Analysis of Efficacy and Safety of Small-Volume-Plasma Artificial Liver Model in the Treatment of Acute-On-Chronic Liver Failure

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Summary

To explore the efficacy and safety of a small-volume-plasma artificial liver support system (ALSS) in the treatment of acute-on-chronic liver failure (ACLF). A retrospective analysis was performed. All ACLF patients received ALSS of plasma exchange & double plasma molecular absorb system (PE+DPMAS) treatment, and successfully completed this treatment. Patients were divided into small-volume and half-volume plasma groups. We compared the changes of the indicators on liver function, kidney function, blood coagulation function, and blood ammonia level before and after PE+DPMAS treatment; we compared the short-term and long-term curative effects between small-volume and half-volume plasma groups; and the factors influencing Week 4 and Week 12 mortality of ACLF patients were analyzed. The Week 4 improvement rates were 63.96 % and 66.86 % in the small-volume and half-volume plasma groups, respectively. The Week 12 survival rates in the small-volume-plasma and half-volume plasma groups were 66.72 % and 64.61 %, respectively. We found several risk factors affecting Week 4 and Week 12 mortality. Kaplan–Meier survival curves suggested no significant difference in Week 4 and Week 12 survival rates between the small-volume and half-volume plasma groups (P=0.34). The small-volume-plasma PE+DPMAS treatment could effectively reduce bilirubin and bile acids, and this was an approach with high safety and few complications, similar to the half-volume-plasma PE+DPMAS treatment. The small-volume-plasma PE+DPMAS has the advantage of greatly reducing the need for intraoperative plasma, which is especially of importance in times of shortage of plasma.

Keywords

Acute-on-chronic liver failure • Artificial liver support system (ALSS) • PE+DPMAS • Small volume plasma • Half volume plasma

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Introduction

Acute-on-chronic liver failure (ACLF) refers to the rapidly deteriorating liver failure (LF) syndrome, which caused by various acute injury factors in chronic liver disease patients with relatively stable liver function; and it has a higher short-term mortality than decompensated cirrhosis, similar to acute LF [1]. ACLF has become the most common type of LF in China, with an incidence rate of 2.53 out of 100,000 [2,3], and it can rapidly progress to a more serious condition, with a short-term mortality rate of 50 % to 90 % [4,5]. At present, the treatment of ACLF is comprehensive medical therapeutic measures, including symptomatic treatment, treatment of complications, event prediction, and liver transplantation (LT); and among them, LT is the only definitive and curative therapeutic option for patients with ACLF [6]. However, patients who needs LT faces some factual problems, such as the severe shortage of donor livers, the excessive economic burden of liver transplantation, the possibility of fatal complications in living donors, and the short "organ transplantation window" period; and many patients die while waiting for a donor liver [6-12].

Over the past 30 years, the artificial liver support system (ALSS) has emerged as an alternative to abnormal liver. ALSS uses external mechanical, physical, chemical or biological methods to remove toxic substances and provide essential substances, thereby improving the internal environment, and temporarily restoring the

function of the failing liver. ALSS is a highly promising and effective bridging therapy for LT [13-15]. ALSS has been widely used in clinical practice, and its effectiveness has been confirmed in some studies. For example, studies have reported that ALSS treatment can improve the short-term prognosis of patients with ACLF [13-19]. Plasma exchange (PE) is one of the methods recommended for the treatment of LF in China and the United States [20-24]. PE removes small- and medium-molecule metabolic toxins and immune complexes as well as other macromolecular substances in LF patients. What's more, plasmapheresis can also correct electrolytic disorders, balance pH, and stably maintain homeostasis. However, it may result in the loss of useful substances, such as coagulation factors and proteins, and has limited ability to remove blood ammonia, creatinine and inflammatory mediators, and cannot prevent and treat cerebral edema and HRS; and even, excessive plasma infusion can also cause hypocalcemia and brain edema [17,18]. In addition, due to the increasing shortage of plasma supply in our country, the development of PE treatment has been restricted to a certain extent because the PE artificial liver model requires a large amount of plasma [25]. Therefore, how to reduce the plasma volume required by PE and the adverse effects of PE are urgent problems that we need to solve. In this regard, an ALSS model that uses less or no plasma is becoming increasingly attractive [22].

The double plasma molecular absorption system (DPMAS) integrates plasma separation, plasma perfusion, and bilirubin adsorption to comprehensively and continuously remove medium and large molecular substances, and specifically remove bilirubin bile acids. The DPMAS can process more than 6000 mL of plasma at a time. The combination of DPMAS and PE can effectively reduce the plasma volume during the ALSS treatment, improve the therapeutic effects of the ALSS treatment, and reduce side effects. It has been reported that in the period of plasma scarcity, half-volume-plasma PE+DPMAS can effectively treat patients with ACLF [26], and even small-volume-plasma PE+DPMAS is also safe [27]. However, studies on small-volume-plasma PE+DPMAS are still scarce.

Therefore, this study aimed to investigate the efficacy and safety of a small-volume-plasma PE+DPMAS in the treatment of ACLF by analyzing and comparing the clinical data of ACLF patients treated by different-volume-plasma PE+DPMAS and performing survival analysis. Subgroup analyses were performed according to the etiology and stage of ACLF to explore the effect of plasma volume on short-term and long-term mortality during PE+DPMAS treatment. The influencing factors related to the death of patients with ACLF were explored, so as to identify what kind of patients could benefit more from PE+DPMAS treatment, hoping to provide a reference for clinicians in treating ACLF to a certain extent.

Materials and methods

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethic committee of the First Affiliated Hospital of Kunming Medical University, with approval No. 2022-L-41. Written informed consents to treatment and subsequent anonymous processing of patients' data were obtained from the participants and next of kin for all vulnerable participants.

Study design and patients

The clinical data of ACLF patients who received PE+DPMAS treatment in the Department of Infectious Diseases, First Affiliated Hospital of Kunming Medical University from November 2013 to January 2021 were retrospectively analyzed. The clinical diagnosis of all patients met the diagnostic criteria of ACLF from the "Guidelines for Diagnosis and Treatment of Liver Failure of the Chinese Medical Association" [23]. Regardless of the presence of cirrhosis, patients with chronic liver disease (diagnosed based on medical history, clinical signs and laboratory inspection indicators) develop rapid deepening of jaundice [total serum bilirubin ≥ 10× upper limit of normal (ULN) (ULN=17.1μmol/L) or daily increase ≥ 17.1 μmol/L] or coagulation dysfunction (Prothrombin activity (PTA) ≤ 40 % or international normalized ratio for blood coagulation (INR) ≥ 1.5), it is diagnosed as ACLF, which may be accompanied by complications, such as ascites, infection, hepatic encephalopathy (HE), electrolyte disturbance, hepatorenal syndrome (HRS), hepatopulmonary syndrome (HPS), and failure of extrahepatic organs.

All patients were divided into two groups: the small-volume (dosage of plasma: 600–800 mL) and half-volume plasma groups (dosage of plasma: 1000–1500 mL). In addition, according to the LF guidelines, they were further divided into mild [30 % < PTA ≤ 40 % (or 1.5 ≤ INR < 1.9), and no complications or failure of other extrahepatic organs], moderate [20 % < PTA ≤ 30 % (or 1.9 ≤ INR < 2.6 and with one complication and/or one

extrahepatic organ failure], and severe [PTA ≤ 20 % (or INR ≥ 2.6 and with more than two complications and/or failure of more than two extrahepatic organs] stages. The exclusion criteria: patients with active bleeding or disseminated intravascular coagulation; patients with unstable cardiovascular and cerebrovascular accidents; patients with severe sepsis; allergic patients to plasma, heparin, and protamine; patients with cholestasis caused by extrahepatic obstruction; patients with cancer; patients living with human immunodeficiency virus (HIV).

All enrolled patients were followed up from the first session of ALSS therapy to either death or 12 weeks after completing ALSS treatment. The flowchart of the research process is shown in the Figure 1.

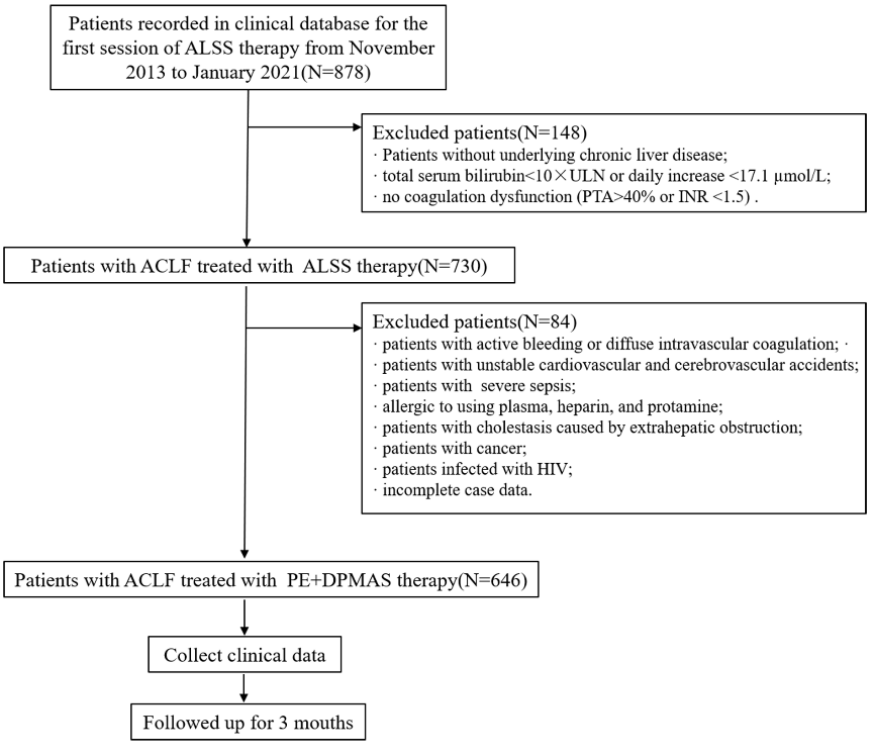

Fig. 1. The flowchart of the research process.

Treatments

After admission, all patients received comprehensive medical treatment, including bed rest, protection of the liver, elimination of jaundice, correction of hypoproteinemia, supplementation of coagulation factors, maintenance of water–electrolyte and acid-base balance, and prevention of infection. Appropriate treatment measures should be taken for patients with ACLF whose exact etiology is clear. For example, for ACLF patients with positive hepatitis B virus (HBV) deoxyribonucleic acid (DNA), nucleoside (acid) drugs should be administered immediately as antiviral therapy, regardless of the detected HBV DNA level [24]. At the same time, hepatic encephalopathy (HE), hepatorenal syndrome (HRS), gastrointestinal bleeding, spontaneous peritonitis and other complications should be prevented or treated accordingly. Based on these factors, all patients included in this study received the ALSS of PE+DPMAS treatment.

The PE+DPMAS treatment was put into practice as followings. We established a cardiopulmonary bypass under constant temperature conditions, and then used an artificial liver treatment machine and a plasma separation device (membrane plasma separator EC-4A20, Jafron Biomedical Co., Ltd., https://www.jafron international.com) for plasma separation. Subsequently, fresh frozen plasma was infused for plasma exchange. This process is PE. Before PE, the circulation line was pre-flushed with normal saline and heparin. 5mg dexamethasone was injected intravenously to prevent allergic reactions. The plasma volume of each PE was approximately 600-1500 mL, the plasma pump flow rate (BP) was 80-120 mL/min, and the plasma separation speed was 28-30 mL/min. After PE, DPMAS was performed for the adsorption of bilirubin, blood ammonia, creatinine, etc. In this process, we usually use a disposable hemoperfusion device (HA330-II produced by Langfang Aier Medical Technology Co., LTD) and a disposable anion resin

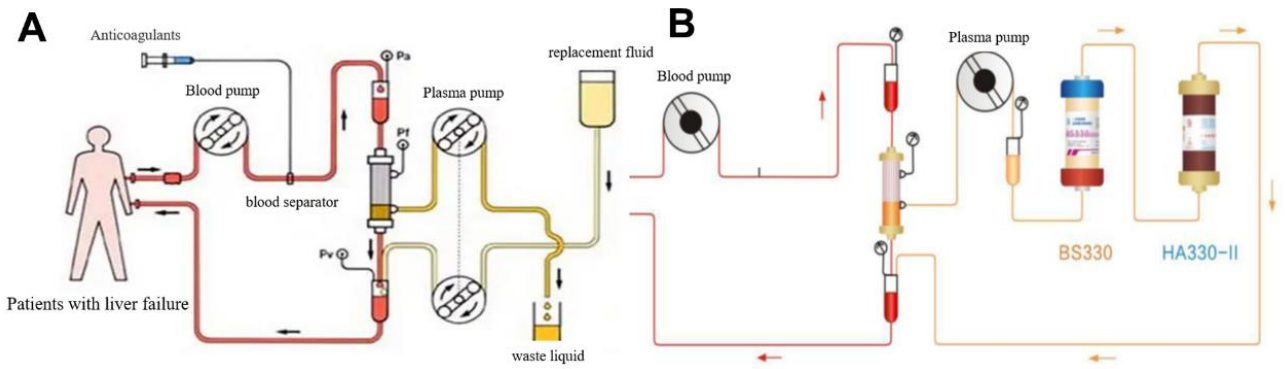

Fig. 2. The diagram of plasma exchange & double plasma molecular absorb system (PE+DPMAS) artificial liver support system. A: PE; B: DPMAS.

plasma adsorption column (BS330, Langfang Aier Medical Technology Co., LTD). The schematic diagram of the artificial liver model is shown in Figure 2.

Based on the patient's body weight (kg) and hematocrit (Hct), the non-biological artificial liver plasma requirements are accurately calculated, as follows: circulating blood volume = patient weight (kg) × 70 mL, circulating plasma volume = circulating blood volume × ([1.0–Hct] × 0.91), displacement plasma volume = 1.3 × circulating plasma volume, and the usual plasma volume required for PE is 2500-4000 mL [28]. Based on fresh frozen plasma dosage during the ALSS treatment, patients were divided into small-volume plasma (1/3 of the full-volume plasma, 600–800 mL usually) and half-volume plasma (1/2 of the full-volume plasma, 1000–1500 mL usually) groups. The duration of each ALSS treatment was approximately 6 to 8 hours, and the interval between each ALSS was determined by the patient's condition, which is generally about 2 to 5 days.

ALSS treatment could be terminated if the patient's condition improves, there is a significant reduction in total bilirubin (TB), the prothrombin time (PT) -INR decreases, worsening of the disease or other complications preclude further ALSS treatment, or the patients or their family members refuse further ALSS treatment.

Data collection

We collected demographic baseline data (age and gender), clinical parameters, LF stages, causes of chronic liver disease, liver cirrhosis, ascites, infections, HE, HRS, hepatopulmonary syndrome (HPS), spontaneous peritonitis, and the number of extrahepatic failing organs. In addition, we obtained laboratory test results (PT, INR, albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), TB, total bile acid (TBA), creatinine (Cr), ammonia (AM), electrolytes, white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, and hemoglobin (Hb), severity scores (Child-Turcotte-Pugh (CTP), Model for End-stage Liver Disease (MELD), and Chronic Liver Failure Consortium (CLIF-C) ACLF (Supplementary Table 1), and treatment strategy. Furthermore, data on the frequency and number of ALSS treatments and adverse events were collected. The condition of each patient was recorded at the Week 4 and Week 12 follow-ups, respectively.

Statistical analysis

The continuous variables were presented as mean ± standard deviation ($\bar{X}$±S) for normal distribution, and comparison between the small-volume-plasma and half-volume-plasma groups was performed using two independent sample t-test when the distribution was normal. The continuous variables with non-normal distribution were presented as median and quartile M (Q1, Q3), and comparison between the small-volume-plasma and half-volume-plasma groups was performed using the Mann-Whitney U test. Categorical variables were presented as counts (percentages), and compared using Pearson's chi-square test. Kaplan-Meier method was used to draw the Week 4 and Week 12 survival curves of the small-volume-plasma and half-volume-plasma ALSS treatments, and survival rates were compared using the log-rank test. The COX proportional hazards regression model was used to calculate hazard ratios (HRs) and 95 % confidence intervals of independent factors to determine whether the plasma volume of ALSS in ACLF patients was independently associated with Week 4 and Week 12 mortality. The crude model, model 1, and model 2 were constructed using the small-volume-plasma ALSS treatment group as the reference, adjusting for the baseline variables of imbalance between groups. The crude model

was adjusted for no variables; Model 1 was adjusted for stages of liver failure, ascites, infection, and spontaneous peritonitis; and Model 2 was adjusted for Model 1 plus ALT, AST, and Hb levels. Subgroup analysis was performed to explore the effects of different-volume-plasma ALSS treatment models on Week 4 and Week 12 mortality in ACLF patients with different etiologies and stages. COX regression analysis was used to screen risk factors associated with Week 4 and Week 12 mortality in ACLF patients. Statistical analyses were performed using the R software (version 3.6.1). For all analyses, a two-sided probability value of $P<0.05$ was considered statistically significant.

Results

Description of the subjects and comparison of baseline parameters between groups

According to the diagnostic criteria of ACLF, 730 patients diagnosed with ACLF were included in this study. Of these, 84 patients were excluded due to exclusion criteria such as incomplete case data, etc., and finally, 646 patients were enrolled in this paper. Among these 646 patients, 498 (77.09 %) were male and 148 (22.91 %) were female. The oldest was 79 years old, and the youngest was 13 years old, with an average age of 45 years old. Patients with HBV and hepatitis C virus (HCV) infections and patients complicated with other diseases such as autoimmune liver disease, alcoholic liver disease, and drug-induced liver disease, were included in the study. In addition, patients with other definite causes or unknown causes were included. 98 patients (15.17 %) had compensated liver cirrhosis, 185 patients (28.64 %) had decompensated cirrhosis, and 363 patients (56.19 %) did not suffer from concomitant liver cirrhosis. The complications included ascites, infections, HE, HRS, HPS, gastrointestinal bleeding, and spontaneous bacterial peritonitis (SBP). The lowest and maximum number of ALSS treatment for each patient were 1 and 15, respectively. Most of patients received 1-3 times ALSS treatment. All these details are showed in the Table 1.

All patients were divided into a small-volume-plasma group (600-800 mL) and a half-volume-plasma group (1000-1500 mL) according to the amount of plasma used during the ALSS treatment. The differences in the composition ratios of ascites (P = 0.008), infection (P = 0.001), and SBP (P = 0.006) were statistically significant between the two groups. The differences in the overall mean ALT (P = 0.015), AST (P = 0.021), and HB (P = 0.030) levels were statistically significant between the two groups. There were no statistical differences in the other variables between the two groups. All these details are showed in the Table 1 and Table 2.

Comparison of changes of the indicators on liver function, kidney function, blood coagulation function, and blood ammonia level before and after ALSS treatment in the two groups, and their improvement degree after ALSS treatment between groups

Table 3 shows the changes in liver function, kidney function, blood coagulation function, and blood ammonia levels before and after performing ALSS in the small-volume-plasma and half-volume-plasma groups. There were significant differences in the levels of PT, PTA, TB, direct bilirubin or conjugated bilirubin (DB), TBA, ALT, AST, AM, and blood urea nitrogen (BUN) before and after ALSS treatment in the two groups according to the paired t-test (P < 0.05). There were no significant differences in the levels of ALB and Cr before and after ALSS treatment in the two groups (P = 0.806 and P = 0.854 in the small-volume-plasma group; P = 0.622 and P = 0.491 in the half-volume-plasma group).

A between-group independent samples t-test was used to compare the improvement degree in liver function, renal function, coagulation function, and blood ammonia levels between the small-volume-plasma and half-volume-plasma groups, the results of which showed that there were significant differences in PT (P = 0.007), PTA (P = 0.001), TBA (P = 0.044), ALT (P = 0.002) and AST(P < 0.001) between the two groups (Table 3).

All patients in two groups successfully completed treatment. During the treatment, 15 patients in the small-volume-plasma group and 18 patients in the half-volume-plasma group suffered from allergic reactions, manifested as skin rash, pruritus, or numbness of the mouth. These symptoms resolved after anti-allergic treatment was administered, and these patients also completed the ALSS treatment. After the ALSS treatment, 10 patients had hemorrhage at the catheterization site, and of whom 3 patients developed a hematoma at the catheterization site, which was improved after the corresponding treatment. None of the patients had active bleeding, and a few patients had low blood pressure during the ALSS treatment, which could be corrected by fluid supplementation.

Table 1. Comparison of patients' clinical characteristics before treatment between a small-volume-plasma group (600–800 mL) and a half-volume-plasma group (1000–1500 mL)

Variables	Total	Small-volume-plasma group n=308	Half-volume-plasma group n=338	t/Z/c2	P
Age		45.17±12.56	44.17±12.88	0.99*	0.323
Gender					
Female	148	69(22.4)	79(23.37)	0.086	0.770
Stage					
Mild	411	190(61.69)	221(65.38)	1.673	0.433
Moderate	117	62(20.13)	55(16.27)		
Severe	118	56(18.18)	62(18.34)		
Liver cirrhosis					
None	363	169(54.87)	194(57.4)	0.636	0.728
Compensated	98	50(16.23)	48(14.2)		
Decompensated	185	89(28.9)	96(28.4)		
Ascites	180	101(32.79)	79(23.37)	7.114	0.008
Infection	118	73(23.7)	45(13.31)	11.647	0.001
HE	73	33(10.71)	40(11.83)	0.202	0.653
HRS	30	17(5.52)	13(3.85)	1.019	0.313
HPS	9	3(0.97)	6(1.78)	0.771	0.380
Gastrointestinal bleeding	9	6(1.95)	3(0.89)	1.336	0.248
SBP	77	48(15.58)	29(8.58)	7.531	0.006
Other organs failure apart from liver					
<2	633	304(98.7)	329(97.34)	1.568	0.211
≥2	13	4(1.3)	9(2.66)		
Times of ALSS					
1	121	54(17.53)	67(19.82)	0.074	0.780
2	244	107(34.74)	137(40.53)		
3	140	76(24.68)	64(18.93)		
4	74	38(12.34)	36(10.65)		
≥5	67	33(10.71)	34(10.06)		
Survival situation in Week 4	553	259(84.09)	294(86.98)	0.761	1.167
Survival situation in Week 12	431	199(64.61)	232(68.64)	0.316	1.003
CTP		10 (9, 11)	10 (10, 11)	0.0082	0.994
MELD		22.69 (20.02, 27.03)	22.63 (20.19, 26.35)	-0.0184	0.985
CLIF-C ACLFs		26.01±6.44	25.5±6.07	1.03*	0.302

Categorical variables are expressed as number (%), non-normal continuous variables as median (interquartile ranges: P25, P75) and normal continuous variables as mean ± SD. Abbreviations: ALSS, artificial liver support system; CHB, chronic hepatitis B, CHC, chronic hepatitis C; HE, Hepatic encephalopathy; HRS, hepatorenal syndrome; HPS, hepatopulmonary syndrome; SBP, spontaneous bacterial peritonitis; CTP score, Child-Turcotte-Pugh score; MELD score, End-Stage Liver Disease score. CHB + other causes: including CHB + hepatitis A, CHB + hepatitis E, CHB + alcoholic liver disease. Other causes: Cholestasis, hepatolenticular degeneration, biliary tract infection, Epstein–Barr virus infection, adult Still's disease, cholestatic hepatitis, cholestatic liver disease. Note: *Represents the comparison method between the two means using t-test.

Table 2. Comparison of patients' laboratory baseline data before treatment between a small-volume-plasma group (600–800 mL) and a half-volume-plasma group (1000–1500 mL)

Variables	Small-volume-plasma group n=308	Half-volume-plasma group n=338	t/Z	P
PT, S	19.15 (18.3, 24.65)	18.8 (18.3, 24)	1.393	0.164
PTA	0.35 (0.25, 0.38)	0.36 (0.25, 0.38)	-1.391	0.164
INR	1.65 (1.53, 2.27)	1.59 (1.53, 2.21)	1.300	0.194
ALB, g/L	31.15±5.87	31.23±5.32	-0.18*	0.859
ALT, U/L	148.9 (64.85, 472.6)	248.2 (74.9, 612.5)	-2.436	0.015
AST, U/L	161.1 (84.1, 378.85)	200.15 (96, 517.9)	-2.315	0.021
TB, umol/L	284.4 (203.35, 393.55)	298.6 (200.7, 391.6)	-0.743	0.457
TBA, umol/L	196.4 (124.4, 272)	192.1 (134.9, 256.3)	0.435	0.663
BUN, mmol/L	3.96 (2.96, 5.27)	3.7 (2.68, 5.3)	1.544	0.123
Cr, umol/L	68.5 (57.95, 84)	69.75 (58.3, 81.8)	-0.007	0.994
K, mmol/L	3.69 (3.35, 4.02)	3.65 (3.34, 4.09)	-0.225	0.822
Na, mmol/L	137.7 (135.3, 140.3)	137.85 (135.2, 140)	0.608	0.543
Cl, mmol/L	102.4 (99.5, 104.9)	101.8 (98.9, 104.5)	1.393	0.164
AM, umol/L	65.55 (46.25, 91)	58.7 (40, 92)	1.053	0.292
WBC, $\times 10^9$/L	6.71 (5.25, 9.02)	6.61 (5.23, 8.75)	0.402	0.688
Hb, g/L	127 (110.5, 143.5)	132 (117, 147)	-2.172	0.030
PLT, $\times 10^9$/L	123 (82.5, 180)	137 (89, 201)	-1.527	0.127
CTP	10 (9, 11)	10 (10, 11)	0.008	0.994
MELD	22.69 (20.02, 27.03)	22.63 (20.19, 26.35)	-0.018	0.985
CLIF-C ACLFs	26.01±6.44	25.5±6.07	1.03*	0.302

Non-normal continuous variables as median (interquartile ranges: P25, P75) and normal continuous variables as mean ± SD. Abbreviations: PT, prothrombin time; PTA, Prothrombin activity; INR, international normalized ratio for blood coagulation; Alb, Albumin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TB, Total bilirubin; DB, Direct bilirubin or Conjugated bilirubin; TBA, total bile acid; BUN, Blood Urea Nitrogen; Cr, Creatinine; K, Serum potassium; Na, Serum sodium; Cl, Serum chloride; AM, ammonia; WBC, white blood cell count; Hb, Hemoglobin; PLT, Platelets; CTP score, Child-Turcotte-Pugh score; MELD score, End-Stage Liver Disease score. Note: * Represents the comparison method between the two means using t-test.

Comparison of the changes of the indicators on routine blood tests, and electrolytes were performed before and after ALSS treatment in the two groups, which showed that there were significant difference in serum potassium (K), serum sodium (Na), WBC, neutrophils (N), and Hb before and after ALSS treatment in the small-volume-plasma group ($p < 0.05$), and in K, and Hb before and after ALSS treatment in the half-volume-plasma group ($p < 0.05$). A between-group independent samples t-test was used to compare the improvement degree in the levels of K, Na, serum chloride (Cl), WBC, N, lymphocytes (L), platelets (PLT) and Hb between the small-volume-plasma and half-volume-plasma groups, the results of which showed that there was significant difference in WBC ($P = 0.006$), N ($P < 0.001$), and Hb ($P = 0.001$) between the two groups, and there were no significant differences in the levels of K, Na, Cl, L, and PLT between the two groups (Table 3).

Table 3. Comparison of the improvement degree in liver function, kidney function, blood coagulation function, blood ammonia, electrolytes, and blood routine between a small-volume-plasma group (600–800 mL) and a half-volume-plasma group (1000–1500 mL)

	Small-volume-plasma group (n=308)			Half-volume-plasma group (n=338)			P between groups
Variables	**Before ALSS**	**After ALSS**	**P**	**Before ALSS**	**After ALSS**	**P**	
PT, S	19.15 (18.3, 24.65)	18.85 (15.75, 25.7)	<0.001	18.8 (18.3, 24)	17.6 (14.8, 22.8)	<0.001	0.007
PTA	0.35 (0.245, 0.38)	0.36 (0.23, 0.48)	<0.001	0.36 (0.25, 0.38)	0.4 (0.27, 0.54)	<0.001	0.001
ALB, g/L	30.7 (27.2, 34.9)	30.55 (26.95, 34.7)	0.806	31.4 (27.3, 34.9)	31.1 (27.5, 35)	0.662	0.599
TB, umol/L	284.4 (203.35, 393.55)	163.6 (90.65, 275.95)	<0.001	298.6 (200.7, 391.6)	136.15 (76.7, 315.1)	<0.001	0.081
DB,umol/L	223.05 (160.7, 322.1)	129.45 (68.8, 217)	<0.001	225 (157.8, 308.5)	101.5 (58.4, 226.9)	<0.001	0.12
TBA, umol/L	196.4 (124.4, 272)	138.4 (75, 209.15)	<0.001	192.1 (134.9, 256.3)	111.55 (54.1, 175.9)	<0.001	0.044
ALT, U/L	148.9 (64.85, 148.9)	70.8 (40.7, 70.8)	<0.001	248.2 (74.9, 612.5)	63.1 (37.7, 103.7)	<0.001	0.002
AST, U/L	161.1 (84.1, 348.85)	99.9 (60.8, 169.3)	<0.001	200.15 (96, 517.9)	87.45 (56.3, 138.3)	<0.001	<0.001
AM, umol/L	65.55 (46.25, 91)	44.75 (31.6, 67)	<0.001	58.7 (40, 92)	42.2 (27, 65)	<0.001	0.769
BUN, mmol/L	4.675 (3.245, 6.3)	3.955 (2.96, 5.27)	<0.001	3.92 (2.93, 5.66)	3.695 (2.68, 5.3)	0.013	0.078
Cr, umol/L	68.5 (57.95, 84)	68.7 (58.1, 81.9)	0.854	69.75 (58.3, 81.8)	69.45 (55.9, 82.6)	0.491	0.546
K, mmol/L	3.685 (3.345, 4.02)	3.88 (3.5, 4.275)	<0.001	3.65 (3.34, 4.09)	3.885 (3.52, 4.28)	<0.001	0.638
Na, mmol/L	137.7 (135.3, 140.3)	137 (134.25, 139.55)	0.004	137.85 (135.2, 140)	138.1 (135.4, 140.9)	0.265	0.051
Cl, mmol/L	102.4 (99.5, 104.9)	102.2 (99.3, 105.15)	0.874	101.8 (98.9, 104.5)	102.85 (99.5, 105.5)	0.065	0.051
WBC, ×109/L	6.705 (5.245, 9.015)	7.91 (5.65, 11.22)	<0.001	6.61 (5.23, 8.75)	6.95 (5.07, 9.87)	0.217	0.006
N, ×109/L	4.33879 (3.13, 6.28)	5.53 (3.50, 8.83)	<0.001	4.412975 (3.05, 6.06)	4.5 (3.13, 7.20681)	0.49	<0.001
L, ×109/L	1.3 (0.97, 1.825)	1.34 (0.92, 1.81)	0.602	1.41965 (1.03, 1.87)	1.445 (0.99, 1.88)	0.754	0.34
PLT, ×109/L	123 (82.5, 180)	113 (71, 190.5)	0.131	137 (89, 201)	130.5 (83, 216)	0.593	0.55
Hb, g/L	127 (110.5, 143.5)	116 (99, 130)	<0.001	132 (117, 147)	115.5 (101, 130)	<0.001	0.001

Non-normal continuous variables as median (interquartile ranges: P25, P75). PT, prothrombin time; PTA, Prothrombin activity; Alb, Albumin; TB, Total bilirubin; DB, Direct bilirubin or Conjugated bilirubin; TBA, total bile acid; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AM, ammonia; BUN, Blood Urea Nitrogen; Cr, Creatinine; K, Serum potassium; Na, Serum sodium; Cl, Serum chloride; WBC, white blood cell count; N, Neutrophils; L, Lymphocytes; PLT, Platelets Hb, Hemoglobin.

Comparison of short- and long-term efficacy of PE+DPMAS treatment between groups

The Week 4 improvement rate after PE+DPMAS treatment was used as an index to evaluate short-term efficacy. The Week 12 survival rate after PE+DPMAS treatment was used as an index to evaluate long-term efficacy [29]. We used the degree of TB clearance and the patient's clinical symptoms to evaluate the efficacy of treatment. When the TB reduction rate reached 50 %, and skin yellowing and gastrointestinal symptoms were significantly improved, it is evaluated as improvement; when TB reduction rate was less than 10 %, and gastrointestinal symptoms were not improved, it was evaluated as ineffectiveness; and when TB rebound rose more than 30 %, gastrointestinal symptoms became worsen, and even complications such as hepatorenal syndrome appeared, it was evaluated as deterioration.

The Week 4 improvement rates were 63.96 % and 66.86 % in the small-volume-plasma and half-volume-plasma groups, respectively, and there was no significant difference in this index between the two groups. The Week 12 survival rates were 64.61 % and 68.64 % in the small-

volume and half-volume plasma groups, respectively, and there was no significant difference in this index between the two groups (Table 4).

Based on different severity of ACLF, all patients were divided into mild, moderate, and severe stages. Moreover, the short-term and long-term efficacies of the small-volume-plasma and half-volume-plasma groups were compared. Kaplan–Meier survival curves for patients in different stages and different plasma-volume groups are shown in Figure 3. We observed a significantly higher cumulative survival rate in patients in mild stage of ACLF at Week 4 and Week 12 ($P < 0.001$) (Fig. 3A). However, we found no significant differences in Week 4 and Week 12 survival between the small-volume-plasma and half-volume-plasma groups (P=0.34) (Fig. 3B).

Table 4 Comparison of curative effect between a small-volume-plasma group (600–800 mL) and a half-volume-plasma group (1000–1500 mL)

Varibles	Total	Small-volume-plasma group (n, %) n=308	Half-volume-plasma group (n, %) n=338	c2	P
Week 4				0.761	1.167
Improvement	423 (65.48)	197 (63.96)	226 (66.86)		
Ineffectiveness	91 (14.09)	43 (13.96)	48 (14.2)		
Deterioration	39 (6.04)	19 (6.17)	20 (5.92)		
Death	93 (14.4)	49 (15.91)	44 (13.02)		
Week 12				0.316	1.003
Survivors	431 (66.72)	199 (64.61)	232 (68.64)		
Death	215 (33.28)	109 (35.39)	106 (31.36)		

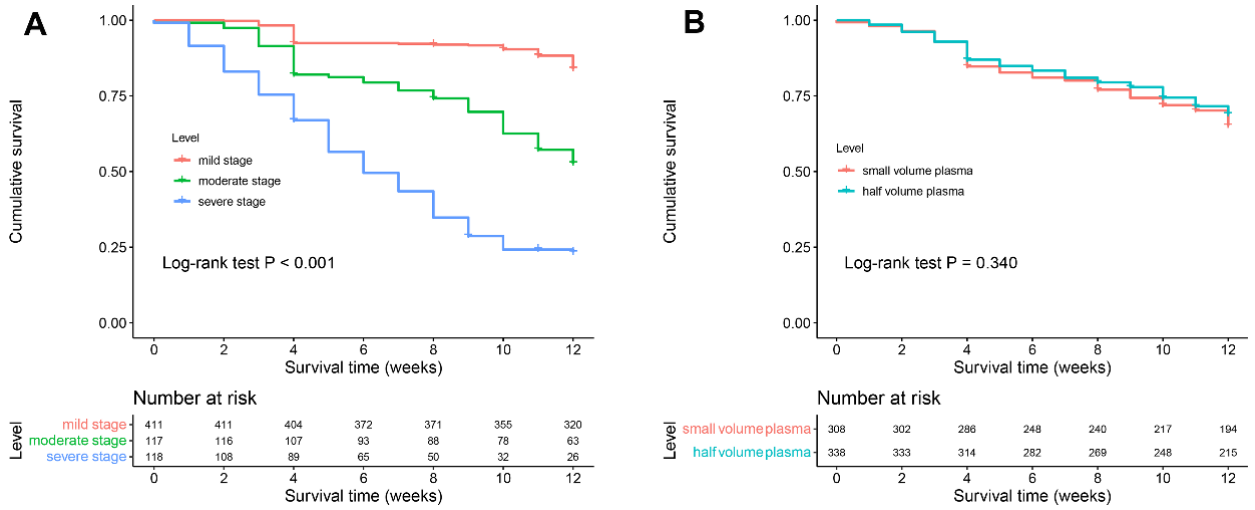

Fig. 3. Kaplan–Meier survival curves. A: different stages; B: treatment with different plasma volumes.

COX proportional hazards regression analysis

COX proportional hazards regression analysis of the overall samples showed that there were no significant differences between the small-volume-plasma and half-volume-plasma groups in the risk of mortality in ACLF patients at Week 4 (HR, 95 %CI: 0.83, 0.55-1.25; P=0.369), and Week 12 (HR, 95 %CI: 0.88, 0.67-1.15; P=0.339) for the crude model. After adjusting for confounding factors, there were still no significant differences between the small-volume-plasma and half-

volume-plasma groups in the risk of mortality in patients with ACLF at Week 4 and Week 12 for the model 1 and 2 (Table 5).

HBV infection is the main cause of liver failure in China, accounting for approximately 90 % of all ACLF cases. All ACLF patients were divided into chronic HBV (CHBV) -induced and non-CHBV-induced ACLF groups. According to different causes, further subgroup analysis was performed, which suggested that the plasma volume of ALSS treatment was not a related factor for Week 4 and Week 12 mortality in ACLF patients with CHBV (HR, 95 %CI: 0.87, 0.53-1.43, *P*=0.585; and HR, 95 %CI: 0.85, 0.61-1.20, *P*=0.354), and after adjusting for confounding factors, the plasma volume of ALSS treatment was still not a related factor for Week 4 and Week 12 mortality in ACLF patients with CHBV (all *P*>0.05). In ACLF patients without CHBV, we also observed that the plasma volume of ALSS treatment was not a related factor for Week 4 and Week 12 mortality (HR, 95 %CI: 0.78, 0.37-1.64, *P*=0.520; and HR, 95 %CI: 0.95, 0.59-1.52, *P*=0.828), and after adjusting for confounding factors, the plasma volume of ALSS treatment was not a related factor for Week 4 and Week 12 mortality (all *P*>0.05) (Table 6).

Analysis of influencing factors of therapeutic efficacy of ALSS

Gender, age, etiology, PT, PTA, TB, INR, Alb, Cr, Na, PLT, CTP score, MELD score, CLIF-C ACLF score, neutrophil-to-lymphocyte ratio (NLR), the number of artificial livers, complications, combined cirrhosis, decompensated liver cirrhosis, the number of extrahepatic organ failures, and LF stages were included in the stepwise logistic regression analysis to screen the influencing variables of therapeutic efficacy of ALSS. The logistic model was established with Week 4 mortality and Week 12 mortality as dependent variables. Univariate logistic regression analysis showed that ascites (*P*=0.006), infections (*P*=0.008), HPS (*P*=0.001), SBP (*P*=0.001), times of ALSS treatments (*P*=0.001), CTP score (*P*=0.008), and MELD score (*P*<0.001) were the influencing factors for Week 4 mortality; HE (*P*=0.002), HRS (*P*=0.002), cirrhosis (*P*=0.021), number of ALSS (*P*=0.019), PTA (*P*<0.001), Na (*P*=0.009), NLR (*P*=0.006), and CTP score (*P*=0.012) were the influencing factors for Week 12 death (Table 7 and Table 8). Variables with a P value of less than 0.05 in the univariate model were included into the multivariate model, and the multivariate logistic regression analysis showed that except for SBP, ascites (*P*=0.012), infections (*P*=0.011), HPS (*P*=0.004), number of ALSS treatments (*P*<0.001), CTP score (*P*=0.001), and MELD score (*P*<0.001) were the independent influencing factors of Week 4 mortality; except for PTA, HE (*P*<0.001), HRS (*P*<0.001), cirrhosis (*P*<0.001), number of ALSS (*P*=0.014), Na (*P*=0.005), NLR (*P*=0.002), and CTP score (*P*<0.001) were the independent influencing factors of Week 12 mortality (Table 7, Table 8).

Table 5. COX proportional hazards regression analysis for different plasma ALSS treatment in Week 4 and Week 12 prognosis based on all patients

	Crude model		**Model 1**		**Model 2**	
Variables	**HR (95 % CI)**	**P**	**HR (95 % CI)**	**P**	**HR (95 % CI)**	**P**
Week 4						
small volume plasma	Ref		Ref		Ref	
half volume plasma	0.83 [0.55, 1.25]	0.369	0.90 [0.59, 1.36]	0.61	0.95 [0.62, 1.44]	0.808
Week 12						
small volume plasma	Ref		Ref		Ref	
half volume plasma	0.88 [0.67, 1.15]	0.339	0.95 [0.72, 1.26]	0.714	0.99 [0.74, 1.31]	0.924

Crude model adjusted for no variables; Model 1 adjusted for stages of liver failure, ascites, infection, spontaneous peritonitis; Model 2 adjusted for Model1 plus alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin (Hb)

Table 6. COX proportional hazards regression analysis for different plasma ALSS treatment in Week 4 and Week 12 prognosis based on subgroups of different etiologies

	Crude model		Model 1		Model 2	
Variables	**HR (95% CI)**	**P**	**HR(95% CI)**	**P**	**HR(95% CI)**	**P**
CHBV Etiology						
Week 4						
small volume plasma	Ref		Ref		Ref	
half volume plasma	0.87 (0.53, 1.43)	0.585	0.90 (0.55, 1.49)	0.692	1.00 (0.60, 1.66)	0.999
Week 12						
small volume plasma	Ref		Ref		Ref	
half volume plasma	0.85 [0.61, 1.20]	0.354	0.91 (0.65, 1.29)	0.6	0.95 (0.67, 1.35)	0.784
Other Etiology						
Week 4						
small volume plasma	Ref		Ref		Ref	
half volume plasma	0.78 (0.37, 1.64)	0.52	0.97 (0.44, 2.16)	0.945	0.99 (0.45, 2.17)	0.981
Week 12						
small volume plasma	Ref		Ref		Ref	
half volume plasma	0.95 (0.59, 1.52)	0.828	1.09 (0.67, 1.78)	0.734	1.18 (0.72, 1.94)	0.518

Crude model adjusted for no variables; Model 1 adjusted for stages of liver failure, ascites, infection, spontaneous peritonitis; Model 2 adjusted for Model1 plus alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin (Hb)

Table 7. Parameter and OR estimations of a univariate and multivariate analyses with Week 4 mortality data as the dependent variable

	Univariate analysis			Multivariate analysis		
Intercept	**OR**	**95 %CI**	**P**	**OR**	**95 %CI**	**P**
Ascites	3.327	1.419-7.801	0.006	2.171	1.187-3.971	0.012
Infection	0.319	0.138-0.741	0.008	0.460	0.253-0.835	0.011
HPS	0.026	0.003-0.198	0.001	0.080	0.014,0.444	0.004
SBP	0.231	0.099-0.536	0.001			
Times of ALSS treatment	0.695	0.576-0.84	0.001	0.779	0.697-0.895	<.001
CTP	0.034	0.003-0.409	0.008	0.540	0.371-0.787	0.001
MELD	0.071	0.035-0.144	<.001	0.880	0.843-0.919	<.001

Abbreviations: HPS, hepatopulmonary syndrome; SBP, spontaneous peritonitis; ALSS, artificial liver support system; CTP score, Child-Turcotte-Pugh score; MELD score, End-Stage Liver Disease score.

Table 8. Parameter and OR estimations of a univariate and multivariate analyses with Week 12 mortality data as the dependent variable

	Univariate analysis			Multivariate analysis		
variable	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
HE	0.34	0.169-0.682	0.002	0.166	0.090-0.308	<.001
HRS	0.15	0.044-0.506	0.002	0.121	0.038-0.382	<.001
Cirrhosis	0.756	0.596-0.96	0.021	0.683	0.548-0.851	<.001
Times of ALSS	0.858	0.755-0.975	0.019	0.863	0.767-0.970	0.014
PTA	3.078	2.329-4.066	<.001			
Na	1.763	1.152-2.699	0.009	1.071	1.022-1.123	0.005
NLR	0.706	0.55-0.907	0.006	0.924	0.879-0.972	0.002
CTP	0.464	0.254-0.847	0.012	0.591	0.445-0.784	<.001

HE, Hepatic encephalopathy; HRS, hepatorenal syndrome; ALSS, artificial liver support system; PTA, Prothrombin activity; Na, Serum sodium; NLR, neutrophil-to-lymphocyte ratio; CTP score, Child-Turcotte-Pugh score.

Discussion

Although the main effective treatment for ACLF is liver transplantation, clinical application of liver transplantation is limited due to the influence of some clinical factors. ALSS can replace the decompensated liver and is an effective bridging therapy for ACLF patients before liver transplantation. The treatment model of ALSS should be selected individually according to different clinical manifestations and severity of liver failure. Our study found that the combination of PE and DPMAS could reduce plasma volume use without reducing the efficacy.

In this study, we found that the PE+DPMAS of artificial liver model significantly eliminated bilirubin and bile acids; these results are consistent with those of previous studies [30,31]. For the PE+DPMAS treatment in this study, we observed there was no significant difference in the albumin level before and after the ALSS treatment, and the coagulation function was improved to a certain extent after treatment, which might be attributed to the fact that the PE model can supplement a large volume of plasma to compensate for the excessive loss of albumin and coagulation factors caused by DPMAS. Thus, we also believe that PE and DPMAS in the PE+DPMAS treatment are complementary to compensate for each other's shortcomings, which is consistent with the results of the previous studies [30,27]. Most patients with ACLF have coagulation dysfunction due to hyperbilirubinemia, and the PE+DPMAS model is a better choice. In the present study, we also observed that the blood ammonia and BUN levels were largely cleared after ALSS treatment. Our results are consistent with a previous study, the PE+DPMAS of artificial liver model is suitable for patients with HE, hyperammonemia, LF, and renal insufficiency [32].

During the ALSS treatment, the allergic reactions in different-plasma-volume groups were equal. After the ALSS treatment, the Hb level in the two groups decreased significantly. Both PE and DPMAS can damage the blood cells. In the present study, the PE+DPMAS treatment was found to significantly reduced the Hb level, which might be related to blood cell damage caused by the plasma separator and the adsorption column. However, we still found that the safety of the PE+DPMAS model was very good for both small- and half-volume plasma.

In this study, we found no difference in the Week 4 and Week 12 curative effects for ACLF patients between the two groups; and the Kaplan–Meier curve also showed no difference in patients' survival rates between the two groups. These suggested the efficacy of the small-volume group was equivalent to that of the half-volume plasma group.

A large number of studies have been conducted on the relationship between the clinical stage and prognosis of liver failure [33, 34]: the later the stage, the higher the mortality rate. In this study, the mortality rate of patients with severe-stage liver failure was significantly higher than that with mild- and moderate-stage liver failure. Kaplan–Meier analysis also showed that there is a significant difference in survival rate for patients with mild-, moderate-, and severe-stage ACLF. However, it is important to note that we found no difference in the Week 4 and Week 12 efficacies between the small- and half-volume-plasma groups for patients with mild--, moderate-, and severe-stage ACLF. Subgroup analysis of patients with different-stage ACLF was performed, and we found that the plasma volume in ALSS treatment was not an independent factor affecting the Week 4 and Week 12 mortality of patients. The patient's condition in the first three months is crucial for the long-term prognosis of ACLF [35,36]. The PE+DPMAS model improved the short-term prognosis of ACLF, increased the number of patients with ACLF who did not require liver transplantation within 4 weeks, and provided more waiting time for ACLF patients to receive liver transplantation. Our study found that consistent with the efficacy of PE+DPMAS treatment with half-volume plasma, PE+DPMAS treatment with low-volume plasma greatly reduced plasma volume. Therefore, PE+DPMAS might be an ideal ALSS for the treatment of mild ACLF. Moreover, it might be also used in the ALSS treatment for patients with moderate and severe ACLF.

The etiology of liver failure is complex and diverse. Viral infection, drugs, alcoholic drugs, other hepatotoxic substances and metabolic liver diseases can lead to liver failure. China is the country with the heaviest burden of liver diseases in the world, and the incidence of various chronic liver diseases is increasing year by year. According to the World Health Organization and various studies, there were approximately 250 million HBV infections worldwide in 2019, of which about 70 million were in China, including about 20-30 million CHBV patients [37]. HBV infection is the main cause of liver failure in China, accounting for approximately 90 % of the causes of ACLF, and is becoming the main cause of HBV infection-related death [38, 39]. The aim of this study was to investigate whether the plasma volume of ALSS

treatment was independently associated with the prognosis of ACLF. The COX proportional hazards regression analysis showed that for ACLF patients with various etiologies, the plasma volume of ALSS treatment was not a relevant factor affecting the prognosis of ACLF.

In this study, the independent influencing factors of Week 4 mortality were ascites, infection, HPS, times of ALSS treatments, CTP score, and MELD score. Among these, infection has been reported as a major prognosis-affected factor in the ALSS treatment for patients with liver failure [40], whereas HPS, as an influencing factor of Week 4 mortality, has not been reported previously. The CTP and MELD scores are commonly used scoring systems to predict the prognosis of liver failure, and reflect the severity of liver failure, liver functional reserve, and liver complications. The present study demonstrated that higher CTP and MELD scores were associated with a higher Week 4 mortality rate of ACLF patients. The number of ALSS treatments was an influencing factor for the Week 4 mortality rate, which was not been reported in previous studies, the reasons for which might be that a higher frequency of ALSS treatment was associated with a higher severity of ACLF, or this might be related to the poor response of the patient to ALSS treatment.

The independent influencing factors affecting the Week 12 mortality rate were HE, HRS, cirrhosis, number of artificial liver treatments, Na, NLR, and CTP scores. ACLF Patients with cirrhosis had a higher Week 12 mortality rate. Among the complications, the major factors influencing the Week 12 mortality rate of ACLF patients were HE and HRS, of which HE was reported as an independent risk factor in several studies [41-43], while HRS has rarely been reported as an influencing factor of Week 12 mortality. Renal function has long been proposed as an influencing factor for poor prognosis [44]. Some study groups have proposed that Na concentration might be a useful predictor of mortality in patients with end-stage liver disease when they wait for liver transplantation [45]. CTP score reflects the reserve function of the liver, and the higher the score, the worse the prognosis. The NLR is a systemic inflammatory index reflecting the immune status of the body. NLR is associated with the progression of non-alcoholic fatty liver and liver cirrhosis, and its high level serves as an independent prognostic factor, affecting the mortality of patients with liver cirrhosis, ACLF, and liver cancer after liver transplantation [46-48]. The severities of liver cirrhosis, comorbidities, inflammation, and of liver failure affects the long-term prognosis of ACLF, and might be responsible for the poor efficacy of ALSS treatment. Such patients should be considered for early liver transplant evaluation.

In the present study, we found that the PE+DPMAS treatment effectively removed bilirubin and bile acids, improved coagulation function to a certain extent, and had little effect on albumin. There was no significant difference in the efficacy and safety between the small-volume-plasma and half-volume-plasma PE+DPMAS treatments. COX proportional hazards regression analysis showed that the plasma volume during ALSS treatment was not a factor affecting the prognosis of ACLF patients. The independent influencing factors for the Week 4 mortality were ascites, infections, HPS, number of ALSS treatments, CTP score, and MELD score. The independent influencing factors for Week 12 mortality were HE, HRS, cirrhosis, times ALSS treatments, Na, NLR, and CTP score.

Our study has certain limitations. First, it was a retrospective study, with data collected only from patients with ACLF who underwent ALSS treatment at one medical center. Second, patients with ACLF who were not treated with ALSS were not included as the control to do the comparison analysis. Third, the patient's allergic symptoms may be caused by low calcium. However, because the blood calcium was not routinely detected after artificial liver treatment in the patients included in this study, there was no analysis for blood calcium in this paper. Therefore, in the future study, a large sample size with multiple centers and more complete data is necessary to analyze the efficacy, safety, and influencing factors of the small-volume-plasma PE+DPMAS treatment.

In conclusion, the small-volume-plasma PE+DPMAS model could effectively remove bilirubin and bile acids, and it was a therapeutic method with high safety and few complications, similar to the half-volume-plasma PE+DPMAS model. However, this small-volume-plasma ALSS treatment has the advantage of greatly reducing the need for intraoperative plasma, which is especially of importance in times of plasma shortage.

Ethics approval and consent to participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethic committee of the First Affiliated Hospital of Kunming Medical University, with approval No. 2022-L-41. Written informed consents were obtained from the participants and next of kin for all vulnerable participants.

Conflict of Interest

There is no conflict of interest.

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