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Original Article

Efficacy and Economic Evaluation of Nonbiological Artificial Liver Therapy in Acute-on-chronic Hepatitis B Liver Failure

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Abstract

Background and Aims: Nonbiological artificial liver (NBAL) is frequently used as a first-line treatment for hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF). This study aimed to compare the therapeutic efficacy and cost-effectiveness ratio (CER) of comprehensive medical treatment, plasma exchange (PE), and double plasma molecular adsorption system (DPMAS) plus half-dose PE (DPMAS+PE) in patients with HBV-ACLF. ***Methods:*** A total of 186 patients with HBV-ACLF randomly received comprehensive medical treatment, PE, or DPMAS+PE and were prospectively evaluated. Patients were divided into four subgroups based on the pretreatment prothrombin activity (PTA): Group I (PTA>40%), group II (PTA 30–40%), group III (PTA 20–30%), and group IV (PTA<20%). The main outcome measures were 28 day effectiveness; 90 day liver transplantation-free survival; change of biochemical parameters; and CER. ***Results:*** DPMAS+PE treatment was associated with significantly higher 28 day effectiveness and 90 day liver transplantation-free survival compared with PE treatment in patients with group I liver failure. Clearance of serum total bilirubin (TBIL), AST, and creatinine (Cr) were significantly higher in the DPMAS+PE group than in the PE group. For subjects with group I liver failure, DPMAS+PE treatment had advantages of lower CER values and better cost-effectiveness. ***Conclusions:*** Compared with comprehensive medical treatment and PE alone, DPMAS with half-dose sequential PE treatment more effectively improved TBIL, AST, and Cr in HBV-ACLF patients, improved 28 day effectiveness and 90 day survival rates in patients with group I liver failure, and was more cost effective. DPMAS+PE is a viable NBAL approach for treatment of HBV-ACLF.

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Keywords: Nonbiological artificial liver; Acute-on-chronic liver failure; Double plasma molecular adsorption system; Plasma exchange.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; CER, cost-effectiveness ratio; Cr, creatinine; Ca^{2+}, serum calcium; DPMAS, double plasma molecular adsorption system; HBV-ACLF, hepatitis B virus-associated acute-on-chronic liver failure; HBV, hepatitis B virus; INR, international normalized ratio; K^+, serum potassium; NBAL, nonbiological artificial liver; PE, plasma exchange; PLT, platelets; P^{3+}, serum phosphorus; PTA, prothrombin activity; TBIL, total bilirubin; WBC, white blood cells.

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Introduction

Hepatitis B virus (HBV) infection is a global public health problem. According to the World Health Organization, there were an estimated 296 million HBV carriers worldwide in 2019.[1] HBV-related acute-on-chronic liver failure (HBV-ACLF) is the most common type of liver failure in China owing to the high prevalence of HBV infection.[2] The disease progresses rapidly and is associated with high short-term rate (50–70%) in the absence of timely intervention.[3,4] However, there is lack of specific or effective therapies for HBV-ACLF. Although liver transplantation is an ideal option for patients with HBV-ACLF, the high cost, shortage of donor livers, and post-transplantation immune rejection are key limitations to its wider use.[5] Therefore, nonbiological artificial livers (NBALs) are useful for first-line treatment of HBV-ACLF.

NBAL refers to the use of *in vitro* mechanical, chemical, and biological devices to clear harmful substances, supply essential substances, stabilize the internal environment, and partially replace the liver function temporarily. NBAL may help liver function recovery or act as a bridge to liver transplantation.[5,6] In previous studies, NBAL combined with general medical treatment was found to improve short-term and long-term outcomes, and to decrease mortality in patients with liver failure.[7,8]

There are various types of NBAL, and plasma exchange (PE) is the most widely used technique in clinical practice. PE entails the use of a plasma separator membrane to filter the plasma from whole blood and infusion of the same amount of fresh frozen plasma (FFP). PE therapy supplies essential substances such as albumin and coagulation factors that are lacking in liver failure.[9] However, PE therapy requires large amounts of fresh plasma and is usually limited by inadequate plasma supply. The double plasma molecular absorption system (DPMAS) is a relatively new NBAL technology. It uses a hemoperfusion cartridge and bilirubin adsorption column to remove medium- and macro-molecular toxins, and bilirubin.[10] Although DPMAS clears multiple harmful substances and saves large amounts of plasma, it adversely affects coagulation function because of the loss of coagulation factors and the use of anticoagulants during treatment.[11]

Based on limited evidence, use of a combination of differ-

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ent types of NBAL may offer a viable alternative for treatment of patients with HBV-ACLF because their respective advantages to complement each other. Recently, the combination of low volume (1,000–1,500 mL) PE and DPMAS has been widely used to treat HBV-ACLF patients. In some studies, DPMAS+PE treatment was found to more effectively improve temporary total bilirubin (TBIL) and 28 day survival compared with simple PE in patients with early-stage HBV-ACLF.[10,12] However, studies that have investigated the combination of DPMAS and PE in the treatment for HBV-ACLF have yielded inconsistent results. Of note, the high cost of NBAL is another crucial consideration for clinical decision-making. There is a paucity of studies related to the economic evaluation of different NBAL models. Therefore, this study aimed to investigate the differences between the clinical outcomes of comprehensive medical treatment, PE, and DPMAS plus half-dose sequential PE, and to compare the economic characteristics and evaluate the safety of the three treatment models.

Methods

Research subjects and study design

This was a nonblinded, prospective clinical study that screened 254 patients with HBV-ACLF who were treated at the Department of Infectious Diseases, Xiangya Hospital, Central South University (Changsha, China) between June 2020 and October 2021. Of those, 186 who satisfied the enrollment criteria were included in the study. The inclusion criteria were: (1) age 18–65 years; (2) ACLF caused by HBV infection; and (3) meeting the ACLF diagnostic criteria of the Asian Pacific Association for the Study of Liver (APASL).[5] The exclusion criteria were: (1) pregnancy or current lactation; (2) previous liver transplantation; (3) hepatocellular carcinoma or other malignancy; (4) human immunodeficiency virus infection or other immunocompromised state; or (5) concomitant underlying diseases such as severe heart, respiratory, or hematological diseases. Based on the inclusion and exclusion criteria, we randomly assigned patients in a 1:1:1 ratio to three groups with comparable age, sex distribution, complications, and liver function: comprehensive medical treatment (control group), PE, or DPMAS plus half-dose sequential PE (DPMAS+PE). Sixty-two patients were assigned to each group. This study was approved by the Clinical Research Ethics Committee of the Xiangya Hospital, Central South University with informed content obtained from all participants (No. 202201022). The study protocol complied with the ethical principles of the Helsinki Declaration and registered at ClinicalTrials.gov (registration No. NCT05392673, https://clinicaltrials.gov/show/NCT05392673).

Treatment

Comprehensive medical treatment: All 186 enrolled patients received comprehensive medical treatment after admission to the hospital, including antiviral treatment, general supportive treatment, supplementation of blood products (such as albumin and plasma), and symptomatic treatment.

Nonbiological artificial liver treatment: In addition to comprehensive medical treatment, the other two groups were treated with PE or PE plus half-dose sequential PE. In the current study, PE was carried out with a KM-8800 plasma exchange device (Kuraray, Tokyo, Japan). The device was preflushed with 2,000 mL of normal saline and 20 U/mL heparin dilution. The blood pump speed was 100–120 mL/min and the PE speed was 25–30 mL/min. Before PE, calcium gluconate and diphenhydramine were routinely administered to prevent allergic reactions. For each PE session, 2,800 mL fresh frozen plasma was administered. DPMAS with half-dose sequential PE was administered using an EC-40W plasma separator (Asahi Kasei Medical, Tokyo, Japan), BS330 bilirubin adsorption column (Jianfan Biotechnology, Zhuhai, China), and the neutral microporous adsorption resin HA330-II (Jianfan Biotechnology). After the bilirubin adsorption and hemoperfusion treatment, sequential half-dose PE treatment was initiated. 1,400 mL plasma replacement was conducted each time.

Follow-up

Participants returned to the hospital for follow-up every 28 to 90 days after starting medication. The clinical outcomes (survival without liver transplantation) of each participant and the relevant follow-up indicators of survivors were recorded.

Observation indicators

The main biochemical indices were measured before and after treatment, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), TBIL, albumin (ALB), prothrombin activity (PTA), international normalized ratio (INR), creatinine (Cr), white blood cell (WBC) count, hemoglobin (HGB), platelet (PLT) count, serum potassium (K^+), serum calcium (Ca^{2+}), and serum phosphorus (P^{3+}). The degree of improvement of each indicator was calculated as the difference between pre- and post-treatment level/pretreatment level. The primary endpoint was the 90 day survival rate (liver transplantation-free survival rate). The secondary endpoints were the improvement of biochemical indices and coagulation function. The model for end-stage liver disease (MELD) score was calculated as: MELD = 9.57 × $\log_e$ (CR, mg/dL) + 3.78 × $\log_e$ (TBIL, mg/dL) + 11.20 × $\log^e$ (INR) + 6.43.[13]

Treatment effectiveness assessment criteria

The criteria of clinical effectiveness against liver failure were: (1) Improvement of clinical symptoms, including fatigue, anorexia, abdominal distension, and bleeding; absence of hepatic encephalopathy; (2) subsidence of jaundice and normalization of liver size; and (3) improvement of liver function indicators (TBIL<5 × upper limit of normal, PTA>40% or INR<1.5). The survival rate in this study refers to the liver transplantation-free survival rate.

Economic evaluation of NBAL treatment

In the current study, the cost-effectiveness ratio (CER) and incremental cost-effectiveness ratio (ICER) were used for the cost-effectiveness analysis in the three treatment groups, where CER = total cost/effectiveness rate and ICER = differences in cost/differences in effectiveness rate. The smaller the CER value, the lower the cost to obtain a unit effect and the more economical is the corresponding treatment. A smaller ICER value indicated less additional cost to add to effectiveness and indicated that the treatment regimen was relatively more economical compared with the alternatives. Internationally, the cost-effectiveness threshold-willingness to pay (WTP) was used to indicate the cost

that patients/physicians/medical insurance were willing to bear for better curative effect. As there is no unified standard in China, according to the World Health Organization's recommendation, the WTP threshold was set as 3-times the gross domestic product (GDP) per capita. If the ICER was less than GDP per capita, the increased cost was considered completely worth it. If the per capita GDP was less than ICER and more than 3-times the per capita GDP, the increased cost was acceptable. If the ICER was more than 3-times the per capita GDP, the increased cost was not considered worth it. The study was based on the 2021 National Economic and Social Development Statistical Bulletin issued by the National Bureau of Statistics and the national per capita GDP of 80,976 Yuan in 2021. The WTP of the study was 3-times the per capita GDP-242,928 Yuan. The dominant strategy means that when there are multiple strategies to choose from, the dominant strategy is better than the others. An absolute disadvantage indicates that when there are multiple strategies to choose from, there is always a strategy that is better than one with an absolute disadvantage.

Statistical analysis

Sample size was estimated using software G*Power version 3.1 (Heinrich-Heine-Universität Düsseldorf, Germany). The effect size f was set as a range from medium (0.24) to large (0.4), with a type I error (alpha) of 0.05 and a power of 0.80. The number of independent groups was 3 (Control, PE, and DPMAS+PE). Using a one-way analysis of variance model, the estimated required total sample size ranged from 66 to 159 (large to medium effect size). The final recruited number of patients in this study was 186.

Continuous variables were reported as means±standard deviation (SD). Intragroup comparisons between pretreatment and post-treatment values were performed with paired *t*-tests. Between-group differences were assessed using independent *t*-tests. If normality was not assumed, the nonparametric Mann-Whiney test was used. Differences in ratios (%) between groups were analyzed using chi-squared tests. Data were analyzed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA), and *p*-values <0.05 were considered statistically significant.

Results

General characteristics of the study population

The baseline characteristics of the study population are summarized in Table 1. A total of 186 eligible patients with HBV-ACLF were enrolled, with 62 patients each in the control group, PE group, and DPMAS+PE group (Fig. 1). There were no significant differences between the three groups with respect to any clinical characteristics or baseline parameters, including age, sex distribution, serum CR, blood urea nitrogen (BUN), AST, ALT, TBIL, PTA, PT, INR, K^+, Ca^{2+}, P^{3+}, WBC, PLT, Child-Pugh score, or MELD score ($p>0.05$ for all, Table 1). The results indicate that the three treatment groups were comparable.

Comparison of treatment effectiveness and liver transplantation-free survival rates in the three groups

To investigate the prognosis of different degrees of liver failure, we classified liver failure into four subgroups, group I (PTA>40%), group II (PTA 30–40%), group III (PTA 20–30%), and group IV (PTA<20%) according to the pretreatment PTA level, and compared the short-term (28 day) and long-term (90 day) effectiveness, the liver transplantation-free survival rate of the different NBAL strategies in different liver failure groups (Table 2). The 28 day effectiveness in the DPMAS+PE group was significantly greater than that in the comprehensive medical treatment group in the overall comparison (DPMAS+PE: 27.42% vs. control: 12.90%, $p=0.044$). Notably, 28 day effectiveness in the DPMAS+PE group (50%) was significantly greater than that in the PE group (50% vs. 0%, $p=0.019$) in liver failure group I (PTA>40%) In liver failure group II (PTA 30–40%), 28 day effectiveness was greater in the PE group than in the control group (37.5% vs. 9.09%, $p=0.024$). However, there were no significant differences in 28 day effectiveness in liver failure group III (PTA 20–30%). The 90 day survival rates in the three groups did not differ significantly. Nevertheless, the 90-day survival rate in the DPMAS+PE group was significantly greater than that in the PE or comprehensive medical treatment in liver failure group I (PTA>40%) (DPMAS+PE: 100.00% vs. PE: 77.78% vs. control: 36.64%, $p<0.05$). There were no significant differences in the 90 day survival rates of the three study groups.

Post-treatment changes in serum biochemical indices in comprehensive medical treatment, PE, and PE+DPMAS groups

Changes in the serum biochemical parameters of subjects in the three treatment groups are summarized in Table 3. Post-treatment serum levels of ALT and AST were significantly lower than the corresponding pretreatment levels, and the post-treatment levels of ALB, K^+, and Ca^{2+} were significantly higher than the corresponding pretreatment levels in all three treatment groups ($p<0.05$). Furthermore, in the DPMAS+PE group, the post-treatment levels of TBIL and PLT were significantly lower than the pretreatment levels (Table 3, $p<0.05$). There were no significant differences of the pre- and post-treatment INR and Cr levels in the three groups ($p>0.05$).

Comparison of the post-treatment rates of decline in serum biochemical parameters in the three groups

After calculating the rate of decline in biochemical parameters in the three groups, the differences between the PE and control groups as well as between the PE and DPMAS+PE groups were analyzed (Table 4). The rates of decrease in TBIL and Cr in the DPMAS+PE group were significantly greater than those in the PE group (59.97 vs. 12.37, 7.76 vs. 0.74, $p<0.05$). The rate of decline in AST in the DPMAS+PE group was lower than that in PE group (60.11 vs. 73.99, $p<0.05$). When compared with comprehensive medical treatment, the rate of decline in AST in the PE group was significantly greater than that in the control group (73.99 vs. 57.10, $p<0.05$). There were no significant differences in the rates of decrease in INR, ALT, and ALB for any comparisons (Table 4).

Economic evaluation of the treatments in the three groups

To characterize the cost and effect of the corresponding treatment, the average total costs, effective rates, CER, and ICER of all groups were summarized and calculated[14,15]

Table 1. Comparison of pretreatment clinical data of patients in the control group, PE group, and DPMAS+PE group

	Control group (*n*=62)	PE group (*n*=62)	DPMAS+PE group (n=62)	*p*-value
Treatment times	-	2.58±1.24	2.27±1.23	0.118
Male, *n* (%)	54 (87.10)	56 (90.32)	56 (90.32)	0.646
Age (years)	49.06±13.72	48.23±11.44	44.37±11.71	0.054
WBC ($\times10^9$/L)	5.81±2.55	6.14±2.22	6.75±3.2	0.150
PLT ($\times10^9$/L)	95.56±54.89	101.61±43.68	110.18±47.04	0.082
Albumin (g/L)	30.01±4.53	30.57±3.31	30.5±3.61	0.436
Globulin (g/L)	29.23±6.73	28.77±5.97	27.9±6.04	0.521
TBIL (μmol/L)	397.39±154.16	413.59±174.23	384.11±117	0.355
DBIL (μmol/L)	224.73±83.57	223.22±95.51	229.14±78.01	0.924
ALT (U/L)	457.30 (122.35,780.25)	370.80 (179.48,634.33)	496.20 (208.83,946.93)	0.058
AST (U/L)	288.80 (152.60,531.75)	267.55 (165.73,480.75)	309.65 (165.05,782.25)	0.398
Urea (mmol/L)	6.09±4.8	4.81±3.08	4.21±1.6	0.051
Creatinine (μmol/L)	94.35±45.41	92.37±27.79	90.86±16.79	0.565
PTA (%)	39.69±12.57	39.89±15.04	41.09±18.72	0.888
PT (sec)	23.91±8.81	23.21±6.67	24.94±16.81	0.705
INR	2.12±0.94	2.03±0.61	2.2±1.23	0.969
K^+ (mmol/L)	3.83±0.49	3.74±0.46	3.8±0.47	0.445
Ca^{2+} (mmol/L)	2.14±0.16	2.13±0.13	2.11±0.11	0.552
P^{3+} (mmol/L)	0.77±0.26	0.79±0.25	0.78±0.22	0.949
Child-Pugh score	10.92±1.86	10.85±1.91	10.89±1.85	0.561
MELD score	19.93±4.55	21.33±3.28	21.21±2.34	0.069
Group of liver failure				
Group I	11 (17.74)	9 (14.52)	12 (19.35)	11 (17.74)
Group II	22 (35.48)	24 (38.71)	18 (29.03)	22 (35.48)
Group III	18 (29.03)	17 (27.42)	19 (30.65)	18 (29.03)
Group IV	11 (17.74)	12 (19.35)	13 (20.97)	11 (17.74)

Data are frequency (%), median M (P25, P75), or mean±standard deviation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ca^{2+}, serum calcium; DBIL, direct bilirubin; DPMAS, double plasma molecular adsorption system; INR, international normalized ratio; K^+, serum potassium; MELD, model for end-stage liver disease; PE, plasma exchange; PLT, platelets; PTA, prothrombin activity; PT, prothrombin time; P^{3+}, serum phosphorus; TBIL, total bilirubin; WBC, white blood cells.

(Table 5). For subjects in liver failure group I (PTA>40%), the CER value in the DPMAS+PE group was significantly lower than that in the PE and control groups, which indicates a better cost-effectiveness advantage. Additionally, the ICER in the DPAMS+PE group (59,118.2) was less than the *per capita* GDP, indicating that the increased cost was completely worth it. In the PE group, the ICER value of the patients with liver failure in all groups was higher than the *per capita* GDP, which was indicative of an absolute disadvantage strategy. In patients with group II (PTA 30–40%) and group III (PTA 20–30%) liver failure, the PE CERs were 92,213.82 and 174,538.14, respectively, which indicates a cost-effectiveness advantage compared with the DPMAS+PE group. Moreover, the ICER values of the PE group were between 1- and 3-times the per capita GDP for patients with group II (PTA 30–40%) and group III (PTA 20–30%) liver failure, which was acceptable for the increased cost. However, in the subjects with group IV (PTA<20%) of liver failure, the comprehensive medical treatment group showed a lower CER value and a better cost-effectiveness advantage compared with the PE and DPMAS+PE groups (Table 5).

Safety

The 62 patients in the PE group received a total of 160 treatments, and 29 patients (18.13%) developed adverse reactions. Of those, 26 developed chills, urticaria, and fever, which improved after anti-allergy treatment, and three developed hypotension, which improved after anti-allergy and vasopressor treatment). The 62 patients in the DPMAS+PE group received 140 treatments. Of those, 25 (17.86%) developed cold urticaria, which improved after antiallergy treatment. None of the patients in the medical treatment group experienced any adverse reactions. During the 90 day observation period, no serious treatment-related adverse events, such as coagulation dysfunction or hypotension, were observed in the two kinds of abiotic artificial livers used to treat HBV-ACLF patients.

Discussion

The treatment of liver failure is inherently challenging and

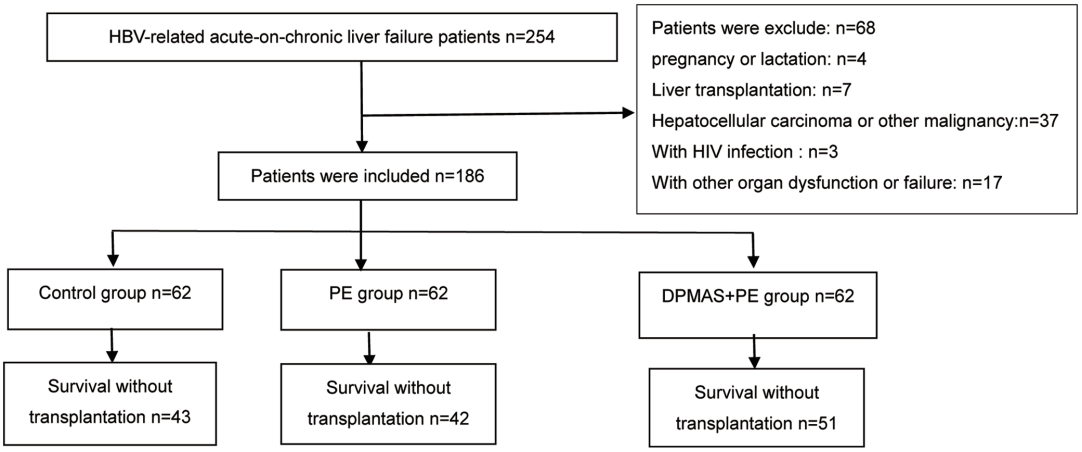

Fig. 1. Flow chart of patient inclusion.

Table 2. Treatment effectiveness in different groups according to the degree of liver failure

Liver failure group	Group	N	28 day effectiveness (%)	*p*-value	90 day survival (%)	*p*-value
Total	Control	62	8/62 (12.90)		43/62 (69.35)	
	PE	62	13/62 (20.97)	0.231[a]	42/62 (67.74)	0.847
	DPMAS+PE	62	17/62 (27.42)	0.044[a]	51/62 (82.26)	0.093[a]/0.062[b]
Group I	Control	11	3/11 (27.27)		4/11 (36.36)	
	PE	9	0/9 (0)	0.089[a]	7/9 (77.78)	0.037
	DPMAS+PE	12	6/12 (50.00)	0.019[b]	12/12 (100.00)	<0.001[a]/0.086[b]
Group II	Control	22	2/22 (9.09)		18/22 (81.82)	
	PE	24	9/24 (37.50)	0.024[a]	20/24 (83.33)	0.892
	DPMAS+PE	28	6/18 (33.33)	0.057[a]	16/18 (88.89)	0.533[a]/0.611[b]
Group III	Control	18	2/18 (11.11)		14/18 (77.78)	
	PE	17	3/17 (17.65)	0.658[a]	10/17 (58.82)	0.227
	DPMAS+PE	19	6/19 (31.58)	0.232[a]	15/19 (78.95)	0.931[a]/0.191[b]
Group IV	Control	11	0/11 (0)		7/11 (63.64)	
	PE	12	1/12 (8.33)	1.000[a]	5/12 (41.67)	0.292
	DPMAS+PE	13	2/13 (15.38)	0.482[a]	8/13 (61.54)	0.916[a]/0.320[b]

Data are frequency (%). DPMAS, double plasma molecular adsorption system; PE, plasma exchange; [a]Comparison with comprehensive medical group; [b]Comparison with PE group. Control, comprehensive medical treatment group.

Table 3. Serum biochemical indices in the three study groups before and after NBAL treatment

	Group	n	TBIL (mmol/L)	ALT (U/L)	AST (U/L)	INR	Cr (mg/dL)
Control	Before	62	397.39±154.16	457.30 (122.35, 780.25)	288.80 (152.60, 531.775)	2.12±0.94	94.35±45.41
	After	62	256.2±206.52	59.20 (42.70, 88.10)	111.20 (77.80, 167.70)	2.01±1.3	79.99±16.33
	p-value		0.07	<0.001	<0.001	0.592	0.135
PE	Before treatment	62	413.59±174.23	370.80 (179.48, 634.33)	267.55 (165.73, 480.75)	2.03±0.61	92.37±27.79
	After Treatment	62	360.14±194.35	56.80 (40.38, 77.38)	105.35 (75.55, 148.85)	1.9±0.88	88.28±22.47
	p-value		0.219	<0.001	<0.001	0.067	0.389
DPMAS +PE	Before treatment	62	384.11±117	496.20 (208.83, 946.93)	309.65 (165.05, 782.25)	2.2±1.23	90.86±16.79
	After	62	228.22±117.65	70.90 (47.70, 112.20)	122.40 (82.50, 190.7)	1.84±0.59	89.53±28.2
	p-value		<0.001	<0.001	<0.001	0.056	0.229

Data are frequency (percentage), medians M (P25, P75), or means±standard deviation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; DPMAS, double plasma molecular adsorption system; INR, international normalized ratio; PE, plasma exchange; TBIL, total bilirubin.

Table 4. Comparison of the rate of decline in biochemical parameters after NBAL treatment

Group	n	INR (%)	TBIL (%)	ALT (%)	AST (%)	ALB (%)	Cr (%)
Control	62	9.12 (−7.5, 22.66)	47.17 (−102.7,178.8)	80.16 (67.28, 94.40)	57.10 (19.92, 74.51)	−20.60 (−30.99, −8.91)	5.56 (−4.02, 12.85)
PE	62	6.36 (−14.73, 26.29)	12.37 (−35.27, 32.85)	83.90 (67.85, 93.66)	73.99 (41.89, 98.54)	−10.78 (−23.85, 3.53)	0.74 (−11.12, 8.43)
DPMAS +PE	62	8.63 (−8.78, 30.12)	59.97 (28.63, 79.11)	84.58 (49.21, 93.11)	60.11 (−10.04, 87.14)	−12.42 (−25.13, −1.73)	7.76 (−1.54, 15.61)
P-value		0.558[a]	<0.001[b]	0.253[a]	<0.001[a,b]	0.632[a]	<0.001[a,b]

Data are medians M (P25, P75). [a]Comparison between comprehensive medical and PE group; [b]comparison PE and DPMAS+PE group. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; Cr, creatinine; DPMAS, double plasma molecular adsorption system; INR, international normalized ratio; PE, plasma exchange; TBIL, total bilirubin.

the prognosis is poor, which imposes great pain and economic burden on the patients. hepatitis B virus infection is the main causative factor of ACLF. Systemic inflammatory response syndrome plays a key role in the pathophysiology of the condition, in which cytokines play a particularly important role. The inflammatory response leads to a series of chain reactions, causing massive necrosis of hepatocytes, inflammatory cell infiltration, and hepatic ischemic injury, as well as enterogenous endotoxemia caused by injury of the intestinal mucosal barrier. The accumulation of many nonspecific inflammatory cytokines in the liver results in secondary damage to the liver, resulting in liver failure.[16] Patients with ACLF have significant impairment of the detoxification function of the liver, leading to the accumulation of a large number of toxic substances in the body, including various water-soluble toxins, protein-bound toxins, and metabolites that seriously affect regeneration and function recovery.[17] NBAL is important method for the treatment of liver failure. The rapid development of this technology has greatly improved the treatment of liver failure in patients with severe hepatitis.[17] NBALs that include PE are widely used because of the low cost and simple operation. PE effectively scavenges toxic metabolites and supplements biologically active substances.[18,19] However, inadequate availability of plasma and adverse reactions are key limitations that prevent the wider clinical use of PE.

In recent years, with the popularization and application of artificial liver treatment without PE, has led to increasing use of DPMAS in clinical settings. That model has low requirements for equipment and shows good compatibility. The basic feature of the technical application is plasma separation and adsorption of inflammatory media through an adsorption system. Many studies have shown that DPMAS effectively removes serum cytokines and inflammatory mediators, improves liver function, saves plasma resources, and reduces related virus infections and allergic reactions. However, DPMAS also binds to protein toxins, resulting in a huge loss of albumin in the body and affecting coagulation function. The combination of DPMAS and PE can make up for their respective shortcomings to a great extent, effectively eliminating toxins and inflammatory factors, and supplementing nutrients at the same time.[20]

In our study, the DPMAS+PE and PE treatment increased the 28 day effectiveness and 90 day liver transplantation-free survival rates compared with the control group in patients with PTA>40 (group I). That is consistent with a pre-

Table 5. CER and ICER in all treatment groups

Liver failure group failure	Group	Total cost (C_1, yuan)	Effectiveness (%) (E)	CER (C_1/E)	ΔC	ΔE	ICER (ΔC/ΔE)
Total	Control	30,505.11	0.53	57,308.12			
	PE	77,698.00	0.53	145,966.57	47,192.89		
	DPMAS+PE	98,447.98	0.61	160,626.49	67,942.87		
Group I	Control	31,177.81	0.27	114,288.16			
	PE	94,530.20	0.56	170,140.75	63,352.39	0.28	224,018.36
	DPMAS+PE	74,168.58	1.00	74,168.58	42,990.77	0.73	59,118.22
Group II	Control	26,775.40	0.55	49,084.15			
	PE	76,841.78	0.83	92,213.82	50,066.37	0.29	173,962.38
	DPMAS+PE	98,778.88	0.78	126,997.78	72,003.47	0.23	309,958.99
Group III	Control	33,716.04	0.61	55,181.73			
	PE	71,874.81	0.41	174,538.14	38,158.77	0.20	190,793.86
	DPMAS+PE	117,557.64	0.37	319,103.26	83,841.60	0.24	349,340.02
Group IV	Control	32,329.50	0.27	118,553.37			
	PE	79,243.88	0.33	237,755.42	46,914.38	0.06	774,164.66
	DPMAS+PE	98,929.8	0.62	160,756.91	66,600.30	0.34	194,339.94

Data are medians M (P25, P75). CER, cost-effectiveness ratio; C_1, total cost; PE, plasma exchange; DPMAS, double plasma molecular adsorption system; E, effective rate; ICER, incremental cost-effectiveness ratio.

vious study in which PE+DPMAS was found to significantly reduce 28 day mortality in patients with mild ACLF.[12] Another study showed that PE improved the prognosis of ACLF patients to a certain extent.[21] The effectiveness of DPMAS+PE in the initial stages of HBV-ACLF is likely attributable to blocking hepatocellular damage caused by the inflammatory factor storm. Previous studies have shown that inflammatory damage caused by the hyperimmune response has an important role in the initial stages of HBV-ACLF.[22,23] Artificial livers effectively remove inflammatory factors, bilirubin, and other harmful substances and block the inflammatory factor storm.[24,25] In addition, compared with groups II, III, and IV, group I represents the initial stage of disease development. The second reason is that with the aggravation of liver damage, the ability of liver regeneration is gradually reduced or even lost.[26,27] The degree of liver injury in the initial stage of HBV-ACLF (group I) is milder than that in groups II, III, and IV. The artificial liver creates conditions for hepatocyte regeneration in patients with initial-stage HBV-ACLF.[28]

In this study, both DPMAS+PE and PE effectively reduced ALT and AST levels in patients with ACLF, which is consistent with previous studies. However, in contrast to other studies, there was no significant difference in the reduction of TBIL level in the PE compared. with the control group, which may be attributable to the death of patients with severe disease before the end of follow-up. Previous studies have shown that PE effectively adsorbs bilirubin and improves liver function. However, in this study, DPMAS+PE had a significantly better ability to reduce bilirubin than PE alone. When different modes of NBAL are used, the respective advantages to complement each other. Combined use overcomes the limitations of traditional treatment and achieves the best curative effect, which is the future direction of artificial liver technology development.

However, although DPMAS is believed to reduce the amount of plasma required, it increases the cost of treatment. At present, there is a paucity of econometric evaluations of the combined NBAL therapies worldwide.[29] In our study, DPMAS with half-dose sequential PE combination treatment was found to save fresh frozen plasma and reduce the treatment cost. In addition, in patients with PTA>40%, DPMAS+PE treatment had a lower CER value and a better cost-effectiveness advantage. At the same time, DPMAS+PE significantly improved effectiveness and the liver transplantation-free survival of patients with PTA>40%. Therefore, DPMAS with half-dose sequential PE combination treatment may be a viable option for patients with HBV-ACLF, especially those with PTA>40%.

Some limitations of this study should be acknowledged. Foremost among them, it was a single-center study with a relatively small sample size and short follow-up period. A larger multicenter study is required to provide more robust evidence.

In conclusion, compared with PE treatment alone, DPMAS+PE was found to be more effective in improving liver function and creatinine levels in patients with ACLF, and was found to be more effective in improving the 90 day liver transplantation-free survival rate in HBV-ACLF patients with PTA>40% (group I), with a cost-effectiveness advantage. DPMAS+PE was found to be effective only in the initial stages of HBV-ACLF. Therefore, DPMAS+PE may be a potential NBAL approach for the treatment of HBV-ACLF patients with a PTA of >40% (group I). Further prospective studies are required to investigate the effect of DPMAS+PE on long-term survival.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Designed the experiments and supervised the study (LF), collected the clinical data (HG, FL), performed the experiments and wrote the manuscript (CW, TP), and assisted in experiments (DC).

Ethical statement

This study was approved by the Clinical Research Ethics Committee of the Xiangya Hospital, Central South University with informed content obtained from all participants (No. 202201022). The study protocol complied with the ethical principles of the Helsinki Declaration and registered at ClinicalTrials.gov (registration No. NCT05392673, https://clinicaltrials.gov/show/NCT05392673).

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] Akbar SMF, AL-Mahtab M, Khan S, Yoshida O, Hiasa Y. "Elimination of Hepatitis by 2030": Present Realities and Future Projections. Infect Dis Immun 2022;2(1):3–8. doi:10.1097/ID9.0000000000000028.
[2] Guideline for diagnosis and treatment of liver failure. Zhonghua Gan Zang Bing Za Zhi 2019;27(1):18–26. doi:10.3760/cma.j.issn.1007-3418.2019.01.006, PMID:30685919.
[3] Wu T, Li J, Shao L, Xin J, Jiang L, Zhou Q, *et al*. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut 2018;67(12):2181–2191. doi:10.1136/gutjnl-2017-314641, PMID:28928275.
[4] Li H, Chen LY, Zhang NN, Li ST, Zeng B, Pavesi M, *et al*. Characteristics, Diagnosis and Prognosis of Acute-on-Chronic Liver Failure in Cirrhosis Associated to Hepatitis B. Sci Rep 2016;6:25487. doi:10.1038/srep25487, PMID:27146801.
[5] Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, *et al*. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int 2019;13(4):353–390. doi:10.1007/s12072-019-09946-3, PMID:31172417.
[6] Li LJ, Zhang YM, Liu XL, Du WB, Huang JR, Yang Q, *et al*. Artificial liver support system in China: a review over the last 30 years. Ther Apher Dial 2006;10(2):160–167. doi:10.1111/j.1744-9987.2006.00358.x, PMID:16684218.
[7] Karvellas CJ, Subramanian RM. Current Evidence for Extracorporeal Liver Support Systems in Acute Liver Failure and Acute-on-Chronic Liver Failure. Crit Care Clin 2016;32(3):439–451. doi:10.1016/j.ccc.2016.03.003, PMID:27339682.
[8] Keklik M, Sivgin S, Kaynar L, Pala C, Solmaz M, Cetin M, *et al*. Treatment with plasma exchange may serve benefical effect in patients with severe hyperbilirubinemia: a single center experience. Transfus Apher Sci 2013;48(3):323–326. doi:10.1016/j.transci.2013.04.009, PMID:23602141.
[9] Reeves HM, Winters JL. The mechanisms of action of plasma exchange. Br J Haematol 2014;164(3):342–351. doi:10.1111/bjh.12629, PMID:24172059.
[10] Yao J, Li S, Zhou L, Luo L, Yuan L, Duan Z, *et al*. Therapeutic effect of double plasma molecular adsorption system and sequential half-dose plasma exchange in patients with HBV-related acute-on-chronic liver failure. J Clin Apher 2019;34(4):392–398. doi:10.1002/jca.21690, PMID:30758886.

[11] Xu W, Li Y, Wang L, Gao H, Chen J, Yuan J, *et al*. Efficacy and safety of combination treatment of double plasma molecular adsorption system and low volume plasma exchange for patients with hepatitis B virus related acute-on-chronic liver failure: a multicentre randomised controlled clinical trial. BMJ Open 2021;11(12):e047690. doi:10.1136/bmjopen-2020-047690, PMID:34907041.
[12] Guo X, Wu F, Guo W, Zhang J, Yang Y, Lu Y, *et al*. Comparison of plasma exchange, double plasma molecular adsorption system, and their combination in treating acute-on-chronic liver failure. J Int Med Res 2020; 48(6):300060520932053. doi:10.1177/0300060520932053, PMID:32552092.
[13] Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31(4):864–871. doi:10.1053/he.2000.5852, PMID:10733541.
[14] Marsden G, Wonderling D. Cost-effectiveness analysis: role and implications. Phlebology 2013;28(Suppl 1):135–140. doi:10.1177/0268355512475119, PMID:23482549.
[15] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ 2010;19(4):422–437. doi:10.1002/hec.1481, PMID:19382128.
[16] Casulleras M, Zhang IW, Lopez-Vicario C, Claria J. Leukocytes, Systemic Inflammation and Immunopathology in Acute-on-Chronic Liver Failure. Cells 2020;9(12):2632. doi:10.3390/cells9122632, PMID:33302342.
[17] Shen Y, Wang XL, Wang B, Shao JG, Liu YM, Qin Y, *et al*. Survival Benefits With Artificial Liver Support System for Acute-on-Chronic Liver Failure: A Time Series-Based Meta-Analysis. Medicine (Baltimore) 2016;95(3):e2506. doi:10.1097/MD.0000000000002506, PMID:26817889.
[18] Winters JL. Plasma exchange: concepts, mechanisms, and an overview of the American Society for Apheresis guidelines. Hematology Am Soc Hematol Educ Program 2012;2012:7–12. doi:10.1182/asheducation-2012.1.7, PMID:23233554.
[19] Inoue K, Watanabe T, Hirasawa H, Yoshiba M. Liver support systems as perioperative care in liver transplantation-historical perspective and recent progress in Japan. Minerva Gastroenterol Dietol 2010;56(3):345–353. PMID: 21037550.
[20] Yang CF, Zhang Z, Zhang XY, Li YM. Artificial liver support system in pediatric acute liver failure due to mushroom poisoning: Case series. Ann Hepatol 2021;23:100290. doi:10.1016/j.aohep.2020.100290, PMID:33221398.
[21] Zhong S, Wang N, Zhao J, Zhang L, Luo L, Zeng WQ, *et al*. [Plasma exchange combined with double plasma absorption therapy improve the prognosis of acute-on-chronic liver failure]. Zhonghua Gan Zang Bing Za Zhi 2018;26(10):744–749. doi:10.3760/cma.j.issn.1007-3418.2018.10.003, PMID:30481880.
[22] Arroyo V, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, *et al*. The systemic inflammation hypothesis: Towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol 2021;74(3):670–685. doi:10.1016/j.jhep.2020.11.048, PMID:33301825.
[23] Clària J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, *et al*. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology 2016;64(4):1249–1264. doi:10.1002/hep.28740, PMID:27483394.
[24] Vaninov N. In the eye of the COVID-19 cytokine storm. Nat Rev Immunol 2020;20(5):277. doi:10.1038/s41577-020-0305-6, PMID:32249847.
[25] Zhe-Bin W, Ke W, Mo ZS, Zhen X, Yu-Bao Z, Ying Y, *et al*. Early, short-term, low-dose glucocorticoid therapy effectively blocks progression of severe acute exacerbation of chronic hepatitis B to liver failure. Clin Res Hepatol Gastroenterol 2021;45(5):101505. doi:10.1016/j.clinre.2020.07.010, PMID:32896504.
[26] Michalopoulos GK, Bhushan B. Liver regeneration: biological and pathological mechanisms and implications. Nat Rev Gastroenterol Hepatol 2021;18(1):40–55. doi:10.1038/s41575-020-0342-4, PMID:32764740.
[27] Miyajima A, Tanaka M, Itoh T. Stem/progenitor cells in liver development, homeostasis, regeneration, and reprogramming. Cell Stem Cell 2014;14(5): 561–574. doi:10.1016/j.stem.2014.04.010, PMID:24792114.
[28] Tandon R, Froghi S. Artificial liver support systems. J Gastroenterol Hepatol 2021;36(5):1164–1179. doi:10.1111/jgh.15255, PMID:32918840.
[29] Kong LX, Qiu F, Wang HM, Shan XF, Hu P, Zhong S, *et al*. [Economic evaluation of plasma exchange combined with dual plasma adsorption therapy for early, mid and late stage liver failure]. Zhonghua Gan Zang Bing Za Zhi 2020; 28(5):434–440.doi:10.3760/cma.j.cn501113-20190122-00025,PMID:32536061.