Research Article
Cirrhosis and Liver Failure

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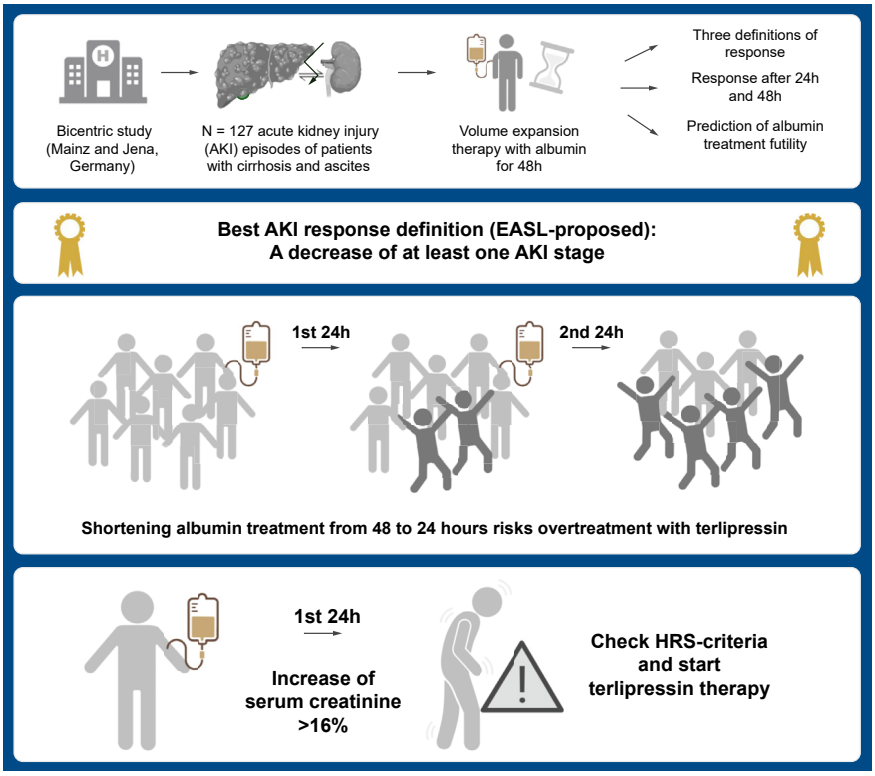
Authors

Eva Maria Schleicher, Henrik Karbannek, Julia Weinmann-Menke, …, Alexander Zipprich, Cristina Ripoll, **Christian Labenz,**

Correspondence

Christian.labenz@unimedizin-mainz.de (C. Labenz).

Graphical abstract



Highlights

- 18-28% of patients with AKI who eventually responded to albumin did not show early response.
- Shortening albumin treatment from 48 to 24 hours risks overtreatment with terlipressin.
- The EASL-proposed AKI response definition of at least one stage improvement was linked to a better prognosis.
- Even patients with a lack of decrease of SCr at 24 hours or minor increases (<16%) may respond within 24-48 hours.

Impact and implications

This study provides valuable insights into the optimal duration of albumin treatment for patients with cirrhosis and acute kidney injury, challenging the recent recommendation to shorten the duration of albumin treatment. Furthermore, the optimal definition for response to albumin (reduction of at least one acute kidney injury stage) has been assessed. The results of this study are highly clinically relevant since shortening albumin therapy may lead to overtreatment with terlipressin, and evidence to support a specific definition of response to albumin was lacking. Clinicians can use these findings to predict treatment outcomes better, avoid fluid overload, and improve patient prognosis, while also considering the potential risks of early intervention with terlipressin.

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Effect of albumin treatment duration on response rates and outcomes in patients with cirrhosis and acute kidney injury

Eva Maria Schleicher[1,2], Henrik Karbannek[3], Julia Weinmann-Menke[1,4], Peter Robert Galle[1,2], Andreas Stallmach[3], Simon Johannes Gairing[1,2], Alexander Zipprich[3], Cristina Ripoll[3,†], Christian Labenz[1,2,*,†]

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Background & Aims: Guidelines recommended volume expansion with albumin for 48 hours for patients with cirrhosis and acute kidney injury (AKI) to correct hypovolemia and rule out prerenal AKI. A recent update in the ADQI-ICA consensus guidelines suggested shortening this duration to 24 hours, primarily based on expert opinion. This study aimed to evaluate the response rates to albumin treatment after 24 and 48 hours and to compare and assess the prognostic significance of three different definitions of response to albumin therapy.

Methods: Data from 127 prospectively recruited patients with cirrhosis and AKI from two German centers were analyzed. We examined three response definitions after 24 and 48 hours: (1) serum creatinine (SCr) decrease >0.3 mg/dl, (2) SCr decrease >25%, and (3) SCr decrease in at least one AKI stage. Follow-up was prolonged until liver transplantation, death or hemodialysis.

Results: Overall, 30-54% of the patients responded to albumin treatment depending on the definition, and response rates were balanced across AKI stages. Notably, a relevant number of patients who responded at 48 hours did not respond within the first 24 hours. Additional responses to albumin during the second 24 hours according to definitions 1, 2, and 3 were 28%, 22%, and 18%, respectively. Response according to definition 3 was associated with higher hemodialysis- and transplantation-free survival rates.

Conclusion: A substantial proportion of patients require 48 hours to respond to albumin treatment. Shortening the duration of albumin therapy may lead to overtreatment with terlipressin.

Introduction

Acute kidney injury (AKI) is a frequent, serious, and prognostically relevant complication of cirrhosis.[1] Approximately 20-50% of patients hospitalized for decompensated cirrhosis develop AKI.[2,3] Different forms of AKI can be distinguished from a clinical and a pathophysiological point of view. In the context of decompensated cirrhosis with ascites, massive splanchnic vasodilation leads to central hypovolemia and reduced renal perfusion, with compensatory activation of vasoactive systems. These systems can compensate for central hypovolemia, but in some instances, these mechanisms are insufficient, leading to a special form of renal dysfunction known as hepatorenal syndrome (HRS).[4,5] One of the most lethal complications of cirrhosis is the acute form, referred to as hepatorenal syndrome-acute kidney injury (HRS-AKI). The diagnosis of HRS-AKI is based on ruling out other causes of AKI, mainly hypovolemia, ongoing infection, nephrotoxic medications, and intrinsic renal disease. Due to the high mortality rate associated with AKI, a rapid work-up and diagnosis of its cause are crucial to ensure timely recognition and treatment. The recent ADQI (Acute Disease Quality Initiative)-International Club of Ascites (ICA) consensus paper has proposed changes in the diagnostic criteria, including using albumin to rule out hypovolemia.[6] The previous guidelines recommended a volume expansion with albumin at a dosage of 1 g/kg body weight per day for 48 h to rule out prerenal AKI (*e.g.* diuretic-induced, diarrhea from lactulose).[7,8] The current consensus paper recommends shortening the albumin treatment to a maximum of 24 hours and against 48 hours of albumin administration, in order to avoid delaying the diagnosis of HRS-AKI.[6] However, this recommendation is only based on expert opinion. In addition, there is no evidence to support a certain definition for a response to albumin treatment, neither after 24 nor 48 hours. Therefore, this study had three aims: 1) to investigate the response rates to albumin treatment after 24 and 48 hours of treatment, 2) to compare three different response definitions and assess the prognostic impact of response according to those definitions, and 3) to find a cut-off to define a group of patients in whom further treatment with albumin would be futile.

* Corresponding author. Address: Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg-University, Langenbeckstraße 1, 55131 Mainz, Germany; Tel.: +49 (0) 6131 17 2380, fax: +49 (0) 6131 17 477282.
E-mail address: Christian.labenz@unimedizin-mainz.de (C. Labenz).
† Authors share senior authorship.
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Patients and methods

Patient cohort

For this study, data from two prospectively enrolled cohorts were merged and retrospectively analyzed. The first cohort included patients from the prospective ongoing LIVKID study. LIVDKID is a prospective observational study including consecutive hospitalized patients with decompensated cirrhosis and AKI at the normal wards of the Cirrhosis Center Mainz (Germany). LIVKID aims to investigate the natural trajectory of different forms of AKI in patients with cirrhosis, with an additional goal being to investigate novel biomarkers in the future. The patients included in this current study were recruited for LIVKID between 04/2022 and 06/2024. The second cohort included patients from the randomized-controlled Liver-HERO study screening phase in the Jena University Hospital. This study is a prospective, multicenter, open-label, 1:1 randomized, controlled parallel-group trial. The main endpoint is to compare 12-month liver transplant-free survival in patients assigned to transjugular intrahepatic portosystemic shunt (TIPS) compared to the standard of care (terlipressin and albumin).[9] Liver-HERO started in the Jena University Hospital in 01/2023, with systematic screening of all potential candidates. The study population included in the present study are the screened patients. During this time period a total of three patients were finally randomized to TIPS. In both studies, the leading etiology of the underlying liver disease was determined according to clinical, serological, and histological findings. Diagnosis of cirrhosis was established by histology or a combination of conclusive appearance in ultrasound, radiological imaging, endoscopic features of portal hypertension, and medical history. Blood biochemistry was assessed in all patients. This patient group consisted exclusively of patients not hospitalized in an intensive or intermediate care unit (ICU). Treatment with albumin was done using 20% albumin solution. Once diagnosed with HRS-AKI, patients received drug therapy with terlipressin in continuous infusion and albumin according to guidelines. If patients had a history of TIPS implantation, only those with TIPS dysfunction and ascites were included in the analysis.

Patients were excluded from the current analysis if they fulfilled one or more of the following criteria: no ascites, no albumin therapy (due to prior diagnosis of HRS-AKI in an external hospital, due to signs of volume overload based on clinical examination or pulmonary edema), incomplete laboratory parameters, the presence of hepatocellular carcinoma outside of the Milan criteria, terlipressin therapy due to variceal bleeding, existing dialysis requirement, or AKI in patients with prior TIPS without signs of TIPS dysfunction. The study flowchart is displayed in Fig. 1.

Definition of AKI

AKI was defined by the KDIGO (Kidney Disease Improving Global Outcomes) criteria, which have been endorsed by the ICA as an increase in serum creatinine (SCr) of at least 0.3 mg/dl (26.5 mmol/L) within 48 hours or a percentage increase in SCr of at least 50% from baseline, which is already known or presumed to have occurred within the prior 7 days.[10] These criteria classify AKI into stages (AKI Stage 1A and B, AKI Stage 2, and AKI Stage 3), which are prognostically relevant.[11–13] For the present study, Stage 1A and 1B were combined and referred to as Stage 1 for further analysis.

Stage 1 (definitions for substages A and B merged): Increase in SCr ≥0.3 mg/dl from baseline to a value <1.5 mg/dl or an increase in SCr ≥1.5-fold to 2-fold from baseline or an increase in SCr of ≥0.3 mg/dl from baseline to a value ≥1.5 mg/dl or an increase in SCr of ≥1.5-fold to 2-fold from baseline.

Stage 2: Increase in SCr of >2-fold to 3-fold from baseline.

Stage 3: Increase in SCr of >3-fold from baseline or SCr ≥4.0 mg/dl with an acute increase of ≥0.3 mg/dl or initiation of renal replacement therapy.

In the absence of baseline values and in cases of existing AKI at hospital admission, we used the lowest SCr value of the previous 3–6 months as a baseline. The difference in SCr was calculated by subtracting the baseline value from the measurement taken at 24 or 48 hours, respectively (SCr at 24 or 48 hours minus SCr at baseline).

Definition of response to albumin treatment

Currently, there is no standard response definition (defined by kidney function as expressed by SCr) to volume expansion.[7,8] We therefore examined three different definitions of response after 24 and 48 hours. The initial time for starting the observation period was the time of diagnosis of AKI and initiation of subsequent albumin treatment. In the first definition, a decrease in SCr of more than 0.3 mg/dl from the time of AKI was considered a response. The second is adopted from the ongoing Liver-HERO study, where lack of response is defined as an improvement of SCr of <25% from the peak value.[9] The third definition of response is based on the algorithm proposed in the EASL clinical practice guidelines derived from expert opinions for treating AKI in patients with cirrhosis[7]: a full response was defined as SCr decreasing back to within 0.3 mg/dl of the baseline value; a partial response was defined as a SCr decrease of at least one AKI stage without reaching an SCr within 0.3 mg/dl of baseline SCr (see Table S1).[14] For the present study, full and partial responses were combined and referred to as response for further analysis.

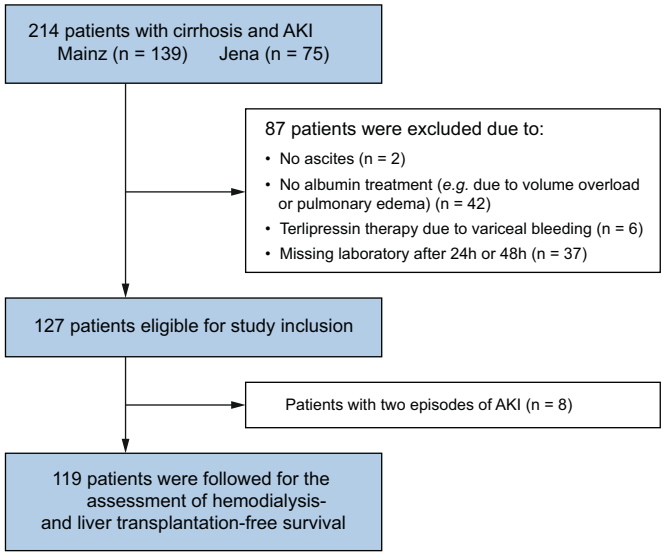

Fig. 1. Flowchart of the study. AKI, acute kidney injury.

Follow-up evaluations

All patients from the LIVKID study were followed up for the placement, initiation of hemodialysis (HD), and liver transplantation (HD-free/LT-free survival). In the Jena University Hospital, this was filled in retrospectively. Patients who were discharged and not rehospitalized or had no visits to the outpatient clinic of the Cirrhosis Center Mainz were contacted by phone (for Mainz) or censored at the time of the last visit (for Jena). Follow-up continued until the composite endpoint was reached or the last contact was made (data collected until 10/2024).

Ethics

The studies were conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and its later amendments. The LIVKID study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz (2022-16356). The Liver-HERO study was approved by all participating German centers (NCT05346393). For the sake of the present study, further approval from the ethics committee in Jena was obtained for the retrospective collection of the data (2024-34585-BO-D) with informed consent waived. Written informed consent was obtained from all participants from Mainz.

Statistical analyses

All data were analyzed using IBM SPSS Statistics Version 29.0 (Armonk, NY: IBM Corp.), GraphPad Prism Version 8.0.2 (GraphPad Software, California, US), and R Software Version 4.4.2 (R Core Team, 2024). Sankey plots were created with sankeymatic.com.

Categorical variables are presented as numbers and percentages. Continuous variables are presented as medians (IQR). Normal distribution was tested using the Shapiro-Wilk normality test, and subsequent comparisons between groups were made using a Mann-Whitney *U* test, an unpaired t-test, or a chi-squared test.

To identify variables associated with response to albumin treatment after 48 hours according to various definitions, multivariable logistic regression models were fitted including all univariable significant variables.

For HD-/LT-free survival analyses, Kaplan-Meier curves, and Cox proportional hazards regression models were built. The tidycmprsk R package was used for cumulative incidence functions of death for competing risk analyses. Here, LT was handled as a competing event for death. For the aforementioned analyses, patients with repeated AKI episodes were only included in the first episode. Multiplicative interaction between response and administration of terlipressin was assessed and ruled out. Evaluation of the impact of terlipressin included as a time-dependent covariate was performed. The log-rank test was used to test for differences between groups in Kaplan-Meier curve analysis.

To investigate how a SCr change after 24 hours of albumin treatment discriminates between patients with or without response after 48 hours according to the three definitions, we calculated the AUC of receiver-operating characteristic curves, and respective 95% CIs. Additionally, the negative predictive values and positive predictive values, as well as cut-offs with a sensitivity of 100% were defined.

For all tests, we used a 0.05 level to define statistically relevant deviations from the respective null hypotheses. Given that our complete data analysis is exploratory, *p* values must be interpreted in the context of the study design. No adjustments for multiple testing were performed.

Results

Demographics and baseline characteristics

For this study, 214 patients with cirrhosis and AKI were available for analyses from Mainz (n = 139) and Jena (n = 75). As described in the study flowchart (Fig. 1), 127 patients remained for final analyses after applying the exclusion criteria. Eight patients had more than one episode of AKI. Baseline characteristics are displayed in Table 1. A comparison between patients from Mainz and Jena is provided in Table S2. Most patients had Child-Pugh B or C cirrhosis, and the predominant etiology of the cohort was alcohol-related liver disease (63.0%). Acute-on-chronic liver failure (ACLF) was detected in 82 (64.6%) patients. AKI stages at diagnosis of AKI were as follows: AKI 1, 40.9%; AKI 2, 33.9%; AKI 3, 25.2%.

Table 1. Demographics and clinical characteristics of the cohort at the time of study inclusion.

Variable	Total cohort N = 127
Age, y (IQR)	60 (54, 67)
Sex (female) n (%)	57 (44.9)
Etiology	
Alcohol, n (%)	83 (65.4)
Viral hepatitis, n (%)	7 (5.5)
MASLD/cryptogenic, n (%)	25 (19.7)
Cholestatic/	4 (3.1)
Autoimmune, n (%)	6 (4.7)
Other/mixed, n (%)	2 (1.6)
Median MELD score (IQR)	22 (18, 26)
Child-Pugh A/B/C, n (%)	8/56/63 (6.3/44.1/49.6)
ACLF, n (%)	82 (64.6)
ACLF grades:	
1a	62 (48.4)
1b	8 (6.3)
2	9 (7.1)
3a	3 (2.4)
MAP, mmHg (IQR)	80 (72, 92)
Infection, n (%)	51 (40.2)
History of HRS-AKI, n (%)	8 (6.3)
CKD, n (%)	58 (45.7)
Sodium, mmol/L (IQR)	133 (130, 138)
Albumin, g/L (IQR)	28 (24, 32)
Bilirubin, mg/dl (IQR)	2.6 (1.1, 5.1)
INR (IQR)	1.5 (1.3, 1.9)
Hemoglobin, g/dl (IQR)	8.9 (7.7, 10.2)
Platelets/nl (IQR)	89 (58, 140)
WBC,/nl (IQR)	6.8 (4.5, 9.3)
CRP, mg/L (IQR)	22.7 (8.9, 49.4)
SCr, mg/dl (IQR)	2.1 (1.6, 2.7)
Albumin dose (g/kg BW within 24h) (IQR)	0.84 (0.69, 0.98)
Albumin dose (g/kg BW within 48h) (IQR)	1.67 (1.38, 1.97)

Data are expressed as medians and interquartile ranges or as frequencies and percentages.

ACLF, acute-on-chronic liver failure; BW, body weight; CKD, chronic kidney disease; CRP, C-reactive protein; HRS-AKI, hepatorenal syndrome-acute kidney injury; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; INR, international normalized ratio; SCr, serum creatinine; WBC, white blood cell count.

Response to albumin treatment within 24 and 48 hours

All patients received treatment with albumin on the day of AKI diagnosis. The median applied albumin dose was 0.84 g/kg body weight (IQR 0.69, 0.98) over 24 hours and 1.67 g/kg body weight (IQR 1.38, 1.97) over 48 hours. According to the different response definitions, 69 (54.3%) patients responded to albumin treatment after 48 hours according to definition 1, 39 (30.7%) according to definition 2, and 59 (46.5%) according to definition 3. Response according to the three definitions on an individual patient level is displayed in Fig. S1, and SCr trajectories during the treatment period with albumin are shown in Fig. S2. Baseline characteristics stratified by response within 48 hours are displayed in Tables S4–6. Irrespective of the definition, a relevant subset of patients with a response after 48 hours did not show a response within the first 24 hours of albumin treatment. The distribution of the response rates within the first or second 24 hours of albumin treatment and the response trajectories within 24 and 48 hours stratified by different AKI stages for the three definitions are displayed in Fig. 2 and S3.

To identify predictors of treatment response to the albumin therapy within 48 hours, we conducted univariable comparisons between patients with and without a response according to the different definitions (Tables S4–6). Afterwards, we built multivariable logistic regression models, including univariable significant variables. Here, the SCr decrease in percent after 24 hours of albumin treatment was the only variable consistently associated with response across all three definitions (Tables 2 and S7). Of note, a higher SCr at AKI diagnosis was associated with a poorer response rate according to definition 3 (Table 2). We also conducted multivariable logistic regression models that included ACLF (Tables 2 and S7). In these models, we excluded SCr at AKI diagnosis due to collinearity with ACLF. Here, the presence of ACLF was independently associated with a poorer response rate according to definition 3 (Table 2).

We found that 28%, 22%, and 18% of the cohort responded to albumin therapy during the second 24 hours of treatment according to definitions 1, 2, and 3, respectively. Therefore, we aimed to identify variables predicting a treatment response after the first 24 hours to guide the management of the patient group that did not respond within the first 24 hours. For this analysis, we consequently compared the patients with a response in the second 24 hours of albumin treatment to the patients without a response at all. The analyses for each definition are displayed in Tables S8–10. Here, the SCr decrease in percent after 24 hours of albumin treatment differed significantly between both groups in the analyses for definitions 2 and 3, while in the analysis for definition 1, significance was missed ($p = 0.051$). We did not proceed with multivariable logistic regression analyses due to potential overfitting due to the number of events.

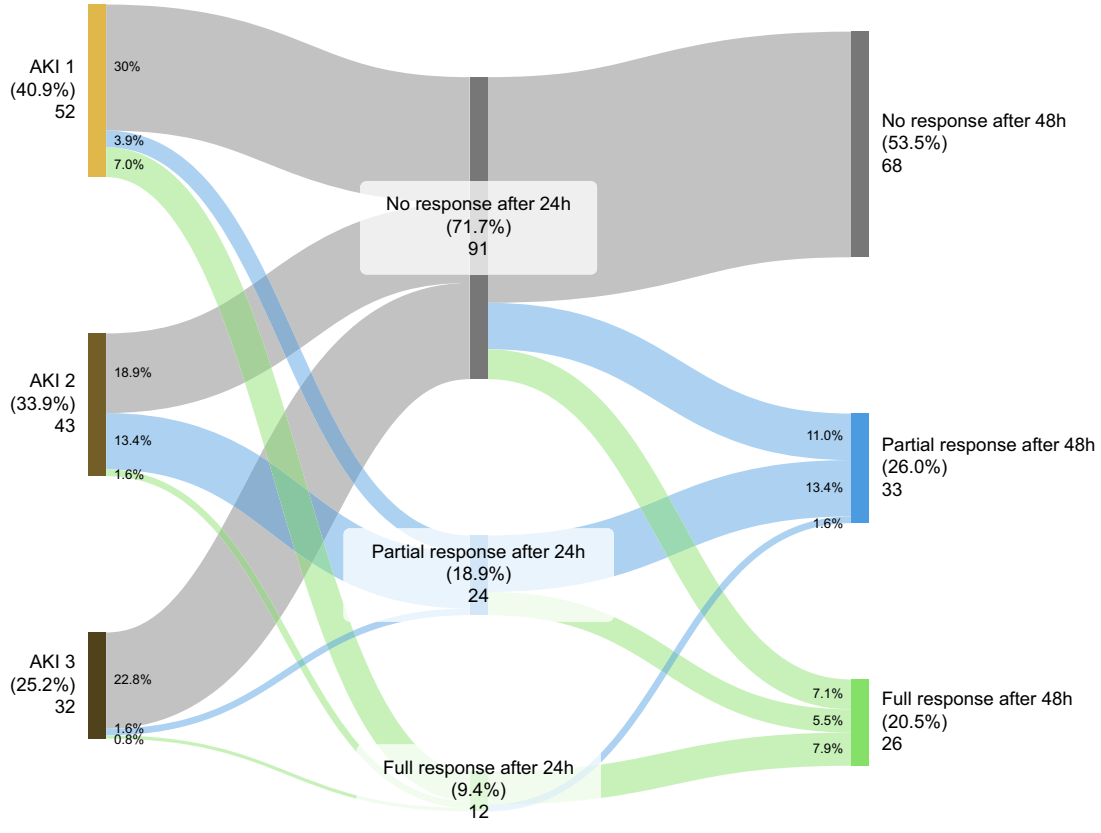

Fig. 2. Response rates to albumin treatment within 24 or 48 hours in percent and per AKI stage according to definition 3 (EASL-proposed definition). Sankey plot with the comparison of response rates in different AKI stages according to definition 3. Definition 3: SCr decrease in at least one AKI stage. AKI, acute kidney injury; EASL, European Association for the Study of the Liver; SCr, serum creatinine. (This figure appears in color on the web.)

Table 2. Multivariable logistic regression analysis for identifying variables associated with response after 48 hours of albumin treatment according to definition 3 (EASL-proposed definition).

Variable	OR (95% CI)	*p* value
Model 1. Outcome: EASL-proposed definition (decrease in at least one AKI stage)		
Hemoglobin, g/dl	1.138 (0.898, 1.442)	0.284
SCr, mg/dl	0.420 (0.227, 0.777)	**0.006**
SCr decrease in% after 24 hours	0.902 (0.865, 0.941)	**<0.001**
Model 2. Outcome: EASL-proposed definition (decrease in at least one AKI stage)*		
Hemoglobin, g/dl	1.107 (0.865, 1.417)	0.419
ACLF	0.100 (0.033, 0.297)	**<0.001**
SCr decrease in% after 24 hours	0.899 (0.860, 0.939)	**<0.001**

p values in bold designate statistical significance of <0.05.
Model 1: R2 0.494; Model 2: R2 0.561.
ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; EASL, European Association for the Study of the Liver; OR, odds ratio; SCr, serum creatinine.
*Model includes ACLF instead of SCr at baseline in order to avoid collinearity.

Prognosis of patients with cirrhosis and AKI stratified by response to albumin treatment

For survival analyses, only patients with a first AKI episode in the study were selected for further analysis (n = 119) (Fig. 1). The baseline characteristics of this cohort are displayed in Table S3. Overall, patients were followed for a median of 75 days (IQR 24, 247), and 36 (30.3%) patients received terlipressin treatment after establishing non-response to albumin. During that period, 38 patients (31.9%) died, 24 (20.2%) received LT, and 11 (9.2%) needed HD. The outcome events at the respective centers were as follows: Mainz (21 deaths, 18 LT, 5 HD), Jena (17 deaths, 6 LT, 6 HD).

Kaplan-Meier curves were plotted to compare the prognosis regarding HD- and LT-free survival of patients with or without response to albumin treatment after 48 hours according to the three definitions. Here, the prognosis did not differ between patients with and without response to albumin treatment according to definitions 1 and 2. In contrast, patients with a response according to definition 3 had a better prognosis than patients without a response at all (Fig. 3, *p* <0.001). The same results were found when analyzing the impact of response according to the three definitions on LT-free survival or death considering LT as a competing event (Figs. S4 and S5). We also compared the prognosis of the group of patients with a response to albumin treatment within the first 24 hours to patients with a response within the second 24 hours and the

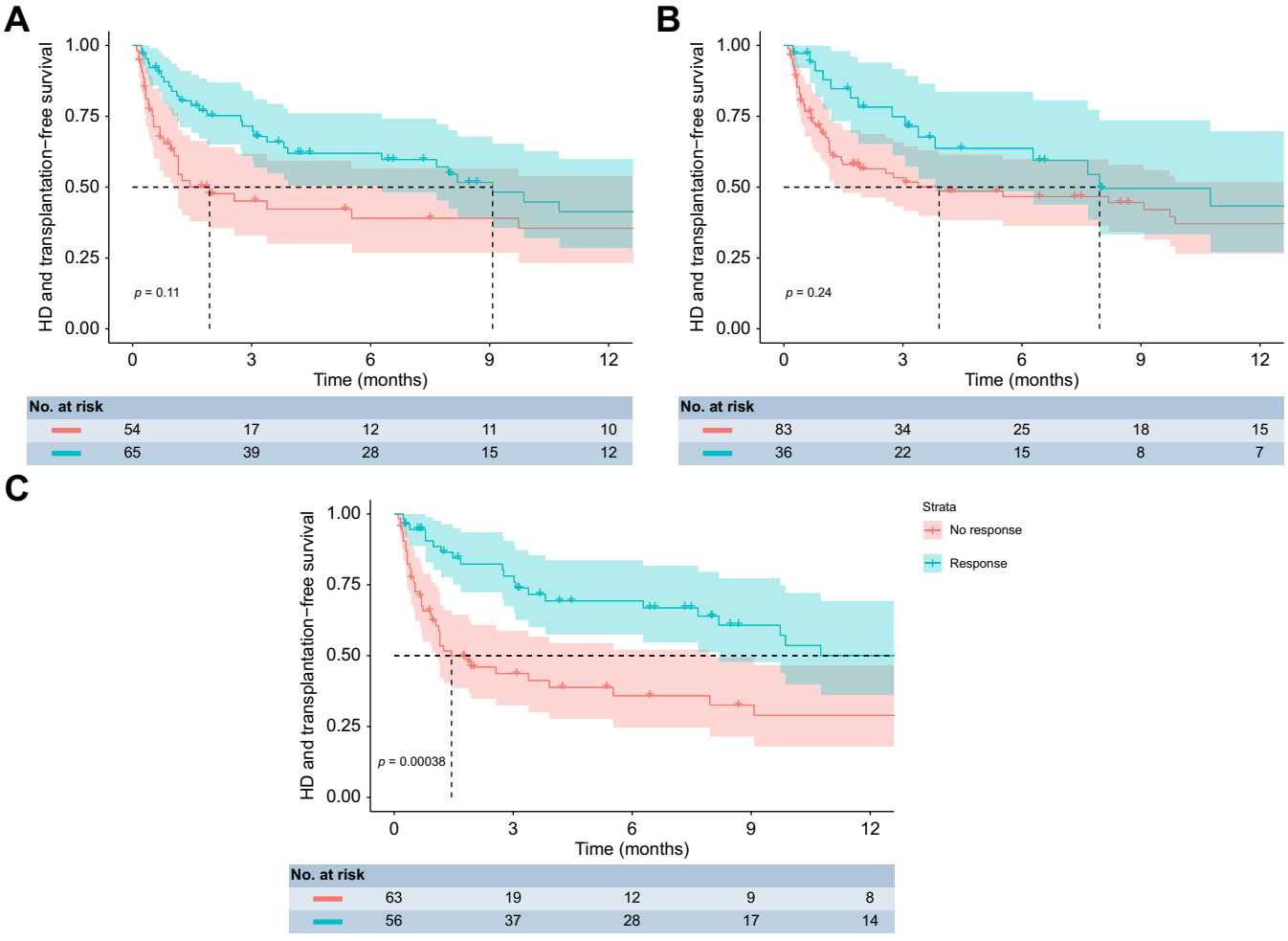

Fig. 3. HD/LT-free survival of patients with AKI stratified by response to albumin treatment within 48 hours according to the three response definitions. Kaplan-Meier curves showing the incidence of need for HD/LT or death in (A) patients with and without response to albumin treatment within 48 hours according to definition 1 (*p* = 0.11, log-rank test), (B) definition 2 (*p* = 0.24, log-rank test) or (C) definition 3 (*p* <0.001, log-rank test). Definition 1: >0.3 mg/dl SCr decrease; definition 2: >25% SCr decrease; definition 3: SCr decrease in at least one AKI stage. AKI, acute kidney injury; HD hemodialysis; LT, liver transplantation; SCr, serum creatinine. (This figure appears in color on the web.)

patients without a response at all (Fig. S6). Again, there was no difference regarding prognosis between the three groups according to definitions 1 and 2, while patients with a response within 24 or 48 hours according to definition 3 had a better prognosis compared to patients without a response at all (Fig. 4, p <0.01). This univariable finding was also found in a multivariable Cox regression analysis for identifying variables associated with a higher risk of reaching the composite endpoint of HD, LT, or death (Table 3). Here, response according to definition 3 (hazard ratio 0.316, 95% CI 0.179–0.556, p <0.001) was independently associated with a poorer prognosis. Other variables associated with poorer prognosis were platelets, sodium, model for end-stage liver disease score, and etiology of cirrhosis. We also repeated the multivariable analysis and added terlipressin therapy to the model. Here, terlipressin therapy was not independently associated with prognosis (Table 3). We also investigated terlipressin therapy in a time-dependent multivariable Cox regression analysis (cut-off 30 days). Again, lack of terlipressin therapy did not turn out to be significantly associated with a better prognosis.

The predictive usefulness of SCr changes after 24 hours

In the next step, we evaluated those patients who had met the response criteria within the initial 24-hour period to determine whether the initial changes in SCr observed at 24 hours could help identify those who would or would not respond at 48 hours. For this purpose, we calculated the respective AUC for creatinine decrease at 24 hours in percent. For definition 1, the AUC for SCr decrease in percent at 24 hours for identifying patients with a response at 48 hours was 0.621 (95% CI 0.509–0.734). For response definition 2 (>25% SCr decrease), the AUC for SCr decrease in percent at 24 hours for identifying patients with a response at 48 hours was 0.871 (95% CI 0.807–0.936), while it was 0.690 (95% CI 0.567–0.812) for definition 3. We identified cut-offs for SCr decrease in percent at 24 hours with sensitivity and negative predictive values of 100% to define a group of patients in whom further treatment with albumin would be futile. The cut-off for the only prognostically relevant definition (definition 3/EASL-proposed definition) was a 16% increase in SCr from baseline to 24 hours after treatment initiation (Table 4). Using this futility cut-off in clinical practice, terlipressin treatment could have been initiated in 12% of the patient cohort even after 24 hours. The respective cut-offs (definition 1: 16%, definition 2: -4.5%, definition 3: 16%), sensitivities, specificities, negative predictive values, and positive predictive values for the other two response definitions are displayed in Table S11.

Discussion

EASL and AASLD guidelines recommend treatment with albumin for 48 hours in patients with AKI and suspected HRS-AKI or hypovolemia.[7,8] Recently, a multidisciplinary consensus meeting recommended reducing the duration of systematic volume expansion therapy from 48 hours to 24 hours.[6] The findings of our current study argue strongly against a universal shortening of the duration of albumin treatment for each patient

Table 3. Cox regression analysis of variables associated with a higher risk for reaching the composite endpoint of HD, LT or death during the complete follow-up.

Variable	Univariable Cox regression analysis HR (95% CI)	p value	Multivariable Cox regression analysis* HR (95% CI)	p value	Multivariable Cox regression analysis# HR (95% CI)	
Age (years)	1.025 (0.998, 1.053)	0.073				
Sex (female)	0.725 (0.432, 1.217)	0.223				
MAP (mmHg)	0.985 (0.965, 1.005)	0.141				
Alcoholic etiology (*vs.* other)	0.470 (0.283, 0.783)	**0.004**	0.397 (0.232, 0.679)	**<0.001**	0.379 (0.215, 0.668)	**<0.001**
MELD	1.102 (1.055, 1.151)	**<0.001**	1.076 (1.024, 1.131)	**0.004**	1.081 (1.029, 1.136)	**0.002**
History of HRS-AKI	0.953 (0.298, 3.047)	0.935				
CKD	0.977 (0.591, 1.614)	0.926				
Albumin dose (g/kg BW within 48 h)	1.066 (0.638, 1.780)	0.807				
Albumin response 48 h (*vs.* no response) (0.3 mg/dl definition)	0.664 (0.402, 1.097)	0.110				
Albumin response 48 h (*vs.* no response) 25% definition	0.716 (0.409, 1.254)	0.243				
Albumin response 48 h (*vs.* no response) EASL-proposed definition	0.399 (0.236, 0.674)	**<0.001**	0.316 (0.179, 0.556)	**<0.001**	0.273 (0.141, 0.527)	**<0.001**
Infection	1.090 (0.652, 1.822)	0.743				
WBC (/nl)	0.996 (0.967, 1.027)	0.821				
Platelets (/nl)	0.994 (0.990, 0.998)	**0.005**	0.992 (0.987, 0.997)	**<0.001**	0.991 (0.986, 0.996)	**<0.001**
Hemoglobin (g/dl)	0.919 (0.811, 1.042)	0.186				
Sodium (mmol/L)	0.939 (0.898, 0.982)	**0.006**	0.932 (0.888, 0.978)	**0.004**	0.932 (0.887, 0.978)	**0.004**
SCr (mg/dl)	1.146 (0.888, 1.478)	0.294				
Bilirubin (mg/dl)	1.021 (0.987, 1.055)	0.227				
Albumin in serum (g/L)	0.979 (0.942, 1.018)	0.287				
CRP (mg/L)	0.997 (0.990, 1.003)	0.328				
Terlipressin treatment	1.816 (1.051, 3.137)	**0.032**			0.728 (0.379, 1.399)	0.341

Definition 1: >0.3 mg/dl SCr decrease; Definition 2: >25% SCr decrease; Definition 3: SCr decrease in at least one AKI stage.
p values in bold designate statistical significance of <0.05.
BW, body weight; CKD, chronic kidney disease; CRP, C-reactive protein; HR, hazard ratio; HRS-AKI, hepatorenal syndrome-acute kidney injury; MAP, mean arterial pressure; MELD, model for end-stage liver disease; INR, international normalized ratio; SCr, serum creatinine; WBC, white blood cell count.
*This model includes all univariable significant variables, but not terlipressin treatment (yes *vs.* no).
#This model includes all univariable significant variables (with terlipressin treatment (yes *vs.* no).

Table 4. Discriminative ability of a cut-off with 100% sensitivity for identifying patients with potential response to albumin treatment within the second 24 hours of therapy.

Definition	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI
Definition 3/EASL-proposed definition Cut-off: 16% increase of SCr after 24 hours	100 (82–100)	22 (13–34)	30 (21–42)	100 (75–100)

Response definition 3: SCr decrease in at least one AKI stage.
AKI, acute kidney injury; EASL, European Association for the Study of the Liver; NPV, negative predictive value; PPV, positive predictive value; SCr, serum creatinine.

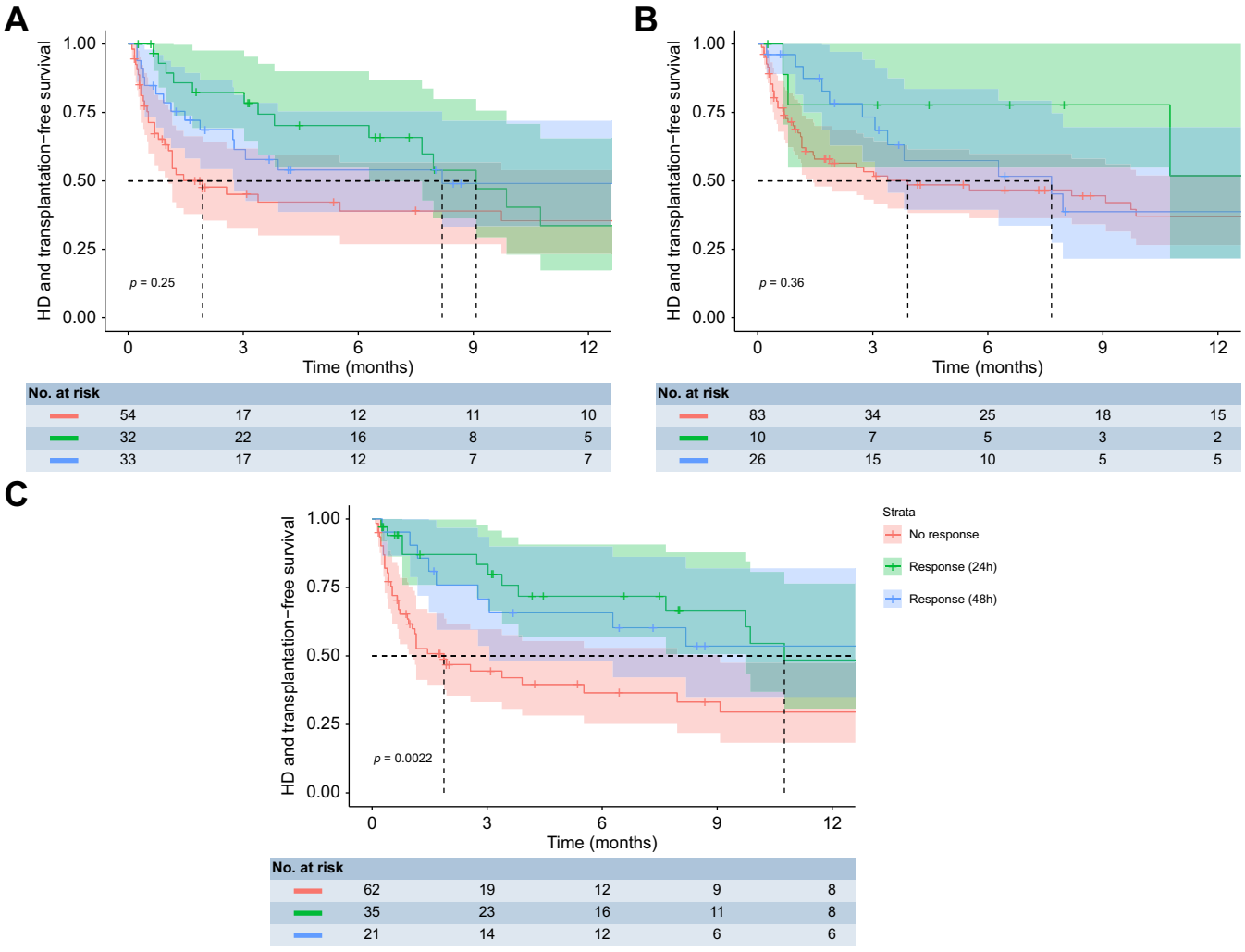

Fig. 4. HD/LT-free survival of patients with AKI stratified by response to albumin treatment within 24 or 48 hours according to the three response definitions. Kaplan-Meier curves showing the incidence of need for HD/LT or death in (A) patients with response within 24 hours or 24-48 hours or no response at all according to definition 1 ($p = 0.25$, log-rank test), (B) definition 2 ($p = 0.36$, log-rank test) or (C) definition 3 ($p = 0.0022$, log-rank test). Definition 1: >0.3 mg/dl SCr decrease; definition 2: >25% SCr decrease; definition 3: SCr decrease in at least one AKI stage. AKI, acute kidney injury; HD hemodialysis; LT, liver transplantation; SCr, serum creatinine. (This figure appears in color on the web.)

with AKI before initiating combination therapy with terlipressin since up to 30% of responders will do so between 24 and 48 hours. Another important finding is that only response definition 3 (the EASL-proposed definition: a SCr decrease in at least one AKI stage) was associated with a better prognosis. In comparison, a reduction in SCr of 0.3 mg/dl or by 25% was not associated with survival. Finally, we also identified futility cut-offs to identify patients who will not benefit from albumin treatment during the second 24 hours of therapy. Here, a SCr increase of at least 16% from the peak value after 24 hours identifies patients in whom further treatment with albumin is futile, and subsequently treatment with terlipressin should be started. On the other hand, a lack of changes of SCr after 24 hours of albumin or minor increases (<16%) are not sufficient to identify a lack of response at 48 hours.

Irrespective of the applied definition, 18-28% of patients who responded after 48 hours did not show a response within the first 24 hours of albumin treatment. This is in line with the recently published findings of Ma *et al.* in a letter to the editor, where almost 40% of the patients who responded to albumin treatment by 48 hours did not show early response at the 24-hour mark.[15] When comparing our current study with the

study published by Ma *et al.*, it is important to note that our study only included patients treated in normal wards in liver units. This excludes patients treated in ICUs with a higher likelihood of acute tubular necrosis, which will not improve with albumin. Nevertheless, both studies underscore the fact that shortening the albumin challenge period would significantly increase the number of unnecessarily treated patients. This is of pivotal importance, given that terlipressin is associated with potentially severe and frequent side effects and incurs substantial costs. In this context, it is also noteworthy that a recent large multicenter retrospective study showed that the occurrence of HRS-AKI is the exception rather than the rule, as its incidence is only 12-15%.[14,16] Therefore, terlipressin should only be prescribed in confirmed cases of HRS-AKI where its benefits outweigh its risks. Interestingly, according to the three definitions used in our study, 47-69% of the patients did not respond to therapy within 48 hours of albumin treatment.

Currently, the definition of response to albumin treatment is not standardized. In addition, albumin also has well-known volume expansion effects and these may cause a simple dilution of SCr, which is dependent on the volume used and the body weight of the respective patient.[17,18] The EASL guidelines and ICA criteria suggest that a response should be defined as a full response (SCr decreasing back to within 0.3 mg/dl of the baseline value) or partial response (defined as a SCr decrease in at least one AKI stage without reaching <0.3 mg/dl of baseline SCr).[1,7,10] According to these guidelines, any response (both partial and full) would be considered a response to albumin. The AASLD guideline does not provide any guidance in this sense.[8] Expert opinions suggest that the resolution of AKI (full response according to EASL-proposed definition) should be considered as response to albumin.[1,4] In a recently published clinical trial, the definition of full response to albumin therapy was in line with the EASL-proposed definition, whereas for albumin-treated AKI, partial response was defined differently as returning to AKI stage 1A.[14] Therefore, we examined three different definitions of response in this study. Definitions 1 and 2 are applied from clinical settings in Jena and Mainz. Definition 3 was based on the EASL-proposed algorithm.[7] All in all, response rates varied between 31-53%, depending on the respective response definition. However, responses according to definition 1 and 2 were not linked to a better prognosis, while response to definition 3 was. This highlights that definition 3 seems to be the most appropriate for use in routine care as a partial or full response according to this definition was independently associated with better HD- and LT-free survival. This is likely explained by the fact that definition 3 reflects recovery from AKI, resulting in a better prognosis than the other two definitions used.[19]

Of note is that terlipressin therapy was not independently associated with prognosis in this multivariable analysis; however, it has to be acknowledged that the decision to initiate terlipressin was made according to local practice. Nevertheless, this result further emphasizes the lack of difference in the LT-free survival observed in the CONFIRM trial.[20] As a side note, in our study, prognosis also remained comparably poor even in patients with response to albumin treatment according to definition 3, underlying the need to consider listing for liver transplantation as early as possible.

Given that response rates to terlipressin decrease with increasing SCr, it would be desirable to identify patients without a response to albumin after 24 hours.[21,22] Therefore, we aimed to identify variables predicting a treatment response within the second 24 hours of albumin treatment among those who did not respond within the first 24 hours. Not surprisingly, predicting response was difficult, and the trajectory of SCr from baseline to 24 hours after treatment initiation seemed to be the most promising variable across all three response definitions. As an example, for predicting response to definition 3: patients with an increase of SCr of at least 16% after 24 hours of albumin treatment will not respond to treatment after 48 hours. Using this cut-off, 12% of patients who had not responded already at 24 hours could be fast-tracked to terlipressin treatment at this time point.

Current guideline recommendations are heterogeneous regarding the stage of AKI and the need for treatment with albumin. While EASL guidelines recommend the administration of albumin for AKI stages 1B and above, the AASLD only recommends administration for stage 2 and above, whereas the recently published consensus guidelines recommend treatment in all AKI stages.[6–8] Additionally, recent secondary analyses from the CONFIRM trial highlighted that terlipressin treatment seems to be futile in patients with SCr >5 mg/dl.[21] Although these findings cannot be completely extrapolated from terlipressin to albumin treatment, it is a notable finding of our study that response rates to albumin treatment were well-balanced across AKI stages for all response definitions. Importantly, even patients with AKI stage 3 showed a relevant response rate despite the fact that a higher baseline SCr was associated with a poorer response rate. This emphasizes that an albumin challenge should not be dispensed even in patients with higher-grade AKI if there are no signs of pulmonary volume overload. Identifying AKI as early as possible is of utmost importance for achieving a response to treatment, not only to albumin but also to terlipressin in the case of HRS-AKI.[21] In this context, biomarkers identifying patients at risk for the development of AKI during their hospital stay would be desirable. Potential candidate biomarkers include urinary neutrophil gelatinase-associated lipocalin or serum uromodulin.[23,24] Though further validation in diverse multicenter cohorts would be desirable.

One of the key strengths of our study is the prospectively recruited, relatively homogeneous, cohort. Indeed, we decided to exclude patients treated in an ICU since acute tubular necrosis is the most common cause of AKI in this population, and they are less likely to benefit from albumin treatment.[16] Additionally, we did not include patients without ascites because these patients also benefit from intravenous fluid, and the costly use of albumin is not necessary for these patients.

The limitation of our study is that we did not assess the side effects of albumin treatment in our current study in a structured manner. Therefore, we are unable to answer the question of whether albumin treatment is associated with a higher frequency of side effects in patients with higher-grade AKI. Another limitation is that our analyses remain retrospective, and the endpoints used differ from those used in the original studies, especially in Liver-HERO. Additionally, the urinary output criterion of KDIGO to define AKI was not used to define AKI in this study. Moreover, urinary neutrophil gelatinase-associated lipocalin levels were not available for this study, and we were therefore unable to analyze the diagnostic and prognostic implications of this biomarker.

In conclusion, the key finding of our current study is that about one-quarter of patients (depending on the definition used) who respond to albumin will have this response in the second 24 hours of albumin treatment. Therefore, shortening the duration of volume expansion therapy may lead to overtreatment with terlipressin. Finally, our results also highlight that the best response definition seems to be the improvement of at least one AKI stage. Given that this was the only one associated with a better prognosis, it seems to be the most reasonable definition for implementation in clinical practice.

Affiliations

[1]*Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany;* [2]*Cirrhosis Center Mainz (CCM), University Medical Center of the Johannes Gutenberg-University, Mainz, Germany;* [3]*Clinic for Internal Medicine IV, Jena University Hospital, Friedrich-Schiller University Jena, Germany;* [4]*Research Center of Immunotherapy, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany*

Abbreviations

AASLD, American Association for the Study of Liver Diseases; ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HD, hemodialysis; HRS-AKI, hepatorenal syndrome-acute kidney injury; ICA, International Club of Ascites; SCr, serum creatinine; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflict of interest

E.M.S., H.K., J.W-M., P.R.G., S.J.G., A.S., C.L. disclose no potential financial or non-financial conflict of interests regarding this study. C.R. has held lectures for Gore, Bristol-Myers Squibb, and Falk, achieved funding from German Research Foundation (DFG) and served as an advisory board member for Boehringer-Ingelheim. A.Z. has held lectures for Gore and Falk Foundation and obtained advisory grants from CLS Behring.

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

Authors' contributions

Performed research: E.M.S; C. R., C.L. Contributed to acquisition of data: all authors. Designed the experiments and analyzed the data: E.M.S, C.R., C.L. Contributed reagents/materials/analysis tools: E.M.S, J.W.-M., P.R.G., A.Z., A.S., C.R., C.L. Wrote the paper: E.M.S, C.R., C.L. Critical revision of the draft: all authors. Statistical analysis: E.M.S., C.L. All authors approved the final version of the manuscript and the authorship list. Guarantor of the article: C.L.

Data availability statement

Raw data are available from the corresponding author on reasonable request.

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Supplementary data

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Author names in bold designate shared co-first authorship

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