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A study of Acute Liver Failure in adults in a tertiary care hospital

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Abstract

Acute liver failure (ALF) is a condition with rapid deterioration of liver function resulting in hepatic encephalopathy and/or coagulopathy in patients with previously normal liver. Acute liver failure (ALF) is an uncommon condition associated with high morbidity and mortality. The prognosis is poor for untreated cases of Acute liver failure, so early recognition and management of patients with acute liver failure is crucial. A cause for acute liver failure can be identified in 60 to 80 percent of patients. Identifying the underlying cause of the liver failure is important because it influences the approach to management and provides prognostic information. **Aims and Objectives:** The aim of our study is to identify the clinical features, etiology and outcome of acute liver failure in a tertiary care hospital. **Materials and Methods:** This study is an observational study where patients with Acute Liver Failure admitted in ICU in our institution after meeting the diagnostic criteria for Acute liver failure were included in the study. Details of history, relevant symptoms and baseline investigations included, complete blood count, blood glucose, renal function test, serum electrolytes, liver function test (LFT), prothrombin time, international normalized ratio (INR), lactate dehydrogenase (LDH), creatine kinase (CK)], arterial blood gas analysis, arterial lactate, arterial ammonia, amylase and lipase level and pregnancy test (if female) and ultrasonography (USG) abdomen were recorded, MRI brain and other investigations relevant to the admission diagnosis, co morbidities and aetiology if needed were recorded. All the patients received standard supportive treatment for ALF. **Results:** In this study of 57 patients, majority of the patients were from the age group 41 to 50 years (17 patients) and 31 to 40 years (13 patients). 36 patients were male and 21 patients were females. Jaundice and encephalopathy was observed in all 57 (100%) patients, 24 (42%) patients had INR >2.5, 27 (47%) patients had serum creatinine >1.2 mg/dl and 18 (31.5%) patients had serum ammonia levels >100 micromol/L. The lowest value for serum aminotranferase was observed in infections (other than viral hepatitis) and maximum value was observed in drugs leading to ALF.In 20 (35%) patients viral hepatitis was the cause for ALD, followed by drugs and toxins which was the cause of ALD in 18 (31.5%) patients. Infections other viral hepatitis as the aetiology for ALF was observed in 16 (28%) of patients. Ischemic hepatitis was observed in 1 and Wilson's disease was noted in 2 patients. Total 6 (10.5%) patients out of 57 patients had died, 4 patients with hepatitis B infection, 1 patient with paracetamol over dosage and 1 patient with dengue fever had died. **Conclusion:** Viral hepatitis and drugs are the commonest cause for acute liver failure. The aetiology of ALF varies significantly worldwide. Determining the etiology of acute liver failure requires a combination of detailed history taking and investigations. A broad evaluation is required to identify a cause of the acute liver failure, as the prognosis is poor in untreated cases of acute liver failure, so early recognition and management of patients with acute liver failure is crucial.

Keywords: Acute liver failure, Fulminant hepatic failure, Viral hepatitis, Paracetamol overdose.

INTRODUCTION

The definition of Acute liver failure includes evidence of coagulation abnormality (international standardized ratio of prothrombin time (INR) > 1.5) and any degree of mental alteration in a patient without preexisting cirrhosis and with an illness of < 26 weeks duration [1, 2]. It is also referred to as acute hepatic necrosis, fulminant hepatic failure, and fulminant hepatitis. The cause for ALF varies worldwide. Paracetamol overdose is the commonest cause of ALF in the United Kingdom (UK) and the United States (US). In developing countries, Viral aetiology is the most commonest cause. The prognosis is poor in untreated cases of acute liver failure, so early recognition and management of patients with acute liver failure is crucial [3]. The incidence of ALF is between one and six cases per million people per year in developed world [4]. Incidence may be higher in developing world, but data are lacking [5, 6].

MATERIALS AND METHODS

The current study is a retrospective observational study between January 2018 to December 2018. 57 patients with Acute Liver Failure admitted in ICU in our institution after meeting the diagnostic criteria for Acute liver failure were included in the study.

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Inclusion criteria

- Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥1.5) in a patient without cirrhosis or preexisting liver disease
- The time course of the illness duration of <26 weeks.

Exclusion criteria

- Patients with chronic liver disease were excluded.

Detailed history which also included extensive drug history to exclude intake of any medications, herbal or dietary supplements that could cause ALF, clinical, and laboratory data were recorded. Baseline investigations included, complete blood count, blood glucose, renal function test, serum electrolytes, liver function test (LFT), prothrombin time, international normalized ratio (INR), lactate dehydrogenase (LDH), creatine kinase (CK)], arterial blood gas analysis, arterial lactate, arterial ammonia, amylase and lipase level and pregnancy test (if female) and ultrasonography (USG) abdomen were recorded. Additional tests to confirm etiological diagnosis were ordered when needed, such as serological markers of Hepatitis A, B, C and E viral infections, including IgM antibodies against HAV and HBV (HIV, IgM anti HAV, HBsAg, IgM anti HBc, antiHCV, IgM anti HEV and anti HDV). Autoimmune markers (ANA, ASMA, Anti LKM1, p-ANCA), tests for Wilson disease (serum ceruloplasmin, slit lamp study, urinary copper). In addition, specific diagnostic tests for infectious diseases causing ALF: IgM Dengue virus antibody; IgM Leptospirosis antibody, peripheral smears for malarial parasites; Widal test and blood culture for Salmonella; and blood culture for bacteria and fungus were ordered when needed. Computerized tomography of head was performed in cases with worsening of mental status to exclude intracranial haemorrhage and other causes. All the patients received standard supportive treatment for ALF.

RESULTS

This study included 57 patients between the age group of 18 to 71 years and it was observed that 5 (8.7%) patients were from the age group 18 to 20 years, 9 (15.7%) patients were from the age group 21 to 30 years. 13 (22.8%) patients were from the age group 31 to 40 years and 17 (29.8%) patients were from the age group 41 to 50 years. Age group 51 to 60 years included 11 (19.2%) patients and only 2 (3.5%) patients were from the age group 61 to 71 years. This study included 21 (36.8%) females and 36 (63.1%) male patients.

Table 1: Aetiology of Acute liver failure

AETIOLOGY	NO. OF PATIENTS
Hepatitis A	4 (7%)
Hepatitis B	12 (21%)
Hepatitis B and Hepatitis C co-infection	3 (5.2%)
Hepatitis E and Hepatitis B co-infection	1 (1.7%)
Wilson's disease	2 (3.5%)
Paracetamol	6 (10.5%)
Anti tubercular drugs	5 (8.7%)
Phenytoin	2 (3.5%)
Unknown	4 (7%)
Mushroom poisoning	1 (1.7%)
Dengue	5 (8.7%)
Enteric fever	1 (1.7%)
Leptospirosis	2 (3.5%)
Sepsis	3 (5.2%)
Falciparum Malaria	4 (7%)
Scrub typhus	1 (1.7%)
Ischemic hepatitis	1 (1.7%)

In this study it was observed that viral hepatitis leading to ALF included 20 (35%) patients. Infections other that viral hepatitis accounted for 16 (28%) cases of ALF. In 18 (31.5%) patients drugs were the cause for ALF. Ischemic hepatitis and Wilson's disease include 1 (1.7%) and 2 (3.5%) patients respectively as the cause for ALF.

Table 2: Symptoms and signs of Acute liver failure

Symptoms and Signs	Percentage
Jaundice	57 (100%)
Abdominal discomfort	23 (40.3%)
Myalgia	16 (28%)
Nausea	27 (47.3%)
Vomiting	14 (24.5%)
Hepatomegaly	27 (47.3%)
Splenomegaly	10 (17.5%)
Ascites	38 (66%)
Encephalopathy	57 (100%)
Encephalopathy grade I	33 (57.8%)
Encephalopathy grade II	15 (26.3%)
Encephalopathy grade III	7 (12.2%)
Encephalopathy grade IV	2 (3.5%)

In this study it was observed that encephalopathy and jaundice was present in all the 57 (100%) patients and gradeIII/IV encephalopathy was observed in 9 patients and grade I/II encephalopathy as observed in 48 patients. Ascites was observed in 38 (66%) patients followed by nausea and hepatomegaly which was observed in 27 (47.3%) patients each. Abdominal discomfort was observed in 23 (40.3%) patients. Cerebral edema was observed in 3 patients of which 2 patients were from grade III encephalopathy and 1 patient had grade IV encephalopathy.

Table 3: Serum Aminotransferase levels in different etiologies of ALF

ETIOLOGY OF ALF	RANGE
Viral hepatitis	983 – 3794 units/L
Genetic disorder (Wilson's disease)	407 – 625 units/L
Drugs	798 – 5043 units/L
Ischemic hepatitis	4631 units/L
Infections (other than viral hepatitis)	388 – 1055 units/L

Serum aminotransferase levels range noted in this study was from 388 units/L to 5043 units/L. The lowest value for serum aminotranferase was observed in infections (other than viral hepatitis) and maximum value was observed in drugs leading to ALF.

Table 4: Baseline characteristics in Acute liver Failure.

Baseline characteristics	Range	
INR	**1.5 – 2.5**	**> 2.5**
	33 (57.8%)	24 (42%)
Serum Creatinine	**< 1.2 mg/dl**	**> 1.2 mg/dl**
	30 (52%)	27 (47%)
Serum Ammonia	**< 100 micromol/L**	**> 100 micromol/L**
	39 (68%)	18 (31.5%)

In this study it was observed that out of 57 patients with ALF, 24 (42%) patients had INR >2.5, 27 (47%) patients had serum creatinine >1.2 mg/dl and 18 (31.5%) patients had serum ammonia > 100 micromol/L.

Total 6 (10.5%) patients out of 57 patients had died, 4 patients with hepatitis B infection, 1 patient with paracetamol overdosage and 1

patient with dengue fever had died. Of the 6 patients who died, 3 patients had grade III encephalopathy, 2 patients had grade IV encephalopathy and 1 patient had grade II encephalopathy. 4 patients were from the age group 51 to 60 years, 1 patient each was from the age group 41 to 50 years and 61 to 71 years. All the 6 patients who dies had serum creatinine levels more than >1.2 mg/dl, INR > 2.5 and serum ammonia levels > 100 micromol/L.

DISCUSSION

In this study it was observed that out of 57 patients, viral hepatitis was the cause for acute liver failure in 20 (35%) patients, of which hepatitis B was observed in 12(21%) patients, hepatitis C was the cause for ALF in 4 (7%) patients. Co-infection was observed in 4 patients (hepatitis B with hepatitis C co-infection in 3 (5.2%) patients and hepatitis E with hepatitis B co-infection in 1(1.7%).It was noted in this study that in 18 (31.5%) patients drug was the cause of acute liver failure of which paracetamol accounted for ALF in 6 (10.5%) of patients, antitubercular drugs in 5 (8.7%) patients, unknown drugs in 4 (7%) patients, phenytoin in 2 (3.5%) patients and mushroom poisoning accounted for in 1(1.7%) patient. Infections as a cause for ALF was observed in this study in 16 (28%) patients of which dengue accounted for ALF in 5(8.7%) of patients, falciparum malaria in 4(7%) patients, sepsis in 3(5.2%) patients and leptospirosis in 2(3.5%) patients. Only 1(1.7%) patient each with enteric fever and scrub typhus had developed ALF. Ischemic hepatitis accounted for 1.7% of cases of ALF

Acute liver failure can result from a wide variety of causes [7], in adults drug-induced and viral hepatitis are the most common causes of acute liver failure. In developed countries like, the United Kingdom, Australia and the United States, acetaminophen is the most common cause of acute liver failure, whereas in developing countries and some other parts of Europe, viral hepatitis predominates [8, 9]. In a study from Japan between 1998 and 2006, among 856 patients with acute liver failure, 51 percent of cases were due to viral hepatitis (42 percent hepatitis B), and 10 percent were due to drugs (including acetaminophen) [10]. Date collected between 1998 and 2007 by the US Acute Liver Failure Study Group from 1147 cases of acute liver failure from 23 sites observed that the most common causes of acute liver failure were acetaminophen overdose (46 percent), indeterminate (14 percent), idiosyncratic drug reactions (12 percent), hepatitis B virus (7 percent), and hepatitis A virus (3 percent) (3). In India, Acute viral hepatitis is the most common cause of ALF [11, 12].

It was observed that hepatitis A and E infections are probably responsible globally for the majority of cases of acute liver failure, with rates of death of more than 50% reported from the developing world [13, 14]. It was observed that hepatitis B infection [11], was a common cause for acute liver failure in some Asian and Mediterranean countries. However, the incidence of acute liver failure from hepatitis B may be underestimated. Precore or pre-S mutant hepatitis B viruses that are able to produce infection but do not produce hepatitis B e antigen (precore mutants) or surface antigen (pre-S mutants) may be difficult to diagnose by routine serology. Thus, liver failure in such patients may be attributed to cryptogenic causes [15]. This was illustrated in a study in patients who underwent liver transplantation, where hepatitis B infection was detected by polymerase chain reaction (PCR) in 6 of 17 patients (35 percent) who were initially thought to be non-A, non-B hepatitis [16].

In developing countries like India, infections like falciparum malaria, typhoid fever, leptospirosis, and dengue fever can present with ALF; and so they should be considered for in cases presenting as ALF [1]. In a study by Amarapurkar Deepak N *et al*. [1] ALF was seen in 1 patient with enteric fever, 4 patients with ricketsial infection (scrub typhus = 2, endemic typhus = 2), 5 patients with leptospirosis and dengue fever each, 4 patients with amoebic liver abscess and in 8 patients with falciparum malaria. In a study by Soek - Siam Tan *et al*, 8 patients with dengue fever had developed Acute liver failure [17].

In this study it was observed that the signs and symptoms of acute liver failure were similar to a study conducted by Amarapurkar Deepak N *et al.* [1] where jaundice was observed in 56 (100%) patients, abdominal discomfort in 19 (33.9%) patients, hepatomegaly in 25 (44.6%) patients, splenomegaly was observed in 12 (21.4%) patients and encephalopathy was 54 (96.4%) patients. Our study showed that encephalopathy and jaundice was present in all the 57 (100%) patients. Hepatomegaly which was observed in 27 (47.3%) patients and splenomegaly was observed in 10 (17.5%). Abdominal discomfort was observed n 23 (40.3%) patients. Cerebral edema was present in 75% of those with grade IV encephalopathy and in 25-35% of patients with grade III encephalopathy [18]. Cerebral edema in ALF is caused by a combination of vasogenic and cytotoxic edema [19, 20]. Excess ammonia and glutamine disturb cerebral osmolality, leading to increase free radical production, and also alter glucose metabolism, leading to calcium-mediated mitochondrial injury leading to astrocyte swelling [19, 20]. Alteration in cerebral blood flow and activation of inflammatory cytokines can aggravate cerebral edema [20]. In our study it was observed that 3 patients had cerebral edema and of which 2 (28.5%) patients out of 7 patients with grade III encephalopathy had cerebral edema and 1 (50%) patient with cerebral edema had grade IV encephalopathy which was observed in 2 patients in this study.

In this study it was observed that markedly elevated aminotransferase levels were observed in drug induced and ischemic hepatitis cause for ALF followed by Viral hepatitis. Ischemic or toxic liver injury in indicated by very high aminotransferase levels (> 75 times the upper reference limit) in more than 90% of cases of acute hepatic injury, whereas they are less commonly observed with acute viral hepatitis [21]. In ischemic or toxic liver injury, AST levels usually peak before those of ALT because of the enzyme's peculiar intralobular distribution [22, 23, 24]. Zone 3 of the acinus is more vulnerable to both hypoxic and toxic damage. Reducing aminotransferase levels may indicate spontaneous recovery but could also reflect worsening of the liver failure with loss of hepatocyte mass.

Decreased synthesis and increased consumption of fibrinolytic proteins, anticoagulant proteins and procoagulant factors occurs in ALF. In this study it was observed that out of 57 patients 33 patients had INR between the range of 1.5 to 2.5 and 24 patients had INR >2.5. Out of 57 patients included in this study, 27 (47%) patients had serum creatinine >1.2mg/dl. Acute kidney injury complicates acute liver failure in approximately 30 to 70 percent of patients (25-28). It has been observed that renal dysfunction is associated with increased mortality, but the resolution of liver failure is accompanied by a return to pre-existing levels in most cases [29].

This study included 18 (31.5%) patients with serum ammonia levels > 100 micromol/L. In liver failure, the normal detoxification of ammonia to urea is impaired, and levels of circulating ammonia increase. Ammonia increases intracellular osmolarity through its cerebral metabolism to glutamine and induces changes in neurotransmitter synthesis and release and in mitochondrial function; altered cerebral function and swelling result [30, 31]. It has been observed that with rise in arterial ammonia level the development of encephalopathy occurs, and with a sustained level of ammonia of 150 to 200 µmol per liter (255 to 340 µg per deciliter) there is a greater risk of intracranial hypertension [32, 33].

Overall, survival rates in patients treated for acute liver failure are greater than 60 percent [34, 35]. Approximately 55 percent of patients will survive without needing a liver transplantation [35]. The most important factors for predicting the outcome in acute liver failure are the patient's age, the degree of encephalopathy, and the aetiology of the acute liver failure. These factors in part reflect the importance of the severity of the hepatic injury and the likelihood of reversal of the underlying process either spontaneously or with specific therapy. Of the 6 patients who died in this study, 3 patients had grade III

encephalopathy, 2 patients had grade IV encephalopathy and 1 patient had grade II encephalopathy. 4 patients were from the age group 51 to 60 years, 1 patient each was from the age group 41 to 50 years and 61 to 71 years.

Total 6 (10.5%) patients out of 57 patients had died in this study, 4 patients with hepatitis B infection, 1 patient with paracetamol over dosage and 1 patient with dengue fever had died. The importance of the etiology of the acute liver failure was demonstrated in a study of 308 patients with acute liver failure [34]. The short-term (three-week) transplant-free survival rate overall was 43 percent. The transplant free survival rate was ≥50 percent in patients with acute liver failure due to acetaminophen, hepatitis A, ischemia, or pregnancy-related acute liver failure. On the other hand, it was <25 percent for those whose liver failure was due to hepatitis B, autoimmune hepatitis, Wilson disease, Budd-Chiari syndrome, cancer, or an indeterminate cause. Death extremely rare if N-acetylcysteine is administered within eight hours following acetaminophen overdose [36, 37, 38]. 1 patient with paracetamol over dosage died in our study and he had presented 72 hours after ingestion and hence the treatment was delayed.

All the 6 patients who dies had serum creatinine levels more than >1.2 mg/dl, INR > 2.5 and serum ammonia levels > 100 micromol/L. Several other variables, such as the prothrombin time/INR and arterial ammonia levels, have been used to predict the probability of recovery, but their predictive accuracy has not been well established [15, 33, 39-42].

CONCLUSION

In adults Viral and drug-induced hepatitis are the most common causes of acute liver failure. In developing countries, ALF-mimicking infections should be looked for in differential diagnosis of ALF. The rarity, severity and heterogeneity of acute liver failure, has resulted in a very limited evidence to guide supportive care. However, rates of survival have improved substantially in recent years through advances in critical care management and the use of emergency liver transplantation.

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