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Impact of plasma adsorption volumes (5 L vs. 6 L) on the prognosis of patients with liver failure.

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Keywords: Plasma Adsorption; Liver Failure; Complications; Duration of Therapy; Blood Platelets.

Abstract. Plasma adsorption (PA) is used to improve outcomes in liver failure (LF). Data on adsorption capacity and its relationship to patient outcomes are limited. This single-center retrospective study included patients with LF who received PA at the First Affiliated Hospital of Zhejiang University School of Medicine in Hangzhou City, China, between October 2020 and October 2022, and examined the impact of adsorption volume (5 L vs. 6 L) on prognosis. The study included 230 PA treatments, of which nine were excluded due to missing data. The 5L column was used in 60 patients (118 treatments, 47 male), and the 6L column was used in 50 patients (103 treatments, 31 male). Treatment effectiveness was evaluated using length of hospital stay, liver transplantation, death, and improvement in disease-related symptoms. In both groups, PA increased white blood cells (WBC), international normalized ratio (INR), activated partial thromboplastin time (APTT), and prothrombin time (PT) but decreased hemoglobin, total bile acids, total bilirubin, and fibrinogen (all $p<0.05$). Platelet levels decreased after 6L PA ($p=0.033$) but not after 5L PA ($p=0.116$). After PA, the 6L group had lower WBC than the 5L group ($p=0.003$), but there were no significant differences in the other parameters. The 5L and 6L columns did not differ significantly in hospital stay duration, liver transplantation, mortality, or symptom improvement. However, the 5L column significantly reduced platelet destruction, shortened treatment time, and reduced the occurrence of complications, particularly thrombocytopenia-related risks. Hence, the results indicate that the 5L volume would be preferable clinically.

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Impacto de los volúmenes de adsorción plasmática (5 L vs. 6 L) en el pronóstico de pacientes con insuficiencia hepática.

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Palabras clave: Adsorción Plasmática; Insuficiencia Hepática; Complicaciones; Duración de la Terapia; Plaquetas.

Resumen. La adsorción plasmática (AP) se utiliza para mejorar los resultados en la insuficiencia hepática (IH). Faltan datos relevantes sobre las diferentes capacidades de adsorción y su efecto en la recuperación de los pacientes. Este estudio retrospectivo unicéntrico incluyó a pacientes con IH que recibieron AP en el First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou City, China, entre octubre de 2020 y octubre de 2022, y examinó el impacto del volumen de adsorción (5 L frente a 6 L) en el pronóstico. El estudio incluyó 230 tratamientos de AP, de los cuales nueve fueron excluidos por falta de datos. Se utilizó la columna de 5 L en 60 pacientes (118 tratamientos) y la de 6 L en 50 pacientes (103 tratamientos). La efectividad se evaluó mediante la duración de la estancia hospitalaria, el trasplante hepático, la muerte y la mejoría de los síntomas relacionados con la enfermedad. En ambos grupos, la AP aumentó los leucocitos, el INR, la APTT y el PT, y disminuyó la hemoglobina, los ácidos biliares totales, la bilirrubina total y el fibrinógeno (todos $p<0,05$). Los niveles de plaquetas disminuyeron después de la AP de 6 L ($p=0,033$), pero no con la de 5 L ($p=0,116$). Tras la AP, el grupo de 6 L mostró leucocitos más bajos ($p=0,003$). Las columnas de 5 L y 6 L no mostraron diferencias significativas en los resultados clínicos principales. Sin embargo, la columna de 5 L redujo significativamente la destrucción plaquetaria y acortó el tiempo de tratamiento, lo que sugiere que el volumen de 5 L podría ser clínicamente preferible.

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INTRODUCTION

Liver failure (LF) is the leading cause of death in patients with liver disease. It often progresses rapidly, with a poor prognosis and severe cases that are life-threatening[1,2]. High mortality associated with LF results from severe impairment or decompensation of hepatic synthesis, detoxification, excretion, and biotransformation functions. Among these, the accumulation of bile acids, bilirubin metabolites, and ammonia in the body is a major factor [3-5]. These metabolites are normally managed by the liver, and abnormal liver function can lead to brain dysfunction (hepatic encephalopathy), renal dysfunction (hepatorenal syndrome), and eventually death [6, 7].

Plasma adsorption (PA) has been established as a treatment for various LF conditions, providing patients with additional treatment options by temporarily and partially replacing liver function [8-12]. These treatments can remove toxins, endotoxins, and bilirubin metabolites from the blood, allowing time for liver cell recovery and function, or providing support while awaiting a donor liver. PA is preferred because it avoids plasma-dose limitations, plasma allergies, and blood transfusion-related infections [8, 11]. This method introduces the patient's blood into the external pipeline, and the plasma to be processed is separated by the plasma component separator. The separated plasma is then passed through a bilirubin adsorption column to remove pathogenic substances and returned to the patient without requiring allogeneic plasma or albumin.

Plasorba BR-350 is a commonly used bilirubin adsorption column capable of processing large volumes of plasma to remove bilirubin effectively [13, 14]. PA mainly uses an adsorption column to remove toxins from patients' plasma, including substances such as albumin-bound bilirubin, thereby improving liver cells and liver function. According to this principle, the role of the plasma bilirubin adsorption column is particularly critical [8-11]. In lipoprotein (a) apheresis, different treatment volumes affect the lipid removal rate, as well as the removal of fibrinogen and other macromolecules [15]. Data are available regarding the curative effect of the adsorption column material itself [13, 14], but there remains a lack of data on whether different adsorption capacities will produce different curative effects. Although an adsorption capacity below 7 L can be treated using the BR-350 adsorption column, current studies mostly show that the treatment adsorption time is 3-4 h (representing about 5-6 L) [13, 16-18]. In patients on hemodialysis, the volume of blood treated is associated with various outcomes, such as hemodialysis efficacy and intradialytic hypotension [19, 20]. Hence, optimizing benefits and limiting complications is an important goal during blood purification therapies.

Therefore, this study aimed to examine how adsorption volume (5 L vs. 6 L) affects clinical outcomes in patients with LF. The results could help improve treatment and nursing during PA.

MATERIALS AND METHODS

Study design and patients

This single-center retrospective study included patients with LF who received PA treatment at the First Affiliated Hospital of Zhejiang University School of Medicine from October 2020 to October 2022.

The inclusion criteria were 1) patients diagnosed with LF according to the Chinese Guidelines for Diagnosis and Treatment of Liver Failure (2018) [21], 2) aged ≥18 years, and 3) who underwent PA only. The exclusion criteria were 1) patients with incomplete clinical data, 2) patients with a malignant tumor, 3) patients with severe infection, such as pulmonary infection, or 4) patients in the ICU.

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine. Patient informed consent was waived due to the retrospective nature of the study. All authors had full control of the data and information for this study.

Data collection and definition

According to the infection department's artificial liver center standard operating procedure and guidelines [21], an Artificial Liver Support System (ALSS) was considered for patients with LF. Vascular access was obtained with a double-lumen hemodialysis catheter placed in the femoral veins. Blood anticoagulation was managed with unfractionated heparin. The anticoagulant regimen consisted of an initial 2000 U of heparin sodium, followed by maintenance at 1000 U/h. The PA treatment device consisted of a standard hemodialysis machine with the appropriate tubing and plasma filter. The Plasorba BR-350 (B-Braun Carex) was used as the bilirubin absorption column during the study period, with a plasma processing volume of 5L or 6L. The selection of 5L versus 6L plasma processing volume was determined by the attending physician based on clinical judgment and the department's standard operating procedures during the study period, rather than being predetermined by patient anthropometric characteristics such as height or body weight.

The patients' identities were protected. The demographic and clinical characteristics were collected from the medical records, including sex, age, height, weight, hypertension, allergies, diabetes, heart disease, kidney disease, viral hepatitis, hepatocirrhosis, hematocrit, and blood volume. The blood volume was estimated using 0.65×weight×(1-hematocrit) [22].

Blood routine and coagulation function indicators were collected, including white blood cells (WBC), hemoglobin (HGB), platelets (PLT), total bile acid (TBA), total bilirubin (TB), potassium (K+), sodium (Na+), chlorine (Cl-), calcium (Ca^{2+}), phosphorus (P), international normalized ratio (INR), fibrinogen (Fib), activated partial thromboplastin time (APTT), and prothrombin time (PT). Percentage differences were calculated as [(after treatment - before treatment) / before treatment].

Outcomes

The outcomes of this study were the length of hospital stay, liver transplant, death, and improvement in disease-related symptoms. Symptom improvement was defined as 1) clinical symptoms such as fatigue, poor appetite, abdominal distension, and bleeding were significantly improved, and hepatic encephalopathy disappeared; 2) signs such as jaundice and ascites improved significantly; and 3) liver function indices improved significantly, such as TBil <5 the upper limit of normal (ULN), PTA >40%, or INR <1.5 [21].

Statistical analysis

Continuous data were tested for normality using the Shapiro-Wilk test. Continuous variables with a normal distribution were expressed as means ± standard deviations (SD) and analyzed using Student's t-test; otherwise, they were presented as medians (interquartile ranges) and analyzed using the Mann-Whitney U-test. Categorical variables were presented as n (%) and analyzed using the chi-square test or Fisher's exact test. Data processing was performed in Python, and data analysis was conducted in SPSS 26.0 (IBM, Armonk, NY, USA). Two-sided P-values <0.05 were considered statistically significant.

RESULTS

During the study period, 230 plasma adsorption (PA) treatments were performed in 110 patients. Nine treatments were excluded for missing data, leaving 221 for analysis of laboratory parameters (118 in the 5L group and 103 in the 6L group). For patient-level analyses of baseline characteristics and clinical outcomes, 60 patients received 5L PA and 50 received 6L PA. Patients in the 5L group were significantly taller than those in the 6L group (166.14±7.18 cm vs. 163.13±7.24 cm, p=0.031), but the estimated systemic blood volume (0.65×weight×(1-hematocrit)) did not differ significantly between groups (2732.29±453.71 mL vs. 2683.34±508.21 mL, p=0.595). Other baseline characteristics, including the prevalence of viral hepatitis, hypertension, diabetes, and renal disease, were comparable between groups (Table 1).

The majority of patients were male (70.9%), and males had a higher mean systemic blood volume than females (2838±452 mL vs. 2395±387 mL). The mean age of the entire cohort was 55.4±13.8 years. Patients in the 5L group were significantly taller than those in the 6L group (p=0.031). Viral hepatitis was the most common underlying disease (30%). No significant differences were observed between groups in the prevalence of hypertension, diabetes, heart disease, or kidney disease (all p>0.05) (Table 1). Baseline laboratory parameters, including total bile acid and total bilirubin levels, were comparable between the two groups prior to treatment (all p>0.05).

Table 1. Baseline characteristics.

Variable	5L group (n=60)	6L group (n=50)	p
Sex, n (%)			
Female	13 (21.7%)	19 (38%)	0.065
Male	47 (78.3%)	31 (62%)	
Age, year, mean ± SD	54.00±12.53	57.17±15.20	0.233
Height, cm, mean ± SD	166.14±7.18	163.13±7.24	0.031
Weight, kg, mean ± SD	61.57±10.24	60.41±2.48	0.592
Hypertension, n (%)	12 (20%)	9 (18%)	0.793
Allergy, n (%)	1 (1.7%)	2 (4%)	0.459
Diabetes, n (%)	7 (11.7%)	6 (12%)	0.957
Heart disease, n (%)	1 (1.7%)	1 (2%)	0.898
Kidney disease, n (%)	4 (6.7%)	1 (2%)	0.224
Virus hepatitis, n (%)	19 (31.7%)	14 (28%)	0.679
Hepatocirrhosis, n (%)	0	1 (2%)	0.275
Hematocrit, median (interquartile range)	31.44 (5.74)	30.99 (7.49)	0.730
Blood volume, median (interquartile range)	2732.29 (453.71)	2683.34 (508.21)	0.595

Continuous variables were analyzed using Student's t-test for normally distributed data (expressed as mean ± SD) and the Mann-Whitney U-test for non-normally distributed data (expressed as median with interquartile range). Categorical variables were analyzed using the chi-square test or Fisher's exact test.

In both groups, PA treatment significantly increased white blood cell counts, INR, APTT, and PT, while decreasing hemoglobin, total bilirubin, total bile acids, and fibrinogen (all $p<0.05$) (Supplementary Table 1). Notably, platelet levels decreased significantly after 6L PA ($p=0.033$), whereas no significant reduction was observed after 5L PA ($p=0.116$).

Post-treatment comparisons between groups showed significantly lower white blood cell counts in the 6L group than in the 5L group ($p=0.003$). No significant between-group differences were observed in other post-treatment laboratory parameters, including hemoglobin, platelets, bilirubin, coagulation indices, or electrolytes (Table 2).

At the patient level, no significant differences were observed between the 5L and 6L groups in length of hospital stay, liver transplantation rates, in-hospital mortality, or improvement in disease-related symptoms (all $p>0.05$) (Table 3). Although the 5L group had a numerically longer mean hospital stay and higher transplantation and mortality rates, and the 6L group showed a slightly higher improvement rate, none of these differences reached statistical significance.

DISCUSSION

The 5L and 6L columns yield similar outcomes in terms of hospital stay duration, liver transplantation, mortality, and symptom improvement. The 5L column can reduce platelet destruction, shorten treatment time, and reduce the occurrence of complications.

In patients with LF, high bilirubin levels can be fatal in the short term [13, 14]. Low bilirubin levels can promote hepatocyte regeneration, whereas high bile acid levels can induce hepatocyte apoptosis and necrosis and delay regeneration [3, 23, 24]. Excessive bilirubin

Table 2. Laboratory indices after treatment.

Variable	5L group (n=118)	6L group (n=103)	p
WBC, x10^9/L	11.57±10.29	8.29±3.84	0.003
HGB, g/L	107.61±22.76	102.42±26.12	0.116
PLT, x10^9/L	166.43±88.66	155.70±84.15	0.359
TBA, μmol/L	170.04±115.27	152.53±104.54	0.241
TB, μmol/L	251.16±107.54	238.27±106.26	0.372
Na, mmol/L	136.81±4.6	137.79±3.25	0.068
Cl, mmol/L	101.99±4.55	102.01±3.97	0.975
Ca, mmol/L	2.13±0.12	2.15±0.13	0.493
P, mmol/L	0.98±0.24	0.92±0.26	0.125
INR	1.80±3.55	1.44±0.38	0.301
Fib, g/L	1.80±0.68	1.92±0.74	0.224
APTT, s	45.69±19.07	42.68±12.76	0.167
PT, s	17.00±4.19	16.53±4.19	0.413

White blood cells (WBC), hemoglobin (HGB), platelets (PLT), total bile acid (TBA), total bilirubin (TB), sodium (Na^+), chlorine (Cl^-), calcium (Ca^{2+}), phosphorus (P), international normalized ratio (INR), fibrinogen (Fib), activated partial thromboplastin time (APTT), and prothrombin time (PT). Between-group comparisons of post-treatment laboratory parameters were performed using Student's t-test for normally distributed continuous variables, with data presented as mean ± standard deviation.

Table 3. Clinical outcomes.

Variable	5L group (n=60)	6L group (n=50)	p
Length of stay (days)	23.7±19.86	19.4±8.78	0.135
Liver transplant	6 (10%)	3 (6%)	0.451
In-hospital mortality	8 (13.3%)	4 (8%)	0.376
Good prognosis	45 (75%)	42 (85%)	0.245

Length of hospital stay was analyzed using Student's t-test, and categorical outcomes (liver transplant, in-hospital mortality, and good prognosis) were analyzed using the chi-square test or Fisher's exact test. All data are presented as mean ± SD or n (%).

itself does not cause multiple organ failure, but in patients with LF it has neurotoxic and encephalopathic effects. Therefore, removing bilirubin and bile acids seems a reasonable therapeutic goal. ALSS can help remove toxic metabolites in patients with LF, which is beneficial for liver cell regeneration and functional recovery, buys time for liver transplantation, and can even allow some patients to avoid liver transplantation [8, 10, 25]. PA can selectively adsorb lipid-soluble substances such as bilirubin, aromatic amino acids, and other toxic metabolites that are tightly bound to proteins. Although many studies have examined the efficacy of ALSS [3, 8, 10,13,26,27], there are few data on different PA amounts and even fewer studies in large populations. It is unclear whether the amount of adsorption in the clinic will have the same effect across patients with LF. In the present study, bilirubin decreased in both groups after treatment, which is the goal of treatment. WBCs increased, probably due to an immune insult from the treatment. Fibrinogen decreased, and PT and APPT increased, suggesting reduced coagulation function, probably due to adsorption of coagulation factors by the column. HGB also decreased.

The PA treatment mode is a mature, classic method that addresses the issue of scarce plasma supply. The 5-L and 6-L adsorption capacities are routine choices in adults. This study showed that 1) the 5-L and 6-L adsorption doses could be considered effective strategies for treating patients with LF, with no differences in treatment outcomes; 2) there might be a risk of thrombocytopenia after treatment with a PA volume of 6 L, but not with 5 L; and 3) since the treatment time is shorter with 5 L, the 5-L volume could be associated with lower complication rates.

BR-350 is an anion resin plasma adsorption column with styrene-divinylbenzene as the main material. The effective use of BR-350 in LF dates back more than 30 years[8,10,25]. Previous studies have reported that the amount of PA in LF treatment ranges from 2 to 7 L, and the clearance rate of BR-350 for bilirubin decreases with increasing treatment volume and eventually tends to saturate [13]. As shown in the present study, there were no significant differences in post-treatment bilirubin and TBA between 5 and 6 L. Some researchers have suggested that a longer PA treatment time can lead to a higher incidence of complications [28]. Therefore, in the case of the same treatment effect, a 5L treatment capacity seems to be a better choice because of the shorter treatment time. Nursing care for ALSS treatment needs to be refined and individualized, and timely analysis of the cause of alarms in the treatment system and handling of emergencies are required to ensure patient safety and the smooth progress of treatment.

The most critical safety distinction between the two treatment volumes lies in their differential effects on hematological parameters. While both 5L and 6L PA effectively reduced bilirubin and bile acids, the 6L volume was associated with a significant decrease in platelet counts ($p=0.033$), whereas the 5L volume preserved platelet levels ($p=0.116$). This finding carries substantial clinical significance for patients with liver failure, who already exhibit compromised hemostasis due to impaired synthesis of coagulation factors and often baseline thrombocytopenia [29]. Further platelet reduction in this vulnerable population increases the risk of spontaneous bleeding and procedure-related hemorrhage and may necessitate platelet transfusions, thereby increasing treatment costs and risks[30,31]. Additionally, the 6L group demonstrated significantly lower post-treatment white blood cell counts compared to the 5L group ($p=0.003$). Although we did not observe a statistically significant increase in infection rates in the 6L group during the study period, leukopenia theoretically elevates infection risk, which is particularly concerning in patients with liver failure who exhibit immune dysfunction. The combination of thrombocytopenia and leukopenia suggests that the 6L volume may impose greater hematological stress or more pronounced activation of cellular adhesion to the adsorption column and extracorporeal circuit. Patients with LF are at risk of thrombocytopenia due to factors such as decreased thrombopoietin synthesis from massive necrosis of liver cells[32,33]. Blood purification treatments such as bilirubin adsorption will cause increased platelet consumption, and at the same time, there is an increased risk of HIT due to heparin anticoagulation. A researcher found that the proportion of patients with amputation or death due to HIT was as high as 20%-30% [33]. At the same time, an elevated time-to-risk of transient thrombocytopenia associated with separation membranes was associated [31]. This study found a statistically significant decrease in platelet counts with 6-L PA, suggesting that 5-L PA may be safer. A previous study of lipoprotein(a) apheresis showed that larger treatment volumes were associated with larger decreases in the levels of fibrinogen and other blood macromolecules [15], but no significant differences were observed in the present study. The 6L group had lower WBC levels than the 5L group after treatment. Although our study did not find a significant increase in infection rates in the 6 L group, we acknowledge that leukopenia may theoretically elevate infection risk [34]. Future studies with larger cohorts and longer follow-up may further elucidate this relationship. Nevertheless, differences could be observed in larger cohorts or with longer follow-up.

We acknowledge that the 5L group had a significantly greater mean height than the 6L group. Although height can correlate with blood volume, we believe this difference is unlikely to have influenced the choice of adsorption volume or the study outcomes for several reasons. First, the estimated systemic blood volume, calculated using the formula 0.65×weight×(1-hematocrit), showed no significant difference between groups ($p=0.595$), suggesting that the height disparity did not translate into clinically relevant differences in total circulating volume. Second, in clinical practice, the decision to use 5L versus 6L adsorption is typically based on the severity of liver failure, baseline bilirubin levels, and physician preference rather than patient height. Nevertheless, we recognize this baseline imbalance as a limitation of our retrospective design, and we cannot entirely exclude the possibility of unmeasured confounding factors that may influence both patient selection and volume determination.

This study had limitations. It was a single-center study with a small sample size. The retrospective design limited the data to what was available in the charts. The 5-L and 6-L capacities are the most common at the authors' center, but future studies should also examine other capacities.

In conclusion, PA therapy can remove a large amount of bilirubin and also reuse the patient's plasma and albumin to reduce allergic reactions. Treatment with a 5-L plasma adsorption capacity yields outcomes similar to those of the 6-L treatment for length of stay, liver transplantation, in-hospital mortality, and prognosis. However, given smaller post-treatment platelet changes and a shorter treatment duration, the 5-L treatment volume might be more appropriate than the 6-L volume.

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Author's contributions

XZ: Conceptualization, Methodology, Investigation, Formal Analysis, Writing – Original Draft; ZYZ: Methodology, Investigation, Formal Analysis; HC: Methodology, Investigation, Formal Analysis; HFZ: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Supervision, Project Administration. All authors contributed to resources, reviewed and edited the manuscript, and approved the final version for submission.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Ethic Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (IIT20230143A). The requirement for informed consent from the patients was waived due to the retrospective nature of the study. All authors had full control of the data and information regarding this study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article and supplementary information files.

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