Journal of Gastroenterology and Hepatology

WILEY

JGHF Journal of Gastroenterology and Hepatology Foundation

ORIGINAL ARTICLE - HEPATOLOGY (CLINICAL)

Artificial Liver Support System Improves One-Year Prognosis of Patients With Hepatitis B Virus-Associated Acute-on-Chronic Liver Failure

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Received: 24 July 2024 | **Revised:** 10 December 2024 | **Accepted:** 4 January 2025

Funding: This study was supported by the National Science and Technology Major Project (2022YFC2304800 and 2018ZX10723203) and the National Natural Science Foundation of China (82370614 and 82300698).

Keywords: double plasma molecular adsorption system | liver failure | one-year mortality | plasma exchange | short-term mortality

ABSTRACT

Background & Aims: Acute-on-chronic liver failure (ACLF) is a complex syndrome with limited treatment options. This study aims to investigate the impact of artificial liver support system (ALSS) on the one-year prognosis of patients with Hepatitis B virus (HBV)-associated ACLF.

Method: A retrospective study was conducted on 239 patients with HBV-ACLF in Nanfang Hospital from January 2016 to June 2021. Patients were divided into the ALSS group ($n = 103$) and the Standard Medical Therapy (SMT group, $n = 136$). Demographic, clinical, and laboratory data were collected before the first ALSS treatment for patients in ALSS group, while baseline data were collected in SMT group. According to receiving different ALSS modes, patients in ALSS group were divided into plasma exchange (PE) group and non-PE group.

Result: The 12-week and 1-year liver transplant (LT) free survival rates in the ALSS group were significantly higher than that in the SMT group (65.05% vs 52.21%, $p = 0.0011$; 63.11% vs. 48.53%, $p = 0.0006$). ALSS therapy was the independent predictive factors associated with 12-week and 1-year mortality (hazard ratio, HR: 0.59, $p = 0.04$, and HR: 0.54, $p = 0.01$). Comparatively more ALSS-related complications were observed in PE group. After Propensity Score Matching, the 12-week and 1-year LT-free survival rates between PE and non-PE group were similar (88% vs. 80%, $p = 0.227$, 88% vs. 80%, $p = 0.227$).

Conclusion: ALSS therapy is a safe and effective treatment for HBV-ACLF. ALSS improves 1-year prognosis of patients with HBV-ACLF.

1 | Introduction

Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterized by acute deterioration of liver function, extrahepatic organ failure and high short-term mortality on the basis of chronic liver disease. The CANONIC study carried out by European associations for the study of liver disease (EASL) showed that the overall incidence rate of ACLF was 33.9%, and the 90-day mortality was 51.2% [1]. The COSSH study in China redefined hepatitis B virus-related ACLF, and the results showed

that the short-term mortality rate of HBV-ACLF was similar to that of CANONIC study [2].

So far, liver transplantation (LT) is the only proven effective treatment that can improve the prognosis of patients with ACLF. However, due to the shortage of liver donors and excessive economic burden, LT is less accessible to most of patients with ACLF. A large collaborative study showed 24% patients with ACLF on waitlist for LT in Europe died in 1 year [3]. Therefore, it is necessary to explore more treatment methods to maintain liver function, prevent multiple organ failures and bridge to LT.

Artificial Liver Support System (ALSS) had been developed as a treatment option since 40 years ago [4]. Previous studies have shown that ALSS is well-tolerated and may improve short-term LT-free survival rates for acute liver failure (ALF) and patients with ACLF [5–8]. However, there are few studies regarding the efficacy of ALSS treatment to improve 1-year prognosis of patients with HBV-ACLF.

This study aims to evaluate the safety and efficacy of ALSS in improving 12-week and 1-year prognosis of patients with HBV-ACLF.

TABLE 1 | The clinical baseline characteristics in participants of SMT group and ALSS group.

Parameters	ALSS (n = 103)	SMT (n = 136)	All (*n* = 239)	*p*
Age, years	46.64 ± 10.69	48.51 ± 13.11	47.7 ± 12.14	0.24
Sex				0.23
Male (%)	87 (84.47%)	122 (89.71%)	209 (87.45%)	
Cirrhosis				0.09
No	56 (54.37%)	88 (64.71%)	144 (60.3%)	
Yes	45 (43.69%)	42 (30.88%)	87 (36.4%)	
Uncertain	2 (1.94%)	6 (4.41%)	8 (3.3%)	
HBVDNa, IU/mL	8.08 + E04 (2.27 + E03, 2.82 + E06)	3.89 + E04 (1.35 + E03, 1.53 + E06)	4.76 + E04 (1.76 + E03, 1.92 + E06)	0.372
ALT, U/L	108 (67, 366)	190.5 68, 630.5)	154 (68, 491)	0.046
AST, U/L	135 (86, 232)	186.5 (101.25, 417)	157 (92, 350)	0.025
TBIL, mg/dL	24.03 (18.48, 28.63)	22.29 (17.49, 30.25)	23.37 (17.96, 30.01)	0.508
ALB, g/L	33.60 (31.2, 38)	32.8 (29.23, 36.95)	33.2 (29.7, 37.2)	0.049
Na, mmol/L	137 (134, 140)	137 (134, 140)	137 (134, 140)	0.83
CR, mg/dL	0.78 (0.69, 0.94)	0.84 (0.72, 1.09)	0.8 (0.69, 1.03)	0.028
INR	2.23 (1.89, 2.93)	2.17 (1.78, 2.87)	2.19 (1.83, 2.9)	0.505
D-dimer	2.56 (1.23, 4.64)	3.15 (1.37, 6.26)	2.96 (1.34, 5.38)	0.181
White blood cell, 10^9/L	7.37 (5.54 9.14)	7.32 (5.99, 10.27)	7.32 (5.65, 9.77)	0.241
Hemoglobin, g/L	114.11 ± 19.67	115.37 ± 22.29	114.82 ± 21.16	0.65
Platelet, 10^9/L	97 (71, 140)	108.5 (75.5, 150)	104 (74, 147)	0.212
MELD	24.14 (22.91, 28.93)	25.89 (22.18, 30.68)	25.33 (22.64, 29.76)	0.35
MELD-Na	26.9 (23.96, 29.53)	27.18 (23.85, 31.35)	26.99 (23.92, 30.47)	0.402
EASL ACLF				0.504
NO	59 (57.28%)	72 (52.94%)	131 (54.81%)	
YES	44 (42.72%)	64 (47.06%)	108 (45.19%)	
ACLF-1	1 (2.27%)	3 (4.69%)	4 (3.7%)	
ACLF-2	32 (72.73%)	28 (43.75%)	60 (55.56%)	
ACLF-3	11 (25%)	33 (51.56%)	44 (40.74%)	

Note: Independent sample *t*-test and Mann–Whitney U test were used to compare between-group differences in continuous variables. Data are mean ± standard deviation, medians (interquartile range); categorical variables are frequency (percentage) and were compared by the chi-square tests.
Abbreviations: TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; INR, international normalized ratio; Cr, creatinine; Na, serum sodium; MELD, model for end-stage liver disease score; MELD-Na, Model for End Stage Liver Disease-Sodium score; EASL ACLF, European associations for the study of liver disease of acute-on-chronic liver failure; ACLF, acute-on-chronic liver failure; ALSS, Artificial Liver Support System; SMT, Standard Medical Therapy.

2 | Methods and Patients

2.1 | Study Design and Patients

This is a single center, retrospective, observational study. ACLF inpatients at Nanfang Hospital were screened from January 2016 to June 2021. Only patients who met the COSSH criteria are eligible enrolled in this study [2]: 1) age > 18 years old; 2) chronic hepatitis B virus infection; 3) total bilirubin (TBIL) ≥ 12 mg/dL and international normalized ratio (INR) ≥ 1.5. The exclusion criteria are: 1) chronic extrahepatic organs failure; 2) malignancy; 3) biliary obstructive disease; 4) pregnancy; 5) HIV infection; 6) not suitable to participate in this study judging by the researchers.

Three hundred and ninety-five patients with ACLF were consecutively screened and 239 patients were enrolled in this study (Figure S1). Patients were divided into the ALSS group ($n = 103$) and the Standard Medical Therapy (SMT) group ($n = 136$).

ALSS group: Except for SMT, all patients were treated with ALSS, including PE and non-PE modes. When PE was performed, whole blood was centrifuged at a certain speed to separate plasma and blood cells. Next, discarded the plasma from patients and then mixed fresh plasma with blood cells in an equal amount of exchange solution before transfusion back into patients. The exchange volume of plasma was 3000 mL. The non-PE mode was Double Plasma Molecular Adsorption System (DPMAS) or DPMAS combined with a low volume of PE (less than 3000 mL plasma per time). DPMAS is an extracorporeal procedure that combines an HA330-II hemoperfusion cartridge (Jafron, Zhuhai City, China) with a BS330 plasma bilirubin adsorption column (Jafron, Zhuhai City, China) [9]. During the procedure, toxic plasma was separated and cleansed by perfusion over two absorbers, and the final cleansed plasma was then returned to patients.

During ALSS treatments, unfractionated heparin sodium was used for anticoagulation, with the specific dosage tailored to the coagulation status of each individual patient. The frequency of ALSS treatments was mainly determined by the patient's condition and the assessment of treatment effectiveness, generally one to two times per week, with an average total of two to five times per patient. Before 2019, PE mode is the only choice in Nanfang Hospital. Since 2019, patients with prothrombin time (PT) ≥ 30 s had been received ALSS with PE mode when plasma supply was sufficient. However, during periods of extreme plasma shortage, such as during the COVID-19 pandemic, we had to use the combination mode of low-dose plasma PE with DPMAS for ALSS treatment. The specific amount of plasma used was based on the maximum standard available from the blood transfusion department at the time. For patients with PT < 30 s, we generally applied only 1000–1500 mL of plasma per treatment session for PE, combined with DPMAS therapy, though the total plasma volume was still limited by the maximum standard available from the blood transfusion department at the time.

This research protocol complies with the ethical guidelines of the Helsinki Declaration of 1975 and has been approved by the Ethics Committee of Nanfang Hospital, Southern Medical University. Ethics Committee Approval Number: NFEC-2020-143.

2.2 | Follow-Up and Data Collection

The baseline time point was within 24–48 h before the first ALSS treatment in ALSS group and within 24–48 h after admission in SMT group.

In addition, all patients were followed up for 1 year through phone calls or WeChat, which is the most widely used social media in China. The primary endpoint was the cumulative LT-free

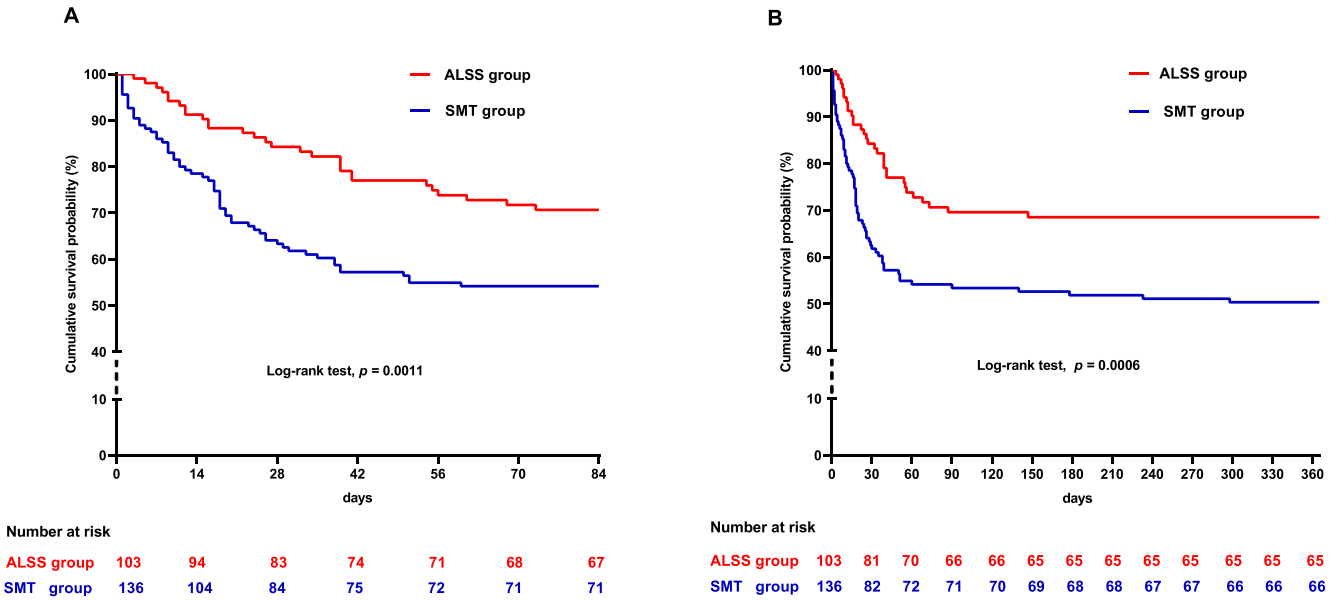

FIGURE 1 | Kaplan–Meier survival analysis in the SMT and ALSS groups. (A) Compared to the SMT group, the patients with ALSS therapy had a higher 12-week LT-free survival rate (65.05% vs. 52.21%, $p = 0.0011$). (B) Compared to the SMT group, the patients with ALSS therapy also had a higher 1-year survival rate (63.11% vs. 48.53%, $p = 0.0006$).

survival rates at 1 year, and the secondary endpoints were the cumulative LT-free survival rates at week 12 and the safety of ALSS. No patients were lost to follow-up in this study.

The demographic data, clinical parameters, and laboratory biochemical data were recorded at baseline. ALSS treatment details, including frequency, patterns, plasma volume, and adverse events, were recorded at each time of treatment.

2.3 | Statistical Analysis

Normally distributed continuous variables were expressed as mean ± standard deviation, whereas abnormally distributed continuous variables were expressed as median (interquartile range). Categorical data were presented as count and percentage (%). Comparisons between two continuous variables were carried out using Mann–Whitney U test. Categorical variables

TABLE 2 | The independent predictive factors associated with 1-year LT-free mortality.

	Univariate		Multivariate	
Parameters	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
ALSS				
No	Reference		Reference	
Yes	0.51 (0.34 to 0.79)	0.002	0.54 (0.33 to 0.86)	0.01
Age, years	1.05 (1.03 to 1.07)	< 0.001	1.03 (1.01 to 1.05)	0.001
Sex				
Male	Reference			
Female		0.83		
Cirrhosis		0.02		
No	Reference			0.12
Yes	1.27 (0.84 to 1.93)	0.25		0.65
Uncertain	3.39 (1.46 to 7.93)	0.01		0.04
HBVDNa, IU/mL		0.25		
ALT, U/L		0.18		
AST, U/L		0.57		
TBIL, mg/dL	1.00 (1.00 to 1.01)	< 0.001		
ALB, g/L		0.66		
Na, mmol/L		0.84		
CR, mg/dL	1.01 (1.00 to 1.01)	< 0.001		
INR	2 (1.67 to 2.39)	< 0.001		
D-dimer	1.13 (1.08 to 1.19)	< 0.001	1.07 (1.00 to 1.13)	0.05
White blood cell, 10^9/L	1.13 (1.1 to 1.17)	< 0.001	1.08 (1.03 to 1.12)	0.001
Hemoglobin, g/L	0.99 (0.98 to 1.00)	0.005		0.53
Platelet, 10^9/L		0.1		
EASL ACLF				
NO	Reference			
YES	5.79 (3.64 to 9.22)	< 0.001	2.68 (1.55 to 4.65)	< 0.001
MELD	1.2 (1.16 to 1.24)	< 0.001		
MELD-Na	1.2 (1.16 to 1.25)	< 0.001	1.11 (1.06 to 1.16)	< 0.001

Note: Univariate and multivariate Cox proportional-hazards model were used to investigate the independent variable associated to LT-free survival. Spearman's correlation coefficient was used to check the correlations among independent variables.
Abbreviations: HR, hazard ratio; CI, confidence interval; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; INR, international normalized ratio; Cr, creatinine; Na, serum sodium; MELD, model for end-stage liver disease score; MELD-Na, Model for End Stage Liver Disease-Sodium score; EASL ACLF, European associations for the study of liver disease of acute-on-chronic liver failure; ACLF, acute-on-chronic liver failure; ALSS, artificial liver support system.

were presented as absolute frequencies and percentage and were compared by using Chi-square test or Fisher's exact test. Univariate and multivariate Cox proportional-hazards model were used to investigate the independent variable associated to LT-free survival rates. The comparison of survival rates were analyzed using Kaplan–Meier method followed by the log-rank test. Propensity score matching (PSM) procedure was used to select paired cases from two groups while Model for End-stage Liver Disease (MELD) score was controlled. Statistical analyses were conducted using IBM SPSS version 25 and software R version 4.3.0.

3 | Results

3.1 | Baseline Characteristics and Clinical Outcomes in Patients of SMT Group and ALSS Group

A total of 239 patients with HBV-ACLF were included in this study, with 209 males (87.45%) and 30 females (12.55%). Among them, 103 patients received ALSS treatment, and the remaining 136 patients were defined as SMT group, 60.3% patients without cirrhosis. The baseline characteristics were comparable between these two groups, except the levels of albumin were higher in the ALSS group and the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine (CR) were higher in the SMT group (Table 1). Comparing to the SMT group, the patients with ALSS therapy had a higher 12-week and 1-year liver transplant (LT) free survival rates (65.05% vs. 52.21%, $p=0.0011$; 63.11% vs. 48.53%, $p=0.0006$, respectively; Figure 1).

3.2 | Independent Predictive Factors Associated With 12-Week LT-Free Mortality

Table S1 indicated the independent variables to patient's LT-free mortality at week 12. It seemed that patients with older age (HR: 1.04, $p<0.001$), higher levels of white blood cell (WBC) (HR: 1.09, $p<0.001$), MELD-Na (HR: 1.12, $p<0.001$), and met EASL ACLF diagnostic criteria (HR: 2.39, $p=0.003$) were associated to higher risk of death outcome at week 12. However, ALSS treatment was the only protective factor for the mortality risk of 12 weeks (HR: 0.59, $p=0.04$).

3.3 | Independent Predictive Factors Associated With 1-Year LT-Free Mortality

Table 2 indicated the independent variables to patient's LT-free mortality at 1 year. It seemed that patients with older age (HR: 1.03, $p=0.001$), higher levels of WBC (HR: 1.08, $p=0.001$), MELD-Na (HR: 1.11, $p<0.001$), and met EASL ACLF diagnostic criteria (HR: 2.68, $p<0.001$) were associated to higher risk of death outcome at 1 year. Similar with week 12, ALSS treatment was the only protective factor for the mortality risk of 1 year (HR: 0.54, $p=0.01$).

3.4 | ALSS Treatment was Associated With a Lower Risk of All-Cause Mortality

Compared to the SMT group, the individuals with ALSS therapy had a lower 12-week and 1-year mortality (34.95% vs. 47.79%, $p=0.0011$; 36.89% vs. 51.47%, $p=0.0006$). Using a Cox model with adjustment for baseline differences, ALSS treatment was associated with lower mortality compared to SMT treatment group during 12-week (Table S1) and 1-year (Table 2) follow-up (aHR 0.59, 95% CI, 0.36 to 0.97; $p=0.04$ and aHR 0.54, 95% CI, 0.33 to 0.86; $p=0.01$).

3.5 | Details About the ALSS Treatment

The median times of artificial liver was two times (Table 3). Average plasma dosage is 3000 mL per time in PE group and 800 mL per time in non-PE group. Comparatively more ALSS-related complications were observed in PE group (34.62% vs. 12%, $p=0.04$). Overall, the complications include 13 hepatic encephalopathy, four infection, seven allergic reaction, one tetany, and two other complications. There were three patients combined with two or more kinds of adverse reactions.

TABLE 3 | Details about the ALSS treatment.

Parameters	Type of ALSS		
	PE ($n=78$)	Non-PE ($n=25$)	p
Times of ALSS	2 (1, 3)	2 (1, 3)	0.99
1	24 (30.77%)	8 (32%)	0.99
2	33 (42.31%)	10 (40%)	
3	13 (16.67%)	4 (16%)	
4	8 (10.26%)	3 (12%)	
Average plasma dosage/time(ml)	3000	800 (500, 1250)	
ALSS related complications			
No	51 (65.38%)	22 (88%)	0.04
Yes	27 (34.62%)	3 (12%)	
Hepatic encephalopathy	12 (15.38%)	1 (4%)	0.33
Infection	3 (3.85%)	1 (4%)	
Allergic reaction	7 (8.97%)	0	
Tetany	1 (1.28%)	0	
Others	2 (2.56%)	0	
Two or more kinds of adverse reactions	2 (2.56%)	1 (4%)	

Note: Independent sample t-test and Mann–Whitney U test were used to compare between-group differences in continuous variables. Data are mean ± standard deviation, medians (interquartile range); categorical variables are frequency (percentage) and were compared by the chi-square tests.
Abbreviations: ALSS, artificial liver support system; PE, plasma exchange.

3.6 | Clinical Characteristics of Different Clinical Outcomes in ALSS Group

During 1-year follow-up, 65 (63.11%) patients survived and 38 (36.89%) dead or underwent LT in ALSS group. Table S2 showed clinical characteristics of these two groups of patients. As indicated, patients who survived had lower levels of TBIL, PT, INR, MELD, and MELD-Na. Moreover, fewer patients in survival group met EASL-ACLF criteria or had higher grade of EASL-ACLF and underwent PE treatment. Using a Cox model with adjustment for baseline differences, as indicated in Table 4, it seemed that patients who were older (aHR: 1.04, $p = 0.034$) and had higher levels of WBC (aHR: 1.12, $p = 0.02$) and MELD-Na (aHR: 1.15, $p = 0.001$) were associated to higher risk of LT-free mortality during 1-year follow-up. However, we did not find association between the mode of ALSS and mortality.

TABLE 4 | The independent predictive factors associated with 1-year LT-free mortality of patients in ALSS group.

	Univariate		Multivariate	
Parameters	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age, years	1.05 (1.01 to 1.09)	0.006	1.04 (1.00 to 1.08)	0.034
Sex				
Male	Reference			
Female		0.3		
Cirrhosis		0.236		
No	Reference			
Yes		0.09		
Uncertain		0.692		
HBVDNa, IU/mL		0.132		
ALT, U/L		0.341		
AST, U/L		0.93		
TBIL, mg/dL	1.01 (1.00 to 1.01)	< 0.001		
ALB, g/L		0.6		
Na, mmol/L		0.424		
CR, mg/dL		0.212		
PT, s	1.05 (1.02 to 1.08)	< 0.001		
INR	1.75 (1.27 to 2.41)	0.001		
D-dimer		0.21		
White blood cell, 10^9/L	1.15 (1.06 to 1.25)	0.001	1.12 (1.02 to 1.23)	0.02
Hemoglobin, g/L	0.98 (0.97 to 1.00)	0.042		0.819
Platelet, 10^9/L		0.464		
EASL ACLF				
NO	Reference		Reference	
YES	2.53 (1.32 to 4.86)	0.005		0.128
MELD	1.15 (1.08 to 1.23)	< 0.001		
MELD-Na	1.14 (1.07 to 1.23)	< 0.001	1.15 (1.06 to 1.24)	0.001
Type of ALSS				
PE	Reference			
Non-PE		0.062		

Note: Univariate and multivariate Cox proportional-hazards model were used to investigate the independent variable associated to LT-free survival. Spearman's correlation coefficient was used to check the correlations among independent variables.
Abbreviations: HR, hazard ratio; CI, confidence interval; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; INR, international normalized ratio; Cr, creatinine; Na, serum sodium; MELD, model for end-stage liver disease score; MELD-Na, Model for End Stage Liver Disease-Sodium score; EASL ACLF, European associations for the study of liver disease of acute-on-chronic liver failure; ACLF, acute-on-chronic liver failure; ALSS, artificial liver support system; PE, plasma exchange.

3.7 | The Clinical Characteristics of Two ALSS Groups Patients Before and After PSM

A total of 103 patients had ALSS treatment. Seventy-eight patients received PE treatment and 25 received non-PE treatment. Propensity score matching (PSM) procedure was used to select paired cases from two groups while MELD score were controlled. There was no difference in the survival rates at week 12 and 1 year between the PE and non-PE group after PSM (88% vs. 80%, $p = 0.227$, 88% vs. 80%, $p = 0.227$, Figure 2).

4 | Discussion

The pathogenesis of ACLF is complex and has not been fully elucidated yet. It is usually described based on the PIRO concept [9], including predisposition, injury, response, and organ failure. After excessive systemic inflammatory stage, patients with ACLF enter a state of immune exhaustion or paralysis, and become vulnerable to bacterial infections, ultimately leading to multiple organ failures and death [10,11]. The short-term mortality rate of ACLF is high and correlated with the number of organ failures [1,11]. However, due to the complex mechanism, there are currently no specific and effective therapies for ACLF.

The first LT was conducted in humans 60 years ago. There was no difference of the 1-year survival rates after LT between patients with ACLF with one or two organ failures and patients without ACLF [12,13]. For patients with three or more organ failures, the 1-year post-transplantation survival rate may approach 80% [12–14]; the data in patients without received transplantation was lower than 20% [12,13]. These data provided compelling evidence in favor of transplantation for patients with ACLF [15]. However, in patients with ACLF, difficulties in urgent transplantation assessment, paucity of organ donors, sepsis, circulatory failure and great expense often preclude emergency LT [16]. In this study, only 3% of patients with HBV-ACLF in our center ultimately underwent LT.

ALSS has been widely used, and a large number of clinical studies had shown that it could improve the short-term prognosis of patients with ACLF and bridge to LT effectively [5–8,17–21]. There are many ALSS modes among which PE is the most commonly used. A randomized controlled trial in India demonstrated that standard volume PE improved the prognosis of patients with non-acetaminophen ALF [22]. The 21-day LT-free survival rate in the PE group was 75%, while in the STM group it was only 45% [22]. PE has been one of the recommended ALSS for patients with liver failure in China. PE treatment provides basic substances such as albumin and coagulation factors that are insufficient in liver failure. However, PE treatment requires a large amount of fresh plasma, so it is often limited by insufficient plasma supply. Meanwhile, DPMAS is a relatively new ALSS technology. It uses a blood perfusion device and a bilirubin adsorption column to remove inflammatory cytokines and middle-large molecule toxins, bilirubin and bile acid. Although DPMAS can remove various harmful substances and save a large amount of plasma, it still has adverse effects on coagulation function due to the loss of coagulation factors and the use of anticoagulants during the treatment process. Therefore, combinations of different ALSS modes, like DPMAS and PE, might reduce related complication of DPMAS and cope with the shortage of plasma in clinical setting due to their complementary characters. In recent years, the combination therapy of low volume (1000–1500 mL) PE (LPE) and DPMAS has been widely used in the treatment of patients with HBV-ACLF. Some studies had documented that DPMAS plus PE treatment was more effective in improving TBIL and 28-day survival rate in early stage of HBV-ACLF compared to pure PE treatment [21]. DPMAS with LPE significantly improved the 4-week cumulative survival of early HBV-ACLF and improved the inflammatory response of patients [6].

There was limited research on the impact of ALSS on 1-year LT-free prognosis in patients with HBV-ACLF. Our research showed that the 12-week LT-free survival rate in the ALSS group was 65.05%, significantly higher than that in the SMT group 52.21%.

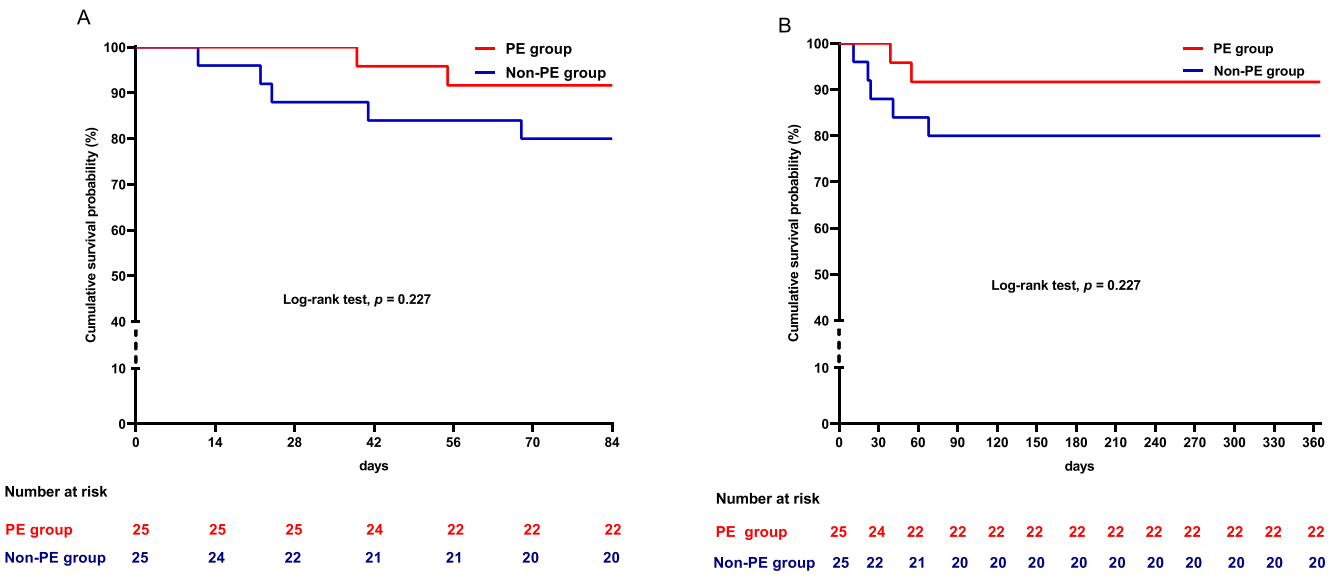

FIGURE 2 | Kaplan–Meier survival analysis in the PE group and Non-PE group. (A) The LT-free survival rate at 12 week 88% (PE group) vs. 80% (Non-PE group), LogRank $p = 0.227$. (B) The LT-free survival rate at 1 year 88% (PE group) vs. 80% (Non-PE group), LogRank $p = 0.227$.

The 1-year LT-free survival rate of the ALSS group was 63.11%, significantly higher than that of the SMT group 48.53%. The results of the 12-week multivariate analysis (Table S1) indicated that older age (HR: 1.04, $p < 0.001$), higher levels of WBC (HR: 1.09, $p < 0.001$), MELD-Na (HR: 1.12, $p < 0.001$) and met EASL ACLF diagnostic criteria (HR: 2.39, $p = 0.003$) are positively correlated with a higher risk of 12-week mortality. ALSS was the only protective factor of 12-week mortality (HR: 0.59, $p = 0.04$). Similarly, the results of the 1-year multivariate analysis (Table 3) indicated that older age (HR: 1.03, $p = 0.001$), higher levels of WBC (HR: 1.08, $p = 0.001$), MELD-Na (HR: 1.11, $p < 0.001$) and met EASL ACLF diagnostic criteria (HR: 2.68, $p < 0.001$) were positively correlated with a higher risk of 1-year mortality. ALSS is also the only protective factor of 1-year mortality (HR: 0.54, $p = 0.01$). It suggested that if ALSS can intervene early, it might win better 1-year survival opportunities for some patients with HBV-ACLF.

There are many modes of ALSS, and the safety and effectiveness of different modes of ALSS also need to be paid attention to. The common adverse reactions of artificial liver are mainly related to the use of plasma, so the proportion of complications related to ALSS was relatively higher in the PE group. The incidence of these adverse reactions in the non-PE group was extremely low and easy to be detected and corrected. After PSM while MELD score were controlled, we found that the 12-week and 1-year LT-free survival rates of the two modes of ALSS groups were similar at 88% (PE group) vs. 80% (non-PE group). This indicated that DPMAS or low volume PE combined with DPMAS might be effective enough compared to PE. In patients with severe hepatic encephalopathy or plasma allergies, or when plasma extremely shortages, DPMAS combined or not combined with low volume PE treatment seemed to be a more ideal choice. In order to clarify which factors might affect the effectiveness of ALSS, furtherly, we conducted a multivariate analysis (Table 4). In the ALSS group, that patients who were older (HR: 1.04, $p = 0.034$) and had higher levels of WBC (HR: 1.12, $p = 0.02$), and MELD-Na (HR: 1.15, $p = 0.001$) were associated with a higher risk of 1-year mortality.

In conclusion, ALSS, such as PE, DPMAS or DPMAS combined with a low volume of PE, is a safe and effective method for the treatment of patients with HBV-ACLF. It can significantly improve 1-year LT-free prognosis of patients with HBV-ACLF.

Conflicts of Interest

The authors declare no conflicts of interest.

Financial Interests

The authors have no relevant financial or non-financial interests to disclose.

References

1. R. Moreau, R. Jalan, P. Gines, et al., "Acute-On-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis," *Gastroenterology* 144, no. 7 (2013): 1426–1437, 1437.e1–9, https://doi.org/10.1053/j.gastro.2013.02.042 Epub 2013 Mar 6. PMID: 23474284, 1437.e9.

2. T. Wu, J. Li, L. Shao, et al., "Chinese Group on the Study of Severe Hepatitis B (COSSH). Development of Diagnostic Criteria and a Prognostic Score for Hepatitis B Virus-Related Acute-On-Chronic Liver Failure," *Gut* 67, no. 12 (2018): 2181–2191, https://doi.org/10.1136/gutjnl-2017-314641 Epub 2017 Sep 19. PMID: 28928275.

3. L. S. Belli, C. Duvoux, T. Artzner, et al., "Liver Transplantation for Patients With Acute-On-Chronic Liver Failure (ACLF) in Europe: Results of the ELITA/EF-CLIF Collaborative Study (ECLIS)," *Journal of Hepatology* 75, no. 3 (2021): 610–622, https://doi.org/10.1016/j.jhep.2021.03.030 Epub 2021 May 2. PMID: 33951535.

4. L. J. Li, Y. M. Zhang, X. L. Liu, et al., "Artificial Liver Support System in China: A Review Over the Last 30 Years," *Therapeutic Apheresis and Dialysis* 10 (2006): 160–167.

5. G. Qin, J.-G. Shao, B. Wang, et al., "Artificial Liver Support System Improves Short and Long-Term Outcomes of Patients With HBV-Associated Acute-On-Chronic Liver Failure: A Single-Center Experience," *Medicine* 93 (2014): e338.

6. W. Xu, S. Zhu, L. Yang, et al., "Safety and Efficacy of Double Plasma Molecular Adsorption System With Sequential low-Volume Plasma Exchange in Intermediate-Stage Hepatitis B Virus-Related Acute-On-Chronic Liver Failure," *Journal of Medical Virology* 95, no. 3 (2023 Mar): e28650, https://doi.org/10.1002/jmv.28650 PMID: 36897008.

7. F. S. Larsen, L. E. Schmidt, C. Bernsmeier, et al., "High-Volume Plasma Exchange in Patients With Acute Liver Failure: An Open Randomised Controlled Trial," *Journal of Hepatology* 64, no. 1 (2016): 69–78.

8. J. J. Chen, J. R. Huang, Q. Yang, et al., "Plasma Exchange-Centered Artificial Liver Support System in Hepatitis B Virus-Related Acute-On-Chronic Liver Failure: A Nationwide Prospective Multicenter Study in China," *Hepatobiliary & Pancreatic Diseases International* 15, no. 3 (2016 Jun): 275–281, https://doi.org/10.1016/s1499-3872(16)60084-x PMID: 27298103.

9. R. Jalan, V. Stadlbauer, S. Sen, L. Cheshire, Y. M. Chang, and R. P. Mookerjee, "Role of Predisposition, Injury, Response and Organ Failure in the Prognosis of Patients With Acute-On-Chronic Liver Failure: A Prospective Cohort Study," *Critical Care* 16, no. 6 (2012): R227, https://doi.org/10.1186/cc11882 PMID: 23186071; PMCID: PMC3672612.

10. A. J. O'Brien, J. N. Fullerton, K. A. Massey, et al., "Immunosuppression in Acutely Decompensated Cirrhosis Is Mediated by Prostaglandin E2," *Nature Medicine* 20, no. 5 (2014): 518–523.

11. J. Clària, R. E. Stauber, M. J. Coenraad, R. Jalan, et al., "Systemic Infammation in Decompensated Cirrhosis: Characterization and Role in Acute-On-Chronic Liver Failure," *Hepatology* 64, no. 4 (2016): 1249–1264.

12. F. Artru, A. Louvet, I. Ruiz, et al., "Liver Transplantation in the Most Severely ill Cirrhotic Patients: A Multicenter Study in Acute-On-Chronic Liver Failure Grade 3," *Journal of Hepatology* 67 (2017): 708–715.

13. V. Sundaram, R. Jalan, T. Wu, et al., "Factors Associated With Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation," *Gastroenterology* 156, no. 5 (2019): 1381–1391.e3.

14. P. J. Thuluvath, A. J. Thuluvath, S. Hanish, and Y. Savva, "Liver Transplantation in Patients With Multiple Organ Failures: Feasibility and Outcomes," *Journal of Hepatology* 69 (2018): 1047–1056.

15. V. Arroyo, R. Moreau, and R. Jalan, "Acute-On-Chronic Liver Failure," *New England Journal of Medicine* 382, no. 22 (2020): 2137–2145, https://doi.org/10.1056/NEJMra1914900 PMID: 32459924.

16. B. William, J. Rajiv, Q. Alberto, et al., "Acute-on-chronic liver failure," *Lancet* 1000 (2015): 1576–1587, https://doi.org/10.1016/S0140-6736(15)00309-8.

17. G. Li, P. Zhang, and Y. Zhu, "Artificial Liver Support Systems for Hepatitis B Virus-Associated Acute-On-Chronic Liver Failure: A meta-Analysis of the Clinical Literature," *Journal of Viral Hepatitis* 30, no. 2 (2023): 90–100, https://doi.org/10.1111/jvh.13767 Epub 2022 Nov 18. PMID: 36327289.

18. Y. Shen, X. L. Wang, B. Wang, et al., "Survival Benefits With Artificial Liver Support System for Acute-On-Chronic Liver Failure: A Time Series-Based meta-Analysis," *Medicine* 95, no. 3 (2016): e2506, https://doi.org/10.1097/MD.0000000000002506.

19. R. Bañares, L. Ibáñez-Samaniego, V. Arroyo, et al., "Meta-Analysis of Individual Patient Data of Albumin dialysis in Acute-On-Chronic Liver Failure: Focus on Treatment Intensity," *Therapeutic Advances in Gastroenterology* 12 (2019): 1756284819879565, https://doi.org/10.1177/1756284819879565 PMID: 31632458; PMCID: PMC6767713.

20. L. Yang, T. Wu, J. Li, J. Li, et al., "Chinese Group on the Study of Severe Hepatitis B (COSSH). Artificial Liver Treatment Improves Survival in Patients With Hepatitis B Virus-Related Acute-On-Chronic Liver Failure: A Case-Control Matched Analysis," *Hepatology Research* 50, no. 6 (2020): 656–670, https://doi.org/10.1111/hepr.13497 Epub 2020 Mar 31. PMID: 32134538.

21. Y. M. Wan, Y. H. Li, J. H. Yang, et al., "Therapeutic Plasma Exchange Versus Double Plasma Molecular Absorption System in Hepatitis B Virus-Infected Acute-On-Chronic Liver Failure Treated by Entecavir: A Prospective Study," *Journal of Clinical Apheresis* 32, no. 6 (2017): 453–461, https://doi.org/10.1002/jca.21535 Epub 2017 Mar 17. PMID: 28304106.

22. R. Maiwall, M. Bajpai, S. K. Sarin, et al., "Standard-Volume Plasma Exchange Improves Outcomes in Patients With Acute Liver Failure: A Randomized Controlled Trial," *Clinical Gastroenterology and Hepatology* 20, no. 4 (2022): e831–e854, https://doi.org/10.1016/j.cgh.2021.01.036 Epub 2021 Jan 29. PMID: 33524593.

Supporting Information

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