Systemic arterial blood pressure determines the therapeutic window of non-selective beta blockers in decompensated cirrhosis

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Summary

Background: The safety of non-selective β-blockers in patients with advanced cirrhosis has been questioned in recent years. It was hypothesised that there is a particular therapeutic window. However, the specific limits still need to be determined.

Aim: To evaluate potential limits of the therapeutic window of non-selective β-blocker therapy in patients with cirrhosis and ascites

Methods: The impact of non-selective β-blockers on 28-day transplant-free survival was analysed in a cohort of 624 consecutive patients with decompensated cirrhosis and ascites. Three potential limits were investigated: spontaneous bacterial peritonitis, acute-on-chronic liver failure, mean arterial blood pressure ≤ 82 and < 65 mm Hg.

Results: Treatment with non-selective β-blockers was associated with a higher 28-day transplant-free survival in the overall cohort (hazard ratio: 0.621; P = .035) as well as in patients with acute-on-chronic liver failure (hazard ratio: 0.578; P = .031) and those with spontaneous bacterial peritonitis (hazard ratio: 0.594; P = .073). In contrast, survival benefits were markedly attenuated in patients with a mean arterial blood pressure ≤ 82 mm Hg and completely lost in those with mean arterial blood pressure < 65 mm Hg (P = .536). In spontaneous bacterial peritonitis patients with a mean arterial blood pressure < 65 mm Hg non-selective β-blocker treatment was associated with renal impairment. Of note, among those with a mean arterial blood pressure ≥ 65 mm Hg non-selective β-blocker intake was consistently associated with superior transplant-free survival (hazard ratio: 0.582; P = .029) irrespective of the presence of spontaneous bacterial peritonitis (hazard ratio: 0.435; P = .028) or acute-on-chronic liver failure (hazard ratio: 0.480 P = .034).

Conclusions: Ascites, acute-on-chronic liver failure and spontaneous bacterial peritonitis do not limit the safe use of non-selective β-blockers in
patients with cirrhosis. Mean arterial blood pressure might represent a better indicator to determine the therapeutic window of non-selective β-blocker treatment.

1 | INTRODUCTION

Non-selective β-blockers (NSBB) lower portal pressure and significantly reduce the incidence of variceal bleeding in selected patients with cirrhosis. Therefore, they are the cornerstone of primary and secondary prophylaxis of variceal bleeding. However, some data indicate that NSBB may not always be beneficial in patients with cirrhosis. Especially in those with decompensated liver disease, important safety concerns have been raised. In 2010, Serste et al suggested that NSBB intake is linked to higher mortality among patients with refractory ascites.

These data initiated the hypothesis of a certain therapeutic window for NSBB in patients with cirrhosis. The suggested window opens with the development of oesophageal varices and closes at advanced stages of cirrhosis indicated by the onset of refractory ascites. However, in particular the upper limit of such a window was challenged in the following years by a couple of studies. Leithead et al showed improved survival in patients taking NSBB with decompensated cirrhosis and ascites awaiting liver transplantation. Therefore, refractory ascites alone seems to be inaccurate in defining the therapeutic window for NSBB. Madorfer et al suggested that the adverse effects of NSBB in patients with ascites might be limited to those with spontaneous bacterial peritonitis (SBP). SBP may cause circulatory dysfunction as a result of the inflammatory response and is associated with a high risk for acute kidney injury (AKI). Madorfer et al documented that the circulatory dysfunction after paracentesis is further impaired by NSBB intake, which leads to a higher risk for AKI and subsequently also increased overall mortality. Similar to SBP, a hyperinflammatory status can be found in patients with acute-on-chronic liver failure (ACLF), which is also often associated with renal failure and circulatory dysfunction. Moreover, SBP is one of the most frequent triggers for ACLF in Europe. However, a sub-analysis of the CANONIC study documented improved survival in ACLF patients using a NSBB.

Currently, it is common consensus in the field of hepatology that there is a certain therapeutic window for the treatment of NSBB in patients with liver cirrhosis, the upper limit of this window remains highly controversial. Therefore, we aimed to investigate different potential window limits for the use of NSBB in patients with decompensated cirrhosis in a large, well-defined cohort.

2 | PATIENTS AND METHODS

2.1 | Study cohort

Patients were recruited from the Hannover ascites cohort (HAC). The inclusion and exclusion criteria have been described previously. Briefly, all 1011 consecutive, hospitalised patients that underwent paracentesis at the Hannover Medical School between January 2012 and June 2016 were considered. In the far majority of patients primary reason for hospitalisation was hepatic decompensation (n = 601 (96%), eg ascites (84%), alcoholic hepatitis (4%) or GI bleeding (4%)). A total of 23 patients (4%) were initially admitted for nonliver-related reasons but developed hepatic decompensations during hospitalisation. Data collection was conducted in a retrospective manner. Individuals without evidence of liver cirrhosis were excluded, as well as patients with secondary intraabdominal infection, hepatic or extrahepatic malignancy (except for hepatocellular carcinoma within the MILAN criteria), HIV infection, nonliver solid organ transplantation and congenital immune dysfunction. Figure S1 further illustrates patients’ recruitment.

2.2 | Data assessment

Patients’ medical records were used to assess data regarding presence of oesophageal varices, history of variceal bleeding, presence of HCC, aetiology of liver cirrhosis and medication. Laboratory values and vital signs were assessed at the time of the first paracentesis and, if applicable, at the time of first SBP development. Diagnosis of SBP was made by paracentesis. ACLF was diagnosed according to EASL guidelines. Diagnosis of AKI was based on the criteria of the International Ascites Club. Primary end point of the study was liver transplant or death (LTx-free survival). Patients receiving a liver transplant had a mean MELD score of 30 at the time of data collection. Short time mortality must be expected to have been very high in those selected for a donor liver in this cohort, if no transplantation would have been performed. Thus, death and liver transplant were considered as equal endpoints in this study. A number of 15 patients received a donor liver during the follow-up time.

2.3 | Study design

Three potential limits for the therapeutic window for NSBB in cirrhotic patients were investigated:

2.3.1 | Mean systemic arterial blood pressure

We further analysed the impact of the MAP on the effects of NSBB in patients with cirrhosis. For this purpose, MAP was assessed at the time of the first paracentesis and impact of NSBB was analysed in the subgroup of patients with a MAP ≤ 82 mm Hg and in those with <65 mm Hg. Both cut-offs have previously been associated with an increased mortality in patients with cirrhosis.
2.3.2 Spontaneous bacterial peritonitis

To analyse whether the development of a SBP closes the therapeutic window of NSBB, impact of NSBB was analysed among patients who either already had a SBP at the time of the first paracentesis or developed a SBP later during hospitalisation. For this analysis, baseline was defined as the time point of SBP diagnosis.

2.3.3 Acute-on-chronic liver failure

ACLF was tested as a potential limit of the therapeutic window for NSBB. For this analysis, only patients who fulfilled the ACLF diagnosis criteria were included. ACLF criteria were assessed at two occasions: at the time of the first paracentesis and at the time of SBP diagnosis (in patients with SBP). The time of ACLF diagnosis was considered as baseline for further analysis.

2.4 Statistics

GraphPad Prism (version 5.0; GraphPad Software Inc.), SPSS (Version 22.0; IBM) and Microsoft Excel (Microsoft, Redmond) were used to analyse the data. P-values were considered to be significant. Continuous variables are presented as mean with standard deviation. Categorical variables are listed as proportions. Paired and unpaired t test were used to analyse continuous variables and Pearson’s chi-squared test for categorical variables. Kaplan-Meyer curves were generated to illustrate incidences of specific endpoints (ie survival). The attached P-values were calculated with the log-rank test. Whenever a log-rank test implicated a significant difference between two compared groups, univariate and multivariate Cox-regression were performed, using backwards stepwise regression. Parameters included in the multivariate analysis were MELD score, platelet count, presence of oesophageal varices, leucocyte count and NSBB intake. The MELD score was included because it indicates the severity of the liver disease and correlates with the short-term survival. Platelet count and presence of oesophageal varices were included to adjust for the degree of portal hypertension, since both have already been associated with the respective parameter. The leucocyte count was included to adjust for the degree of inflammation and because the leucocyte count was previously associated with the short-term mortality in patients with ACLF. Competing risk analysis was conducted with R (crrstep-package). To create Hazard ratios and P-values from the data crrstep.output was applied.

2.5 Ethics

The study was approved by the local ethics committee as well as the data protection officer and followed the declaration of Helsinki.

3 RESULTS

3.1 Impact of NSBB intake on 28-day LTx-free survival in the entire study cohort

A number of 255 (41%) patients used a NSBB at baseline, which was either Propanolol (n = 147; 58%; median dose 30 mg/d) or Carvedilol (n = 108; 42%; median dose 12.5 mg/d). Patients with NSBB intake had a significantly lower leucocyte count, heart rate, prevalence of alcoholic hepatitis and bilirubin levels. The presence of oesophageal varices and history of variceal bleeding were more frequent in the NSBB group. The proportion of patients with recurrent ascites was comparable in both groups, as well as the proportion of patients listed for a liver transplantation (Table 1).

Overall, patients with NSBB treatment had a significantly higher 28-day LTx-free survival compared with patients in the No NSBB group (P = .014) (Figure 1A). In the multivariate analysis, only MELD (HR: 1.120; P < .001) was associated with an impaired LTx-free survival, whereas NSBB intake was identified as a protective factor (adjusted HR: 0.621; P = .035) (Table 2). There was no significant difference between patients using Propanolol and those using Carvedilol (Figure S2). Moreover, 28-day LTx-free survival was comparable in a Cox-regression analysis between patients with oesophageal varices or a history of variceal bleeding that received NSBB either as a primary prophylaxis or as a secondary prophylaxis (HR: 1.701; P = .286). In 53 (9%) individuals, NSBB were discontinued within 48 hours after baseline. Withdrawal of NSBB was associated with a lower 28-day LTx-free survival (P = .001) (Figure S3A). Of note, the 28-day incidence of variceal bleeding was comparable between patients with and without NSBB intake (NSBB: 3.9% vs No NSBB: 2.2%; P = .228).

3.2 Impact of NSBB intake on 28-day LTx-free survival depending on the MAP

There were 398 patients with a MAP ≤ 82 mm Hg, of whom 171 (43%) individuals used NSBB (Table 3). In patients with a MAP > 82 mm Hg, NSBB intake was linked to a numerically higher 28-day LTx-free survival (P = .050) (Figure S4A). However, in case of a lower MAP of ≤ 82 mm Hg the link between NSBB intake and LTx-free survival was attenuated (P = .135) (Figure S4B).

When analysing the lower MAP threshold of 65 mm Hg differences became more prominent. In patients with a MAP < 65 mm Hg, no positive effect of NSBB on LTx-free survival was documented (P = .536) (Figure 1B). In contrast, among those with a MAP ≥ 65 mm Hg NSBB treatment was associated with a superior LTx-free survival (P = .021; Figure 2C). This association remained statistically significant, even after adjusting for potential confounders (HR: 0.582; P = .029) (Table 4). Early discontinuation of NSBB was associated with a lower LTx-free survival in patients with a MAP ≥ 65 mm Hg (P = .004), whereas no difference was documented among those with a MAP < 65 mm Hg (P = .842) (Figure S3B,C).
3.3 | Impact of NSBB intake on 28-day LTx-free survival in patients with SBP

Of the 624 patients, 257 (41%) individuals developed a SBP during hospitalisation, of whom 103 (40%) individuals used NSBB. Patients with NSBB had a lower heart rate, systolic blood pressure and leucocyte count, whereas the presence of oesophageal varices and history of variceal bleeding were more prevalent in the respective group (Table S1A).

SBP patients receiving a NSBB had a higher 28-day LTx-free survival ($P = .027$) (Figure 2A). However, after adjusting for other potential confounders in the multivariate analysis this closely failed to reach statistical significance (adjusted HR: 0.594; $P = .073$) (Table S1B).

Of note, there were no survival benefits in patients with a NSBB and a MAP < 65 mm Hg ($P = .967$) (Figure 2B). Even negative associations were identified with regard to the renal function. In NSBB patients with SBP and a MAP < 65 mm Hg there was a significant increase
in the serum creatinine level from baseline (first paracentesis) to SBP diagnosis (125-188 µmol/l; \( P = .027 \)) (Figure S5A). This was not the case in the No NSBB group (\( P = .585 \)) (Table S2). In addition, we observed a numerically higher frequency of severe AKI among the NSBB users (HR: 2.957; \( P = .085 \)) (Figure S5B). In contrast, patients with a MAP ≥ 65 mm Hg and a NSBB had a higher 28-day LTx-free survival (\( P = .008 \)) (Figure 2C), which remained statistically significant in the multivariate analysis (HR: 0.435; \( P = .028 \)) (Table 4). Furthermore, no adverse impact of NSBB treatment on creatinine values was documented in this group (Figure S5A and Table S2). Of note, NSBB withdrawal was associated with a lower 28-day LTx-free survival, especially in those with a MAP ≥ 65 mm Hg (\( P = .004 \)) (Figure S6A-C).

### 3.4 Impact of NSBB intake on 28-day LTx-free survival in patients with ACLF

ACLF was diagnosed in 254 (41%) individuals. In this cohort, patients with NSBB intake had a lower heart rate, systolic blood
pressure, MAP, leucocyte and MELD score. Subsequently, oesophageal varices and history of variceal bleeding were more prevalent in the NSBB group (Table S3A). Intake of a NSBB was associated with an increased 28-day LTx-free survival in the log-rank test ($P = .004$) (Figure 3A) and the univariate Cox-regression (HR: 0.475; $P = .003$). Of note, NSBB intake remained a positive prognostic factor even after adjusting for several potential confounders in the multivariate model (HR: 0.578; $P = .031$) (Table S3B).

Individuals with and without a NSBB in their medication and a MAP < 65 mm Hg had a comparable 28-day LTx-free survival ($P = .151$) (Figure 3B). Twenty-eight-day incidence of grade 3 AKI was also comparable in the respective cohort (HR: 0.497; $P = .151$) (Figure 3B). Twenty-eight-day incidence of grade 3 AKI was also comparable in the respective cohort (HR: 0.497; $P = .151$) (Figure 3B). Twenty-eight-day incidence of grade 3 AKI was also comparable in the respective cohort (HR: 0.497; $P = .151$) (Figure 3B). Twenty-eight-day incidence of grade 3 AKI was also comparable in the respective cohort (HR: 0.497; $P = .151$) (Figure 3B). Twenty-eight-day incidence of grade 3 AKI was also comparable in the respective cohort (HR: 0.497; $P = .151$) (Figure 3B). Twenty-eight-day incidence of grade 3 AKI was also comparable in the respective cohort (HR: 0.497; $P = .151$) (Figure 3B).

### TABLE 2

| Risk factors for 28-day mortality/LTx | Univariate | Multivariate |
|-------------------------------------|------------|--------------|
|                                     | HR         | 95% CI       | adjusted HR | 95% CI       | $P$  |
| Platelets ($10^{12}/µL$)            | 0.997      | 0.994-0.999  | 0.998       | 0.996-1.001  | .157 |
| Leucocytes ($10^{9}/µL$)            | 1.023      | 1.008-1.038  | 0.995       | 0.961-1.031  | .793 |
| Presence of oesophageal varices     | 0.680      | 0.445-1.039  | 0.709       | 0.452-1.112  | .134 |
| MELD                                | 1.121      | 1.095-1.148  | <.001       | 1.120       | 1.093-1.147 | <.001 |
| NSBB intake                         | 0.573      | 0.371-0.885  | 0.621       | 0.398-0.967  | .035 |

### DISCUSSION

NSBB treatment in patients with decompensated cirrhosis and SBP is currently highly controversial. It is widely accepted that there is a certain therapeutic window for the usage of NSBB in patients with cirrhosis. However, the limits of this window still remain to be better defined.7,8,15,18 The present study investigated three potential window limits and suggests that NSBB are in general safe to use in most patients with liver cirrhosis and ascites. We were able to demonstrate for the first time that NSBB are overall not associated with lower 28-day LTx-free survival in patients with ascites and SBP. Furthermore, we confirmed data from Mookerjee et al showing a positive association between survival and NSBB in patients with ACLF.17 However, we also documented that survival benefits of NSBB treatment in cirrhotic patients are limited to those without significant hypotension. Subsequently, NSBB intake was beneficial in all of our investigated cohorts with a MAP ≥ 65 mm Hg, even after adjusting for the stage of the liver disease, the degree of inflammation and the severity of the portal hypertension. A low MAP, although already discussed as a mortality/LTx risk factor, was independently associated with a lower 28-day LTx-free survival in the multivariate analysis (HR: 0.578; $P = .031$) (Table S3B).

### TABLE 3

Baseline characteristics of all patients with a mean arterial pressure < 82 mm Hg and nonselective β-Blocker intake or nonselective β-Blocker intake at the time of their first paracentesis. Unpaired t test for continuous data, chi-squared test for categorical data. Parameters are shown in mean and with standard deviation.

| NSBB | No NSBB | $P$ value |
|------|---------|-----------|
| Patients (n, %)                  | 171 (43) | 227 (57)  |
| Age (y)                         | 56.33 ± 11.38 | 54.26 ± 11.79 | .079 |
| Male/female (n, %)               | 105 (61)/66 (39) | 126 (56)/101 (45) | .238 |
| Aetiology                        |          |           |
| Viral (n, %)                     | 28 (16)  | 35 (15)   | .796 |
| ALD (n, %)                       | 86 (50)  | 108 (48)  | .592 |
| Other (n, %)                     | 57 (33)  | 84 (37)   | .449 |
| Heart rate (bpm)                 | 75 ± 13  | 87 ± 16   | <.0001 |
| BP systolic (mm Hg)              | 99 ± 13  | 100 ± 8   | .438 |
| BP diastolic (mm Hg)             | 56 ± 9   | 55 ± 8    | .850 |
| MAP (mm Hg)                      | 70 ± 9   | 70 ± 9    | .781 |
| Leucocytes ($10^{9}/µL$)         | 8.21 ± 5.13 | 10.21 ± 9.43 | .014 |
| Platelets ($10^{9}/µL$)          | 128 ± 95 | 145 ± 105 | .100 |
| Haemoglobin (g/dL)               | 10.04 ± 1.77 | 9.87 ± 1.96 | .371 |
| INR                              | 1.59 ± 0.49 | 1.60 ± 0.46 | .820 |
| Creatinine (µmol/L)              | 154 ± 95 | 155 ± 122 | .989 |
| CRP (mg/L)                       | 45 ± 54  | 39 ± 36   | .175 |
| Bilirubin (µmol/L)               | 107 ± 159 | 118 ± 148 | .464 |
| Albumin (g/L)                    | 25 ± 6   | 25 ± 7    | .951 |
| MELD                             | 19.26 ± 8.13 | 19.77 ± 8.30 | .540 |
| Presence of SBP (n, %)           | 37 (22)  | 49 (22)   | .991 |
| Presence of oesophageal varices (n, %) | 152 (89) | 142 (63) | <.0001 |
| History of variceal bleeding (n, %) | 49 (29)  | 14 (6)    | <.0001 |
| HCC (n, %)                       | 2 (1)    | 10 (4)    | .062 |
| Presence of AKI at baseline (n, %) | 56 (33)  | 72 (32)   | .823 |
a potential window limit, has never been investigated in detail, so far. According to our data, NSBB may safely be used in ACLF and even SBP patients unless severe hypotension occurs.

Our study is in line with Leithead et al, who investigated the survival of patients with refractory ascites awaiting liver transplantation. Intake of NSBB at the time of the listing was associated with an improved survival. However, the potential impact of the MAP in the cohort could not be analysed in detail because data on blood pressure was only available in 81 of the 208 patients. Krag et al reported an association between MAP and renal function and hypothesised that NSBB could potentially worsen hemodynamics. Other studies suggested that negative impacts of NSBB on renal function might particularly occur in case of additional intercurrent conditions like severe ASH or SBP. In our study, we only documented a significant increase in serum creatinine levels as well as a numerically higher incidence of severe AKI among patients with

**FIGURE 2** Twenty-eight-day liver transplant-free survival after the first paracentesis in all patients with spontaneous bacterial peritonitis (n = 257) (A) and patients with a MAP < 65 mm Hg (n = 59) (B) or ≥ 65 mm Hg (n = 196) (C). P values were calculated with the log-rank test. Two patients had insufficient data regarding the mean arterial pressure
NSBB intake in case of a MAP < 65 mm Hg and SBP. In a large post hoc analysis of 1198 patients, Bossen et al did not find any association between NSBB intake and an increased survival in the overall cohort. However, there was a positive impact among patients with a MAP of 81-90 mm Hg, which was not further discussed or analysed.7

It has to be considered that the NSBB doses in our study were lower compared with some other trials.7,12 In a letter by Madsen et al, a high dose of Propanolol (160 mg/d) was associated with an increased mortality in SBP patients, whereas this was not the case among those taking a low dose (80 mg/d).17 Other studies also observed a reduced mortality in cirrhotic patients if lower propranolol doses were used.32,33 This might help to explain the differences between the present study and the results in the cohorts of Mandorfer et al and Serste et al, in which higher NSBB dosages were used.6,7,12 It seems well possible that the proposed detrimental hemodynamic effects of NSBB that lead to a decreased cardiac index and in the course to an increase of the incidence of hepatorenal syndrome or even death in decompensated cirrhosis, escalates with higher NSBB doses.1,19,29 Furthermore, it has to be considered that Propanolol and Carvedilol get metabolised in the liver. Decompensated liver disease can result in a decreased clearance of the NSBB and thus, increases the effective dose of the prescribed substance by an unknown fold. This might be particularly relevant for those with a high daily dose, which could increase the risk for deleterious hemodynamic effects of NSBB as described by Serste et al and Mandorfer et al.7,12

While our results do not confirm the findings from Mandorfer et al in terms of the impact of NSBB on survival in patients with SBP, there were still some similarities with regard to renal failure but also the superior overall survival in patients with ascites.12 We documented a significant worsening of renal function in the subgroup of SBP patients with a NSBB and a low MAP, which, importantly, did not occur in those with normal MAP. In ACLF patients, NSBB had at least no positive impact on the incidence of renal failure. However, other positive effects of NSBB seem to weight out this disadvantage to quite some extend. In ACLF patients, we observed positive effects of NSBB treatment even with regard to lung failure or coagulation failure, which might hardly be explained just by a decrease in portal pressure. Thus, there must be some non-pressure related positive effects of the NSBB: A recently published, well conducted study by Mookerjee et al associated NSBB intake with a higher 28-day survival in patients with advanced liver cirrhosis during follow-up and these patients had a significantly lower survival compared with those who maintained NSBB intake.17 The higher survival was explained through the lower grade of inflammation as indicated by the lower leucocyte count in patients with NSBB intake. Downregulation of the sympathetic nervous system in the splanchnic area through sympathectomy or NSBB intake have been associated with less bacterial translocation and less bacterial overgrowth in the past.34-36 Intake of NSBB was also associated with a lower leucocyte

| Risk factors for 28-day mortality/LTx | Univariate | Multivariate |
|-------------------------------------|------------|--------------|
|                                     | HR         | 95% CI       | adjusted HR | 95% CI       | P  |
| (A) The first analysis was conducted with all patients with a mean arterial pressure ≥65 mm Hg | | | | |
| Platelets (10^3/µL) | 0.997 | 0.994-1.000 | .062 | 0.999 | 0.996-1.001 | .378 |
| Leucocytes (10^3/µL) | 1.064 | 1.029-1.101 | <.001 | 0.990 | 0.944-1.039 | .692 |
| Presence of oesophageal varices | 0.539 | 0.322-0.905 | .019 | 0.708 | 0.405-1.237 | .225 |
| MELD | 1.122 | 1.092-1.153 | <.001 | 1.121 | 1.091-1.153 | <.001 |
| NSBB intake | 0.590 | 0.364-0.956 | .032 | 0.582 | 0.358-0.946 | .029 |
| (B) The second analysis included all patients with a spontaneous bacterial peritonitis and a mean arterial pressure ≥65 mm Hg | | | | |
| Platelets (10^3/µL) | 0.992 | 0.987-0.998 | .004 | 0.996 | 0.992-1.000 | .072 |
| Leucocytes (10^3/µL) | 1.061 | 1.027-1.097 | <.001 | 1.045 | 0.993-1.099 | .091 |
| Presence of oesophageal varices | 0.753 | 0.397-1.431 | .387 | 0.624 | 0.321-2.121 | .164 |
| MELD | 1.119 | 1.079-1.160 | <.001 | 1.101 | 1.060-1.114 | <.001 |
| NSBB intake | 0.383 | 0.183-0.801 | .011 | 0.435 | 0.206-0.915 | .028 |
| (C) The third model included all patients who met the criteria of an acute-on-chronic liver failure and a mean arterial pressure ≥65 mm Hg | | | | |
| Platelets (10^3/µL) | 0.998 | 0.994-1.001 | .233 | 0.998 | 0.995-1.002 | .351 |
| Leucocytes (10^3/µL) | 1.054 | 1.021-1.089 | .001 | 1.025 | 0.975-1.076 | .255 |
| Presence of oesophageal varices | 0.815 | 0.442-1.502 | .512 | 0.872 | 0.458-1.659 | .676 |
| MELD | 1.119 | 1.075-1.165 | <.001 | 1.112 | 0.243-0.947 | <.001 |
| NSBB intake | 0.378 | 0.193-0.742 | .005 | 0.480 | 0.243-0.947 | .034 |
count in another study. This is further supported by our data: The overall leucocyte count was also lower in every investigated group with NSBB intake compared with those without a NSBB in their medication. However, further studies are needed to conclude on the impact of an anti-inflammatory effect that results in a lower risk for organ failure and a better survival.

Our study has some important limitations that need to be considered when interpreting the results. Although we minimised the potential selection bias with a consecutive assessment and automated patient identification the data were collected in a retrospective manner. Due to the retrospective data collection, we could not assess the presence of ACLF at every day during hospital treatment. Hence, a few ACLF patients might have been missed for the respective analysis. Furthermore, the majority of patients used low dosages of NSBB, thus we are unable to draw final conclusions on the consequences of the use of high NSBB dosages. However, propranolol
is often not well tolerated at higher dosages in real-world clinical practice because of side effects like orthostatic hypotension. This may be relevant why our and several other studies reported the usage of relatively low dosages in routine clinical practice. Of note, in patients with severe ascites higher NSBB dosages (>80 mg Propanolol/d) are no longer recommended by the recent EASL guideline. We think that this study has valuable clinical implications. Our data provide some evidence for the current EASL recommendation to limit NSBB intake to those without severe hypotension. In contrast, in cirrhotic patients with normal MAP NSBB discontinuation might not be necessary even in the case of additional intercurrent conditions like SBP or ACLF. NSBB discontinuation in patients with normal MAP was even associated with an impaired survival in our cohort irrespective of the presence of SBP or ACLF. However, this observation might well be biased, as it seems likely that physicians may have preferably stopped NSBB in patients who follow a more severe clinical course (ie indicated by progressive hypotension). A recent study by Payancé et al showed that at least no increase in the risk of variceal bleeding nor a hemodynamic rebound must be expected in those with abrupt interruption. However, this study consisted mostly out of patients with compensated cirrhosis and also included those with cardioselective beta-blockers. Yet, more and prospective studies are needed, that is, to properly address the question whether NSBB should be discontinued in patients with sepsis or GI-bleeding and to identify further valuable marker for the therapeutic window.

In summary, our study indicates that NSBB are in general safe and associated with an improved LTx-free survival in cirrhotic patients in most subgroups. In a setting of severe hypotension however, the beneficial effects of the NSBB treatment cease to exist and might even increase the probability of kidney failure in particular among those with SBP. Our study implies that not a clinical condition like ascites, ACLF or SBP per se, but rather the MAP might be used to determine the therapeutic window of NSBB treatment.

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