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Clinical characteristics, outcomes, and liver transplantation in pediatric acute liver failure: a retrospective single-center cohort study

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Abstract

Objectives

Pediatric acute liver failure (PALF) is a rapidly progressive, life-threatening condition with heterogeneous causes and challenging treatment decisions. This study aimed to describe the etiological spectrum and clinical outcomes of PALF and summarize outcomes after auxiliary partial orthotopic liver transplantation (APOLT).

Methods

This retrospective single-center cohort study included 86 children with PALF treated at Beijing Friendship Hospital between November 2016 and April 2026. Clinical characteristics, etiologies, survival, and liver-transplantation outcomes were reviewed. Liver-tissue metagenomic next-generation sequencing (mNGS) was performed in children with indeterminate PALF. APOLT recipients were evaluated for survival, immunosuppression withdrawal, and available longitudinal histopathological findings.

Results

Indeterminate PALF was the most common etiology (43/86, 50.0%), followed by genetic or metabolic disorders (19/86, 22.1%) and drug-induced liver injury (14/86, 16.3%). Viral sequences were detected by liver-tissue mNGS in 24 of 26 children (92.3%) with indeterminate PALF. HHV-6 was detected in 23, including 5 with HHV-6 as the only viral finding and 18 with viral co-detections. Liver transplantation was performed in 49 children (57.0%); estimated survival in the transplantation group was 83%, 77%, and 73% at 1, 3, and 12 months, respectively. Among 22 APOLT recipients, 15 (68.2%) survived. Eleven of the 15 survivors (73.3%) had completely discontinued immunosuppression by the last follow-up. Serial histopathology in 15 recipients showed variable native-liver recovery and acute cellular rejection in some graft biopsies.

Conclusion

Indeterminate PALF was common, and HHV-6 was frequently detected in liver tissue from this subgroup. However, viral detection alone does not establish causation. Liver transplantation was associated with better observed survival among children with severe PALF, while APOLT offered the possibility of native-liver recovery and immunosuppression withdrawal in selected survivors. Long-term monitoring of both the native liver and graft remains important.

Introduction

Pediatric acute liver failure (PALF) is a critical condition characterized by rapid deterioration of liver function, coagulopathy, and progressive hepatic encephalopathy, occurring in previously healthy children of all ages. Although its incidence is low, PALF is associated with a high mortality rate. Genetic and metabolic liver diseases are more common in neonates and infants, whereas drug-induced liver injury and autoimmune hepatitis are frequently observed in older children[1]. Viral infection is the predominant cause for PALF in developing countries, whereas it accounts for a smaller proportion of cases in developed countries. The incidence of acute hepatitis caused by non-hepatotropic viruses has increased since 2019, suggesting the presence of other potential triggers for such cases[2]. Herpesviruses have also been detected in the plasma or liver tissue of ALF patients, with separate or co-infections of human herpesvirus 7 (HHV-7), human herpesvirus 6 (HHV-6), and CMV[3,4]. Assessing the etiology of PALF is of vital importance in determining whether to perform liver transplantation (LT).

Timely decision-making is critical to avoid unnecessary transplantation in patients who may recover spontaneously or benefit from auxiliary partial orthotopic liver transplantation (APOLT), which is suitable for patients with PALF and can offer them the opportunity to avoid lifelong immunosuppression. Prognostic assessment of PALF includes international normalized ratio (INR), hepatic encephalopathy (HE), factor V, and pediatric end-stage liver disease (PELD) score. However, accurate prognosticsation remains challenging due to the multifactorial pathogenesis of the disease [5].

We conducted a retrospective cohort study to describe the etiological spectrum and clinical outcomes of PALF, characterize viral findings from liver-tissue mNGS in children with indeterminate PALF, and evaluate outcomes after APOLT, including survival, immunosuppression withdrawal, and longitudinal histopathological changes in the native liver and graft.

Methods

1. Study design and inclusion criteria

This retrospective study included pediatric patients (< 18 years) diagnosed with acute liver failure between November 2016 and April 2026. PALF was defined according to the 2017 guidelines of the European Association for the Study of the Liver (EASL): hepatic-based coagulopathy with PT > 15 s or INR > 1.5 not corrected by vitamin K in the presence of hepatic encephalopathy (HE), or PT ≥ 20 s or INR ≥ 2.0 irrespective of HE. Patients with underlying chronic liver disease were excluded.

2. Liver transplantation and clinical management

Upon admission, all patients underwent evaluation for potential liver transplantation. Liver transplantation was performed in patients with progressive hepatic encephalopathy or neurological impairment with persistent coagulopathy that was refractory to intensive medical management.

3. Data collection

Clinical data included demographics, etiological diagnosis, organ support, peak hepatic encephalopathy (HE) grade, survival, transplantation details, and immunosuppression withdrawal. No patients were lost to follow-up. Frozen liver tissue from 26 patients with indeterminate PALF was subjected to mNGS, and microbial sequence data were normalized as reads per million. For APOLT recipients, available serial biopsies of the native liver and graft were reviewed separately. The histopathological findings were summarized from the original reports.

4. Statistical analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using the Student's t-test or Wilcoxon rank-sum test, as appropriate. Survival was analyzed using the Kaplan–Meier method. All statistical analyses were performed using Stata version 14, and a two-sided P value < 0.05 was considered statistically significant.

5. Ethics Statement

Our study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the Istanbul Declaration regarding donor sources. It was approved by the Medical Ethics Committee of Beijing Friendship Hospital, Capital Medical University (ID: 2026-P2-148-01).

Results

1.Clinical characteristics

A total of 86 pediatric patients diagnosed with acute liver failure were included, comprising 47 (54.7%) males and 39 (45.3%) females. The median age at onset was 6 years (range, 1 month–17 years). The age distribution was as follows: infancy (1–12 months), 11 patients (12.8%); early childhood (1–5 years), 28 (32.6%); and childhood (> 5 years), 47 (54.6%). Jaundice was the most common initial presentation (n = 38, 44.2%), followed by fever (n = 25, 29.1%), vomiting (n = 13, 15.1%), and other symptoms such as abdominal pain and diarrhea. Overall, 37 patients (43.0%) required endotracheal intubation, 40 (46.5%) received continuous renal replacement therapy, 60 (69.7%) underwent artificial liver support therapy, and 49 (57.0%) underwent liver transplantation. Detailed clinical characteristics are summarized in Table 1.

Table 1
Clinical characteristics of 86 children with pediatric acute liver failure

Clinical characteristics	Total(n = 86)	IND-PALF(n = 43)	Defined etiology(n = 43)
Age, years	6 (0.1–17)	6 (0.1–17)	6 (0.3–17)
Infancy	11 (12.8%)	10 (23.3%)	1 (2.3%)
Early childhood	28 (32.6%)	10 (23.3%)	18 (41.9%)
Childhood	47 (54.6%)	23 (53.5%)	24 (55.8%)
Sex, male	47 (54.7%)	26 (60.5%)	21 (48.8%)
Grade 3–4 HE	50 (58.1%)	27 (62.8%)	23 (53.5%)
CRRT	40 (46.5%)	21 (48.8%)	19 (44.2%)
Artificial liver support therapy	60 (69.7%)	34 (79.1%)	26 (60.5%)
Mechanical ventilation	37 (43.0%)	22 (51.2%)	15 (34.9%)
Liver transplantation	49 (57.0%)	23 (53.5%)	26 (60.5%)

IND-PALF, indeterminate pediatric acute liver failure; HE, hepatic encephalopathy; CRRT, continuous renal replacement therapy.

2. Etiologies of PALF

Indeterminate PALF was the most common etiology, accounting for 43 cases (50.0%), followed by genetic or metabolic disorders in 19 cases (22.1%) and drug-induced liver injury in 14 cases (16.3%). Other etiologies included mushroom poisoning (n = 3), hemophagocytic lymphohistiocytosis (n = 2), viral hepatitis (n = 2; one cytomegalovirus-associated and one varicella-zoster virus-associated), Budd–Chiari syndrome (n = 1), autoimmune liver disease (n = 1), and primary immunodeficiency associated with a STAT1 mutation (n = 1).

Among the 19 patients with genetic or metabolic disorders, 11 had Wilson disease, four had ornithine transcarbamylase deficiency, one had mitochondrial DNA depletion syndrome type 6, one had pediatric liver failure syndrome type 2, one had familial hypercholanemia type 2, and one had porphyria.

Indeterminate PALF accounted for 90.9% of cases in infancy, 35.7% in early childhood, and 48.9% in childhood. Drug-induced liver injury was absent in infancy but accounted for 25.0% of cases in early childhood and 14.9% in childhood. Wilson disease occurred predominantly in children older than 5 years.

3. Liver Transplantation

Liver transplantation was performed in 49 patients, including 13 (26.5%) deceased-donor liver transplants, 35 (71.4%) living-donor liver transplants, and one (2.0%) domino liver transplant. 22 children underwent APOLT and 27 underwent non-auxiliary liver transplantation. The detailed APOLT characteristics and outcomes are summarized in Table 2.

Disease severity differed significantly between the transplantation and non-transplantation groups. Blood ammonia [(198.50, range: 53.00-1466.00) vs. (168.00, range: 32.00-737.00), P = 0.036], INR [(4.98, range: 1.63–18.82) vs. (2.42, range: 1.23–12.60), P < 0.001]and PELD score [(37, range: 4–68) vs. (23, range: 2–98), P < 0.001] in the transplantation group were significantly higher than those in non-transplantation group.

The 22 APOLT recipients had a median age of 6.85 years (IQR, 4.83–10.58; range, 0.75–15.00) and a median body weight of 27.5 kg (IQR, 20.0–45.8; range, 10.5–78.0). 17 grafts (77.3%) were obtained from living donors, four (18.2%) from deceased donors (including one split graft), and one (4.5%) was a domino graft. Graft types included right-lobe grafts in eight patients (36.4%), left-lobe grafts in six (27.3%), and left-lateral-section grafts in eight (36.4%). Sixteen patients (72.7%) had grade 3–4 HE before transplantation, including 13 (59.1%) with grade 4 HE.

7 APOLT recipients died, yielding an overall survival rate of 68.2% (15/22). Estimated survival was 81.8% at 1 month and 72.7% at both 3 and 12 months. Eleven recipients completely discontinued immunosuppression at a median of 20.0 months (IQR, 18.5–40.0; range, 14–62) after APOLT; all were alive at the last follow-up and represented 73.3% of APOLT survivors. The other four survivors were undergoing immunosuppression tapering. Exploratory comparisons showed no statistically significant differences between survivors and non-survivors in age (P = 0.180), body weight (P = 0.072), or the proportion with grade 3–4 HE (P = 0.616). Among survivors, age, body weight, and grade 3–4 HE were not significantly associated with complete immunosuppression withdrawal (all P > 0.05).

Serial liver histopathology was available for 15 of the 22 APOLT recipients (68.2%), comprising 41 native-liver and 45 graft biopsies. Native-liver biopsies demonstrated heterogeneous recovery: extensive or bridging necrosis present in early specimens resolved to preserved lobular architecture or minimal nonspecific changes in several children, whereas residual fibrosis (reported stage S0–1 to S3), portal-hypertensive vascular changes, steatosis, or cholangiolar reaction persisted in others.

In graft biopsies, definite acute cellular rejection was reported in six patients across 14 biopsy episodes, with reported RAI scores ranging from 4/9 to 9/9; borderline rejection was described in two additional patients. One patient developed polymorphic post-transplant lymphoproliferative disorder. Patient-level longitudinal pathological findings are summarized in Supplementary Table 1.

Table 2
Clinical characteristics and outcomes of APOLT recipients (n = 22)

Characteristic	Value
Age, years	6.85 (4.83–10.58)
Body weight, kg	27.5 (20.0–45.8)
Donor source	LDLT, 17 (77.3%); DDLT, 4 (18.2%); domino, 1 (4.5%)
Graft type	Right lobe, 8 (36.4%); left lobe, 6 (27.3%); left lateral section, 8 (36.4%)
Grade 3–4 HE	16 (72.7%)
Survived	15 (68.2%)
Complete immunosuppression withdrawal	11/22 (50.0%); 11/15 survivors (73.3%)
Time to complete withdrawal, months	20.0 (18.5–40.0); range, 14–62
Definite acute cellular rejection	6/15
Borderline acute cellular rejection	2/15

APOLT, auxiliary partial orthotopic liver transplantation; HE, hepatic encephalopathy;

4. Clinical outcomes and survival

The overall mortality rate was 32.6% (28/86), with indeterminate PALF being the leading cause of death. In the indeterminate-PALF group, 16 patients (37.2%) died and 27 (62.8%) survived. In the defined-etiology group, 12 patients (27.9%) died and 31 (72.1%) survived. According to Kaplan–Meier analysis, overall survival rates in the indeterminate-PALF group were 72.1%, 67.4%, and 62.4% at 1, 3, and 12 months, respectively, compared with 78.9%, 76.5%, and 71.7% in the defined-etiology group. There was no significant difference in the distribution of survival curves (P = 0.371) or the reported survival duration (P = 0.387) between the two groups.

Among 49 patients underwent LT, 36(73.5%) survived and 13(26.5%) died. While, 22(59.5%) survived and 15(40.5%) died in the non-transplant group (n = 37). According to Kaplan-Meier curve, postoperative survival rates in the transplant group were 83%, 77%, and 73% at 1, 3, and 12 months, respectively. In contrast, the non-transplant group had a 1-month survival rate of 59%. The median survival time in transplant group was significantly higher than that in non-transplant group [(34.4 months, range: 0.1-109.1) vs. (16.0 months, range: 0.1–84.0), *P* = 0.009)]. The severity of HE is of great significance in determining the prognosis of patients. In transplant group, there were 3 (15.8%) patients died and 16 (84.2%) patients survived in grade 0–2 HE group (n = 19), and 10 (33.3%) patients died and 20 (66.7%) patients survived in grade 3–4 HE group (n = 30). The median survival time in patients with grade 0–2 HE

was significantly higher than that in patients with grade 3–4 HE [(52.1 months, range: 0.2–77.4) vs. (15.3 months, range: 0.1-109.10), P = 0.012)]. In non-transplant group, 2 (11.8%) patients died and 15 (88.2%) patients survived in grade 0–2 HE group (n = 17). In grade 3–4 HE group (n = 20), there were 13 (65.0%) patients died and 7 (35.0%) patients survived). The median survival time between different HE grade has significant difference [grade 0–2 (24.0 months, range: 0.1–84.0) vs. grade 3–4 (0.75 months, range: 0.2–36.0), *P* = 0.004)]. These results indicate that grade 3–4 HE is associated with a poorer prognosis, both in the transplant group and the non-transplant group.

Further subgroup analysis of patients with grade 3–4 HE demonstrated that postoperative survival rates in the transplant group (n = 30) were 80.0%, 73.1%, and 65.7% at 1, 3, and 12 months, respectively. Among the 20 patients in non-transplant group, survival rates at 1, 3, and 12 months were 40.0%, 35.0% and 35.0%, respectively(*P* = 0.016). The median survival time in transplant group was significantly higher than that in non-transplant group [(15.35 months, range: 0.10-109.10) vs. (0.75 months, range: 0.2–36.00), *P* = 0.007], proving that LT played an important role in severe patients.

At the end of follow-up, 15 of 22 APOLT recipients (68.2%) and 21 of 27 non-auxiliary liver transplant recipients (77.8%) were alive; the difference was not statistically significant (Fisher's exact *P* = 0.525). Given the small groups and differences in operative selection, this unadjusted comparison should be interpreted cautiously. The principal long-term advantage of APOLT was the opportunity for native-liver recovery: 11 APOLT survivors had discontinued immunosuppression completely, whereas four were still undergoing dose reduction.

5. Liver-tissue mNGS findings in indeterminate PALF

Frozen liver tissue from 26 patients with indeterminate PALF, including 24 transplant recipients and two non-transplant patients, was subjected to mNGS. Viral sequences were detected in 24 patients (92.3%), whereas two patients had negative results. HHV-6 was detected in 23 patients, including 22 cases of HHV-6B and one case of HHV-6A. HHV-6 was the sole viral finding in five patients, whereas the remaining 18 had viral co-detections involving cytomegalovirus, Epstein–Barr virus, HHV-7, adenovirus, or human polyomavirus 2. One additional patient had isolated Epstein–Barr virus detection without HHV-6.

Discussion

PALF is a life-threatening condition characterized by acute liver injury in children without preexisting liver disease. Clinical evaluation and diagnostic approaches for PALF differ from those in adults and must take into account patient age, personal and family history, geographic location, and clinical presentation to consider diverse diagnostic factors.

Indeterminate PALF is a diagnosis of exclusion and commonly affects younger children. Approximately 30%–50% of PALF cases remain etiologically undetermined, potentially because of incomplete

diagnostic evaluation or unrecognized causes such as occult drug toxicity, viral infection, autoimmune hepatitis, or metabolic disease[6]. Previous studies have shown that children with indeterminate PALF have lower transplant-free survival than those with an identified etiology. In the present cohort, overall survival was 62.8% in the indeterminate-PALF group and 72.1% in the defined-etiology group, although the difference in survival curves was not statistically significant.

The high frequency of HHV-6 detection in liver tissue in our indeterminate-PALF subgroup is consistent with previous reports describing HHV-6 in explanted livers from children with acute liver failure of unknown etiology[7,8]. In our cohort, HHV-6 sequences were detected in 23 of 26 tested children, but the selected sample and frequent viral co-detections limit etiological interpretation. Detection by mNGS does not by itself establish active infection or demonstrate that HHV-6 caused liver injury.

Recent genomic and histopathologic studies suggest that HHV-6–associated liver injury may be predominantly immune mediated. Low-level HHV-6B reads have been detected in explanted livers accompanied by $CD8^+$ T-cell–predominant inflammatory infiltrate[8], and central perivenulitis with $CD8^+$ T-cell dominance has been described as a characteristic feature of HHV-6–associated acute liver failure[9]. Epidemiological studies and systematic reviews further indicate that HHV-6 is frequently co-detected with other viruses, including adenovirus and adeno-associated virus 2, supporting a contributory or permissive role rather than a solitary etiological agent[3,10,11].

In this cohort, severe hepatic encephalopathy was associated with poor outcomes, and children with grade 3–4 HE had better observed survival when they underwent liver transplantation than when they did not. These findings emphasize the importance of timely multidisciplinary assessment for transplantation in children with rapidly progressive PALF.

Timely liver transplantation is crucial to improve PALF outcomes before multi-organ failure or brain death. After extensive hepatocyte necrosis in ALF, preservation of liver function depends on the survival and regenerative activity of residual hepatocytes and progenitor-cell responses. APOLT provides temporary graft support while retaining the native liver and therefore preserves the possibility of functional recovery and eventual immunosuppression withdrawal. In the present series, 11 of 15 APOLT survivors (73.3%) discontinued immunosuppression completely, at a median of 20 months after transplantation, while the remaining four survivors were being tapered. This proportion is consistent with a systematic review in which native-liver regeneration occurred in 73.3% of surviving pediatric APOLT recipients and 68.6% subsequently discontinued immunosuppression[12].

The longitudinal biopsy findings also illustrate that anatomical preservation does not invariably equate to complete histological normalization. Although early massive or bridging necrosis resolved in several native livers, residual fibrosis, portal-hypertensive changes, steatosis, and cholangiolar reactions were observed in others. Meanwhile, graft biopsies showed a spectrum from no rejection to severe acute cellular rejection, and one child developed polymorphic post-transplant lymphoproliferative disorder. These findings support continued biochemical, imaging, immunological, and histological surveillance of

both liver components during immunosuppression tapering. Decisions to withdraw immunosuppression should therefore be individualized and based on sustained native-liver functional recovery rather than elapsed time alone.

CRRT and PE are key in ALF management, but their efficacy in PALF remains unclear. Artificial liver support shows promise in aiding liver recovery and improving transplant outcomes[13]. In this study, 60 patients received artificial liver therapy, including 35 with combined CRRT and plasma exchange; no significant survival difference was observed, likely due to small sample size. Dynamic monitoring of consciousness before and after therapy is needed to better assess efficacy. Pre-transplant plasma exchange may also enhance neurological recovery and facilitate earlier ventilator weaning.

The retrospective, single-center design carries a risk of selection and information bias. Selection bias may also have arisen because liver-tissue mNGS was limited to patients with available frozen samples. As this was a single-center study conducted at a tertiary liver transplantation center, the patient population may have included a higher proportion of severe cases and transplant candidates. Therefore, the findings may not be fully generalizable to PALF populations in other clinical settings or geographic regions.

Conclusion

In this single-center cohort, half of the children with PALF had an indeterminate etiology. HHV-6 was frequently detected in liver tissue from tested children with indeterminate PALF, often alongside other viral sequences, but its causal role remains uncertain. Liver transplantation was associated with better observed survival in this critically ill population. APOLT preserved the possibility of native-liver recovery and subsequent immunosuppression withdrawal in some survivors, although histological abnormalities in the native liver and graft complications support continued long-term surveillance.

Declarations

Conflict of Interest :

There is no conflict of interest for this work.

Clinical trial number

not applicable.

Ethics approval:

Our study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the Istanbul Declaration regarding donor sources. It was approved by the Medical Ethics Committee of Beijing Friendship Hospital, Capital Medical University (ID: 2026-P2-148-01).

Consent to participate:

Written informed consent was obtained from the parents of all patients included in this study.

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Author Contribution

WTZ and RZM drafted the manuscript. HFX, FH, WQ, and LW managed patients and collected clinical data. ZJZ and LYS conceived and designed the study and contributed to manuscript development. All authors reviewed and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are not publicly available because they contain clinical information from pediatric patients and are subject to patient privacy and institutional ethical restrictions. De-identified data may be available from the corresponding author upon reasonable request, subject to approval by the relevant institutional authorities and applicable ethical requirements.

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14. Supplementary Table 1. Longitudinal histopathological findings in APOLT recipients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx