

## Original Research Article

DOI: <http://dx.doi.org/10.18203/2394-6040.ijcmph20191398>

# Etiological profile and clinical characteristics in fulminant hepatic failure in North India

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**Received:** 28 January 2019

**Accepted:** 02 March 2019

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## ABSTRACT

**Background:** Acute liver failure (ALF) is a rare but severe, life-threatening, multisystemic medical emergency. ALF of duration <8 weeks in a patient is considered as fulminant hepatic failure (FHF). Its rapid progression and high mortality demand early diagnosis and expert management. Clinical and etiological profile varies with geographical area and time. The objective of this prospective study was to determine the clinical characteristics and etiological profile of FHF.

**Methods:** A total of eighty consecutive patients with a diagnosis of FHF were included in the study. The variables evaluated were demographic, signs and symptoms, biochemical parameters (bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), internal normalization ratio (INR) etc.) and etiological profile.

**Results:** Most of the patients were <35 years of age and males. Viral hepatitis 35 (43.8%) was the most common cause of FHF but the majority of the patients 25 (31.2%) had undetermined etiology. Among viral causes, acute hepatitis E was most common followed by hepatitis B and A. Drug or toxic induced liver failure (18.8%) also contributed a significant proportion of cases. The three groups (viral, drug-induced and indeterminate) were comparable for the various baseline characteristics (bilirubin, alanine aminotransferase, INR, creatinine, albumin, grade of encephalopathy, MELD score etc.).

**Conclusions:** Like the rest of India, viral hepatitis was the common cause of FHF but the majority of the patients 25 (31.2%) had undetermined etiology. Our study highlights the differences in the profile of FHF from other earlier studies in India and the west. Each different etiology leads to a similar final common pathway. Trying to determine etiology is essential, however, as outcomes and the use of antidotes depend on the identification of the causative process.

**Keywords:** Acute liver failure, Fulminant hepatic failure, Viral hepatitis, Hepatitis E virus, Drug-induced liver failure

## INTRODUCTION

Acute liver failure (ALF) is a rare but severe, life-threatening, complex, multisystemic medical emergency, in which the rapid deterioration of liver function results in coagulopathy and alteration in the mental status of an individual who previously had normal liver. As a result of

a cataclysmic insult to the liver, previously healthy individuals become deathly ill in a very short period of time.

ALF often affects young people and carries a very high mortality and resource cost. Reports from the developed world suggest an overall incidence of 1-6 cases per

million people every year, although rates are probably high in locations where infective hepatitis is common and medical therapies that interrupt progression of hepatic injury and development of extrahepatic organ dysfunction are not readily available.<sup>1-3</sup> While ALF is a rare event, with an incidence of approximately 2500 cases yearly in the US, yet it accounts for up to 7% of all liver-related deaths and is responsible for 6% of liver transplants.<sup>4,5</sup>

The term acute liver failure is used to describe the development of coagulopathy, usually with an international normalized ratio (INR) of greater than 1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of less than 26 weeks duration.<sup>6</sup> Encephalopathy may vary from only subtle changes in affect, insomnia, and difficulties with concentration (stage 1) to deep coma (stage 4) by West Haven Grading System for hepatic encephalopathy.<sup>7</sup>

O'Grady et al classified ALF into hyperacute, acute, and subacute liver failure on the basis of encephalopathy less than 7, 8–28, and more than 28 days but less than 26 weeks, respectively, from the onset of jaundice.<sup>8,9</sup> Hyperacute and acute ALF have a better prognosis in terms of survival than subacute liver failure.

ALF is a broad term that encompasses both fulminant hepatic failure (FHF) and subfulminant hepatic failure (or late-onset hepatic failure). FHF is generally used to describe the development of encephalopathy within 8 weeks of the onset of symptoms in a patient with a previously healthy liver.<sup>8</sup>

The most important step in the assessment of patients with FHF is to identify the cause. Identifying the underlying etiology of FHF is the most robust prognostic indicator and allows for the implementation of targeted therapies and antidotes, when available. The majority of cases of ALF are young (median age 38 years) and female (73%).<sup>10</sup> FHF, a multisystemic disorder is having multifactorial etiology. The main etiological factor includes:

Viral, which mostly include hepatotropic (HBV, HAV, HEV, HCV, HDV, HGV) and non-hepatotropic (CMV, HSV, EBV etc.). Viral hepatitis is the commonest cause of ALF world-wide and in the Indian subcontinent alone it accounts for 90% of cases.<sup>11</sup> All primary hepatotropic viruses can cause ALF with a different incidence in different countries.<sup>12,13</sup> In developing world Hepatitis B (HBV) predominates as a cause, because of high prevalence of disease, but in India, Pakistan, China and Southeast Asia, Hepatitis E (HEV) is now the most common cause of acute liver failure. Approximately 2.2 million adult cases of HEV hepatitis are believed to occur in India annually. Major epidemics in Indian cities, include Delhi, Ahmedabad, Kolhapur, and some cities in the Kashmir Valley.<sup>14</sup>

Drug related hepatotoxicity accounts for more than 50% of acute liver failure cases, including acetaminophen toxicity (42%) and idiosyncratic drug reactions (12%) in the USA. The drugs responsible vary by location and prevailing drug use, with anti-infectives, anticonvulsants, antituberculosis and anti-inflammatory drugs most commonly implicated; herbal or adulterated traditional or complementary medications are also a notable cause in east Asia.<sup>15,16</sup> Liver damage induced by drugs other than paracetamol has been the most frequent cause of safety-related marketing withdrawals in the past 50 years.<sup>17</sup> Fewer than 10% of drug-induced liver injuries (DILI) progress to ALF.<sup>18-20</sup> However, up to 80% of patients who develop liver failure might die or require transplantation.<sup>16,18</sup>

Other causes include

- Autoimmune hepatitis
- *Toxin- Amanita phalloides* mushroom toxin.
- *Vascular causes-* ischemic hepatitis, hepatic vein thrombosis (Budd-Chiari syndrome), hepatic veno-occlusive disease, portal vein thrombosis, hepatic arterial thrombosis.
- *Metabolic causes-* Alpha1-antitrypsin deficiency, fructose intolerance, galactosemia, lecithin-cholesterol acyltransferase deficiency, reye syndrome, tyrosinemia, Wilson disease.
- *Malignancies-* Primary liver tumor (usually hepatocellular carcinoma, rarely cholangiocarcinoma), secondary tumor (extensive hepatic metastases or infiltration from adenocarcinoma, such as breast, lung, melanoma primaries [common]; lymphoma; leukemia).<sup>21</sup>
- *Indeterminate-* Causation cannot be established in many cases; such seronegative or indeterminate liver failures happens worldwide, and are associated with especially poor survival with medical therapy alone, and frequently need emergency transplantation.<sup>22,23</sup>

Mortality in ALF is usually due to cerebral edema, multiorgan dysfunction syndrome, and sepsis. The management of patients with ALF requires a thorough infrastructure and understanding to deal with the complications.<sup>24</sup> Orthotopic liver transplantation (OLT) has now become an established treatment option in patients with ALF and is becoming increasingly available in developing countries including India. ALF has geographical differences in terms of etiology and outcome as a result of different environment and host (genetic) factors.

The present study was carried out to determine the clinical and etiological profile of FHF in a large cohort of patients with ALF in Kashmir (India), an endemic zone of HEV.

## METHODS

It was a hospital based prospective study of adult patients with ALF. This study was carried out in the Department of Gastroenterology of Sher-I-Kashmir Institute of Medical Science (SKIMS), Soura, J&K. The study was approved by the institutional ethical committee (SKIMS).

### Study subjects

Overall 80 consecutive patients with diagnoses of FHF who fulfilled eligibility criteria were recruited in the study. This study was conducted over a period of three years from 2011 to 2014. Information regarding various demographics characteristics was taken through well structured questionnaires from all subjects. Besides a detailed history, physical examination and biochemical workup which included baseline investigations, liver function test (LFT), coagulogram of subjects was carried out. Informed consent was obtained from all the recruited subjects.

### Eligibility criteria

Inclusion criteria include patients having age  $>18$  years and FHF was defined as biochemical evidence of acute liver injury with INR  $\geq 1.5$  and any degree of encephalopathy caused by the illness of duration  $<8$  weeks in a patient with no prior known liver disease (Fulminant hepatic failure).

Exclusion criteria include acute on chronic liver failure, ALF due to pregnancy

### Detailed study design

After FHF was diagnosed, blood samples of all the patients were taken for the etiological diagnosis, which included hepatitis B surface antigen (HBsAg), hepatitis B core IgM (HBc-IgM), hepatitis A virus IgM (HAV-IgM), and hepatitis E virus IgM (HEV-IgM), hepatitis D virus (IgG and IgM anti-HDV), anti HCV (hepatitis C virus), ANA (anti-nuclear antibody), ASMA (anti smooth muscle antibody), Wilson profile (serum ceruloplasmin, serum copper) and iron profile. HSV (herpes simplex virus), CMV (cytomegalovirus) and EBV (Epstein barr virus) serology were done if non hepatotropic viruses were suspected as a cause of ALF. A detailed history was taken for any hepatotoxic drug intake, including homeopathic, herbal medications and intravenous drug abuse. Indeterminate cause was diagnosed in a patient with: (i) clinical and biochemical features of FHF, (ii) absence of acute viral markers of known hepatitis viruses (A-E), (iii) no exposure to drugs, hepatotoxins, systemic infections, biliary obstruction/infection and metabolic liver diseases. All the ethical considerations were taken care of during the study. Patients were given the option of liver transplant (to be done at the hospital with transplantation facility) at various stages of study when indicated.

### Supportive treatment

All patients were managed with the standard supportive care treatment. The patients received treatment of and prevention for the complications of ALF.<sup>25</sup> The treatment mainly involved continuous intravenous dextrose to prevent hypoglycemia; broad-spectrum prophylactic antimicrobials.<sup>25</sup> Proton pump inhibitors for stress-related ulcers and lactulose enema. With the development of advanced hepatic encephalopathy, intensive care management, fluid and electrolyte balance, midazolam sedation and mannitol infusion in case of raised intracranial pressure. Intracranial hypertension was diagnosed clinically in the presence of clinical signs such as abnormal pupillary reflexes, hypertonia or decerebrate posturing. Fresh frozen plasma was given in only those patients who had a spontaneous bleed. Blood and urine cultures were obtained in suspected cases of sepsis, which were then treated as per sensitivity. Response to treatment was monitored clinically (Grade of encephalopathy) and biochemically (bilirubin, PT, INR etc.).

### Statistical analyses

Frequency distribution was assessed in terms of means $\pm$ SD for quantitative variables and number (percentages) for categorical variables. In univariate analysis, the categorical variables were compared by using  $\chi^2$  test or Fisher exact test where appropriate. For continuous variables, the independent sample t-test was used. P $<0.05$  was considered statistically significant. All the analyses were performed by the Statistical Package for Social Sciences (SPSS; 2004).

## RESULTS

There were 80 patients of FHF in total. Table 1 demonstrates the etiologies of FHF. Viral hepatitis 35 (43.8%) was the most common cause of FHF. Majority of the patients 25 (31.2%) had undetermined etiology. Among viral causes Acute HEV-induced FHF (22.5%) was most common followed by hepatitis B and A. Drug or toxic induced liver failure (18.8%) also contributed significant proportion of cases (12 patients had Anti-tuberculosis therapy (ATT) induced FHF and 3 patients had ayurvedic induced FHF). HBV- induced ALF (11.2%) and HAV-induced FHF (10%). Other etiology included FHF due to Wilson (2 patients) and one patient each of Autoimmune, CMV (cytomegalovirus), and HSV (Herpes simplex virus).

Table 2 shows the distribution of baseline characteristics (both categorical and continuous) of three major groups of FHF. All the patients were of Kashmiri ethnicity. Majority of the patients were male (51.2%). About 62.8% and 56% were males in viral hepatitis and indeterminate cause of FHF, respectively. The mean age FHF patients were  $39.48\pm20.11$  years. Coma grade at the time of

admission showed that majority (38.8%) of patients (study group) had grade I encephalopathy. There were 42.8%, 46.7% and 24% Grade I encephalopathy patients in viral hepatitis, drug-induced and indeterminate cause of FHF, respectively. The three groups did not differ significantly with respect to, vomiting, MELD Score, interval between jaundice and encephalopathy and biochemical measures of liver injury (INR, Bilirubin, AST, ALT, and albumin). Mean MELD score in FHF patients was  $31.83 \pm 6.74$ .

**Table 1: Etiology of FHF (n=80).**

Etiology	N (%)
Acute hepatitis E	18 (22.5)
Acute hepatitis A	8 (10)
Acute hepatitis B	9 (11.2)
Drug-induced ALF	15 (18.8)
Undetermined etiology	25 (31.2)
Others*	5 (6.25)

\*Two patient of Wilson induced ALF. One patient each of autoimmune, CMV, and HSV.

**Table 2: Baseline characteristics of study subjects.**

Characteristics	ALF (n=80)	Hepatitis virus (n=35)	Drug-induced ALF (n=15)	Indeterminate (n=25)
<b>Categorical variables [N (%)]</b>				
Male gender	41 (51.2)	22 (62.8)	4 (26.7)	14 (56)
<b>Hepatic- encephalopathy</b>				
Grade I	31 (38.7)	15 (42.8)	7 (46.7)	6 (24)
Grade II	21 (26.2)	9 (25.7)	3 (20)	9 (36)
Grade III	14 (17.5)	7 (20)	2 (13.3)	4 (16)
Grade IV	14 (17.5)	4 (11.4)	3 (20)	6 (24)
Fever	29 (36.2)	13 (37.1)	6 (40)	10 (40)
Vomiting	22 (27.5)	8 (22.8)	4 (26.7)	10 (40)
<b>Continuous variables (mean<math>\pm</math>SD)</b>				
Age (years)	39.48 $\pm$ 20.11	35.50 $\pm$ 11.64	38.60 $\pm$ 13.60	36.60 $\pm$ 16.04
INR	2.87 $\pm$ 1.89	2.21 $\pm$ 0.78	2.57 $\pm$ 1.39	2.67 $\pm$ 1.16
Bilirubin (mg/dl)	21.12 $\pm$ 10.94	18.12 $\pm$ 8.94	20.72 $\pm$ 8.60	19.56 $\pm$ 9.34
AST (mg/dl)	1726 $\pm$ 983.40	1576 $\pm$ 784	1520 $\pm$ 834.60	1675 $\pm$ 943.66
ALT (mg/dl)	1050.78 $\pm$ 717.46	1010.56 $\pm$ 678.76	990.62 $\pm$ 666.40	987.88 $\pm$ 710.46
Albumin (g/dl)	2.96 $\pm$ 0.75	2.63 $\pm$ 0.65	2.13 $\pm$ 0.42	2.43 $\pm$ 0.67
Creatinine (mg/dl)	1.45 $\pm$ 0.81	1.31 $\pm$ 0.57	1.23 $\pm$ 0.70	1.35 $\pm$ 0.78
Interval between jaundice and encephalopathy (days)	36 $\pm$ 11.40	32 $\pm$ 15.80	28 $\pm$ 18.30	24 $\pm$ 13.90
MELD Score	31.83 $\pm$ 6.74	29.60 $\pm$ 6.54	27.45 $\pm$ 5.85	30.13 $\pm$ 5.94

N= Number; SD= Standard deviation; \*Two patient of Wilson induced ALF. One patient each of autoimmune, CMV, and HSV.

## DISCUSSION

FHF is a rare but dramatic and challenging syndrome with rapid progression and high mortality necessitates early diagnosis and expert management. OLT has now become an established treatment option in patients with ALF. Due lack of OLT facility N-acetylcysteine (NAC) has emerged as a beneficial treatment for ALF.<sup>26</sup> Clinical and etiological profile varies with geographical area and time.<sup>27</sup> Each different etiology leads to a similar final common pathway. Trying to determine etiology is essential, however, as outcomes and the use of antidotes depend on the identification of the causative process. So the prospective study was carried out to determine the clinical and etiological profile of FHF in a large cohort of patients of Kashmir (India)

Most of the patients in our study were  $<35$  years of age and males (51.2%) which is similar to the study was Das et al and Acharya et al.<sup>11,28</sup> FHF in all the patients in our

study was etiologically associated with either known or putative hepatitis viruses. FHF can result from diverse etiological agents. The most common cause of ALF in the United Kingdom is related to acetaminophen toxicity in association with suicidal episodes.<sup>8,29</sup> None of our patients had FHF caused by acetaminophen. This may be related to very low suicidal rates or practice of using alternative agents for suicidal intents in this community.

HEV was etiologically associated with FHF in 18 (22.5%) patients. HEV is endemic in Kashmir, India and is the most common cause of acute viral hepatitis in this and other endemic regions of the world.<sup>14,30,31</sup> HAV constituted 8 (10%) FHF cases in the present study. HAV is a ubiquitous agent in developing countries, is highly pathogenic and spreads through person-to-person transmission. Although HAV is a common cause of ALF in children than adults.<sup>32</sup> HCV is a very rare cause of ALF in Europe and the US, although a number of studies

from Japan and India have found evidence of HCV, although no patient of HCV related FHF was found.<sup>33,34</sup>

Alcohol acetaminophen syndrome is emerging as another important cause of ALF in US.<sup>35</sup> but alcohol consumption does not occur in this population because of religious reasons so acetaminophen-alcohol syndrome is not expected to occur in this community. A wide variety of drugs either alone or in combination result in FHF and is a common cause of ALF in the West.<sup>36</sup> The most important of these agents include acetaminophen toxicity (42%) and idiosyncratic drug reactions (12%) with anti-infectives, anticonvulsants, antituberculosis and anti-inflammatory drugs. The frequent use of ATT for tuberculosis has increased the frequency of ATT induced FHF. 12 (15%) patients had ATT induced FHF Ayurvedic or herbal treatment being the treatments of choice for various disorders prescribed by quacks. 3 (3.7%) patients had ayurvedic induced FHF in our study while other studies from East Asia revealed a higher percentage.<sup>15,16</sup>

31.2% patients in the present study lacked acute markers of known hepatitis viruses and were classified as indeterminate. Similar percentage of indeterminate cause of FHF was shown by Khuroo et al while western studies reported less percentage.<sup>10,14</sup> Whether some of these patients were related to exposure to some unidentified herbal agents or toxins could not be ascertained with certainty.<sup>37</sup> The increase in undetermined etiology from western could be because of unexpected acetaminophen toxicity, a novel or unrecognized virus, metabolic or xenobiotic injury.<sup>38</sup> Also, undiagnosed immune dysregulation may result in ALF.<sup>39</sup>

Metabolic, vascular liver diseases and a number of miscellaneous liver diseases cause a small number of the remaining cases.<sup>40</sup> Some of these causes contributed to ALF in our study (two patient of Wilson induced FHF. One patient each of autoimmune, CMV, and HSV).

## CONCLUSION

In conclusion, the current study like rest of India has viral hepatitis as a common cause of FHF but the majority of the patients 25 (31.2%) had undetermined etiology despite geographically defined region endemic for HEV. Trying to determine etiology is essential, however, as outcomes and the use of antidotes depend on the identification of the causative process. Our study highlights the differences in the profile of FHF from other earlier studies in India and west, possibly due to novel or unrecognized virus, metabolic or xenobiotic injury and undiagnosed immune dysregulation.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Nabi T, Rafiq N, Arifa QA. Etiological profile and clinical characteristics in fulminant hepatic failure in North India. *Int J Community Med Public Health* 2019;6:1639-44.