Original Research Article

Comparative study of etiological profile and outcome in acute liver failure

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ABSTRACT

Background: Acute liver failure (ALF) is a clinical syndrome that is marked by the sudden loss of hepatic function in a person without chronic liver disease. Clinical and etiological profile varies with geographical area and over time. The objective of this prospective study was to determine the etiological profile and outcome of ALF and to compare it with other major studies from India and US.

Methods: A total of 84 consecutive patients with a diagnosis of ALF were included in the study. The variables evaluated were demographic, signs and symptoms, biochemical parameters, etiological profile and outcome.

Results: Viral hepatitis 32 (38.1%) was the most common cause of ALF but large number of the patients 30 (35.7%) had indeterminate aetiology. Among viral causes, acute hepatitis E (19.1%) was most common followed by hepatitis B (9.5%) and A (9.5%). Drug or toxic induced liver failure (17.8%) also contributed a significant proportion. Majority of the patients were male (51.9%) and the mean age was 39.48±20.11 years. Aetiology varied with other geographical area and even over time in the same area. Overall mortality was 44 (57.1%) in ALF patients, with highest mortality in indeterminate group (60%).

Conclusions: Like the rest of India, viral hepatitis was the common cause of ALF but a large number of patients 30 (35.7%) had indeterminate aetiology. Overall mortality was 57.1%. Our study highlights the differences in the profile of ALF from other earlier studies in India and the west.

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

INTRODUCTION

ALF is a syndrome characterized by the development of hepatic encephalopathy (HE) and coagulation disorders, in patients without previous liver disease. It is one of the rare gastrointestinal emergencies encountered in clinical practice. ALF often affects young people and carries a very high mortality and resource cost. Reports from the developed world suggest an overall incidence of 1-8 cases per million people every year, although rates are probably high in locations where infective hepatitis is common.¹-⁵ While ALF is a rare event, with an incidence of approximately 2000-3000 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.⁶-⁷

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.⁸ 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.\textsuperscript{7}

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.\textsuperscript{8,9} Hyperacute and acute ALF have better prognosis in terms of survival than subacute liver failure.

The most important step in the management of patients with ALF is to identify the cause. The majority of cases of ALF are young (median age 38 years) and female (73%).\textsuperscript{10} ALF, a multisystemic disorder is having multifactorial etiology. Etiology of ALF is diverse and shows wide geographical variation. 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.\textsuperscript{11} All primary hepatotropic viruses can cause ALF with a different incidence in different countries.\textsuperscript{12,13} Hepatitis E (HEV) is the most common cause of ALF in Southeast Asia including India, Pakistan and China.\textsuperscript{14}

Drug-related hepatotoxicity accounts for more than 50% of ALF 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.\textsuperscript{15,16} Liver damage induced by drugs other than paracetamol has been the most frequent cause of safety-related marketing withdrawals in the past 50 years.\textsuperscript{17} Fewer than 10% of drug-induced liver injuries (DILI) progress to ALF.\textsuperscript{18,20} However, up to 80% of patients who develop ALF might die or require transplantation.\textsuperscript{16,18}

Other causes include Autoimmune hepatitis; toxin-amanita phalloides mushroom toxin; vascular causess-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 acyl-transferase deficiency, Reye syndrome, tyrosinemia, Wilson disease; malignancies-primary liver tumor (usually hepatocellular carcinoma) or secondary tumor (from breast, lung, melanoma), lymphoma, leukemia and Indeterminate—where causation cannot be established; such seronegative or indeterminate liver failures happens worldwide, and are associated with especially poor survival with medical therapy alone, and frequently need emergency transplantation.\textsuperscript{21,23}

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.\textsuperscript{24} Orthotropic liver transplantation (OLT) is an established treatment option in patients with ALF who do not improve with supportive care. 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 etiological profile and outcome of ALF in Kashmir (North India), an endemic zone of HEV and to compare it with other studies from India and US.

**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 and K. The study was approved by the institutional ethical committee. Informed consent was obtained from all the recruited subjects or their next-of-kin.

**Study subjects**

Overall 84 consecutive patients with diagnoses of ALF who fulfilled eligibility criteria were recruited in the study. This study was conducted over a period of three years from May 2011 to June 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.

**Eligibility criteria**

Patients included were age >18 years and ALF was defined as biochemical evidence of acute liver injury with INR ≥1.5 and any degree of encephalopathy caused by the illness of duration <26 weeks in a patient with no prior known liver disease.\textsuperscript{6} Exclusion criteria include acute on chronic liver failure.

**Detailed study design**

After ALF 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. Imaging was obtained.
to rule out biliary processes, hepatic vascular abnormalities, and intrahepatic lesions. 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 ALF, (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.25 The treatment mainly involved continuous intravenous dextrose to prevent hypoglycaemia; broad-spectrum prophylactic antimicrobials; 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±SD for quantitative variables and number (percentages) for categorical variables. All the analyses were performed by the statistical package for social sciences (SPSS, Chicago, IL, USA, version 21.0).

RESULTS

There were 84 patients of ALF in total. Table 1 demonstrates the etiologies of ALF. Viral hepatitis 32 (38.1%) was the most common cause of ALF. Majority of the patients 30 (35.7%) had indeterminate etiology. Among viral causes acute HEV-induced ALF (19.1%) was most common followed by hepatitis B and A. Drug or toxic induced liver failure (17.8%) also contributed significant proportion of cases (12 patients had Anti-tuberculosis therapy (ATT) induced ALF and 3 patients had ayurvedic induced ALF), HBV- induced ALF (9.8%) and HAV-induced ALF (9.5%). Other aetiology included ALF due to Wilson (2.4%), autoimmune hepatitis (2.4%), ALF in pregnancy (1.2%), CMV (cytomegalovirus), and HSV (herpes simplex virus).

| Aetiology                 | Total N (%) |
|---------------------------|-------------|
| Acute hepatitis E         | 16 (19.1)   |
| Acute hepatitis A         | 8 (9.5)     |
| Acute hepatitis B         | 8 (9.5)     |
| Drug-induced ALF          | 15 (17.8)   |
| Autoimmune hepatitis      | 2 (2.4)     |
| Wilson disease            | 2 (2.4)     |
| ALF in pregnancy          | 1 (1.2)     |
| Indeterminate aetiology   | 30 (35.7)   |
| Others*                   | 2 (2.4)     |

*One patient each of CMV and HSV.

Table 2 shows the distribution of baseline characteristics (both categorical and continuous) of three major groups of ALF. All the patients were of Kashmiri ethnicity. Majority of the patients were male (51.9%) and the mean age was 39.5±20.1 years. About 59.4%, 26.7% and 56.7% were males in viral hepatitis, drug and indeterminate cause of ALF, respectively. Coma grade at the time of admission showed that majority (58.4%) of patients had grade I-II encephalopathy. In indeterminate group majority of patients had grade III-IV encephalopathy (60%). Mean MELD score in ALF patients was 31.83±6.74. MELD score was highest for indeterminate followed by viral and drug-induced ALF. Overall mortality was 44 (57.1) in ALF patients. Mortality was highest in indeterminate group (60%) followed by viral (53.1%) and drug (40%) induced ALF.

| Characteristics                      | Viral hepatitis (n=32) | Drug (n=15) | Indeterminate (n=30) |
|--------------------------------------|------------------------|-------------|----------------------|
| Categorical variables [n (%)]        |                        |             |                      |
| Male gender                          | 19 (59.4)              | 4 (26.7)    | 17 (56.7)            |
| Hepatic-encephalopathy               |                        |             |                      |
| Grade I-II                           | 23 (71.8)              | 10 (66.7)   | 12 (40)              |
| Grade III-IV                         | 9 (28.2)               | 5 (33.3)    | 18 (60)              |
| Fever                                | 19 (59.4)              | 6 (40)      | 12 (40)              |
| Vomiting                             | 12 (37.5)              | 4 (26.7)    | 10 (33.3)            |
| Mortality                            | 17 (53.1)              | 6 (40)      | 18 (60)              |

Continued.
The increase in indeterminate etiology from western could be because of unrecognized virus, metabolic or xenobiotic injury. Also, undiagnosed immune dysregulation may result in unexpected acetaminophen toxicity, a novel or indeterminate etiology from western could be because of unidentified herbal agents or toxins could not be ascertained with certainty. Alcohol acetaminophen syndrome is emerging as another important cause of ALF in US 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 ALF and is a common cause of ALF in the West. The most important of these agents include acetaminophen toxicity (42%) and idiosyncratic drug reactions (12%) with anti-infectives, anticonvulsants, anti-tuberculosis and anti-inflammatory drugs. The frequent use of ATT for tuberculosis has increased the frequency of ATT induced ALF. 12 (14.3%) patients had ATT induced ALF. Ayurvedic or herbal medicines are treatments of choice for various disorders, usually prescribed by quacks. 3 (3.6%) patients had ayurvedic induced ALF in our study while other studies from East Asia revealed a higher percentage. Amanita poisoning was a cause of ALF in North-east Indian villages.

About 35.7% patients in the present study lacked acute markers of known hepatitis viruses and were classified as indeterminate. Similar percentage of indeterminate cause of ALF was shown by Khuroo et al, while western studies reported less percentage. Whether some of these patients were related to exposure to some unidentified herbal agents or toxins could not be ascertained with certainty. Metabolic, vascular liver diseases and a number of miscellaneous liver diseases cause a small number of the remaining cases. Some of these causes contributed to ALF in our study (two patient each of Autoimmune and...
Wilson induced ALF. One patient each of CMV and HSV.

Comparison of etiology of ALF of this study with other Indian and US study is shown in Table 3. In studies from the US, major etiological cause of ALF is Acetaminophen toxicity followed by other drugs, indeterminate and viral causes.\textsuperscript{10} In the previous study from Kashmir by Khuroo et al.\textsuperscript{14} reported HEV as a major cause followed by indeterminate and HBV. Acharya et al in his study from Delhi reported HEV, HBV, drugs and HDV (3.8%) as major cause.\textsuperscript{11} Other study from East India reported drugs as major cause including (6.3%) as amanita poisoning followed by viral etiology.\textsuperscript{28}

Table 3: Comparison of causes of acute liver failure.

| Variables              | US n=308 | Kashmir n=180 | Delhi n=423 | East India n=255 | Our study n=84 |
|------------------------|----------|---------------|-------------|------------------|----------------|
| Acetaminophen          | 39       | 0             | 4           | 43.9             | 17.8           |
| Indeterminate          | 17       | 31.1          | 4.5         | 35.7             |                |
| Drugs                  | 13       | 0.6           | 4.5         | 43.9             | 17.8           |
| Ischemic Hepatitis     | 6        |               |             |                  |                |
| HEV                    |          | 43.9          | 62.4        | 13.3             | 19.1           |
| HAV                    | 4        | 2.2           | 1.7         | 29.8             | 9.5            |
| HBV                    | 7        | 13.9          | 27.6        | 3.1              | 9.5            |
| Autoimmune hepatitis   | 4        |               |             | 0.8              | 2.4            |
| Wilson disease         | 3        |               |             |                  | 2.4            |
| Budd-Chiari syndrome   | 2        |               |             |                  |                |
| HELLP syndrome         | 1        |               |             |                  |                |
| Acute fatty liver of pregnancy | 1 |     |             |                  | 1.2            |
| Metastatic cancer      | 1        |               |             |                  |                |
| Others                 | 2        | 7             |             |                  | 2.4            |

Values given as percentage (%).

Table 4: Comparison of overall mortality of acute liver failure.

| Variables          | US n=308 | Kashmir n=180 | Delhi n=423 | East India n=255 | Our study n=84 |
|--------------------|----------|---------------|-------------|------------------|----------------|
| Mortality          | 101 (32.8) | 131 (72.8) | 280 (66.2) | 73 (28.6) | 44 (57.1) |

Overall mortality was 44 (57.1) in ALF patients. Mortality was highest in indeterminate group (60%) followed by viral (53.1%) and drug (40%) induced ALF. In our study the mortality of ALF patients was 44 (57.1%). Mortality was 32.8% in the study by Ostapowicz et al.\textsuperscript{10} which is lower than our study. The reason may be that 29% of their patients received liver transplant which improved survival. While the previous study from Kashmir by Khuroo et al reported mortality of 72.8% which is higher than ours.\textsuperscript{14} Due to improvement in the supportive care for ALF might have reduced the mortality rates in our study. Other study from East India reported lower mortality of 73 (28.6%) but the reason for this was not explained.\textsuperscript{28} Acharya et al in his study reported the mortality of 280 (66.2%).\textsuperscript{11} Comparison of mortality outcome is shown in Table 4.

CONCLUSION

In conclusion, the current study like rest of India has viral hepatitis as a common cause of ALF but a large number of the patients had indeterminate etiology (35.7%) despite geographically defined region endemic for HEV. Indeterminate etiology has poorer prognosis as compared to other etiology. 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 ALF from other earlier studies in India and west, possibly due to novel or unrecognized virus, metabolic or xenobiotic injury and undiagnosed immune dysregulation.

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