Research Article
Cirrhosis and Liver Failure

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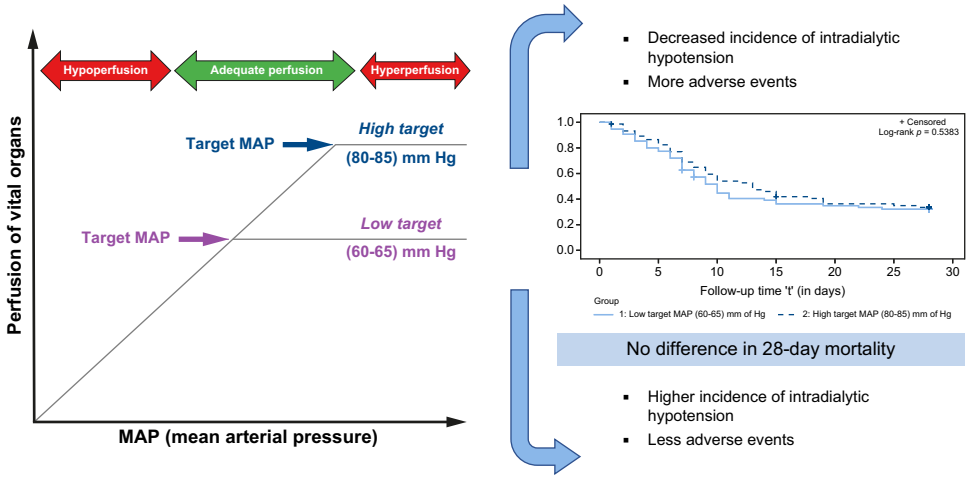
Graphical abstract



Cirrhosis with septic shock? High MAP- Splanchnic vasodilatation or low MAP-chronic adaptation

Highlights

- A higher target MAP strategy does not confer any survival benefit in patients with cirrhosis and septic shock.
- A higher target MAP strategy was associated with more frequent adverse events.
- This strategy was associated with decreased incidence of intradialytic hypotension, better tolerance of dialysis, and improved renal recovery.
- A higher target MAP strategy can be considered alongside careful monitoring for adverse events.

Impact and implications

Maintaining an appropriate organ perfusion pressure during sepsis is the ultimate goal of haemodynamic management. A higher mean arterial pressure (MAP) improves renal outcomes in patients with hepatorenal syndrome. Patients with cirrhosis and septic shock have severe circulatory disturbances, low MAP, and poor tissue perfusion. In these patients, targeting higher MAP *vs.* lower MAP does not confer any survival benefit but is associated with more adverse events. A higher target strategy was associated with better tolerance and lesser episodes of hypotension on dialysis. Patients who could achieve the higher target MAP, without the development of adverse events, had improved renal outcomes and better lactate clearance. Higher MAP was also associated with improvements in markers of endothelial function. A higher target MAP strategy, with close monitoring of adverse events, may be recommended for patients with cirrhosis and septic shock.

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A randomised-controlled trial (TARGET-C) of high *vs.* low target mean arterial pressure in patients with cirrhosis and septic shock

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Background & Aims: A high mean arterial pressure (MAP) target has been associated with improved renal outcomes in patients with cirrhosis, though it has not been studied in critically ill patients with cirrhosis and septic shock (CICs). We compared the efficacy of a high (80-85 mmHg; H-MAP) *vs.* low (60-65; L-MAP) target MAP strategy in improving 28-day mortality in CICs.
Methods: We performed open-label 1:1 randomisation of 150 CICs (H-MAP 75; L-MAP 75). The primary endpoint was 28-day mortality and secondary endpoints included reversal of shock, acute kidney injury (AKI) at day 5, the incidence of intradialytic hypotension (IDH), and adverse events. Endothelial markers were analysed in a subset of patients.
Results: The baseline characteristics were comparable. On intention-to-treat analysis, 28-day mortality (65% *vs*. 56%; $p = 0.54$), reversal of shock (47% *vs*. 53%; $p = 0.41$) and AKI development (45% *vs.* 31%;$p = 0.06$) were not different between the H-MAP and L-MAP groups, respectively. A lower incidence of IDH (12% *vs.* 48%; $p < 0.001$) and higher adverse events necessitating protocol discontinuation (24% *vs.* 11%; $p = 0.031$) were noted in the H-MAP group. On per-protocol analysis (L-MAP 67; H-MAP 57), a significantly higher reversal of AKI (53% *vs.* 31%; $p = 0.02$) and a lower incidence of IDH (4% *vs.* 53%; $p < 0.001$) were observed in the H-MAP group. Endothelial repair markers such as ADAMTS (2.11 ± 1.13 *vs.* 1.15 ± 0.48; $p = 0.002$) and angiopoietin-2 (74.08 ± 53.00 *vs.* 41.80 ± 15.95; $p = 0.016$) were higher in the H-MAP group.
Conclusions: A higher MAP strategy does not confer a survival benefit in CICs, but improves tolerance to dialysis, lactate clearance and renal recovery. Higher adverse events indicate the need for better tools to evaluate target microcirculation pressures in CICs.
Clinical trial number: NCT03145168.

Introduction

A target mean arterial pressure (MAP) of 65-70 mmHg has been suggested for patients with septic shock undergoing resuscitation, except for patients with chronic hypertension.[1,2] In these patients, a higher target of 80-85 mmHg is a reasonable approximation that preserves the perfusion of kidneys.[3] A high target strategy is associated with a higher risk of arrhythmias. Maintaining an appropriate organ perfusion pressure during sepsis is the ultimate goal of haemodynamic management.[1,2] The surviving sepsis campaign recommends initial resuscitation with crystalloids at 30 ml/kg followed by the institution of vasoactive agents. Norepinephrine is usually considered the first-choice vasopressor to target a MAP of 65-70 mmHg.[1] Despite this, the appropriate blood pressure target in patients with septic shock is controversial. In a large French multicentric trial that enrolled around 776 patients, Asfar *et al.* reported that a target MAP of 65-70 mmHg was the most reasonable strategy, except in patients with chronic hypertension. In a subgroup analysis that included patients with cirrhosis, targeting a higher MAP was not associated with improved renal outcomes.[4]

Patients with cirrhosis are in a hyperdynamic circulatory state, with severe vasodilatation and high cardiac output.[4] These haemodynamic perturbations get further exaggerated in the presence of severe sepsis. The systemic and splanchnic vasodilatation causes venous pooling. The vasodilatation leads to decreased kidney perfusion, causing vasoconstriction in the renal vascular bed. Therefore, the use of vasoconstrictors counteracts vasodilatation and improves renal perfusion.[5,6] At the same time, these patients are chronically vasodilated and adapted to low mean arterial blood pressure. Patients with cirrhosis and sepsis-induced hypotension respond less well to

Keywords: Lactate; Sepsis; AKI; Dialysis; NGAL; Cystatin C; ACLF.
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crystalloids.[5,6] In a large randomised-controlled trial evaluating the FRISC (Fluid Resuscitation in Cirrhosis with Septic Shock) protocol, we demonstrated the superiority of 5% albumin over normal saline for volume expansion in these patients.[5] In a subsequent study, the use of 20% albumin was associated with a higher incidence of discontinuation due to pulmonary complications compared to plasmalyte.[6] Critically ill patients with cirrhosis have distinct haemodynamic alterations and immunological profiles, and determination of an appropriate target MAP warrants investigation. In cirrhosis patients with sepsis have severe circulatory disturbances, including exaggerated systemic and splanchnic vasodilatation, low MAP, poor tissue perfusion, and failure of microcirculation.

We hypothesised that a higher target MAP would be associated with improved survival compared to a lower target strategy, owing to improved renal outcomes. We designed the current prospective randomised open-label trial to explore the efficacy of two target strategies of MAP, *i.e*. 60-65 mmHg and 80-85 mmHg. Our primary objective was to evaluate the impact of target MAP on 28-day survival. Our secondary objectives were to compare the effect of the two strategies on the reversal of shock and acute kidney injury (AKI), the incidence of intradialytic hypotension (IDH) in patients undergoing renal replacement therapy (RRT), the incidence of adverse effects, the sequential organ failure assessment score (SOFA), and the duration of mechanical ventilation and L-ICU stay. In a subset of patients, we also evaluated markers of endothelial dysfunction.

Patients and methods

Study design

We designed the current study as an open-label, randomised-controlled trial. The trial was conducted at the Institute of Liver and Biliary Sciences in the liver intensive care unit (L-ICU), New Delhi, from September 2018 to March 2021. The study was approved by the Institutional Ethics Board-IEC/2017/53/NA04. The protocol was registered with ClinicalTrial.gov (identifier: NCT03145168). All authors had access to the study data and reviewed and approved the final manuscript.

Participants

We screened and enrolled consecutive patients with cirrhosis, septic shock, and AKI admitted to the L-ICU. The cirrhosis diagnosis was based on clinical (presence of ascites, jaundice, splenomegaly, *etc.*), biochemical, imaging (ultrasonography, computed tomography, or magnetic resonance imaging showing features of chronic liver disease), and endoscopic evidence of varices or liver histology (when available). Patients with cirrhosis and septic shock with persisting hypotension requiring vasopressors (norepinephrine at a minimum infusion rate of 0.01 μg/kg/min to maintain MAP ≥65 mmHg) and arterial lactate >2 mmol/L, despite adequate volume resuscitation using standard criteria, were screened for randomisation. In all patients, the radial artery or, rarely, the femoral artery was used to measure the MAP.

We excluded patients aged less than 18 years, with severe known cardiopulmonary disease, pregnant patients, patients with chronic heart and lung diseases, extremely moribund patients with an expected life expectancy of fewer than 24 h, and those with refractory shock. Failure to provide informed consent by the legal representative or the patient's next of kin was also an exclusion criterion.

Randomisation and masking

The trial was designed as an open-label randomised-controlled trial. Randomisation was performed by the clinical trial coordinator using a block randomisation method with a block size of 5 with ten blocks. Allocation concealment was performed by the SNOSE technique (sequentially numbered opaque sealed envelopes).

Interventions: In the high target group, the vasopressor dose was adjusted to target a MAP between 80-85 mmHg (high target MAP [H-MAP]) until day 5 or reversal of shock or the development of adverse effects. Similarly, in the low target group, the MAP was kept between 60-65 mmHg (low target MAP [L-MAP]) until the reversal of shock or until day 5 or the development of adverse effects.

Outcome measures: The primary outcome of the study was 28-day survival, while secondary outcome measures included duration of mechanical ventilation and L-ICU stay, reversal of shock and AKI at day 5, the incidence of IDH in patients undergoing dialysis and adverse effects.

Renal and cardiac biomarkers: We also aimed to study the role of renal biomarkers, *i.e*., urine neutrophil gelatinase-associated lipocalin (NGAL), cystatin c (CysC), and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) in predicting clinical outcomes in patients with cirrhosis and septic shock. CysC was evaluated using nephelometry, uNGAL by spectrophotometry, and NT-pro-BNP by ELISA. In a subset of patients (n = 40), we also analysed markers of endothelial dysfunction and vascular shear stress.

Endothelial injury, repair and norepinephrine levels: We measured the plasma levels of endothelin-1 (EDN-1), angiopoietin-2 (ANGPT-2), von-Willebrand factor (vWF), and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS). We also measured monocyte chemoattractant protein-1 (MCP-1) and endotoxin levels. We, in addition, measured the level of norepinephrine spectrophotometrically using pre-coated competitive ELISA of plasma samples in both patient groups. Baseline plasma samples of both cases were considered for the analysis. The reaction and colour change were measured at a wavelength of 450 nm. The noradrenaline concentrations in the samples were then determined by comparing the samples' optical density to the standard curve.

Protocol of dialysis

RRT was performed for standard renal indications. These included severe metabolic acidosis, hyperkalemia refractory to medical management, volume overload non-responsive to intravenous diuretics or progressive or worsening azotemia and for complications of uraemia. Patients requiring two vasopressors or a norepinephrine dose >0.5 ug/kg/min and with arterial lactate >4 mmol/L were considered for continuous renal replacement therapy (CRRT). In patients who developed haemodynamic instability, contraindicating sustained low-efficiency dialysis (SLED), or in patients developing hypotension on SLED, CRRT was administered as the rescue strategy. SLED was considered as a step-down strategy in patients who exhibited haemodynamic improvement on CRRT. SLED sessions were targeted to 8-10 h in duration with blood and dialysate flows of 150-200 ml/min and 300 ml/min, respectively. SLED was delivered using the dialysis

machines (Fresenius, 4008S, Dialyser F6 HPS). The minimum frequency of SLED treatments was three times per week. CRRT was administered as continuous venovenous hemodiafiltration using Prisma and Prismaflex (Gambro) devices, with blood flows ranging from 150–180 ml/h and target effluent rates of 20–25 ml/kg/hour. Anticoagulation was not used during dialysis. The dialysis sessions were continued until renal recovery, liver transplant, or death. The dialysis sessions were also discontinued in patients wherein end-of-life care was considered based on futility of intensive care.

Sample size

We assumed an alpha error of 5% and power of 80%, with a 25% difference in survival (hazard ratio [HR] 2.06) to calculate the sample size. We calculated the sample size by assuming a 28-day survival of 60% in the H-MAP group *vs.* 35% in the L-MAP group and a 10% dropout rate. The sample size was calculated as a minimum of 75 patients in each group. The sample size and power calculation was performed using the nMaster 2.0 developed by Christian Medical College Vellore, India, and Stata by stataCorp USA.

Statistical analysis

Continuous variables were compared between groups using independent samples Student's *t* test or Mann-Whitney *U* test for normal or non-normally distributed data, respectively. Categorical variables were analysed using Fischer's exact test or the Chi-square test between the two randomised groups of patients. Intention-to-treat and per-protocol analyses were performed. Survival analysis was performed using Cox regression, and Kaplan-Meier survival curves were compared using the log-rank test. All tests were 2-tailed, and p <0.05 was considered significant. Statistical analysis was performed using the statistical package for social sciences (IBM corp Ltd. Armonk, NY version 22.0).

Results

From the period of September 2018 to March 2021, we screened a total of 604 patients with septic shock, of whom 150 were randomised (75 in the L-MAP *vs.* 75 in the H-MAP group) (Fig. 1). The baseline characteristics were comparable. Mean age was (46.7 ± 9.1 *vs.* 45.0 ± 12.9; p = 0.38); most patients were male (87% *vs.* 91%; p = 0.44) and had alcohol-

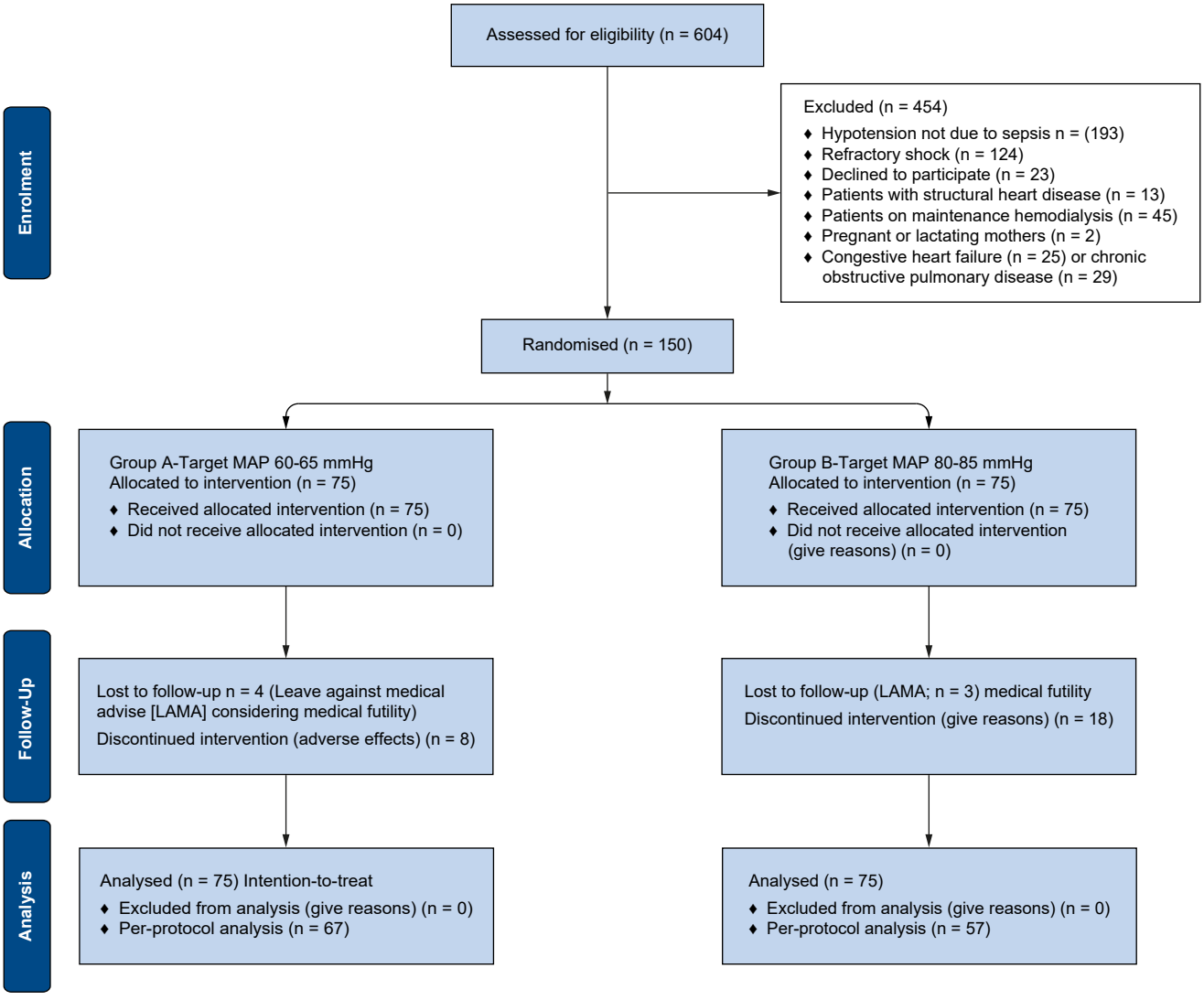

Fig. 1. Consort diagram demonstrating patient enrolment and follow-up in the trial.

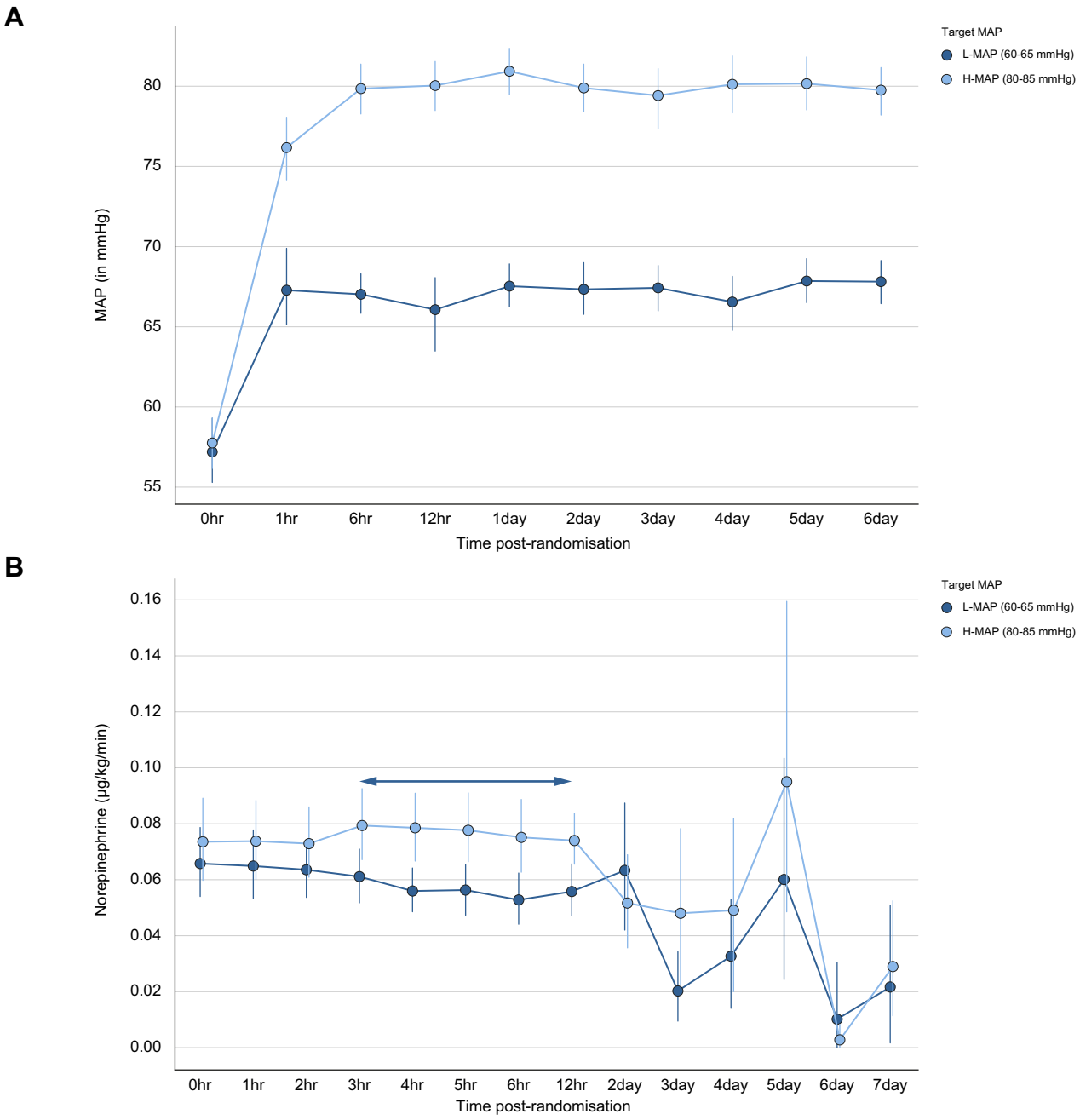

Fig. 2. MAP and norepinephrine dose stratified by the target MAP strategy from day 0 to 7 post-randomisation. (A) The target MAP was significantly higher at all time points between the two randomisation groups. (B) The dose of norepinephrine required to target the required MAP was significantly different and higher in the high target group from 3 h to 48 h (p <0.05) compared to the low target group. At the rest of the time points it was similar. Independent sample t tests were used to test the difference in the mean values of the relevant parameters between the two randomisation groups, at different time points. MAP, mean arterial pressure.

associated disease (64% *vs.* 65%; p = 0.86), in L-MAP *vs.* H-MAP, respectively. Patients had severe liver disease with high model for end-stage liver disease (32.2±5.5 *vs.* 31.5±7.3; p = 0.35) and SOFA (12.04±3.0 *vs.* 12.3±3.4; p = 0.58) scores. At enrolment, the requirement for mechanical ventilation (38 [51%] *vs.* 48 [64%]; p = 0.10) and RRT (9 [12%] *vs.* 5 [6.7%]; p = 0.26) was similar between L-MAP and H-MAP groups, respectively. The use of second-line agents, namely intravenous steroids (56 [75%] *vs.* 51 [68%]; p = 0.37), terlipressin (22 [29%] *vs.* 27 [36%]; p = 0.86), and vasopressin (49 [65%] *vs.* 41 [55%]; p = 0.18) was also not significantly different between the L-MAP and H-MAP groups, respectively. The use of inotropes and vasodilatory agents was also not significantly different between the two groups (dopamine 4 [5.3%] *vs.* 3 [4%]; adrenaline 2 [2.7%] *vs.* 6 [8%]; and dobutamine in 0 [0%] *vs.* 4 [5.3%]; p = 0.08 in the L-MAP and H-MAP groups, respectively). The MAP at enrolment was also comparable (57.2 ± 10.8 *vs.* 57.8 ± 6.8; p = 0.18) in the L-MAP and H-MAP groups, respectively. The MAP at subsequent time points showed a significant difference between the two groups (Fig. 2A). The mean dose of norepinephrine was significantly different from 3 to 48 h between the two groups to target the required MAP (Fig. 2B).

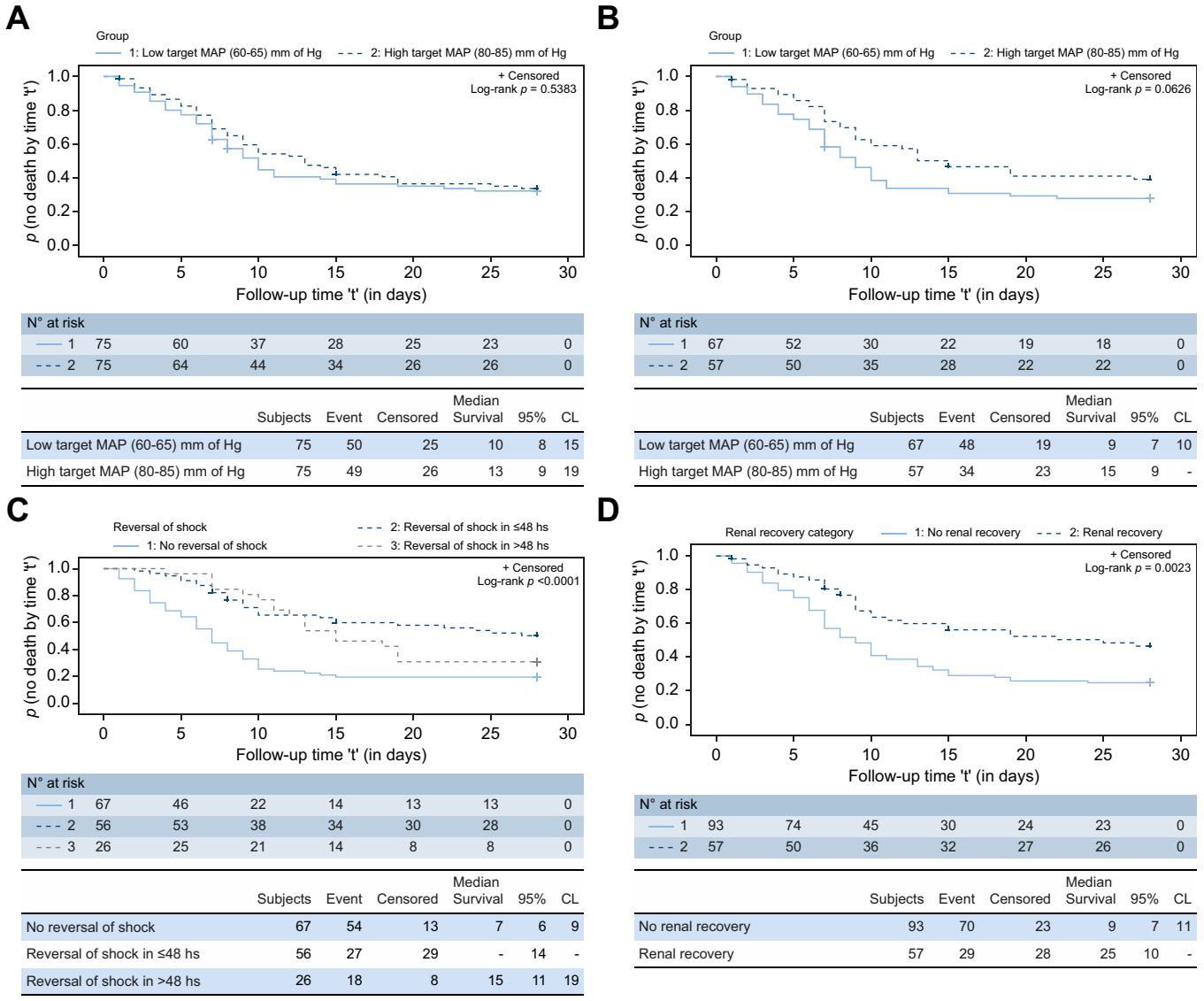

Fig. 3. Kaplan-Meier survival analysis stratified by different groups for 28-day mortality. (A) Low *vs.* high target MAP on intention-to-treat analysis. (B) Low *vs.* high target MAP on per-protocol analysis. (C) Patients stratified based on time to shock reversal (reversal within 24 h, late reversal and no reversal). (D) Patients stratified based on recovery of renal function. Log-rank test was used to test whether the pattern of survival is significantly different across various categories of the considered categorical variable and the results were reported in the form of *p* values. MAP, mean arterial pressure.

Intention-to-treat analysis (Table 2)

Primary outcome

The mortality at 28 days was not different between the two groups. At 28 days, mortality was similar in the L-MAP *vs.* H-MAP group (42 [56%] *vs.* 49 [65%], respectively; p = 0.54) (Fig. 3A).

Impact of target MAP on AKI reversal and incidence of IDH

Though not statistically significant at a 5% level of significance, a trend toward higher AKI reversal at day 5 was observed in the H-MAP *vs.* L-MAP group (34 [45%] *vs.* 23 [31%], respectively; p = 0.06); the proportion of patients who required RRT was not different between the two groups (43 [57%] *vs.* 40 [53%], respectively; p = 0.62). The incidence of IDH was significantly lower in the H-MAP *vs.* L-MAP group (5 [7%] *vs.* 19 [48%], respectively; p <0.001). Of the total patients who underwent dialysis, the mode of first dialysis was not significantly different between the H-MAP *vs.* L-MAP group (requirement of CRRT; 12/43 [27.9%] *vs.* 5/40 [12.5%], respectively; p = 0.08). The remaining patients underwent SLED. The number of patients who were escalated from SLED to CRRT (20 (50%) *vs.* 18 (41.9%); p = 0.46) and those who were stepped down from CRRT to SLED (2 (5%) *vs.* 5 (11.6%); p = 0.28) were not significantly different in the L-MAP *vs.* H-MAP group, respectively. As a protocol, sicker patients were considered for CRRT, but the incidence of hypotension during dialysis was significantly higher in those receiving SLED *vs.* CRRT (23 (34.8%) *vs.* 1 (5.9%), respectively; p = 0.019). Of the patients who were escalated from SLED to CRRT, 15 (39.5%) had developed IDH after the first session. The median duration of SLED sessions was not significantly different (2 range (1-12) *vs.* 2 (1-11); p =

Table 1. Baseline characteristics of the study cohort (n = 150).

	Low target MAP (n = 75)	High target MAP (n = 75)	*p* value
Variables			
Age (in years)	46.7 ± 9.1	45.0 ± 12.9	0.38
Sex (Males)	65 (87%)	68 (91%)	0.44
Aetiology (alcohol)	48 (64%)	49 (65%)	0.86
Ascites; n (%)			0.43
Grade 1-2	61 (81%)	57 (76%)	
Grade 3	14 (19%)	18 (24%)	
Source of admission			0.62
Emergency	65 (87%)	67 (89%)	
Wards	10 (13%)	8 (11%)	
Liver severity scores			
MELD	32.5 ± 5.5	31.5 ± 7.3	0.35
Child-Pugh	12.8 ± 1.5	12.6 ± 1.8	0.45
SOFA	12.0 ± 3.0	12.3 ± 3.4	0.58
CLIF-SOFA	10.7 ± 2.4	10.6 ± 2.5	0.72
CLIF-C-ACLF	40.8 ± 9.6	39.9 ± 10.1	0.58
AARC	9.8 ± 1.5	10.0 ± 1.4	0.39
Comorbid diseases			
Diabetes; n (%)	18 (24%)	14 (19%)	0.43
Hypertension; n (%)	7 (9%)	7 (9%)	1.00
Physiological variables			
MAP (mmHg)	57.2 ± 8.8	57.8 ± 6.8	0.66
Heart rate (beats/min)	94.2 ± 19.5	90.3 ± 20.5	0.24
Respiratory rate (breaths/min)	19.0 ± 3.5	19.6 ± 3.5	0.31
Arterial lactate (mmol/L)	3.5 ± 2.2	3.9 ± 2.7	0.38
Central venous pressure (cm of H_2O)	14.5 ± 4.2	14.4 ± 4.3	0.86
PaO_2:FiO_2	311.4 ± 185.6	307.1 ± 218.6	0.91
Inferior vena cava diameter (in mm)	16.8 ± 4.5	16.1 ± 3.8	0.31
Norepinephrine dose (μg/kg/min)	0.065 ± 0.056	0.073 ± 0.065	0.44
Terlipressin; n (%)	22 (29%)	27 (36%)	0.38
Vasopressin; n (%)	49 (65%)	41 (54.7%)	0.18
Intravenous steroids	56 (75%)	51 (68%)	0.37
Biochemical parameters			
Haemoglobin (g/dl)	8.0 ± 1.3	7.7 ± 1.5	0.26
Total leucocyte count (x10^3 cells/mm^3)	16.4 ± 10.9	18.4 ± 11.8	0.29
Platelet count (x10^3 cells/mm^3)	50.6 ± 26.2	59.0 ± 58.0	0.26
Serum total bilirubin (mg/dl)	13.6 ± 8.2	13.9 ± 9.8	0.80
International normalized ratio	3.7 ± 1.9	4.2 ± 2.9	0.22
Serum sodium (mEq/L)	130.9 ± 10.0	132.1 ± 11.2	0.48
Serum potassium (mEq/L)	3.9 ± 0.7	3.9 ± 0.9	0.98
Serum bicarbonate (mEq/L)	20.5 ± 5.2	19.2 ± 4.3	0.098
Anion gap	6.6 ± 6.1	7.3 ± 6.7	0.47
Serum calcium (mg/dl)	1.1 ± 0.1	1.1 ± 0.2	0.56
Serum magnesium (mg/dl)	1.9 ± 0.4	2.2 ± 1.2	0.16
Serum phosphate (mg/dl)	3.4 ± 0.9	3.2 ± 1.6	0.48
Serum creatinine (mg/dl)	0.9 ± 0.4	0.9 ± 0.5	0.76
Serum urea (mg/dl)	74.0 ± 56.2	83.7 ± 58.8	0.40
Serum chloride (mEq/L)	104.0 ± 9.1	105.4 ± 12.1	0.42
Cause of sepsis			0.17
Pneumonia	57 (77%)	48 (64%)	
Spontaneous bacterial peritonitis	5 (7%)	9 (12%)	
Urinary tract infection	4 (5%)	0 (1.3%)	
Spontaneous bacterial empyema	0 (0)	1 (1%)	
Spontaneous bacteremia	1 (1%)	1 (1%)	
Cellulitis	1(1%)	1 (1%)	
Others	5 (7%)	10 (13%)	
>1 site	2 (2%)	5 (4%)	
Culture positive infections; n (%)	46 (61%)	45 (60%)	0.92
Renal biomarkers			
Urine NGAL (ng/ml)	1,523.2 ± 1,869.9	1,725.8 ± 1,735.6	0.49
Serum Cystatin C (mg/L)	2.0 ± 0.8	2.0 ± 0.9	0.96
Cumulative fluid (in ml)	1,095.5 ± 1,272.3	1,364.3 ± 1,330.0	0.22
Crystalloids + colloids (albumin)			

(*continued on next page*)

Table 1. (*continued*)

	Low target MAP (n = 75)	High target MAP (n = 75)	*p* value
Organ support			
Mechanical ventilation[#]	38 (51%)	48 (64%)	0.10
Renal replacement therapy	9 (12%)	5 (6.7%)	0.26

Descriptive statistics have been presented as n (%) for categorical variables and mean ± SD for continuous variables.
Independent samples *t* tests were used to test the difference in the mean values of the considered parameters between the two MAP groups (low MAP *vs.* high MAP). Chi-square tests/Fisher's exact test, whichever is suitable for the considered problem, were used to test the bivariate association of MAP group with various individual categorical variables considered.
AARC, Asia Pacific Research Consortium; CLIF-C-ACLF, chronic liver failure-acute on chronic liver failure; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NGAL, neutrophil gelatinase associated lipocalin; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; SOFA, sequential organ failure assessment.
[#]All patients were ventilated using the synchronized intermittent mandatory ventilation mode post-intubation.

0.73); however, the median duration of CRRT was significantly lower in the L-MAP *vs.* H-MAP group (24 (5-98) hours *vs.* 36 (6-65) hours; $p = 0.04$), respectively (Table S1).

Duration of mechanical ventilation and L-ICU stay
The duration of mechanical ventilation (6.6±5.5 *vs.* 5.3±4.4 days; $p = 0.12$) and L-ICU stay (7.4±5.2 *vs.* 6.2±3.9 days; $p = 0.11$) were not different between the H-MAP and L-MAP group, respectively.

Reversal of shock and improvement in SOFA score
The frequency of reversal of shock (35 [47%] *vs.* 40 [53%]; $p = 0.10$) and improvement in SOFA score by at least two points (31 [41%] *vs.* 32 [43%]; $p = 0.87$) was not significantly different between the H-MAP and L-MAP group, respectively.

Impact on arterial lactate
On repeated measures ANOVA, the time trends in mean arterial lactate were not significantly different ($p > 0.05$) between the two groups. The mean arterial lactate showed an increase in the L-MAP group while a decreasing trend was observed in the H-MAP group. The mean arterial lactate at different time points, however, was not significantly different between the two groups on the intention-to-treat analysis (Table S2). After excluding patients who had protocol violations, a significantly lower lactate was observed in the H-MAP group from day 4 to day 7 (Fig. S1). Interestingly, the daily cumulative fluid balance was not significantly different either at enrolment or at subsequent time points till day 5 in both groups (Table S3).

Changes in liver severity scores
The liver severity scores – the chronic liver failure-sequential organ failure assessment (CLIF-SOFA), the chronic liver failure-acute on chronic liver failure (CLIF-C-ACLF) and the Asia pacific association research consortium (AARC) score were not significantly different between the two groups at enrolment (Table 1). The CLIF-SOFA and the CLIF-C-ACLF scores were higher at day 2 (11.2±2.8 *vs.* 10.2± 2.6; $p = 0.018$ and 40.8±9.6 *vs.* 39.9±10.1; $p = 0.58$), day 3 (11.4 ±3.2 *vs.* 10.3 ± 2.7; $p = 0.029$ and 42.3±10.4 *vs.* 38.5±10.7; $p = 0.026$), and day 5 (11.7±3.1 *vs.* 10.6±2.9; $p = 0.036$ and 42.6±11.7 *vs.* 38.8±11.2; $p = 0.044$) in the L-MAP *vs.* H-MAP group, respectively. However, there was no difference in the proportion of patients with different ACLF grades and AARC scores at each time point (Table S3).

Adverse events
A significantly higher incidence of adverse events requiring protocol violation was observed in the H-MAP *vs.* L-MAP group (18 (24%) *vs.* 8 (10.6%), respectively; $p = 0.03$) (Table 2 and Table S4). The adverse events were reported according to the standard criteria for adverse events (CTCAE). The total number of patients who developed any adverse event (19 [25.3%] *vs.* 10 [13.3%]; $p = 0.06$) and the total number of observed adverse events (23 (30.7%) *vs.* 14 (18.7%); $p = 0.09$) were higher in the H-MAP *vs.* L-MAP group, respectively (some patients developed more than one adverse event). Grade 4 adverse events which included digital ischaemia (8 [10.6%] *vs.* 3 [4%]; $p = 0.12$), mesenteric ischaemia (1 [1.3%] *vs.* 0 [0%]), tachyarrhythmias (4 [5.3%] *vs.* 3 [4.0%]; $p = 1.00$), bradyarrhythmias (0 [0%] *vs.* 1 [1.3%]), and hypertension (3 [4.0%] *vs.* 0 [0%]; $p = 0.24$) were more frequently observed in the H-MAP *vs.* L-MAP group, respectively. However, the incidence of rebound hypotension was much more frequent in the L-MAP *vs.* H-MAP group (4 [5.3%] *vs.* 0 [0%], respectively; $p = 0.12$). On multivariable analysis, higher SOFA score (odds ratio [OR] 1.28, 1.06-1.55), use of terlipressin (*vs.* vasopressin) as second vasopressor (OR 6.72, 2.07-21.83), higher serum sodium (OR 1.08, 1.03-1.13) and randomisation group (H-MAP *vs.* L-MAP) (OR 3.21, 1.03-10.06) were independent predictors of adverse events in these patients (Table S5).

Per-protocol analysis

A total of 67 (89%) and 57 (76%) patients were analysed in the per-protocol analysis. At 28 days, mortality was similar in the L-MAP *vs.* H-MAP group (40 [60%] *vs.* 35 [61%], respectively; Log-rank $p = 0.63$) (Fig. 3B). A significantly higher AKI reversal on day 5 was observed in the H-MAP *vs.* L-MAP group (30 [53%] *vs.* 21 [31%]; $p = 0.018$); the proportion of patients who required RRT was not different between the two groups (28 [49%] *vs.* 34 [51%], respectively; $p = 0.10$), while the incidence of IDH was significantly lower in the H-MAP *vs.* L-MAP group (1 [4%] *vs.* 18 [53%], respectively; $p < 0.001$). The duration of mechanical ventilation (5.6±5.2 *vs.* 5.4±4.6 days; $p = 0.79$) and L-ICU stay (6.6±4.7 *vs.* 6.3±4.0 days; $p = 0.71$) were not different between the H-MAP and L-MAP group, respectively. The frequency of reversal of shock (31 [54%] *vs.* 37 [55%]; $p = 1.0$) and improvement in SOFA score by at least two points (29 [51%] *vs.* 27 [40%]; $p = 0.24$) was not significantly different between the H-MAP and L-MAP group, respectively (Table 2).

Predictors of 28-day mortality
Time to shock reversal is essential in predicting mortality (HR 0.99, 95% CI 0.98-0.99). Each hour delay in shock reversal was

Table 2. Differences between the two randomisation groups for secondary outcome measures for intention-to-treat and per-protocol analysis.

Secondary outcome measures	Intention-to-treat analysis			Per-protocol analysis		
	Low MAP (n = 75)	High MAP (n = 75)	*p* value	Low MAP (n = 67)	High MAP (n = 57)	*p* value
AKI recovery	23 (31)	34 (45%)	0.064	21 (31)	30 (53)	0.016
Renal replacement therapy	40 (53)	43 (57%)	0.62	34 (51)	28 (49)	0.86
Intradialytic hypotension*	19/40 (48)	5/43 (12)	<0.001	18/34 (53)	1/28 (4)	<0.001
Duration of mechanical ventilation (in days)	5.3 ± 4.4	6.6 ± 5.5	0.12	5.4 ± 4.6	5.7 ± 5.2	0.73
Length of stay in the intensive care unit (days)	6.2 ± 3.9	7.4 ± 5.2	0.11	6.3 ± 4.0	6.6 ± 4.7	0.71
Reversal of shock at day 5	40 (53)	35 (47)	0.10	37 (55)	31 (54)	1.00
Improvement in SOFA score at 48 h	32 (43)	31 (41)	0.87	27 (40)	29 (51)	0.24
Adverse events	8 (11)	18 (24)	0.03	—	—	—

Descriptive statistics have been presented as number (%) for categorical variables and mean ± SD for continuous variables.
Independent samples t tests were used to test the difference in the mean values of the considered parameters between the two MAP groups (low MAP vs. high MAP). Chi-square tests/Fisher's exact test, whichever is suitable for the considered problem, were used to test the bivariate association of MAP group with various individual categorical variables considered.
The *p* values have been derived from Chi-square test for categorical variables and independent Student's *t* test for continuous variables.
AKI, acute kidney injury; MAP, mean arterial pressure; SOFA, sequential organ failure assessment.
*Restricted to dialysis patients only (n = number of patients who underwent dialysis in that group).

associated with a 2% increase in 28-day mortality in patients with cirrhosis and septic shock. Patients who had an early reversal of shock within 24 h (HR 0.35; 95% CI 0.22-0.55; *p* <0.001) had better 28-day survival outcomes than those patients with late reversal (HR 0.49; 95% CI 0.29-0.84; *p* <0.009) *vs*. those with no reversal of shock (Fig. 3C). Similarly, renal recovery was associated with improved outcomes (HR 0.53; 95% CI 0.34-0.81; *p* = 0.004) (Fig. 3D). On multivariable analysis, in model-1, higher SOFA score (HR 1.14, 95% CI 1.06-1.22) and reversal of shock (HR 0.44, 95% CI 0.28-0.70) were independent predictors of 28-day mortality. The target MAP strategy was not significant for mortality either on univariate or multivariate analysis. In model 2, the presence of diabetes (HR 1.88, 95% CI 1.19-2.95), arterial lactate (at 24 h) (HR 1.32, 95% CI 1.01-1.71), lower partial pressure of oxygen (HR 0.99, 95% CI 0.99-1.00) and lower serum bicarbonate (HR 0.95, 95% CI 0.91-0.99) were independent predictors of 28-day mortality (Table 3). The same factors were found significant for 28-day mortality in the per-protocol analysis (Table S6).

Factors predicting shock reversal

On multivariable analysis, avoiding multicollinearity, the presence of grade 2 or 3 ascites (OR 0.22, 95% CI 0.08-0.62 and OR 0.29, 95% CI 0.10-0.82), higher arterial lactate at 24 h (OR 0.33, 95% CI 0.19-0.58 and OR 0.32, 95% CI 0.18-0.58) and lower urine NGAL (OR 0.70, 0.52-0.94 and OR 0.73, 0.54-0.99) were independent predictors of shock reversal in model-1 and model-2, respectively (Table S7). The same factors were significant in the per-protocol analysis (Table S8). We also observed a substantial and direct correlation of NGAL with NT-pro-BNP (r = 0.431, *p* = 0.004) (Fig. S2).

Factors predicting AKI recovery

Renal recovery was assessed at day 14. Patients with shock reversal had significantly higher renal recovery compared to those with no reversal of shock (OR 7.88, 95% CI 3.64-17.03). Of the patients with AKI recovery, 23 (40%) required RRT (13/34 [38.2%] *vs.* 10/23 [43.5%]; *p* = 0.69) in the H-MAP *vs.* L-MAP group, respectively. We created two multivariable models for identification of factors predicting renal recovery. In both models, we forced the randomisation group to understand the impact of the target strategy on renal outcomes. On intention-to-treat analysis, in the first model, we included SOFA score, and, in the second model, the components of the SOFA score. It was interesting to find that a high target MAP (compared to L-MAP) was an independent predictor of renal recovery in both models; OR 2.36 (95% CI 1.11-5.04) in model 1, and OR 2.47 (95% CI 1.15-5.34) in model 2. Lower arterial lactate and leucocyte counts were associated with higher renal recovery in both the models. Apart from these factors, in model 1, lower SOFA score and, in model 2, type of dialysis modality, *i.e.* SLED, were associated with significantly lower renal recovery compared to CRRT and no dialysis (as the ref.) (Table 4).

Endothelial, inflammatory markers, and norepinephrine levels (n = 40)

The subgroup of patients in whom we measured markers of endothelial injury and repair had comparable clinical and biochemical characteristics. The initial MAP (67.15±10.18 *vs.* 73.45±8.30; *p* = 0.039), EDN-1, vWF, ANGPT2, ADAMTS, and MCP-1 were also comparable in the L-MAP and H-MAP groups, respectively (Table S9). Post-randomisation, the endothelial injury markers, *i.e.* EDN-1 (3.02±1.14 *vs.* 2.19±0.54; *p* = 0.007) and vWF (54.17±12.82 *vs.* 40.58±14.07; *p* = 0.003) were significantly elevated in the plasma samples of the L-MAP *vs.* H-MAP group, respectively. On the contrary, the endothelial repair markers such as ADAMTS (2.11±1.13 *vs.* 1.15±0.48; *p* = 0.002) and ANGPT2 (74.08±53.00 *vs.* 41.80±15.95; *p* = 0.016) were significantly higher in the H-MAP *vs*. L-MAP group, respectively (Fig. 4A,B). MCP-1 was not different between the two groups, and the ADAMTS/vWF was significantly higher in the H-MAP group compared to the L-MAP group (Fig. 4C and D). Comparison of norepinephrine levels in the plasma showed considerably higher levels in the L-MAP *vs.* H-MAP group (7,477±2,665 pg/ml *vs.* 3,777±2,342 pg/ml, respectively; *p* <0.001) (Fig. 4E) (Table S10).

Discussion

The current large prospective randomised-controlled trial performed in patients with cirrhosis and septic shock did not demonstrate the superiority of targeting a higher MAP compared to a lower MAP in improving survival at 28 days. A higher target strategy was associated with more adverse events requiring protocol violations. Apart from this, higher SOFA score and serum sodium, and the use of terlipressin (*vs.*

Table 3. Predictors of 28-day mortality-Cox-proportional regression analysis.

	Crude hazard ratio		Adjusted hazard ratio		Adjusted hazard ratio	
	Crude HR	95% CI		Model-1		Model-2
Variables						
Age (in years)	0.999	0.982-1.017				
Sex (males)	1.554	0.753-3.205				
Etiology (alcohol)	1.015	0.670-1.536				
Ascites (grade 2-3 *vs*. 0-1)						
Liver severity scores						
MELD	1.038*	1.004-1.072			1.023	0.988-1.058
CTP score	1.224**	1.077-1.390				
SOFA score	1.156**	1.087-1.228	1.136**	1.060-1.218		
Comorbid diseases						
Diabetes	1.901**	1.218-2.964	1.393	0.877-2.211	1.878**	1.194-2.954
Hypertension	0.772	0.254-2.345				
Physiological variables						
Mean Arterial Pressure (mmHg)	0.990	0.965-1.016				
Heart rate (beats/min)	1.000	0.984-1.016				
Arterial lactate 0 h (mmol/L)	1.056	0.979-1.139				
Arterial lactate (mmol/L) at 6 h	1.073*	1.002-1.149				
Arterial lactate mmol/L at 12 h	1.076*	1.010-1.147				
Arterial lactate mmol/L at 24 h	1.393*	1.080-1.795	1.007	0.762-1.331	1.316*	1.012-1.710
Central venous pressure (cm of H_2O)	0.982	0.936-1.030				
PH	1.152	0.163-8.149				
Partial pressure of CO_2 (PCO_2) mmHg	0.988	0.964-1.013				
Partial pressure of oxygen (PO_2) mmHg	0.996*	0.992-1.000	0.996	0.993-1.000	0.996*	0.992-1.000
PaO_2:FiO_2						
Inferior vena cava diameter (in mm)	0.987	0.940-1.035				
Norepinephrine dose (ug/kg/min)	1.010	0.961-1.062				
Terlipressin *vs*. vasopressin	0.987	0.624-1.561				
Biochemical parameters						
Hemoglobin (gm/dl)	0.962	0.850-1.088				
Total leucocyte count (x10^3 cells/mm^3)	1.030**	1.013-1.046				
Platelet count (x10^3 cells/mm^3)	0.998	0.994-1.003				
Serum total bilirubin (mg/dl)	1.030**	1.008-1.053				
International normalized ratio	1.055	0.980-1.136				
Serum sodium (mEq/L)	0.994	0.976-1.012				
Serum potassium (mEq/L)	0.870	0.672-1.125				
Serum bicarbonate (mEq/L)	1.055	0.984-1.132	0.990	0.944-1.038	0.954*	0.911-0.999
Anion gap	1.007	0.978-1.038				
Serum calcium (mg/dl)	0.166**	0.048-0.570	0.305	0.066-1.414		
Serum magnesium (mg/dl)	1.038	0.878-1.227				
Serum phosphate (mg/dl)	1.006	0.910-1.111				
Serum creatinine (mg/dl)	1.035	0.673-1.591				
Serum urea (mg/dl)	1.003*	1.000-1.006				
Serum chloride (mEq/L)	0.980*	0.962-0.999	0.995	0.976-1.015		
Biomarkers						
Urine neutrophil gelatinase lipocalin (ng/ml)	1.015	0.901-1.144				
Serum cystatin c (mg/L)	0.837	0.672-1.042				
NT-pro-BNP (pg/ml)						
Randomization group	0.948	0.500-1.799			0.892	0.597-1.333
L-MAP *vs*. H-MAP						
Reversal of shock	0.401**	0.267-0.604				
Time to reversal of shock	0.392**	0.263-0.585	0.440**	0.279-0.696		

Binary and multivariate Cox proportional hazards models were used to identify factors associated with 28-day mortality.
Log transformation of lactate was considered.
Exponentiated coefficients; *p <0.05, **p <0.01.
FiO_2, fraction of inspired oxygen; H-MAP, high target MAP; L-MAP, low target MAP; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NGAL, neutrophil gelatinase associated lipocalin; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; SOFA, sequential organ failure assessment.

vasopressin) as a second vasopressor were independent predictors of adverse events. We observed the benefits of a higher MAP approach in reducing IDH incidence, which possibly led to better dialysis tolerance and a longer duration of dialysis. The higher target MAP strategy was associated with improved renal recovery after adjusting for other factors.

Multiple studies have suggested a higher MAP improves renal outcomes and decreases the requirement for RRT in patients with hepatorenal syndrome-AKI.[7–10] We observed a significant improvement in kidney outcomes in patients who tolerated the higher MAP in our study. The renal perfusion pressure is governed by the difference between the MAP and

Table 4. Predictors of AKI recovery-intention-to-treat by binary logistic regression analysis.

			Model-1		Model-2	
	Crude OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Variables						
Age (in years)	0.99	0.963-1.022				
Sex (male)	0.656	0.238-1.812				
Aetiology (alcohol)	0.704	0.355-1.396				
Ascites (grade 2-3 *vs.* 0-1)	0.469	0.195-1.132				
Liver severity scores						
MELD	0.925**	0.876-0.976				
Child-Pugh	0.724**	0.583-0.899				
SOFA	0.839**	0.750-0.938	0.866*	0.767-0.978		
Comorbid diseases						
Diabetes	0.571	0.243-1.340				
Hypertension	0.897	0.285-2.825				
Physiological variables						
MAP (mmHg)	0.990	0.948-1.033				
Heart rate beats/min	1.007	0.991-1.024				
Arterial lactate 0 h (mmol/L)	0.919	0.796-1.062				
Arterial lactate 6 h (mmol/L)	0.815*	0.689-0.964				
Arterial lactate 12 h (mmol/L)	0.764**	0.634-0.920				
Arterial lactate mmol/L at 24 h	0.720**	0.586-0.884	0.592*	0.351-0.999	0.566*	0.333-0.962
Central venous pressure (cm of H_2O)	0.979	0.904-1.060				
PH	0.817	0.032-20.866				
Partial pressure of CO_2 (PCO_2) mmHg	1.007	0.970-1.045				
Partial pressure of oxygen (PO_2) mmHg	1.005*	1.000-1.010				
PaO_2:FiO_2	1.002*	1.000-1.004			1.001	0.999-1.003
Inferior vena cava diameter (in mm)	1.036	0.958-1.121				
Norepinephrine dose (μg/kg/min)	1.070	0.978-1.170				
Terlipressin *vs.* vasopressin	1.050	0.521-2.118				
Biochemical parameters						
Haemoglobin (gm/dl)	0.991	0.783-1.253				
Total leucocyte count (x10^3 cells/mm^3)	0.942**	0.908-0.978	0.948**	0.912-0.986	0.950*	0.911-0.990
Platelet count (x10^3 cells/mm^3)	1.001	0.993-1.008				
Serum total bilirubin (mg/dl)	0.955*	0.917-0.995			0.978	0.937-1.021
International normalized ratio	0.887	0.763-1.032				
Serum sodium (mEq/L)	0.988	0.957-1.020				
Serum potassium (mEq/L)	1.233	0.815-1.865				
Serum bicarbonate (mEq/L)	1.064	0.991-1.142				
Anion gap	0.975	0.924-1.029				
Serum calcium (mg/dl)	1.447	0.159-13.205				
Serum magnesium (mg/dl)	0.832	0.530-1.306				
Serum phosphate (mg/dl)	0.944	0.795-1.121				
Serum creatinine (mg/dl)	0.615	0.271-1.397				
Serum urea (mg/dl)	0.999	0.994-1.005				
Serum chloride (mEq/L)	1.003	0.972-1.034				
Biomarkers						
Urine neutrophil gelatinase lipocalin (ng/ml)	0.768*	0.624-0.946	0.865	0.680-1.101	0.896	0.692-1.160
Serum cystatin c (mg/L)	0.754	0.507-1.120				
NT-pro-BNP (pg/ml)	1.007	0.782-1.297				
Cumulative fluid balance day 1	0.986	0.760-1.279				
Cumulative fluid balance day 2	0.991	0.836-1.176				
Cumulative fluid balance day 3	0.964	0.853-1.089				
Cumulative fluid balance day 4	1.014	0.919-1.120				
Cumulative fluid balance day 5	1.002	0.930-1.080				
Type of dialysis (no dialysis as ref. category)	1	1.000-1.000			1	1.000-1.000
CRRT	0.506	0.217-1.181			1.117	0.393-3.180
SLED	0.289**	0.126-0.659			0.360*	0.139-0.928
Intradialytic hypotension	0.626	0.242-1.618				
Duration of dialysis	0.992	0.979-1.006				
Randomisation group (H-MAP *vs.* L-MAP)	1.875	0.960-3.660	2.366*	1.110-5.043	2.472*	1.145-5.337

Log transformation of lactate was considered. In the first model SOFA score and in model-2 the components of the score were considered in the multivariable analysis. Exponentiated coefficients; *p <0.05, **p <0.01.

Binary and multivariate logistic regression analyses were performed to identify factors associated with AKI recovery at day 14. The randomisation group was considered in the multivariable analysis in both the models.

CRRT, continuous renal replacement therapy; FiO_2, fraction of inspired oxygen; H-MAP, high target MAP; L-MAP, low target MAP; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NGAL, neutrophil gelatinase associated lipocalin; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; SLED, sustained low-efficiency dialysis; SOFA, sequential organ failure assessment.

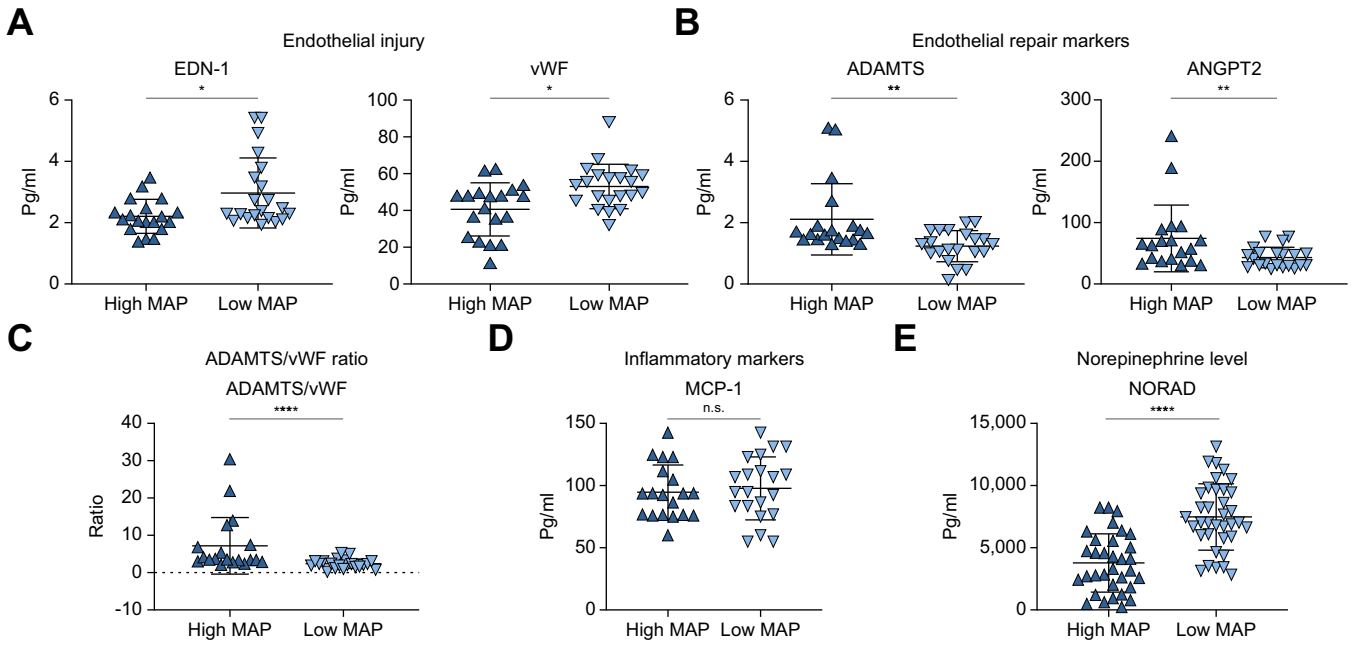

Fig. 4. Graphs showing the differences in the endothelial injury and repair markers and MCP-1 between low and high MAP groups. We performed independent-sample *t* tests between patients with H-MAP and L-MAP. (A) Endothelial injury markers EDN-1 (3.02±1.14 *vs.* 2.19±0.54; $p = 0.007$) and vWF (54.17 ± 12.82 *vs.* 40.58 ± 14.07; $p = 0.003$) are significantly elevated in plasma of patients with low MAP, while (B) endothelial repair markers ADAMTS (2.11±1.13 *vs.* 1.15±0.48; $p = 0.002$) and ANGPT-2 (74.08±53 *vs.* 41.8±15.94; $p = 0.016$) are significantly higher in plasma of patients with high MAP. (C) The inflammatory marker MCP-1 (96.08±24.76 *vs.* 96.56±22.72; $p = 0.950$) shows no significant difference between the groups. (D) The dot plot of ADAMTS/vWF ratio (7.19±2.38 *vs.* 2.38±1.26; $p < 0.001$) shows a significantly higher ratio for the high MAP group. (E) Level of noradrenaline (7,477±2,665 *vs.* 3,777±2,342; $p < 0.001$) was significantly higher in the low MAP target group.

intraabdominal pressure (IAP). We did not measure IAP in our study, which is a limitation. The role of IAP monitoring should be explored in future studies. Also, the correlation of IAP with renal resistive index and cardiocirculatory dysfunction in these patients could have been interesting.[12]

Patients who tolerated a higher target MAP strategy without adverse events had improved renal outcomes and lactate clearance. The concept of fluid responsiveness is used to guide fluid administration in critically ill patients.[11] Similar to this, vasopressor responsiveness can be determined by measuring the parameters of microcirculation (lactate, urine output etc.) which in-turn could guide an appropriate target MAP for each patient.[8,11] The prognostic relevance of arterial lactate is known for patients with cirrhosis admitted to the L-ICU with sepsis and organ failures.[13–15] We found that post-resuscitation lactate level was a better surrogate of 28-day mortality, shock and AKI reversal than the lactate level at enrolment. Based on the results of our study, the levels at 24 h could be considered for prognostication of these patients.

Higher SOFA scores, the use of terlipressin, hypernatremia, and a high target MAP strategy, were independent predictors of adverse events. A recent large randomised-controlled trial investigated a combination of terlipressin and albumin in patients with hepatorenal syndrome-AKI. Terlipressin was associated with a significantly higher incidence of pulmonary complications.[10] Similarly, compared to norepinephrine, the use of terlipressin as the first-choice vasopressor in patients with cirrhosis and sepsis, even though more effective in reversing MAP and improving microcirculation, was associated with more adverse events.[16] In our study, terlipressin was used as the second vasopressor and its use was not different between the two groups.

Our study also identified NGAL as an independent predictor of shock reversal. However, NGAL did not predict AKI reversal. Studies have demonstrated the correlation of NGAL with myocardial function and the severity of multiorgan dysfunction in patients with sepsis.[17,18] The levels are indicative of renal tubular injury but do not correlate with renal repair in these patients. It was interesting to observe a direct and positive correlation of NGAL with NT-pro-BNP, a biomarker of cardiac dysfunction in these patients.[18,19]

Higher SOFA score, presence of diabetes, lower bicarbonate, and partial pressure of oxygen and higher arterial lactate were identified as independent predictors of 28-day mortality. Pulmonary involvement is associated with worse outcomes in patients with cirrhosis admitted to the L-ICU.[20–23] Apart from these factors, akin to the previous studies, we found early shock reversal was associated with improved outcomes. Each hour delay in shock reversal correlated with higher mortality. The shock reversal also directly correlated with AKI reversal. Even though the norepinephrine dose required to maintain the target MAP was higher in the high target group, the serum levels of norepinephrine were much higher in the low MAP group. This suggests the exogenous norepinephrine, does not correlate with the endogenous levels. Higher plasma norepinephrine can predict septic shock and correlates with worse outcomes and a higher incidence of cardiopulmonary dysfunction.[24,25] Injury and repair markers were also improved in the high target MAP group. The ratio of ADAMTS to vWF, which is known to correlate with the degree of endothelial dysfunction and severity of inflammation, was higher in the high MAP group.[26,27] The findings support targeting a higher MAP; however, the experiments were performed in only a subset of the enrolled patients, which is a limitation.

The incidence of IDH was significantly lower in the high MAP group. IDH is associated with adverse cardiovascular outcomes, impairs cerebral perfusion, and causes renal ischaemia impairing the chances of renal recovery.[28] IDH could be prevented by choosing a continuous mode of dialysis. We observed patients who underwent SLED compared to CRRT had a significantly higher incidence of hypotension during dialysis and decreased renal recovery. Therefore, CRRT could be the preferable mode of dialysis in critically ill patients with cirrhosis; however, randomised-controlled trials comparing CRRT to SLED are required to validate these findings. It was also very interesting to observe that the higher target MAP strategy was an independent predictor of AKI recovery after adjusting for other factors in patients with cirrhosis and septic shock. Together, the findings indicate the benefits of targeting a higher MAP on renal outcomes.

The limitation of our study is the lack of data on echocardiographic parameters and IAP and renal resistive index, which could have further added strength to the observations. Despite some benefits noted in improving AKI and better tolerance on dialysis, we could not demonstrate a mortality benefit with a high target MAP strategy. The other limitation of our study is we used the definition proposed by the acute disease quality initiative group (ADQI) for defining AKI recovery in patients on dialysis. We defined renal recovery in these patients as spontaneous improvement in laboratory and clinical parameters within 3 days (no later than 7 days) of discontinuation of RRT with improvement of urine output >400 ml/day. We considered these definitions because a very small proportion of patients met the definitions of complete renal recovery as proposed by the International Club of Ascites despite the fact that they had improvement in renal function after discontinuation of RRT.[29,30]

Future studies should explore combining markers of endothelial function with the surrogates of microcirculation to determine vasopressor responsiveness and hence guide the target MAP in critically ill patients with cirrhosis. Also, careful monitoring is warranted if using terlipressin as a second vasopressor in septic shock, as it was identified as an independent predictor of adverse events.

In summary, the current randomised trial demonstrates that a higher target MAP strategy was associated with improved renal outcomes, a decrease in the incidence of IDH, and better tolerance of dialysis, but did not confer any survival benefit. Adverse events are a significant limitation in the routine application of a higher target approach to all patients. We propose targeting a MAP that improves organ perfusion and microcirculation, as a safe and effective strategy in most critically ill patients with cirrhosis and septic shock.

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Abbreviations

AARC, Asia Pacific Research Consortium; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AKI, acute kidney injury; ANGPT-2, angiopoietin-2; CLIF-C-ACLF, chronic liver failure-acute on chronic liver failure; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; CRRT, continuous renal replacement therapy; CysC, Cystatin C; EDN-1, endothelin-1; H-MAP, high target MAP; HR, hazard ratio; IAP, intraabdominal pressure; IDH, intradialytic hypotension; L-ICU, liver intensive care unit; L-MAP, low target MAP; MAP, mean arterial pressure; MCP-1, monocyte chemoattractant protein-1; NGAL, neutrophil gelatinase-associated lipocalin; NT, pro, BNP, N, terminal pro, brain natriuretic peptide; OR, odds ratio; RRT, renal replacement therapy; SLED, sustained low-efficiency dialysis; SOFA, sequential organ failure assessment; vWF, von, Willebrand factor.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

RM and SKS made the study concept and design; the acquisition of data was made by AKH, AP, RPM, and AM. Statistical analysis was done by SSP, GK; ST performed the analysis of biomarkers and drafting of the manuscript was done by RM, SSP, and SKS. The study of endothelial injury and repair markers done by AKH and AK. Critical revision of manuscript done for crucial intellectual content done by SKS, administrative and technical support by SKS.

Data availability statement

All data can be made accessible in excel format on request.

Disclaimer

The results were presented as an oral paper in AASLD 2021.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.04.006.

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Author names in bold designate shared co-first authorship

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