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Acute Liver Failure in Children: Clinico-epidemiological Profile and Prognostic Markers

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ABSTRACT

Background: Prospective observational study to evaluate the clinical, etiological and epidemiological profile as well as different prognostic markers for children with acute liver failure in a PICU of a tertiary care hospital in eastern India. **Methods:** 54 children were included in the study, using a predesigned structured study proforma. Routine tests including viral markers, autoimmune, metabolic studies and imaging were done. Standard treatment protocol was followed. **Results:** Of the 54 children mean age was 7.90 +/- 2.54 years, male female ratio was 1.12: 1. The etiology could be detected in 43 of 54 cases (79.6%). Of them hepatotropic viruses accounted for 35 of 43 cases (81.4%) with known etiology with Hepatitis A, E, both A and E, B accounting for 14(25.9%), 9(16.7%), 6(11.1%) and 6(11.1%) cases respectively. Invasive ventilation was required in 30 of 54 (55.6%) patients and the mortality was 27 of 54 cases (50%). Lower age of presentation, decreased liver span, ascites, cerebral edema, hepatic encephalopathy, bleeding manifestations were significant poor prognostic indicators while gender, presence of prodrome, AKI, SBP were not significant. Peak TSB values, prothrombin time, serum albumin, lowest platelet count achieved were significantly bad prognostic markers but hypoglycemia was not. The mean age, ascites, presence of Stage 4 encephalopathy, cerebral edema differed significantly between survivors and non-survivors. **Conclusion:** In the subcontinent water borne hepatotropic viruses continue to predominate as the main cause of pediatric acute liver failure and contributes to its mortality. Despite advances in intensive care, there is a lack of affordable hepatic transplant facilities.

Keywords: *Acute liver failure, viral hepatitis, Wilsons disease.*

INTRODUCTION

Acute liver failure is a clinical syndrome that was initially characterized by severe hepatic dysfunction complicated by hepatic encephalopathy that develops within 8 weeks of onset of signs and symptoms of liver disease.[1-3] However recognition of hepatic encephalopathy in children is difficult and may not be clinically apparent until the terminal stages of the disease.[4,5]

The Pediatric Acute Liver Failure (PALF) Study Group was formed in 2000 as a multisite, multinational consortium to prospectively study ALF in children from birth to 18 years of age. A consensus was reached by the 21 members of the PALF group regarding the entry criteria which has henceforth been used in several studies as well as in the present study.[6]

Etiology varies in adults and children as well as according to the country of origin. In North America and Europe, acetaminophen toxicity comprises 20% of total cases and metabolic disease, autoimmune disease, infectious hepatitis and other causes while in India the most common cause is viral hepatitis.[7-9] A significant group of indeterminate cause remains despite detailed investigation.[6,8] In infants however, metabolic cause remains as the major etiology causing ALF.[8]

Liver transplantation has been found to be the definitive management, however, spontaneous native liver survival over a period of time is increasingly reported.[10,11] This study evaluates the various etiology of acute liver failure in children along with the different clinical features. It also records the management given and the varied outcomes of these children.

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MATERIALS AND METHODS

This prospective observational study was conducted in the PICU of a tertiary care centre in eastern India over a period of two year from December'17 to November'19. 54 consecutive patients who satisfied the following criteria were enrolled in the study: a. biochemical evidence of liver injury with alteration of liver function test, b. children with no evidence of chronic liver disease, c. prothrombin time (PT) >15 seconds or International Normalised Ratio (INR) >1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy or PT >20 seconds or INR >2.0 regardless of presence of clinical hepatic encephalopathy. Children below 1 year or above 12 years were excluded.

A study proforma was made and maintained to study the progress of each patient starting from detailed clinical history and thorough clinical examination and routine investigations were performed. Viral markers

of hepatotropic viruses like HBsAg, Anti HBc IgM, Anti HAV IgM, Anti HEV IgM, Anti HCV IgM, Anti HDV IgM were tested on each patient.

Autoimmune hepatitis was diagnosed with raised IgG, positive family history, ANA>1:40, Anti liver kidney microsomal antibody, Anti smooth muscle antibody >1:20. Wilson's disease was diagnosed in those with a Ferenci score of 4 or more.[12] Liver biopsy and bone marrow aspiration studies, serum ferritin and triglyceride level were done. 2D echocardiography with color Doppler was done. Direct ophthalmoscopy and slit lamp examination for KF ring were also performed. CT scan was done for intracranial hemorrhage and cerebral oedema and MRI brain was done where CT scan was inconclusive. Outcome and mortality was studied after 3 weeks from admission.

Spontaneous bacterial peritonitis was defined as combination of positive culture, an ascitic fluid neutrophil count of >250 cells/mm3, and no evidence of a source of infection.[13] Culture negative neutrocytic ascites (CNNA) was defined as ascitic fluid infection in which the neutrophil count was >250 cells/mm3 with no growth of ascitic fluid culture.[14] Encephalopathy was graded from grade I to IV according to the criteria of Teasdale and Jennett.[15]

Institutional Ethical and Scientific Committee clearance was obtained. Consent of the parents of the children was taken.

Statistical analysis was done using SPSS (version 25.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5.

RESULTS

During the study period 62 children were admitted with liver failure. Eight patients were excluded due to past history of liver disease or physical signs of chronic liver disease, expiry within few hours of admission and refusal of consent. There were 54 patients enrolled in the present study during the study period of two year [December 2017 to November 2019]. Detailed epidemiological and clinicopathological data is available in [Table 1]. Etiological profile of the study patients is found in [Table 2].

Among 21 patients of cerebral oedema 16(30% of total study population) needed mannitol and 5 patients required 3% NaCl infusion to reduce the increased intracranial tension. Regarding respiratory care 30 (55.6%) children required invasive mechanical ventilation (IMV) and 2 (3.7%) child required non-invasive ventilation (NIV) during their course of the illness. 4 (7.4%) children needed moist O2 inhalation and 18 (33.3%) children did not require any respiratory support, not even moist oxygen. Regarding the outcome of the study population 27 (50.0%) children with acute liver failure died and 27 (50.0%) children survived. All parameters and its relation with the outcome including statistical significance is given in detail in [Table 3].

Table 1: Epidemiological and clinico -pathological data

Number of cases	**54 (males= 29, females = 25)**
Age group in years, mean	1 – 12 years , 7.90 +/- 2.54 years
Prodrome	43 patients (79.6%)
Liver Span	
Increased	24 patients (44.4%)
Decreased	20 patients (37.0%)
Normal	10 patients (18.5%)
Splenomegaly	18 patients (33.3%)
Highest stage of Encephalopathy	
Stage 1/Stage 2/Stage 3/Stage 4	19/8/3/24 patients (35.2%/14.8%/5.6%/44.4%)
Cerebral edema	21 patients (38.9%)
Acute Kidney Injury	5 patients (9.3%)
Ascites	29 patients (53.7%)
Spontaneous Bacterial Peritonitis	4 patients (7.4%)
Bleeding manifestations	23 patients (42.6%)
Peak Prothrombin Time (Mean +/-SD)	56.75 +/- 35.24 sec
Peak TSB peak (Mean +/-SD)	21.97 +/- 13.4 mg/dL
Hypoglycemia	9 patients (16.7%)
Serum Albumin (Mean +/-SD)	2.75 +/- 0.8 gm/dL
Electrolyte abnormalities	
Hypo/Hypernatremia/Hypo/Hyperkalemia	5/2/9/5 patients (9.2%/3.7%/16.7%/ 9.2%)
Invasive mechanical ventilation	30 (55.6%)
Mortality	27 patients (50%)

Severe hyponatremia and hypernatremia has been defined as <120 mEq/L and > 155 mEq/L respectively. Severe hypokalemia and hyperkalemia has been defined as <2.5 mEq/L and >5.5 mEq/L respectively.

Table 2: Etiological profile of Paediatric Acute Liver Failure

Etiology		**Frequency (%)**	**Death**
Viral Hepatitis	Hepatitis A	14 (25.9%)	2(14.3%)
	Hepatitis E	9 (16.7%)	3(33.3%)
	Hep A & E co-infection	6 (11.1%)	3(50%)
	Hepatitis B	6 (11.1%)	5(83.3%)
Wilson's disease		5 (9.2%)	4(80%)

Autoimmune Hepatitis		2 (3.7%)	0(0%)
Drug induced ALF		1 (1.9%)	1(100%)
Idiopathic		11 (20.4%)	9(81.8%)
Total		54 (100%)	27 (50%)

Table 3: Association between clinico-pathological features and outcome in terms of survival.

Clinical features		Non-survivors (n=27)	Survivors (n=27)	Chi-square value(where applicable)	p-value
Age in years (mean±SD)		6.28±2.45	9.53±1.33		<0.0001
Sex M:F		15:12	14:13	0.1115	<0.7384
Prodrome		19(44.2)	24(55.8)	1.5961	0.2064
Liver Span	Normal	6(60)	4(40)	25.3929	<0.0001
	Increased	2(8.3)	22(91.7)		
	Decreased	19(95)	1(5)		
Splenomegaly		11(61.1)	7(38.9)	0.5	0.4795
Ascites		23(79.3)	6(20.7)	13.4861	0.0002
Cerebral Edema		19(90.5)	2(9.5)	16.8312	<0.0001
AKI		5(100)	0(0)	3.2727	0.0704
Bleeding Manifestation		23(100)	0(0)	25.7143	<0.0001
Hypoglycemia (< 45 mg/dL)		9(100)	0(0)	7.2000	0.0072
SBP		4(100)	0(0)	3.2727	0.0704
Hepatic Encephalo-pathy	Stage-1	1(5.3)	18(94.7)	30.3077	<0.0001
	Stage-2	0(0)	8(100)		
	Stage-3	2(66.7)	1(33.3)		
	Stage-4	24(100)	0(0)		
		Non survivors	Survivors		
Peak value of TSB (mean±SD)		32.9333 ±9.9294	11.0111 ±4.2240		<0.0001
Prothrombin Time (mean±SD)		86.8889 ±24.4514	26.6111 ±5.9125		<0.0001
Serum Albumin (mean±SD)		2.0944 ±0.4856	3.4111±0.4057		<0.0001
Lowest platelet count (mean±SD)		111472±65492	193333±52650		0.0002

DISCUSSION

In this study, 54 patients with pediatric acute liver failure (PALF) were studied. The mean age of the present study population was 7.9 ± 2.5 years (Mean ± SD) (range 2 years to 11.5 years and median age is 8.25 years) which is similar to Samanta et al.[16] .The mean age of our study was considerably higher as compared to other previous studies.[9,17-19] The mean age difference between the survivors (9.53±1.33 years) and non survivors(6.28±2.45 years) is statistically significant (p value <0.0001). Younger age group shows significant increased mortality. The male female ratio of this study was 1.12: 1 similar to the study by Yasmin et al,[20] (1.14:1) although other studies had shown slight female preponderance in their studies.[16,21,22]

Prodrome in the form of fever, anorexia and vomiting was present in 79.6 % cases of the present study (43 out of 54 total cases) compared to 95.5% (64 out of 67 children) of cases by Poddar et al.[17] In this study liver span, either normal, increased or decreased was found in 18.5%, 44.4 % and 37 % respectively similar to the study of Samanta et al.[16] Decreased liver span is significantly associated with higher mortality (all 20 cases with decreased liver span died) with a p value of < 0.0001. Splenomegaly was present in 33.3 % (16 out of 54 cases) compared to 24.44 % by Samanta et al.[16] Ascites was diagnosed in 53.7 % similar to Poddar et al.[17] who detected it in 51% of cases. In the study by Samanta et al,[16] ascites was seen in 40 % of all cases. On the contrary, a study by Yasmin et al,[20] found ascites in 83.9 % cases, ascites was higher in frequency in their study perhaps because a large number were suffering from Wilson's disease and hepatitis A infection. Presence of ascites is significantly associated with mortality (p = 0.0002).

In our series, one of four cases of SBP was culture positive for E. coli and three were CNNA. The reason for culture negativity may have been the routine use of antibiotics for gut sterilization. Poddar et al,[17] also reported one third SBP and two thirds CNNA although they had 9 of 67 cases in their series which increased mortality significantly (p<0.001). However unlike Poddar et al,[17] our study showed the increase in mortality due to SBP was not statistically significant(p=0.0704).

All patients of this study experienced some stages of hepatic encephalopathy (HE) during their course of illness. The frequency of HE in this study is higher than the findings of Kaur et al,[9] and Yasmin et al,[20] (83.7 % and 75.8% respectively) although the study of Kulkarni et al,[22] reported only 38.6 % to have HE. High incidence of HE is seen in this study is probably because of referral bias as the present study centre is a tertiary care teaching institute.

HE stage 3 and 4 were seen in 50% of the study population in this study (27 out of total 54 cases ; 24 of them were in stage 4 and 3 cases in stage 3) which is almost similar with the studies of Samanta et al,[16]

(48.88% ≥ stage 3 HE) and Poddar et al,[17] (53.7% ≥ stage 3 HE). All studies as well as our study have confirmed that presence of HE as a poor prognostic marker (p<0.0001).[9,16,17]

Bleeding manifestations were seen in 42.6 % of study population similar to another study by Kaur.[9] However, others found less incidence of bleeding manifestations in their studies which was also statistically significant like our present study (p<0.0001).[16,17,20] Lowest platelet counts in our study was 111472±65492 in non survivors as compared to 193333±52650 in survivors. There was a statistically significant difference between survivors and non survivors (p=0.0002) in our study as also noted by Poddar.[17] Samanta et al found thrombocytopenia in 18.8% of the deceased but association between mean platelet counts and deaths were not studied.[16]

The etiology of PALF was detected in 43 out of the 54 cases (79.6 %). Diagnosis of acute liver failure due to hepatotropic viruses (Hepatitis A to E viruses) was made in 35 patients out of 43 cases with known etiology (81.4 %). In the present study, hepatitis A virus predominates with 20 of 35 cases (57.1%), 14 as mono-infection and 6 in combination with hepatitis E virus. Hepatitis E & B virus has an incidence of 42.9 % (n=15) & 17.1% (n=6) among the hepatotropic viruses respectively. Various studies also showed hepatitis A virus as the predominant cause of PALF.[16-18] Viruses transmitted via the enteric route, i.e. hepatitis A and E viruses, accounted for 29 out of 35 (82.9%) viral hepatitis patients of the present study. This finding is similar with Samanta et al,[16] where hepatitis A and E accounted for 24 out of 30 (80%) viral hepatitis patients. On the contrary, Kulkarni et al,[22] and Squires et al,[6] had shown acetaminophen toxicity as the most common identifiable etiology. In the present study one case of drug induced PALF was seen due to antitubercular drugs who died before serum drug samples could be collected. So it is seen that the most common etiology of pediatric ALF differs from developed countries to developing countries. This is perhaps because of improved drinking water supply, good sanitations and community hygiene, strong health infrastructure and excellent vaccination coverage against the hepatotropic viruses in the developed nations. The mortality from Hepatitis A, Hepatitis E, Hepatitis A and E co infection, Hepatitis B was 11.1%,33.3%,50% and 75% in this study which is similar to studies in the subcontinent,[5] although the small sample size prevents us from drawing inferences. Mixed infection with Hepatitis A & E was found to be fatal by Arora et al,[23] but Poddar et al in their series found that all survived. Hepatitis A was found to be a good prognostic marker by Pandit et al as well as our study, as also Hepatitis E by Samanta et al.[16,17]

In the present study Wilson's disease (WD) is diagnosed in 5/54 patients (9.3 %) similar to Samanta et al 3/45 cases (6.67%) although less than Yasmin et al who found WD in 39 of 62 children (63 %).[16,20] According to Yasmin et al, Wilson's disease was the most common cause in their study possibly due to referral bias and consanguineous marriage. In the present study highest mortality was seen in WD (100%) which is similar to Samanta et al (100%) and Yasmin et al (59%) who also concluded that if the etiology is WD then the outcome would be fatal.[16,20]

The incidences of autoimmune hepatitis (AIH) were higher in the studies from US (9.3 % and 6% of total by Kulkarni et al,[22] and Squires et al,[6] respectively) than the present one. In the present study only one case of AIH was detected which survived.

The mean highest value of TSB (peak value) in this study is 21.9 ± 13.4 mg/dl. In the present study, mean peak value (highest value) of TSB of survivors and non-survivors are 11 ± 4.2 mg/dl and 32.9 ± 9.9 mg/dl respectively which is statistically significant (p value < 0.0001). Similar findings were observed by others (p value < 0.001). The study of Kaur et al,[9] found that the prognosis of ALF worsens if TSB levels increase beyond 10mg/dl (p value = 0.014).

Mean peak value of PT of the present study is 56.8 ± 35.2 sec (range 18 to 120 sec). In this study, mean peak value of PT of survivors and non-survivors are 26.6 ± 5.9 sec and 86.9 ± 24.5 sec respectively which is statistically significant (p value < 0.0001).

Mean serum albumin (drawn at admission) of the present study is 2.75 ± 0.80 g/dl (range 1.5 – 3.9 g/dl). Present study is corroborating with the study of Samanta et al,[16] where hypoalbuminemia (<2.5g/dl) was found in 42.2% cases. Mean serum albumin of the survivors and the deceased are 3.41±0.40 g/dl and 2.09 ± 0.49 g/dl respectively (p value <0.0001). Hence, outcome of ALF is dependent on serum albumin. Episodes of hypoglycaemia (blood glucose < 45mg/dL) were observed in 16.7% in the present study which is significantly associated with death (p = 0.0072). This was also confirmed by Shrivastava et al.[24]

Electrolyte abnormalities have been found in 38.9 % (21 of 54 cases) of present study population. Hyponatremia (serum Na < 120 mEq/L) corroborates with Samanta et al (9.2% vs 8.8%) as also hypokalaemia (serum K< 2.5 mEq/L) (16.7% vs 15.5%). Only Yasmin et al reported a hypokalaemia incidence of 56%.[22] Hypokalemia may be caused by dilution from renal wasting, volume overload or ascites. Serum sodium > 155 meq/L was found in only two cases (3.7%) and serum potassium > 5.5 meq/L was seen in five cases (9.2%). All cases with hyperkalemia (serum K > 5.5 meq/L) showed features of altered renal function similar to Samanta et al.[16]

As our centre does not have hepatic transplant facilities and is unaffordable for the majority it is imperative to have an universal Hepatitis A vaccination policy although there are views to the contrary.[25,26] Limitations of this study include it being a single centre study, longer study duration

would have been preferred and a lack of transplant facilities.

CONCLUSION

Hepatotropic viruses continues to remain the most common etiological agents of pediatric acute liver failure of which hepatitis A and E viruses predominate. Lower age of presentation, decreased liver span, ascites, cerebral edema, hepatic encephalopathy, bleeding manifestations were significant poor prognostic indicators while gender, presence of prodrome, AKI, SBP were not significant. Peak TSB values, prothrombin time, serum albumin, lowest platelet count achieved were significantly bad prognostic markers but hypoglycemia was not. Early recognition, appropriate management in intensive care unit and more affordable facilities for liver transplantation are necessary to reduce the mortality of acute liver failure.

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