Pediatr Gastroenterol Hepatol Nutr. 2024 Jan;27(1):43-52
https://doi.org/10.5223/pghn.2024.27.1.43
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Original Article

Check for updates

Clinical Profile and Outcomes of Children with Acute Liver Failure in a Tertiary Care Center in South India: A Retrospective Study

Anitha Abimannane,[1] **Bobbity Deepthi**,[2] **Rohit Bhowmick**,[3] **and Narayanan Parameswaran**[2]

[1]Department of Pediatrics, Pondicherry Institute of Medical Sciences, Puducherry, India
[2]Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
[3]Department of Pediatrics, All India Institute of Medical Sciences (AIIMS) Kalyani, Kalyani, India

OPEN ACCESS

Received: Jan 29, 2023
Revised: Aug 20, 2023
Accepted: Sep 8, 2023
Published online: Jan 9, 2024

Correspondence to
Narayanan Parameswaran
Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India.
Email: narayanan.p@jipmer.edu.in

ORCID iDs
Anitha Abimannane
https://orcid.org/0000-0003-0490-8211
Bobbity Deepthi
https://orcid.org/0000-0002-0071-2134
Rohit Bhowmick
https://orcid.org/0000-0002-2589-4499
Narayanan Parameswaran
https://orcid.org/0000-0002-8297-5789

Funding
None.

ABSTRACT

Purpose: In this study, we investigated the clinical profile, survival at discharge, and proportion of children with acute liver failure (ALF) meeting the criteria for, yet surviving without, liver transplantation (LT).
Methods: Medical case records of children aged >28 days to ≤15 years over a period of 7 years, identified from pediatric admission and discharge registers, were screened. Children satisfying the criteria for ALF were included in this study.
Results: A total of 71 records meeting the pediatric ALF (PALF) criteria were included. The survival rate at discharge was 61% (n=44). A considerable proportion of children satisfied the King's College Criteria (KCC) (56.3%) and the European Association for the Study of the Liver (EASL) criteria (7%) for LT at admission. Nonetheless, the survival rate in the absence of LT was 42.5% in children who satisfied the KCC and 20% in those who met the EASL criteria. Infection (29.5%) and paracetamol overdose (19.7%) were the major identifiable causes of PALF. Hepatitis A was the most common infection identified. No significant predictors of poor outcomes were identified in multivariable analysis.
Conclusion: Our study highlights the changing survival rates and the clinical and etiological profiles of patients with PALF. In areas with poor access to LT services, survival in these children could be improved through early referral to centers with adequate intensive care facilities. Preventing ALF and referring patients to LT services are paramount to reducing mortality.

Keywords: Liver failure; Acute; Child survival; Liver transplantation

INTRODUCTION

In the current era of advanced critical care, pediatric acute liver failure (PALF) remains a disease with high mortality. Developing countries face unique challenges in managing this disease owing to the lack of access to timely liver transplantation (LT). In addition, the outcome depends on the underlying etiology, disease severity at presentation, and—most importantly—availability of adequate supportive care. The published literature shows survival rates ranging from 25 to 33% in the absence of LT [1-3]. A considerable increase in survival

Conflict of Interest
The authors have no financial conflicts of interest.

rates (58%) has been shown with timely LT in developed countries [2]. Infective causes constitute the most common etiology of PALF in developing countries [1,2,4]. Drugs, toxins, metabolic disorders, and autoimmune diseases are other commonly identified causes [2,4]. Sparse literature exists on the survival rates of patients with PALF in South India. We aimed to study the survival rates of patients with PALF, determine the proportion of children surviving without LT, describe the clinical and etiological profiles of PALF, and identify risk factors for poor outcomes.

MATERIALS AND METHODS

This was a retrospective study conducted at a tertiary care center in South India. All children aged >28 days to ≤15 years admitted in the department of pediatrics with a diagnosis of PALF between January 2014 and December 2020 were identified from admission and discharge registers. The institutional ethics committee provided a waiver of consent as this study involved a retrospective review of patients' medical records. Medical records were retrieved and screened to select children satisfying the criteria for PALF, defined as acute liver injury evidenced by clinical features or laboratory parameters, including elevated international normalized ratio (INR) ≥1.5 with hepatic encephalopathy (HE) or INR ≥2 with or without HE, not corrected by vitamin K administration and occurring within 8 weeks of symptom onset, with no evidence of underlying chronic liver disease [4,5]. Data from medical records were collected in a deidentified manner into a spreadsheet. For the subset of children who were discharged against medical advice, an outcome of death was recorded.

Children with altered sensorium were categorized into one of five HE grades by using the Whitington scale for children younger than 3 years and the standard clinical scale for HE for children aged >3 years [6]. Data on clinical features and investigations (first tier: liver function tests, renal function tests, electrolytes, blood gas, lactate, viral hepatitis markers [hepatitis A, B, C, D, E], complete blood count with smear, blood culture, tropical infections [e.g., dengue, scrub typhus, enteric fever, malaria, leptospirosis]; second tier: serum ceruloplasmin, 24-hours urinary copper, autoimmune hepatitis panel [antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsome 1 antibody], inborn errors of metabolism, other hepatotropic viruses [e.g., cytomegalovirus, Epstein-Barr virus]; third tier: liver biopsy and genetic testing) were collected.

Statistical analysis

According to previously published data from our institute, the mortality rate of PALF was 65.5% [5]. Our admission records for the last 1 year revealed an admission rate of 14–15 cases of PALF per year. Assuming a 35% survival rate in our population, with an absolute precision of 5% and a confidence level of 90%, we estimated that the required sample size was 72.

The number of children with PALF who survived without LT and the number of children who survived among those who met the criteria for LT (King's College Criteria [KCC] and European Association for the Study of the Liver–[EASL] criteria) were expressed as proportions. Clinical and laboratory parameters were compared between children who survived (group A) and those who died (group B). The observed differences in these parameters were tested for statistical significance through appropriate tests. Categorical variables were compared using the chi-square test, and continuous variables were compared using Student's *t*-test (if normally distributed) or the Mann–Whitney U-test (if nonnormally

Pediatric Gastroenterology, Hepatology & Nutrition pghn

distributed). A two-sided $p<0.050$ was considered significant. A multivariable analysis was used to identify independent predictors of survival.

RESULTS

A total of 77 children with a diagnosis of ALF were assessed for eligibility; 6 children were excluded (acute-on-chronic liver disease), and 71 children were enrolled.

The baseline characteristics of the enrolled children are summarized in **Table 1**. The median age of the cohort was 3.5 years, with 57.7% being boys. Significantly more male than female children died of the illness ($p=0.002$). The most common symptom at presentation was fever (77%), followed by altered sensorium (70%) and bleeding manifestations (40.8%). Severe HE (grade 3 or 4) at admission was found in 36.3% of group A children (survivors) and 66.6% of group B children (nonsurvivors). Hyperacute liver failure (onset of encephalopathy

Table 1. Baseline characteristics and clinical profile of patients with pediatric acute liver failure

Variable	All patients (n=71)	Group A (survivors, n=44)	Group B (nonsurvivors, n=27)	*p*-value
Age (mo)	42 (12–84)	48 (15–84)	36 (10–84)	0.376
Male:female	41:30	19:25	22:5	0.002
Weight (kg)	12 (8–17)	13.25 (8.8–16.9)	12 (8–19)	0.376
Weight Z score				0.116
0 to −2	40 (56.3)	25 (56.8)	15 (55.6)	
−2 to −3	20 (28.2)	15 (34.1)	5 (18.5)	
<−3	11 (15.5)	4 (9.1)	7 (25.9)	
Height (cm)	94 (74–116.7)	96 (80–116)	93 (71–122)	0.560
Clinical presentation				
Altered sensorium	53 (74.6)	32 (45)	21 (77)	0.635
Bleeding	28 (39.4)	13 (18.3)	15 (55)	0.029
Jaundice	47 (66.2)	26 (59)	21 (77)	0.062
Edema	16 (22.5)	6 (13)	10 (37)	0.017
Hepatomegaly	52 (73.2)	35 (79)	17 (62)	0.167
Splenomegaly	14 (19.4)	9 (2)	5 (18)	0.842
Ascites	14 (19.4)	7 (15)	7 (25)	0.303
GCS at admission	12 (9–15)	14 (10.25–15)	11 (6.5–14)	0.120
Lowest GCS	5.5 (3–11)	9.5 (5.25–13)	3 (3–3)	<0.001
BP at admission				0.022
Normotension	63 (88.7)	42 (95.5)	21 (77.8)	
Hypotension	4 (5.6)	0 (0.0)	4 (14.8)	
Hypertension	4 (5.6)	2 (4.5)	2 (7.4)	
AKI	29 (40.3)	12 (27)	17 (62)	0.003
MODS	23 (31.9)	7 (15)	16 (59)	<0.001
DIC	4 (5.6)	1 (2)	3 (11)	0.151
Sepsis	15 (20.8)	5 (11)	10 (37)	0.033
HE grade at admission				0.025
0	23 (32.3)	17 (38.6)	6 (22.2)	
1	12 (16.9)	9 (20.4)	3 (11.1)	
2	2 (2.8)	2 (4.5)	0 (0.0)	
3	30 (42.2)	16 (36.3)	14 (51.8)	
4	4 (5.6)	0 (0.0)	4 (14.8)	
Jaundice and HE duration				0.398
No HE	18 (25.3)	13 (29.5)	5 (18.5)	
<7 d	44 (61.9)	27 (61.3)	17 (62.9)	
>7 d	9 (12.6)	4 (9)	5 (18.5)	

Values are presented as median (interquartile range), number only, or number (%).
GCS: Glasgow Coma Scale, BP: blood pressure, AKI: acute kidney injury, MODS: multiorgan dysfunction syndrome, DIC: disseminated intravascular coagulation, HE: hepatic encephalopathy.

https://doi.org/10.5223/pghn.2024.27.1.43

Pediatric Gastroenterology, Hepatology & Nutrition pghn

within 7 days of first symptom onset) was noticed in 61.9% of the children. Icterus, edema, hepatomegaly, splenomegaly, and ascites were observed in 66%, 22%, 73%, 19%, and 19%, respectively. Of these clinical signs, edema was significantly more prevalent in group B children (**Table 1**). The proportion of children who had received any native treatment before hospital admission was 28%. The incidence of complications, such as hypoglycemia, acute kidney injury (AKI), multiorgan dysfunction syndrome (MODS), sepsis, and requirement for mechanical ventilation and renal replacement therapy (RRT), was significantly higher in group B than in group A.

A definitive cause for ALF could not be established in most children. Infection was the predominant identifiable cause (29.5%), followed by paracetamol overdose (19.7%) (**Table 2**). A diagnosis of metabolic disorder was made in four children. Two children had Wilson's disease, and two other children who presented with developmental delay, hepatomegaly, and hypoglycemia were suspected of having inborn errors of metabolism. Type 1 autoimmune hepatitis was diagnosed in two children. Of 34 children with an idiopathic etiology of ALF, 9 were screened for Wilson's disease, 6 were evaluated for other inborn errors of metabolism, 3 were investigated for evidence of an autoimmune etiology, 8 had features suggestive of viral hepatitis (fever and jaundice) at admission but recovered spontaneously, and 8 also presented with fever and jaundice and rapidly deteriorated within a few days of admission (all 8 children tested negative for viral hepatitis A, B, C, D, and E markers, and 1 child was discharged against medical advice without further evaluation). Thrombocytopenia and abnormal leukocyte counts were significantly more frequent in children who died than in those who survived. The median bilirubin levels at admission and the maximum recorded values during hospitalization were significantly higher in group B (9 and 9.5 mg/dL, respectively; p=0.020) than in group A (3.7 and 5.3 mg/dL, respectively; p=0.020). The median alanine aminotransferase (ALT) and aspartate aminotransferase (ALP) levels were significantly lower in group B. A trend of decreasing liver enzyme levels with clinical worsening was observed in 18.3%, and a deranged INR without bleeding manifestation was observed in 56.3% (**Table 2**).

The rate of survival without LT was 61% (n=44). Among all the children included, 56.3% satisfied the KCC and 7% met the EASL criteria for LT. Of the children who satisfied the KCC and the EASL criteria, 42.5% and 20% survived without LT, respectively (**Table 3**). All probable candidates for LT at admission were counseled about the need for an early transplant; however, none of them opted for transfer to a facility with LT due to financial and access constraints.

ALF treatment included adequate supportive care for associated complications. All children with ALF due to paracetamol overdose and 22.8% of children with non-paracetamol-induced ALF had received *N*-acetylcysteine. A total of 12 children (17%) underwent RRT, and 33% of these children survived without LT. Peritoneal dialysis was used in 50% of those who underwent RRT. Other RRT modalities included continuous kidney replacement therapy in six children and hemodialysis in one child. All children who required RRT had HE, and 11 of the 12 children also had AKI. One child who underwent peritoneal dialysis and three children who underwent other modes of RRT survived.

Variables that were significantly associated with mortality in univariable analysis (male sex, grade 3–4 HE, presence of edema at admission, hypotension, hypoglycemia, MODS, need for mechanical ventilation, AKI, RRT, abnormal total leukocyte count, thrombocytopenia, idiopathic etiology, and total bilirubin, ALT, and ALP at admission) were included in logistic

https://doi.org/10.5223/pghn.2024.27.1.43

Pediatric Gastroenterology, Hepatology & Nutrition pghn

Table 2. Laboratory parameters and etiology of pediatric acute liver failure

Parameters	Total (n=71)	Group A (survivors, n=44)	Group B (nonsurvivors, n=27)	*p*-value
Hypoglycemia	28 (38.9)	9 (2)	19 (70)	<0.001
Thrombocytopenia	28 (39.4)	13 (29)	15 (55)	0.029
Anemia*	60 (83.3)	37 (84)	23 (85)	0.471
Abnormal leukocyte count	25 (35.2)	12 (27)	13 (48)	0.014
Increased	19 (26.7)	11 (25)	8 (29.6)	
Decreased	6 (8.4)	1 (2.2)	5 (18.5)	
Maximum creatinine (mg/dL)	0.81 (0.59–1.26)	0.7 (0.52–1.010)	0.98 (0.7–1.47)	0.282
Hyponatremia at admission	35 (49.3)	24 (54)	11 (40)	0.330
Potassium at admission	4.01 (3.7–4.8)	4 (3.67–4.62)	4.3 (3.7–4.89)	0.549
Phosphate (mg/dL)	3.4 (2.16–4.32)	3.6 (2.8–4.7)	3.2 (1.7–3.8)	0.463
Total bilirubin (mg/dL)				
Admission	4.8 (1.98–11.55)	3.7 (1.5–7)	9 (3.87–16.37)	0.020
Maximum	6.3 (3.35–12.87)	5.3 (2.4–9.9)	9.5 (5.17–19)	0.020
Maximum bilirubin >10 mg/dL	22 (30.9)	9 (20.4)	13 (48.1)	0.012
Maximum bilirubin >17.6 mg/dL	11 (15.4)	3 (6.8)	8 (29)	0.015
Albumin at admission (g/dL)	2.9 (2.6–3.4)	3.1 (2.7–3.6)	2.8 (2.25–3.2)	0.183
AST (IU/L)				
Admission	845 (357.75–2,092.25)	1,366 (377.25–3,058.75)	686 (253.75–1,379)	0.212
Maximum	1,398 (605–3,501)	1,775 (709.5–4,112.5)	756 (505.5–3,408.75)	0.097
ALT (IU/L)				
Admission	764 (201–2,202)	1,398 (381.5–3,364.25)	571 (84–787)	0.003
Maximum	1,194 (575–3,394)	2,014 (804–3,869)	622 (135.25–1,482.75)	0.008
ALP (IU/L)				
Admission	440 (265.25–776.25)	388.5 (232.5–633.5)	582 (382.5–934)	0.025
Maximum	522 (315.25–876.75)	454 (287.75–803.25)	664 (401.5–1,090.75)	0.212
GGT (IU/L)				
Admission	80.5 (43.75–147.750)	86 (57.75–153.75)	47 (27–113.25)	0.434
Maximum	133 (66.5–218)	172 (90–332.75)	47 (30.25–156)	0.019
PT (s)				
Admission	30.1 (22.65–41.1)	28.5 (21.5–38)	32.85 (27.6–46.75)	0.248
Maximum	31.71 (24–43.5)	30.21 (24–39.58)	44 (22.6–53.33)	0.693
INR				
Admission	2.7 (1.9–3.73)	2.41 (1.89–3.3)	2.79 (2.06–4.2)	0.367
Maximum	2.79 (1.92–3.46)	2.75 (1.93–3.5)	3.65 (1.63–4.6)	0.940
Coagulopathy				0.003
With bleeding	29 (40.8)	12 (27)	17 (62)	
Without bleeding	40 (56.3)	31 (70)	9 (33)	
Lactate at admission (mmol/L)	4.3 (2.65–6.71)	4 (2.37–5.06)	6.81 (3.6–10.7)	0.021
Etiology				0.013
Idiopathic	34 (47.8)	16 (36.3)	18 (66.6)	
Infectious	17 (23.9)	16 (36.3)	1 (3.7)	
Drugs/toxins	10 (14)	6 (13.6)	4 (14.8)	
Metabolic	4 (5.6)	2 (4.5)	2 (7.4)	
Autoimmune	2 (2.8)	1 (2.2)	1 (3.7)	
Both infections and drugs	4 (5.6)	3 (6.8)	1 (3.7)	
Infections				0.203
Hepatitis A	11 (50.5)	10 (0.22)	1 (0.03)	
Dengue	6 (27.2)	5 (0.11)	1 (0.03)	
CMV	3 (13.63)	2 (0.04)	1 (0.03)	
Hepatitis E	2 (9.09)	4 (0.09)	2 (0.03)	

Values are presented as number (%) or median (interquartile range).
AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, PT: prothrombin time, INR: international normalized ratio, CMV: cytomegalovirus.
Some children had more than one etiology; hence, the total number may exceed the sample size.
*The World Health Organization cutoff for anemia in different age groups was used.

regression analysis. None of these factors were identified as a predictor of poor outcomes on multivariable analysis.

Pediatric Gastroenterology, Hepatology & Nutrition pghn

Table 3. Treatment and outcomes of pediatric acute liver failure

Parameters	Total (n=71)	Group A (survivors, n=44)	Group B (nonsurvivors, n=27)	*p*-value
Osmotherapy	39 (54.1)	21 (47)	18 (66)	0.249
Blood product transfusion	44 (61.1)	20 (45)	24 (88)	<0.001
NAC	27 (38)	19 (43.1)	8 (29.6)	0.539
Rifampicin/metronidazole	20 (27.8)	13 (29)	7 (25)	0.569
Lactulose	36 (50)	21 (47)	15 (55)	0.522
Mechanical ventilation indication	37 (51.4)	12 (27)	25 (92)	<0.001
HE	35	12	23	
HE with shock	2	0	2	
RRT				0.047
Total	12 (16.9)	4 (9)	8 (29)	
PD	6 (8.4)	1 (2)	5 (18)	
CKRT	6 (8.4)	3 (6.8)	3 (11)	
HAI	6 (8.2)	5 (11)	1 (90.03)	0.397
Duration of hospital stay	7 (4–11)	8.5 (6–13.5)	4 (3–7.5)	0.017
LT requirement by the KCC at admission				<0.001
Required	40 (56.3)	17 (38.6)	23 (85.1)	
Not required	31 (43.6)	27 (61.3)	4 (14.8)	
LT requirement by the EASL criteria at admission				0.066
Required	5 (7)	1 (2)	4 (14.8)	
Not required	66 (92.9)	43 (97.7)	23 (85.1)	

Values are presented as number (%), number only, or median (interquartile range).
NAC: *N*-acetylcysteine, HE: hepatic encephalopathy, RRT: renal replacement therapy, PD: peritoneal dialysis, CKRT: continuous kidney replacement therapy, HAI: hospital-acquired infection, LT: liver transplantation, KCC: King's College Criteria, EASL: European Association for the Study of the Liver.

DISCUSSION

ALF is a life-threatening disease in children. However, over the years, the survival rates have increased with the advent of LT and improvements in critical care services. The etiological profile and outcome of PALF differ between developing and developed countries [1,4,5].

Clinical profile

ALF was reported to be more prevalent in children aged between 1 and 5 years than in other pediatric age groups [1]. Our study also observed a similar median age at the presentation of ALF (47 months). The predilection of this age group for ALF is probably due to the increased risk of acquiring infections, particularly those caused by feco-orally transmitted hepatotropic viruses. The higher incidence of paracetamol overdose in this age group is due to the availability and incorrect use of different strengths of paracetamol syrups. Sex has not been shown to be associated with survival, except in a few studies reporting higher survival among girls, which is similar to the finding of increased mortality in male patients in our study [7]. Children with ALF commonly present with jaundice, bleeding, or altered sensorium [1,2,8]. In our study, the most common symptom at initial presentation was fever, followed by altered sensorium, jaundice, and bleeding manifestations. ALF presenting with fever could be caused by infections, overdose of paracetamol administered for other febrile illnesses, and autoimmune abnormalities. The presence of edema, hypotension, coagulopathy, or grade 3–4 HE at admission was significantly associated with poor outcomes in our children and reflects the severity of the disease at admission. Delayed onset of encephalopathy from the initial symptom has been reported to be associated with poor survival [1,4]. However, no such association was found in our study; in most children, the onset of HE was hyperacute. Significant improvements in sensorium and survival were observed in 11.2% of children with ALF and grade 3 HE caused by either paracetamol overdose or hepatitis A. This finding

Pediatric Gastroenterology, Hepatology & Nutrition pghn

agrees with the previously reported good survival outcomes associated with ALF induced by hepatitis A or paracetamol overdose [1-4]. We also observed that 40% of children who died had received native medicines before presenting to our center. Native medicine use could potentially worsen the outcomes by delaying the initiation of appropriate therapy. However, in our study population, the observed difference in native medicine use between nonsurvivors and survivors was not statistically significant.

Laboratory profile

We observed hematological abnormalities, including thrombocytopenia, leukocytopenia, or leukocytosis, more commonly in children who died of idiopathic ALF. Thrombocytopenia in liver disease occurs due to reduced thrombopoietin synthesis, splenic sequestration (portal hypertension), virus-induced suppression of megakaryopoiesis, and disseminated intravascular coagulation, with the latter two being reported as important causes of ALF [9]. Studies have shown that the development of thrombocytopenia early in the course of ALF is associated with poor outcomes and is a potential predictor of multiorgan failure [10]. Similarly, leukocytosis or leukopenia in ALF indicates an infectious etiology or a result of a systemic inflammatory response. Findings of altered liver function, such as elevated total bilirubin and a decreasing trend of liver enzyme levels with clinical deterioration, have been reported to be predictors of mortality in ALF [1,4]. Elevated total bilirubin levels at admission, at various cutoffs ranging from >5 mg/dL in some studies to >10 or >17 mg/dL in others, have been shown to predict increased mortality in ALF [1,4]. In univariable analysis, we found that a cutoff of either >10 or >17 mg/dL was associated with poor survival in our children; however, in multivariable analysis, high serum bilirubin levels at admission was not a predictor of mortality. Similar to the findings of other studies, decreasing ALT levels were also associated with poor survival in our study [1,11].

Etiological profile

The underlying etiology was elusive in most cases (47.8%), although infections contributed to a considerable proportion (29.5%), followed by drug-induced liver failure (19.7%). This contrasts with the profile observed in developed countries, where, after an idiopathic etiology, metabolic causes in young infants and autoimmune or drug-induced liver failure in older children were commonly identified [7,8]. Ciocca et al. [2] observed that children with an idiopathic etiology of ALF deteriorate rapidly and die before a diagnosis can be reached. This may indicate an insufficient understanding of the natural course and pathogenesis of PALF. Moreover, a rapid and aggressive diagnostic evaluation may be needed to identify treatable causes and help improve the management and prognostication of patients with PALF. The presence of fever, thrombocytopenia, and leukocyte abnormalities (more commonly found in children with idiopathic ALF) could indicate an unknown infectious etiology in this group of children. The most common infectious etiology identified in our study was hepatitis A, consistent with previous reports [2,4,7,12]. This contrasts with the finding from a recently published study from South India, in which a predominance of dengue-induced PALF was demonstrated [13]. Although the incidence of hepatitis A infection has decreased over the years in developing countries, it remains the primary infectious cause of PALF [8]. Drug-induced liver failure was another preventable cause, with paracetamol being the most common drug implicated in our study. The common reasons for paracetamol overdose in our study were accidental ingestion of a single large dose, use of an incorrect dosage for a prolonged duration and at frequent intervals for fever (due to the parents' poor understanding of the doctors' advice or self-medication), availability of higher-strength paracetamol drops (1 mL=100 mg), and parents' mistake in administering the proper amount

https://doi.org/10.5223/pghn.2024.27.1.43

Pediatric Gastroenterology, Hepatology & Nutrition pghn

of the drug (number of drops vs. milliliters of the paracetamol-containing solution). Dengue was another important infectious cause of PALF in our study. Preventable causes such as hepatitis A and paracetamol overdose contributed to 14% of PALF deaths in this study. Cytomegalovirus hepatitis, hepatitis E, and malaria were the other infections identified. The etiological profile observed in our population suggests the need for implementing public health measures, such as improvement in sanitation, vaccination against hepatitis A, avoidance of self-medication and over-the-counter drug use, promotion of public awareness of the need to improve health-seeking behaviors, and early referral to centers with facilities for adequate supportive/intensive care and LT, to decrease the mortality rates at a global level.

Outcomes

With the increasing availability of LT services, the survival of children with ALF has increased worldwide, especially in developed countries [1-3]. Interestingly, recent studies have shown an important increase in the proportion of children with spontaneous recovery, from 28% in the pre-LT era to 56–73% currently [14]. Many of these studies were from developed countries, and there is a lack of studies on the survival of patients with PALF in developing countries. A study from our center in 2013 showed a survival rate of 34% with supportive care alone [5]. The current study from the same center with no LT facility showed a marked increase (to 61%) in the proportion of children recovering spontaneously from ALF. Despite the absence of an LT facility, our center could achieve improved patient survival through adequate supportive and intensive care. The previous study from the same institute had a higher proportion of children with severe HE, respiratory failure, and MODS, indicating that delayed referral to a tertiary care center contributes to higher mortality. The previous study also had a higher rate (68.9%) of complications related to culture-proven infections, such as bloodstream infection, urinary tract infection, spontaneous bacterial peritonitis, and ventilator-associated pneumonia. However, in the current cohort, 21% of the children were suspected of having an infection and 8.4% had a culture-proven infection (five children had a bloodstream infection, and one child had a urinary tract infection). Half (50%) of these children had received intravenous antibiotics elsewhere before admission, and 90% received antibiotics after admission; the rate of antibiotic administration was not significantly different between patients who survived and those who died. Strict adherence to ventilator-associated pneumonia/central line-associated bloodstream infection prevention bundle measures might have contributed to the reduced infection rate and improved survival. Other medical measures, such as administration of drugs including lactulose, rifampicin for HE, and *N*-acetylcysteine for non-paracetamol-induced ALF, did not contribute to improved survival in our children. In this study, approximately 33% of children who underwent RRT survived without LT. Interventions such as continuous RRT, continuous venovenous hemofiltration, plasma exchange, and various artificial liver support systems can serve as a useful bridge to LT in children [14-17]. Although RRT is an obvious choice when HE is accompanied by severe AKI, its role in children with PALF without AKI is controversial. Our study had insufficient numbers to draw any reasonable conclusions on the role of RRT in PALF.

Predictors of poor outcomes

Previous studies on predictors of mortality in PALF have identified factors such as higher grade of HE, HE onset >7 days from symptom onset, coagulopathy, ALT at admission, higher total serum bilirubin, and hypoglycemia as predictors of poor outcomes [1,2,4,18]. In our study, univariable analysis identified male sex, grade 3–4 HE, presence of edema at admission, hypotension, hypoglycemia, MODS, need for mechanical ventilation, AKI, abnormal total leukocyte count, thrombocytopenia, idiopathic etiology, total bilirubin, ALT,

https://doi.org/10.5223/pghn.2024.27.1.43

Pediatric Gastroenterology, Hepatology & Nutrition pghn

and ALP to be significantly associated with poor outcomes. However, a multivariable analysis including all these factors did not identify any significant predictor of poor outcomes. The findings of our study suggest a complex interplay among multiple factors contributing to the poor predictive value of any model.

Various prognostic modeling scores, including the KCC for paracetamol- and non-paracetamol-induced ALF, model for end-stage liver disease score, pediatric end-stage liver disease score, and Clichy criteria, have been devised to predict the need for LT in ALF. However, none of these are sufficiently accurate to make such predictions [6,13]. Studies analyzing the sensitivity and specificity of the KCC have shown good specificity (95% for paracetamol-induced ALF and 81% for non-paracetamol-induced ALF) and poor sensitivity (58% for paracetamol-induced ALF and 68% for non-paracetamol-induced ALF) [14,18]. The KCC was more specific when applied dynamically and in studies with more patients with high-grade HE [18]. When applied to our patients, the sensitivity and specificity of the KCC were 85% and 61%, respectively, and those of the EASL criteria were 14.8% and 97.7%, respectively. The higher sensitivity of the KCC in our study could be attributed to the lower proportion of children with grade 3–4 HE at admission, the large proportion of children with idiopathic ALF (47.8%), and the predominance of the <10 years age group. These findings indicate the need for better scoring systems or newer markers/predictors of LT in children with ALF, especially in developing countries.

This study has the inherent limitations of retrospective studies. In addition, being an observational study from a single center, the findings need to be confirmed by a prospective study with a large sample size, preferably involving multiple centers.

In conclusion, this study demonstrates improved survival of children with ALF and the unchanged etiological profile of the disease over a decade. The improvement in survival in the absence of LT could be attributed to early referral to a center with adequate intensive and supportive care facilities. An equal emphasis on strategies to prevent infection- and drug-related ALF is imperative. Our study also highlights the critical need to develop effective prognostic scoring models and better access to LT facilities in developing countries.

REFERENCES

1. Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United Kingdom. J Pediatr Gastroenterol Nutr 2005;40:575-81.
PUBMED | CROSSREF
2. Ciocca M, Ramonet M, Cuarterolo M, López S, Cernadas C, Alvarez F. Prognostic factors in paediatric acute liver failure. Arch Dis Child 2008;93:48-51.
PUBMED | CROSSREF
3. Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010;52:2065-76.
PUBMED | CROSSREF
4. Kaur S, Kumar P, Kumar V, Sarin SK, Kumar A. Etiology and prognostic factors of acute liver failure in children. Indian Pediatr 2013;50:677-9.
PUBMED | CROSSREF
5. Mekala S, Jagadisan B, Parija SC, Lakshminarayanan S. Surveillance for infectious complications in pediatric acute liver failure - a prospective study. Indian J Pediatr 2015;82:260-6.
PUBMED | CROSSREF

6. Ng VL, Li R, Loomes KM, Leonis MA, Rudnick DA, Belle SH, et al.; Pediatric Acute Liver Failure Study Group (PALFSG). Outcomes of children with and without hepatic encephalopathy from the pediatric acute liver failure study group. J Pediatr Gastroenterol Nutr 2016;63:357-64.
PUBMED | CROSSREF
7. Bitar R, Thwaites R, Davison S, Rajwal S, McClean P. Liver failure in early infancy: aetiology, presentation, and outcome. J Pediatr Gastroenterol Nutr 2017;64:70-5.
PUBMED | CROSSREF
8. Scharf RE. Thrombocytopenia and hemostatic changes in acute and chronic liver disease: pathophysiology, clinical and laboratory features, and management. J Clin Med 2021;10:1530.
PUBMED | CROSSREF
9. Stravitz RT, Ellerbe C, Durkalski V, Reuben A, Lisman T, Lee WM; Acute Liver Failure Study Group. Thrombocytopenia is associated with multi-organ system failure in patients with acute liver failure. Clin Gastroenterol Hepatol 2016;14:613-620.
PUBMED | CROSSREF
10. Zahmatkeshan M, Serati Z, Freydooni S, Safarpour AR, Esmailnejad A, Haghbin S. Prediction of early liver failure in pediatric patients admitted to intensive care unit. Middle East J Dig Dis 2019;1:141-6.
PUBMED | CROSSREF
11. Pandit A, Mathew LG, Bavdekar A, Mehta S, Ramakrishnan G, Datta S, et al. Hepatotropic viruses as etiological agents of acute liver failure and related-outcomes among children in India: a retrospective hospital-based study. BMC Res Notes 2015;8:381.
PUBMED | CROSSREF
12. Amatya P, Kapalavai SK, Deep A, Sankaranarayanan S, Krupanandan R, Sadasivam K, et al. Pediatric acute liver failure: an experience of a pediatric intensive care unit from resource limited settings. Front Pediatr 2022;10:956699.
PUBMED | CROSSREF
13. Jain V, Dhawan A. Prognostic modeling in pediatric acute liver failure. Liver Transpl 2016;22:1418-30.
PUBMED | CROSSREF
14. Ide K, Muguruma T, Shinohara M, Toida C, Enomoto Y, Matsumoto S, et al. Continuous veno- venous hemodiafiltration and plasma exchange in infantile acute liver failure. Pediatr Crit Care Med 2015;16:e268-74.
PUBMED | CROSSREF
15. Deep A, Stewart CE, Dhawan A, Douiri A. Effect of continuous renal replacement therapy on outcome in pediatric acute liver failure. Crit Care Med 2016;44:1910-9.
PUBMED | CROSSREF
16. Podoll AS, DeGolovine A, Finkel KW. Liver support systems--a review. ASAIO J 2012;58:443-9.
PUBMED | CROSSREF
17. Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr 2006;148:652-8.
PUBMED | CROSSREF
18. McPhail MJ, Wendon JA, Bernal W. Meta-analysis of performance of Kings's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure. J Hepatol 2010;53:492-9.
PUBMED | CROSSREF