Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/x1wjd609

CLINICO EPIDIMIOLOGICAL AND ETIOLOGICAL PROFILE OF ACUTE LIVER FAILURE IN CHILDREN

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Abstract

Background: Pediatric Acute Liver Failure (PALF) represents one of the most challenging of all pediatric critical illnesses. It combines the management of rapidly progressive, severe multisystem organ failure, unpredictable and potential devastating complications.

Aim: To find out the clinical, epidemiological and Etiological profile of Pediatric Acute Liver Failure.

Methods: A profile of 65 consecutive children in this Hospital-based cross sectional observational study diagnosed with Pediatric acute liver failure at Postgraduate Department of Pediatrics, Children hospital Srinagar over a period of 18 months were taken up for the study. The children were followed up to their discharge, death or referral to higher center. A predesigned pro forma was used to record the socio-demographic details, detailed history , examination and investigations of the enrolled patients. Children with the past history of liver disease or physical signs of chronic liver disease were excluded from the study.

Results: Mean age of the study subjects was 7.0± 3.3 years. Majority of the patients in our study were from district Anantnag (21.5%) followed by Budgam (18.5%). The most common clinical presentation was anorexia which was present in 50 of the patients that is 76.9%, followed next in frequency by Vomiting (75.4%), jaundice in 47patients (72.3%), fever (60%), abdominal pain (40%) and features of Hepatic Encephalopathy that is Irritability (10.8%), Sleep cycle change (33.8%) and behaviour changes in 23.1%. Hepatic encephalopathy present at admission was observed to be significant predictor of mortality. Higher grade of encephalopathy present at admission was a significant predictor of mortality. Serum bilirubin was high in 98.5% of the patients whose trend correlated with the clinical profile and outcome of patients. Hepatitis A was diagnosed as cause of ALF in 72.3% patients followed by Indeterminate in 7.7% of patients, GALD in 4.6%, Wilsons and Autoimmune as cause in 4.6 % respectively.

Conclusion: In conclusion, PALF is a life-threatening condition. For this reason, referring the patient to a liver transplant center on time, estimating the likelihood of spontaneous survival, and identifying patients who cannot recover without LT is necessary.

Keywords: Pediatric Acute Liver Failure (PALF), Pediatrics, epidemiology, etiology, prevalence

Introduction:

Acute liver failure (ALF) results from rapid death or injury to a large proportion of hepatocytes, leaving insufficient hepatic parenchymal mass to sustain liver function.

Pediatric Acute Liver Failure (PALF) represents one of the most challenging of allpediatric critical illnesses. It combines the management of rapidly progressive, severe multisystem organ failure, unpredictable and potential devastating complications, as well as the need for urgent decision making in regards to emergent liver transplantation.

In adults, it was initially characterized by signs of severe hepatic dysfunction, including jaundice and coagulopathy, accompanied by development of hepaticencephalopathy within 8 weeks of onset of the signs and symptoms of liver disease. [1] The inability to assess the age-appropriate mental status and the exact duration of illness in children has made it challenging to apply this definition to children. [2,3]

The etiology of ALF varies according to the age of patient and health standards and practices of the country. [4,5] The survival rate of ALF also varies according to etiology – survival is better in few etiologies like paracetamol poisoning whereas it is poor in metabolic diseases. [5] The incidence in developing countries is suspected to be higher due to increased rates of infectious hepatitis. Improvements in health management can affect incidence and etiology. For example, in Argentina, implementing a Hepatitis A virus (HAV) immunization program resulted in a drop of transplant listing rates due to HAV from 60% to 0%. [6]

In developed countries, acetaminophen toxicity is the most frequently identified cause of PALF accounting for 13.3% of the cases, with no etiology identified in 30- 50%. However, studies in India show viral infections as the most common cause followed by metabolic liver diseases and drug induced liver injury with only 9-14.6% cases being of indeterminate etiology. [7]

There is a massive scope of studies which needs to be done for better understanding nature, prognostic factors, early predictors of mortality, timeline and better management of Acute liver Failure. This study is done for better understanding of Acute liver failure in children, its etiology, clinical profile, epidemiological factors affecting the disease and the outcome of the disease.

Methods:

This hospital based cross sectional observational study was conducted in the Postgraduate Department of Pediatrics, Government Medical College Srinagar from September 2022 to February 2024. All patients fitting in inclusion criteria from birth to 18 years admitted to the Children Hospital Srinagar were included in the study. The children were followed up to their discharge, death or referral to higher center. Children with the past history of liver disease or physical signs of chronic liver disease were excluded from the study.

All children presenting to hospital fulfilling the inclusion criteria were enrolled in the study. An informed consent was taken from parents or guardians of the patients.

A predesigned pro forma was used to record the socio demographic details, detailed history, examination and investigations of the enrolled patients.

After detailed history and physical examination, all the patients were subjected to haematological and biochemical investigations. The investigations included complete blood count (CBC), arterial blood gas (ABG), serum electrolytes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total and conjugated bilirubin, prothrombin time (INR), blood group, direct coombs test (DCT), blood and urine cultures, chest X-ray, lactate, blood ammonia and urine for reducing substances. All the patients were tested for viral markers for hepatitis: IgM anti-hepatitis A virus, IgM anti-hepatitis E virus, hepatitis B virus surface antigen, IgM anti-hepatitis B core antibody. Positive blood cultures were taken as diagnostic of enteric fever.

Statistical analysis:
All the collected data was recorded in Microsoft Excel and analyzed using SPSS v23. Categorical variables were described as frequencies and percentages. Discrete variables were described in terms of median and interquartile range. Continuous variables were summarized as mean and standard deviation and finally, the appropriate statistical tests were applied for data analysis. Statistical significance was set at $P<0.05$.

Results:
A total of 65 patients were enrolled in the study with female preponderance. The mean age of the study subjects was 7.0± 3.3 years, the highest number of patients being in the age group of 5 years to 10 years [Table 1].

Table 1: Demographic characteristic of the study population

Variables	Mean ±SD (%)
Age (years)	**7.0±3.3**
Male	41.5%
Female	58.5%

The clinical profile of the patients indicated that a substantial proportion, approximately (72.3-76.9%), exhibited symptoms characterized by Anorexia, vomiting and yellow discoloration of sclera and body. This was followed by manifestations of fever, observed in 60.0% of the patients, lethargy in 49.25% and Pain abdomen in 40.05% of the patients. The mean duration of illness before hospitalization came to be 5.5 days [Table 2].

Table 2: Distribution of Clinical Presentation (symptoms) in study population

Clinical Presentation (symptoms)	Frequency	(%)
Anorexia	50	76.9%
Vomiting	49	75.4%
Yellow Discoloration	47	72.3%
Fever	39	60.0%
Lethargy	32	49.2%
Pain Abdomen	26	40.0%
Sleepcycle change	22	33.8%
Behaviour change	15	23.1%
Loss of consciousness	3	4.6%
Irritability	7	10.8%
Bleeding	6	9.2%
Any Drug Intake	6	9.2%

Initial PT mean came to be 34.3 while as standard deviation was 15.89, for Initial INR mean came to be 3.33 and std dev of 1.99. Patients were followed for peak PT and INR which came to have mean of 21.96 and 1.86 respectively [Fig 1].

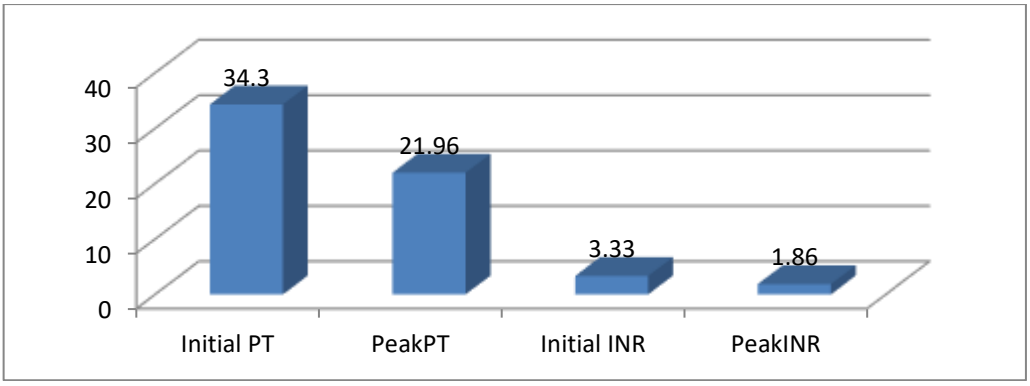

Fig 1

Etiology of acute liver disease was predominantly attributed to hepatitis A in 72.3% of patients. Additionally, 7.7% of cases were classified as indeterminate, while 4.6% each were attributed to Gestational Alloimmune Liver Disease (GALD), Wilson's disease, and autoimmune causes. The remaining cases were associated with various factors including sepsis, hemophagocytic lymphohistiocytosis (HLH), Tyrosinemia, and poisoning [Table 3].

Table 3: Pattern of Etiology in Acute Liver Patients cohort

Etiology	**Frequency**	**(%)**
Hepatitis A	47	72.3%
Indeterminate	5	7.7%
Gestational Alloimmune	3	4.6%
Wilson's disease	3	4.6%
Autoimmune	3	4.6%
Sepsis	1	1.5%
Hemophagocytic Lymphohistiocytosis	1	1.5%
Tyrosenemia	1	1.5%
Poisoning	1	1.5%

A robust association was observed between the outcomes of acute liver failure and its causative factors, Cremer's V value=0.51. Specifically, a survival rate of approximately 91% was noted among patients with hepatitis A as the etiological agent, whereas approximately 53% of patients expired when acute liver failure was attributed to other causes such as GALD, Wilson's Disease, indeterminate factors, sepsis, and autoimmune conditions, as detailed in the pertinent table. This discrepancy suggests a lower mortality associated with hepatitis A compared to alternative causes. Importantly, the observed contrast was statistically significant, as indicated by a p-value < 0.001 [Table 4].

Table 4: Association of Outcomes with Cause of Acute Liver failure among the in study population

Etiology		Hepatitis A	GALD	Wilson's	Autoimmune	Indeterminate	Sepsis	HLH	Tyrosinemia	Poisoning	Total
Outcomes	Survived	30	0	2	0	0	0	0	0	1	33
		90.90%	0.00%	6.10%	0.00%	0.00%	0.00%	0.00%	0.00%	3.00%	100.00%
	Expired	15	2	1	1	4	1	1	1	0	26
		57.70%	7.70%	3.80%	3.80%	15.40%	3.80%	3.80%	3.80%	0.00%	100.00%
Total		45	2	3	1	4	1	1	1	1	59
		76.30%	3.40%	5.10%	1.70%	6.80%	1.70%	1.70%	1.70%	1.70%	100.00%

Fischer'sExactTest=141,p-value<0.001,Cremer's V value=0.51

In conjunction with the standard management protocol employed for acute liver failure patients, additional intensive care unit (ICU) care was necessitated for 80.0% of the patients while as rest were kept in High Dependency Unit. Blood transfusions were administered to 10.8% of the cohort, while 46.2% required inotropic support. Intravenous immunoglobulin (IVIG), continuous renal replacement therapy (CRRT), and coconut oil as special case management being employed in approximately 10.0% of cases. Mechanical ventilation was initiated for 40.0% of the study population [Fig 2].

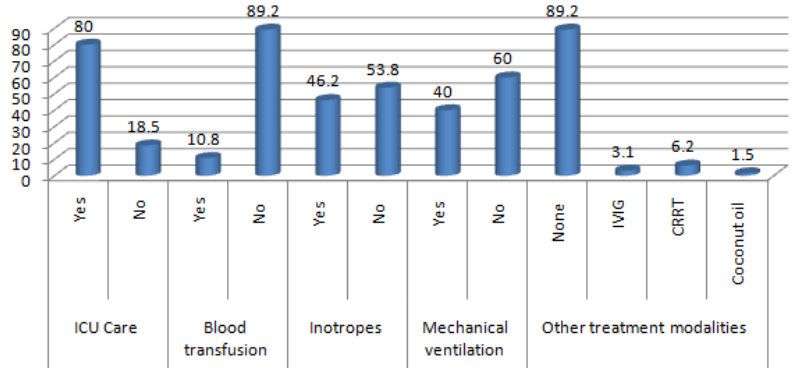

Fig 2

In our analysis, we observed a moderate association between the severity grades of encephalopathy and mortality rates. Notably, among patients without encephalopathy, there was a 0.00% mortality rate, contrasting with increasing mortality rates as the grades of encephalopathy escalated, ranging from 23.1% to 50.0%. This observed trend in mortality rates achieved statistical significance (p-value < 0.001), underscoring the prognostic importance of encephalopathy severity in cases of acute liver failure [Table 5].

Table 5: Association of Outcomes with Grades of Encephalopathy

Encephalopathy		Not Present	Grade 1	Grade 2	Grade 3	Grade 4	Total	Statistical test
Outcomes	Survived	11 33.30%	11 33.30%	10 30.30%	1 3.00%	0 0.00%	33 100.00%	Fischer's Exact Test=17.84
	Expired	0 0.00%	6 23.10%	13 50.00%	5 19.23%%	2 7.6%	26 100.00%	p-value=0.001
Total		11 18.60%	17 28.80%	23 39.00%	6 10.16%	2 3.3%	59 100.00%	Cremer's V=0.53

Discussion:

In our study 65 patients were taken based on predefined inclusion and exclusion criteria, out of 65 patients 58.5 % were females and 41.5% male. Female preponderance was in consistent with **Mendizabal et al.**, [8] **Rajanayagam, Jeremy, et al., [9]Tryambak Samanta et al., [10]**and other studies.

In our study mean age of the patients was 7.02 years with a standard deviation of 4.1 year (7.02 ± 4.1 years), Distribution seen in such a way that max patients were from age group 5 to 10 years that is 26, followed by 1 to 5 years as 20 patients. This pattern is seen in studies like **Kaur, Sharandeep, et al.** [11] In this study it was also observed that the max patients of PALF were from age group of 1 to 10 yr, while as it was also seen that the study had male preponderance in patients.

When we discuss about the clinical profile of patients in our study we start with the symptoms which the patients had and it is observed that 76.9 % of our patients had anorexia as symptom followed by vomiting in 49 % and Yellow discoloration jaundice in 47%. Other symptoms in decreasing order was fever, lethargy, pain abdomen, behavioral change was seen in 60%,49.2%, 40% and 23.1% respectively. This was characteristically seen in the study of **Poddar U et al**., [12] which stated that prodromal symptoms (fever, anorexia, vomiting) were present in 95.5% cases. While when we analyze the most common sign which was present in the patients of our study, it is seen as icterus was present in 95.4% and specific signs like ascitis in 21.5%, Edema in 15.4%, Hepatomegaly in 52% and splenomegaly in 24.6 % which is also in consistency with studies like **Lee WS et al., [13]** who conducted a study in United Kingdom where in the commonest presenting features on admission were jaundice (71%), hepatomegaly (54%), splenomegaly (20%) and ascites (10%). A study conducted by **Ozcay F et al**., [14] in Turkey observed that the most common clinicalfindings during presentation were jaundice (92.3%), hepatomegaly (70.3%), splenomegaly (35.2%), ascites (19.8%), edema (13.1%) and fever (13.1%).

Elevated liver enzymes is observed in our study which in many studies has been analyzed along with serum billirubin being high which is also in correlation with our studies. Studies done which analyze such factors are like **Kaur, Sharandeep, et al**., [11] in which it was observed that if bilirubin increases more than 10 mg/dl has a poor prognostic value. Another prominent study which was done by **Simone Kathemann et al**., [15] illustrated that high AST and ALT levels are not associated with a worse outcome. Persistent elevated liver enzymes are usually associated with liver damage and could therefore be interpreted as worse outcome in PALF. Study found that patients with spontaneous recovery had higher AST and ALT levels on admission and decreased during course of illness, which was statistically significant. This data supports the findings of **Rajanayagam, et al., [9]** who found that AST and ALT levels were higher in PALF patients initially who survived spontaneously. Lower liver enzymes in pre-damaged livers such as

gestational alloimmune liver disease and Wilson's disease, which are commonly associated with worse outcome.

In our study when we discuss about the etiology of PALF we come across the observation that the etiology of acute liver disease was predominantly attributed to Hepatitis A in 72.3% of patients. Additionally, 7.7% of cases were classified as indeterminate, while 4.6% each were attributed to Gestational Alloimmune Liver Disease (GALD), Wilson's disease, and autoimmune causes. The remaining cases were associated with various causes including sepsis, Hemophagocytic Lymphohistiocytosis (HLH), Tyrosinemia, and poisoning. The results correlate well with the studies conducted by **Kaur S et al., [11] Poddar B et al., [12] Bendre SV et al., [16] Ciocca M et al. [17]** But it did not correlate well with the study conducted by **Bravo LCet al., [18]**in which infections were reported in 23% of cases. **Ozcay F et al., [14]** reported infections in 33% of cases. **Lee WS et al., [13]** observed infections in 54.6% of cases. Studies conducted by **Ciocca M et al., [17]**in which Hepatitis A was reported in 60.9% cases.

In our study when we discuss the immediate outcome we come across the observation that approximately half of the study population was discharged, while 40.0% of patients succumbed to their condition. Additionally, 9.2% of individuals were referred to a higher centre for further treatment who were lost to follow up. This correlates with studies like **Kaur S et al., [11]**in which mortality was 44.2%. Similarly, **Silverio CE et al., [19]** observed mortality in 41.9% cases. A study conducted **by Ozcay F et al., [14]** reported that 31.9% cases expired.

In our study, a robust association was observed between the outcomes of acute liver failure and its causative factors, Cremer's V value=0.51. Specifically, a survival rate of approximately 91% was noted among patients with hepatitis A as the etiological agent, whereas approximately 53% of patients expired when acute liver failure was attributed to other causes such as GALD, Wilson's Disease, indeterminate factors, sepsis, and autoimmune conditions, as detailed in the pertinent table. This discrepancy suggests a lower mortality associated with hepatitis A compared to alternative causes. Importantly, the observed contrast was statistically significant, as indicated by a p-value < 0.001. Consequently, etiological agents exhibit promise as prognostic indicators within this study cohort. Similar results were seen in the studies of **Anand Pandit et al., [20]**and **Kaur S et al., [11]** in which there was a more spontaneous resolution of disease seen in the Hepatitis A causal ALF while as in other etiologies survivability was less.

Conclusion:

In conclusion, PALF is a life-threatening condition. For this reason, referring the patient to a LT center on time, estimating the likelihood of spontaneous survival, and identifying patients who cannot recover without LT is necessary.

In our study we found infections were the most common causes of ALF in children. Hepatitis A virus was found to be the most common etiological agent. Improving sanitary conditions, providing safe drinking water facilities, creating awareness about practicing hygienic practices like hand washing, drinking boiled water and providing HAV immunization may help eradicate Hepatitis A.

Conflict of interest: Nil

Funding: Nil

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