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Molecular Adsorbent Recirculating System Can Reduce Short-Term Mortality Among Patients With Acute-on-Chronic Liver Failure—A Retrospective Analysis*

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Objectives: Acute-on-chronic liver failure is associated with numerous consecutive organ failures and a high short-term mortality rate. Molecular adsorbent recirculating system therapy has demonstrated beneficial effects on the distinct symptoms, but the associated mortality data remain controversial.

Design: Retrospective analysis of acute-on-chronic liver failure patients receiving either standard medical treatment or standard medical treatment and molecular adsorbent recirculating system. Secondary analysis of data from the prospective randomized Recompensation of Exacerbated Liver Insufficiency with Hyperbilirubinemia and/or Encephalopathy and/or Renal Failure trial by applying the recently introduced Chronic Liver Failure-criteria.

Setting: Medical Departments of University Hospital Muenster (Germany).

Patients: This analysis was conducted in two parts. First, 101 patients with acute-on-chronic liver failure grades 1–3 and Chronic Liver Failure-C-Organ Failure liver subscore equals to 3 but stable pulmonary function were identified and received either standard medical treatment (standard medical treatment, $n = 54$) or standard medical treatment and molecular adsorbent recirculating system ($n = 47$) at the University Hospital Muenster. Second, the results of this retrospective analysis were tested against the Recompensation of Exacerbated Liver Insufficiency with Hyperbilirubinemia and/or Encephalopathy and/or Renal Failure trial.

Interventions: Standard medical treatment and molecular adsorbent recirculating system.

Measurements and Main Results: Additionally to improved laboratory variables (bilirubin and creatinine), the short-term mortality (up to day 14) of the molecular adsorbent recirculating system group was significantly reduced compared with standard medical treatment. A reduced 14-day mortality rate was observed in the molecular adsorbent recirculating system group (9.5% vs 50.0% with standard medical treatment; $p = 0.004$), especially in patients with multiple organ failure (acute-on-chronic liver failure grade 2–3). Concerning the affected organ system, this effect of molecular adsorbent recirculating system on mortality was particularly evident among patients with increased kidney, brain, or coagulation Chronic Liver Failure-C-Organ Failure subscores.

***See also p. 1776.**

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Subsequent reanalysis of the Recompensation of Exacerbated Liver Insufficiency with Hyperbilirubinemia and/or Encephalopathy and/or Renal Failure dataset with adoption of the Chronic Liver Failure-classification resulted in similar findings.

Conclusions: Molecular adsorbent recirculating system treatment was associated with an improved short-term survival of patients with acute-on-chronic liver failure and multiple organ failure. Among these high-risk patients, molecular adsorbent recirculating system treatment might bridge to liver recovery or liver transplantation. (*Crit Care Med* ; 45:1616–1624)

Key Words: acute-on-chronic liver failure; albumin dialysis; molecular adsorbent recirculating system; multiple organ failure

Acute-on-chronic liver failure (ACLF) is characterized by an acute deterioration in liver function and organ system failures in patients with preexisting chronic liver disease. ACLF is associated with a high short-term (28-day) mortality rate of 30–40% (1, 2). The clinical management of ACLF is not limited to the underlying liver disease because patients often require multiple organ supportive care for consecutive organ failures, including those involving the kidney, brain, coagulation, and so on. As the number of organ failures increases, multiple complex physiological disturbances can develop, leading to increased mortality (2).

The overall therapeutic goal regarding ACLF is to gain time until a donor organ is available or the native liver regenerates. The current standard medical treatment (SMT) involves treating the associated complications, addressing organ failures, and liver transplantation. Because the outcomes for patients with ACLF who receive SMT are poor, unmet medical needs exist for new therapeutic options.

Extracorporeal albumin dialysis (ECAD) is one option that improves specific symptoms of liver disease such as hepatic encephalopathy (HE) (3–5), although the results of survival outcome studies are controversial. Some studies have found a positive association between ECAD and improved survival among patients with ACLF (6–8). Additionally, two recently published meta-analyses found that ECAD significantly reduces the risk of short-term mortality (9, 10). However, the largest randomized multicenter trial that evaluated the use of molecular adsorbent recirculating system (MARS) among patients with ACLF, the Recompensation of Exacerbated Liver Insufficiency with Hyperbilirubinemia and/or Encephalopathy and/or Renal Failure (RELIEF), failed to demonstrate a reduction in short-term mortality although improvements in HE and renal function were observed after MARS therapy (11).

Even if MARS therapy does not improve overall survival (OS) in general, specific patient subgroups might still benefit from its use (12). For example, we do not know the best patient subgroup to select the indications for therapy and the exact treatment schedule.

In the current study, we sought to identify certain patient subgroups who would benefit from MARS treatment and response predictors to this therapy. Thus, we intended to generate new hypotheses that would form the basis for better management strategies to reduce the high-mortality rate associated with ACLF.

PATIENTS AND METHODS

This study was conducted in two parts. First, a retrospective analysis was based on patients treated at the University Hospital Muenster (Muenster cohort) from January 2009 to July 2015. Second, all analyses were repeated equally on the dataset of the RELIEF trial (RELIEF cohort).

Study Design

Patients with ACLF receiving MARS treatment at our hospital were identified retrospectively using the German modification of the International Statistical Classification of Diseases and Related Health Problems. Thus, cirrhosis was present in each analyzed patient. Assessment of each organ failure (OF) subscore and ACLF grade was adopted retrospectively according to the current Chronic Liver Failure-Consortium (CLIF-C) criteria (details are provided in **Supplemental Methods**, Supplemental Digital Content 1, http://links.lww.com/CCM/C680) (13).

Analysis of the patient characteristics revealed a predominant presence of hyperbilirubinemia greater than or equal to 12 mg/dL (CLIF-C-OF liver subscore = 3) (13) and stable respiratory/circulatory status (CLIF-C-OF subscore < 3). Subsequently, all patients with these conditions were considered for analysis (MARS group). To evaluate the impact of MARS treatment, a control group (SMT group) with equal patient characteristics except the application of MARS was mandatory. Therefore, a second database search with both selection criteria was performed. Except MARS treatment, all of the other therapies and supportive care were provided to both groups according to identical institutional guidelines. A more detailed description of SMT is provided in the Supplemental Digital Content (Supplemental Methods, Supplemental Digital Content 1, http://links.lww.com/CCM/C680).

Hepatorenal syndrome (HRS) was diagnosed according to the criteria of the International Ascites Club. HE was graded by adapting the West Haven Criteria, and the Model of End-Stage Liver Disease (MELD) score was performed according to Kamath et al (2, 14, 15).

All the results observed in our retrospective cohort were additionally tested in an independent external population—the per-protocol (PP) population of the prospective RELIEF trial.

All patients provided written informed consent prior to the initiation of any medical treatment. Ethical approval was obtained from the local Ethics Board (Reference Number: 2015-725-f-S).

Extracorporeal Treatment

MARS therapy was performed almost daily (at least three procedures within 5 d) using a Fresenius 5008 dialysis machine (FMC GmbH, Bad Homburg/Germany) and a MARS treatment kit (Gambro Lundia AB, Lund/Sweden). Treatment was

performed according to the manufacturer's instructions. The corresponding treatment times were 360 minutes on average. More detailed information on MARS can be found in the Supplemental Methods (Supplemental Digital Content 1, http://links.lww.com/CCM/C680). MARS treatment was usually discontinued as soon as the bilirubin level decreased significantly (> 30% of initial values) or in the event of no response (i.e., no change in bilirubin level after three consecutive sessions).

Platelet count was monitored closely, and any platelet count below 50,000/µL resulted in the discontinuation of MARS.

Outcome

The primary endpoint was liver transplant-free survival analyzed as mortality rate at 7, 14, 21, and 28 days. OS was defined as survival until death due to any cause, with censoring of patients on the date of liver transplantation or if they were known to be alive at the time of the last follow-up assessment.

Statistical Analyses

Differences between the MARS and SMT groups were analyzed using a two-tailed Mann-Whitney *U* test in the case of continuous variables. The chi-square test was used to compare categorical variables. The distribution of the time-to-event variables was estimated using the Kaplan-Meier method with log-rank testing.

A univariate analysis of the short-term mortality rate was performed using the chi-square test for the four time points at day 7, 14, 21, and 28. *p* values were adjusted using Bonferroni correction to control for multiple comparisons. To determine the predictors of short-term mortality, a multivariate Cox regression model was applied—as outcome the OS with adding censoring for events greater than or equal to 14 days was adopted.

In an explorative approach, all the variables incorporated in the multivariate Cox regression model were concurrently subjected to a decision tree analysis (exhaustive chi-square automatic interaction detection, split $\alpha = 0.05$, no correction for multiple tests) to recursively identify the best predictors and patient subgroups with different prognoses with regard to short-time mortality.

Two-tailed *p* values less than 0.05 were considered as significant. Statistical analyses were performed using SPSS-Statistics, version 22.0 (IBM, Armonk, NY).

RESULTS

Study Population

The final cohort consisted of 101 patients with ACLF and organ failure liver subscore equals to 3 adapted to the current CLIF-criteria. A total of 54 patients from this sample received SMT exclusively, and 47 patients were treated with SMT and MARS. Within the MARS group, the median number of extracorporeal therapy sessions was three (range = 2–5 sessions).

Table 1 displays the baseline patient criteria in detail. Briefly, both groups were equally balanced with regard to baseline patient characteristics except for gender and initial bilirubin values. Patients in the MARS group had higher bilirubin values with a mean of 22.80 mg/dL than 19.49 mg/dL in the SMT group ($p = 0.004$). With regard to the ACLF grade, all patients had a minimum of one organ failure (grade 1). Grades 2–3 were observed in 44.7% and 40.7% of the MARS and SMT groups, respectively. In addition to liver failure (which was mandatory for inclusion), approximately 30% of all patients had kidney failure, and nearly 17% had evidence of coagulopathy. No patient exhibited circulatory or respiratory organ failure (according to the CLIF-C-OF score system).

Outcome

A significant reduction in average bilirubin values was observed on day 4 in the MARS group (–17.7% vs –4.1% in the SMT group; $p = 0.013$). Additionally, a trend toward reduced creatinine values was observed on day 4 (–9.4% vs +7.6% in the SMT group; $p = 0.182$); however, no significant changes in international normalized ratio (INR), platelets hemoglobin, or serum sodium were found.

The short-term mortality rate (up to day 14) was significantly reduced for the MARS group. This effect was less significant at day 21 but still showed a trend toward reduced mortality compared with the SMT group ($p = 0.080$) (**Table 2**). The corresponding Kaplan-Meier plots also reflected a trend toward an increased cumulative probability of 28-day transplant-free survival ($p = 0.163$) (**Fig. 1**). Within the first 28 days of follow-up, 34.0% of patients ($n = 16$) in the MARS group were censored because of a successful liver transplantation compared with 9.3% ($n = 5$) in the SMT group ($p = 0.002$).

In some cases, filter clotting ($n = 6$ MARS sessions) led to early termination of extracorporeal therapy. One patient in the MARS group suffered from catheter-related infection; another patient collapsed some hours after therapy and developed a traumatic subarachnoid bleeding. Specifically, no cases of bleeding disorders, sepsis, or death related to MARS therapy were observed. Compared with the SMT group, no differences in cause of death between both treatment groups were observed (Table 2).

Predictors of Mortality

Patients with HRS (13.6% vs 42.1%; $p = 0.040$) or a MELD score greater than 20 (7.3% vs 29.3%; $p = 0.008$) showed a significantly reduced short-term mortality at day 14 when treated with MARS. Concerning the affected organ system, a therapeutic effect of MARS was observed in patients with increased kidney, brain, or coagulation CLIF-C-OF subscores. Mortality was reduced in the MARS group, especially among patients with multiple organ failure (ACLF grade ≥ 2; 9.5% vs 50.0% in the SMT group; $p = 0.004$).

Importantly, multivariate Cox regression models that assessed the effect of the independent risk factors on the 14-day mortality rate indicated an independent beneficial effect of MARS treatment on short-term mortality (hazard ratio [HR] = 0.17, 95% [CI] = 0.05–0.60; $p = 0.006$). In addition, patients with an increased ACLF grade ($p < 0.001$) and especially brain failure (subscore, 3 vs 1; HR = 16.00; 95%

TABLE 1. Baseline Patient Characteristics: Comparison of Molecular Adsorbent Recirculating System and Standard Medical Treatment

Parameter	Molecular Adsorbent Recirculating System (*n* = 47)	Standard Medical Treatment (*n* = 54)	*p*
Age (yr)	53.10 (12.5)	53.67 (13.3)	0.764
Male sex, *n* (%)	40 (85.1)	24 (44.4)	**< 0.0001**
Body weight (kg)	85.49 (17.4)	80.09 (19.8)	0.287
Etiology of liver disease, *n* (%)			0.774
Alcohol	24 (51.1)	24 (44.4)	
Hepatitis B virus	1 (2.1)	3 (5.6)	
Hepatitis C virus	5 (10.6)	2 (3.7)	
Autoimmune hepatitis	3 (6.4)	4 (7.4)	
Nonalcoholic steatohepatitis	2 (4.2)	1 (1.9)	
Primary biliary cirrhosis	0 (0)	1 (1.9)	
Primary sclerosing cholangitis	3 (6.3)	5 (9.3)	
Hemochromatosis	1 (2.1)	2 (3.7)	
Cryptogenic	4 (8.4)	7 (13.0)	
Drug toxicity	3 (6.3)	2 (3.7)	
Other	1 (2.1)	3 (5.6)	
Hepatorenal syndrome, *n* (%)	22 (46.8)	19 (35.2)	0.235
Hepatic encephalopathy, *n* (%), grade ≥ 2	9 (19.2)	13 (24.1)	0.786
Ascites, *n* (%)			
None	10 (21.3)	12 (22.2)	
Moderate	10 (21.3)	18 (33.3)	
Severe	26 (55.3)	24 (44.4)	0.383
Pulse oximetric saturation (%)	95.06 (0.4)	95.35 (2.1)	0.667
Mean arterial pressure (mm Hg)	90.00 (15.5)	87.94 (15.9)	0.569
Heart rate (beats/min)	79.71 (12.4)	83.22 (15.5)	0.438
Laboratory data			
Bilirubin (mg/dL)	22.80 (9.3)	19.49 (5.7)	**0.004**
Serum sodium (mmol/L)	135.17 (6.2)	133.46 (5.4)	0.116
Serum potassium (mmol/L)	3.98 (0.6)	4.17 (0.7)	0.283
Creatinine (mg/dL)	1.91 (1.5)	1.74 (1.3)	0.427
Blood urea nitrogen (mg/dL)	39.50 (28.5)	32.30 (22.6)	0.262
White blood count (10^3 cells/μL)	10.78 (6.0)	11.94 (7.2)	0.412
Hemoglobin (g/dL)	10.72 (1.8)	10.74 (1.9)	0.963
Platelets (10^3 cells/μL)	121.70 (70.1)	129.54 (70.4)	0.474
Albumin (g/dL)	3.18 (0.6)	2.84 (0.6)	0.064
Quick (%)	49.49 (21.8)	43.15 (16.0)	0.416
International normalized ratio	1.83 (0.61)	1.98 (0.9)	0.487

(*Continued*)

TABLE 1. (*Continued*). Baseline Patient Characteristics: Comparison of Molecular Adsorbent Recirculating System and Standard Medical Treatment

Parameter	Molecular Adsorbent Recirculating System (*n* = 47)	Standard Medical Treatment (*n* = 54)	*p*
Model of End-Stage Liver Disease score	29.19 (6.9)	28.37 (7.0)	0.406
> 20, *n* (%)	41 (87.2)	51 (94.4)	
> 25, *n* (%)	30 (63.8)	30 (55.6)	
> 30, *n* (%)	18 (38.3)	18 (33.3)	
CLIF Consortium score system			
Organ failure subscore, *n* (%)			
Liver, subscore = 3	47 (100)	54 (100)	0.999
Kidney, subscore ≥ 2	15 (31.9)	16 (29.6)	0.999
Brain, subscore = 3	2 (4.3)	5 (9.3)	0.453
Coagulation, subscore = 3	8 (17.0)	9 (16.7)	0.999
Circulatory, subscore = 3	0 (0)	0 (0)	–
Respiratory, subscore = 3	0 (0)	0 (0)	–
ACLF grade			
1	26 (55.3)	32 (59.3)	0.413
2	17 (36.2)	14 (25.9)	
3	4 (8.5)	8 (14.8)	
CLIF-C ACLF score	47.63 (7.4)	47.97 (9.7)	0.610
Calculated 28-d mortality	25.66 (15.6)	28.63 (19.1)	0.610

ACLF = acute-on-chronic liver failure, CLIF = chronic liver failure.
Patient baseline characteristics are shown as the number of patients (%) or mean ± SD.
Boldface values were considered as significant ($p < 0.05$).

CI = 1.54–166.08; $p = 0.020$) are at high risk (**Table 3**). In particular, these patients had a significant benefit in 14-day mortality if being treated with MARS therapy (Table 2).

The corresponding Kaplan-Meier estimates of the 28-day survival rate showed almost no difference in the outcome of patients with single organ failure (ACLF grade 1; Fig. 1). However, in patients with ACLF grade greater than or equal to 2, MARS treatment was associated with an improved the 28-day mortality rate ($p = 0.022$).

Finally, all of the clinically relevant variables that were significant for the 14-day mortality rate were concurrently subjected to a decision tree analysis with recursive partitioning. Using this approach, we recursively identified a sequence of two split variables (ACLF grade, 1 vs ≥2) and a treatment regimen (MARS vs SMT) that best separated patient subgroups with different prognoses (**Fig. 2**).

RELIEF Cohort

A comparison of our cohort with the RELIEF population revealed important differences (**Supplementary** Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/C680). In detail, concerning the CLIF-C-OF subscores, patients in the RELIEF study (PP population, $n = 156$) presented with lower hyperbilirubinemia levels (liver subscore < 3; 14.1% in the RELIEF study vs 0% in our cohort; $p < 0.001$) but a trend to higher creatinine values (kidney subscore ≥ 2; 37.2% vs 30.7% in our cohort; $p = 0.286$) and increased encephalopathy (brain subscore = 3; 19.9% in the RELIEF study vs 6.9%; $p = 0.004$). Patients with INR values greater than 2.3 were excluded in the RELIEF trial but not in our study. In addition, our cohort was restricted to patients with stable pulmonary function, whereas 9.0% of the patients in the PP population had severe respiratory problems (respiratory subscore = 3; $p = 0.002$). This finding resulted in a broader distribution of ACLF grades in the RELIEF trial (eight patients [5.1%] with no ACLF and six patients [3.8%] with ACLF grade ≥ 4), whereas ACLF was limited to grades 1–3 in our cohort.

While in the RELIEF trial, no significant differences were found in mortality, analysis according to ACLF grade showed the same tendency like the significant difference in the Muenster cohort. In detail, patients with an increased ACLF grade benefit from MARS on 14-day mortality (22.6% in the MARS group vs 38.9% in the SMT group, $p = 0.151$; **Supplementary** Fig. 1, Supplemental Digital Content 1, http://links.lww.com/CCM/C680). Oppositely, application of MARS was unfavorable in patients with ACLF grade less than 2 (14-day mortality rate of 20.0% in the MARS group vs 10.2% in the SMT group;

TABLE 2. Mortality at Predefined Time Points, Cause of Death, and Mortality According to the Predetermined Subgroups (14-D Mortality)

Parameter	Molecular Adsorbent Recirculating System (*n* = 47)	Standard Medical Treatment (*n* = 54)	*p*
Mortality (*n*, %)			
Day 7	0 (0.0)	10 (18.5)	0.008
Day 14	3 (6.4)	15 (27.8)	0.020
Day 21	7 (14.9)	19 (35.2)	0.080
Day 28	10 (21.3)	21 (38.9)	0.224
Causes of death (day 28)			
Hemorrhage/bleeding	2 (20.0)	3 (14.3)	0.686
Infection/sepsis	5 (50.0)	10 (47.6)	0.901
Neurologic disorder (HE)	0 (0.0)	2 (9.5)	0.313
Cardio respiratory disorder	3 (30.0)	6 (28.6)	0.935
Subgroup analysis			
Hepatorenal syndrome	3/22 (13.6)	8/19 (42.1)	0.040
HE grade ≥ 2	2/9 (22.2)	8/13 (61.5)	0.069
Model of End-Stage Liver Disease score > 20	3/41 (7.3)	15/51 (29.4)	0.008
CLIF-C ACLF score > 47.5	2/22 (9.1)	10/27 (37.0)	0.024
CLIF-organ failure subscore			
Kidney, subscore ≥ 2	1/15 (6.7)	8/16 (50.0)	0.008
Brain, subscore ≥ 2	3/31 (9.7)	14/38 (36.8)	0.009
Coagulation, subscore ≥ 2	2/19 (10.5)	8/16 (50.0)	0.010
Circulatory, subscore ≥ 2	0/3 (0.0)	2/4 (50.0)	0.147
Respiratory, subscore ≥ 2	1/2 (50.0)	1/2 (50.0)	–
CLIF-ACLF grade ≥2	2/21 (9.5)	11/22 (50.0)	0.004

ACLF = acute-on-chronic liver failure, CLIF = chronic liver failure, HE = hepatic encephalopathy.

$p = 0.193$). Although these results are not statistically significant, it is remarkable that this splitting according ACLF grade seems to be a capable tool to discriminate between patients benefitting from MARS (compared with SMT). A decision tree with the identical split variables as developed in our cohort was also computed for the PP population of the RELIEF trial and is displayed in **Supplementary** Fig**ure** 2 (Supplemental Digital Content 1, http://links.lww.com/CCM/C680).

However, none of the individual organ failures was found to be significantly associated with the observed differences in 14-day mortality rate (**Supplementary** Table 2, Supplemental Digital Content 1, http://links.lww.com/CCM/C680).

DISCUSSION

Results of this analysis demonstrate that MARS therapy is associated with a reduced short-term mortality in a large cohort of patients with ACLF. However, this effect is temporary and deteriorates over time after discontinuing this therapy. By adopting the CLIF-organ failure scoring system, we could identify subgroups of patients benefitting from MARS treatments, whereas others do not.

Over the last few years, a new diagnostic score, the CLIF-C ACLF score has been developed for classification and prognostic assessment of patients with ACLF (13). It measures both hepatic and extrahepatic organ dysfunction, and it discriminates significantly better between survivors and nonsurvivors than did MELD and the Child-Pugh systems, which underestimated the risk of death in ACLF. This progress has helped to improve the identification of patients in need of multiple organ supportive care, but despite these improvements, the prognoses of patients with ACLF remain poor (2).

In our study, application of MARS was safe with adverse events being rare, as also found in some other studies (5, 6). However, our results indicate that patients with a low ACLF grade do not benefit from the addition of MARS to SMT. In the RELIEF trial, SMT was even more favorable than MARS.

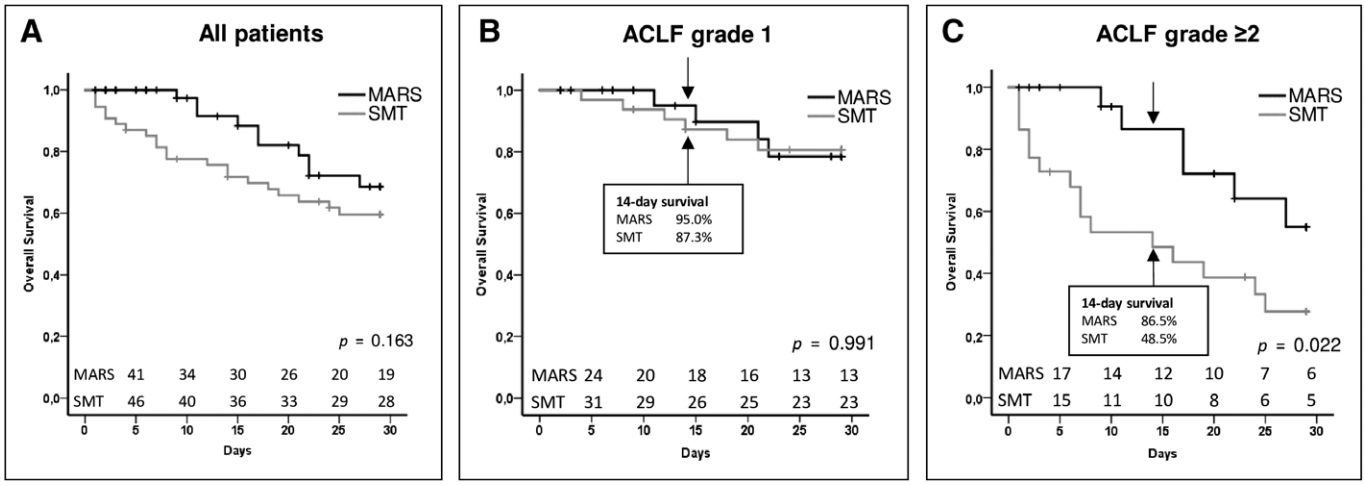

Figure 1. Cumulative probability of the 28-d transplant-free survival rate. **A**, Cumulative probability of 28-d transplant-free survival rate for the entire cohort. **B** and **C**, Influence of the chronic liver failure (CLIF)-acute-on-chronic liver failure (ACLF) grade on the 28-d mortality rate: Subgroups classified based on CLIF-ACLF grade are depicted. In addition, the estimated probability of 14-d survival is displayed. *Black line* indicates molecular adsorbent recirculating system (MARS) therapy plus standard medical treatment (SMT). *Gray line* indicates SMT alone.

TABLE 3. Multivariate Cox Regression Model Evaluating Independent Risk Factors for 14-D Mortality

	All patients ($n = 101$)		
Parameter	**Hazard Ratio**	**95% CI**	***p***
Bilirubin (per point increase)	1.03	0.94–1.14	0.500
Molecular adsorbent recirculating system (vs standard medical treatment)	0.17	0.05–0.60	**0.006**
Acute-on-chronic liver failure			**< 0.001**[a]
Grade 2 (vs 1)	1.45	0.40–5.28	0.575
Grade 3 (vs 1)	11.29	3.10–41.06	**< 0.001**
Chronic liver failure-organ failure			
Liver			
Subscore 3	–	–	–
Kidney			0.167[a]
Subscore 2 (vs 1)	2.49	0.75–8.26	0.136
Subscore 3 (vs 1)	3.80	0.76–19.00	0.104
Brain			0.051[a]
Subscore 2 (vs 1)	5.29	0.66–42.18	0.116
Subscore 3 (vs 1)	16.00	1.54–166.08	**0.020**
Coagulation			0.774[a]
Subscore 2 (vs 1)	1.78	0.36–8.75	0.479
Subscore 3 (vs 1)	1.42	0.22–9.07	0.709
Circulatory			
Subscore 2 (vs 1)	3.65	0.70–19.09	0.126
Respiratory			
Subscore 2 (vs 1)	5.35	0.59–48.48	0.136

ACLF = acute-on-chronic liver failure.

[a]*p* value for the whole category, the other *p* values indicate comparisons between the first subcategory and the subcategory mentioned in the same line.

All patients in our cohort fullfilled this variable (Liver Subscore 3). Therefore a multivariate Cox regression model was not possible. Boldface values were considered as significant ($p < 0.05$).

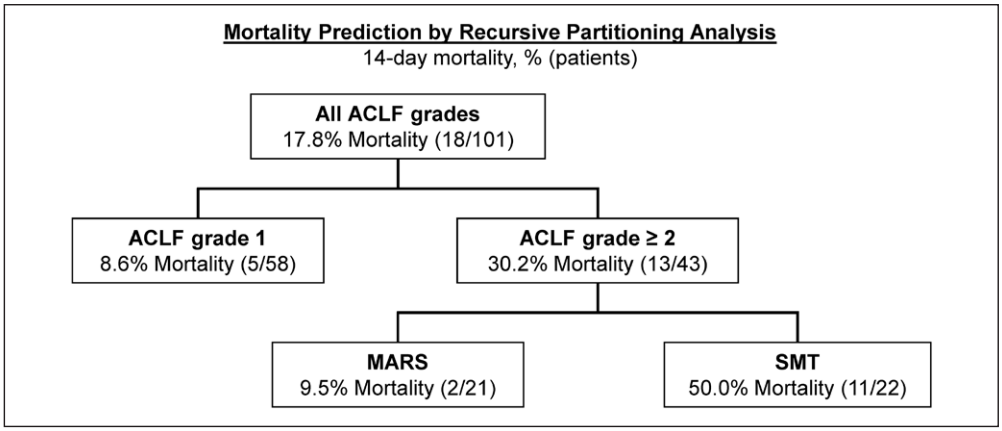

Figure 2. Prediction of the 14-d mortality rate via a recursive partitioning analysis. Acute-on-chronic liver failure (ACLF) grade (1 vs ≥ 2) and treatment mode (molecular adsorbent recirculating system [MARS] vs standard medical treatment [SMT]) served as split variables ($p < 0.05$).

This is in accordance with results of a study by Gustot et al (16), who found these patients to have a lower rate of worsening of ACLF and a low-to-moderate 28-day transplant-free mortality. Therefore, patients with a low ACLF grade should be stabilized using SMT alone to provide them with a chance of liver recovery. By contrast, ACLF grades 2 and 3 are associated with a lower probability of improvement and resolution of ACLF (16). Especially, these patients require extensive clinical resources and might benefit from MARS dialysis. MARS therapy in this subgroup was associated with a reduction in 14-day mortality rate (from 38.9% to 22.6%; $p = 0.022$). Since high MELD scores are correlated with an increased CLIF-ACLF grade, our results corroborate the findings of a previous study reporting a trend of a better 2-week transplant-free survival rate among patients with MELD scores greater than or equal to 30 who received MARS (5). Although the effects were temporary, this gain in time might enable patients to obtain liver transplants or achieve liver recovery.

The results of the current study seem to contradict those from the RELIEF trial, in which MARS did not decrease the mortality rate at day 28. How MARS treatment resulted in improved biochemical parameters and the resolution of encephalopathy but not significantly improves survival remains unclear. One relevant aspect highlighted in the trial was the difficulty of distinguishing ACLF from chronic decompensated liver disease, two entities that have different natural histories and prognoses. With the help of the CLIF-C criteria, distinction of both entities has been facilitated. Retrospectively applying the CLIF-C criteria of ACLF to the RELIEF cohort revealed that not all included patients would have fulfilled the CLIF-ACLF criterion. Thus, the ACLF grade was heterogeneously distributed across the trial. Rather than questioning the findings of the RELIEF trial, the aim of our study is to provide an additional approach for identifying patients.

The results of this study indicate that, in addition to the CLIF-ACLF grade, the specific type of organ failure might be relevant. An analysis of our cohort identified impairments in kidney function, brain function, or coagulation as predictors of short-term survival. Thus, these important factors should be evaluated before patient selection to identify potential MARS responders. Especially, aggravation of HE was the only concomitant organ failure with an independent risk for 14-day mortality. This observation corroborates results from previous studies that have demonstrated the beneficial effects of MARS in a selected group of patients with HE (3, 5) or HRS (4). Notably, patients with additional kidney dysfunction, HRS, or both have a high-mortality rate (2).

In ACLF, a variety of toxins accumulate as a result of impaired hepatic function and clearance (e.g., ammonia, toxic bile acids, inflammatory cytokines, aromatic amino acids, vasoactive substances, and endotoxines), which have been linked to the development of HE or circulatory/renal dysfunction (17, 18). MARS has the ability to remove these toxic substances and restore the albumin-binding capacity (19, 20). In addition, MARS improves the portal and systemic hemodynamics resulting in an improved organ perfusion (6, 21, 22). Although not further analyzed in this study, the therapeutic effects of these changes can result in an improvement of different organ systems (renal function, encephalopathy, and liver function) (3, 5, 11, 23) and might be the rationale for critical ill patients with multiple organ failure to benefit from MARS.

We hypothesize that the benefits of MARS treatment depend on the type of affected CLIF-C-OF system. For example, severe respiratory failure might have a completely different effect on the outcomes and responses to MARS treatment than an asymptomatic coagulation failure (both classified as CLIF-C-OF subscore = 3). Our analyzed cohort and the RELIEF cohort were imbalanced regarding the different organ failures as patients with severe respiratory or circulatory failure (CLIF-C-OF subscores = 3) were underrepresented. However, these special subgroups are also of high interest as these patients are at high risk of death. In our cohort, patients with coagulopathies especially benefited from MARS treatment. Since the RELIEF trial excluded patients with an INR greater than 2.3 and was performed prior to publication of the CLIF-C-OF system, future studies are needed to analyze the effect of different types of organ failure on patient outcomes.

Certain limitations of the current study deserve discussion. Allocation to MARS therapy at our center was not random and may have caused a potential selection bias. In addition, this analysis was retrospective and can only provide associations resulting in the hypothesis that selected ACLF patients may benefit from MARS. However, we attempted to balance this potential limitation by testing our results in the PP population of the randomized RELIEF trial. Patients' characteristics of both cohorts showed important differences. By retrospective

adoption of the current CLIF-scoring system, we tried to compare equal subgroups and partially compensated for this limitation. But general recommendations for/against MARS therapy deserve further prospective randomized trials.

The results of this study suggest that MARS treatment has a beneficial effect on the short-term survival of selected patients with ACLF. In particular, patients with CLIF-ACLF grades 2–3 were identified as a potential target population for MARS therapy bridging to liver recovery or transplantation. These findings should encourage new trials to analyze the role of MARS therapy in patients with different types of organ failure.

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