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ORIGINAL ARTICLE

Treatment with carvedilol improves survival of patients with acute-on-chronic liver failure: a randomized controlled trial

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Abstract

Background and aims In addition to the portal pressure reducing effect, non-selective beta blockers (NSBBs) have possible immunomodulatory and effect in reducing bacterial translocation. Recently, it has been shown that patients who are already on NSBBs should be continued on them (if feasible), if acute-on-chronic liver failure (ACLF) develops. It, however, remains unknown if patients with ACLF and no or small esophageal varices at presentation will benefit from the use of NSBBs. We studied the efficacy and safety of carvedilol in patients with ACLF in reducing mortality, variceal bleeding and non-bleeding complications.

Methods 136 patients with ACLF (with no or small esophageal varices and HVPG $\geq$ 12 mmHg) were randomized to either carvedilol ($n=66$) or placebo arms ($n=70$).

Results Within 28 days, 7 (10.6%) of 66 patients in the carvedilol group and 17 (24.3%) of 70 in the placebo group died ($p=0.044$). Fewer patients in the carvedilol compared to placebo group developed acute kidney injury (AKI) (13.6% vs 35.7%, $p=0.003$ and spontaneous bacterial peritonitis (SBP) (6.1% vs 21.4%, $p=0.013$). Significantly, more patients in the placebo group had increase in APASL ACLF Research Consortium-ACLF grade (22.9% vs 6.1%, $p=0.007$). There was no significant difference in the 90-day transplant-free survival rate and development of AKI, SBP, non-SBP infections (including pneumonia) and variceal bleed within 90 days, between the two groups.

Conclusions In ACLF patients with either no or small esophageal varices and HVPG $\geq$ 12 mmHg, carvedilol leads to improved survival and fewer AKI and SBP events up to 28 days.

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Keywords Acute-on-chronic liver failure · Beta blockers · Carvedilol

Manoj Kumar and Sumit Kainth contributed equally to this work and are joint first authors.

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Abbreviations

AARC	APASL ACLF Research Consortium
ACLF	Acute-on-chronic liver failure
AKI	Acute kidney injury
APASL	Asian Pacific Association for the Study of the Liver
CLIF-C	Chronic Liver Failure Consortium
DILI	Drug-induced liver injury
FHVP	Free hepatic venous pressure
HBV	Hepatitis B virus
HE	Hepatic encephalopathy
HEV	Hepatitis E virus
HVPG	Hepatic venous pressure gradient
INR	International normalized ratio
LT	Liver transplantation
NASH	Non-alcoholic steatohepatitis

NSBB Non-selective beta blocker
WHVP Wedged hepatic venous pressure

Background and objectives

Acute-on-chronic liver failure (ACLF) occurs in patients with chronic liver disease (both cirrhotic and pre-cirrhotic) and is characterized by a precipitating event (identified or surreptitious) often resulting in acute deterioration in liver function, multiorgan system failure and high short-term mortality.

Non-selective beta blockers (NSBBs) have beneficial effects on the severity of portal hypertension, which requires both the beta-1 and beta-2 actions of the drug to ameliorate splanchnic vasodilatation and high cardiac output [1]. In addition to the portal pressure reducing effect, NSBBs have possible immunomodulatory and effect in reducing bacterial translocation [2–4]. These hemodynamic and non-hemodynamic effects of NSBBs may reduce systemic inflammation and may have beneficial effects in ACLF patients over and above its hemodynamic effects. In cirrhosis, NSBB-induced reductions in portal pressure have been associated not only with a decreased incidence of variceal hemorrhage, but also with a reduction in the development of other complications of cirrhosis (ascites, spontaneous bacterial peritonitis, encephalopathy) and improved survival [5–7].

ACLF patients have been shown to have increased hepatic venous pressure gradient (HVPG) as compared to compensated cirrhotics [8]. High baseline HVPG has been shown to be a predictor of mortality in ACLF [9]. Patients with ACLF have marked ongoing hepatic inflammation that leads to increased generation of reactive oxidant species, especially superoxide, which, by reducing nitric oxide bioavailability, may contribute to acute rise in intra-hepatic vascular resistance, and the increased portal pressure in ACLF may contribute to not only variceal bleeding, but also other systemic complications and organ failures of ACLF [10].

There is scant data on the effect of NSBBs in ACLF patients. In one retrospective study, Mookerjee et al. used a subgroup of patients enrolled in the CANONIC study, a European consortium that collects data prospectively from patients hospitalized with decompensated cirrhosis (ascites, variceal hemorrhage, encephalopathy) [11]. 47% of ACLF patients were on NSBBs (most of them having been started at least 3 months prior to admission, and the short-term (28-day) mortality was significantly lower in patients on NSBBs compared to those not on NSBBs and was lower for every degree of severity of ACLF. Also, patients on NSBB had less severe ACLF and a slower progression of ACLF during the study period. Patients who were receiving NSBBs in the previous 3 months and discontinued NSBBs after development of ACLF had a higher mortality and the main difference between those who discontinued and did not discontinue BB was the presence of circulatory dysfunction (hypotension requiring pressors) and respiratory failure [11]. Importantly, the rates of spontaneous bacterial peritonitis were the same in patients on NSBBs and those not being on NSBBs. The rates of bacterial infection, though statistically insignificant, were also noted to be higher in patients on NSBBs than those not on NSBBs.

Variceal bleeding may occur in ACLF even in the presence of small varices. In one study from India, of 57 ACLF patients, the median grade of varices was 2 (0–3); and 6 of these (25%) developed variceal bleed during follow-up. All of these six patients had small varices at baseline [median grade of varices: 1 (0–2)] which had progressed to a median grade of 2 (2–3) at the time of variceal bleed [9]. The rapid development of varices and bleeding is a matter of great concern; it is important to determine the need of acute portal pressure reduction in these patients. In the study by Mookerjee et al., the variceal status of the patients was not reported and HVPG was also not measured. But it is obvious that patients with previous variceal bleeders or non-bleeders with large/high risk varices are more likely to be prescribed NSBBs in clinical practice.

Thus, overall it seems that patients who are already on NSBBs (likely with patients with large/high risk varices or prior variceal bleeders) should be continued on them (if feasible), if ACLF develops. However, it remains unknown if patients presenting with ACLF and who are not already on NSBBs will benefit from the addition of beta blockers (in terms of mortality reduction and development of variceal bleeding and non-bleeding complications), especially those patients with no or small esophageal varices at presentation. Also, whether the use of NSBBs in patients with no or small varices presenting as ACLF will benefit these patients with respect to variceal progression and development of variceal bleed remains unknown.

So, although Mookerjee et al. have studied the effect of NSBBs in the ACLF setting in a retrospective manner, there have been no randomized controlled studies, specifically in patients with no or small esophageal varices and ACLF. So, equipoise remains in the field of use of NSBBs in ACLF with regard to mortality and development of complications (SBP, AKI, infections, variceal progression, and variceal bleed). Also, feasibility of starting NSBBs and their safety in such a setting remain an unmet need.

The aim of the study was to evaluate the efficacy and safety of carvedilol in patients of ACLF with and either no or small esophageal varices and HVPG $\geq$ 12 mmHg in improving survival and reducing complications (variceal bleeding and other non-bleeding complications) by day 28, 60 and 90.

Methods

Trial design

This was a single-center double-blind, randomized placebo-controlled trial.

Participants

The study was conducted in the Department of Hepatology, Institute of Liver and Biliary Sciences (ILBS), New Delhi from 25 October 2015 to 1 July 2017. The study was approved by the ILBS Institutional Review Board (Letter no. F.25/5/80/ILBS/AC/2015/711) and registered with ClinicalTrials.gov (ClinicalTrials.gov identifier number: NCT02583698). Informed consent was taken from the participants and the work was done in accordance with the Declaration of Helsinki.

ACLF was defined as per Asian Pacific Association for the Study of the Liver (APASL) criteria [12].

Patients who fulfilled the following inclusion criteria were eligible to participate in the study: age 18–70 years, ACLF as per APASL criteria, either no or small (< 5 mm) esophageal varices and HVPG ≥ 12 mmHg. Exclusion criteria were the following: contraindications to beta blockers (bradycardia with heart rate < 55/min, hypotension, asthma, heart failure, acute kidney injury, large ascites, spontaneous bacterial peritonitis, past history of endoscopic variceal ligation or sclerotherapy, portal vein thrombosis, presence of grades 3–4 hepatic encephalopathy, pregnancy, lactating mothers, patients planned for liver transplant in the next 12 weeks and no consent).

Interventions

After fulfilling all inclusion and exclusion criteria, patients were randomized to either carvedilol ($n = 66$) or placebo ($n = 70$) in a 1:1 proportion.

Protocol for specific etiological treatment

During the study period, the use of corticosteroids was considered to be the standard of care for severe alcoholic hepatitis. Accordingly, patients were administered 40 mg of prednisolone daily for 28 days. Lille scores were calculated at day 7, as previously described [13]. Corticosteroid treatment was continued for 28 days if patients responded to treatment (Lille score less than 0.45). In cases of non-response to medical therapy, patients were treated with pentoxifylline and counseled for liver transplantation (LT).

Patients with autoimmune flare were counseled for LT and started treatment with 40 mg prednisolone daily for a period of 1 month, followed by a tapering dose. If at any time any complications developed [infections, acute kidney injury (AKI), bleed, encephalopathy grade 3 or above] or if pre-treatment hyperbilirubinemia failed to improve during a 2-week treatment trial, steroids were stopped.

Patients with reactivation of hepatitis B virus infection (HBV) were counseled for LT and tenofovir 300 mg daily was started.

All patients were treated and managed for complications as per standard institutional protocols.

Follow-up of patients

Both the group of patients underwent the following investigations at baseline: hemogram, renal and liver function tests, INR, serum electrolytes, blood sugar fasting, alpha-fetoprotein, thyroid function tests, workup for etiology of acute and chronic components of ACLF as needed, ultrasound abdomen with Doppler of the splenoportal axis and hepatic veins, chest X-ray, arterial ammonia level, arterial blood gas analysis, procalcitonin levels, blood and urine cultures, upper GI endoscopy, and HVPG.

Follow-up of patients was done at weekly intervals till 90 days.

During each follow-up visit, the following were assessed: compliance, history and clinical examination, any adverse drug effect, hemogram, renal and liver function tests, INR, serum electrolytes, and blood sugar fasting.

At the end of 90 days, in addition to the ultrasound of the abdomen with Doppler splenoportal axis and hepatic veins, chest X-ray, arterial blood gas analysis, procalcitonin levels, blood and urine cultures, upper GI endoscopy, and HVPG were repeated.

At each visit, any complications (like acute kidney injury, infections, bleeding, and encephalopathy) that developed were managed according to standard institutional protocols.

The patients and their relatives were instructed to contact us immediately in the event of any alteration in the patient's mental state, any GI bleeding in the form of hematemesis or melena, giddiness, fever, decreased urine output, shortness of breath or any other abnormal events.

Study assessments and methods

ACLF grading

APASL ACLF Research Consortium (AARC) score and ACLF grade were calculated as described previously [14, 15]. Chronic Liver Failure Consortium (CLIF-C) ACLF score and grades were also calculated as described previously [16, 17].

Varices grading

Esophageal varices were classified into one of two grades: small (less than or equal to 5 mm) or large (greater than 5 mm).

Ascites grading

Grading of ascites was done as: Grade 1 ascites (mild ascites only detectable by ultrasound), Grade 2 ascites (moderate ascites evident by moderate symmetrical distension of abdomen) or Grade 3 ascites (large or gross ascites with marked abdominal distension).

AKI diagnosis

We have used the International Club of Ascites criteria for the diagnosis of AKI (defined as an absolute increase in serum creatinine of 0.3 mg/dl within 48 h or by percentage increase in serum creatinine of more than 50% from baseline, which is known, or presumed, to have occurred within the previous 7 days) in our study [18].

HVPG measurement

HVPG measurement was done in accordance with a standardized operating procedure using a 7 F balloon-tipped HVPG catheter. HVPG measurements were performed without sedation and after an overnight fast. Correct positioning of the balloon catheter was confirmed by fluoroscopy. Free hepatic venous pressure (FHVP) and balloon occluded wedged hepatic venous pressure (WHVP) were traced for at least 60 s. Measurements were performed in triplicate and the mean values were used for analysis. HVPG was calculated as the difference between the mean WHVP and FHVP values.

Outcomes

The primary outcome measure was occurrence of death or liver transplant (i.e., patients not having transplant-free survival) at 28 days of enrollment. The secondary outcome measures studied were: occurrence of complications [development of AKI, occurrence of infectious and other complications, and occurrence of variceal bleeding] within 28, 60 and 90 days; transplant-free survival rate within 60 and 90 days; and development or progression of esophageal varices and reduction of HVPG at 90 days.

Sample size

Occurrence of death or liver transplant (i.e., patients not having transplant-free survival) at 28 days was used as the primary outcome to calculate sample size. We analyzed the data of consecutive 50 patients [patients with ACLF with either no or small (< 5 mm) esophageal varices at presentation and not having any of the following at presentation: heart rate < 55/min, hypotension, asthma, heart failure, acute kidney injury, large ascites, spontaneous bacterial peritonitis, past history of endoscopic variceal ligation or sclerotherapy, portal vein thrombosis and presence of grades 3–4 hepatic encephalopathy)] managed without using any beta blockers at ILBS, New Delhi, before the start of this trial. At 28 days, 15 (30%) of such patients died (none could undergo liver transplant). Assuming that, at 28 days, carvedilol would reduce the proportion of patients dying or undergoing liver transplant for 30% to 10%, with alpha 5% and power 80%, we needed to enroll 124 cases with 62 in each group. Assuming a 5% dropout rate after randomization, it was planned to randomize 66 patients in each group.

Randomization

Sequence generation

Random allocation sequence was done by computer-generated random numbers code with an equal number of the alternative treatments with a block size of 10. Patients were randomized to either of the two groups in a 1:1 ratio.

Allocation concealment mechanism

Sequentially numbered sealed, opaque, thick-papered envelopes were used to conceal the sequence until interventions were assigned.

Implementation

The random allocation sequence was computer-generated by Mr Sandip Kumar from the Information Technology Department; Dr Ankit Bhardwaj from the Clinical Research Department assigned participants to interventions; Dr Shiv K Sarin, Dr Sumit Kainth and Dr Manoj Kumar from the Department of Hepatology enrolled participants in the study.

Blinding

The participants, investigator clinicians, data collectors and data analysts were blinded in this trial. After assigning of the patients to intervention or placebo limbs (by Dr Ankit Bhardwaj), the pharmacist provided the drug and nurse in charge of the ward administered the drug till the patient was in the hospital, and then the patient was provided the medicine for home use. Placebo was identical in appearance to carvedilol tablets. The senior resident in-charge of the ward collected and recorded the data of the patients while hospitalized and thereafter during outpatient visits, and managed the patients according to the protocol. The code was not broken until the end of the study.

Medication preparation

The Institute Pharmacy procured and prepared the study medication. Placebo was identical in appearance to carvedilol tablets.

Compliance and dose titration

Pills were supplied to the patients for 1 week at one time. Compliance was checked every week by interview and pill count technique. Carvedilol was started at a dose of 3.125 mg twice daily and the doses titrated on weekly basis by monitoring the heart rate (kept ≥ 55/min) and systolic BP (kept ≥ 90 mmHg). The target was to take the carvedilol dose up to a maximum of 25 mg daily. If systolic blood pressure was lower than 90 mmHg or heart rate below 55/min, the dose was tapered. The drugs were decreased in dose (as per tolerance) or stopped if any complications occurred (such as SBP, AKI, pneumonia, variceal bleeding, hypotension), and after resolution of that complication the drug was again restarted and titrated as stated above.

Statistical methods

Data were processed using the software packages SPSS version 20.0. For comparison of categorical variables, Chi square and Fisher's exact tests were used. For comparison of continuous variables, *t* test for normally distributed continuous variables and Mann–Whitney test for continuous variables not normally distributed were used. Wilcoxon rank sum test for paired continuous data and McNemar test for paired categorical variables were used. Kaplan–Meier curves for 28-day and 90-day survival were plotted. A univariate logistic-regression analysis was performed for the end points of 28-day mortality and 90-day mortality. Separate models were fitted for conventional prognostic scores [AARC-ACLF score, CLIF-C score, Model for End-Stage Liver Disease Sodium score (MELD-Na)] and for clinical and laboratory variables (age, total leukocyte count, creatinine, albumin, total bilirubin, hepatic encephalopathy, lactate, INR and sodium) to investigate whether they were significant predictors of mortality. Individual and treatment variables that were found to be significant in univariate analyses (at 25% significance level) were used in multivariate logistic regression analysis, and backward elimination was applied at a 5% significance level.

Results

Baseline characteristics of patients

280 patients with ACLF as defined by the APASL criteria were screened for enrollment in the study, and 136 patients who fulfilled the inclusion and exclusion criteria were randomized to the carvedilol arm ($n = 66$) and placebo arms ($n = 70$) (Fig. 1). The recruitment period for the trial was from 25 October 2015 to 15 March 2017, and last data collected was on 1 July 2017. The trial was stopped after attainment of the appropriate sample size. Table 1 shows the

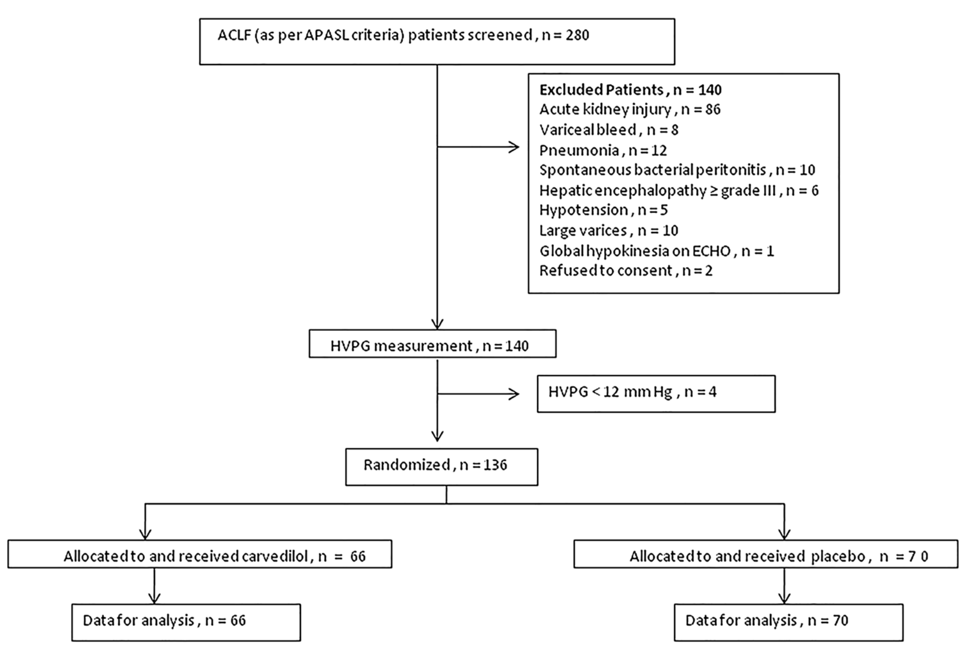

Fig. 1 Participant flow in the study

Table 1 Baseline characteristics of ACLF patients receiving carvedilol and placebo

Characteristics	Carvediol, $N=66$	Placebo, $N=70$	*p* value
Age (year)	44.0 (22.0–64.0)	43.0 (24.0–66.0)	0.543
Male sex	62 (93.9)	64 (91.4)	0.746
Laboratory data			
Hemoglobin (g/dL)	10.5 (8.8–13.9)	10.3 (8.9–14.2)	0.533
Total leukocyte count ($\times 10^9$/L)	10.55 (2.5–32.0)	11.4 (1.6–34.2)	0.269
Platelet count ($\times 10^9$/L)	124.0 (42.0–310.0)	121.5 (40.0–312.0)	0.539
Serum bilirubin (mg/dl)	18.1 (6.2–42.7)	20.7 (6.8–41.0)	0.524
International normalized ratio	2.1 (1.5–4.3)	1.9 (1.5–4.6)	0.423
Aspartate aminotransferase (U/L)	155.0 (45.0–1246.0)	148.5 (21.0–976.0)	0.816
Alanine aminotransferase (U/L)	65.0 (15.0–1115.0)	61.0 (20.0–644.0)	0.789
Serum albumin (g/L)	2.3 (1.5–3.7)	2.3 (1.3–3.9)	0.500
Serum creatinine (mg/dl)	0.6 (0.27–0.92)	0.6 (0.23–1.0)	0.939
Serum sodium (mmol/L)	132.0 (113.0–141.0)	131.0 (118.0–143.0)	0.879
Serum potassium (mmol/L)	3.9 (2.9–5.01)	4.0 (2.6–5.4)	0.267
Serum lactate (mmol/L)	1.3 (0.8–2.6)	1.3 (0.7–2.3)	0.594
Arterial ammonia	101.5 (49.0–255)	101.0 (55.0–212.0)	0.986
Etiology chronic component			
Alcohol	46 (69.7)	52 (74.3)	0.943
NASH	9 (13.6)	8 (11.4)	
Chronic HBV	4 (6.1)	5 (7.1)	
Autoimmune hepatitis	3 (4.5)	2 (2.9)	
Cryptogenic	4 (6.1)	3 (4.3)	
Etiology acute component			
Alcoholic hepatitis	46 (69.7)	49 (70.0)	0.908
Reactivation of HBV	4 (6.1)	5 (7.1)	
DILI	3 (4.5)	6 (8.6)	
Autoimmune flare	3 (4.5)	2 (2.9)	
Acute HEV	9 (13.6)	7 (10)	
Unknown	1 (1.5)	1 (1.4)	
Etiology chronic + acute component combinations			
Alcohol–alcoholic hepatitis	46 (69.7)	49 (70.0)	0.756
Chronic HBV–reactivation of HBV	4 (6.1)	5 (7.1)	
NASH–DILI	3 (4.5)	4 (5.7)	
NASH–acute HEV	6 (9.1)	4 (5.7)	
Atoimmune hepatitis–autoimmune flare	3 (4.5)	2 (2.9)	
Cryptogenic–acute HEV	3 (4.5)	1 (1.4)	
Cryptogenic–unknown	1 (1.5)	1 (1.4)	
Alcohol–DILI	0	1 (1.4)	
Alcohol–acute HEV	0	2 (2.9)	
Cryptogenic–DILI	0	1 (1.4)	
Treatment with steroids	49 (74.2)	51 (72.8)	1.00
Steroid response	31/49 (63.2)	25/51 (49.0)	0.165
Alcohol recidivism	4/46 (8.7)	2/49 (4.1)	0.346
Ascites at presentation	66 (100)	70 (100)	1.00
Ascites grade [1/2/3]	15 (22.7)/45 (68.2)/6 (9.1)	16 (22.9)/52 (74.3)/2 (2.9)	0.298
West Haven HE grade [0/1/2]	56 (84.8)/7 (10.6)/3 (4.5)	59 (84.3)/8 (11.4)/3 (4.3)	0.986
Esophageal varices			
None/small varices	8 (12.1)/58 (87.9)	12 (17.1)/58 (82.9)	0.473
Mean arterial pressure (mmHg)	82.0 (70.0–118.0)	82.0 (66.0–120.0)	0.228
Heart rate (bpm)	89.5 (70.0–113.0)	90.0 (70.0–112.0)	0.138
AARC-ACLF score	8 (5–12)	8 (5–12)	0.722

Table 1 (continued)

Characteristics	Carvediol, $N = 66$	Placebo, $N = 70$	p value
AARC-ACLF grade: 1/2/3	30 (45.5)/31 (47.0)/5 (7.5)	31 (44.3)/35 (50.0)/4 (5.7)	0.811
CLIF-C ACLF score	8 (7–11)	8 (7–11)	0.523
CLIF ACLF grade: 0/1/2	46 (69.7)/5 (7.6)/15 (22.7)	56 (80.0)/7 (10.0)/7 (10.0)	0.128
HVPG (mmHg)	19.5 (12.0–37.0)	18.0 (12.0–36.0)	0.141

Data are *n* (%) or median (range)

NASH nonalcoholic steatohepatitis, *HBV* hepatitis B virus, *DILI* drug-induced liver injury, *HEV* hepatitis E virus, *HE* hepatic encephalopathy, *AARC* APASL ACLF Research Consortium, *ACLF* acute on chronic liver failure, ***CLIF-C*** chronic Liver Failure Consortium, *HVPG* hepatic venous pressure gradient

baseline characteristics for each group. The most common etiological combination for chronic and acute component was alcohol and alcoholic hepatitis [46 of 66 (69.7%) in the carvedilol and 49 of 70 (70.0%) in the placebo group].

The distribution of AARC-ACLF grades 1, 2 and 3 at baseline was 30 (45.5%), 31 (47.0%) and 5 (7.5%) in the carvedilol group, and 31 (44.3%), 35 (50.0%) and 4 (5.7%) in the placebo group (Table 1). At baseline, the distribution of patients to CLIFF-ACLF grades 0, 1 and 2 was 46 (69.7%), 5 (7.6%) and 15 (22.7%) in the carvedilol, and 56 (80.0%), 7 (10.0%) and 7 (10.0%) in the placebo groups (Table 1). Median maximum carvedilol dose was 12.5 (3.125–25.0) mg.

Clinical course and mortality

Two patients underwent liver transplant (on day 54 and day 83), both were in the carvedilol group. Within 28 days, 7 of 66 (10.6%) patients in the carvedilol group and 17 of 70 (24.3%) in the placebo group died ($p = 0.044$) (Table 2). Kaplan–Meier curve for survival in both the groups is provided in Fig. 2.

AKI development was significantly less in the carvedilol group within 28 days [9/66 (13.6%) in the carvedilol group vs 25/70 (35.7%) in the placebo group, $p = 0.003$] and within 60 days [11/66 (16.7%) in the carvedilol group vs 26/70 (37.1%) the placebo group, $p = 0.012$]. However, there was no significant difference in AKI development by day 90 (Table 2).

Overall, development of any infection was significantly less in the carvedilol group within 28 days [11/66 (16.7%) in the carvedilol group vs 27/70 (38.6%) in the placebo group, $p = 0.007$] and within 60 days [13/66 (19.7%) in the carvedilol group vs 30/42.9 (37.1%) in the placebo group, $p = 0.005$], whereas there was no significant difference by day 90 (Table 2). Development of SBP was significantly less in the carvedilol group within 28 days [4/66 (6.1%) in the carvedilol group vs 15/70 (21.4%) in the placebo group, $p = 0.013$], whereas there was no significant difference by day 60 and day 90 (Table 2).

Table 2 shows infections other than SBP that developed in both the groups. There was no significant difference in the development of non-SBP infections (including pneumonia, spontaneous bacterial empyema, cellulitis, urinary tract infection, invasive maxillary aspergillosis/mucormycosis and disseminated tuberculosis) between the two groups at any of the time points (Table 2).

There was no significant differences in 90-day transplant-free survival rate and development of AKI, SBP, pneumonia and variceal bleed within 90 days, between the two groups (Table 2).

Supplementary Table 1 shows the causes of death in both the groups.

Evolution of the AARC-ACLF grade up to 2 weeks after diagnosis

Supplementary Table 2 shows the improvement or worsening in ACLF severity observed up to 1 week from the start of treatment. There was no significant difference in the proportion of patients having improvement and no change or worsening of AARC-ACLF grade from baseline.

Table 3 and Fig. 3 show the improvement or worsening in ACLF severity observed up to 2 weeks from the start of treatment. Significantly, more patients in the placebo group had a 1-grade worsening [14/70 (20.0%) versus 2/66 (3.0%), $p = 0.003$) or any increase in AARC-ACLF grade [16/70 (22.9%) versus 4/66 (6.1%), $p = 0.007$].

HVPG responses and variceal progression

At baseline, in the carvedilol group, 8 (12.1%) patients had no varices and 58 (87.9%) had small varices, whereas in the placebo group, 12 (17.1%) patients had no varices and 58 (82.9%) had small varices ($p = 0.473$) (Supplementary Fig. 1). At the end of the study, 45 patients in the carvedilol group (6 with no varices and 39 with small varices) and 46 patients in the placebo group (7 with no varices and 39 with small varices) did not have variceal bleeding and were alive with native liver (i.e., transplant free). Only these

Table 2 Clinical course and mortality of ACLF patients receiving carvedilol and placebo

Variables	Carvediol, $N=66$	Placebo, $N=70$	*p* value
Mortality or liver transplant[a]			
Within 28 days	7 (10.6)	17 (24.3)	0.044
Within 60 days	10 (15.1)	18 (25.7)	0.127
Within 90 days	18 (27.2)	21 (30.0)	0.725
Acute kidney injury development			
Within 28 days	9 (13.6)	25 (35.7)	0.003
Within 60 days	11 (16.7)	26 (37.1)	0.012
Within 90 days	18 (27.3)	27 (38.6)	0.202
Any infection development			
Within 28 days	11 (16.7)	27 (38.6)	0.007
Within 60 days	13 (19.7)	30 (42.9)	0.005
Within 90 days	21 (31.8)	34 (48.6)	0.055
Spontaneous bacterial peritonitis development			
Within 28 days	4 (6.1)	15 (21.4)	0.013
Within 60 days	6 (9.1)	15 (21.4)	0.058
Within 90 days	10 (15.2)	16 (22.9)	0.282
Any infection, excluding spontaneous bacterial peritonitis, development			
Within 28 days	7 (10.6)	12 (17.1)	0.327
Within 60 days	7 (10.6)	15 (21.4)	0.105
Within 90 days	11 (16.6)	18 (25.7)	0.215
Pneumonia development			
Within 28 days	7 (10.6)	16 (22.9)	0.069
Within 60 days	9 (13.6)	17 (24.3)	0.131
Within 90 days	13 (19.7)	18 (25.7)	0.422
Other infections			
Within 28 days			
Total other infections	3 (4.5)	7 (10.0)	0.223
Spontaneous bacterial empyema	1 (1.5)	2 (2.8)	1.000
Cellulitis	1 (1.5)	2 (2.8)	1.000
Urinary tract infection	0 (0)	2 (2.8)	0.496
Invasive maxillary aspergillosis/mucormycosis	1 (1.5)	1 (1.4)	1.000
Within 60 days			
Total other infections	5 (7.5)	10 (14.2)	0.212
Spontaneous bacterial empyema	1 (1.5)	2 (2.8)	1.000
Cellulitis	2 (3.0)	3 (4.3)	1.000
Urinary tract infection	1 (1.5)	3 (4.3)	0.620
Invasive maxillary aspergillosis/mucormycosis	1 (1.5)	1 (1.4)	1.000
Disseminated tuberculosis	0 (0)	1 (1.4)	1.000
Within 90 days			
Total other infections	9 (13.6)	13 (18.5)	0.435
Spontaneous bacterial empyema	2 (3.0)	2 (2.8)	1.000
Cellulitis	3 (4.5)	4 (5.7)	1.000
Urinary tract infection	3 (4.5)	4 (5.7)	1.000
Invasive maxillary aspergillosis/mucormycosis	1 (1.5)	2 (2.8)	1.000
Disseminated tuberculosis	0 (0)	1 (1.4)	1.000
Variceal bleed development			
Within 28 days	3 (4.5)	3 (4.3)	1.000
Within 60 days	4 (6.1)	3 (4.3)	0.713
Within 90 days	5 (7.6)	5 (7.1)	1.000

[a]Two patients underwent liver transplant (on day 54 and day 83), both were in carvedilol group

Fig. 2 Kaplan–Meier curve showing overall transplant free survival rate according to study group. Kaplan–Meier survival curve shows a significant survival advantage during the first 28 days among patients who received carvedilol as compared with placebo

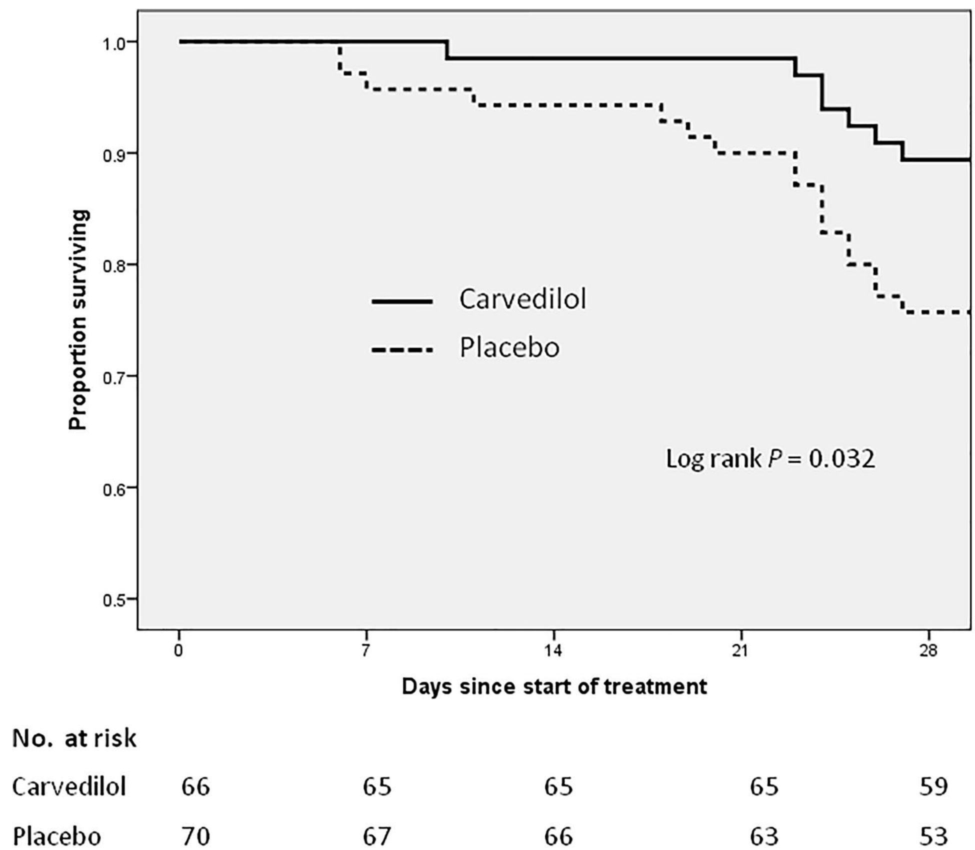

Table 3 Evolution of AARC-ACLF grade up to 2 week after start of treatment among patients receiving carvedilol and placebo

ACLF grade at the 1st onset	ACLF grade after up to 2 weeks from the start of treatment[a]			ACLF grade at the 1st onset	ACLF grade after up to 2 weeks from the start of treatment[a]		
Carvediol, $N=66$				Placebo, $N=70$			
	ACLF-1	ACLF-2	ACLF-3		ACLF-1	ACLF-2	ACLF-3
ACLF-1 ($n=30$)	27 (90.0%)	1 (3.3%)	2 (6.7%)	ACLF-1 ($n=31$)	25 (80.6%)	4 (12.9%)	2 (6.5%)
ACLF-2 ($n=31$)	16 (51.6%)	14 (45.2%)	1 (3.2%)	ACLF-2 ($n=35$)	17 (48.6%)	8 (22.8%)	10 (28.6%)
ACLF-3 ($n=5$)	2 (40.0%)	1 (20.0%)	2 (40.0%)	ACLF-3 ($n=4$)	0 (0.0%)	1 (25.0%)	3 (75.0%)
Evolution of the initial ACLF grade				Evolution of the initial ACLF grade			
Reduction in the ACLF grade-19 (28.8%)				Reduction in the ACLF grade-18 (25.7%) $p=0.704$			
Increase in ACLF grade-4 (6.1%)				Increase in ACLF grade-16 (22.9%) $p=0.007$			
No change in ACLF grade-43 (65.2%)				No change in ACLF grade- 36 (51.4%) $p=0.120$			

[a]For patients who were alive at 2 weeks AARC-ACLF grade at 2 weeks was considered and for those who died earlier AARC-ACLF grade on the day of death was considered

AARC APASL ACLF Research Consortium, *ACLF* acute on chronic liver failure

patients were considered for analysis of HVPG responses and variceal progression (Supplementary Fig. 1).

HVPG decrease of ≥ 10% or to ≤ 12 mmHg at the end of the study was seen in 36/45 (80.0%) of the patients in the carvedilol group and 24/46 (52.2%) in the placebo group ($p=0.008$). Variceal progression was seen in 5/45 (11.1%) in the carvedilol group and 15/46 (32.6%) in the placebo group ($p=0.021$) (Table 4).

Analysis of variables influencing 28-day mortality

The baseline variables that influenced 28-day mortality in univariate analyses (at 25% significance) were total leukocyte count, total bilirubin, INR and treatment with carvedilol (Table 5). Baseline AARC-ACLF score, baseline CLIF-C ACLF score and change in AARC-ACLF grade up to week 1 and week 2 also influence the 28-day mortality. Significant

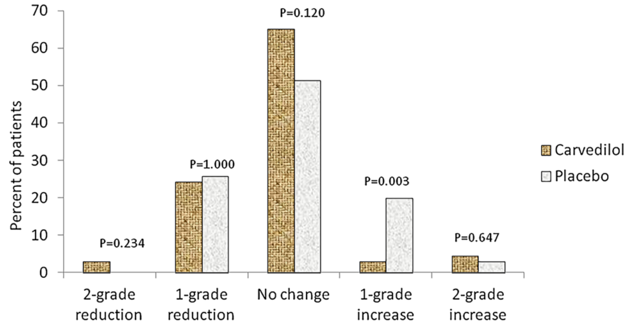

Fig. 3 Evolution of AARC-ACLF grade up to 2 weeks after start of treatment among patients receiving carvedilol and placebo. Significantly, more patients in the placebo group had a 1-grade worsening ($p=0.003$)

variables in the univariate analysis (at 25% significance, i.e., total leukocyte count, total bilirubin, INR, treatment with carvedilol) were added to a multivariate model, and backward elimination was applied. Prognostic scores (MELD-Na, AARC-ACLF score, CLIF-C ACLF score) were excluded from the multivariate analysis owing to multicollinearity with individual component variables. In the multivariate logistic-regression model that adjusted for these prognostic variables (total leukocyte count, total bilirubin and INR), we found that the odds ratio for 28-day mortality among the patients who received carvedilol as compared with those who did not was 0.335 (95% CI, 0.118 to 0.956, $p=0.041$) (Table 5).

Discussion

The results of this study show that carvedilol use among patients presenting with ACLF and no or small esophageal varices (and HVPG ≥ 12 mmHg) led to improved 28-day survival as compared to placebo. Also, fewer patients in the carvedilol group developed AKI, SBP and pneumonia within 28 days as compared to placebo, although there was no difference in the variceal bleeding rates between the two groups.

There are numerous definitions of ACLF (we have used the APASL definition) and ACLF comprises varied diseases such as chronic and acute insults, leading to different specific initial and subsequent therapeutic interventions (such as steroids for alcoholic hepatitis and autoimmune flares, and antivirals for reactivation of HBV). However, a majority of patients in this RCT had the etiology of chronic and acute component combination of alcohol and alcoholic hepatitis [69.7% in the carvedilol group and 70% in the placebo group).Moreover, once ACLF develops, the etiology has no effect on the prognosis [19], in effect making ACLF a prognostically homogenous group.

In this study, we found that up to 2 weeks from the start of treatment, as compared to carvedilol, significantly more patients in the placebo group had a 1-grade worsening [14/70 (20.0%) versus 2/66 (3.0%), $p=0.003$) or any increase in AARC-ACLF grade [16/70 (22.9%) versus 4/66 (6.1%), $p=0.007$]. The dynamic nature of ACLF has important implications. Patients can move rapidly from higher to lower stage or can deteriorate to a more advanced stage. Since carvedilol improves the ACLF grades by week 2, it could provide the opportunity to intervene and select patients for liver transplantation.

In this study we found that carvedilol use decreases the short-term (28 day) survival among patients presenting with ACLF and no or small esophageal varices (and HVPG ≥ 12 mmHg). There is scanty data on the effect of NSBBs in ACLF patients. In one study, Mookerjee et al. used a subgroup of patients enrolled in the CANONIC study, a European consortium that collects data prospectively from patients hospitalized with decompensated cirrhosis (ascites, variceal hemorrhage, encephalopathy) [11]. From a total of 1343 patients from 21 centers enrolled in the study, 349 were deemed to have ACLF per criteria established by the consortium. Of these, 164 (47%) were on NSBB (most of them having been started at least 3 months prior to admission) and 185 were not. Short-term, 28-day

Table 4 Analysis of HVPG changes and variceal progression among ACLF patients (who did not bleed and survived with native liver) receiving carvedilol and placebo

Variables	Carvedilol, $N=45$	Placebo, $N=46$	p value
HVPG baseline, mmHg	19.0 (12.0–33.0)	18.0 (12.0–32.0)	0.134
% change HVPG from baseline to end of study	− 21.7 (− 78.6 to +31.3)	− 11.3 (− 46.2 to +50)	0.003
HVPG decrease ≥ 10% at end of study	35 (77.8)	24 (52.2)	0.015
HVPG decrease ≥ 20% at end of study	26 (57.8)	14 (30.4)	0.011
HVPG ≤ 12 mmHg at end of study	15 (33.3)	10 (21.7)	0.247
HVPG decrease ≥ 10% or to ≤ 12 mmHg at end of study	36 (80.0)	24 (52.2)	0.008
HVPG decrease ≥ 20% or to ≤ 12 mmHg at end of study	28 (62.2)	14 (30.4)	0.003
Variceal progression at end of study	5 (11.1)	15 (32.6)	0.021

Table 5 Analysis of factors associated with mortality at 28 Days

Variable	Univariate analysis[a] OR (95% CI), *p* value	Multivariate analysis# OR ([95% CI), *p* value
Age	0.977 (0.935–1.020), 0.291	
Total leukocyte count	1.054 (0.993–1.118), 0.084	1.023 (0.958–1.093), 0.496
Creatinine	0.738 (0.073–7.493), 0.797	
Albumin	0.638 (0.236–0.1.722), 0.375	
Total bilirubin	1.088 (1.029–1.151), 0.003	1.082 (1.019–1.149), 0.010
Hepatic encephalopathy	1.117 (0.124–10.066), 0.894	
Lactate	1.843 (0.623–5.451), 0.269	
INR	1.490 (0.813–2.730), 0.197	1.668 (0.838–3.318), 0.145
Sodium	0.985 (0.902–1.076), 0.740	
Carvedilol vs placebo	0.370 (0.142–0.961), 0.041	0.335 (0.118–0.956), 0.041
MELD-Na	1.067 (0.953–1.193), 0.261	
CLIF-C ACLF score	3.316 (0.928–11.843), 0.065	
AARC-ACLF score	1.565 (1.156–2.120), 0.004	
AARC-ACLF grade		
1	1	
2	2.248 (0.796–6.350), 0.126	
3	11.458 (2.404–54.618), 0.002	
Change in AARC-ACLF grade up to week 1		
Decrease or same	1	
Increase	12.111 (2.777–52.826), 0.001	
Change in AARC–ACLF grade up to week 2		
Decrease or same	1	
Increase	54.00 (14.570–200.142), < 0.001	

[a]A separate univariate model was fitted for all baseline prognostic factors

Significant variables in the univariate analysis (at 25% significance i.e., total leckocyte count, total bilirubin, INR, treatment with carvedilol) were added to a multivariate model, and backward elimination was applied. Prognostic scores (MELD-Na, AARC-ACLF score, CLIF-C ACLF score) were excluded from the multivariate analysis owing to multicollinearity with individual component variables

mortality (the main outcome in ACLF) was significantly lower in patients on NSBB compared to those not on NSBB (24% vs. 34%, $p = 0.048$) and was lower for every degree of severity of ACLF. Also, patients on NSBB had less severe ACLF and a slower progression of ACLF during the study period. Patients who were receiving NSBBs in the previous 3 months and discontinued NSBBs ($n = 78$) after development of ACLF had a higher mortality (37% vs. 13%) and the main difference between those who discontinued and did not discontinue BB was the presence of circulatory dysfunction (hypotension requiring pressors) and respiratory failure.

There was no significant difference in the 60-day and 90-day transplant-free survival rate between the carvedilol and placebo groups. These findings are similar to the study by Mookerjee et al., who also found that only 28-day mortality was significantly lower in patients on NSBB compared to those not on NSBB, whereas the 90-day mortality was similar between the two groups. The reasons for the loss of efficacy of carvedilol over time are speculative. Increased intestinal permeability is one of the most important events in the pathophysiology of ACLF. An acute hepatic insult activates Kupffer cells present in hepatic sinusoids, resulting in increased release of inflammatory mediators, regulatory cytokines, eicosanoids and lysosomal/proteolytic enzymes. Increased gut permeability in the altered milieu allows immune cells as well as endotoxins and LPS to migrate toward the liver. Activation of hepatic stellate cells by Kupffer cells produces endothelin-1, thromboxane A2, nitric oxide and prostaglandins, leading to hepatic microcirculatory dysfunction and an increase in portal pressure. This leads to inflammation-induced death of hepatocytes as well as other parenchymal and non-parenchymal liver cells. Ongoing hepatocyte loss and cytokine release lead to persistent injury, immunoparalysis, with systemic inflammatory response syndrome, compensatory anti-inflammatory response syndrome and high probability of sepsis. Unabated hepatic injury and sepsis lead to multiorgan dysfunction syndrome and eventually to organ failure.[20]. It is possible that carvedilol's effects on the decrease in intestinal permeability are lost beyond few weeks in the setting of ACLF. But this needs to be verified in well-designed studies in future.

In this study, we found that, within 28 days, significantly fewer patients in the carvedilol group developed SBP [4/66 (6.1%) vs 15/70 (21.4%) in the placebo group, $p = 0.013$], whereas there was no significant difference in the development of non-SBP infections (including pneumonia between the two groups at any of the time points). A recent meta-analysis showed that NSBBs reduced the risk of development of spontaneous bacterial peritonitis (SBP) in susceptible cirrhotic patients independent of hemodynamic responses [7]. It has been shown that in cirrhotics, an 11% reduction in HVPG from baseline was the best cutoff in predicting the absence of risk of SBP [21], which is markedly less than the threshold of 20% reduction considered protective for variceal bleeding [22]. Thus NSBBs may be protective against infection in a larger group of patients than it is protective against bleeding [23]. NSBBs might reduce bacterial translocation from the gut by reducing splanchnic blood flow and thus intestinal mucosa edema and congestion and also by increasing intestinal transit stimulating the beta-adrenoceptor-mediated pathway [3]. The treatment with NSBBs of patients with cirrhosis has also been associated with decreased serum levels of lipopolysaccharide-binding protein (LBP) and IL-6 [4]. Experimental models of bacterial peritonitis or splanchnic sympathectomy have shown that sympathetic nervous system activation is followed by lower levels of peritoneal secretion of TNF-alpha and limited phagocytic activity of peritoneal macrophages [24], while sympathetic nervous system suppression is associated with a reduced rate of *Escherichia coli* bacterial translocation [25]. The sympathetic nervous system is known to produce most of these effects through beta-adrenergic receptors [26]. NSBBs have been hypothesized to enhance performance of the immune system by inhibiting the stress-related cyclic adenosine mono phosphate protein kinase A pathway, which has an inhibitory effect on the immune system [27]. Esmolol, a selective beta-1 blocker was studied in patients with severe septic shock (without underlying cirrhosis) and shown to be safe with potentially beneficial effects on multiorgan function and inflammatory markers [28].

One novel finding of this study was that, within 28 days, fewer patients in the carvedilol group developed AKI [9/66 (13.6%) vs 25/70 (35.7%) in the placebo group, $p = 0.003$]. This result is in contrast to one previous nonrandomized retrospective cohort study among severe alcoholic hepatitis patients, which has suggested that the 168-day cumulative incidence of AKI was higher among patients who were on NSBB (propranolol) as compared to those patients who were not on propranolol [89.6% (95% CI, 74.9–95.9%) vs 50.4% (95% CI 39.0–60.7), $p = 0.0001$] [29]. However, the effects of NSBBs on renal function is complex. Administering beta blockers cause increased level of nor-adrenaline and, as a consequence, sodium and water retention. The other effect is reduction in plasma renin, angiotensin, and aldosterone levels (β1 blockade), which increase salt and water excretion. On the other hand, renal vasoconstriction due to β2 blockade has been proposed as a mechanism by which β blockers may impair renal blood flow (RBF) and glomerular filtration rate (GFR) [30]. In a study on effects of propranolol in cirrhotics, it was found that at baseline as compared to compensated cirrhotics, decompensated patients had significantly higher renal resistive index (0.64 ± 0.03 vs. 0.72 ± 0.02, $p \leq 0.001$) and lower GFR (72.80 ± 21.49 vs. 60.53 ± 10.24 mL/min, $p = 0.089$) After 1 month of propranolol use, as compared to baseline, in compensated cirrhotics there was no significant change in renal resistive index (0.64 ± 0.03 vs. 0.64 ± 0.02, $p = 0.270$) and GFR (72.80 ± 21.49 vs. 68.57 ± 9.41, $p = 0.333$), whereas in decompensated patients, there was significant decrease in renal resistive index (0.72 ± 0.02 vs. 0.66 ± 0.04, $p \leq 0.01$) and significant increase in GFR (60.53 ± 10.24 vs. 74.02 ± 10.10, $p < 0.01$) [32]. Increased RI seems to be correlated with a higher risk of subsequent impairment of kidney function [32]. However, contradictory data has also been reported, showing that after administering propranolol, resistive index decreased in the compensated patients but increased in the decompensated ones [33]. Further studies are needed to confirm findings of this study and to elucidate the mechanisms of reno-protection of NSBBs in the setting of ACLF.

Ours is the first study focussing on effects of NSBBs on variceal progression and HVPG in ACLF patients. Although there was no significant difference in incidence of variceal bleeding between carvedilol and placebo groups; among the patients who did not bleed and were alive with native liver, there was greater decrease in HVPG [HVPG decrease of ≥ 10% or to ≤ 12 mmHg at the end of the study seen in 36/45 (80.0%) of patients in the carvedilol group vs. 24/46 (52.2%) in the placebo group ($p = 0.008$)] and fewer patients had variceal progression [5/45 (11.1%) in carvedilol group vs. 15/46 (32.6%) in placebo group, $p = 0.021$]. This reduction in variceal progression is a novel finding of the current study. A recent meta-analysis of 5 RCTs concluded that NSBBs are not effective in preventing growth of small varices in patients with cirrhosis and may lead to significant adverse effects [34]. Our study found that carvedilol was effective in preventing variceal progression in ACLF patients. Whether these HVPG changes and changes in variceal progression lead to fewer episodes of variceal bleeding on long term follow-up needs further longer duration studies.

There are a few limitations of this study. This study did not dwell into mechanistic basis of beneficial effects of carvedilol in ACLF patients. Around 2/3rd of the patients had alcoholic hepatitis as the cause of ACLF in this study. It is possible that the effects of carvedilol on other causes of ACLF (especially without steroid therapy) might be different. Further studies are needed to address this issue.

In conclusion, in ACLF patients with either no or small esophageal varices and HVPG ≥ 12 mmHg, carvedilol leads to improved 28 day survival, and less development of AKI and SBP up to 28 days. There was no significant differences in the 60-day and 90-day transplant free survival rate; and development of AKI and SBP within 60 days and 90 days, between the two groups. Also, there was no significant difference in development of non-SBP infections (including pneumonia between the two groups at any of time points). Although there was no significant difference in incidence of variceal bleeding between carvedilol and placebo groups; among the patients who did not bleed and were alive with native liver, there was greater decrease in HVPG and fewer patients had variceal progression.

We feel that carvedilol should be used in ACLF patients with no or small esophageal varices and HVPG > 12 mmHg. However, careful monitoring for development of complications is needed and appropriate dose modification should be done according to the tolerance of the patient.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The study has been approved by the institutional ethics committee of the Institute of Liver and Biliary Sciences (Letter no. F.25/5/80/ILBS/AC/2015/711) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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