Therapeutic Plasma Exchange in Pediatric Acute Liver Failure

Chun-Feng Yang

Jilin University

Yu-Ao MD

Jilin University

Lin-Mei Jin

Jilin University

Yumei Li (✉ ym_li@jlu.edu.cn)

Jilin University First Hospital <https://orcid.org/0000-0002-7705-4950>

Research Article

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1 **Therapeutic Plasma Exchange in Pediatric Acute Liver Failure**

2 **Chun-Feng Yang MD, Yu-Ao MD, Lin-Mei Jin MD, Yu-Mei Li MD***

3 Department of Pediatric Intensive Care Unit, First Hospital of Jilin University, Changchun 130021,
4 Jilin, China

5 ***Corresponding Author:** Yu-Mei Li M.D.

6 Department of Pediatric Intensive Care Unit, First Hospital of Jilin University, No. 1 Xinmin Street,
7 Changchun 130021, Jilin, China.

8 Tel.: +86-0431-88783975

9 E-mail: ym_li@jlu.edu.cn

10 ORCID: 0000-0002-7705-4950

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27 **Key words:** pediatric acute liver failure, therapeutic plasma exchange, continuous renal replacement

28 therapy, extracorporeal purification.

29 **What is Known.**

30 Acute liver failure is a rare but devastating disease. Many studies in critically ill adults have
31 demonstrated the benefits of TPE for improving the clinical outcomes of acute liver failure.

32 **What is New.**

33 The literature on TPE are limited in the pediatric acute liver failure. In addition, few papers have
34 examined the safety of TPE in younger children with PALF. Our experience suggests that protocolized
35 use of TPE, which necessarily combines CRRT, can be effectively and safely performed in PALF
36 children including those younger than 2 years old.

Abstract

We aim to assess the efficacy and safety of therapeutic plasma exchange (TPE) in pediatric acute liver failure (PALF) and to examine possible risk factors for mortality. Similar data are limited in PALF. Thirty-three cases diagnosed with PALF who received TPE from June 2011 to June 2021 in the pediatric intensive care unit (PICU) of the First Hospital of Jilin University were included in this retrospective cohort analysis. Descriptive statistics were used for the clinical features of these patients and TPE related variables. The effect of TPE was measured by the difference tests before and after treatment. Survivors with native livers and nonsurvivors were also compared by the difference tests. In the TPE combined with continuous renal replacement therapy (CRRT) group (21/33, 63.6%), the patients were older, and more patients had multiple organ dysfunction syndrome (76.2% vs 25%, $P=0.009$) and a greater need for mechanical ventilation (86.2% vs 8.3%, $P<0.001$). TPE can significantly reduce alanine aminotransferase, total bilirubin, and international normalized ratio. The most common complication in the overall population was hypocalcemia ($n=12$, 36%), while the most common complication in children under 2 years of age was hypotension ($n=3$, 40%). The mortality of liver transplant-free patients was 10/30 (30%). The nonsurvivor group had significantly more failed organs, longer PICU stays and more patients requiring ventilatory support.

Conclusions: TPE alone or combined with CRRT can effectively improve liver function and may reduce mortality. TPE can be performed relatively safely in critically ill children, including younger patients.

56 **Abbreviations**

57 AKI, acute kidney injury

58 ALT, alanine aminotransferase

59 CRRT, continuous renal replacement therapy

60 HE, hepatic encephalopathy

61 INR, international normalized ratio

62 MODS, multiple organ dysfunction syndrome

63 PALF, pediatric acute liver failure

64 PICU, pediatric intensive care unit

65 PRISMIIL, pediatric risk of mortality III

66 TBIL, total bilirubin

67 TPE, therapeutic plasma exchange

Introduction

Pediatric acute liver failure (PALF) is a rare but devastating disease that occurs in previously healthy children and rapidly leads to multiple organ dysfunction syndrome (MODS) and death^[1]. The exact pathophysiology of MODS in PALF remains elusive, but toxins and metabolites leading to a systemic inflammatory response are well understood to play a greater role in hepatocyte damage^[2]. Therapeutic plasma exchange (TPE) can remove part of a patient's plasma to clear circulating pathogenic molecules and toxic substances, which is replaced with equivalent amounts of fresh frozen plasma to replenish important physiological components^[3]. In recent guidelines proposed by the American Society of Apheresis, high-volume TPE was accepted as a strong grade 1A/III recommendation for acute liver failure, and non-High volume-TPE was regarded as a weak grade 2B/III recommendation due to a lack of reliable evidence^[4, 5].

Although many studies in critically ill adults have demonstrated the benefits of TPE for improving the clinical outcomes of acute liver failure, similar data are lacking in PALF^[6]. However, children are not simply small adults, and PALF also differs from adult liver failure in etiologies, pathophysiology, comorbidities, treatment and prognosis. TPE in children is more technically challenging^[7]. In particular, TPE is rarely performed in younger children due to concern regarding potential hemodynamic instability caused by the extracorporeal procedure.

The first aim of this study was to characterize the clinical features and outcomes of PALF children who received TPE at our institution. We also retrospectively analyzed the efficacy and safety of a TPE strategy in patients with PALF with a particular focus on the safety of TPE in children under two years old.

Materials and Methods

Patients and Setting

This single-center retrospective observational study was conducted in a tertiary referral 20-bed pediatric intensive care unit (PICU) over a 10-year period in northeast China. We reviewed all hospitalized pediatric patients diagnosed with PALF who underwent TPE from June 2011 to June 2021 in the PICU of the First Hospital of Jilin University. PALF was defined according to the Pediatric Acute Liver Failure Study Group criteria^[8]. The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University. Because the study was retrospective, our committee waived the requirement for patient consent.

Data Collection

Patient records in the institutional electronic health record database were manually extracted and reviewed by two investigators. Data elements included demographic data (age, weight, gender), pediatric risk of mortality III (PRISMIII) scores, primary diagnoses, hepatic encephalopathy (HE), the number of failed organs, the need for mechanical ventilation, TPE-related variables (the number of TPE sessions per patient, TPE duration, TPE complications such as hypotension, hypocalcemia, allergic reactions or any other significant adverse event), the need for continuous renal replacement therapy (CRRT), CRRT duration, vasopressor use, length of PICU stay, length of hospital stay, and outcomes.

Procedure

All patients received comprehensive medical treatment, including energy and vitamin supplementation, infection control, blood glucose and blood pressure regulation, prevention of gastrointestinal bleeding and HE, and blood product supplementation, such as albumin, plasma and prothrombin complex.

To investigate the etiology of PALF, a history including toxin and/or drug exposure was taken, and pathogen screening, including serological viral markers and blood culture, was performed. Possible metabolic diseases, autoimmune hepatitis, and mitochondrial disorders were also evaluated.

The decision to perform TPE was made by the pediatric intensivist when the diagnosis of PALF was confirmed. After the parents' consent was obtained, preparation for TPE was initiated.

Blood access was established by inserting a double-lumen catheter into the left or right femoral vein. The size of the catheter varied according to the patient's age.

TPE was performed using a continuous renal replacement machine (MultiFiltrate, Fresenius Medical Care AG&Co. KGaA, Germany), extracorporeal circuits (MPS Substitute System multiFiltrate and Multifiltrate Cassette, Fresenius Medical Care AG&Co. KGaA, Germany), and a membrane filter (Plasma Flux P1/P2 dry, Fresenius Medical Care AG&Co. KGaA, Germany). The volume of fresh frozen plasma exchanged per procedure was 50 ml/kg. Each TPE session lasted 1.5 to 2 hours. The blood flow rate was maintained at 3–5 ml/kg/min. The plasma exchange rate was set at 15%~25% of the blood flow rate. Circuits were primed with saline with sodium heparin, followed by the administration of packed red blood cells in small children (< 10 kg). No anticoagulants were used. Before TPE, the patient was given intravenous dexamethasone and oral calcium to prevent allergies and hypocalcemia, respectively. Blood gas analysis results and activated clotting time were assessed approximately one hour after treatment initiation. When ionized calcium was less than 0.8 mmol/L, calcium gluconate was given intravenously. Additional heparin was administered through an extracorporeal line as necessary to maintain an activated clotting time of 160–180 seconds.

The TPE interval between each treatment was determined by the pediatric intensivist depending on the patient's condition. TPE was performed until coagulation and liver function improved or the

outcome event (liver transplantation or death) occurred.

Patients with hypotension were managed with saline supplementation and blood flow adjustments or vasopressors. Promethazine was given intravenously when the patient presented with an itchy rash indicative of an allergy. If anaphylactic shock occurred, the patient was given intravenous epinephrine.

We added CRRT if the patients had (1) elevated ammonia accompanied by grade III or IV HE; (2) MODS; (3) acute kidney injury (AKI); and (4) a risk of fluid overload. CRRT and TPE were performed sequentially. The CRRT filter was replaced after each TPE session.

CRRT was performed using a continuous renal replacement machine (MultiFiltrate, Fresenius Medical Care AG&Co. KGaA, Germany), an extracorporeal circuit (Multifiltrate Cassette, Fresenius Medical Care AG&Co. KGaA, Germany), and a membrane filter (Ultraflux AV paed/AV400S/AV600S, Fresenius Medical Care AG&Co. KGaA, Germany). In patients weighing more than 10 kg, continuous veno-venous hemodiafiltration was performed with a dialysate flow rate of 20~30 ml/kg/hr and a predilution filtration rate of 30~50 ml/kg/hr. In patients weighing less than 10 kg, continuous veno-venous hemofiltration was performed with a predilution filtration rate of 30~50 ml/kg/hr. The blood flow rate was 3~5 ml/kg/min. Anticoagulation was achieved by regional citrate infusion. Target postfilter ionized calcium concentrations were 0.4~0.6 mmol/L. Circuits were also primed with packed red blood cells in children with low body weights (<10 kg). Nurses prepared the dialysate and replacement fluid. Based on blood gas analysis, pediatric intensive care physicians adjusted electrolyte concentrations and sodium bicarbonate such that sodium, potassium, magnesium, calcium, and pH were within the normal ranges.

Statistical Analysis

Statistical analysis was performed using SPSS 24.0 software (SPSS Inc., Chicago, Illinois). The

hypothesis of a normal distribution was tested with the Kolmogorov-Smirnov test and histograms. Continuous variables are expressed as the means with standard deviations or the medians with interquartile ranges (IQRs). Categorical variables are expressed as numbers and percentages. When testing the significance of differences, for data that did not follow a normal distribution, the Mann-Whitney rank sum test was used, and for data following a normal distribution, an independent sample t test was used. The *P* values of categorical variables (i.e., sex, etiology) were calculated using Fisher's exact test since the total sample included fewer than 40 patients. Differences were considered statistically significant at *P* values less than 0.05.

Results

Patient Characteristics

From June 2011 to June 2021, a total of 54 patients were diagnosed with PALF in the PICU of our hospital. Thirty-three (61%) patients who received TPE were analyzed (see the patient flowchart in Fig. 1). The most common cause of PALF was genetic metabolic diseases (*n*=11, 34%), followed by undetermined cause (*n*=9, 18%), infection (*n*=8, 24%) and toxins (*n*=5, 15%). The patients' ages varied from 6 months to 14 years, with a median of 7 years. The median body weight was 24 kg (range 14–39 kg). Of note, seven patients were younger than 2 years old with a body weight under 12 kg. Patient characteristics are shown in Table 1. The median PRISMIII score was 13 (7, 17). Patients with grade III and IV HE at admission accounted for 33% of all cases. MODS was present in 19 (57.6%) patients, and AKI was present in 15.2% of the patients. Nearly half of the patients (17/33, 51.5%) were mechanically ventilated, and 15 of 33 (45.5%) patients required vasopressor support. A total of 21/33 (63.6%) patients underwent CRRT combined with TPE, and the median CRRT duration was 3 (2, 5) days. The median PICU length of stay was 13 (6, 17.5) days. Exposure to CRRT was used to assign the patients

to the TPE group or TPE+CRRT group. In the TPE+CRRT group, the patients were older, more patients had MODS (76.2% vs 25%, $P = 0.009$), and more patients required mechanical ventilation (86.2% vs 8.3%, $P < 0.001$).

Effects of TPE

In the overall population, alanine aminotransferase (ALT) before TPE was significantly decreased compared to that after the procedure [before: 1231 (434, 2668) vs after: 184 (124, 873), $P < 0.001$], and a significant decline in total bilirubin (TBIL) was observed [before: 152 (58, 259) vs after: 110 (65, 195), $P = 0.002$]. Significant improvement in coagulation was characterized by a reduction in the international normalized ratio (INR) [before: 2.3 (1.8, 3.3) vs after: 1.6 (1.3, 1.9), $P < 0.001$]. No significant reduction in ammonia was noted during the observation period [before: 113 (74, 172) vs after: 89 (66, 131), $P = 0.096$]. No differences in ALT, TBIL, the INR, or ammonia were identified between the TPE and TPE+CRRT groups at baseline or after treatment.

TPE Complications

TPE was performed as a sole procedure in 21 sessions (27.6%) and in combination with CRRT in 55 sessions (72.4%) in 21 patients. Ten patients (30%) had only one TPE session. Three (9%) patients with Wilson's disease had more than 5 sessions. Among these patients, one died, and two received liver transplantation. The etiologies and outcomes according to different TPE frequencies are summarized in Table 2. TPE was well tolerated in children. No patient experienced severe adverse effects such as anaphylactic shock. TPE complications are shown in Table 3. The most common complication was hypocalcemia ($n=12$, 36%), followed by allergic rash ($n = 6$, 18%) and hypotension ($n=3$, 9%). We observed increased hypotension in patients younger than 2 years old, but this observation did not warrant premature discontinuation of the procedure. Interestingly, we found a relatively low incidence

of allergic rashes in these younger patients. In terms of catheter-related complications, only access malfunction in 2 (6%) patients was observed, which did not lead to significant problems.

Survivors Versus Nonsurvivors

The mortality of liver transplant-free patients was 10/30 (30%). Patients younger than 2 years old had a lower mortality rate (2/8, 25%) than those older than 2 years (8/22, 36%). The primary causes of death were indeterminate (3/10, 30%), genetic metabolic diseases (3/10, 30%), drug/mushroom toxicity (2/10, 20%), and infection (2/10, 20%). Three patients were successfully transplanted due to Wilson's disease (n=2) and an indeterminate cause (n=1), with a 1-year posttransplant survival rate of 100%. When comparing survivors with native livers (n=20) and nonsurvivors (n=10), we found that nonsurvivors had significantly more failed organs and longer PICU stays and more often required ventilatory support (Table 4).

Discussion

PALF is a rare but fatal disease with mortality varying from 24%-75%^[6, 9]. Standard medical therapies have been demonstrated to be inadequate. Liver transplantation is the ultimate treatment, but spontaneous recovery with a native liver is the ideal outcome, which avoids complications and mortality^[7, 10]. The main mechanisms of PALF include toxin accumulation and the release of proinflammatory cytokines, which ultimately lead to MODS and death. Thus, using various extracorporeal purification modalities to remove these toxins and immune substances is becoming a promising technique, and TPE is the most common method of extracorporeal purification in liver failure. TPE in adult liver failure has been implemented for decades and has been demonstrated to improve biochemical and clinical parameters while a patient is being bridged to liver transplantation or recovery^[11]. The literature on TPE mainly focuses on adults, and reports of TPE are limited in the

pediatric literature. In addition, few papers have examined the safety of TPE in younger children with PALF. Our experience suggests that protocolized use of TPE, which necessarily combines CRRT, can be effectively and safely performed in PALF children including those younger than 2 years old.

TPE has a beneficial effect by delivering biologically active substances contained in fresh frozen plasma and removing toxic factors, cytokines, vasoactive substances, etc. Various studies have shown that TPE can significantly improve biochemical parameters and stabilize hemodynamics^[11, 12]. A recently published prospective, randomized, controlled, multicenter trial by Larsen et al demonstrated that high-volume TPE improved not only hemodynamic and biochemical parameters but also liver transplant-free survival in patients with acute liver failure^[13]. Some recent reports also showed that standard-volume TPE was associated with amelioration of systemic inflammatory response syndrome and higher transplant-free survival both in patients with acute liver failure and patients with acute-on-chronic liver failure^[14]. In the few available studies of TPE-based artificial liver support systems focusing on pediatric patients, the authors also reported improvements in biochemical parameters^[9, 15]. We found that TPE effectively reduced ALT, TBIL, and the INR but had no significant effect on reducing blood ammonia concentrations. This may be due to the fact that some patients only underwent TPE without CRRT. TPE can clear small, medium and large molecular substances, but the clearance of small molecules is far lower than that achieved with hemodialysis and hemofiltration. The shorter duration of TPE (2 hours) is also one of the reasons for the insignificant decrease in blood ammonia.

When PALF is complicated by AKI, MODS, fluid overload, hyperammonemia and so on, TPE alone is not sufficient. Therefore, combination with CRRT, which will help optimize fluid balance and electrolytes and remove water-soluble small-molecule toxins, including ammonia, urea and creatinine,

must be considered. CRRT can also enhance the removal of inflammatory mediators^[7, 10]. In 2018, a multicenter cohort study of consecutive acute liver failure patients from the United States Acute Liver Failure Study Group registry revealed that hyperammonemia was associated with high-grade HE and worse 21-day transplant-free survival, and CRRT was associated with a reduction in serum ammonia levels and improvement in 21-day transplant-free survival^[16]. Kentaro Ide described 17 PALF infants undergoing TPE and CRRT and revealed that bilirubin, ammonia, PT/INR, and creatinine significantly decreased after CRRT and TPE^[15].

No definitive criteria for initiation or discontinuation of CRRT in PALF patients have been established^[17]. In most studies, indications for CRRT initiation in children with PALF include metabolic abnormalities, grade III or IV HE, hyperammonemia, kidney dysfunction, etc^[10]. We implemented similar initiation standards in our institution. We did not observe differences in the main liver injury-related biochemical markers between the TPE group and the TPE combined with CRRT group at baseline or after treatment, suggesting that the combination of CRRT and TPE did not optimize the effects of reducing ALT and TBIL and improving coagulation. Interestingly, although not statistically significant, we observed a higher mortality rate in patients who received TPE combined with CRRT. The explanation may be that patients in the CRRT group had more failed organs and more severe disease, which is consistent with the findings of previous worldwide studies^[10].

Although we did not have a control group to confirm that the effect of TPE was better than that of standard medical treatment, we found a relatively low mortality rate compared to those in the published literature (30% vs 75%)^[6, 9]. TPE-based artificial liver therapy plays a key role to some extent. We attempted to analyze the clinical characteristics of survivors and nonsurvivors and found that nonsurvivors had significantly more failed organs and more frequently required ventilation, which

supported the finding that MODS is a risk factor for death in PALF patients^[6].

In the largest prospective study of PALF, the most common cause was indeterminate^[17]. In the present study, we found that most PALF patients were admitted for metabolic diseases (34%), followed by indeterminate causes (27%). The explanation may be that our hospital has the only liver transplant center in northeast China, and some PALF patients with Wilson's disease visit our department for perioperative management before transplantation. Overall survival is etiology-dependent. Patients with indeterminately caused liver failure had the worst outcome^[10]. Here, we also confirmed this observation.

Our data suggested that PALF due to Wilson's disease required more TPE sessions. The reason may be that toxicity and infection are "pure" acute causes and the patient either improves or dies quickly after TPE treatment. This resulted in a lower frequency of TPE. However, liver failure caused by Wilson's disease has a "relatively" chronic course. Liver function of these patients may temporarily improve after TPE, but the patient's condition will deteriorate again soon; thus, so multiple TPE sessions may be required to maintain liver function while awaiting liver transplantation. We also found that more TPE sessions seem to be associated with poor outcomes, which is consistent with the findings of a previous study. Chien retrospectively analyzed 23 PALF patients and found that fewer than 6 TPE sessions can predict native liver recovery in PALF children with a sensitivity of 100% and a specificity of 66.7%^[9]. The need for multiple TPE sessions is speculated to imply that PALF is less responsive to TPE, which may result in failed treatment.

Hypocalcemia is common in patients receiving TPE. In our study, hypocalcemia (36%) was the most common complication in all populations, followed by allergic rash (18%) and hypotension (9%). Although the incidence of hypocalcemia was high, hypocalcemia was not serious because of the

prophylactic administration of calcium before TPE. The incidence of allergic reactions in the whole population was higher than that in the population under 2 years old, suggesting that allergic reactions are more common in older populations, which may be due to mature immune function in older children. Although the plasma had been cross-matched, using plasma from different donors may still increase the chance of allergy. Extracorporeal therapies are highly challenging in younger patients. Therefore, we assessed the safety of TPE in children under 2 years of age. In this subgroup, hypotension was the most common complication mainly because the ratio of extracorporeal circulation to blood volume is relatively high in small children (usually <10 kg). With the administration of vasopressors or saline, hypotension often improves quickly without adverse consequences, including discontinuation of the procedure or death. Therefore, TPE is still safe in young and small children.

This study has some limitations that must be acknowledged. First and foremost is the small sample size and single-center design. Some differences may not be observed between survivors and nonsurvivors, and we were not able to perform a multivariate regression to analyze risk factors for death. Due to the relatively low prevalence of PALF and the retrospective design, we did not have a control group for comparison. Nevertheless, our study is significant in contributing to the limited reports of PALF treated with TPE. We hope that our experience will inspire further discussions and multicenter randomized trials of TPE in PALF.

Conclusion

Our experience suggests that TPE alone or in combination with CRRT can effectively reduce ALT, TBIL, and the INR and may reduce mortality. TPE can be performed relatively safely in critically ill children, including patients younger than 2 years. Further studies are needed to examine the efficacy of TPE and TPE frequency in prospective multicenter studies.

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311 **References**

- 312 1. Alonso EM, Horslen SP, Behrens EM, Doo E. Pediatric acute liver failure of undetermined
313 cause: A research workshop. *Hepatology*. 2017;65(3):1026-37.
- 314 2. Veeramachaneni H, Subramanian RM. Combined High-Dose Continuous Renal
315 Replacement Therapy and Plasma Exchange in the Management of Severe Multiorgan System
316 Dysfunction Associated With Acute Liver Failure. *Hepatology*. 2021.
- 317 3. Yang CF, Zhang Z, Zhang XY, Li YM. Artificial liver support system in pediatric acute liver
318 failure due to mushroom poisoning: Case series. *Ann Hepatol*. 2020;23:100290.
- 319 4. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, Pham HP,
320 Schneiderman J, Witt V, Wu Y, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical
321 Practice - Evidence-Based Approach from the Writing Committee of the American Society for
322 Apheresis: The Eighth Special Issue. *J Clin Apher*. 2019;34(3):171-354.
- 323 5. Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, Dunbar NM,
324 Witt V, Wu Y, Shaz BH. Guidelines on the Use of Therapeutic Apheresis in Clinical
325 Practice-Evidence-Based Approach from the Writing Committee of the American Society for
326 Apheresis: The Seventh Special Issue. *J Clin Apher*. 2016;31(3):149-62.
- 327 6. Jain V, Dhawan A. Extracorporeal Liver Support Systems in Paediatric Liver Failure. *J Pediatr*
328 *Gastroenterol Nutr*. 2017;64(6):855-63.
- 329 7. Akcan Arian A, Srivaths P, Himes RW, Tufan Pekkucuksen N, Lam F, Nguyen T, Miloh T,
330 Braun M, Goss J, Desai MS. Hybrid Extracorporeal Therapies as a Bridge to Pediatric Liver
331 Transplantation. *Pediatr Crit Care Med*. 2018;19(7):e342-e9.
- 332 8. Squires RH, Jr., Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, Dhawan A,
333 Rosenthal P, Rodriguez-Baez N, Murray KF, et al. Acute liver failure in children: the first 348
334 patients in the pediatric acute liver failure study group. *J Pediatr*. 2006;148(5):652-8.
- 335 9. Chien MM, Chang MH, Chang KC, Lu FT, Chiu YC, Chen HL, Ni YH, Hsu HY, Wu JF. Prognostic
336 parameters of pediatric acute liver failure and the role of plasma exchange. *Pediatr Neonatol*.
337 2019;60(4):389-95.
- 338 10. Zoica BS, Deep A. Extracorporeal renal and liver support in pediatric acute liver failure.
339 *Pediatr Nephrol*. 2021;36(5):1119-28.
- 340 11. Stahl K, Hadem J, Schneider A, Manns MP, Wiesner O, Schmidt BMW, Hoepfer MM, Busch M,
341 David S. Therapeutic plasma exchange in acute liver failure. *J Clin Apher*. 2019;34(5):589-97.
- 342 12. Squires JE, McKiernan P, Squires RH. Acute Liver Failure: An Update. *Clin Liver Dis*.
343 2018;22(4):773-805.
- 344 13. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, Triantafyllou E,
345 Bernal W, Auzinger G, Shawcross D, et al. High-volume plasma exchange in patients with acute
346 liver failure: An open randomised controlled trial. *J Hepatol*. 2016;64(1):69-78.
- 347 14. Maiwall R, Bajpai M, Choudhury AK, Kumar A, Sharma MK, Duan Z, Yu C, Hu J, Ghazinian H,
348 Ning Q, et al. Therapeutic plasma-exchange improves systemic inflammation and survival in
349 acute-on-chronic liver failure: A propensity-score matched study from AARC. *Liver Int*.
350 2021;41(5):1083-96.
- 351 15. Ide K, Muguruma T, Shinohara M, Toida C, Enomoto Y, Matsumoto S, Aoki K, Fukuda A,

352 Sakamoto S, Kasahara M. Continuous Veno-Venous Hemodiafiltration and Plasma Exchange in
353 Infantile Acute Liver Failure. *Pediatr Crit Care Med*. 2015;16(8):e268-74.
354 16. Cardoso FS, Gottfried M, Tujios S, Olson JC, Karvellas CJ, Group USALFS. Continuous renal
355 replacement therapy is associated with reduced serum ammonia levels and mortality in acute
356 liver failure. *Hepatology*. 2018;67(2):711-20.
357 17. Lutfi R, Abulebda K, Nitu ME, Molleston JP, Bozic MA, Subbarao G. Intensive Care
358 Management of Pediatric Acute Liver Failure. *J Pediatr Gastroenterol Nutr*. 2017;64(5):660-70.
359

Table1 Patient Characteristics

Patient Characteristics	Median (interquartile range)/No (%)			<i>P</i> value
	All (n = 33)	TPE only (n=12)	TPE+CRRT (n=21)	
Age (yr)	7(0.5, 14)	2.75(0.9, 7)	8(5.5, 11)	0.012^a
Weight (kg)	24(14, 39)	15 (10.6, 29.6)	28(19.3, 44)	0.041^a
Male, n (%)	14(42.4%)	6(50%)	8(38.1%)	0.716 ^b
PRISM III score	13(7, 17)	11.5(4.2, 16)	13(6.5, 18)	0.485 ^c
AKI, n (%)	5(15.2%)	0	5 (23.8%)	0.133 ^b
MODS, n (%)	19(57.6%)	3(25%)	16(76.2%)	0.009^b
No. organ failed	3(0, 4)	0(0, 2)	3(2, 5)	0.002^c
Grade III and IV Encephalopathy, n (%)	11(33.3%)	6(50%)	5(23.8%)	0.149 ^b
Ventilated, n (%)	17(51.5%)	1(8.3%)	16(76.2%)	0.000^b
vasopressor support,n (%)	15(45.5%)	3(25%)	12(57.1%)	0.145 ^b
PICU stay (d)	13(6, 17.5)	12(7.2, 17)	15(5.5, 19.5)	0.75 ^c
Mortality	10(30.3%)	2(16.7%)	8(38.1%)	0.259 ^b

361 Note:a: independent sample t test . b: Fisher's exact test. c: Mann-Whitney rank sum.

Table 2 Etiologies and outcomes of different TPE sessions

TPE sessions/per patients	etiology	Transplant-free survival
1 session (n=10)	Infection, n=4 drug/mushroom toxicity, n=1 indeterminate cause, n=3 genetic metabolic diseases, n=2	6/10 (60%)
2 sessions (n=15)	Infection, n=3 drug/mushroom toxicity, n=4 indeterminate cause, n=7 genetic metabolic diseases, n=1	10/15 (66.7%)
3 sessions (n=1)	Indeterminate cause, n=1	1/1 (100%)
4 sessions (n=4)	Wilson's disease, n=3 Infection, n=1	3/4 (75%)
5 sessions (n=1)	Wilson's disease, n=1	0
6 sessions (n=2)	Wilson's disease, n=2	0

Table 3 TPE Complications

Patient Characteristics	Total n=33	0–24 mo old n=7
Hypotension (n,%)	3(9%)	3(40%)
Hypocalcemia (n,%)	12(36%)	2(28%)
Allergic rash (n,%)	6(18%)	1(14%)
Circuit complications (n,%)	1(3%)	0
Circuit clotting (n,%)	1(3%)	0
Access malfunction (n,%)	2(6%)	1(14%)
Increased pressure leading to discontinuation of the procedure (n,%)	2(6%)	1(14%)

Table 4 Survival Analyses

Variables	Survivors (n=20)	Nonsurvivors (n=10)	<i>P</i>
Age (yr), Median (range)	6.5(1.3, 9.5)	7.5(3.4, 10)	0.607 ^a
Body weight (kg), Median (range)	21.2(12.2, 36.6)	26.5(15, 42)	0.439 ^a
Male, n (%)	9(45%)	4(40%)	1 ^b
PRISMIII at admission, Median (range)	13(3, 19)	13(7.2, 17)	0.985 ^c
Grade III or IV Encephalopathy, n (%)	13(65%)	1(10%)	0.064 ^b
Indetermined Cause	7(35%)	3(30%)	1 ^b
Biochemical parameters at admission			
ALT	1489(572, 4750)	1101(138,1953)	0.258 ^c
TBIL	107(54.8, 252)	170(77, 340)	0.167 ^a
INR	2(1.5, 2.8)	3(1.7, 4.05)	0.325 ^c
ammonia	112(62, 172)	122(80, 163)	0.955 ^c
No. organ failed, n (%)	0(0, 3)	4(2, 5)	0.041^b
Vasopressors, n (%)	6(30%)	8(80%)	0.019^b
CRRT, n (%)	10(50%)	8(80%)	0.235 ^b
Ventilated, n (%)	8(40%)	8(80%)	0.05^b
PICU stay (d)	15(9.5, 20.7)	5.5(4, 16.2)	0.006^c

367 Note: a: independent sample t test .b: Fisher's exact test.c: Mann-Whitney rank sum

368 **Figure legends**

369 **Figure 1 Flow chart of study participants.**

Figures

Flow chart demonstrates inclusion of patients into the retrospective analysis.

Abbreviations

PALF, pediatric acute liver failure;

TPE, therapeutic plasma exchange;

CRRT, continuous renal replacement therapy

Figure 1

Flow chart of study participants.