International Journal of Contemporary Pediatrics
Wani K et al. Int J Contemp Pediatr. 2024 Jun;11(6):794-799
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20241366

Original Research Article

Clinico-etiological profile of acute liver failure in children in a tertiary care hospital of northernmost India

Khurshid Wani, Jawad Nazir Wani, Bashir U. Zaman*, Naseer Yousuf Mir

Department of Pediatrics, Government Medical College, Srinagar, Jammu and Kashmir, India

Received: 24 April 2024
Revised: 16 May 2024
Accepted: 20 May 2024

***Correspondence:**
Dr. Bashir U. Zaman,
E-mail: drbashiruzaman@gmail.com

ABSTRACT

Background: Acute liver failure is a life-threatening condition with sudden onset liver injury, decreased liver functions, hepatic encephalopathy, and coagulopathy in patients without preexisting liver disease. The objective of this study was to find out the clinical and etiological factors of acute liver failure in children.
Methods: This study was a hospital based prospective observational study conducted from November 2017 to October 2019 at Pediatric Intensive Care Unit (PICU) of Postgraduate Department of Pediatrics, Government Medical College Srinagar, Kashmir. Fifty-one consecutive patients of ALF in the age group of 1 to 18 years were included in this study.
Results: The most common clinical presentation in our study was jaundice which was present in all cases followed by anorexia (90.2%), vomiting (84.3%), fever (76.5%) and abdominal pain (64.7%). HE was present at admission in 54.9% cases and exaggerated DTR's was present in 49% cases. Of the other clinical manifestations, bleeding was present in 49% cases, ascites in 33.3% cases and edema in 5.9% cases. Infections (76.5%) were the most common cause of ALF in children followed by indeterminate (9.8%), autoimmune (5.9%), drug induced (3.9%), Wilson's disease (2%) and HLH (2%). In infectious etiology, the most common cause was Hepatitis A (66.7%) followed by Enteric fever (7.8%) and Hepatitis E (2%).
Conclusions: The most common clinical manifestation of ALF in children is Jandice. Hepatitis A is the most common cause of ALF in children.

Keywords: Acute liver failure, Hepatitis A, Hepatic encephalopathy

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.[1] The Pediatric Gastroenterology Chapter of IAP defines acute liver failure in the presence of (a) evidence of liver dysfunction within 8 weeks of onset of symptoms (neonates may have only deranged liver functions without overt symptoms) (b) uncorrectable (6-8 hours after administration of one dose of parenteral vitamin K) coagulopathy with International Normalized Ratio (INR) >1.5 in patients with hepatic encephalopathy, or INR>2.0 in patients without encephalopathy and (c) no evidence of chronic liver disease either at presentation or in the past.[2]

Acute liver failure (ALF) is a rapidly progressive, potentially fatal syndrome caused by a large variety of insults. The etiology of ALF varies according to the age of patient and development of the country.[3-5] In developing countries, hepatitis A is the most significant etiological agent causing acute liver failure (ALF) in children, however, infectious causes are rarely seen in developed countries.[6-8] Pediatric ALF study group data indicated that metabolic diseases were the most common cause of ALF in children under 3 years.[8] In children older than 3 years, acetaminophen intoxication was the main cause.

However, the cause of ALF still remains undetermined in a large proportion of children.[9] 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.[10,5] Because of the shortage of facilities of liver transplantation (LT), a large number of patients of ALF die without undergoing LT. Determining the prognosis of ALF is vital when considering the patient for LT so as to identify those patients who are unlikely to survive without LT and assessing the probability of successful LT.

Five studies published between 1996 and 2007 studies from India (Chandigarh, Vellore, Delhi, Kolkata and Pune). enrolling 215 children showed acute viral hepatitis to be the commonest cause, either alone or in combination (overall 61-95%: hepatitis A 10-54%; hepatitis E 3-27%; hepatitis B 8-17%; and multiple viruses 11-30%-commonest being hepatitis A+E).[11-18] Drugs were responsible for ALF in 6-8% cases and other causes in 9-10.5%. Etiology remained unestablished in 6-22% patients. There are no published data from India on ALF in neonates and infants.

ALF's clinical manifestations are common to all causes, although there may be subtle differences, such as the characteristic prodromes in viral hepatitides (low-grade or high fever, nausea, vomiting and abdominal pain), or a history of exposure to toxic substances or drugs. In general, children with ALF are previously healthy; they often exhibit rapidly worsening jaundice, accompanied by abdominal pain, anorexia, fever, and vomiting. In infants, jaundice may be mild or absent, and the predominant symptoms are hypoglycemia, vomiting, refusal to eat, irritability, changes in sleep patterns, and seizures. Hepatic encephalopathy is the complex of neuropsychiatric alterations stemming from altered liver function. It is functional in nature and potentially reversible; has a broad spectrum of severity, ranging from mild sensory alteration to coma; and can be of late onset in infants and small children. Altered coagulation is present in all patients, clinically manifested by ecchymosis, petechiae, bleeding at puncture sites, and gastrointestinal or other internal organ hemorrhage. Gastrointestinal hemorrhage can be observed in up to 70% of pediatric ALF patients.[19]

There is lack of data on clinico-etiological profile of acute liver failure in children from the region of Jammu and Kashmir. Therefore, we tried to explore the clinical profile and etiological factors of acute liver failure in PICU setting where significant mortality is due to this disease.

METHODS

The study was conducted at Pediatric Intensive Care Unit (PICU) of Department of Pediatrics in G. B. Pant Hospital, an associated hospital of Government Medical College Srinagar, after obtaining institutional ethical clearance and consent from guardians. The study was a hospital based prospective observational study conducted from November 2017 to October 2019. All children older than one year and ≤18 years of age were included and liver failure was defined as: 1) absence of a previously known history of chronic liver disease, 2) biochemical evidence of acute liver injury, and 3) hepatic-based coagulopathy defined as PT≥15s or INR≥1.5 not corrected by vitamin K in the presence of encephlopathy or PT≥20s or INR≥2 regardless of the presence or absence of clinical HE (12).

Grading of hepatic encephalopathy was done using the standard criteria.[20]

Patients younger than 1 year were excluded as they have different clinical characteristics and aetiology.

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.[2]

Wilson's disease profile was done in patients with alkaline phosphatase/bilirubin ratio <4.0, AST/ALT ratio >2.2± evidence of Coombs negative hemolysis. This included ophthalmological examination for KF rings, 24-hour urinary copper estimation and serum ceruloplasmin. Investigations for autoimmune hepatitis were sent in the following: female sex, age >6 years, positive family history, raised immunoglobulin G levels and positive direct Coombs test. This included anti-nuclear antibody (>1:40), liver kidney microsomal antibody, smooth muscle antibody (>1:20) and Ig G levels. HLH was diagnosed by having 5 of the following 8 signs or symptoms: fever, splenomegaly, cytopenia (affecting ≥2 cell lineages; hemoglobin ≤9 g/dl, platelets <100,000/microlitre, neutrophils <1,000/microlitre), hypertriglyceridemia (265 mg/dl) and/or hypofibrinogenemia (≤150 mg/dl), hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy, low or absent natural killer cell cytotoxicity, hyperferritinemia (≥500 ng/ml) and elevated soluble CD25 (interleukin-2Rα chain; ≥2,400 U/Ml). Young adults and adolescents with history of drug intake and abnormal renal function, drug levels (valproate) were done. In cases where no positive viral markers, no history of toxin or drug exposure, and no metabolic cause were detected, the etiology of PALF was classified as indeterminate.[2,21]

All the patients were managed according to the standard ICU protocols.[15]

RESULTS

During the study period 51 children with acute liver failure were admitted out of which 27 (52.9%) were males and 24 (47.1%) were females as depicted in Figure 1. The mean age of the study population was 7.0±3.3 years. Majority of the study subjects were in age group 6 to 10 years as shown in Figure 2. Most of the patients were from rural than urban areas.

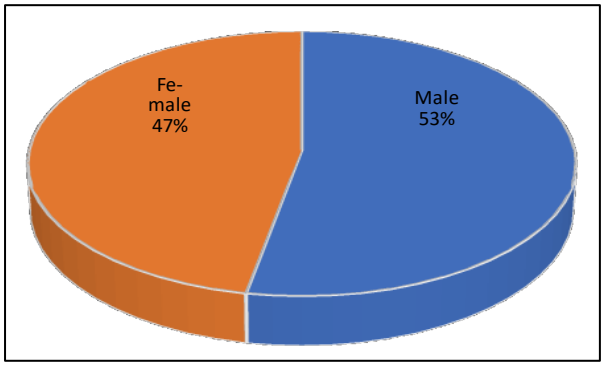

Figure 1: Gender distribution of study subjects.

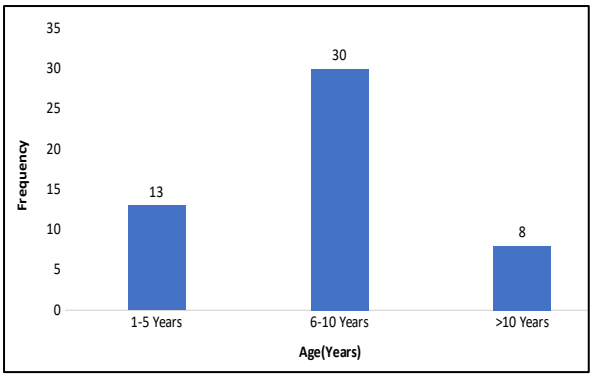

Figure 2: Age distribution of study subjects.

Table 1: Clinical presentation of study subjects.

Presentation	Frequency	Percentage (%)
Jaundice	51	100.0
Anorexia	46	90.2
Vomiting	43	84.3
Fever	39	76.5
Abdominal pain	33	64.7
Bleeding	10	19.6
Hepatic encephalopathy	28	54.9
Ascites	17	33.3
Edema	3	5.9
Exaggerated DTR	25	49.0

The most common clinical findings during presentation were jaundice (100.0%, n=51) followed by anorexia (90.2%, n=46), vomiting (84.3%, n=43), fever (76.5%, n=39), abdominal pain (64.7%, n=-33), hepatic encephalopathy (54.9%, n=28), ascites (33.3%, n=17), bleeding (19.6%, n=10), edema (5.9%, n=3) (Table 1). Hepatic encephalopathy was present in 54.9% (n=28) patients at admission of which grade I HE was seen in 29.4% (15/51), grade II HE in 9.8% (5/51), grade III HE in 11.8% (6/51) and grade IV HE in 3.9% (2/51) as shown in Figure 3 and 4.

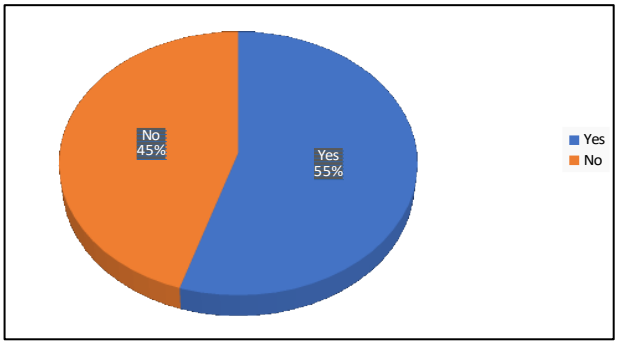

Figure 3: Presence of HE at admission in study subjects.

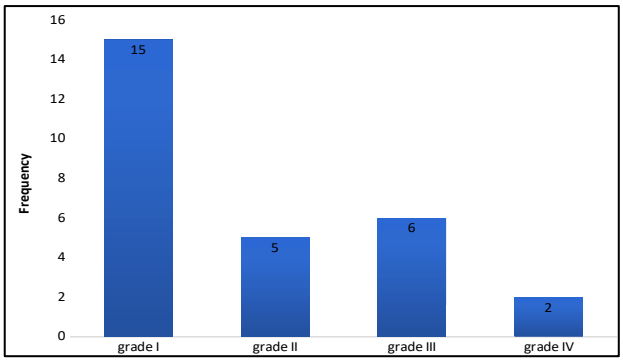

Figure 4: Grade of HE at admission in study subjects.

Table 2: Laboratory parameters of study subjects.

Parameter	Mini-mum	Maxi-mum	Mean	SD
Total Bilirubin at Admission (mg/dl)	3.2	26.6	13.93	5.85
Peak Bilirubin (mg/dl)	4.7	36.7	20.96	7.20
INR at Admission	1.2	4.5	2.27	.61
Peak INR	1.6	5.5	3.74	1.07
BSR at Admission (mg/dl)	32.0	187.0	98.20	39.82
pH	7.10	7.65	7.37	0.14

In our study, the mean total serum bilirubin at admission was found to be 13.93±5.85 mg/dl while as the mean of peak serum bilirubin was found to be 20.96±7.20 mg/dl. The mean INR at admission was 2.27±0.61 while as the mean peak INR was 3.74±1.07. The mean BSR at admission was 98.20±39.82 mg/dl with minimum of 32 mg/dl and maximum of 187 mg/dl. The mean Ph was 7.37±0.14 (Table 2).

The etiologies of PALF included infectious (76.5%, n=39), indeterminate (9.8%, n=5), autoimmune (5.9%, n=3), drug induced (3.9%, n=2). Wilson's disease (2%, n=1) and HLH (2%, n=1) as shown in Figure 5. Among infections the most common etiology was found to be Hepatitis A virus (66.7%, n=34) followed by Hepatitis E virus (2%, n=1) and enteric fever (7.8%, n=4) as shown in Figure 6.

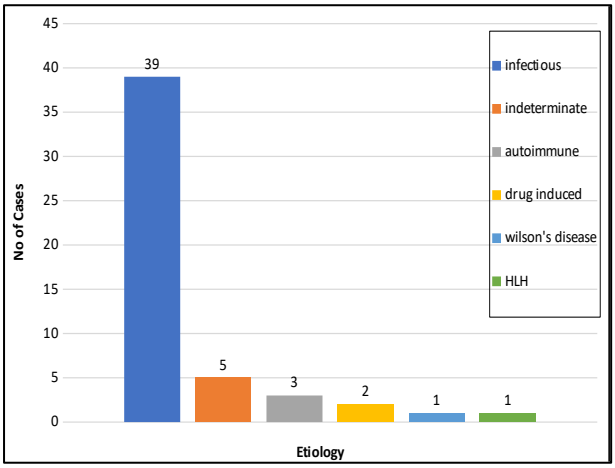

Figure 5: Etiology of ALF in study subjects.

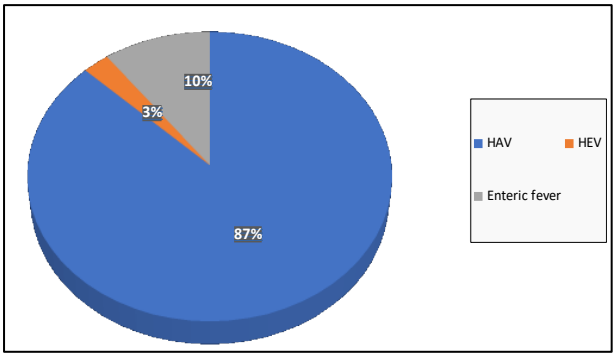

Figure 6: Infectious causes of ALF in study subjects.

DISCUSSION

Our study comprised a total of 51 patients out of which 27 (52.9%) were males and 24 (47.1%) were females. The male to female ratio in our study was approximately 1:1 which was similar to a study conducted by Ozcay et al in which 50.5% of the study population comprised of males and 49.5% females.[22] A study conducted by Ciocca et al in Argentina also found similar results wherein 51% of the total study population comprised of males and 49% females.[6] The mean age of the study subjects in our study was 7.0±3.3 years, the highest number of patients being in the age group of 6 to 10 years comprising 30 patients which was 58.8% of the total study population which was comparable to the studies conducted by Ozcay et al and Ciocca et al.[6,22] Although study cases presented from all the parts of the Kashmir valley, majority of the patients were from rural than urban regions. This could be attributed to poor access of people to safe drinking water facilities, rivers and springs as source of drinking water, unhygienic practices, poor sanitation and low socioeconomic standards.

The most common clinical presentation of our study cases was jaundice which was present in all cases (n=51, 100%) followed by anorexia (n=46, 90.2%), vomiting (n=43, 84.3%), fever (n=39, 76.5%), and abdominal pain (n=33, 64.7%). HE was present at admission in 54.9% (n=28) cases and exaggerated DTR's was present in 49% (25) cases. Of the other clinical manifestations, bleeding was present in 45.1% (n=10) cases, ascites (n=17, 33.3%) and edema (n=3, 5.9%). Lee et al conducted a study in United Kingdom wherein the commonest presenting features on admission were jaundice (71%), hepatomegaly (54%), splenomegaly (20%) and ascites (10%).[10] A study conducted by Ozcay et al in Turkey observed that the most common clinical findings during presentation were jaundice (92.3%), hepatomegaly (70.3%), splenomegaly (35.2%), ascites (19.8%), edema (13.1%) and fever (13.1%).[22] Poddar et al stated that prodromal symptoms (fever, anorexia, vomiting) were present in 95.5% cases.[17] A study conducted by Bravo et al reported that on admission, jaundice and encephalopathy (any grade) were present in 84.6% and 46.2% of subjects respectively.[23]

Out of the total 51 patients admitted with the diagnosis of acute liver failure, HE was present in 55% (n=28) of study subjects at admission which was consistent with the results obtained in a study conducted by Ciocca et al wherein 58% of study subjects had HE at admission.[6] Similar results were reported in a study conducted by Bravo et al in which 46.2% of study subjects presented with HE on admission.[23] Among the patients who presented with HE at admission, grade I HE was present in 53.6% (n=15), grade II in 17.9% (n=5), grade III in 21.4% (n=6) and grade IV HE in 7.1% (n=2) of study subjects. Similar results were obtained among patients who presented with HE at admission in a study conducted by Ozcay et al in which grade I and II HE was observed in 60.9% cases and grade III and IV in 39.1% cases.[22]

In our study we found that infections were the most common cause of ALF in children comprising 39 cases which is 76.5% of the total study population followed by indeterminate (9.8%, n=5), autoimmune (5.9%, n=3), drug induced (3.9%, n=2), Wilson's disease (2%, n=1) and HLH (2%, n=1). Two cases of drug induced ALF were reported both due to sodium valproate toxicity. The results correlate well with the studies conducted by Kaur et al, Poddar et al, Bendre et al, Ciocca et al.[6,14,24,25] In infectious

etiology, the most common cause was found to be Hepatitis A virus comprising 34 cases which is 66.7% of the total study population followed by Enteric fever (7.8%, n=4) and Hepatitis E virus (2%, n=1). The results were consistent with the study conducted by Ciocca et al in which Hepatitis A was reported in 60.9% cases.[6] Similarly, Kaur et al found Hepatitis A in 58% cases. Poddar et al also reported Hepatitis A in 54% cases.[17,24]

As viral hepatitis was the most common etiological agent in our study, it highlights the fact that simple interventions like improving hygienic practices and immunization coverage can substantially decrease ALF. Our study carries various limitations because of the small sample size and hence generalization of our study results needs further research using a larger sample size.

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 practising hygienic practices like hand washing, drinking boiled water and providing HAV immunization may help eradicate Hepatitis A.

ACKNOWLEDGEMENTS

Authors would like to thank faculty and staff members in the Department of Paediatrics, Government Medical College, Srinagar, Jammu and Kashmir. Author thank the guardians of the children for their cooperation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Bucuvalas J, Yazigi N, Squires RH. Acute liver failure in children. Clin Liver Dis. 2006;10:149-68.
2. Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics; Bhatia V, Bavdekar A, Yachha SK; Indian Academy of Pediatrics. Management of acute liver failure in infants and children: consensus statement of the pediatric gastroenterology chapter, Indian academy of pediatrics. Indian Pediatr. 2013;50(5):477–82.
3. Acharya SK, Dasarathy S, Kumar TL, Sushma S, Presanna U, Tandon A, et al. Fulminant hepatitis in a tropical population: clinical course, cause and early predictors of outcome. Hepatology. 1996;23:1448-55.
4. Ostapowicz J, Lee WM. Acute hepatic failure: a western perspective. J Gastroenterol Hepatol. 2000;15;480-8.
5. Dhiman RK, Seth AK, Jain S, Chawla YK, Dilawari JB. Prognostic evaluation of early indicators in fulminant hepatic failure by multivariate analysis. Dig Dis Sci. 1998;43:1311-6.
6. Ciocca M, Ramonet M, Cuarterolo M, López S, Cernadas C, Alvarez F. Prognostic factors in paediatric acute liver failure. Arch Dis Child. 2008;93:4851.
7. Shah U, Habib Z, Kleinman RE. Liver failure attributable to hepatitis A virus infection in a developing country. Pediatrics. 2000;105:436-8.
8. Squires RH, 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.
9. Dhawan A. Etiology and prognosis of acute liver failure in children Liver Transpl. 2008;14:80-4.
10. 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.
11. Wilson DC, Phillips MJ, Cox DW, Roberts EA. Severe hepatic Wilson's disease in preschool-aged children. J Pediatr. 2000;137:719-22.
12. Arora NK, Mathur P, Ahuja A, Oberoi A. Acute liver failure. Indian J Pediatr. 2003;70:73-9.
13. Arora NK, Nanda SK, Gulati S, Ansari IH, Chawla MK, Gupta SD, et al. Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in north India. J Med Virol. 1996;48:215-21.
14. Bendre SV, Bavdekar AR, Bhave SA, Pandit AN, Chitambar SD, Arankalle VA. Fulminant hepatic failure: etiology, viral markers and outcome. Indian Pediatr. 1999;36:1107-12.
15. Bhatia V, Lodha R. Intensive care management of children with acute liver failure. Indian J Pediatr. 2010;77:1288-95.
16. Bhowmick K, Mammen A, Moses PD, Agarwal I, Mathew L, Kang G. Hepatitis A in pediatric acute liver failure in southern India. Indian J Gastroenterol. 2005;24:34.
17. Poddar U, Thapa BR, Prasad A, Sharma AK, Singh K. Natural history and risk factors in fulminant hepatic failure. Arch Dis Child. 2002;87:54-6.
18. Samanta T, Ganguly S. Aetiology, clinical profile and prognostic indicators for children with acute liver failure admitted in a teaching hospital in Kolkata. Trop Gastroenterol. 2007;28:135-9.
19. Alonso E, Squires R, Whitington P. Acute Liver Failure in Children. In: Suchy FJ, Sokol RJ, Balistreri WF, editors. Liver Disease in Children. 3rd ed. Cambridge: Cambridge University Press; 2007: p.71–96.
20. Squires RH. Acute liver failure in children. Seminars in Liver disease June 2008; doi:10.1055/9-2008-10/3115.

21. Lehmberg K, Ehl S. Diagnostic evaluation of patients with suspected haemophagocytic lympho-histiocytosis, Br J Haematol. 2013;160:275-87.
22. Ozçay F, Karadag-Oncel F, Baris S, Canan O, Moray G, Haberal M. Etiologies, outcomes, and prognostic factors of pediatric acute liver failure: A single center's experience in Turkey. Turk J Gastroenterol. 2016;27:450-7.
23. Bravo LC, Gregorio GV, Shafi F, Bock HL, Boudville I, Liu Y, et al. Etiology, incidence and outcomes of acute hepatic failure in 0–18 year old Filipino children. Southeast Asian J Trop Med Public Health. 2012;43(3):764-72.
24. Kaur S, Kumar P, Kumar V, Sarin SK, Kumar A. Etiology and prognostic factors of acute liver failure in children. Indian Pediatr. 2013;50(7):677-9.
25. Poddar B, Saigal S, Kumar A, Singh RK, Azim A, Gurjar M, et al. Factors associated with outcome in acute liver failure in an intensive care unit. Indian J Gastroenterol. 2013;32(3):172-8.

Cite this article as: Wani K, Wani JN, Zaman BU, Mir NY. Clinico-etiological profile of acute liver failure in children in a tertiary care hospital of northernmost India. Int J Contemp Pediatr 2024;11:794-9.