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The Role of Non-Selective Beta-Blockers (NSBBs) in Liver Cirrhosis

Anak Agung Yunda Prabundari[1]*, Dewa Nyoman Wibawa[2]

[1]Department of Internal Medicine, H. Marsidi Judono District Hospital, Belitung, Indonesia; [2]Department of Internal Medicine, Gastro-Entero-Hepatology Division, Udayana University, Sanglah Hospital, Denpasar, Bali, Indonesia

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***Correspondence:** Anak Agung Yunda Prabundari, Internal Medicine Department, H. Marsidi Judono District Hospital, Belitung, Indonesia.
E-mail: anakagungyundaprabundari@gmail.com
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Abstract

Non-selective beta-blockers (NSBBs) are one of the recommended treatments for portal hypertension in liver cirrhosis (LC). NSBB plays the role of primary as well as secondary prophylactic upper gastrointestinal bleeding in LC. NSBB therapy has been shown to effectively reduce the risk of variceal bleeding, reduction of portal pressure, and treat other complications of portal hypertension. The safety of NSBB therapy in cirrhosis requires a good therapeutic guide and considers the side effects. The indication of NSBB administration is adjusted according to the cirrhosis stage and the specific pathophysiology that occurs in cirrhosis. Conventional NSBBs such as propranolol and nadolol which are antagonists of β1 and β2 adrenergic receptors would induce decreased cardiac output and splanchnic vasoconstriction. Carvedilol is an NSBB with the addition of α1-adrenergic activity in reducing portal pressure stronger than conventional NSBB, so carvedilol can cause greater systemic arterial pressure reduction when compared to conventional NSBB. The appropriate treatment strategies can be applied in the use of NSBB to prevent more severe complications and reduce morbidity and mortality.

Introduction

Liver cirrhosis (LC) is the final stage of the diffuse process of progressive liver fibrosis which is characterized by abnormalities of liver architecture and the formation of regenerative nodules. The morphological features of the LC include diffuse processes, regenerative nodules, altered lobular architecture, and the formation of intrahepatic vascular connections. LC is clinically divided into two, which are compensated LC and decompensated LC with signs of hepatocellular failure and portal hypertension [1], [2].

After cardiovascular disease and cancer, in patients aged 45–46 years, the third leading cause of death is LC. Worldwide, LC is the seventh leading cause of death. LC patients are more male than the female with a ratio of 1.6: 1, with 30–59 years average age and peaks after 40–49 years. The incidence of LC in America is estimated at 360/100,000 population. The main causes of LC in Southeast Asian countries are hepatitis B and hepatitis C [3].

Chronic liver disease and LC have high morbidity and mortality due to their complication. The two main causes of death are portal hypertension and liver dysfunction (decreased liver cell reserves). LC with portal hypertension who experience esophageal variceal bleeding reaches 20–40% and the mortality rate reaches 75% who will die within 1 year [1], [4].

One of the recommended therapies for LC is non-selective beta-blockers (NSBBs). The role of NSBB can be as primary or secondary prophylaxis. NSBB therapy aims to reduce the portal pressure and prevent variceal bleeding, as well as treat other complications of portal hypertension such as ascites, hepatorenal syndrome (HRS), and spontaneous bacterial peritonitis (SBP) [5], [6]. Conventional NSBBs such as propranolol and nadolol which are β1 and β2 adrenergic receptor antagonists induce decreased cardiac output and splanchnic vasoconstriction. Carvedilol is an NSBB with added α1-adrenergic activity in reducing portal pressure stronger than conventional NSBB, so it can cause a greater decrease in systemic arterial pressure when compared to conventional NSBB. Treatment with NSBB reduces the risk of variceal bleeding by 16% [7], [8]. Based on the above explanation, it is necessary to have a better understanding of LC so that an appropriate treatment strategy can be made in the use of NSBB to prevent more severe complications and reduce morbidity and mortality.

LC

LC is the most frequent consequence of the long clinical course of all chronic liver diseases

characterized by liver parenchyma damage [3]. In the past, LC was considered a passive and irreversible process but it is now considered an active form of response to recoverable chronic liver injury, but the determinants of regression are not clear yet, when cirrhosis recovers properly has not been determined in terms of morphological and functional because it is not yet certainly known the degree of fibrosis which is still reversible [8].

LC patients were divided into two staged groups based on the presence or absence of decompensation signs (ascites, variceal bleeding, hepatic encephalopathy, and jaundice), the 1-year survival in compensated patients was 95%, whereas in decompensated patients was 61%. Furthermore, two prospective Italian cohort studies involving 1600 patients showed a median survival of more than 12 years in compensated patients, but only 1.8 years in decompensated patients [9].

Compensated LC is often asymptomatic and found on routine biochemical tests, physical examination, transient elastography, and abdominal ultrasonography [1], [9]. In the decompensated stage of LC, the patient may experience shortness of breath, which can be caused by large ascites, pleural effusions, or disturbed pulmonary circulation. On physical examination, in patients with decompensated LC, it can be found impaired consciousness (hepatic encephalopathy), severe anemia (gastrointestinal bleeding both acute and chronic), jaundice, malnutrition to hypotension, or shock due to severe hemodynamic disorders [1], [9].

Compensated and decompensated LC was further stratified according to clinical characteristics and risk of death in five stages. The current development of science shows a more comprehensive division of stages (Figure 1). Compensated LC is divided into two stages based on the presence or absence of esophageal varices (EV). Compensated LC without EV is mild portal hypertension with a hepatic venous pressure gradient (HVPG) >5 and <10 mmHg. Stage 2 is seen with clinically significant portal hypertension (CSPH) with HVPG ≥10 mmHg or with already occurring EV. The next three stages are in decompensated LC, variceal bleeding (without clinical decompensation), first non-bleeding events with clinical decompensation (such as ascites), or second bleeding events with clinical decompensation. The last stage is advanced decompensation with clinical refractory ascites, renal failure, infection, and acute on chronic liver failure (ACLF). ACLF is characterized by multiorgan failure in cirrhosis which is a different form of decompensated hepatic cirrhosis [9], [10].

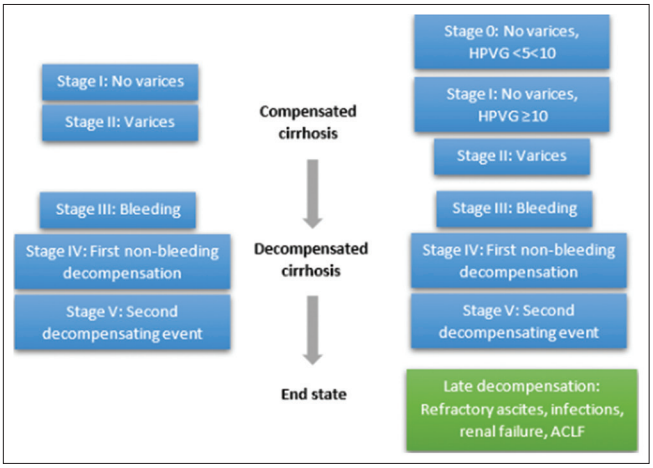

Figure 1: Schematic drawing of the stages of the LC [9]

NSBB

Beta-blockers, also known as beta-adrenergic blocking agents, are drugs that block the chronotropic, inotropic, and vasoconstrictor response to catecholamines, epinephrine, and norepinephrine. Most beta-blockers have a half-life of more than 6 h. The shortest action is propranolol (3–5 h). Beta-blockers are mostly metabolized in the liver and kidneys. Beta-blockers affect three adrenergic receptors, namely, β1, β2, and α. Selective beta-blockers have a higher affinity for β1 receptors than β2. Conventional NSBB, such as propranolol, nadolol, and timolol, have the same affinity for both β1 and β2 receptors. A class of drugs such as carvedilol, apart from blocking β receptors, also blocks α-adrenergic receptors by reducing peripheral vascular resistance [11], [12], [13].

The increment of intrahepatic vascular resistance along with the flow of portal blood involved in the elevation of portal pressure for patients with LC. In patients with CSPH, characterized by HVPG ≥10 mmHg, the condition of ascites and EV may eventually develop. Progressive vasodilatation of splanchnic and peripheral may lead to hyperdynamic circulation, with the compensation of heart rate elevation and cardiac output. Although NSBB may not effective to prevent varices for LC patients, it may prevent the progression of large varices from the small varices in CSPH patients. The blockade of β-adrenergic may result in a decrease in HVPG since CSPH patients possess vasodilatation of splanchnic and hyperdynamic circulation (Figure 2) [5], [14], [15].

A compensatory adaptation of elevation of cardiac output comes from adrenergic occurs, as a result of reduced effective circulatory blood volume. It may be associated with the activity of the sympathetic nervous system. A critical situation may occur, for instance, excessive volume loss that occurs after paracentesis, or massive blood loss due to the bleeding of variceal or SBP. In these situations, it may result in acute kidney injury (AKI) as well as organ failures [16]. The elevation in cardiac output due to β-adrenergic may be interfered with NSBB. This is essential for the perfusion

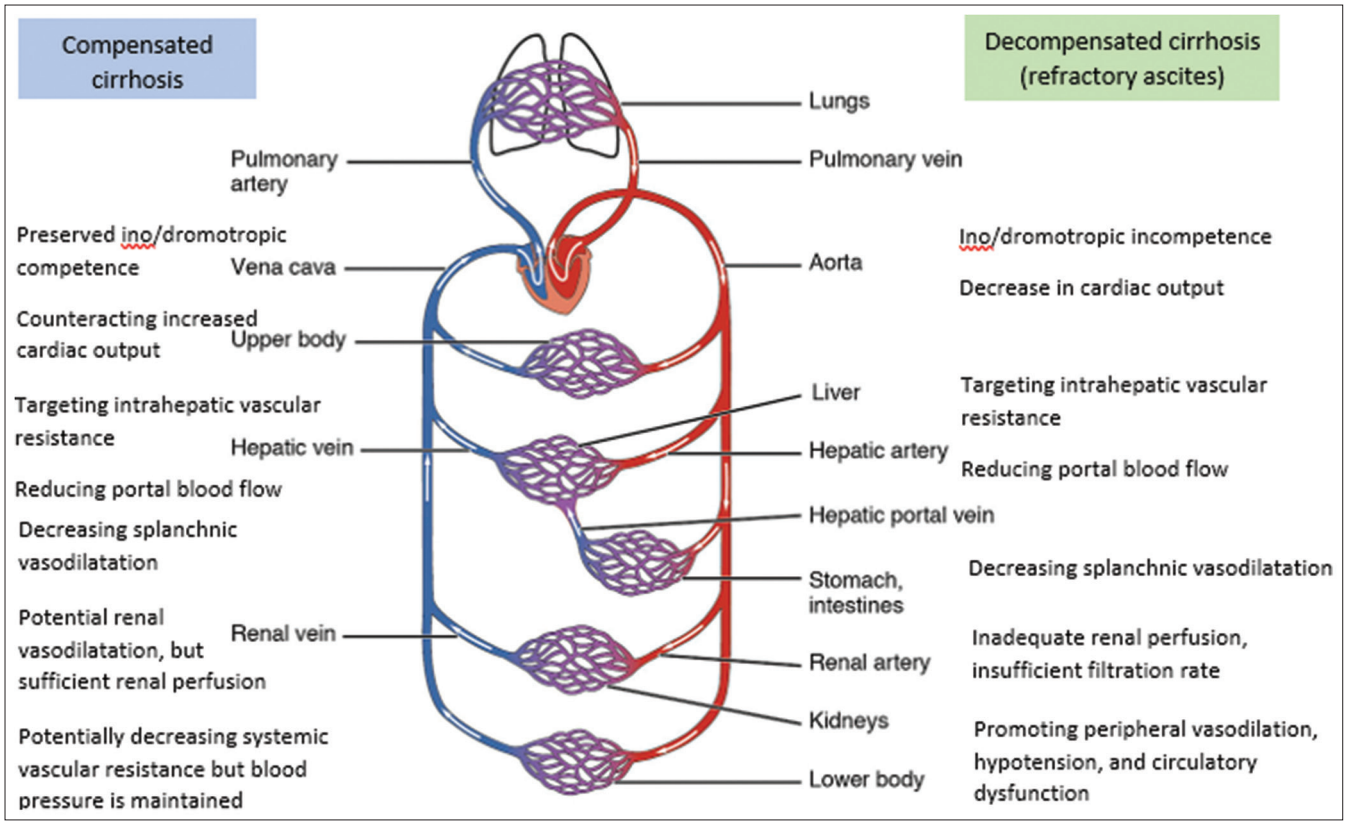

Figure 2: Effects of NSBB on LC [15]

of kidneys and other systemic mechanisms, especially for LC patients. When arterial hypotension took place, the influence of noradrenalin in HRS along with the indirect effect of reducing the function of the kidney is beneficial, underlining the significant involvement of the sympathetic nervous system to maintain a sufficient systemic circulation during SBP [15].

NSBB has been evaluated for the long-term treatment of decompensated LC. It may be used for the prevention of variceal bleeding. The fundamental mechanism in producing such an effect may occur through the blockade of β-1 and β-2 adrenergic. The blockade of β-1 resulted in reduced portal hypertension through decreasing cardiac output. Meanwhile, the blockade of β-2 resulted in the vasoconstriction of splanchnic, due to unopposed α-adrenergic activity. The use of NSBB, such as timolol, propranolol, and nadolol, is preferred since it may reduce the HVPG compared to β-1 adrenergic blockers, for instance, atenolol and metoprolol. The effect of β-2 blockade served a more important role, further evidenced by the lack of correlation between reduced heart rate due to propranolol (β-1 effect) with the reduction in HVPG [15].

The mortality rate for hospitalized patients with LC is 12%, which is significantly better than that of outpatients who do not receive NSBB therapy, where the mortality rate increases by 2–3 times. In LC patients with EV, the incidence rate of variceal bleeding is 12–15%/year despite the improvement in the management of complications, but the mortality rate associated with variceal bleeding is still high, reaching 15–20%, therefore, primary prophylaxis with NSBB which is for the prevention of variceal bleeding is given. Secondary prophylaxis with NSBB has been proven to reduce the risk of recurrent bleeding and reduce mortality number. Secondary prophylaxis, which is the combination of NSBB and EBL, is more effective than the provision of NSBB therapy alone [5], [16].

Several studies studying the effects of giving NSBB on the development of large variceal veins can be seen as follows:

A study by Merkel *et al*. reported that NSBB (nadolol) showed efficacy as the preventive strategy for the development of large varices from small varices. The study showed efficacy in patients who have not bled. However, different results showed in the study conducted by Sarin *et al*., in which propranolol showed no effect (Table 1). A meta-analysis study reported that NSBB did not prevent the establishment of large varices in patients who did not experience bleeding. However, the meta-analysis put in the study by Groszman *et al*., in which timolol was used, and Calès *et al*., in which propranolol was used. The studies included patients without varices, in which the likelihood to develop large varices was lower (Table 1). The efficacy of conventional NSBB is modest when used to reduce HVPG in populations with subclinical portal hypertension. This is due to the absence of hyperdynamic circulation. A study by Groszman *et al*. reported that only a total of 4%

Table 1: Randomized controlled trials studying the effects of non-selective beta-blocker [12]

Study	Cales *et al*.	Merkel *et al*.	Groszmann *et al*.	Sarin *et al*.	Bhardwaj *et al*.
Study and patient characteristics					
n, NSBB versus placebo	102 versus 104	83 versus 78	108 versus 105	77 versus 73	70 versus 70
NSBB	Propranolol	Nadolol	Timolol	Propranolol	Carvedilol
NSBB dose	160 mg	62 mg	11 mg	120 mg	12 mg
HVPG	Not assessed	12 mmHg	11 mmHg	15 mmHg	15 mmHg
Follow up	2 years	36 month	55 month	25 month	21 month
Endpoints, NSBB versus placebo					
Large varices	31% versus 14%	11% versus 37%	4% versus 4%	23% versus 19%	20% versus 36%
Variceal bleeding	2% versus 2%	2% versus 12%	2% versus 3%	5% versus 1%	0% versus 0%
Mortality	9% versus 10%	29% versus 40%	3% versus 2%	3% versus 4%	3% versus 11%

NSBB: Non-selective beta-blocker, HVPG: Hepatic venous pressure gradient.

develop into large varices, with the median follow-up in the study is more than 4 years [12].

In the study conducted by Groszmann *et al*., LC patients with portal hypertension were randomly assigned to timolol or placebo. The median follow-up in the study was nearly 5 years. After the follow-up, as many as 40% of patients both in the timolol and placebo group met the composite primary endpoint, which is the development of variceal bleeding. In patients who received timolol, the relative HVPG-decreases >10% were more often found, that is, 53% versus 38%. In patients without varices, NSBB should not be used. Due to the reduction of portal pressure by a decrease in cardiac output (anti-β1) as well as reduced splanchnic vasodilation (anti-β2), the absence of hyperdynamic circulation attenuates NSBB anti-portal hypertensive effect. A study comparing timolol with placebo using an average dose of 11 mg and followed for a median of 55 months, found as many big variceal veins as placebo (4%), and the incidence of variceal bleeding on timolol was 1% lower than placebo, but the mortality rate 1% greater compared to placebo [12] (Table 1).

A study by Bhardwaj *et al*., which implemented a randomized single-blind placebo-controlled study design, found a lower proportion of large varices progression from small varices in the carvedilol group compared to the placebo. The current guideline did not support carvedilol or conventional NSBB. In patients with compensated LC, it has been shown that carvedilol is well tolerated. This is evidenced by only one patient who did not resume the medication due to adverse events. One hemodynamic study on the use of carvedilol raised awareness regarding the ascites worsening during carvedilol medication. A study reported the efficacy of NSBBs to prevent variceal growth, along with the assessment of HVPG-response (Table 1) [12].

The role of NSBB in management of LC

NSBB therapy aims to reduce portal pressure and prevent variceal bleeding, as well as treat other complications of portal hypertension such as ascites, HRS, and SBP, so the role of NSBB can be as primary and secondary prophylaxis [17]. The recommended primary prophylaxis is NSBB, not selective beta-blockers such as bisoprolol and metoprolol. This is because, in addition to the β1 inhibitory effect of NSSB which reduces cardiac output and splanchnic blood flow, NSSB also inhibits β2 receptors where inhibition of β2 receptors causes a reduction in inhibition of the vasoconstrictive effect by stimulating α1 adrenergic receptors in the splanchnic circulation [18].

The regiment for NSBB should be implemented with an individual approach, specific for the pathophysiological phase of LC. This approach seems to be the optimal strategy for the management of LC patients. Recommendations for NSBB targeted specifically to the LC phase and pathophysiological phase which happen in LC patients described in Table 2 [15].

Several studies already showed the superiority of carvedilol compared to propranolol to decrease portal pressure, to be used as primary prophylaxis. Important points that should be noted are carvedilol is associated with a stronger reduction in arterial blood pressure and increased diuretics use. Furthermore, it also shows potentially less survival benefit in patients with LC and ascites, compared to propranolol. The use of carvedilol in severe or refractory ascites should become a concern. The same concern applied for patients with progressive arterial hypotension. A low dose of propranolol, which is 680 mg/d, or repetitive EBL is recommended for patients with severe ascites until variceal eradication (Table 2) [15].

NSBB also could be used as secondary prophylaxis. It is used if a strong indication exists (secondary vs. primary prophylaxis). No evidence showed harmful effects for uncomplicated ascites (non-refractory, no SBP). It is recommended to use NSBB for secondary prophylaxis. However, the use of high-dose propranolol, which is >80 mg/d and carvedilol should be avoided in severe or refractory ascites. The management using transjugular intrahepatic portosystemic shunt should be implemented in refractory ascites patients, the same for patients with a history of variceal bleeding. This is due to covered stents that may improve survival [15].

NSBB can be used for primary prophylaxis in patients with ascites and should be used for secondary prophylaxis of variceal bleeding. However, careful monitoring of blood pressure and renal function, as well as screening for infections, should be performed to identify scenarios in which NSBB doses should be

Table 2: Recommendations for giving non-selective beta-blocker based on liver cirrhosis and other clinical stages [15]

Clinical scenario	Recommendation
Decompensation	Evaluate the patient for liver transplantation
First decompensation with ascites (primary prophylaxis)	Screen for varices if not already done
	Medium-large varices: Start primary prophylaxis with either NSBB or EBL according to local expertise and patient preference
	Ascites *per se* is not a contraindication for NSBBs
	If ascites is severe or refractory avoid high doses of propranolol (> 80 mg/d) and do not use carvedilol
Variceal bleeding and ascites (secondary prophylaxis)	Treat variceal bleeding according to recommendations of the Baveno VI consensus
	Establish secondary prophylaxis with a combination of EBL and NSBB
	Ascites *per se* is not a contraindication for NSBBs
	If ascites is severe or refractory avoid high doses of propranolol (> 80 mg/d) and do not use carvedilol
	If a patient is on terlipressin/vasopressors interrupt NSBB treatment – but try to re-establish NSBB treatment
	If variceal bleeding occurs while on adequately dosed NSBB treatment, the patient is considered a "clinical" NSBB non-responder and should be evaluated for TIPS
Progressive arterial hypotension or intolerance of NSBB treatment	Treat other reasons for arterial hypotension (i.e., infections)
	Reduce NSBB dose or discontinue NSBB treatment and monitor changes in blood pressure
	Consider switching from carvedilol to propranolol
	Consider plasma expansion with albumin in case of severe hypoalbuminemia (i.e., serum albumin levels<25 g/dL)
	Primary prophylaxis: Consider switching from NSBBs to EBL
	Secondary prophylaxis: Try to maintain NSBB treatment at a lower dose
NSBB intolerance	Up to 20% of patients with cirrhosis show intolerance to NSBBs
	Try to initiate NSBBs at a low dose (carvedilol: 6.25 mg/d and propranolol 40 mg/d) and follow a slow dose increasing titration protocol until intolerance occurs
	Consider switching from carvedilol to propranolol or use low doses of propranolol (≤80 mg/d)
	Primary prophylaxis: Switch to EBL
	Secondary prophylaxis: Consider TIPS, especially if the patient has severe or refractory ascites
Refractory ascites	Reduce dose of NSBB or discontinue NSBBs in patients with (i) SBP <90 mmHg, or (ii) serum creatinine>1.5 mg/dL, or (iii) hyponatremia <130 mmol/L
	Primary prophylaxis: Consider switching from NSBBs to EBL
	Secondary prophylaxis: Try to maintain NSBB treatment at a lower dose
	Avoid high doses of propranolol (> 80 mg/d) and do not use carvedilol
	Evaluate the patient for TIPS
Spontaneous bacterial peritonitis	Reduce NSBB dose or interrupt NSBB treatment in case of (i) SBP<90 mmHg, or (ii) serum creatinine>1.5mg/dL, or (iii) hyponatremia<130 mmol/L
	In the setting of septic shock when terlipressin or vasopressors are needed to maintain arterial blood pressure stop NSBB treatment and carefully monitor renal function to detect AKI/HRS
	Primary prophylaxis: Consider switching from NSBBs to EBL
	Secondary prophylaxis: Try to reestablish NSBB treatment, eventually at a lower dose
	Establish antibiotic prophylaxis for recurrent SBP
AKI/HRS	Stop diuretics and perform plasma expansion with albumin to establish the diagnosis of HRS-AKI
	Stop NSBBs if terlipressin/vasopressors are needed
	Consider reestablishing NSBBs after AKI/HRS has resolved
	Evaluate the patient for TIPS

EBL: Endoscopic band ligation, AKI: Acute kidney injury, HRS: Hepatorenal syndrome, NSBBs: Non-selective beta-blockers, TIPS: Transjugular intrahepatic portosystemic shunt, SBP: Systolic blood pressure.

reduced or treatment discontinued. Due to the higher risk of inducing arterial hypotension, carvedilol should not be used in patients with severe or refractory ascites. Low doses of conventional NSBBs seem safer in patients with LC and severe or refractory ascites (Table 2) [15].

NSBB treatment must pay attention to the main factors that can predict esophageal variceal bleeding (the presence of red wale signs) and the LC stage. Patients with medium or large variceal veins should receive NSBB therapy as primary prophylaxis [12]. NSBB administration as primary prophylaxis in variceal bleeding is shown in Figure 3.

The combination of NSBB with EBL is the recommended secondary prophylaxis because ligation does not affect the pathophysiological mechanisms that cause portal hypertension. Secondary prophylaxis involves therapy to prevent rebleeding in patients with EV. Intervention is essential because up to 80% of patients who experience rebleeding will bleed again within 2 years [18]. Reduction of portal pressure by NSBB will reduce the incidence of variceal veins and the development of other complications of LC (ascites, hepatic encephalopaty, refractory ascites, HRS, and better survival) [13], [15].

For patients with LC and ascites, the use of NSBB could be implemented as primary prophylaxis in variceal bleeding, if blood pressure <90 mmHg, creatinine serum >1.5 mg/dL, and hyponatremia <130 mmol/L, it is advisable to switch to EBL. NSBB therapy as secondary prophylaxis can be maintained with previous therapeutic doses, however, in LC patients with refractory ascites, it is advised to avoid carvedilol, along with high doses of propranolol (>80 mg/dl) [15]. The current treatment guidelines do not support the therapy of NSBB in LC patients without variceal veins. NSBB should not be given to prevent SBP, although it has an anti-inflammatory effect in LC patients and may be associated with a reduction in bacterial translocation in endothelial dysfunction [11], [15], [19].

In LC patients, the use of NSBB for variceal bleeding primary and secondary prophylaxis is well-established. Research that had been conducted found "window hypothesis" for NSBB medication may improve survival within a narrow window [20], [21]. Medication with NSBB in the early stage of LC not possessed any significant effect on survival. It also may have the effect of increment in an adverse event, along with not preventing varices formation. As for the middle phase of LC, NSBB "window" may open the gastrointestinal bleeding prevention with primary and secondary prophylaxis. Patients with LC and the accompanying condition of decreased perfusion to vital organs, refractory ascites, and reduce mean arterial pressure may possess an increased likelihood of HRS and end-organ damage [17], [21]. The timing of the "window" closed is still unclear. A study that explores the effects of NSBB medication for advanced cirrhosis with refractory ascites also had not

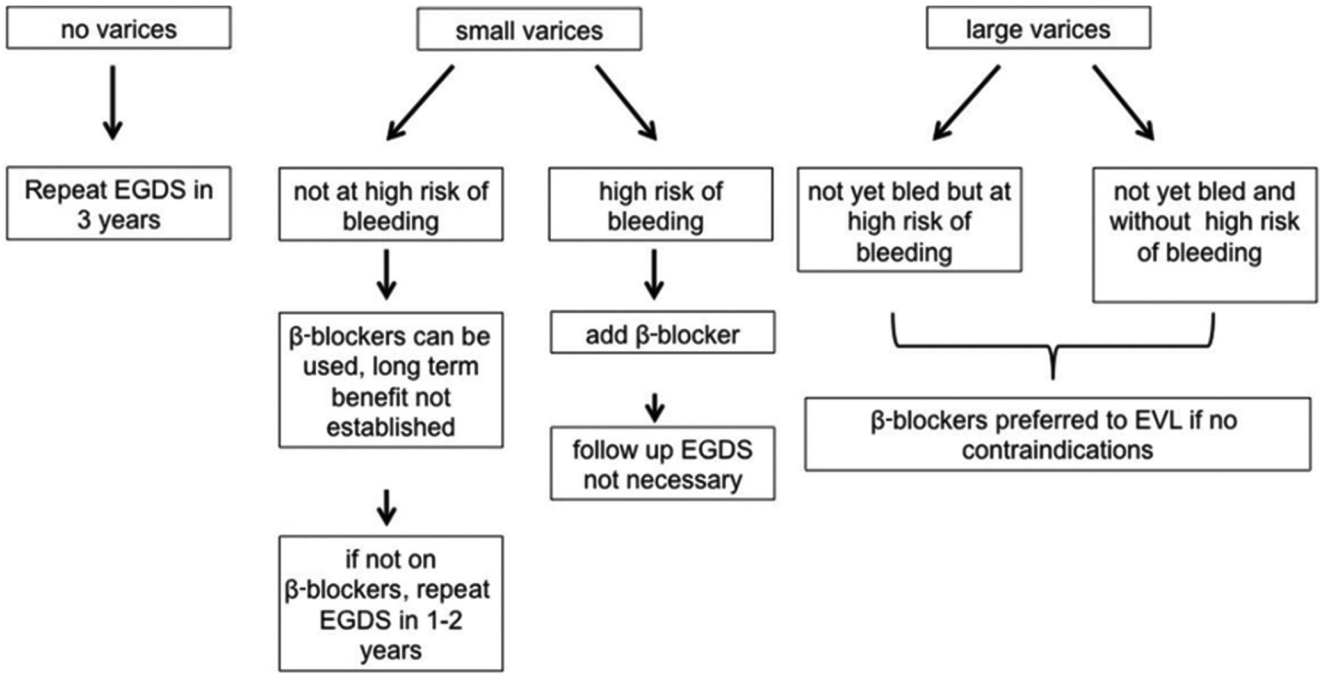

Figure 3: NSBB in primary prophylaxis for variceal bleeding [5]

yet been conducted. Since LC is a dynamic process, it is understandable that early studies conducted previously are too heterogeneous (Figure 4) [21].

The "window hypothesis" should be closed in the presence of refractory ascites, systolic blood pressure <110 mmHg, and arterial <82 mmHg. The same is also for AKI or HRS, along with sepsis, who received intensive medical management or not adherent to treatment, and patients at the first onset of SBP [8], [19]. In the past 2 years, the hypothesis of the "window" therapeutic was reintroduced because there was no association between NSBB therapy and an increased risk of death in decompensated LC patients or an adverse effect on patient survival. The use of NSBB was not associated with a significant increase in all-cause of death in LC patients [15], [21].

Propranolol which is an antagonist of β1 and β2 adrenergic receptors causes decreased cardiac output and

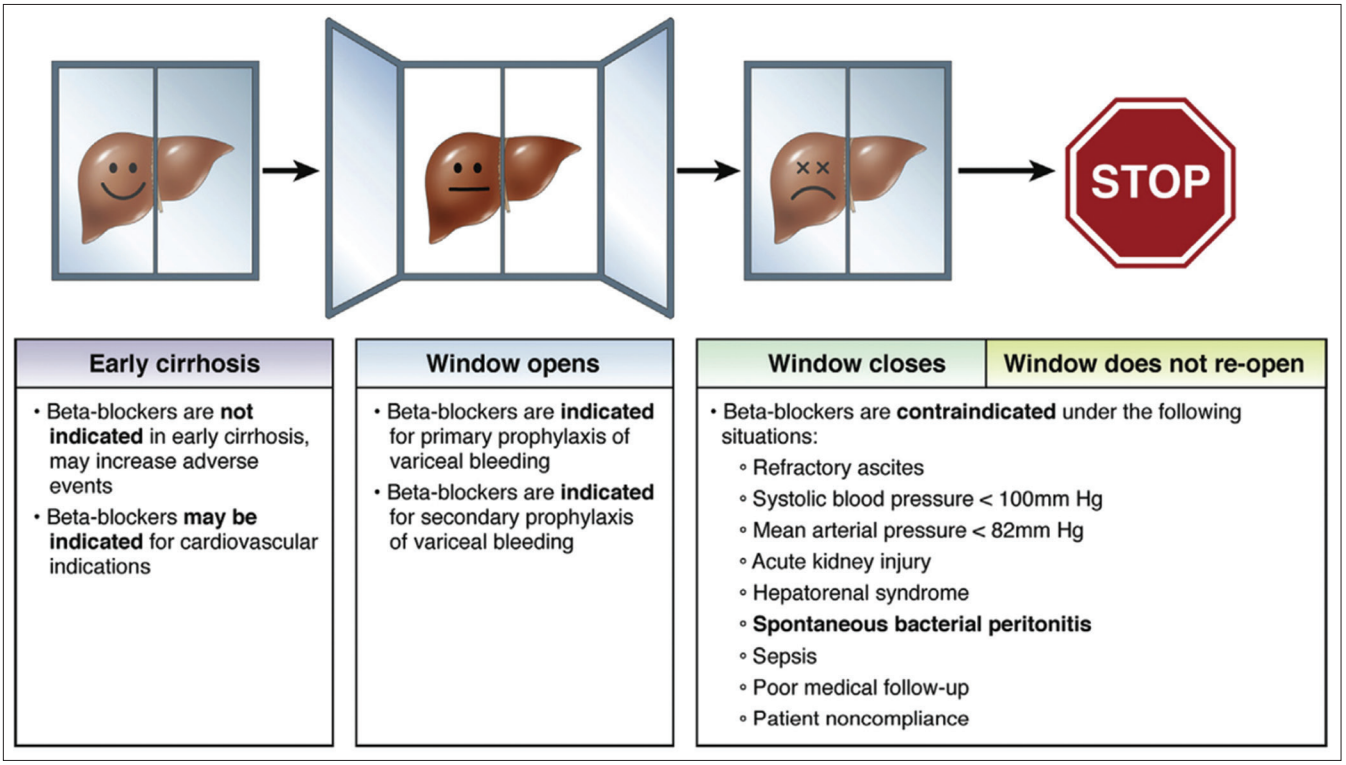

Figure 4: The NSBB of opportunity in the "Window Hypothesis" [21]

splanchnic vasoconstriction. Propranolol is administered up to the maximum tolerable dose (maintaining systolic pressure >100 mmHg and pulse, not below 55 beats/min). The dose should not exceed 320 mg/day. The target is achieved if the HVPG is reduced by <12 mmHg or 20% of the pre-therapy HVPG value [10].

Nadolol is given up to the maximum tolerable dose (maintaining systolic pressure >100 mmHg and pulse, not below 55 beats/min). The dose should not exceed 160 mg/day with the target achieved when the HVPG is reduced by <12 mmHg or 20% of the pre-therapy HVPG value [10].

Carvedilol is a β1 and β2 adrenergic receptor antagonist with an additional α1-adrenergic activity which can reduce cardiac output, splanchnic vasoconstriction, and intrahepatic vasodilation. The maximum dose is 25 mg/day with systolic blood pressure maintained >100 mmHg. However, with carvedilol, the expected target is not yet fully known [10].

Conclusion

LC is the final stage of the diffuse process of progressive liver fibrosis characterized by abnormal liver architecture and regenerative nodule formation. LC is clinically divided into two, compensated LC and decompensated LC with signs of hepatocellular failure and portal hypertension.

The recommended treatment for LC is NSBB. NSBB is primary and secondary prophylaxis. The indication for giving NSBB was adjusted based on the LC stage and the specific pathophysiology that occurred in LC. Conventional NSBBs such as propranolol and nadolol which are β1 and β2 adrenergic receptor antagonists induce decreased cardiac output and splanchnic vasoconstriction. Carvedilol is an NSBB with additional α1-adrenergic activity in reducing portal pressure stronger than conventional NSBB, so carvedilol can cause a greater decrease in systemic arterial pressure when compared to conventional NSBB.

Safety in the use of NSBB therapy in LC requires good therapeutic guidance and considers the side effects caused. The giving of NSBB requires vigilance in LC patients so that appropriate treatment strategies can be made in using NSBB to prevent more severe complications and can reduce morbidity and mortality.

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