Therapeutics and Clinical Risk Management

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Comparative Cost-Effectiveness of Two Artificial Liver Therapies in Early-Stage Hepatitis B Virus-Related Acute-on-Chronic Liver Failure: A Retrospective Cohort Study

Jia Chen[1,*], Qiumin Luo[1,*], Lu Wang[2,*], Lihua Zheng[1], Yeqiong Zhang[1], Ying Liu[1], Liang Peng[1,3], Wenxiong Xu[1]

[1]Department of Infectious Diseases and Guangdong Key Laboratory of Liver Disease Research, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, People's Republic of China; [2]Department of Diagnostics, second School of Clinical Medicine, Binzhou Medical University, Yantai, Shandong, People's Republic of China; [3]Key Laboratory of Tropical Disease Control, Ministry of Education, Sun Yat-sen University, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wenxiong Xu; Liang Peng, Department of Infectious Disease, Third Affiliated Hospital of Sun Yat-sen University, 600# Tianhe Road, Tianhe District, Guangzhou, Guangdong province, 510630, People's Republic of China, Tel +8613760783281; +8613533978874, Email xuwenx@mail.sysu.edu.cn; pliang@mail.sysu.edu.cn

Purpose: This study aimed to compare the cost-effectiveness of the double plasma molecular adsorption system sequential low-volume plasma exchange (DPMAS+LPE) versus conventional plasma exchange (PE) in treating early-stage hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF).

Patients and Methods: A total of 215 early-stage HBV-ACLF patients were assigned to either DPMAS+LPE or conventional PE groups. After propensity score matching (1:1), 101 matched pairs were analyzed. We compared 30- and 90-day survival rates and direct medical costs from the healthcare payer's perspective. Cost-effectiveness analysis was performed with a willingness-to-pay (WTP) threshold of $12,681 and $38,043, equivalent to 1 and 3 times China's 2023 per capita GDP. Univariate and probabilistic sensitivity analyses (Bootstrap method) were used to assess parameter uncertainty.

Results: Over the 90-day follow-up period, the DPMAS+LPE group had numerically higher survival rates compared to the PE group, but this difference was not statistically significant (91.04% vs 83.07%, Logrank: P=0.094). Compared to PE, DPMAS+LPE showed no economic benefit at 30 days. At 90 days, each 1% increase in the survival rate with DPMAS+LPE required an additional $3013.68 in medical costs, demonstrating cost-effectiveness. In the cirrhosis subgroup, the 90-day average total medical cost of the DPMAS+LPE group was lower than that of the PE group. At a WTP threshold of $12,681, the probability of DPMAS+LPE being cost-effective was 14% at 30 days and 75% at 90 days. At a WTP of $38,043, these probabilities increased to 45% and 90%, respectively. Univariate sensitivity analysis demonstrated that variations in the 90-day survival rates and costs for both groups still favored DPMAS+LPE within the 95% confidence interval. However, when the number of DPMAS+LPE treatments exceeded 4.4, it was no longer cost-effective.

Conclusion: Compared to PE, DPMAS+LPE demonstrated cost-effectiveness at 90 days in early-stage HBV-ACLF patients, particularly those with cirrhosis. While DPMAS+LPE can be considered a suitable artificial liver therapy option for early-stage HBV-ACLF, careful consideration must be given to the number of treatments to ensure cost-effectiveness.

Keywords: acute-on-chronic liver failure, double plasma molecular adsorption system, plasma exchange, economic evaluation

Introduction

Acute-on-chronic liver failure (ACLF) is a complex clinical syndrome characterized by acute decompensation in patients with pre-existing chronic liver disease, leading to high short-term mortality rates.[1,2] Globally, ACLF affects

Received: 13 February 2025
Accepted: 4 July 2025
Published: 12 July 2025

approximately 35% of patients admitted with cirrhosis, with mortality rates reaching 45% at 28 days and 58% at 90 days.[3] In the Asia-Pacific region, particularly in China, hepatitis B virus (HBV) infection is a predominant cause of ACLF, accounting for 40% of the underlying chronic liver disease in these patients.[3,4] This condition not only poses a significant threat to patient survival but also imposes substantial financial and emotional burdens on patients and their families.[5]

Artificial liver support systems (ALSS) serve as a temporary supportive therapies, acting as a bridge to liver transplantation or facilitating liver cell regeneration.[6] Systematic reviews and meta-analyses have demonstrated that among various artificial liver treatment modalities, plasma exchange (PE) stands out as the most effective in improving overall 3-month survival rates in ACLF patients.[7] In recent years, combinations of non-bioartificial liver support system, which utilize PE as a core component, have gained traction in clinical practice and research.[8] This approach capitalizes on the synergistic effects of multiple treatment modalities, demonstrating significant improvements in patient outcomes, particularly for those classified as ACLF grades 1 and 2.[9–13] One promising approach is the double plasma molecular adsorption system sequential low-dose plasma exchange (DPMAS+LPE). This system utilizes bilirubin adsorption columns (BS330) and neutral large-pore resin adsorption columns (HA330-II) to eliminate toxins such as inflammatory mediators and bilirubin, while also delivering albumin and clotting factors.[14,15] Studies indicate that DPMAS+LPE not only enhances short-term survival rates but also reduces the total volume of plasma required for treatment, contributing to better management of patients with ACLF.[16–18]

In an era of constrained healthcare resources, treatment decisions for ACLF must balance clinical efficacy with economic considerations. ALSS, such as DPMAS+LPE, offer potential therapeutic advantages for hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF), while the higher costs associated with DPMAS+LPE necessitate a thorough evaluation of its cost-effectiveness compared to PE. Two small-sample studies from China have explored the cost-effectiveness of PE and DPMAS combined with PE, suggesting potential economic benefits for the combined approach in early-stage HBV-ACLF.[17,19] However, these studies did not directly compare DPMAS+LPE with PE head-to-head. Internationally, several European studies have mainly focused on the comparison between molecular adsorbent recirculating system (MARS) and standard medical treatment (SMT).[20–23] Despite these findings, controversy persists regarding MARS's impact on survival rates, and its high cost and prolonged treatment duration limit its use in China.

In light of these gaps, this study aims to assess the cost-effectiveness of DPMAS+LPE in comparison to PE for early-stage HBV-ACLF patients. The 90-day period is particularly significant, as it is when the impacts of clinical interventions become apparent. To investigate this further, we utilize real-world clinical data to analyze 30-day and 90-day survival rates along with the associated direct medical costs. This analysis offers new insights into the practical application of these two artificial liver treatment modalities from a cost-effectiveness perspective.

Methods

Study Design

This retrospective study collected real-world clinical data from early-stage HBV-ACLF patients treated with artificial liver therapy at the Third Affiliated Hospital of Sun Yat-sen University, spanning January 2021 to September 2023. Patients were divided into two groups based on the type of artificial liver treatment received: the DPMAS+LPE group and the PE group. The primary efficacy endpoint was the 90-day survival rate, and the secondary endpoint was the 30-day survival rate. Survival information and direct medical costs were obtained from the hospital information system (HIS) and via telephone follow-ups (Figure 1). The median follow-up duration was 90 days (IQR: 90–90 days).

Study Population and Treatment

Patients selected for the study met the Chinese Group on the Study of Severe Hepatitis B(COSSH) criteria[24] for ACLF (diagnostic criteria in Appendix 1). Inclusion criteria were: (1) age 18–65 years; (2) early-stage HBV-ACLF:[25] total bilirubin (TBIL) > 12 mg/dL and international normalized ratio (INR) between 1.5 and 2.5; or renal dysfunction (creatinine 1.5–1.9 mg/dL), or grade I - II hepatic encephalopathy. (3) positive HBsAg or persistent HBV DNA for more than 6 months; and (4) receiving DPMAS+LPE or PE treatment at least twice. The exclusion criteria were as follows: (1) liver disease due to other

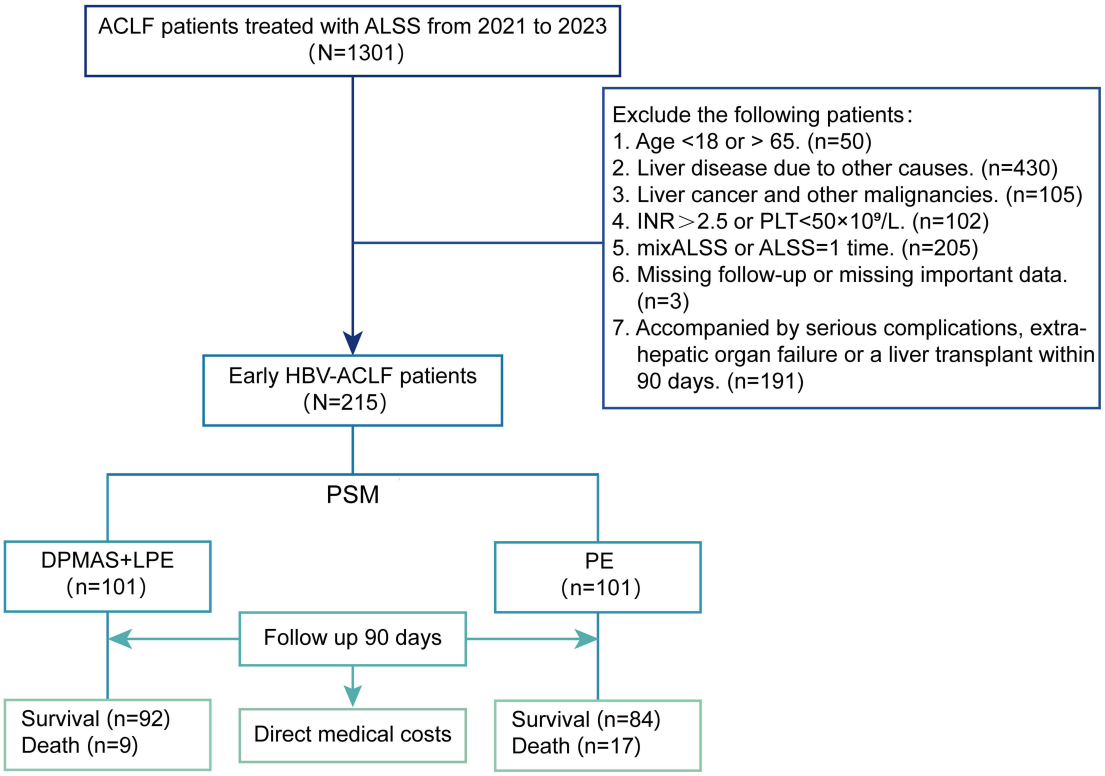

Figure 1 A flowchart of the research.
Abbreviations: DPMAS+LPE, double plasma molecular adsorption system sequential low-dose plasma exchange; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; PE, plasma exchange; PTA, prothrombin activity; ALSS, Artificial liver support systems; PSM, propensity score matching.

causes (eg, hepatitis C, alcohol-related liver disease, drug-induced liver injury); (2) hepatocellular carcinoma or other malignancies; (3) platelet count< 50 × 10E9/L or INR >2.5; (4) grade III–IV hepatic encephalopathy, serum creatinine ≥ 2 mg/dL, active bleeding, or other organ failure; (5) mixed ALSS treatment during hospitalization (ie, receiving different modes of artificial liver therapy); (6) liver transplantation within 90 days; (7) pregnancy or lactation; and (8) unstable chronic diseases (eg, diabetes, hypertension, coronary arteriosclerotic cardiopathy, autoimmune diseases, stroke). (9) Missing follow-up or missing important data.

All patients received comprehensive internal medicine treatment in addition to artificial liver therapy. This includes monitoring vital signs and organ function, plasma transfusion, albumin infusion, nutritional support, removal of precipitating factors (eg, antimicrobial treatment for infections), nucleoside/nucleotide analogues (NAs), hepatoprotective and jaundice-reducing medications to promote liver function recovery, and management of complications.

Both groups underwent central venous or femoral vein catheterization before non-bioartificial liver treatment, with extracorporeal heparin anticoagulation during ALSS treatment (see Appendix 4 for heparin usage principles). In the PE group, partial plasma was separated using a blood plasma separator (MICROPLAS MPS 07, BELLCO S.R.L., Italy), and 2000 mL of fresh frozen plasma was infused, at a plasma exchange rate of 25–30 milliliters/minute. The DPMAS+LPE group used the same extracorporeal circuit, but also employed a plasma bilirubin adsorption column (BS330, Jafron Biomedical Co., Ltd., Zhuhai, China) and a disposable hemoperfusion cartridge (HA330-II, Jafron Biomedical Co., Ltd., Zhuhai, China). DPMAS treatment was performed first, followed by low-dose PE with an additional 1000 mL of fresh frozen plasma. The plasma adsorption rate in DPMAS treatment is 25 to 30 milliliters/minute, with a total of 5000 milliliters of plasma adsorption volume. The ALSS frequency was 2–3 times per week. Adverse reactions during treatment, such as hypotension, plasma allergy, bradycardia, bleeding, or thrombosis, were promptly managed.

https://doi.org/10.2147/TCRM.S521406

Cost Calculation

The cost evaluation in pharmacoeconomics includes direct costs, indirect costs, and "intangible" costs.[26] Direct costs encompass both direct medical costs and direct non-medical costs. Direct medical costs specifically refer to the consumption of medical resources during treatment. Since this study focuses on the consumption of social medical resources by two modes of non-bioartificial liver therapy, we only considered direct medical costs (hospital charges). These costs include detailed expenses from the initial hospitalization, such as medication, medical supplies, bed fees, nursing fees, laboratory and examination fees, treatment costs, and transfusion fees, as well as outpatient treatment and readmission costs within 90 days due to liver disease. The costs were directly obtained from the HIS and telephone interviews.

As shown in Supplementary Table 1, the cost per treatment session for DPMAS+LPE was $1773.5, while for PE it was $945.5. Since the incidence of ALSS-related adverse reactions was not significantly different between the two groups and the cost of managing these reactions was minimal, adverse reaction costs were not included separately in the cost calculations. Given the 90-day study period, discounting was not applied. The cost data span from 2021 to 2023, and all costs were adjusted for inflation to 2023 values using the Chinese healthcare consumer price index (CPI) obtained from the National Bureau of Statistics (Supplementary Table 2). All expenses were converted to USD at the average 2023 exchange rate of 7.0467 RMB to 1 USD.

Cost-Effectiveness Analysis

The economic benefit of the two treatment modes was assessed using cost-effectiveness analysis. The cost-effectiveness ratio (CER) represents the ratio of the total costs to the effectiveness rate, with a lower CER indicating better economic efficiency. The incremental cost-effectiveness ratio (ICER) calculates the cost difference and effectiveness difference between the two groups (ΔC/ΔE) indicating the additional cost required for each unit of effectiveness gained with DPMAS+LPE compared to PE. In decision-making, the ICER is compared to the willingness-to-pay (WTP) threshold. According to the Chinese Pharmacoeconomic Evaluation Guidelines, the WTP threshold is set at 1–3 times the 2023 per capita GDP of China ($12,681-$38,043). An ICER below $12,681 indicates cost-effectiveness, while an ICER between $12,681-$38,043 is considered acceptable, and an ICER above $38,043 is deemed not cost-effective. Additionally, net monetary benefit (NMB) is used to evaluate economic benefit. The incremental net monetary benefit (INMB) compares the net economic benefits of DPMAS+LPE to PE.

The calculation formulae of relevant economic indicators are as follows:

$$ICER = \frac{C1 - C0}{E1 - E0} = \frac{\Delta C}{\Delta E}$$

$$NMB = E \times WTP - C$$

$$INMB = (E1 - E0) \times WTP - (C1 - C0)$$

E stands for effectiveness, C stands for cost. C1 and E1 represent the total cost and survival rate for the DPMAS+LPE group, respectively, while C0 and E0 represent the total cost and survival rate for the PE group, respectively. When calculating NMB, a WTP of $38,043 is used.

Sensitivity Analysis

Sensitivity analysis was conducted to assess the impact of parameter uncertainty on the cost-effectiveness results. Probabilistic sensitivity analysis used the bootstrap method with 5000 resamples to calculate incremental costs and effects, determining the 95% confidence for incremental cost-effectiveness (ICE). The ICER confidence interval is displayed as a wedge-shaped region on the cost-effectiveness plane.[27] One-way sensitivity analysis examined the economic conclusions by varying single parameters within plausible ranges. Survival rates, total costs and average hospital days were varied within the study's 95% CI, ALSS treatment frequencies were adjusted to the lowest and highest

values observed in the study, the cost of HA330-II and BS330 was adjusted by ±25%. The direction and magnitude of the changes in the INMB determined whether the economic conclusions shifted.[28]

Statistical Analysis

Propensity score matching (PSM) based on prognostic predictors (eGFR and COSSH-ACLF II scores) balanced baseline variables between groups, with precise matching achieved by employing caliper matching at a caliper value of 0.05. Continuous variables were analyzed with the Mann–Whitney *U*-test or students' *t*-test. Categorical variables were compared using chi-square or Fisher's exact tests. Linear regression analyzed factors influencing total costs. Kaplan-Meier survival analysis and Log rank tests compared survival between groups. Probabilistic sensitivity analysis was performed using the R package (ICEinfer_1.3) to generate incremental cost-effectiveness planes and cost acceptability curves. Statistical significance was set at $P<0.05$ for two-sided tests. All analyses were conducted using SPSS 26, GraphPad Prism 8, and R-4.3.1.

Results

Patient Characteristics

A total of 215 patients were included in the study, with 114 in the DPMAS+LPE group and 101 in the PE group. Prior to matching, patients in the DPMAS+LPE group had significantly higher hemoglobin levels and the eGFR, and lower COSSH-ACLF II scores compared with those in the PE group. Using eGFR and COSSH-ACLF II scores for propensity score matching at a 1:1 ratio resulted in comparable baseline characteristics between the groups (Table 1). Finally, 202 matched patients were included in the analysis.

Table 1 Clinical Baseline Characteristics of Two Groups Before and After Matching

Variables	Before PSM			After PSM		
	DPMAS+LPE (n=114)	PE (n=101)	*P* value	DPMAS+LPE (n=101)	PE (n=101)	*P* value
Sex						
Male, n(%)	106(92.98)	93(92.08)	0.80	93(92.08)	93(92.08)	1.00
Female, n(%)	8(7.02)	8(7.92)		8(7.92)	8(7.92)	
Age (years)	43.62±9.81	46.38±9.73	0.11	44.85±9.61	46.38±9.73	0.27
NAs, n(%)			0.75			0.99
ETV	68(59.65)	63(62.38)		62(61.39)	63(62.38)	
TDF	14(12.28)	14(13.86)		14(13.86)	14(13.86)	
TAF	22(19.30)	19(18.81)		20(19.80)	19(18.81)	
TMF	10(8.77)	5(4.95)		5(4.95)	5(4.95)	
Ascites, n(%)	55(48.25)	44(43.56)	0.49	50(49.51)	44(43.56)	0.40
Cirrhosis, n(%)	65(57.02)	49(48.52)	0.21	59(58.42)	49(48.52)	0.16
Infection, n(%)	78(68.42)	68(48.51)	0.86	72(60.40)	68(48.51)	0.52
HE, n(%)	5(4.39)	4(3.96)	0.95	4(3.96)	4(3.96)	1.00
WBC (10^9/L)	7.03[5.68,8.70]	7.11[5.60,8.82]	0.88	7.15[5.83,8.82]	7.11[5.60,8.82]	0.70
NEUT (10^9/L)	4.75[3.64,5.91]	4.65[3.79,6.04]	0.89	5.10[3.68,6.07]	4.65[3.79,6.04]	0.65
HGB (g/L)	129[117,138]	122[109,133]	**0.04**	128[115,136]	122[109,133]	0.11
PLT (10^9/L)	144[104,190]	127[91,179]	0.14	139[99,188]	127[91,179]	0.28

(*Continued*)

https://doi.org/10.2147/TCRM.S521406

Table 1 (Continued).

Variables	Before PSM			After PSM		
	DPMAS+LPE (n=114)	PE (n=101)	*P* value	DPMAS+LPE (n=101)	PE (n=101)	*P* value
TBIL (μmol/L)	348.70[261.30,439.10]	377.40[266.70,442.60]	0.24	348.98[265.40,443.60]	377.40[266.70,442.60]	0.39
ALB (g/L)	33.90[31.00,36.40]	33.40[30.50,38.00]	0.44	33.90[31.00,36.40]	33.40[30.50,37.40]	0.64
Cr (μmol/L)	58.00[49.00,72.00]	64.00[51.00,75.00]	0.12	59.00[49.90,73.00]	64.00[51.00,75.00]	0.30
eGFR	116.32[104.27,129.03]	112.10[101.00,121.69]	**0.02**	113.00[103.96,126.70]	112.10[101.00,121.69]	0.15
PT(s)	20.90[18.80,23.60]	20.90[18.60,24.10]	0.87	21.20[18.90,23.70]	20.90[18.60,24.10]	0.89
INR	1.80[1.57,2.09]	1.82[1.55,2.14]	0.91	1.85[1.58,2.12]	1.82[1.55,2.14]	0.78
PTA (%)	43[36,51]	43[35,52]	0.93	42[36,50]	43[35,52]	0.65
MELD score	20.38±3.80	21.25±3.75	0.10	20.75±3.78	21.25±3.75	0.34
COSSH-ACLF II score	6.10±0.63	6.29±0.68	**0.04**	6.19±0.60	6.29±0.68	0.29
Log(HBV DNA)	4.96±1.90	4.78±1.93	0.51	4.89±1.85	4.78±1.93	0.83
Days from baseline for first treatment (days)	3[2,6]	4[3,8]	0.02	4[2,6]	4[3,8]	0.09

Notes: Continuous data are summarized as median and interquartile range (IQR). Categorical data are summarized as numbers and percentages. Formulas for MELD and COSSH-ACLF II scores are provided in Appendices 2 and 3. Bolded numbers indicate $P < 0.05$.

Abbreviations: HE, hepatic encephalopathy; WBC, white blood cell; NEUT, neutrophil; HGB, hemoglobin; PLT, platelet; TBIL, total bilirubin; ALB, albumin; CREA, creatinine; eGFR, estimation of glomerular filtration rate; PT, prothrombin time; INR, international standardized ratio; PTA, prothrombin activity; MELD, model for end-stage liver disease; COSSH, Chinese Group on the Study of Severe Hepatitis B.

At 30 days of follow-up, the mortality rates were 0.99% (1/101, 95% CI [0%, 5.90%]) in the DPMAS+LPE group and 2.97% (3/101, 95% CI [0.99%, 9.90%]) in the PE group. By 90 days, the mortality rates were 8.91% (9/101, 95% CI [4.95%, 15.83%]) and 16.83% (17/101, 95% CI [10.89%, 26.73%]) respectively. Although overall survival rates did not significantly differ between the two groups (P=0.09, Supplementary Figure 1), consistently higher survival rates were observed with DPMAS+LPE treatment at all time points compared with PE.

Treatment Metrics

The average number of artificial liver treatments was 2.88 in the DPMAS+LPE group and 3.15 in the PE group (P=0.09). Mean hospital stay was significantly shorter with DPMAS+LPE (26.89 days) compared with the PE group (30.71 days, P<0.05). Notably, DPMAS+LPE treatment significantly reduced plasma usage per patient during hospitalization compared with PE group (4395 mL vs 7966 mL, P<0.05). Initial hospitalization costs, total costs at 30 days, and total costs at 90 days were all significantly higher in the DPMAS+LPE group compared with PE group (Table 2). The average total costs at 90 days were $12,596 [95% CI: 11,642–13,550] for DPMAS+LPE and $12,356 [95% CI: 11,027–13,685] for PE, with initial hospitalization costs accounting for 87.82% and 85.78% of the total 90-day costs respectively. During the initial hospitalization period, the cost of artificial liver was significantly higher in the DPMAS+LPE group than in the PE group; however, the cost of other treatments and diagnosis and nursing was reduced. Multivariable linear regression identified treatment mode, number of treatments, and hospital stay as key factors influencing 90-day total costs (Supplementary Table 3).

Cost-Effectiveness

At 30 days, increasing survival rates by 1% with DPMAS+LPE treatment required an additional total cost of $41,433.84, resulting in a negative incremental net monetary benefit (INMB) (Table 3). By 90 days, however, the cost-effectiveness of DPMAS+LPE treatment significantly improved, with the additional cost per 1% increase in survival rate falling below

Table 2 90-Day Cost Details for DPMAS+LPE and PE Treatment of Early-Stage HBV-ACLF

Variables	DPMAS+LPE ($)[a]	PE ($)[a]	*P* Value
Cost of the first hospitalization	11063[10,356,11,771]	10,599[9485,11,713]	**0.02**
Artificial liver treatment	5110[4861,5359]	2977[2786,3168]	**<0.0001**
Drugs	2340[1999,2761]	3200[2572,3827]	0.16
Medical consumables	499[394,603]	566[478,654]	0.06
Laboratory and examination	2027[1903,2151]	2261[2095,2427]	0.08
Other treatment	598[499,698]	977[780,1173]	**0.0004**
Diagnosis and nursing	489[439,538]	618[549,687]	**0.02**
Cost of outpatient	534[483,584]	629[553,704]	0.23
Cost of readmission	999[521,1478]	1129[458,1801]	0.92
Total cost for 30 days	10726[10,253,11,198]	9905[9167,10,644]	**0.0055**
Total cost for 90 days[b]	12596[11,642,13,550]	12,356[11,027,13,685]	**0.0015**

Notes: [a]The cost data in the table represent the mean and its 95% confidence interval. [b]Total cost for 90 days = cost of the first hospitalization + cost of outpatient + cost of readmission. Bolded numbers indicate $P < 0.05$.
Abbreviations: DPMAS+LPE, double plasma molecular adsorption system sequential low-dose plasma exchange; PE, plasma exchange.

Table 3 Overview of Calculated Results for Costs, Survival Rates, and Economic Indicators in Two Groups

	Average cost ($) [95% CI]	Effectiveness (%) [95% CI]	CER ($)	ICER ($)	NMB ($)	INMB ($)
Economic analysis for 30 days						
DPMAS+LPE	10725.88 [10,253.01,11,198.45]	99.01 [94.10,1.00]	10,833.13	41,433.83	26,940.49	−67.14
PE	9905.49 [9167.22,10,644.39]	97.03 [90.10, 99.01]	10,208.69		27,007.63	
Economic analysis for 90 days						
DPMAS+LPE	12596.30 [11,642.17,13,550.07]	91.04 [84.17,95.05]	13,836.01	3013.68	22,038.05	2791.84
PE	12356.11 [11,027.02,13,685.36]	83.07 [73.27, 89.11]	14,874.33		19,246.21	

Abbreviations: DPMAS+LPE, double plasma molecular adsorption system sequential low-dose plasma exchange; PE, plasma exchange; CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; INMB, incremental net monetary benefit; ICE, incremental cost-effectiveness; PTA, prothrombin activity.

China's 2023 per capita GDP threshold ($12,681). Positive INMB values indicated an economic advantage of DPMAS+LPE over PE at this stage. Subgroup analysis revealed that DPMAS+LPE treatment yielded average savings of $235.21 per patient among HBV-ACLF patients with liver cirrhosis (Supplementary Table 4). Additionally, early-stage ACLF patients benefited economically from the DPMAS+LPE treatment regardless of their cirrhosis status.

Sensitivity Analysis

Probabilistic sensitivity analysis (Figure 2a) indicated that most data dots fell within quadrant I at 30 days, suggesting higher costs and better efficacy of DPMAS+LPE compared with PE. Economic viability probabilities of DPMAS+LPE at WTP thresholds of $12,681 and $38,043 were 14% and 45% respectively (Figure 2b). Similar patterns were observed at 90 days (Figure 2c), with more dots in quadrant IV, indicating economic superiority of DPMAS+LPE. Economic viability probabilities at WTP thresholds of $12,681 and $38,043 were 75% and 90% respectively (Figure 2d).

One-way sensitivity analysis (Figure 3) demonstrated that changes in 90-day survival rates, number of treatments, and total costs had a significant impact on INMB. When the average treatment frequency of DPMAS+LPE exceeded 4.4, the INMB value shifted from positive to negative, indicating that the economic advantage of DPMAS+LPE was inferior to that of PE (Supplementary Figure 2). For the other parameters, within a certain range, DPMAS+LPE still showed better economic benefits than PE, confirming the robustness of the results.

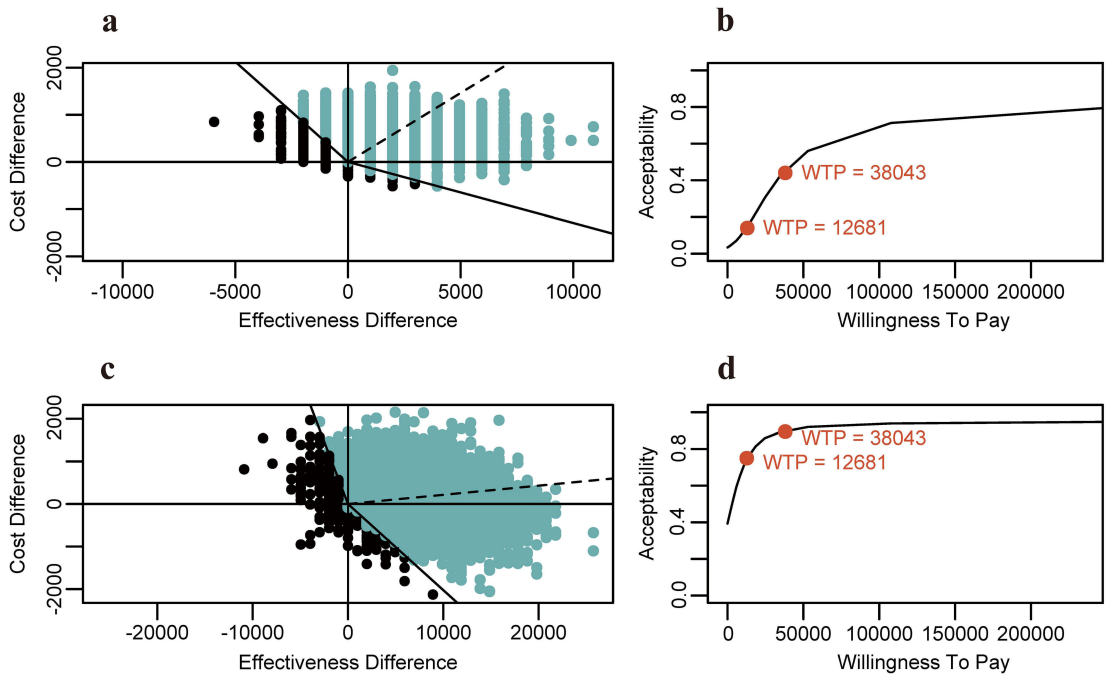

Figure 2 Results of probabilistic sensitivity analysis. (**a**) Cost-effectiveness planes at 30 days. Cost and effect differences are both expressed in cost units, lambda=1e+05. (**b**) Acceptability curve at 30 days. It is the result of Bootstrap uncertainty analysis and represents the probability that DPMAS+LPE has economic benefits under different WTP thresholds. (**c**) Cost-effectiveness planes at 90 days. (**d**) Acceptability curve at 90 days. The cost-effectiveness plane is divided into four quadrants. In quadrants II and IV, the ICER values are negative, indicating that the intervention is absolutely dominated or absolutely dominant, respectively. In quadrants I and III, the ICER values are positive; quadrant I represents a treatment that is more costly yet more effective, while quadrant III indicates one that is less costly but also less effective—thus requiring further economic analysis to determine which option is more cost-effective. The green area represents the 95% confidence interval of the incremental cost-effectiveness (ICE).

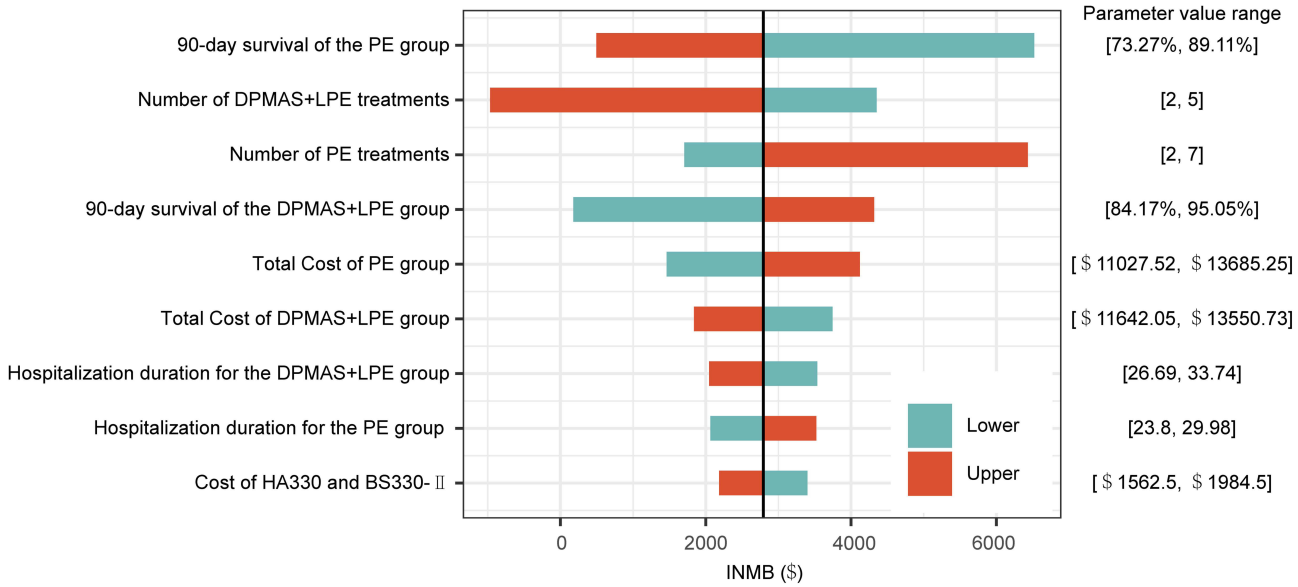

Figure 3 Tornado diagram for one-way sensitivity analysis. The green part of each bar chart indicates that the parameter is lower than the baseline value range, and the Orange part indicates that the parameter is higher than the baseline value range. The solid black line in the middle indicates that the baseline INMB value is $2792.

Discussion

This study documents the 90-day healthcare costs and health outcomes of early-stage HBV-ACLF patients in a real clinical setting. Economic analysis demonstrated that DPMAS+LPE treatment not only alleviated clinical blood product shortages but also proved cost-effective. Furthermore, the economic benefits of DPMAS+LPE treatment were time-

dependent: while no economic advantage over PE was observed at 30 days, superior economic benefit was evident at 90 days. This shift may be attributed to the relatively milder conditions of the early-stage HBV-ACLF patients in our study. Consequently, the 30-day survival rate was high, resulting in only minimal differences between the two groups. By the 90-day mark, however, the differences in treatment effectiveness between the two groups became more apparent. Furthermore, despite higher treatment costs in the DPMAS+LPE group, patients experienced significantly shorter hospital stays and lower costs for additional treatments, diagnosis and nursing during their hospitalization compared with those receiving PE.

These findings reinforce our conclusion that DPMAS+LPE, by enhancing liver function recovery and improving short-term survival rates while reducing hospitalization duration, effectively offsets the costs related to treatments beyond artificial liver therapy. As a result, DPMAS+LPE emerges as a cost-effective option for early-stage HBV-ACLF patients when compared to PE. In another study,[17] the ICER of PE and DPMAS+LPE compared to standard medical treatment (SMT) in HBV-ACLF patients with prothrombin time activity (PTA) > 40% was ¥224,018.36 and ¥59,118.22, respectively. Among patients with PTA 30–40%, the ICER values were ¥173,962.38 and ¥309,958.99, respectively. The results indicate that DPMAS+LPE treatment is cost-effective in patients with PTA > 40%, who have relatively milder disease severity. It is noteworthy that early intervention during the cytokine storm phase of pre-ACLF and early ACLF stages contributes to improved patient outcomes.[29,30] In a prospective cohort of 149 ACLF cases in Europe, the direct medical costs of MARS and SMT were €35,639 and €15,804, respectively. The ICER for MARS treatment was €29,985 per life-year gained, which is below the WTP threshold of €50,000, making it cost-effective.[23] However, MARS is rarely used in China.

Several factors influence the economic conclusions of DPMAS+LPE treatment. First, the greater the disparity in survival rates between the two groups, the more likely DPMAS+LPE shows economic superiority. According to previous studies, the difference in 28-day survival rates between DPMAS combined with PE and PE alone in treating liver failure ranges from 9.5% to 27.5%, with 90-day survival rate differences between 14.4% and 16.3%, all higher than those observed in our study.[16,17,31,32] Second, when the average number of DPMAS+LPE treatments exceeds 4.4, the increased costs outweigh the economic benefits of efficacy, thereby losing economic advantage. Therefore, the economic considerations of DPMAS+LPE treatment need to be balanced when treatment exceeds 4 sessions. Lastly, the WTP value also affects conclusions. Chinese researchers have estimated the WTP per quality-adjusted life year (WTP/QALY). The results indicate that for end-stage diseases, the WTP/QALY threshold is ¥140,800, which is 1.94 times China's per capita GDP.[33] If this threshold is used to assess the cost-effectiveness of DPMAS+LPE, the treatment remains economically beneficial at the 90-day mark.

The treatment modalities chosen in this study were based on actual patient conditions and treatment preferences. Health outcomes and cost expenditures were derived from real medical environments, enhancing the clinical relevance and generalizability of our findings.[34,35] To control confounding factors, propensity score matching was used to reduce bias. However, the study has limitations. First, it was retrospective, excluding patients who received multiple artificial liver treatments during a single hospitalization, potentially introducing selection bias. Second, the single-center design may limit the external validity of the results due to variations in medical service prices and treatment protocols across different hospitals. Nevertheless, sensitivity analysis was conducted to mitigate these influences. Lastly, long-term follow-up was not conducted to assess patient survival quality, indirect costs, and intangible costs.

Conclusion

In conclusion, we found that compared with PE, DPMAS+LPE is cost-effective at 90 days among early-stage HBV-ACLF patients, particularly those with coexisting liver cirrhosis. However, exceeding an average of 4.4 treatments eliminates its economic benefits. In the context of current plasma shortages, DPMAS+LPE emerges as a suitable choice for early-stage ACLF patients. Clinical decision-making and the allocation of medical resources in the future can benefit from our comparison of the economic aspects of DPMAS+LPE and PE in early-stage HBV-ACLF.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Third Affiliated Hospital of Sun Yat-sen University (Approval No. [2020]02-009-01). This study was conducted in accordance with the ethical standards of the Ethics Committee of Third Affiliated Hospital of Sun Yat-sen University and with the Helsinki Declaration. The study did not involve patient privacy or biological samples, and all patients provided informed consent, with some giving written consent and others providing verbal consent.

Acknowledgments

We would like to express our gratitude to Shuo Yang from the Department of Medical Statistics, School of Public Health, Sun Yat-sen University, for providing valuable statistical guidance and consultation.

Funding

This research was financially supported by several grants: the National Natural Science Foundation of China (No. 82070611), Key-Area Research and Development Program of Guangdong Province (No. 2020B0101130015), Guangdong Medical Science and Technology Research Fund (A2021304), Guangzhou Science and Technology Program Key Projects (2023B03J1287 and 2023B01J1007), Sun Yat-Sen University Clinical Research 5010 Program (2020007), Beijing iGandan Foundation (No.iGandanF-1082022-RGG038, No.iGandanF-1082023-RGG049, and No. iGandanF-1082024-RGG050), and the Five-Year Plan of Third Affiliated Hospital of Sun Yat-sen University (2024W106), Shandong Provincial Natural Science Foundation (ZR2024QH660).

Disclosure

The authors affirm that there are no known financial or personal conflicts of interest that could have influenced the work presented in this paper.

References

1. Sarin SK, Choudhury A, Sharma MK, 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
2. Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):131–149. doi:10.1038/nrgastro.2015.219
3. Mezzano G, Juanola A, Cardenas A, et al. Global burden of disease: acute-on-chronic liver failure, a systematic review and meta-analysis. *Gut*. 2022;71(1):148–155. doi:10.1136/gutjnl-2020-322161
4. Tafesh ZH, Salcedo RO, Pyrsopoulos NT. Classification and epidemiologic aspects of acute-on-chronic liver failure. *Clin Liver Dis*. 2023;27(3):553–562. doi:10.1016/j.cld.2023.03.002
5. Allen AM, Kim WR, Moriarty JP, Shah ND, Larson JJ, Kamath PS. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. *Hepatology*. 2016;64(6):2165–2172. doi:10.1002/hep.28812
6. Saliba F, Bañares R, Larsen FS, et al. Artificial liver support in patients with liver failure: a modified DELPHI consensus of international experts. *Intensive Care Med*. 2022;48(10):1352–1367. doi:10.1007/s00134-022-06802-1
7. Ocskay K, Kanjo A, Gede N, et al. Uncertainty in the impact of liver support systems in acute-on-chronic liver failure: a systematic review and network meta-analysis. *Ann Intensive Care*. 2021;11(1):10. doi:10.1186/s13613-020-00795-0
8. Wang X-H, Peng -B-B, Zhang L, et al. Mixed mode of artificial liver support in patients with acute-on-chronic liver failure: a retrospective cohort study. *Hepatol Internat*. 2023;17(5):1241–1250. doi:10.1007/s12072-023-10573-2
9. Chen -Y-Y, Li H, Xu B-Y, et al. Plasma exchange-based non-bioartificial liver support system improves the short-term outcomes of patients with hepatitis b virus-associated acute-on-chronic liver failure: a multicenter prospective cohort study. *Front Med*. 2021;8:779744. doi:10.3389/fmed.2021.779744
10. Yang L, Wu T, Li J, et al. Artificial liver treatment improves survival in patients with hepatitis B virus-related acute-on-chronic liver failure: a case-control matched analysis. *Hepatol Res*. 2020;50(6):656–670. doi:10.1111/hepr.13497
11. Beran A, Mohamed MFH, Shaear M, et al. Plasma exchange for acute and acute-on-chronic liver failure: a systematic review and meta-analysis. *Liver Transpl*. 2024;30(2):127–141. doi:10.1097/LVT.0000000000000231
12. Li G, Zhang P, Zhu Y. Artificial liver support systems for hepatitis B virus-associated acute-on-chronic liver failure: a meta-analysis of the clinical literature. *J Viral Hepat*. 2023;30(2). doi:10.1111/jvh.13767
13. Liu H, Zhang Q, Liu L, et al. Effect of artificial liver support system on short-term prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure. *Artif Organs*. 2020;44(10):E434–E447. doi:10.1111/aor.13710
14. Rosa-Diez GJ, Joannes-Boyau O. The use of adsorption in extracorporeal liver support: the double plasma molecular adsorption system (DPMAS). *Contrib Nephrol*. 2023;200:210–217. doi:10.1159/000529296
15. Marcello M, Ronco C. Bilirubin adsorption with DPMAS: mechanism of action and efficacy of anion exchange resin. *Contrib Nephrol*. 2023;200:201–209. doi:10.1159/000526729

16. Yao J, Li S, Zhou L, 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
17. Wu C, Peng W, Cheng D, et al. Efficacy and economic evaluation of nonbiological artificial liver therapy in acute-on-chronic hepatitis B liver failure. *J Clin Transl Hepatol*. 2023;11(2):433–440. doi:10.14218/JCTH.2022.00106
18. Wang L, Xu W, Zhu S, et al. Double plasma molecular adsorption system with sequential low-dose plasma exchange in patients with hepatitis B virus-related acute-on-chronic liver failure: a prospective study. *J Clin Transl Hepatol*. 2023;11(4):908–917. doi:10.14218/JCTH.2022.00254
19. Kong LX, Qiu F, Wang HM, 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
20. Hessel FP, Mitzner SR, Rief J, Guellstorff B, Steiner S, Wasem J. Economic evaluation and 1-year survival analysis of Mars in patients with alcoholic liver disease. *Liver Int*. 2003;23 Suppl 3:66–72. doi:10.1034/j.1478-3231.23.s.3.5.x
21. Hessel FP. Economic evaluation of the artificial liver support system Mars in patients with acute-on-chronic liver failure. *Cost Eff Resour Alloc*. 2006;4:16. doi:10.1186/1478-7547-4-16
22. Kantola T, Maklin S, Koivusalo AM, et al. Cost-utility of molecular adsorbent recirculating system treatment in acute liver failure. *World J Gastroenterol*. 2010;16(18):2227–2234. doi:10.3748/wjg.v16.i18.2227
23. Hessel FP, Bramlage P, Wasem J, Mitzner SR. Cost-effectiveness of the artificial liver support system Mars in patients with acute-on-chronic liver failure. *Eur J Gastroenterol Hepatol*. 2010;22(2):213–220. doi:10.1097/MEG.0b013e3283314e48
24. Wu T, Li J, Shao L, 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
25. Group AL, Disease SL, Group AL, Chinese Medical Association. Guidelines for diagnosis and treatment of liver failure (2024 version). *Zhonghua Gan Zang Bing Za Zhi*. 2025;33(1):18–33. doi:10.3760/cma.j.cn501113-20241206-00614
26. Luce BR, Elixhauser A. Estimating costs in the economic evaluation of medical technologies. *Int J Technol Assess Health Care*. 1990;6(1):57–75. doi:10.1017/S026646230000893X
27. Obenchain RL, Melfi CA, Croghan TW, Buesching DP. Bootstrap analyses of cost effectiveness in antidepressant pharmacotherapy. *Pharmacoeconomics*. 1997;11(5):464–472. doi:10.2165/00019053-199711050-00008
28. Paulden M. Why it's time to abandon the ICER. *Pharmacoeconomics*. 2020;38(8):781–784. doi:10.1007/s40273-020-00915-5
29. Arroyo V, Moreau R, Kamath PS, et al. Acute-on-chronic liver failure in cirrhosis. *Nat Rev Dis Primers*. 2016;2:16041. doi:10.1038/nrdp.2016.41
30. Moreau R, Tonon M, Krag A. EASL clinical practice guidelines on acute-on-chronic liver failure. *J Hepatol*. 2023;79(2):461–491. doi:10.1016/j.jhep.2023.04.021
31. Guo X, Wu F, Guo W, 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
32. Zhang RX, Liu LX. Meta-analysis of the therapeutic value of plasma exchange simple or combined with dual plasma molecular adsorption system for liver failure. *Zhonghua Gan Zang Bing Za Zhi*. 2022;30(10):1107–1114. doi:10.3760/cma.j.cn501113-20201007-00541
33. Xu L, Chen M, Angell B, et al. Establishing cost-effectiveness threshold in China: a community survey of willingness to pay for a healthylife year. *BMJ Glob Health*. 2024;9(1):e013070. doi:10.1136/bmjgh-2023-013070
34. Ray WA, Griffin MR, Avorn J. Evaluating drugs after their approval for clinical use. *N Engl J Med*. 1993;329(27):2029–2032. doi:10.1056/NEJM199312303292710
35. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med*. 2016;375(23):2293–2297. doi:10.1056/NEJMsb1609216