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Association between volume of processed plasma and total bilirubin reduction during plasma adsorption for severe liver disease

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Abstract

Background The double plasma molecular adsorption system (DPMAS) is a crucial therapeutic modality for the management of severe liver disease. Current literature reports considerable variability in the volume of processed plasma (VPP) utilized during DPMAS treatment, and there is currently no consensus on the appropriate VPP. We aimed to investigate the relationship between VPP and changes in total bilirubin levels during DPMAS treatment.

Methods A prospective observational study with a repeated-measures design was conducted in patients with severe liver disease. The generalized estimation equations were used to evaluate the relationship between VPP and changes in total bilirubin levels during DPMAS treatment. The Bonferroni method was used for multiple comparisons. Tests for linear trends were performed by entering the median value of each category as a continuous variable. Total bilirubin level were detected repeatedly at four different times (four different VPP) (at 0.0 h (0 mL); at 2.0 h (3000 mL); at 2.5 h (3750 mL); at 3.0 h (4500 mL)).

Results Twenty-nine patients who underwent 75 sessions of DPMAS treatment were enrolled. The baseline total bilirubin levels and model for end-stage liver disease score were 426.1 (356.6–487.3) μmol/L and 21.9 (18.7–24.9). The total bilirubin levels and their reduction ratios in all patients (75 sessions) or patients with total bilirubin <425 μmol/L (39 sessions) or ≥425 μmol/L (36 sessions) decreased gradually and significantly at four different times (four different VPP) (all adjusted *P* for pairwise comparisons <0.001; adjusted *P* for trend <0.001). The reduction ratios of total bilirubin in patients with total bilirubin ≥425 μmol/L were similar to those with total bilirubin <425 μmol/L (adjusted OR (95% CI), 1.001 (0.966–1.036)). The positive relationship between the reduction ratios of total bilirubin and VPP was less remarkable in patients with higher height (adjusted *P* for interaction = 0.027) or lower albumin levels (adjusted *P* for interaction = 0.017).

Conclusion The VPP of DPMAS treatment could be more than 4500 mL. Patients with higher height or lower albumin levels might require a higher VPP to achieve sufficient therapeutic efficacy.

Keywords Severe liver disease, Artificial liver support system, Double plasma molecular adsorption system, Volume of processed plasma, Therapeutic dosing

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Introduction

Artificial liver support system (ALSS) treatment is an available method for liver failure, which could improve short-term prognosis and hepatic encephalopathy but does not increase the occurrence of adverse events such as hypotension, bleeding, thrombocytopenia, and catheter-related infections [1]. Although various modes exist, ALSS typically involves the use of single or combined techniques, such as plasma exchange (PE), plasma adsorption, and continuous renal replacement therapy (CRRT), utilizing different consumables [2]. In China, ALSS treatment is based on PE treatment. If the amount of plasma used for PE is less than one plasma volume, plasma adsorption would be added [2, 3]. The primary plasma adsorption method used in ALSS treatment is the double plasma molecular adsorption system (DPMAS). Previous non-randomized controlled studies have suggested that DPMAS treatment may improve short-term prognosis in patients with liver failure [4–9]. A recent randomized controlled trial demonstrates that the combination treatment of DPMAS with sequential low-volume PE could significantly improve short-term prognosis in patients with intermediate-stage acute-on-chronic liver failure [10]. In situations of plasma shortage, the combination of DPMAS with low–volume PE may be an appropriate approach for patients with liver failure.

Therapeutic dosing for plasma adsorption refers to the volume of plasma processed using a perfusion device. The recommended volume of processed plasma for DPMAS, according to the product manual is 3600–5400 mL over 2–3 h. However, there is significant variability in the volume of processed plasma (3000–6000 mL) and duration (2–4 h) in DPMAS treatment (Supplementary file 1: Table S1) [4–20]. The appropriate volume of processed plasma for DPMAS treatment remains unclear. Here, we conducted a prospective observational cohort study to provide a reference for establishing a reasonable volume of processed plasma for DPMAS treatment in patients with severe liver disease.

Methods

Study design

A prospective observational cohort study was conducted to provide a reference for establishing a reasonable volume of processed plasma for DPMAS treatment in patients with severe liver disease at the Center of Infectious Diseases, West China Hospital, Sichuan University.

The study employed a single-group, quantitative, repeated-measures design. The sample size relied on five parameters: the correlation coefficient (ρ), effect size, number of repeated measures (k), significance level (α), and power (β) [21]. The correlation coefficient refers to the correlation between repeated measurement data. The most commonly used correlation coefficients are 0.3, 0.5, and 0.8. Barcikowski et al. [21] recommend using 0.5, which has been proven to be the most conservative yet close to the actual situation. The effect size refers to the degree of change in the measured values over time, which can be classified into small, medium, and large categories. Barcikowski et al. [21] did not recommend this parameter. For this study, with $k=4$, assuming $\rho=0.5$, a medium effect size, $\alpha=0.05$, and $\beta=0.8$, the minimum sample size required utilizing table lookup methods was 27 sessions of DPMAS treatment [21].

Hyperbilirubinemia is not only one of the defining features of severe liver disease but is also associated with disease severity and patient outcome [22]. During ALSS treatment, the most noticeable change was observed in the total bilirubin levels [23]. Therefore, this study assessed the appropriateness of the volume of processed plasma for DPMAS treatment based on changes in total bilirubin levels. Given that a total bilirubin level of 25 mg/dL (approximately 425 umol/L) is an important cutoff value for patients with liver failure [24–26], patients were categorized into two subgroups based on cutoff values: <425 and ≥425 μmol/L. Consequently, the total bilirubin level was stratified into two subgroups (patients with total bilirubin <425 or ≥425 μmol/L), each subgroup required at least 27 sessions.

Ethical approval

This study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (2021-1652), and was conducted in compliance with the Declaration of Helsinki. Written informed consent to participate in this study was obtained from all adult participants.

Patients

The main indications of ALSS treatment in China are pre-, early-, and mid-stage liver failure; perioperative period of liver transplantation for end-stage liver failure; and severe cholestatic liver disease or hyperbilirubinemia with poor response to standard medical treatment [3]. The inclusion criteria were: (1) age between 18 and 75 years, any sex; (2) severe liver disease due to various causes with total bilirubin ≥205 μmol/L (12 mg/dL), no specific requirement for international normalized ratio of prothrombin time (PT-INR); (3) receiving standard medical treatment, currently undergoing or planning to undergo ALSS treatment with the mode of DPMAS followed by PE; and (4) willingness to participate in this study. The exclusion criteria were obstructive jaundice, pregnancy, diagnosed or suspected liver cancer, mental illness, prior organ transplantation, and partial hepatectomy.

From February 14, 2022, to March 13, 2022, it took 4 weeks to screen and enroll patients who fulfilled the criteria (Fig. 1). Medical records were collected from the Hospital Information System and Laboratory Information System. Baseline data, including routine blood tests, liver and kidney function, and coagulation function within 48 h before enrollment, were recorded.

DPMAS treatment and measurements

The DPMAS is composed of a plasma bilirubin adsorption column (BS330, Jafron Biomedical Corp.) and a hemoperfusion device (HA330-II, Jafron Biomedical Corp.), which was the same as previously described [18, 23]. The capacities of BS330 and HA330-II were all 330 mL. BS330, which contains styrene anion exchange resin, could remove bilirubin and bile acid. The adsorption capacity of BS330 for bilirubin and bile acid are not less than 0.8 and 0.3 μmoL/mL, respectively. The HA330-II containing neutral macroporous resin could remove endogenous and exogenous materials such as residual drugs, toxins, and metabolic substances.

Prior to DPMAS treatment, the extracorporeal circuit and plasma separator were primed with 2000 mL of normal saline, and the DPMAS device was rinsed with 5000 mL of normal saline, followed by 500 mL of 4% succinylated gelatin solution (B. Braun Medical (Suzhou) Co., LTD). The parameters of the CRRT machine were set as follows: blood flow, 130 mL/min; plasma separation flow, 1500 mL/h; plasma return flow, 1500 mL/h. The duration of DPMAS treatment was 3 h, and the volume of processed plasma was 4500 mL.

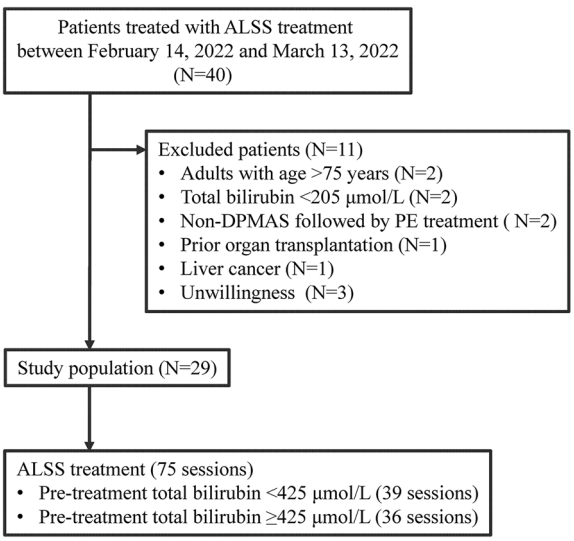

Fig. 1 Patients selection. *ALSS* artificial liver support system, *DPMAS* double plasma molecular adsorption system, *PE* plasma exchange

Blood samples for total bilirubin and other liver function tests, as well as renal function tests, were collected before DPMAS treatment (at 0.0 h, volume of processed plasma: 0 mL), and blood samples for total bilirubin test were collected at 2.0 h (volume of processed plasma: 3000 mL), 2.5 h (volume of processed plasma: 3750 mL), and 3.0 h (volume of processed plasma: 450 mL) into DPMAS treatment.

The calculation formulas used were developed as follow:

Reduction ratio = (1 − bilirubin during treatment (μmol/L)/bilirubin before treatment (μmol/L)) × 100%.

The volume of processed plasma (mL) = plasma separation flow (1500 mL/h) × treatment time (h).

All participants completed the study and were included in the analysis. The dataset was fully intact, with no missing values.

Statistical analysis

Quantitative data are represented as medians (P_{25}–P_{75}), while qualitative data are represented as frequencies (proportions). As a study with a repeated-measures design, individual observations in repeated measurement data were not entirely independent and tended to exhibit convergence. Therefore, the generalized estimating equations with robust estimation and an unstructured working correlation matrix were used to evaluate the relationship between the volume of processed plasma and changes in total bilirubin levels, as well as the reduction ratios of total bilirubin. An adjusted model was established using sex (female vs. male), age (years), height (cm), underlying chronic liver disease (yes vs. no), PT-INR, total bilirubin (μmol/L), albumin (g/L), creatinine (μmol/L), and white blood cell count ($\times 10^9$/L). The Bonferroni method was used for multiple comparisons. Tests for linear trends were performed by entering the median value of each category as a continuous variable in the model. Statistical tests were performed using SPSS version 22 (IBM Corp.). Statistical significance was set at $P < 0.05$.

Results

Patients' characteristics

A total of 29 patients with severe liver disease were enrolled (Fig. 1), including 21 males and 8 females, with a median age of 50.0 (43.0–56.0) years and an age range of 20.0–67.0 years. The median height was 167.0 (161.0–170.0) cm. Baseline (within 48 h before enrollment) total bilirubin levels were 426.1 (356.6–487.3) μmol/L, and the PT-INR was 1.52 (1.39–1.87) (Table 1).

During the study period, patients received one to seven sessions of DPMAS treatment (75 sessions in total). The pre-treatment total bilirubin was 416.0 (342.5–493.4) μmol/L, with 39 sessions having pre-treatment

Table 1 Patients' characteristics

Characteristics	Results (n = 29)
Female	8 (27.6%)
Age (years)	50.0 (43.0–56.0)
Height (cm)	167.0 (161.0–170.0)
Cause of liver disease[§]	
Chronic hepatitis B	15 (51.7%)
Alcoholic liver disease	5 (17.2%)
Drug-induced liver injury	5 (17.2%)
Steatohepatitis	4 (13.8%)
Autoimmune liver disease	3 (10.3%)
Hepatitis A or hepatitis E	2 (6.9%)
Underlying chronic liver disease	21 (72.4%)
Liver cirrhosis	15 (51.7%)
Complications	
Ascites	14 (48.3%)
Hepatic encephalopathy	2 (6.9%)
Upper gastrointestinal bleeding	0 (0.0%)
MELD score	21.9 (18.7–24.9)
Laboratory examination	
Total bilirubin (μmol/L)	426.1 (356.6–487.3)
Alanine aminotransferase (IU/L)	78.0 (40.0–122.5)
Albumin (g/L)	31.4 (28.6–33.5)
Total bile acids (μmol/L)	208.5 (166.5–239.3)
Blood ammonia (mmol/L)	47.9 (38.9–62.9)
PT-INR	1.52 (1.39–1.87)
Serum creatinine (μmol/L)	85.0 (73.5–93.5)
Serum sodium(mmol/L)	134.1 (131.9–135.4)
Serum potassium (mmol/L)	3.41 (3.07–3.86)
White blood cell count ($\times 10^9$/L)	6.16 (5.37–8.72)
Hemoglobin (g/L)	110.0 (101.0–122.5)
Platelet count ($\times 10^9$/L)	84.0 (56.0–130.5)

PT-INR international normalized ratio of prothrombin time

[§] Some patients have more than one cause of liver disease

Quantitative data are represented as median (P_{25}–P_{75})

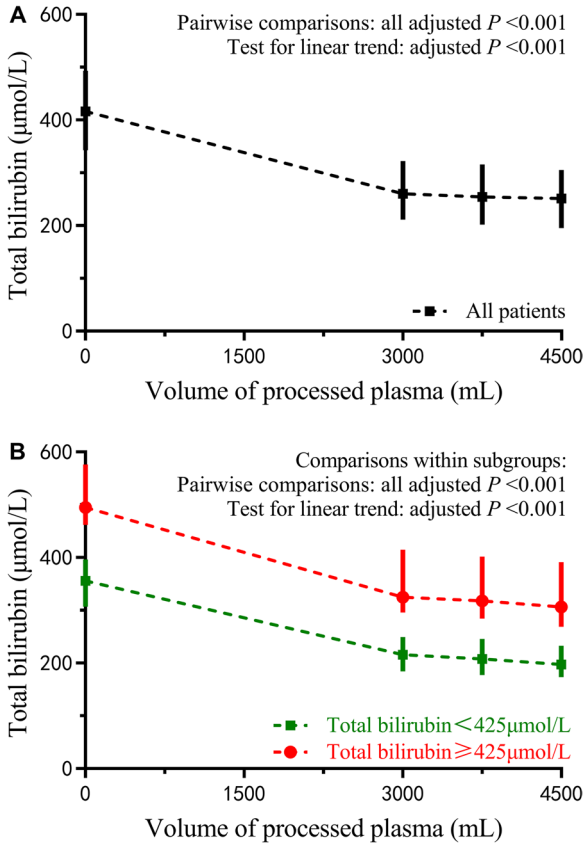

Fig. 2 Changes in total bilirubin levels in all patients (**A**) and patients with total bilirubin <425 μmol/L or ≥425 μmol/L (**B**) during DPMAS treatment. *DPMAS* double plasma molecular adsorption system. Quantitative data are represented as median (P_{25}–P_{75})

total bilirubin <425 μmol/L and 36 sessions having pre-treatment total bilirubin ≥425 μmol/L.

Changes in total bilirubin levels during DPMAS treatment

Of the 75 sessions of DPMAS treatment, the median total bilirubin levels decreased significantly and gradually at the 4 different time (volume of processed plasma) (at 0.0 h (0 mL): 416.0 (342.5–493.4) μmol/L; at 2.0 h (3000 mL): 260.1 (211.1–322.4) μmol/L; at 2.5 h (3750 mL): 254.1 (201.6–315.8) μmol/L; at 3.0 h (4500 mL): 251.2 (195.1–305.2) μmol/L) in pairwise comparisons (all $P < 0.001$) and in test for linear trend (P for trend <0.001). The differences remained significant in the adjusted models (all adjusted $P < 0.001$ and adjusted P for trend <0.001) (Fig. 2A).

Of the 39 sessions of DPMAS treatment in patients with total bilirubin <425 μmol/L, the median total bilirubin levels decreased significantly and gradually at the 4 different time (volume of processed plasma) (at 0.0 h (0 mL): 355.7 (306.5–396.3) μmol/L; at 2.0 h (3000 mL): 215.9 (184.4–249.3) μmol/L; at 2.5 h (3750 mL): 208.0 (177.3–245.5) μmol/L; at 3.0 h (4500 mL): 197.5 (173.3–232.9) μmol/L) in pairwise comparisons (all $P < 0.001$) and in test for linear trend (P for trend <0.001). The differences remained significant in the adjusted models (all adjusted $P < 0.001$ and adjusted P for trend <0.001) (Fig. 2B).

Of the 36 sessions of DPMAS treatment in patients with total bilirubin ≥425 μmol/L, the median total bilirubin levels decreased significantly and gradually at the 4 different time (volume of processed plasma) (at 0.0 h (0 mL): 494.8 (461.6–576.3) μmol/L; at 2.0 h (3000 mL): 324.6 (295.7–414.7) μmol/L; at 2.5 h (3750 mL): 317.6 (284.1–401.9) μmol/L; at 3.0 h (4500 mL): 306.2

(268.7–391.5) μmol/L) in pairwise comparisons (all $P<0.001$) and in test for linear trend (P for trend <0.001). The differences remained significant in the adjusted models (all adjusted $P<0.001$ and adjusted P for trend <0.001) (Fig. 2B).

Changes in reduction ratios of total bilirubin during DPMAS treatment

Of the 75 sessions of DPMAS treatment, the median reduction ratios of total bilirubin increased significantly and gradually at the 4 different time (volume of processed plasma) (at 0.0 h (0 mL): 0%; at 2.0 h (3000 mL): 34.8% (30.7–40.3%); at 2.5 h (3750 mL): 37.7% (32.8–42.7%); at 3.0 h (4500 mL): 40.0% (34.9–45.3%)) in pairwise comparisons (all $P<0.001$) and in test for linear trend (P for trend <0.001). The differences remained significant in the adjusted models (all adjusted $P<0.001$ and adjusted P for trend <0.001) (Fig. 3A).

Of the 39 sessions of DPMAS treatment in patients with total bilirubin <425 μmol/L, the median reduction ratios of total bilirubin increased significantly and gradually at the 4 different time (volume of processed plasma) (at 0.0 h (0 mL): 0%; at 2.0 h (3000 mL): 37.1% (33.2–42.0%); at 2.5 h (3750 mL): 40.0% (34.0–43.6%); at 3.0 h (4500 mL): 41.0% (37.3–45.5%)) in pairwise comparisons (all $P<0.001$) and in test for linear trend (P for trend <0.001). The differences remained significant in the adjusted models (all adjusted $P<0.001$ and adjusted P for trend <0.001) (Fig. 3B).

Of the 36 sessions of DPMAS treatment in patients with total bilirubin ≥425 μmol/L, the median reduction ratios of total bilirubin increased significantly and gradually at the four different times (volume of processed plasma) (at 0.0 h (0 mL): 0%; at 2.0 h (3000 mL): 33.1% (30.4–38.3%); at 2.5 h (3750 mL): 35.1% (31.8–40.5%); at 3.0 h (4500 mL): 37.6% (32.5–44.2%)) in pairwise comparisons (all $P<0.001$) and in test for linear trend (P for trend <0.001). The differences remained significant in the adjusted models (all adjusted $P<0.001$ and adjusted P for trend <0.001) (Fig. 3B).

The reduction ratios of total bilirubin in patients with total bilirubin ≥425 μmol/L were similar to those in patients with total bilirubin <425 μmol/L (odds ratio (OR) (95% confidence interval (CI)): 0.987 (0.965–1.010), $P=0.275$). The difference between the two subgroups remained nonsignificant in the adjusted model (adjusted OR (95% CI): 1.001 (0.966–1.036), adjusted $P=0.977$) (Fig. 3B).

Potential factors modifying the changes in reduction ratios of total bilirubin during DPMAS treatment

In the adjusted models established using sex (female vs. male), age (years), height (cm), underlying chronic liver disease (yes vs. no), PT-INR, total bilirubin (μmol/L), albumin (g/L), creatinine (μmol/L), and white blood cell count ($\times10^9$/L), the volume of processed plasma during DPMAS treatment was positively associated with the reduction ratios of total bilirubin in all patients or in patients stratified by sex, age, height, underlying chronic liver disease, PT-INR, total bilirubin, and albumin (all adjusted $P<0.001$ and all adjusted P for trend <0.001) (Table 2). The stratified adjusted models demonstrated that the positive relationship between the volume of processed plasma and reduction ratios of total bilirubin was less remarkable in patients with higher height (adjusted P for interaction = 0.027) or lower albumin levels (adjusted P for interaction = 0.017).

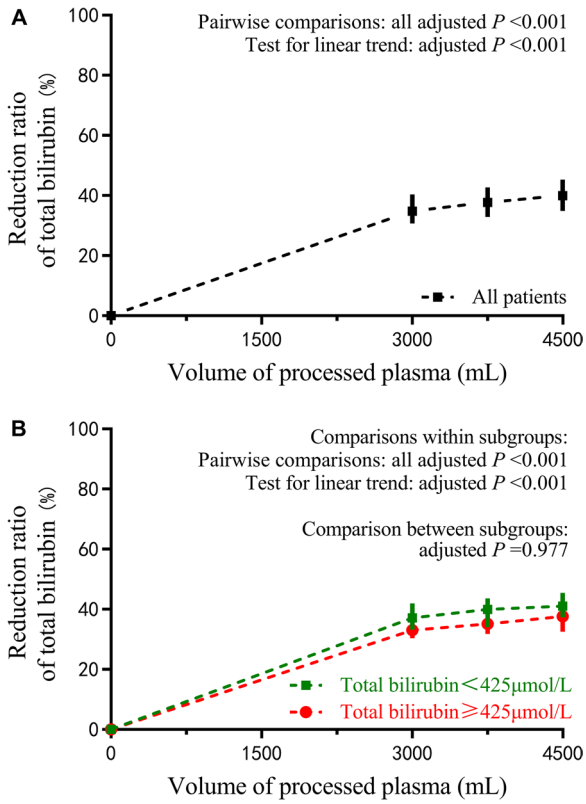

Fig. 3 Changes in reduction ratios of total bilirubin in all patients (**A**) and patients with total bilirubin <425 μmol/L or ≥425 μmol/L (**B**) during DPMAS treatment. *DPMAS* double plasma molecular adsorption system. Quantitative data are represented as median (P_{25}–P_{75})

Discussion

ALSS is a crucial treatment modality for liver failure and plays a role in improving short-term prognosis. Currently, the optimal timing, dosing, frequency, and duration of the three fundamental techniques for ALSS treatment (CRRT, PE, and plasma adsorption) remain unclear [2]. CRRT could significantly reduce blood ammonia,

Table 2 Potential factors modifying the changes in reduction ratios of total bilirubin during DPMAS treatment

	Volume of processed plasma				*P* for trend[#,§]	*P* for interaction[#]
	0 mL (0.0 h)	3000 mL (2.0 h)	3750 mL (2.5 h)	4500 mL (3.0 h)		
All patients	1.0 [Reference]	1.426 (1.398–1.454)	1.456 (1.427–1.485)	1.482 (1.451–1.513)	<0.001	
Sex						0.978
Male	1.0 [Reference]	1.422 (1.391–1.453)	1.452 (1.421–1.485)	1.478 (1.444–1.512)	<0.001	
Female	1.0 [Reference]	1.437 (1.377–1.500)	1.468 (1.404–1.536)	1.493 (1.424–1.566)	<0.001	
Age (year)						0.394
<50	1.0 [Reference]	1.419 (1.376–1.463)	1.449 (1.404–1.494)	1.472 (1.425–1.521)	<0.001	
≥50	1.0 [Reference]	1.432 (1.396–1.467)	1.463 (1.426–1.501)	1.490 (1.451–1.530)	<0.001	
Height (cm)						0.027
<mean stature[&]	1.0 [Reference]	1.485 (1.435–1.536)	1.512 (1.463–1.562)	1.534 (1.486–1.583)	<0.001	
≥mean stature[&]	1.0 [Reference]	1.400 (1.369–1.432)	1.432 (1.399–1.466)	1.459 (1.422–1.497)	<0.001	
Underlying chronic liver disease						0.373
Yes	1.0 [Reference]	1.425 (1.394–1.456)	1.456 (1.423–1.489)	1.485 (1.450–1.521)	<0.001	
No	1.0 [Reference]	1.428 (1.370–1.489)	1.458 (1.398–1.520)	1.473 (1.413–1.536)	<0.001	
PT-INR						0.889
<1.5	1.0 [Reference]	1.422 (1.376–1.468)	1.450 (1.404–1.498)	1.471 (1.421–1.523)	<0.001	
≥1.5	1.0 [Reference]	1.428 (1.394–1.464)	1.460 (1.424–1.497)	1.489 (1.451–1.528)	<0.001	
Total bilirubin (μmol/L)						0.670
<425	1.0 [Reference]	1.440 (1.399–1.482)	1.472 (1.430–1.516)	1.498 (1.452–1.545)	<0.001	
≥425	1.0 [Reference]	1.410 (1.374–1.447)	1.439 (1.402–1.477)	1.464 (1.425–1.505)	<0.001	
Albumin (g/L)						0.017
<30	1.0 [Reference]	1.410 (1.367–1.455)	1.433 (1.390–1.478)	1.461 (1.415–1.508)	<0.001	
≥30	1.0 [Reference]	1.433 (1.398–1.469)	1.468 (1.431–1.505)	1.492 (1.453–1.533)	<0.001	

PT-INR international normalized ratio of prothrombin time

[&] The mean stature of the male is 170 cm and the mean stature of the female is 158 cm

[#] The adjusted models are established using sex (female vs. male), age (years), height (cm), underlying chronic liver disease (yes vs. no), PT-INR, total bilirubin (μmol/L), albumin (g/L), creatinine (μmol/L), and white blood cell count ($\times 10^9$/L)

[§] Tests for linear trends are performed by entering the median value of each category as a continuous variable in the model

intracranial hypertension, and cerebral edema-related mortality in patients with liver failure, potentially significantly enhancing the 21-day transplant-free survival [27, 28]. CRRT should be considered for patients with liver failure and grade III/IV hepatic encephalopathy, or when CRRT is indicated [2]. The therapeutic dosing of CRRT is the effluent volume with a recommended range of 20–25 ml/(kg·h), termed as delivered dose; when the anticipated CRRT duration is less than 24 h, it is advised to increase the prescribed therapeutic dosing, such as 25–30 ml/(kg·h) or higher, to achieve the delivered dose and fulfill therapeutic purpose [29–31]. The therapeutic dosing of PE is the volume of plasma replaced. Recent randomized controlled trials demonstrated that PE with 1–3 plasma volume could significantly improve short-term prognosis in patients with liver failure [32–34]. Therefore, PE is considered essential for ALSS treatment in liver failure [2]. The recommended therapeutic dosing for PE treatment is 1–1.5 plasma volume [3, 29, 35], potentially reaching up to three plasma volumes [35]. Based on evidence-based research, there are relatively clear recommendations regarding therapeutic dosing for CRRT and PE treatment. However, there is a lack of sufficient evidence to establish precise therapeutic dosing for plasma adsorption.

The therapeutic dosing of DPMAS treatment, the volume of processed plasma in the perfusion device, can be expressed in three ways: (1) indirectly hinted: therapeutic dosing (mL) = plasma separation rate (mL/h) × treatment duration (h); (2) direct representation, for example, 4500 mL; and (3) a combination of indirect hint and direct representation, which is the most comprehensive method. The DPMAS product manual suggests a therapeutic dosing of 3600–5400 mL with a treatment duration of 2–3 h. The "Standard Operating Procedures (SOP) for Blood Purification (2021 edition)" proposes a therapeutic dosing for plasma adsorption as 2–3 plasma volume with a treatment duration of 2–3 h [29]; While the "Expert consensus on clinical application of artificial liver and blood purification (2022 edition)" suggests

setting the therapeutic dosing for plasma adsorption at a minimum of 1.2 plasma volume, generally within 2–3 plasma volume, with a minimum treatment duration of 2 h [3]. Nevertheless, there are notable discrepancies between the reported therapeutic dosing of DPMAS treatment in the literature and these recommendations, with large variations (Supplementary file 1: Table S1) [4–20]. Major studies have reported therapeutic dosing directly displayed as 3000–6000 mL [4, 7–18], while indirectly hinted therapeutic dosing are indicated as plasma separation rates of 20–50 mL/min with a treatment duration of 2–4 h [4–6, 10, 11, 18–20]. The normal human plasma volume is approximately calculated as follows: plasma volume (mL) ≈ 65 × ideal body weight (kg) × (1-hematocrit) [29], approximately 4% of the ideal body weight (40 ml/kg). Although the reported therapeutic dosing of DPMAS treatment is generally above 1.2 plasma volume, some therapeutic dosing is below two plasma volumes. This might be related to substantial variations in the treatment efficacy of DPMAS treatment; the immediate reduction ratios of total bilirubin ranged from 30% to 65% pre- and post-treatment (Supplementary file 1: Table S1). This prospective observational cohort study aimed to determine the appropriate therapeutic dosing for DPMAS treatment. Setting the plasma separation rate at 25 mL/min, the total volume of processed plasma for a 3-h session was 4500 mL. The study found that the total bilirubin levels and their reduction ratios in all patients, or patients with total bilirubin <425 μmol/L or ≥425 μmol/L changed gradually and significantly at four different time and different volume of processed plasma of DPMAS treatment (at 0.0 h (0 mL); at 2.0 h (3000 mL); at 2.5 h (3750 mL); at 3.0 h (4500 mL)) (all adjusted *P* for pairwise comparisons <0.001 and all adjusted *P* for trend <0.001), with no rebound in total bilirubin levels observed. These results suggest that at a plasma separation rate of 25 mL/min and a volume of processed plasma of 4500 mL over 3 h, the adsorption capacity of DPMAS remains unsaturated. It is appropriate to continue increasing the volume of the processed plasma of DPMAS treatment.

The DPMAS device has a limited capacity for adsorption, targeting bilirubin in the bloodstream. Once blood bilirubin levels decrease to a certain level, a dynamic equilibrium is reached, manifesting as sustained stability of total bilirubin levels during continuous DPMAS treatment. Given the large apparent distribution volume of bilirubin [36, 37], as blood bilirubin levels decrease, extravascular bilirubin gradually enters the bloodstream. Simultaneously, bilirubin originating from the liver continuously enters the blood stream. Although the apparent blood total bilirubin levels may not decrease, they actually reflect the removal of extravascular and liver-derived bilirubin by DPMAS treatment. Therefore, considering the absence of a statistical inflection point indicating an increase in total bilirubin levels, it is advisable to further increase the volume of processed plasma in DPMAS treatment to eliminate more bilirubin. Jung et al. investigated the capability of the molecular adsorbent recirculating system (MARS) and the fractionated plasma separation and adsorption system (FPSA) in eliminating bilirubin in severe liver disease over a 6-h treatment period [37]. They observed, from the perspective of bilirubin sources and distribution, that assessing treatment efficiency using pre- and post-treatment measurements of blood bilirubin levels significantly underestimated the actual capacity of MARS and FPSA to eliminate bilirubin (48% ± 10% vs. 54% ± 13%, $P < 0.05$) [37]. Because the double absorption technique is also used in MARS and FPSA, the findings from MARS and FPSA support our aforementioned inference during DPMAS treatment. When a patient's blood total bilirubin levels remain stable without an inflection point indicating an increase, it is permissible to continue increasing the volume of processed plasma of DPMAS treatment to further eliminate bilirubin.

Bilirubin binds mainly to albumin in the blood and is transported to the liver for metabolism. The amount and function of albumin affects the metabolism of bilirubin [38, 39]. In this study, we found that the positive relationship between the volume of processed plasma and the reduction ratios of total bilirubin was less remarkable in patients with lower albumin levels (adjusted *P* for interaction = 0.017). This finding suggests that increasing albumin levels might help in bilirubin clearance during DPMAS treatment. We also found that the positive relationship between the volume of processed plasma and the reduction ratios of total bilirubin was less remarkable in patients with higher height (adjusted *P* for interaction = 0.027). A possible reason for this phenomenon is that the relative therapeutic dosing was smaller in patients with a higher height due to their larger plasma volume [29]. This finding suggests that the volume of processed plasma for DPMAS treatment in patients with a higher height should be increased.

DPMAS, PE, and post-dilutional continuous venovenous hemofiltration (post-CVVH), a CRRT method, share similar technical principles and extracorporeal circuit connection methods. The key difference lies in post-CVVH using a hemofilter, discarding separated waste fluid, and replacing it with an equal volume of replacement fluid (with no dehydration) or less than the waste fluid volume of replacement fluid (with dehydration). PE employs a plasma separator, discards separated plasma, and replenishes it with an equal volume of allogeneic plasma (having no dehydration), akin to allogeneic

plasma serving as the replacement fluid in post-CVVH without dehydration. Similarly, DPMAS utilizes a plasma separator, where separated plasma is adsorbed and processed before it is reintroduced into the body (without dehydration), akin to purified autologous plasma serving as the replacement fluid in post-CVVH without dehydration [40]. Consequently, during DPMAS and PE treatments, the fundamental principles of setting the CRRT parameters should be followed. For instance, maintaining an appropriate blood concentration ratio (≤20–25%) and filtration fraction (≤25–30%) to minimize significant blood concentration and blood protein-membrane reactions in the plasma separator area, thereby reducing the patient's blood cell loss [29–31]. In clinical practice, it is more suitable to adjust the blood concentration ratio and control the filtration fraction based on the patient's hematocrit, with the aim of increasing the unit-time volume of processed plasma and the duration to augment the therapeutic dosing of DPMAS treatment (Supplementary file 1: Table S2).

This study had several limitations. (1) Although total bilirubin levels represent the most significant parameter for change during ALSS treatment, bilirubin reduction is not the sole target of DPMAS treatment. The clearance of inflammatory mediators and other factors is equally crucial and should be considered as an assessment criterion for therapeutic dosing. (2) The sample size was based on a moderate effect; therefore, increasing the effect size might yield different results in studies with larger sample sizes. (3) Under the same volume of processed plasma, variations in the plasma separation flow and treatment duration could potentially yield different outcomes. (4) During DPMAS treatment, the change in total bilirubin is the most significant; thus, it is suitable to use it as a surrogate biomarker to find a more appropriate volume of processed plasma in DPMAS treatment. Several studies have focused on the impact of DPMAS plus PE treatment on patient outcomes and have achieved positive results [10, 41, 42]; however, high-quality evidence is still needed. The hypothesis that different volumes of processed plasma for DPMAS treatment may lead to different patient outcomes needs to be tested in the future.

In conclusion, the volume of processed plasma of DPMAS treatment could be more than 4500 mL. While ensuring patient safety, continued efforts could be made to increase the volume of processed plasma in order to enhance treatment efficacy, especially for patients with higher height or lower albumin levels who might require a higher VPP to achieve sufficient therapeutic efficacy. Future prospective multicenter cohort studies are warranted to further elucidate the appropriate therapeutic dosing for DPMAS treatment. Specifically, it is necessary to explore other potential biomarkers or factors in addition to total bilirubin levels. For instance, the role of patient individual characteristics, disease state, combined treatment regimens should be investigated. This approach would facilitate a more comprehensive understanding of the treatment response, thereby enabling the development of personalized treatment strategies. Such studies would provide high-quality evidence to precisely implement DPMAS treatment and improve the prognosis of patients with critically ill liver disease.

Abbreviations

ALSS	Artificial liver support system
CRRT	Continuous renal replacement therapy
CVVH	Continuous veno-venous hemofiltration
DPMAS	Double plasma molecular adsorption system
FPSA	Fractionated plasma separation and adsorption system
MARS	Molecular adsorbent recirculating system
PE	Plasma exchange
PT-INR	International normalized ratio of prothrombin time
SOP	Standard operating procedures

Supplementary Information

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Additional file 1.

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Author contributions
MYJ and DLY: Statistical analysis, drafting of the manuscript, and interpretation of data. MYJ, DLY, and BL: Patient screening and enrollment, full access to all of the data in the study, responsibility for the integrity of the data, and accuracy of the data analysis. MYJ and XY: Data acquisition. MYJ and BL: Study concept and design. BL and TH: Critical revision of the manuscript for intellectual content. All authors have read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Biomedical Research Ethics Committee of the West China Hospital of Sichuan University (2021-1652). All study components were performed according to the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Written informed consent to participate in the study was obtained from all adult participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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