.

Table 2. Comparison of delta Child-Turcotte-Pugh score between No beta-blocker group and Beta-blocker group

	No beta-blocker (n=92)	Beta-blocker (n=86)	*P*-value
Delta CTP class			0.703
No change	57 (62%)	48 (55.8%)	
Improvement	18 (19.6%)	20 (23.3%)	
Deterioration	17 (18.5%)	18 (20.9%)	
Delta CTP score	-0.11±1.9	-0.16±1.9	0.898

Data are presented as n (%), mean±standard deviation.
CTP, Child-Turcotte-Pugh; delta CTP score=baseline CTP score-CTP score after 3 years.

Table 4. Multivariate Cox regression predicting mortality (adjusted HRs with 95% CIs)

Variable	HR (95% CI)	*P*-value
Age	1.062 (1.033-1.091)	<0.001
Gender	1.509 (0.878-2.594)	0.136
CTP score	1.296 (1.061-1.582)	0.011
MELD score	1.085 (1.003-1.173)	0.041
Use of beta-blocker	1.379 (0.487-3.902)	0.545
Presence of esophageal varix	1.002 (0.341-2.940)	0.998
Aspartate aminotransferase	1.002 (0.998-1.006)	0.328

CTP, Child-Turcotte-Pugh; MELD, Model for End-stage Liver Disease.

score were inserted into multivariate Cox regression analysis. In addition, gender and plausible risk factors (presence of esophageal varix, use of beta-blocker) were inserted into multivariate analysis. The independent predictors of mortality according to multivariate analysis were age, CTP score, and MELD score at baseline (Table 4). The presence of varix, an important difference between the two groups in terms of baseline characteristics, was not a predictor of mortality.

DISCUSSION

Low-dose NSBBs had no effect on overall survival and HCC-free survival in cirrhotic patients according to this study. The use of low-dose NSBBs also had no effect on the delta CTP score. The independent predictors of mortality were age, baseline CTP score, and baseline MELD score. Subgroup analysis of survival according to dose of NSBBs showed that the dose difference within 60mg/day have no influence to overall survival or HCC-free survival.

The maximally tolerated dose of NSBBs, as described in the American Association for the Study of Liver Disease guidelines, prevents variceal bleeding and improves survival by reducing portal hypertension in cirrhotic patients with varix.[3] The maximally tolerated dose of NSBBs means a stepwise increase of the dose until the resting heart rate is 55 beats per minute, or decreased to 25% of the baseline heart rate.[4,15] The HVPG is a surrogate marker for portal hypertension and an important prognostic factor in cirrhotic patients.[5,16] A decrease in HVPG below 12 mmHg or by 20% from the baseline is a target value for prevention of variceal bleeding.[3,5] In this study, we used low-dose NSBBs in cirrhotic patients instead of the maximally tolerated dose. According to previous study, optimal required dose of NSBBs in Korean cirrhotic patients was 154.4 mg/day.[17] We could use the value as a reference of

maximally tolerated dose in Korean patients, because there are racial differences in sensitivity to NSBBs.[18,19] Thus, we could consider the dose used in this study as low dose compared to the reference value. The use of low-dose NSBBs would not decrease the HVPG to the target value. Therefore, we could assume the effect of NSBBs, irrespective of the hemodynamic response to NSBBs. We focused on non-hemodynamic related effects, especially in terms of survival.

Many articles have suggested that there are protective mechanisms of NSBBs other than reduction of portal pressure. Several studies[6,20] suggested that NSBBs can prevent spontaneous bacterial peritonitis without marked reduction of portal HTN. The preventive effect of spontaneous bacterial peritonitis is assumed to be due to a decrease of bacterial translocation caused by an increase in intestinal motility or by a decrease in intestinal permeability.[6,12,21,22] Other studies[12,23] showed that NSBBs could reduce bacterial translocation of gut without marked reduction of portal hypertension, and it could reduce variceal bleeding. It was already proven that infection is associated with the cause of variceal bleeding.[24-26] Therefore, less bacterial translocation, irrespective of reduction of portal hypertension, could lead to less variceal bleeding. In a study by Lo et al,[9] patients on the maximally tolerated dose of NSBBs (plus nitrates) showed a better survival than those with band ligation, even though band ligation had a better preventive effect of varix re-bleeding than NSBBs. This suggests that NSBBs have other beneficial effects on survival than the prevention of variceal bleeding.

These non-hemodynamic related benefits of NSBBs, which are not entirely due to reduction of portal hypertension, have been suggested in many studies. In addition, there is an opinion that old-safe drugs, such as NSBBs, antibiotics, statins, and anticoagulants, could be widely used for preventing complications of cirrhosis, similar to aspirin, beta-blocker, and statin for cardiovascular disease.[10] However, currently, universal use of NSBBs in every cirrhotic patient, regardless of the presence of varix, is not recommended.[3] Moreover, in a recent study of cirrhotic patients with refractory ascites, the use of NSBBs showed poor survival compared with the non-NSBBs group.[27] Therefore, we need more research for the possibility of universal use of NSBBs in cirrhotic patients.

This study, which evaluates the effect of low-dose NSBBs on survival in cirrhotic patients, may suggest whether or not low-dose NSBBs can be used as general preventive drugs. Unfortunately, our study showed that there was no effect on survival when low-dose NSBBs were used. In other words, there was no additional non-hemodynamic related benefit of low-dose NSBBs, especially

in terms of survival. This result implies that either the level of the dose in this study is insufficient to obtain the non-hemodynamic related benefits of NSBBs, or the benefits are not strong enough to improve survival.

Thus, we should reconsider the vindication of low-dose NSBBs, which have been broadly used for cirrhotic patients in many clinics. In Korea, NSBBs have been widely prescribed in the low dose instead of the maximally tolerated dose because of concerns regarding clinical side effects such as hypotension, bradycardia, dizziness, fatigue, and shortness of breath.[28] Our institution also used low-dose NSBBs due to concerns for the adverse effects as above, even though we were aware of proper dose of NSBBs. A low dose of NSBBs would not sufficiently reduce the HVPG and may have little effect in prevention of variceal bleeding. In addition, according to our results, the non-hemodynamic related benefits of NSBBs in terms of survival cannot be expected.

There are some reports that NSBBs may have a protective effect on HCC development. Patch et al[29] reported that the medical therapy group (NSBBs and nitrates) showed a lower frequency of HCC development than the band ligation group. In a study by Lo et al,[9] the medical therapy group showed a tendency of less frequent HCC development than the ligation group. In our study, however, the BB group showed no beneficial effect in terms of HCC-free survival compared with the NBB group.

There are some limitations in this study. First, the follow-up time was relatively short. Only 82 (30%) patients died during the follow-up period, even though the follow-up period was at least 4 years. Most patients were in the early stage of cirrhosis and maintained their stable status for a long time; only 10-12% of enrolled patients were CTP class C, and the rest of the patients were CTP class A and B. In addition, some patients refused follow-up, and several patients were transferred. The second limitation is that we did not research the difference in non-hemodynamic related benefits of NSBBs, except survival, HCC-free survival, and change of CTP score. For example, the difference in prevention of spontaneous bacterial peritonitis, which is reported to be a significant non-hemodynamic related benefit of NSBBs in other studies,[6,12,20] was not investigated. However, overall survival or HCC-free survival is more important than prevention of spontaneous bacterial peritonitis. Even though NSBBs could prevent spontaneous bacterial peritonitis, there are no meaningful benefits without improvement of survival. The third limitation is that we could not evaluate the proportion of alcohol abstinence, which might influence survival in alcoholic liver cirrhosis. A retrospective chart review had unclear information on alcohol abstinence.

In conclusion, low-dose NSBBs had no benefits on overall survival and HCC-free survival in cirrhotic patients. In addition, there was no influence on the CTP score after 3 years. Non-hemodynamic related benefits, which are independent of marked reduction in HVPG, were not found, especially in terms of overall survival. Therefore, we should reconsider the use of sub-optimal dose NSBBs in patients with liver cirrhosis.

Conflicts of Interest

The authors have no conflicts to disclose.

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