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ORIGINAL ARTICLE

Hepatology

Role of high-volume plasmapheresis in the management of paediatric acute liver failure

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Abstract

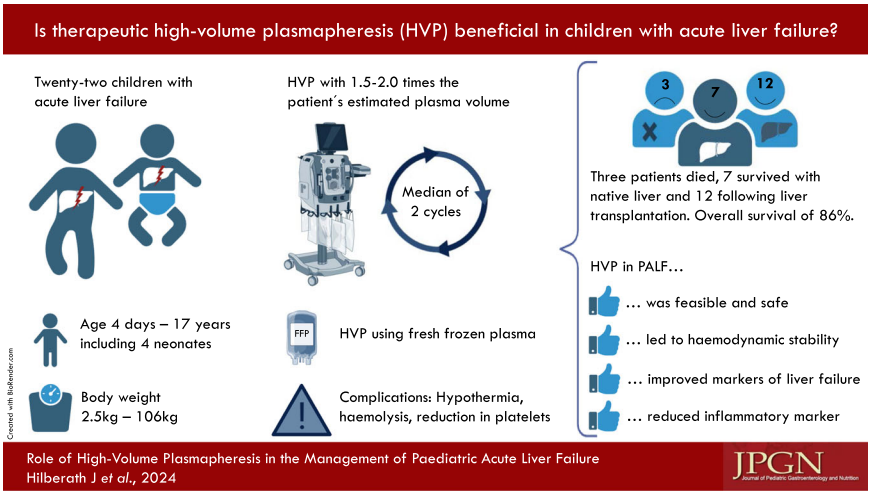
Objectives: Paediatric acute liver failure (PALF) is a life-threatening disease. Management aims to support hepatic regeneration or to bridge to liver transplantation. High-volume plasmapheresis (HVP) removes protein-bound substances, alleviates inflammation, and improves survival in adult acute liver failure. However, experience with HVP in PALF is limited. Aim of this study is to report on feasibility, safety, efficacy and outcomes of HVP in PALF.

Methods: Retrospective observational study in children with PALF. HVP was performed upon identification of negative prognostic indicators, in toxic aetiology or multiorgan failure (MOF). Exchanged volume with fresh-frozen plasma corresponded to 1.5–2.0 times the patient's estimated plasma volume. One daily cycle was performed until the patient met criteria for discontinuation, that is, liver regeneration, liver transplantation, or death.

Results: Twenty-two children with PALF (body weight 2.5–106 kg) received 1–7 HVP cycles. No bleeding or procedure-related mortality occurred. Alkalosis, hypothermia and reduction in platelets were observed. Haemolysis led to HVP termination in one infant. Seven children (32%) survived with their native livers, 13 patients (59%) underwent liver transplantation. Two infants died due to MOF. Overall survival was 86%. International normalization ratio (INR), alanine aminotransaminases (ALT), bilirubin and inotropic support were reduced significantly ($p < 0.05$) after the first HVP-cycle (median): INR 2.85 versus 1.5; ALT 1280 versus 434 U/L; bilirubin 12.7 versus 6.7 mg/dL; norepinephrine dosage 0.083 versus 0.009 µg/kg/min. Median soluble-interleukin-2-receptor dropped significantly following HVP ($n = 7$): 2407 versus 950 U/mL ($p < 0.02$).

Conclusions: HVP in PALF is feasible, safe, improves markers of liver failure and inflammation and is associated with lowering inotropic support. Prospective and controlled studies are required to confirm efficacy of HVP in PALF.

Abbreviations: ELS, extracorporeal liver support; HE, hepatic encephalopathy; HVP, high-volume plasmapheresis; IL-6, interleukin-6; MAS, macrophage activation syndrome; MOF, multiorgan failure; PALF, paediatric acute liver failure; RRT, renal replacement therapy; sIL2-R, soluble interleukin-2 receptor.



KEYWORDS

extracorporeal liver support, hepatic regeneration, HVP, PALF, plasma exchange

1 | INTRODUCTION

Paediatric acute liver failure (PALF) is a rare, life-threatening disease of heterogeneous aetiology.[1,2] Disease progression is driven by the effects of liver necrosis and inflammation, vitally affecting hepatic and extrahepatic organ function which ultimately can lead to multiorgan failure (MOF) and death.[3] The chances of spontaneous recovery without liver transplantation are only 10%–40%.[4] Nontransplant treatment options are limited. Therapy aims at stabilizing vital organ functions, preventing complications and promoting hepatic regeneration.[5] Extracorporeal liver support (ELS) with high-volume plasmapheresis (HVP) offers the potential to remove hepatotoxic substances, pro-inflammatory cytokines, and damage-associated molecular patterns.[6] ELS systems with or without renal replacement therapy (RRT) can potentially mitigate coagulopathy, stabilize cardiovascular function, and serve as a bridge to liver transplantation or liver regeneration.[7–10] One prospective study in adults showed superiority of HVP versus standard treatment in improving the degree of inflammation and transplant-free survival.[11] However, current experience with HVP in children with acute liver failure is limited to small case series which is summarized in Table 1.[7,12–22] A recent study demonstrated feasibility of HVP in 16 such children.[14]

The aim of this single-centre study is to analyse all HVP procedures in PALF between 2010 and 2023 with regard to feasibility, efficacy, safety, and outcome.

What is Known

- Paediatric acute liver failure (PALF) is a rare disease with high mortality, and a low rate of spontaneous recovery.
- Disease progression in PALF is driven by the effects of liver necrosis and inflammation.
- Extracorporeal liver support with high-volume plasmapheresis (HVP) reduces hepatotoxic substances and pro-inflammatory cytokines, and showed improved survival in adults with acute liver failure.

What is New

- HVP in PALF was feasible and safe. No procedure-related serious adverse event or mortality could be attributed to HVP therapy.
- HVP improved markers of liver failure and inflammation.
- HVP allowed reduction of inotropic support in children with PALF.

2 | METHODS

In children ages 0–17 years, PALF was diagnosed according to PALF Study Group criteria.[1] Clinical, biochemical, diagnostic, and management data were

TABLE 1 Overview of studies reporting on plasma exchange in paediatric acute liver failure.

						Plasma exchange			Outcome		
References	**Country and time-frame**	**Study design**	**Number of patients**	**Age**	**Gender (F/M)**	**Dose/volume**	**Duration/frequency**	**Renal replacement therapy (parallel or sequential)**	**Death**	**Survival with native liver**	**Liver transplantation**
Akcan Arikan et al., 2018[20]	USA, 24 months	Retrospective, observational, single-centre	*n* = 15 (study population), *n* = 5 (PALF), *n* = 10 (ACLF)	Median age 3 years	*F* = 4 (27%), *M* = 11 (73%)	1.3–1.5 times plasma volume exchange in tandem with CRRT, FFP replacement	Median of 4 (IQR, 1–8) PE and 6 (IQR, 4–7) MARS treatments	All patients received CRRT (100%)	4/15 (27%)	2/15 (13%)	9/15 (60%)
Atay et Demirkol, 2021[22]	Turkey, 2015–2018	Retrospective, single-centre	*N* = 39 (study population), *n* = 6 (15.4%, PALF)	Median age 80 months (1–198)	*F* = 20 (51.3%), *M* = 19 (48.7%)	1 or 1.5 times the patient's plasma volume exchanged with FFP/albumin according to underlying disease	NS	No	4/6 (67%)	0/6 (0%)	2/6 (33%)
Chien et al., 2019[19]	Taiwan, 2003–2016	Retrospective, observational, single-centre	*n* = 23 (study population), *n* = 18 (with PE), *n* = 5 (no PE)	Median age 1.39 years	*F* = 10 (43%), *M* = 13 (57%)	2–4 times the patient's estimated plasma volume	Daily for first 3 days, then every other day or every 3 days	No	10/23 (43%)	11/23 (48%)	2/23 (9%)
Gün et al., 2023[18]	Turkey, 2016–2021	Retrospective, observational, single-centre	*n* = 34 (study population), *n* = 24 (PALF), *n* = 10 (ACLF)	Median age 54 months (5-211)	*F* = 20 (59%), *M* = 14 (41%)	1.5 times plasma volume, FFP as preferred replacement fluid	Daily PE until LT or self-regeneration	13/34 (38.2%)	6/24 PALF (25%) 5/10 ACLF (50%)	14/24 PALF (58%)	4/24 PALF (17%)
Ide et al., 2015[12]	Japan, 2006–2011	Retrospective cohort study	*n* = 17 infants with PALF who underwent LT	Median age 6 months	*F* = 7 (41%), *M* = 10 (59%)	Plasma exchange and CVVHD in all infants	100 mL/kg of FFP once daily until recovery of coagulopathy	All infants received PE and CVVHDF (100%)	2/17 (12%) post-transplant	n.a.	15/17 (88%)
Jørgensen et al., 2021[14]	Denmark, 2012–2019	Retrospective, observational, single-centre	*n* = 16	Median age 3.7 years	*F* = 5 (31%), *M* = 11 (69%)	Volume corresponding to 10% of body weight exchanged with FFP	Daily on 3 consecutive days, then re-evaluation	4/16 (25%)	6/16 (37.5%)	8/16 (50%)	2/16 (12.5%)
Pawaria et al., 2021[15]	India, 2014–2019	Prospective, nonrandomised interventional study	*N* = 37 PALF due to Wilson's disease (study population),	Median age 9 years (5–15)	*F* = 14 (38%), *M* = 23 (62%)	>1.5 times plasma volume exchanged with FFP	One session on three consecutive days (maximum 3–6 sessions)	No	4/19 (21%) PE group after 2 sessions, 1 patient after 1 session	9/19 (47%) PE group vs. 3/18 (17%) SMT group with transplant-free	4/19 (21%) PE group vs. 5/18 (28%) received LT within 90 days

(Continues)

TABLE 1 (Continued)

References	Country and time-frame	Study design	Number of patients	Age	Gender (F/M)	Plasma exchange			Outcome		
						Dose/volume	Duration/frequency	Renal replacement therapy (parallel or sequential)	Death	Survival with native liver	Liver transplantation
			$n = 19$ (with PE), $n = 18$ (no PE)							survival at 90 days	
Rodriguez et al., 2017[13]	USA, 30 months	Retrospective observational cohort study	$n = 51$ PALF or ACLF (study population), $n = 20$ (with PE)	Median age 3.5 years	$F = 36$ (71%), $M = 15$ (29%)	Plasma exchange with FFP replacement and 1–1.5 times plasma		PE in tandem with CVVHDF	29/51 (57%) hospital mortality	NS	26/51 (51%)
Schaefer et al., 2011[16]	Germany, 2002–2010	Retrospective, observational	$n = 10$ (PALF and ACLF)	Median age 9.7 (0.1–18)	NS	MARS (standard adult for $n = 7$ and MARS Mini for $n = 3$). Plasma exchange 1.5 times plasma volume	5 children with standard MARS underwent six PE/HD sessions. 3 children with Mini-MARS underwent total of 4–11 PE/HD sessions per patient	In 8/10 (80%) MARS alternated with combined PE and HD	5/10 (50%)	2/10 (20%)	3/10 (30%)
Singer et al., 2001[7]	USA, 1987–2000	Retrospective, observational case series	$n = 49$ (study population), $n = 28$ PALF (57%), $n = 21$ ACLF (43%)	Median age 2.9 years (10 days–18.4 years)	$F = 29$ (59%), $M = 20$ (41%)	Removed plasma volume 2.2 ± 0.6 times plasma volume; replacement fluid consisted of 74 ± 11% FFP	Daily until recovery, death or LT	No	14/49 (28%) 15/49 (31%) died post-transplant	3/49 (6%) native liver survival	17/49 (35%) post-transplant survival
Tufan Pekkucuksen et al., 2021[17]	USA, 2013–2016	Retrospective, single-centre	$n = 63$ (study population), $n = 20$ PALF or ACLF	Median age 5 years	$F = 33$ (52%), $M = 30$ (48%)	Mean plasma exchanged: 1.34 ± 0.21. FFP as replacement fluid in patients with liver failure	Median number of sessions per patient was 5	All patients underwent tandem CVVHDF and PE	25/63 (40%)	NS	NS

Abbreviations: ACLF, acute on chronic liver failure; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; F, female; FFP, fresh frozen plasma; FHF, fulminant hepatic failure; HD, haemodialysis; IQR, interquartile range; LT, liver transplantation; M, male; MARS, molecular adsorbent recirculating system; n.a., not applicable; NS, not stated; PALF, paediatric acute liver failure; PE, plasma exchange; SMT, standard medical treatment.

collected from medical records and analysed (*t*-test, Mann–Whitney *U*-test).

All patients were managed according to a local protocol (Table S1) in the paediatric intensive care unit, including inotropic support to address hemodynamic instability. RRT was established in patients with significantly elevated plasma ammonia levels (i.e., 200 µmol/L), renal insufficiency, electrolyte imbalance, fluid overload, metabolic disturbances, or high-grade hepatic encephalopathy (HE ≥ 3). Neuroprotective measures were provided throughout the course.

Aetiology-specific treatment of PALF was provided as soon as a diagnosis was made.

Each patient was evaluated by a multidisciplinary team comprising representatives of paediatric hepatology, transplant surgery, intensive care, nephrology, and neurology. The team made therapeutic management decisions including the time point to employ HVP and RRT and whether to proceed with liver transplantation.

2.1 | High-volume plasmapheresis

PALF patients meeting one or more of the following criteria were considered for HVP: haemodynamic instability; HE grades ≥ 3; severe hyperbilirubinemia (total bilirubin > 12 mg/dL); suspected aetiology of Wilson disease (WD) with the New Wilson Index ≥ 11[23]; and autoimmune/hyperinflammatory or drug-induced liver disease.

HVP was performed using Spectra Optia (Terumo BCT) based on centrifugal apheresis technique by a high-flow double lumen central venous catheter with body-weight-dependent size. Citrate was used for nonsystemic anticoagulation. The volume of centrifugation plasma exchange with fresh-frozen plasma corresponded to 1.5–2.0 times the estimated patient's plasma volume, up to a maximum of 6 L. Below a threshold of 0.9 mmol/L calcium was substituted intravenously.

HVP consisted of one daily cycle over 2–6 h. HVP was discontinued in case of suspected and noncorrectable complications including bleeding and haemolysis, metabolic alkalosis, electrolyte disorders, and hemodynamic instability. Otherwise, HVP was performed until the child improved or was liver-transplanted. If necessary, RRT was performed in between HVP cycles.

2.2 | Statistics

This study was conducted as a retrospective, single-centre, observational study.

Descriptive statistical analysis was performed using IBM SPSS Statistics, version 28.0.

For each individual patient the liver injury unit (LIU) score and paediatric index of mortality score (PIM3) were calculated.[24,25] For comparison, we performed the repeated-measures *t*-test or Mann–Whitney U-test. *p* Values of <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Between 2010 and 2023, of 76 children with acute liver failure treated at our centre, 22 children (29%; 12 male) with a mean age of 11 years and a mean body weight of 34 kg underwent HVP (Table 2). Four children were younger than 3 months. Body weight ranged from 2.5 to 106 kg (including three infants with body weight < 3.5 kg). In six cases (27%), aetiology could not be determined; one recent case was associated with a severe COVID-19 infection (Adenovirus negative) in a chronically ill child (Dravet syndrome).

Eight patients were affected by HE grade ≥ III. Six of them were mechanically ventilated, needed inotropic support and underwent RRT while one patient was on the ventilator but did not require inotropic support. One patient was not on the ventilator and did not need inotropes; he recovered rapidly after the first HVP cycle.

Median number of applied HVP cycles was 2 (range 1–7) and 4 (range 1–7) for children with native liver survival. The median time from establishing a diagnosis of PALF to beginning HVP was 9.5 h (interquartile range [IQR]: 21.25 h).

3.2 | Outcome

The mean duration of follow-up was 50 months (range of follow-up 1–154 months). The overall survival rate in this cohort was 86%, three patients died. All 22 patients met criteria for liver transplantation eligibility, 20 children were granted the highly urgent status on the waiting list and two had contraindications. Seven children (32%) showed sustained regeneration, could be removed from waiting list and survived with native liver. 13 patients (59%) underwent liver transplantation after a median waiting period of 4 days.

Four newborns were included in our study. At time of HVP, their individual ages were 4, 17, 19 and 24 days old at time of diagnosis. The two youngest were too sick to be considered for liver transplantation and died due to MOF: only one full HVP cycle in each could be completed, however, this intervention was not able to permanently stabilize these two infants. The first cycle of HVP led to a reduction of vasoactive support in the 4-day-old patient with familial hemophagocytic

TABLE 2 Patient characteristics.

#	Age	Sex	Body weight (kg)	PALF aetiology	HE grade on admission	Inotropic support	Mechanical ventilation	RRT	LIU score	PIM3 (%)	Criteria for HVP	Listed for LT	HVP cycles	Steroid treatment
Native liver survival														
1	20 m	M	10.9	Non A-E hepatitis	III	Yes	Yes	Yes	157	19.8	1, 2, 3, 8	Yes	4	No
2	17 y	M	106	Indeterminate	II	No	No	No	320	6.4	7, 8	Yes	1	No
3	11 y	F	47	Toxic (PEG-Asparaginase)	II	Yes	Yes	No	189	6.0	1, 3, 4	Yes	4	Yes
4	13 y	F	60	MAS	0	No	No	Yes	200	6.2	6, 7	Yes	7	Yes
5	8 y	F	28	Infection- triggered MOF (Covid-19)	III	Yes	Yes	Yes	203	12.4	1, 2, 3, 8	Yes	2	Yes
6	24d	F	2.5	GALD	I/II	Yes	Yes	No	237	-	1, 3, 7	Yes	4	No
7	40 m	M	13.4	Non A-E hepatitis	III	No	No	No	229	-	2, 8	Yes	2	No
Survival after liver transplant														
8	15 y	F	60	Toxic (Acetaminophen)	III/IV	Yes	Yes	Yes	359	28.5	1, 2, 3, 4, 8	Yes	5	No
9	8 m	M	8.6	Indeterminate	0	No	Yes	No	271	-	3, 7	Yes	1	No
10	12 y	M	50	Indeterminate	III	Yes	Yes	Yes	252	18.0	1, 2, 3	Yes	4	Yes
11	15 y	F	68.2	Wilson's disease	I	No	No	No	268	16.1	5	Yes	4	No
12	15 y	M	74	Wilson's disease	II	No	No	Yes	455	6.2	5, 7, 8	Yes	2	No
13	12 y	M	32	VOD	I	Yes	No	No	135	6.0	1	Yes	1	No
14	19d	F	3.6	GALD	0	Yes	No	Yes	569	13.6	1	Yes	6	No
15	16 y	M	65	Autoimmune hepatitis	II	No	No	Yes	966	5.9	6, 7	Yes	3	No
16	16 y	M	66	Indeterminate	II	Yes	Yes	Yes	545	6.4	1, 3, 6, 8	Yes	4	No
17	10 y	F	31	Wilson's disease	0	No	No	No	183	-	5, 7	Yes	1	No
18	8 y	M	29	Indeterminate	IV	Yes	Yes	Yes	227	-	1, 2, 3, 7	Yes	1	No
19	16 y	M	65	cALL	III	No	Yes	No	284	7.2	2, 3, 7, 8	Yes	1	No
Died														
20	11 y	F	36	Indeterminate	III	Yes	Yes	Yes	283	26.6	1, 2, 3	Yes	1	No

TABLE 2 (Continued)

#	Age	Sex	Body weight (kg)	PALF aetiology	HE grade on admission	Inotropic support	Mechanical ventilation	RRT	LIU score	PIM3 (%)	Criteria for HVP	Listed for LT	HVP cycles	Steroid treatment
21	17 d	M	3.15	Infectious (Parvovirus B19)	-	Yes	Yes	Yes	603	38.6	1, 3, 7	No	1	No
22	4 d	M	3.72	fHLH Type 2	-	Yes	Yes	Yes	573	29.3	1, 3, 6, 7	No	3[1,a]	Yes

Note: 1, Hemodynamic instability; 2, HE grad > 2 on admission; 3, mechanical ventilation; 4, toxic aetiology; 5, (suspected) Wilson's disease with New Wilson Index for predicting mortality ≥ 11 points; 6, (suspected) autoimmune/hyperinflammatory disease; 7, Bilirubin > 12 mg/dL on admission; 8, INR ≥ 4 on admission.

Abbreviations: cALL, common acute lymphocytic leukaemia; d, day; fHLH, familial hemophagocytic lymphohistiocytosis; INR, international normalization ratio; LIU, liver injury unit score; LT, liver transplantation; m, month; MAS, macrophage activation syndrome; MOF, multiorgan failure; PIM3, paediatric index of mortality score; VOD, veno-occlusive disease; y, years; -, data not available.

[a]1 completed HVP cycle; 2 out of 3 cycles had to be sustained due to haemolysis.

lymphohistiocytosis, however, the second and third plasmapheresis cycles had to be suspended due to haemolysis. The other infant showed a very rapid deterioration and decompensated due to sepsis. The two infants with GALD including the smallest patient in our cohort with 2.5 kg of body weight completed 1–4 HVP cycles and survived—one with its native liver. An 11-year-old girl died due to sepsis 4 weeks after a primarily successful liver transplantation.

We calculated the LIU score as a marker of severity of the liver injury. Overall, the median peak LIU score was 269 (IQR: 275) and 125 (IQR: 17) after the last HVP cycle. We found a significant difference between children who survived with their native liver and those children who died or were transplanted (203 [IQR: 48] versus 284 [IQR: 317], $p = 0.026$). Only one patient with a LIU score above 300 survived with native liver.

The calculated predicted death rate (PIM3 Score) was available for 17 patients (median 12.4% [IQR: 17]) and was higher in those patients who died ($n = 3$; median 29.3% [range, 26.6–38.6%]) versus those children who survived with their native liver or after transplantation ($n = 14$; median 6.8% [IQR: 10.4]), which is of statistically significance ($p = 0.012$).

3.3 | Inotropic support and concomitant therapy

13 out of 22 patients needed vasoactive support with norepinephrine. While four children developed vasopressor dependency during their disease course, nine children were on vasopressors pre-HVP. In those, median norepinephrine dosage could significantly be reduced after the first cycle of HVP. Only one of these patients (#16) transiently required higher norepinephrine doses than before first HVP. However, after the second cycle, norepinephrine could be stopped due to haemodynamic stability. Of the remaining four patients, for one (#18) no detailed dosage information is available, in two the norepinephrine dose remained unchanged (#1 and #21) and in one patient it was reduced by 56% (#5).

Thirteen patients underwent RRT for hyperammonaemia and/or renal insufficiency for a median of 5.5 days (IQR: 5.3). Five patients received steroids in hyperinflammatory conditions.

3.4 | Liver function parameters and inflammatory markers

International normalization ratio, alanine aminotransaminases, and bilirubin improved significantly following the first HVP cycle (see Table 3).

TABLE 3 Changes in biochemistry and norepinephrine dosage in children with acute liver failure following HVP.

	Pre HVP			Post HVP			
	n	Median	IQR	n	Median	IQR	*p* Value
INR	22	2.85	1.9	21	1.5	0.4	<0.001
ALT (U/L]	22	1280	3792	21	434	734	<0.001
Bilirubin (mg/dL)	22	12.7	14.4	21	6.7	5.4	0.002
Ammonia (μmol/L)	21	82.0	96	19	82.0	58	0.433
CRP (mg/dL)	21	0.65	1.95	19	0.21	0.71	0.002
Platelets (n/μL)	22	111.500	158.500	21	86.000	97.000	0.004
IL-6 (ng/L)*	5	2892.3	58.715	5	19.5	644	0.138
sIL2-R (U/mL)*	7	2407	950	7	950	977	0.018
Norepinephrine dosage (μg/kg/min)	9	0.083	0.15	9	0.009	0.08	0.012

Note: Parameters were analysed and are shown after 1st HVP-cycle except "*" indicating analysis after last cycle.

Abbreviations: ALT, alanine aminotransaminases; CRP, C-reactive protein; HVP, high-volume plasmapheresis; IL-6, interleukin-6; INR, international normalization ratio; IQR, interquartile range; sIL2-R, soluble interleukin-2 receptor.

However, ammonia (median pre-HVP 82 μmol/l) did not significantly change after one cycle of HVP.

C-reactive protein (CRP) was significantly reduced following the first HVP session ($p < 0.002$). Data for IL-6 and sILR-2 is available in five and seven cases, respectively (Table 3). A nonsignificant decrease in IL-6 levels were found in all but the deceased newborn patient (#22) diagnosed with HLH, a hereditary disorder of immune dysregulation, in which IL-6 increased despite HVP and steroid therapy. The other four survived with their native livers (#3, #5 and #7) or underwent liver transplantation (#16). Soluble ILR-2 levels dropped significantly after HVP. It is noteworthy that four of the children survived with their native liver (#1, #3, #4, #7), while two survived to transplant (#14 and #19).

3.5 | Complications and adverse events

No HVP-related mortality or sepsis was observed. The use of citrate for regional anticoagulation was attributed to two cases of mild and correctable alkalosis (pH 7.5 and 7.52) and hypocalcaemia in two patients (ionized calcium 0.77 and 0.8 mmol/L). No citrate-related cardiovascular instability was observed. There were no cases of HVP discontinuation because of hemodynamic instability or electrolyte or acid–base disbalance. In one 4-day-old newborn, two out of three cycles had to be suspended due to haemolysis.

Transient hypothermia below the targeted core body temperature of 36°C occurred in four out of five infants. A significant reduction of platelet count was observed ($p < 0.005$). However, neither patient had a bleeding episode. Two patients without platelet drop did develop a bleeding episode that was not attributed to HVP: one case was an abdominal bleed following liver biopsy requiring transfusion, and the other a mild nosebleed. There were no instances of bleeding associated with placement of the central venous catheter for HVP.

4 | DISCUSSION

PALF is a rare and life-threatening disease of frequently indeterminate aetiology. No specific therapies are available to promote liver regeneration or bridge to transplantation. This is one of three studies of HVP in PALF reporting on cohorts of 20 or more children, and it is the first to report that HVP may reduce the need for inotropic support and to lower inflammatory activity.

Regarding outcome, no firm conclusions can be drawn due to the uncontrolled design of our study. Spontaneous recovery with native liver in PALF is reported to be only between 10% and 40% depending on age and aetiology and mortality remains high without liver transplantation.[4] However, we found an overall survival rate of 86% and a native liver survival of 32%. Importantly, from the 20 children that were granted the high urgency status for liver transplantation in our cohort, seven patients could be removed from the waiting list due to hepatic regeneration and no patient died on waitlist. In addition, from eight children with grade III-IV hepatic encephalopathy, seven survived (88%) in our cohort, three of them without transplantation (43%). This is in favourable contrast to both, a reported mortality rate of 55% in children with persistent grade III-IV HE and to a published spontaneous recovery rate of 22%–33% for grade III and IV HE.[1,26]

Plasmapheresis may suppress the systemic inflammatory response, thereby limiting the extent of MOF and potentially the need for liver transplantation. HVP trials in adults suffering from acute liver failure have shown anti-inflammatory effects and higher survival: Larsen et al. reported in 182 adult ALF patients, that HVP compared to standard medical treatment alone improved transplant-free survival and led to a reduction in pro-inflammatory cytokines.[11] Interestingly, we also observed reduced levels of a PALF-associated inflammatory marker, soluble interleukin-2 receptor,[27] in our cohort following HVP. In addition, we noted another potential beneficial effect: a significant reduction of inotropic support during HVP. We speculate that these potential mechanisms may contribute to clinical stabilization, supporting hepatic recovery or bridge to transplantation.

Although this may indicate a beneficial effect of HVP on outcome in PALF, the lack of comparative studies makes it unclear which approach or combination of ELS systems is most beneficial for children with PALF. Importantly, experience with renal replacement interventions in PALF have shown benefits. Deep et al. reported increased survival with early initiation of RRT in 45 patients with PALF: 58% of children survived, 27% with their native liver.[9] Although these results are lower than in our cohort, it is noteworthy that 13 out of 22 patients, including those three children that died, received RRT as part of standard medical care for treating hyperammonaemia, kidney injury, fluid overload and metabolic or electrolyte disturbances.

Recently the combination of RRT, plasma exchange and albumin-assisted dialyses has been reported in 15 children with acute or acute-on-chronic liver failure; two patients recovered and four died.[20] An ongoing trial in PALF using steroids to ameliorate the inflammatory cascade in selected patients may also contribute to improved control of inflammation in PALF.[28]

Following plasma exchange, the calculated LIU score improved. Interestingly, the LIU score is significantly different between children who survived with their native liver and those children who died or were transplanted, and only one patient with a peak LIU score above 300 survived with native liver. This is in line with the findings by Jørgensen et al., where seven of eight children who survived with their own liver had an LIU score below 300.[14] As expected, the predicted death rate (PIM3 score), which is calculated within 1 h after admission of intensive care unit and includes acute liver failure as one criterion, was significantly higher in those patients that died. However, the PIM3 score could not differentiate between native liver versus transplant survivors.

HVP was performed in four newborn patients with acute liver failure. While HVP was technically feasible in all neonates with bodyweight between 2.5 and 3.6 kg, outcome for two infants which could only complete one HVP cycle each was not favourable with death due to MOF. Poor outcomes in infants with ALF are frequent.[1] In a study in PALF without plasmapheresis by Rajanayagam et al., age below 3 months and weight below 4.7 kg were significant predictors of death without transplantation and reflected by age-related vulnerability to decompensation and sepsis.[29] Importantly, we observed HVP-related haemolysis in the youngest infant, which did not occur in older children. It is noteworthy that the smallest neonate with ALF due to a refractory GALD survived following treatment with four HVP cycles. However, with four neonates in total, our cohort is too small to draw firm conclusions for this age group.

We found that HVP in PALF is safe and feasible even in infants with a body weight under 3 kg. No bleeding episode, sepsis, or death could be attributed to HVP. However, hypothermia and haemolysis, in particular in young infants, and a reduction in platelets, can occur when performing an extracorporeal treatment like HVP. Therefore, adequate monitoring is recommended.

Limitations of our study include the retrospective and uncontrolled approach. Because PALF is a rare disease, our analysis is limited by the small sample size. A further limitation is that we collected data over 14 years during which management of children with PALF evolved. Details on inflammatory markers were not available in all patients.

5 | CONCLUSION

In summary, our study on HVP treatment in children suffering from PALF shows that this approach is feasible even in young infants. Risks are low, but nonetheless, careful monitoring is required. In patients with indeterminate or inflammatory-type PALF, markers of liver failure, inflammatory activation and inotropic support may improve following one or more HVP cycles. We are confident that our data may stimulate multicentre controlled trials to study efficacy and safety of ELS systems including HVP in PALF.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was approved by the local institutional review board (676/2022BO2).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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