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RESEARCH ARTICLE

Safety and Efficacy of DPMAS in Patients With Acute-on-Chronic Liver Failure Based on Different Platelet Count Levels

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Keywords: acute-on-chronic liver failure | bleeding | double plasma molecular absorption system | platelet count | platelet reduction rate | safety | thromboelastography

ABSTRACT

To investigate the effect of different platelet (PLT) counts on the safety and efficacy of the double-plasma molecular absorption system (DPMAS) in patients with acute-on-chronic liver failure (ACLF). A total of 156 patients with ACLF receiving DPMAS were divided into the observed group (40×10^9/L ≤ PLT < 50×10^9/L) and the control group (PLT ≥ 50×10^9/L) according to PLT count level. The safety and efficacy indices of bleeding-related complications, PLT reduction rate, total bilirubin (TBIL) reduction rate, and 28-days survival rate after DPMAS were analyzed and compared between the two groups. The incidence of bleeding complications during and after DPMAS in the observed and control groups (14.3% vs. 14.9%, $p=0.922$), the decline rate of PLT immediately and 24 h after treatment (0.13 vs. 0.11/0.05 vs. 0.09, $p=0.256/0.161$), and the 28-days survival rate after treatment (76.2% vs. 75.4%, $p=0.923$) were not significantly different. The thromboelastogram before DPMAS showed no significant difference in PLT function between the two groups ($p>0.05$). Although the TBIL level of the two groups rebounded 24 h after treatment compared with immediately after treatment, it decreased significantly immediately and 24 h after treatment compared with pre-treatment levels ($p<0.05$). There was no significant difference in the rate of decline of serum TBIL immediately after treatment and 24 h after treatment between the two groups (0.33 vs. 0.35/0.14 vs. 0.16, $p=0.193$ and 0.653, respectively). DPMAS is safe and effective in patients with ACLF with 40×10^9/L ≤ PLT count < 50×10^9/L.

Abbreviations: ACLF, acute-on-chronic liver failure; APTT, activated partial thromboplastin time; DBIL, direct bilirubin; DPMAS, double-plasma molecular absorption system; MELD, model for end-stage disease; NBAL, non-bioartificial liver support system; PLT, platelet; PT, prothrombin time; PTA, prothrombin activity; TBIL, total bilirubin; TPO-RA, thrombopoietin receptor agonist; TT, thrombin time.

Lingyun Niu and Jiamei Zhou are co-first authors and contributed equally to this work.

1 | Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome arising from chronic liver disease, characterized by acute deepening of jaundice and coagulation dysfunction. This condition may also involve one or more extrahepatic organ failures, representing the most prevalent clinical form of liver failure [1]. Currently, ACLF treatment primarily includes comprehensive medical treatment, artificial liver support, and liver transplantation [2]. However, comprehensive medical treatment is sometimes less effective. Liver transplantation faces issues such as shortage of donor liver resources, high costs, and strict timing requirements for the procedure. Therefore, an artificial liver support system has become an important and effective means of treating ACLF.

ACLF is often accompanied by a decreased platelet (PLT) count to varying degrees. Common causes are infection, decreased thrombopoietin, PLT stasis, destruction of the spleen due to hyposplenism, and PLT depletion due to abnormal coagulation [3]. Artificial liver support therapy may also lead to varying degrees of decline in PLT count [4], which is related to poor histocompatibility of plasma separators. Moreover, heparin anticoagulant therapy not only inhibits PLT aggregation but may also cause heparin-induced PLT reduction [5, 6], which may increase the risk of deep vein catheterization bleeding, digestive tract bleeding, skin and mucous membrane bleeding, and intracranial bleeding. Therefore, for patients with ACLF and PLT count reduction using a non-bioartificial liver support system (NBAL), the safety of treatment needs to be further discussed. The target intervention value for invasive procedures in patients with thrombocytopenia was not clear, but to reduce the risk of postoperative bleeding, it was generally accepted that PLT $\geq 50\times10^9$/L could be used for most invasive procedures [7–9]. Clinically, PLT count $< 50\times10^9$/L in some patients with ACLF remains unclear regarding the bleeding risk when these patients undergo NBAL treatment. If administered a PLT infusion, and an oral thrombopoietin receptor agonist (TPO-RA) [10], the PLT count does not increase in a timely and effective manner, potentially leading to extended waiting periods for NBAL treatment. Thus, the optimal timing for treatment may be delayed. Therefore, it is crucial to further explore the safe range of PLT counts for NBAL therapy.

NBAL presents various patterns, including double-plasma molecular absorption system (DPMAS), plasma exchange, plasma dialysis filters, and the combined application of multiple models. Recently, DPMAS has been extensively employed in treating ACLF [11–13]. This study aimed to retrospectively analyze the safety of DPMAS treatment in patients with ACLF with 40×10^9/L $\leq$ PLT count $< 50\times10^9$/L and to assess any differences in treatment efficacy.

2 | Methods

2.1 | Patients

Patients with ACLF receiving first DPMAS treatment during their admission to the Department of Gastroenterology of Shanxi Bethune Hospital between January 2022 and February 2024 were selected for this study. The observed group was selected with 40×10^9/L $\leq$ PLT count $< 50\times10^9$/L. Concurrently, patients with a PLT count $\geq 50\times10^9$/L were selected as controls. The baseline data included sex, age, etiology, disease severity (Model for End-Stage Liver Disease [MELD] score and MELD-Na score), and proportion of patients with liver cirrhosis. The protocol for this research project was approved by the ethics committee of Shanxi Bethune Hospital and it conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from all participants and/or guardians. (Ethical approval number: YXLL-2024-119).

The inclusion criteria were as follows: a clinical diagnosis of ACLF meeting the diagnostic criteria outlined in the 2018 Guidelines for the Diagnosis and Treatment of Liver Failure [1]. This includes syndromes caused by various inducers with acute, worsening jaundice and coagulation dysfunction, which may be accompanied by complications such as hepatic encephalopathy, ascites, electrolyte disorders, infection, hepatorenal syndrome, hepatopulmonary syndrome, and extrahepatic organ failure. Rapid progression of jaundice was noted with total bilirubin (TBIL) levels $\geq$ 10 times the upper limit of normal or a daily increase $\geq$ 17.1 μmol/L, and with prothrombin activity (PTA) $\leq$ 40% (or international normalized ratio $\geq$ 1.5).

The exclusion criteria comprised the following: (1) complications with primary liver cancer or other systemic or local malignant tumors; (2) liver graft dysfunction post-transplantation; (3) complications with serious underlying diseases such as severe heart, respiratory, and blood system diseases; (4) gastrointestinal hemorrhage, skin and mucous membrane hemorrhage, intracranial hemorrhage, epistaxis, other hemorrhagic diseases, and diffuse intravascular coagulation prior to NBAL treatment; (5) hemodynamic instability; (6) severe allergies to plasma or heparin; and (7) pregnant and lactating women.

2.2 | Treatment Methods

2.2.1 | Routine Comprehensive Medical Treatment

All patients with ACLF were advised to rest in bed, with continuous monitoring of their blood pressure, heart rate, respiration, and blood oxygen saturation. Etiological treatment included antiviral therapy for hepatitis virus infection, cessation of all suspected drugs in cases of drug-induced liver injury, and cessation of alcohol consumption in alcoholic patients.

2.2.2 | NBAL Treatment

A double-lumen central venous catheter was inserted into the femoral or internal jugular vein. DPMAS primarily employs the Plasauto∑ blood purification support system and its associated treatment pipeline (Asahi Kasei Medical Co. Ltd., Tokyo, Japan), plasma separator Plasmaflo OP-08W (Asahi Kasei Medical Co. Ltd., Tokyo, Japan), plasma bilirubin adsorption BS330 (JanFan Organisms, Zhuhai, China), and blood perfusion apparatus HA330-II (JanFan Organisms, Zhuhai, China). The blood pump flow rate was set at 120 mL/min, with a plasma separation rate of 25–30 mL/min. The approximate

plasma processing volume per treatment was 5.0–5.5 L. Conventional heparin sodium injection (2 mL:12500 U, Qianhong Biochemical Pharmaceutical, Changzhou, China) was administered as an anticoagulant to prime the extracorporeal circulation circuit, initially before treatment and for maintenance during the procedure. Close monitoring of vital signs was conducted, alongside observations for complications such as bleeding from deep vein catheterization, skin and mucous petechiae, hematemesis, melena, epistaxis, and intracranial hemorrhage. These were checked pre-treatment, immediately post-treatment, and 24 h following the treatment to assess the relevant venous blood indicators.

2.3 | Observation Index

2.3.1 | Basic Clinical Data

The following basic clinical data were collected: sex, age, etiology, MELD score, and MELD-Na score. The MELD score was established by Malinchoc in 2000 [14]. The formula is expressed as $R = 9.6 \times \ln[\text{creatinine (mg/dL)}] + 3.8 \times \ln[\text{bilirubin (mg/dL)}] + 11.2 \times \ln(\text{international normalized ratio}) + 6.4 \times \text{etiology}$ (0 for cholestasis or alcohol, 1 for other causes). The MELD-Na score is calculated as the MELD score + 1.59 × (137—serum sodium), with a set range of 125 and 137 mmol/L when serum sodium levels are < 125 mmol/L or above > 137 mmol/L, respectively. PLT count was measured using the Beckman DxH800 blood cell analyzer (Beckman Coulter Corporation, USA)and the impedance method.

At baseline, before DPMAS treatment, PLT, coagulation factors, fibrinogen function and fibrinolytic activity were measured using thromboelastography TEG5000 (Haemoscope Corporation, USA) and TEG hemostasis system kaolin (Haemonetics Corporation, USA). The study compared and analyzed differences in coagulation factor function (R value), fibrinogen function (K value and angle-α value), PLT function (mainly MA value), fibrinolytic activity (30-min dissolution ratio of blood clot, and predictive value of blood clot dissolution) between the two groups.

2.3.2 | Safety Index Evaluation

The safety index was evaluated to determine if there was any deep vein catheter bleeding, skin and mucous petechiae, hematemesis, melena, epistaxis, intracranial hemorrhage, or other hemorrhage-related complications and thrombotic events during and after DPMAS treatment.

The total amount of heparin administered (initial dose + maintenance) in both groups was observed and compared. This quantity was calculated based on the PTA level within 24 h before DPMAS treatment. If PTA was ≤ 20%, the base first dose was 2500 U; if PTA was 20%–30%, the base first dose was 3750 U; if PTA was 30%–40%, the base first dose was 5000 U; and if PTA was > 40%, the base first dose was determined based on the actual PTA value. The base maintenance dose for all groups was 625 U/h. The final first dose and maintenance doses were adjusted according to the PLT count level. If the PLT count was $125–325 \times 10^9$/L before treatment, an additional 1250 U was added to the first dose, and 625 U/h to the maintenance dose. If the PLT count was $> 325 \times 10^9$/L before treatment, an additional 5000 U was added to the first dose, and 1250 U/h to the maintenance dose. Final first dose = base first dose + additional first dose; final maintenance dose = base maintenance dose + additional maintenance dose [15]. The total heparin dosage comprised the final first dose and the final maintenance dose.

The rates of PLT decline immediately after DPMAS treatment and at 24 h after treatment were observed and compared between the two groups. The immediate decline rate was calculated as follows: (immediately after treatment—pre-treatment)/pre-treatment × 100%. The decline rate at 24 h was calculated similarly: (24 h after treatment—pre-treatment)/pre-treatment × 100%.

The changes in the coagulation function indices of DPMAS before treatment, immediately after treatment, and 24 h after treatment, were assessed, including prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT).

2.3.3 | Effectiveness Index Evaluation

This study observed changes in the liver function indices of DPMAS before treatment, immediately after treatment, and 24 h after treatment, including TBIL and direct bilirubin (DBIL). The rates of TBIL decline immediately after treatment and at 24 h were also recorded and compared between groups. The immediate TBIL decline rate after treatment was calculated as (immediately after treatment—pre-treatment)/pre-treatment × 100%; similarly, the TBIL decline rate at 24 h was calculated as (24 h after treatment—pre-treatment)/pre-treatment × 100% [11]. A comparative analysis of 28-days survival rate after DPMAS treatment among different PLT groups was performed.

2.4 | Statistical Method

All data were statistically analyzed using SPSS 26.0. Quantitative data that conformed to a normal distribution were described using the mean ± standard deviation. The paired sample t-test was utilized for intra-group comparisons, and the two independent sample t-tests were employed for inter-group comparisons. Non-normally distributed data were described using the median and the first and third quartiles. Comparisons between the two groups were performed using a nonparametric test (Wilcoxon rank sum test). Repeated measurement data were analyzed using generalized estimating equations, with the selection of the appropriate correlation matrix. Qualitative data were described by component ratios, and the χ^2 test was used for comparisons between groups. The Kaplan–Meier method and the log-rank test were utilized for survival analysis. Differences were considered statistically significant when $p < 0.05$.

3 | Results

3.1 | Basic Clinical Data Analysis

A total of 156 patients with ACLF treated with first DPMAS were included in this study. The observed group ($40\times10^9/L \le PLT < 50\times10^9/L$) consisted of 42 patients, including 25 men and 17 women aged 23–80 years. The average PLT count was $(45.17\pm2.77)\times10^9/L$, the proportion of patients with liver cirrhosis was 52.4% (22/42), and the MELD and MELD-Na scores ranged from 14 to 45 and 15 to 53 points, respectively. The control group ($PLT \ge 50\times10^9/L$) comprised 114 patients, with 58 men and 56 women aged 25–78 years. The average PLT count was $(143.83\pm69.66)\times10^9/L$, the proportion of patients with liver cirrhosis was 49.1% (56/114), and the MELD and MELD-Na scores ranged from 11 to 46 and 11 to 63 points, respectively. There were no significant differences in sex, age, disease severity, etiology or proportion of patients with liver cirrhosis between the observed and control groups ($p > 0.05$) (Table 1). This finding indicates that the data in this study are comparable.

The function of PLTs, coagulation factors, and fibrinogen was assessed in 52 patients with ACLF using thromboelastography before DPMAS treatment. Compared with the control group, no significant differences were observed in PLT function, coagulation factor function, fibrinogen function, and fibrinolytic activity in the observed group (Table 2).

TABLE 1 | Basic clinical data of patients with ACLF.

Index	Group		*p*
	Observed group ($n=42$)	Control group ($n=114$)	
Sex [*n*(%)]			
Male	25(59.5)	58(50.9)	0.337
Female	17(40.5)	56(49.1)	
Age (years old)	50.71 ± 11.38	50.19 ± 15.95	0.847
MELD scores	24.0(20.0,28.8)	22.0(19.0,25.0)	0.074
MELD-Na scores	26.0(22.0,31.8)	23.5(20.0,30.8)	0.241
Etiology [*n*(%)]			
Alcohol	9(21.4)	28(24.6)	
Viral hepatitis B	12(28.5)	33(28.9)	0.945
Autoimmune factor	12(28.6)	33(29.0)	
Others	9(21.4)	20(17.5)	
Proportion of liver cirrhosis [*n*(%)]	22(52.4)	56(49.1)	0.718

Abbreviations: ACLF, acute-on-chronic liver failure; MELD, model of end-stage liver disease.

3.2 | Therapeutic Safety Evaluation

3.2.1 | Bleeding-Related Complications During and After DPMAS Treatment

No bleeding occurred during DPMAS treatment or within 24 h following treatment. All of bleeding events occurred during 24–72 h and were classified as delayed bleeding. Bleeding-related complications were observed in 23 patients. The incidence of hemorrhage-related complications in the observed group was 14.3% (6/42). The causes of hemorrhage included bleeding during femoral vein catheterization in two patients, epistaxis in one, and gastrointestinal bleeding in three. In the control group, the incidence rate of bleeding-related complications was 14.9% (17/114). The causes were femoral vein catheterization in two patients, skin and mucous petechial spotting in three, gastrointestinal bleeding in eight, epistaxis in two, bloody pleural effusion in one, and abdominal hemorrhage in one. There was no significant difference in the incidence of hemorrhage-related complications between the observed and control groups ($p = 0.922$) (Table 3).

At the same time, we also monitored the occurrence of thrombotic events during and after DPMAS treatment. We found

TABLE 2 | Comparison of PLT, coagulation factor and fibrinogen functions among groups using thromboelastography before DMPAS treatment.

Index	Group		*p*
	Observed group ($n=11$)	Control group ($n=41$)	
R value (min)	5.9(5.5, 6.8)	5.7(4.8,6.6)	0.324
K value (min)	2.36 ± 0.70	2.08 ± 1.07	0.133
Angle-α value (deg)	58.3(50.6,64.9)	64.9(58.7,68.6)	0.079
MA value (mm)	52.26 ± 7.98	55.0 ± 8.30	0.376
EPL value (%)	0.0(0.0,0.2)	0.0 (0.0,0.0)	0.515
LY30 value (%)	0.0 (0.0,0.0)	0.0(0.0,0.05)	0.434

Note: Reference range: *R* value (5–10 min), *K* value (1–3 min), angle-α value (53–72 deg), MA value (50–70 mm), EPL value [predictive value of blood clot dissolution] (0%–15%), LY30 value [30-min dissolution ratio of blood clot] (0%–8%).
Abbreviation: PLT, platelet.

TABLE 3 | Comparison of bleeding-related complications.

Index	Group		χ^2	*p*
	Observed group ($n=42$)	Control group ($n=114$)		
Bleed [*n*(%)]				
Positive	6(14.3)	17(14.9)	0.010	0.922
Negative	36(85.7)	97(85.1)		

one case of right lower limb venous thrombosis in the observed group, with a thrombosis incidence rate of 2.4% (1/42). Furthermore, there were three cases of right lower limb venous thrombosis and one case of right internal jugular vein thrombosis in the control group, with a thrombosis incidence rate of 2.6% (4/114). No statistically significant difference in the incidence of thrombosis was observed between the two groups ($p = 1.0$).

3.2.2 | Heparin Usage

The average heparin dose in the observed group was 6562.5 U (range: 3750–10 125 U), whereas in the control group it was 8375 U (range: 3750–14 625 U). The heparin dose administered in the observed group was significantly lower than that in the control group ($p < 0.001$).

3.2.3 | PLT Decline Rate

The immediate decline rate after treatment with PLT in the observed group was slightly higher than that in the control group (13% vs. 11%), while that 24 h after treatment was slightly lower than that in the control group (5% vs. 9%); however, there was no statistically significant difference between the two groups ($p = 0.256/0.161$) (Figure 1A,B).

3.2.4 | Indicators of Coagulation Function

A comparison of PT, APTT, and TT between the observed and control groups revealed no significant differences immediately after treatment or 24 h after treatment ($p > 0.05$) (Table 4). PT, APTT, and TT levels in both the observed and control groups showed a significant increase immediately after treatment, demonstrating a statistically significant difference from pre-treatment values ($p < 0.001$). However, 24 h after treatment, these levels returned to pre-treatment values, with no statistical differences observed compared to the baseline ($p > 0.05$) (Figure 2A–C).

3.3 | Evaluation of Treatment Effectiveness

3.3.1 | Liver Function Index

There were no significant differences in TBIL and DBIL levels between the observed and control groups immediately or 24 h after treatment ($p > 0.05$) (Table 4). TBIL and DBIL levels in both the observed and control groups decreased significantly

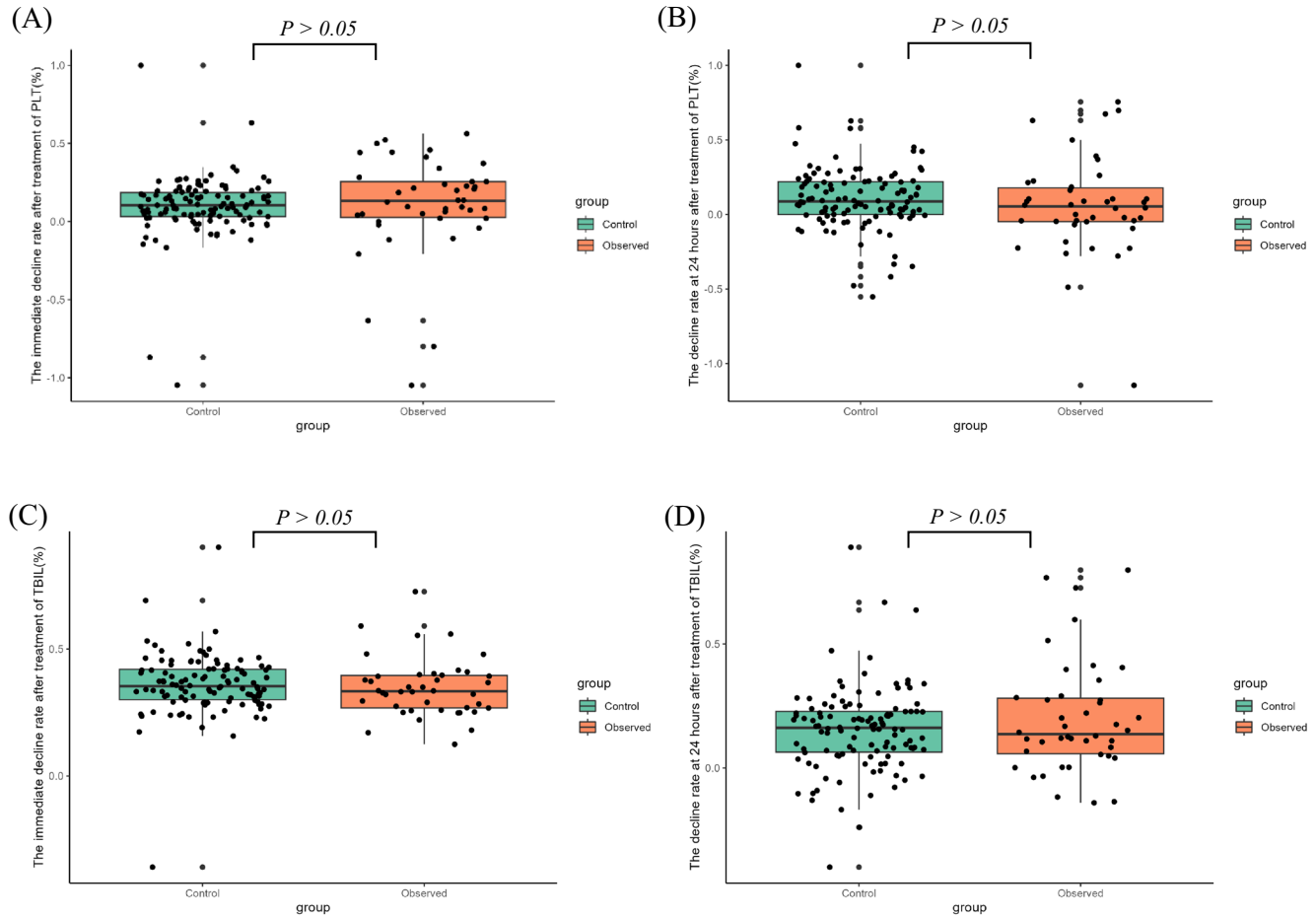

FIGURE 1 | Between-group comparisons of PLT reduction rate, and TBIL decline rate. (A, B) Comparison of PLT reduction rate after DPMAS treatment immediately and 24 h in different PLT groups. (C, D) Comparison of TBIL decline rate after DPMAS treatment immediately and 24 h in different PLT groups. PLT, platelet; TBIL, total bilirubin; DPMAS, double-plasma molecular absorption system.

TABLE 4 | Comparison of PT, APTT, TT, TBIL, and DBIL among groups.

Group		PT(s)	APTT(s)	TT(s)
Observed group	Pre-treatment	20.05 (18.15,23.80)	35.25 (31.25,42.90)	17.20 (15.60,20.08)
	Immediately after treatment	33.55 (27.20,44.18)*	90.85 (54.78,400.00)*	68.45 (22.00,300)*
	24 h after treatment	20.60 (18.00,23.48)	35.60 (30.43,44.80)	18.00 (14.98,19.78)
Control group	Pre-treatment	19.20 (17.90,22.35)	38.40 (34.35,43.55)	17.65 (16.03,20.08)
	Immediately after treatment	33.80 (28.38,44.75)*	112.40 (52.03,400.00)*	56.15 (25.08,300.00)*
	24 h after treatment	19.00 (17.30,23.58)	36.85 (33.50,43.63)	18.10 (16.13,19.98)
p value between the two groups immediately after treatment		0.583	0.875	0.753
p values between the two groups at 24 h after treatment		0.272	0.306	0.311

Group		TBIL(μmol/L)	DBIL(μmol/L)
Observed group	Pre-treatment	314.05 (237.95,437.20)	169.40 (123.45,307.48)
	Immediately after treatment	218.40 (175.33,291.15)*	112.45 (89.78,147.93)*
	24 h after treatment	278.65 (199.38,392.40)*	154.55 (88.70,278.65)*
Control group	Pre-treatment	336.35 (242.83,465.58)	263.20 (128.90,345.43)
	Immediately after treatment	225.05 (158.35,312.65)*	120.40 (88.20,164.40)*
	24 h after treatment	291.80 (203.48,421.28)*	162.55 (111.68,306.00)*
p value between the two groups immediately after treatment		0.981	0.660
p values between the two groups at 24 h after treatment		0.443	0.288

Note: Reference range: PT(9.4–12.5 s), APTT(25.1–36.5 s), TT(10.3–16.6 s), TBIL(≤ 26.0 μmol/L), DBIL(≤ 4.0 μmol/L). * indicates statistically significant difference compared with pre-treatment ($p < 0.05$).
Abbreviations: APTT, activated partial thromboplastin time; DBIL, direct bilirubin; PT, prothrombin time; TBIL, total bilirubin; TT, thrombin time.

immediately after treatment, with statistical differences compared to pre-treatment levels ($p < 0.001$). Although a rebound occurred 24 h after treatment, levels remained significantly lower than pre-treatment values, with statistically significant differences noted ($p < 0.05$) (Figure 2D,E). The decline rate of TBIL immediately after treatment and 24 h after treatment in the observed group was slightly lower than that in the control group (33% vs. 35% and 14% vs. 16%, respectively); however, no statistical difference was observed between the two groups ($p = 0.193$ and 0.653, respectively) (Figure 1C,D).

3.3.2 | Survival Time Analysis

All patients diagnosed with ACLF were monitored for 28 days following DPMAS treatment. In the observed group, there were 10 fatalities, resulting in a survival rate of 76.2%, while the control group experienced 28 fatalities, corresponding to a survival rate of 75.4%. No significant differences were observed in survival rates ($p = 0.923$) or average survival times ($p = 0.0.874$) between the two groups (Table 5). The Kaplan–Meier survival model was developed using the 28-days survival data from both groups (Figure 3).

4 | Discussion

ACLF is characterized by a severe underlying disease, rapid disease progression, and a high short-term fatality rate. Without timely and effective treatment, the prognosis is extremely poor [16, 17]. Notably, timely NBAL treatment can not only improve the survival rate of patients with ACLF but also help patients transition to the liver transplantation stage [13]. At present, the recommended PLT count for most invasive procedures is $\geq 50 \times 10^9$/L, which may cause some patients to miss the optimal treatment opportunity.

In this study, we found no significant differences in the incidence of bleeding-related complications and thrombotic events during and after treatment between patients with ACLF receiving DPMAS with 40×10^9/L ≤ PLT count < 50×10^9/L and those with a PLT count $\geq 50 \times 10^9$/L. Similarly, no statistical differences were observed in the decline of PLT counts immediately after treatment and 24 h later between the observed and control groups. Although the primary coagulation indices—PT, APTT, and TT—increased significantly immediately after treatment, they returned to pre-treatment levels within 24 h, with no significant differences compared to the initial measurements. This notable increase in coagulation indices immediately after treatment is attributed to the anticoagulant effects of heparin sodium used during the procedure, which has a plasma half-life of approximately 1–2 h. As the heparin sodium is metabolized, PT, APTT, and TT swiftly return to pre-treatment levels. Moreover, thromboelastography showed no statistical differences in PLT function, coagulation factor activity, and fibrinogen function between the groups, indicating that despite lower PLT counts in patients with ACLF, their PLT function can still

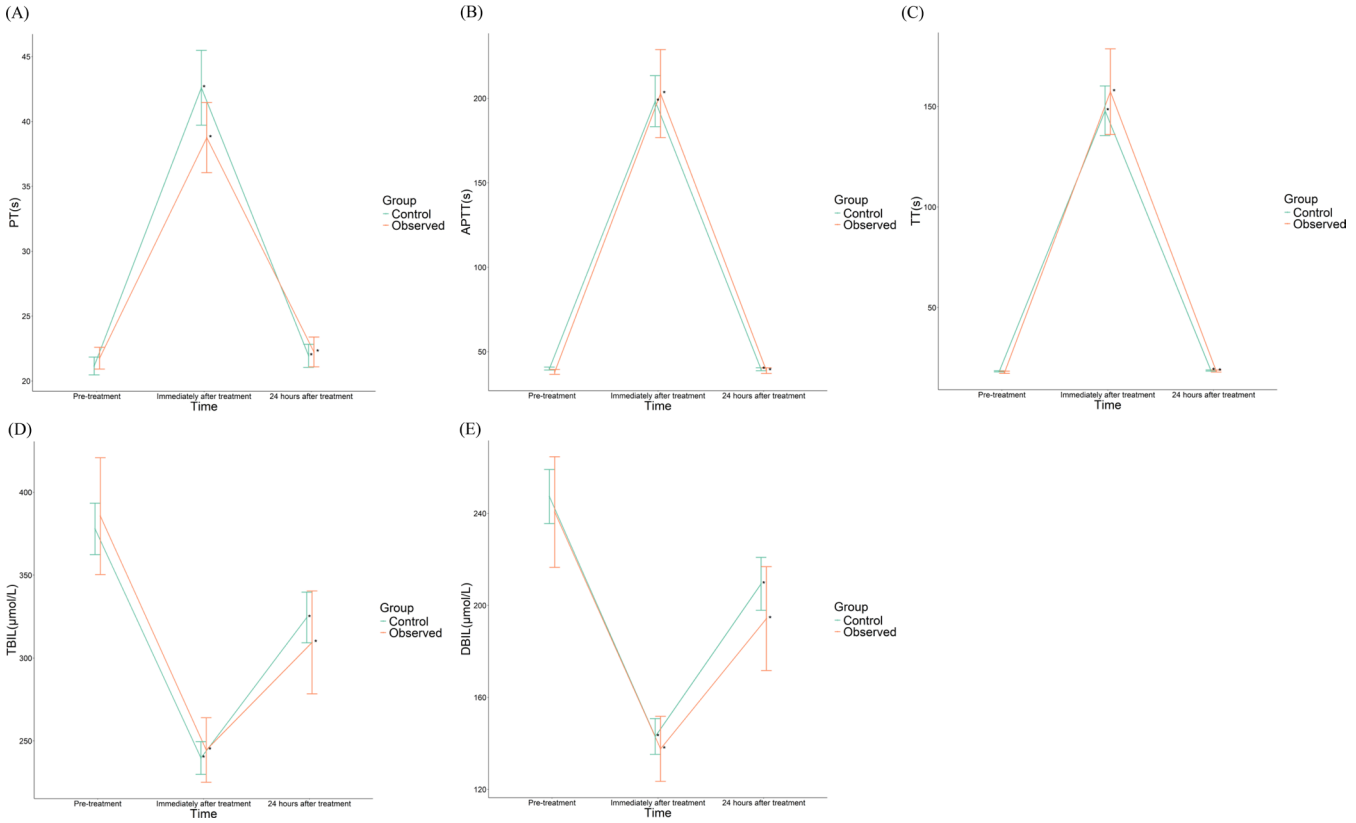

FIGURE 2 | Changes in PT, APTT, TT, TBIL and DBIL in DPMAS pre-treatment, immediately after treatment, and 24 h after treatment. (A, B, C) PT, APTT, and TT levels in both the observed and control groups showed a significant increase immediately after treatment, with a statistically significant difference from pre-treatment values ($p < 0.001$). 24 h after treatment, these levels returned to pre-treatment values, with no statistical differences compared to the baseline ($p > 0.05$). (D, E) TBIL and DBIL levels in both the observed and control groups decreased significantly immediately after treatment, with statistical differences compared to pre-treatment levels ($p < 0.001$). 24 h after treatment, levels remained significantly lower than pre-treatment values, with statistically significant differences noted ($p < 0.05$). PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; TBIL, total bilirubin; DBIL, direct bilirubin; DPMAS, double-plasma molecular absorption system.

TABLE 5 | Comparison of the average survival time.

Index	Average survival time (days)	*Log-Rank*	*p*
Observed group ($n = 42$)	26.21 (24.79,27.64)	0.037	0.85
Control group ($n = 114$)	25.28 (24.14,26.42)		

maintain physiological functionality. These results confirm that DPMAS therapy is feasible and safe for patients with ACLF with $40 \times 10^9/L \leq$ PLT count $< 50 \times 10^9/L$.

Regarding therapeutic efficacy, the main therapeutic indices, TBIL and DBIL, in patients with ACLF with $40 \times 10^9/L \leq$ PLT count $< 50 \times 10^9/L$ decreased significantly immediately after DPMAS treatment and were still significantly lower than pre-treatment, although they rebounded 24 h after treatment. Immediately and 24 h after treatment, the values were significantly different from those before treatment. There was no significant difference in the decline rate of TBIL immediately after treatment and 24 h post-treatment, and the 28-days survival time after DPMAS treatment between the observed and control groups. This finding aligns with the results of previous clinical studies [11, 18]. Thus, the efficacy of DPMAS treatment in patients with $40 \times 10^9/L \leq$ PLT count $< 50 \times 10^9/L$ was determined.

Patients with ACLF with both procoagulant and anticoagulant disorders often have decreased PLT count, and the PLT level decreases with the progression of liver disease; importantly, severe reduction of PLT is associated with adverse clinical outcomes [19]. However, although the PLT count alone can reflect the progression and severity of liver disease, its effectiveness in predicting the risk of bleeding is uncertain. Notably, patients with ACLF accompanied by portal hypertension and hypersplenism have a higher risk of bleeding [20]. In addition, studies have reported that although NBAL treatment may cause a decrease in PLT count, it does not inhibit the bone marrow hematopoietic function of patients; the effect on PLT count is temporary, and the PLT count can be increased to the baseline level approximately 1 week after NBAL treatment [4]. In this retrospective study, we found no statistically significant difference in the decline rate immediately after treatment with PLT and 24 h post-treatment between the observed and control groups. The observed group utilized less heparin than the control group. This finding suggests that standardized and

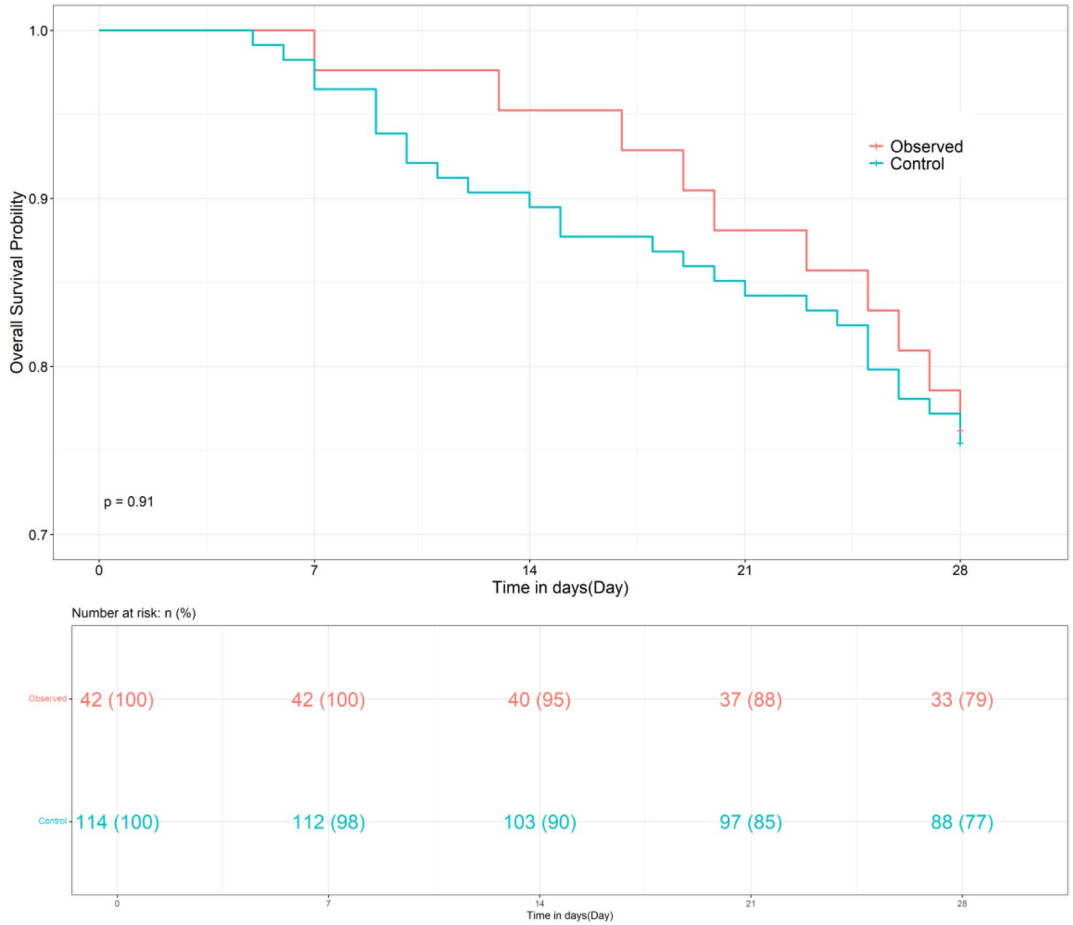

FIGURE 3 | The Kaplan-Meier survival curve depicted the survival status of ACLF patients followed up for 28 days after the first DPMAS treatment.

rational heparin use may contribute to reducing PLT count and bleeding risk after DPMAS.

For patients with a low PLT count, the PLT count is often increased clinically by PLT infusion, oral TPO-RA [21, 22], splenectomy, and partial splenic artery embolization. However, PLT infusion may result in an immune transfusion reaction or ineffective infusion. Studies have reported that the incidence of ineffective PLT infusion in patients with various diseases and a reduced PLT count is 35.7%. The incidence of ineffective infusion is proportional to the number of PLT infusions, and challenges include difficulty in obtaining the blood source, short half-life of PLT, limited shelf life of PLT products, and high costs [23]. Oral TPO-RA requires a wait time of at least 5–9 days or longer, and thrombosis is a potential risk; studies have shown that the risk of thrombotic events within 30 days of TPO-RA treatment is approximately 1% [24, 25]. In 2021, the Journal of "AGA Clinical Practice Guidelines on the Management of Coagulation Disorders in Patients with Cirrhosis" indicated that due to limited clinical benefits, routine use of blood products and TPO-RA for bleeding prevention is not recommended for low-risk procedures [7]. Expanding the treatment population of NBAL could enhance safety and effectiveness for patients with liver failure. Thus, it is necessary to broaden the indications for NBAL therapy in patients with ACLF. Our research has the limitation of being a single-center study with a limited number of cases. A prospective study is being conducted, and more cases and multicenter studies are being planned for later stages to provide further observation and analysis.

5 | Conclusions

DPMAS treatment is safe for patients with ACLF with $40\times10^9/L \leq$ PLT count $< 50\times10^9/L$ under appropriate anticoagulation management and artificial liver care, and does not compromise the therapeutic effect. Treatment should be initiated as soon as possible without exogenous PLT supplementation to impede disease progression and enhance cure and survival rates.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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