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Aetiologies and Outcomes of Acute Liver Failure in Children at a Tertiary Care Hospital in Rawalpindi

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ABSTRACT

Objective: To determine the different aetiologies and outcomes of acute liver failure in children at a tertiary care hospital in Rawalpindi.

Study Design: Cross sectional study.

Place and Duration of Study: Department of Pediatrics, Pak Emirates Military Hospital Rawalpindi, Pakistan from Aug 2020 to Sep 2021.

Methodology: One hundred and twenty-four patients who visited the Department of Pediatrics, and following the exclusion and inclusion criteria were included. Mean and standard deviations were assessed for quantitative variables including age. Percentages and frequencies were computed for qualitative variables.

Results: Out of 124 children, there were 98(79.03%) males and 26(20.97%) females, with a mean age of 5.58±3.63 years. The most common aetiologies were Hepatitis A (n=50, 40.32%) and septicemia (n=16, 12.9%). Eighty-four (68%) had acute presentation (7 to 28 days) while jaundice was observed in 104(84%) patients. There were 32(25.81%) deaths. The mean ALT levels were 1220±1165.52 U/L, mean PT levels were 29.98±9.30 seconds, mean INR levels were 2.8±0.9, mean total bilirubin levels were 22.86±16.11 mg/dl, and mean indirect bilirubin levels were 5.30±4.46 mg/dl. There were 32(25.81%) patients who died, and 92(74.10%) patients who had survived on supportive care.

Conclusion: Our study shows that infective aetiologies are the predominant causes of acute liver failure among Pakistani children.

Keywords: Acute Liver Failure, Bilirubin Levels, Hepatitis A, Septicaemia.

How to Cite This Article: *Babar MW Malik QU, Ikram F, Rehman A, Bashir J, Ghaffor M . Aetiologies and Outcomes of Acute Liver Failure in Children at a Tertiary Care Hospital in Rawalpindi. Pak Armed Forces Med J 2026; 76(3): 298-302. DOI: https://doi.org/10.51253/pafmj.v76i3.7993*

INTRODUCTION

Acute hepatic failure (AHF) refers to an illness which can be life-threatening and is essentially characterized by speedy progression from disturbed function of the liver to a state of coagulopathy and finally resulting in encephalopathy. It is a syndrome in which healthy children liver function is impaired quickly and they become severely ill within a matter of days.[1,2] There is no single etiology, rather there is a diverse array of reasons and causes for AHF including geographical location and the age of the patient among other causes.[3]

Causes of AHF among the pediatric population from North America and Europe include metabolic, infectious, drug-related and cardiovascular reasons.[4] The problem is with the definition of AHF, as most pediatric researches have used the adult classification of AHF.[5] Adult classification tends to rely on the manifestation of hepatic encephalopathy (HE) which occurs within a period of eight weeks after the development of jaundice among the patients. However, HE is rather challenging to assess among infants and children and may not be an essential symptom for the purpose of diagnosis of AHF among children.[6] The AHF prognosis is rather not promising for patients who have suffered from accidental overdose of acetaminophen, for infants who are less than one year old, and patients who are suffering from Wilson's disease and presenting with hepatic encephalopathy.[7,8] Transplantation is usually the only solution, with which only 15% to 20% patients survive.[9,10] Transplantation poses its own challenges, including a dearth of liver donors.[10] Therefore it is crucial that we develop a reliable prognostic score that assists in assigning donor organs to the patients who are ethically the most deserving.

We conducted this study to determine the different aetiologies and outcomes of acute liver failure in children at a tertiary care hospital in Rawalpindi.

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Received: 07 Jan 2022; revision received: 06 Apr 2022; accepted: 08 Apr 2022

METHODOLOGY

This prospective observational study was conducted in the Department of Paediatrics Pak Emirates Military Hospital Rawalpindi, Pakistan, between August 2020 and September 2021. The process of data collection from study respondents was started after obtaining due approval from the Institutional Ethical Review Committee (vide letter number A/28/EC/339/2021).

Inclusion Criteria: Patients of either gender, aged 5 months to 12 years of age with international normalized ratios (INR) of 1.5 or more, prothrombin values of 40% or less, who had a biochemical liver injury without any known co-existing chronic liver disease, those who had a coagulopathy which was not corrected by vitamin K were included

Exclusion Criteria: Patients whose duration of liver related illness was more than 8 weeks were excluded.

Sample size was calculated using the WHO calculator taking Hepatitis A frequency to be 40.32%, which was estimated to be 124.[11] Non-probability convenience sampling was used to enroll children. Informed consent was obtained from the parents. Data was collected on a prevalidated questionnaire for age, sex, residence, liver function tests, for instance alanine aminotransferase, direct bilirubin, total bilirubin, prothrombin time, and INR. Blood culture reports were observed and septic workup was assessed for every subject. Clinical signs and symptoms were noted, grade of encephalopathy was observed, time duration between the appearance of symptoms to the development of encephalopathy and we also took its etiology into consideration. Patient's outcome in terms of survival and/or death was documented from medical records.

Data were analyzed by statistical package for social sciences (SPSS) version 21. Mean and standard deviations were assessed for covariates which were quantitative, like age. Percentages and frequencies were computed for the covariates, which were categorical.

RESULTS

One hundred and twenty-four children who were included in this study. Among them there were 98(79.03%) males and 26(20.97%) females with a mean age of 5.58±3.63 years. Ninety (72.58%) patients lived in urban areas (Table-I). The most common aetiologies were Hepatitis A (n=50, 40.32%), followed by septicemia (n=16, 12.9%) who had septicaemia (Figure). There was a preponderance (n=84, 68%) of acute presentation (7 to 28 days), and jaundice 104(84%) was observed to be the prevalent symptom. There were 32(25.81%) deaths. The mean ALT levels were 1220±1165.52 U/L, mean PT levels were 29.98±9.3 seconds, mean INR levels were 2.8±0.9, mean total bilirubin levels were 22.86±16.11 mg/dl, and mean indirect bilirubin levels were 5.30±4.46 mg/dl. Thirty-two (25.81%) patients from our cohort died, and 92(74.10%) patients survived on supportive care (Table-II).

Table-I: Characteristics of Patients of Acute Liver Failure (n=124)

Variables		Values
Age in years (Mean± SD)	5.58±3.62	
Gender	Males	98(79.03%)
	Females	26(20.97%)
Residence	Rural	34(27.42%)
	Urban	90(72.58%)

Table-II: Aetiologies and Outcomes among Patients of Acute Liver Failure (n=124)

Variables		Values
Septicaemia	No	108(87.10%)
	Yes	16(12.90%)
Hepatitis A	No	74(59.68%)
	Yes	50(40.32%)
ALT (U/L)	Mean±SD	1220.629±1165.52
PT (seconds)	Mean±SD	29.98±9.33
INR	Mean±SD	2.803±0.90
Total Bilirubin (mg/dl)	Mean±SD	22.858±16.11
Indirect Bilirubin (mg/dl)	Mean±SD	5.30±4.46
Mortality	No	92(74.19%)
	Yes	32(25.81%)

**ALT: Alanine Aminotransferase, PT: Prothrombin Time, INR: International Normalized Ratio*

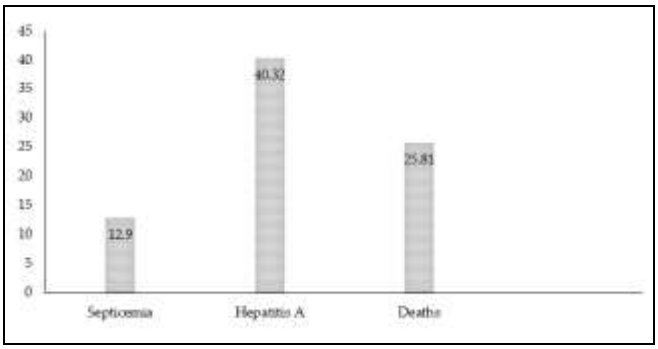

Figure: Percentage Distribution of Aetiologies and Outcomes (n=124)

DISCUSSION

Acute hepatic failure is a life-threatening illness among children in Pakistan. Our research shows

that there can be diverse causes of acute hepatic failure. Similar findings have been noted in prior studies.[12,13] Patients with hepatitis A, should be watched more carefully for acute liver failure (ALF). Some studies suggest that patients should be observed with other aetiologies, such as Wilson's disease or a co-infection with typhoid.[11-13] There are not that many studies conducted in Pakistan that demonstrate the importance of hepatitis A as an important cause for acute liver failure among children. Our population had shown that most patients were from the urban area. This differs across various studies, and some findings are in contrast with our own.[11,12] However, we are unable to comment whether this disparity between rural and urban proportion was due to accessibility or was it a real difference. Due to importance of the study topic, this is something which must be explored in further researches.

Hepatic encephalopathy is rather challenging to assess among children and, it might never be detected clinically in the setting of acute liver failure. Nevertheless, encephalopathy has been noted to be a risk factor by itself for mortality.[14] Hence, in our study we had excluded those children who had hepatic encephalopathy. One study had essentially described that the definition of pediatric acute liver failure does not need hepatic encephalopathy.[2]

An indeterminate cause of acute liver failure (ALF) was assigned to 61(49.19%) of the subjects in our study. Causes that might affect and hence determine the strength of the analytical appraisal among the paediatric population with ALF comprise of prioritising of the list of possible aetiologies, and note the swift progression of illness to the stage of liver transplant or mortality. The group labelled indeterminate might have comprised of patients who were not evaluated well for recognized causes of ALF, or perhaps even those who had immune, metabolic, autoimmune, or genetic disorders. This has been suggested by another study which was conducted in Thailand.[15] Literature has evidence about Epstein Barr virus and Herpes simplex virus, and has shown that the most usual recognizable infections among children.[15]

One study showed that acute viral hepatitis A was about 30% among its population of children.[16] However, in our study the frequency of hepatitis was slightly higher at 40.32%. This could be because our hospital caters to a wide endemic population, and we tend to see more severely ill patients. Another reason for this disparity could be that in the mentioned study, they had further stratified their data, distributing the causes across a variety of aetiologies. For instance, in their research they had explored co-infection of Hepatitis A and Wilson disease which was observed among 2(7%) children and then they noted a co-infection of hepatitis A with typhoid fever that was observed in 1(3%) patient.[16] If we would had stratified our results then perhaps our proportion of patients may have been comparable.

Hepatitis E is described as the chief aetiology among the adult population of India.[17] Amongst the additional infective aetiologies, Talat *et al.,* had observed 2(7%) children with septicemia, and one of these children (3%) was affected with salmonella sepsis with an organism that was ceftriaxone resistant.[1] We did not stratify data according to septicaemia data our study, therefore we do not know the distribution within this category.

In our study, the mean prothrombin time (PT) levels were noted to be 29.98±9.3 seconds, mean International Normalized Ratio (INR) levels were observed at 2.8±0.9. These values were comparable with the values observed in another study from Pakistan.[1] Though evidence suggests that PT-INR tends to offer reliable measurement of liver function, recent trends demonstrate that there is inter-laboratory INR variance.[18]

The etiology of acute liver failure is a significant consideration for management and prognosis. It has been noted that primary reasons of acute liver failure are diverse in every region of the globe.[17,18] Our study found that majority of the cases of acute liver among children are due to infective causes.

Consequently, enhancement in the diagnostic ability would need a rather determined search for causes which are treatable, one that highlights diagnostic illnesses, which are known to cause acute liver failure. It is needed that novel techniques are applied to recognize children who have an underlying metabolic disease, immune dysregulation, acetaminophen toxicity, and thus would enable us to diagnose critically ill children in a more efficient manner.

Based on the findings of this study, we can suggest some important recommendations for the future research. First of all, because this research was conducted in only one tertiary care hospital, it is

highly recommended to carry out multi-center longitudinal studies. This will give a clearer, more accurate picture of acute liver failure in children across the whole Pakistan. Furthermore, since Hepatitis A and septicemia were found as the major causes, future studies should evaluate how the public health interventions and early vaccination programs can help to reduce the burden of these preventable infections. Also, observing the high mortality rate of 25.81% in our patients, it is very necessary to research better intensive care management and the feasibility of pediatric liver transplantation in our local medical centers. Finally, further investigations are advised to identify the rare genetic or metabolic diseases in those children where the infective causes are not present, which can help us to improve the overall survival outcomes.

LIMITATION OF STUDY

We did not collect data on variables such as socioeconomic factors. In addition, this was a single center study, on a relatively small sample size. This limits the generalizability of our study findings. Furthermore, we did not conduct follow-up of our study participants, due to which we could not monitor long-term effects of acute liver failure. Hence, further longitudinal studies should be done to observe any long-term effects of the illness in the diseased population.

CONCLUSION

Our study shows that infective aetiologies are the predominant causes of acute liver failure among Pakistani children, and that the mortality rate was not very high when supportive care was provided to these patients.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MWB & QUM: Data acquisition, data analysis, critical review, approval of the final version to be published.

FI & AR: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

JB & MG: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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