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Research Article

Outcome and Prognostic Factors in Fulminant Hepatic Failure

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Abstract

Background: *Acute liver failure (ALF) is a rare critical illness with high mortality whose successful management requires early recognition and effective initial management. ALF of less than 8 weeks is called Fulminant Hepatic Failure (FHF). Clinical and etiological profile varies with geographical area and over time. Prognostic criteria are applied to identify patients for emergency liver transplantation, and candidates for surgery are prioritized on wait listing schemes.*

Objective: *The objective of this prospective study was to determine the prognostic factors and outcome of FHF.*

Methods: *A total of 84 consecutive patients with a diagnosis of FHF were included in the study. The variables evaluated were etiological profile, outcome and prognostic criteria.*

Results: *Viral hepatitis 32 (38.1%) was the most common cause of FHF but large number of the patients 30 (35.7%) had indeterminate etiology. 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. Overall mortality was 44 (52.4%) in FHF patients. Six variables which predicted the adverse outcome on multivariate analysis were age >60 years, bilirubin >20mg/dl, III–IV grade of encephalopathy, lactate >3.5 mmol/L, MELD score >30 and Non HEV induced FHF.*

Conclusion: *Like the rest of India, viral hepatitis was the common cause of FHF but a large number of patients 30 (35.7%) had indeterminate etiology. Overall mortality was 52.4%. Age >60 years, bilirubin >20mg/dl, III–IV grade of encephalopathy, lactate >3.5 mmol/L, MELD score >30 and Non HEV induced FHF were the independent prognostic factors determining mortality.*

Keywords: *Acute Liver failure (ALF); Fulminant Hepatic Failure (FHF); Viral hepatitis; Survival; Prognostic factors.*

Introduction

FHF is a rare but a life-threatening condition. FHF causes severe injury and massive necrosis of hepatocytes resulting in severe liver dysfunction that can lead to multiorgan failure. FHF 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 and medical therapies that interrupt progression of hepatic injury and development of extrahepatic organ dysfunction are not readily available.[1,2,3] 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[4] and is responsible for 6% of liver transplants.[5]

Acute liver failure is a broad term that encompasses both Fulminant hepatic failure (FHF) and subfulminant hepatic failure (or late-onset hepatic failure). Fulminant hepatic failure 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.[6]

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 FHF are young (median age 38 years) and female (73%).[7] Etiology of FHF is diverse and shows wide geographical variation.

The main etiological factor includes: viral, drugs including herbal and traditional medications, autoimmune, toxin and indeterminate.[7] Acetaminophen overdose is the most common cause of ALF in the United States and Europe, whereas viral hepatitis is more common in Asia and Africa, but numerous other causes have been reported, including drug-induced liver injury, viral hepatitis, ischemic liver injury, Wilson's disease, and acute presentation of autoimmune hepatitis.[8, 9] Viral hepatitis is the commonest cause of ALF world-wide and in the Indian subcontinent alone it accounts for 90% of cases.[10] In India, Pakistan, China and Southeast Asia, Hepatitis E (HEV) is now the most common cause of ALF.[11]

Mortality in FHF is usually due to cerebral edema, multiorgan dysfunction syndrome (MODS), and sepsis. The management of patients with FHF requires a thorough infrastructure and understanding to deal with the complications.[12] Orthotropic liver transplantation (OLT) has now become an established treatment option in patients with FHF.

Prognostic factors in FHF assist in the early identification of patients who would benefit from OLT. They also help identify patients who may recover on their own with supportive care. Such a determination helps in judicious use of resources, avoids OLT and life-long immunosuppression in patients who will recover on their own. The King's College criteria and the Clichy-Villejuif criteria are the most commonly used models while others include MELD score and US-ALF Study Group Index.[13] Unfortunately, despite the presence of numerous clinical indicators and prognostic models, a successful prognostic scoring system has yet to be determined. This is mainly due to the varying etiologies of FHF and the variability in the course and complications of FHF.

The etiology of FHF, age of the patient, and the severity of liver dysfunction has been found to be good predictors of prognosis in FHF. Survival is generally higher in patients with FHF due to acetaminophen toxicity, ischemic hepatitis, or hepatitis A, while survival is lower in patients with FHF due to acute hepatitis B and indeterminate cause. The grade of encephalopathy during presentation also has prognostic value. Patients presenting with grade 3 or 4 encephalopathy are likely to require OLT as compared with patients who present with grade 1 or 2 encephalopathy.[10, 11, 13, 14]

The present study was carried out to determine the prognostic factors and outcome of FHF in Kashmir (North India), an endemic zone of HEV.

Materials and Methods

It was a hospital-based prospective study of adult patients with FHF. 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. Informed consent

was obtained from all the recruited subjects or their next-of-kin.

Study Subjects

Overall 84 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.

Eligibility Criteria

Patients included were age >18 years and FHF was defined as biochemical evidence of acute liver injury with INR ≥1.5 and any degree of encephalopathy caused by the illness of duration <8weeks in a patient with no prior known liver disease.

Exclusion criteria include i) Acute on chronic liver failure

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 FHF. 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 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 FHF.[15] The treatment mainly involved continuous intravenous dextrose to prevent hypoglycemia; broad-spectrum prophylactic antimicrobials.[15] 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

Patients were analyzed in the two groups (survivors and non-survivors). Frequency distribution was assessed in terms of means ± SD for quantitative variables and number (percentages) for categorical variables. In univariate analysis, the categorical variables were compared in the two groups by using $\chi 2$ test or Fisher exact test where appropriate. For continuous variables, the independent sample t test was used to compare the means in the two

groups. P values <0.05 was considered statistically significant. 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 FHF in total. Table 1 demonstrates the etiologies of FHF. Viral hepatitis 32 (38.1%) was the most common cause of FHF. Majority of the patients 30 (35.7%) had indeterminate etiology. Among viral causes Acute HEV-induced FHF (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 FHF and 3 patients had ayurvedic induced FHF), HBV-induced FHF (9.8%) and HAV-induced FHF (9.5%). Other etiology included FHF due to Wilson (2.4%), Autoimmune hepatitis (2.4%), FHF in pregnancy (1.2%), CMV (cytomegalovirus), and HSV (Herpes simplex virus).

Table 1: Etiology of Fulminant Hepatic Failure

Etiology	Total N (%)
Acute Hepatitis E	16 (19.1%)
Acute Hepatitis A	8 (9.5%)
Acute Hepatitis B	8 (9.5%)
Drug-induced FHF	15 (17.8%)
Autoimmune Hepatitis	2 (2.4%)
Wilson Disease	2 (2.4%)
FHF in Pregnancy	1 (1.2%)
Indeterminate etiology	30 (35.7%)
Others[a]	2 (2.4%)

[a]One patient each of CMV, and HSV.

Table 2 shows the distribution of baseline characteristics (both categorical and continuous) of FHF based on survival. All the patients were of Kashmiri ethnicity. Overall mortality was 44 (57.1) in FHF patients. Majority of the patients were female (52.4%) and females were comparable between survived and dead group. The mean age in survived group was 32.6±12.5 years and in dead group was 42.6±14.3 years which was statistically significant ($P = 0.002$). Coma grade at the time of admission showed that majority of patients in dead group had grade III-IV encephalopathy, while patients who survived had grade I-II and the difference was statistically significant ($P < 0.001$). Bilirubin was significantly higher in dead group than survived group ($P = 0.014$). INR, lactate and MELD score was significantly higher in dead group than survived group ($P < 0.05$). The two groups did not differ significantly with respect to creatinine, interval between jaundice and encephalopathy, AST, ALT, and PH).

Table 2: Baseline characteristics of study subjects on the basis of Survival

Characteristics	Survived (N = 32)	Dead (N = 44)	*P-value
Categorical variables **[n (%)]**			
Female Gender	18 (56%)	26 (59%)	0.795
Hepatic-encephalopathy Grade I-II Grade III-IV	23 (71.8%) 9 (28.2%)	12 (27.3%) 32 (72.7%)	< 0.001
Continuous variables **[mean ± SD]**			
Age (Years)	32.6 ± 12.5	42.6 ± 14.3	0.002
INR	2.0 ± 1.1	2.6 ± 1.3	0.037
Bilirubin (mg/dl)	16.4 ± 8.5	21.3 ± 8.4	0.014
AST (mg/dl)	1220 ± 534	1430 ± 645	0.136
ALT (mg/dl)	990 ± 423	1128 ± 489	0.203
Creatinine (mg/dl)	1.23 ± 0.7	1.45 ± 0.8	0.216
Interval between jaundice and encephalopathy (days)	28 ± 18.3	22 ± 11.4	0.083
PH	7.35 ± 0.18	7.31 ± 0.14	0.279
Lactate (mmol/L)	2.3 ± 1.4	3.2 ± 1.9	0.026
MELD Score	27.5 ± 5.8	33.8 ± 4.7	< 0.001

*P-value <0.05 is considered statistically significant n = Number; SD = Standard deviation

Logistic regression analysis was performed in order to study the role of independent risk factors on mortality in FHF patients is shown in table 3. In the study age >60 years, bilirubin >20mg/dl, III–IV grade of encephalopathy, lactate >3.5 mmol/L, MELD score >30 and Non HEV induced FHF were the independent prognostic factors determining mortality.

Table 3: Univariate and Multivariate analysis of Prognostic factors in FHF

VARIABLE	MORTALITY RATE (%)	UNADJUSTED ODDS RATIO	P VALUE	ADJUSTED ODDS RATIO	P VALUE
AGE in years					
<60	36.1%	1	0.002	1	0.026
>60	75.0%	5.308		3.165	
BILIRUBIN					
<20	27.5%	1	0.014	1	0.010
>20	52.5%	2.914		4.650	
GRADE OF ENCEPHALOPATHY					
I and II	28.8%	1	<0.001	1	0.007
III and IV	60.7%	19.812		10.254	
LACTATE in mmol/L					
<3.5	33.3%	1	0.026	1	0.034
>3.5	81.8%	3.130		2.077	
MELD SCORE					
<30	25%	1	< 0.001	1	0.004
>30	52%	15.286		12.964	
INR					
<4	23%	1	0.037	-	-
>4	51%	2.312		-	
ETIOLOGY					
HEV	16.4%	1	0.002	1	0.008
Non HEV	88.7%	14.458		9.980	

Discussion

FHF is a condition of acute hepatic emergency where rapid deterioration of hepatocyte function leads to hepatic encephalopathy, coagulopathy, cerebral edema, infection and MODS resulting in a high mortality rate. The common etiologies of FHF vary in different geographic areas and the course is highly variable. OLT has now become an established treatment option in patients with FHF. Due to lack of OLT facility N-Acetylcysteine (NAC) has emerged as a beneficial treatment for FHF.[16] Clinical and etiological profile varies with geographical area and over time.[17] 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. Prognostic criteria for FHF has come up from both West and East. So the prospective study was carried out to determine the outcome and prognostic factors of FHF in cohort of patients of Kashmir (North India).

FHF in all the patients in our study was etiologically associated with known hepatitis viruses. FHF can result from diverse etiological agents. The most common cause of FHF in the United Kingdom is related to acetaminophen toxicity in association with suicidal episodes.[18] 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 16 (19.1%) 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.[10, 11, 19, 20] HAV constituted 8 (9.5%) 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 FHF in children than adults.[21] Das AK, *et al*.[22] reported higher percentage of HAV (29.8%) as cause for FHF. 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,[23, 24] although no patient of HCV related FHF was found in our study.

In our study 12 (14.3%) patients had ATT induced FHF. Ayurvedic or herbal medicine are treatments of choice for various disorders, usually prescribed by quacks. 3 (3.6%) patients had ayurvedic induced FHF in our study while other studies from East Asia revealed a higher percentage.[25, 26] Amanita poisoning was a cause of ALF in 16 (6.3%) of patients in the study by Das AK, *et al.*[22] because wild mushroom ingestion in rural areas is quite common in North-east Indian villages.

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 MS, *et al.*[11] while western studies reported less percentage.[7] Whether some of these patients were related to exposure to some unidentified herbal agents or toxins could not be ascertained with certainty.[27] The increase in indeterminate etiology from western could be because of unexpected acetaminophen toxicity,[28] a novel or unrecognized virus, metabolic or xenobiotic injury. Also, undiagnosed immune dysregulation may result in ALF.[29] Metabolic, vascular liver diseases and a number of miscellaneous liver diseases cause a small number of the remaining cases.[30] Some of these causes contributed to FHF in our study (two patient each of Autoimmune and Wilson induced FHF. One patient each of pregnancy, CMV and HSV related FHF.

In our study the mortality of FHF patients was 44 (57.1%). Mortality was 32.8% in the study by Ostapowicz G, *et al.*[7] 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 MS, *et al.*[11] reported mortality of 72.8% which is higher than ours. Due to improvement in the supportive care for FHF might have reduced the mortality rates in our study. Other study[22] from East India reported lower mortality of 73 (28.6%) but the reason for this was not explained. Acharya SK, *et al.*[10] in his study reported the mortality of 280 (66.2%).

In our study age >60 years, bilirubin >20mg/dl, III–IV grade of encephalopathy, lactate >3.5 mmol/L, MELD score >30 and Non HEV induced FHF were the independent prognostic factors determining mortality. Khuroo MS, *et al.*[11] reported age >40 years, prothrombin time >30 s, grade of coma >2 and Non HEV etiology as predictors of poor outcome. Acharya SK, *et al.*[10] in his study found prothrombin time >25 s, bilirubin >15mg/dl, age >40 years and cerebal edema to be bad prognostic factors. Anand AC *et al.*[31] reported age >50 years, raised intracranial pressure, prothrombin time >30 s and onset of encephalopathy >7 days after jaundice as bad prognostic factors. Another study from China reported prothrombin time >19 s, bilirubin >23mg/dl, age >43 years as bad prognostic factors.[32] On comparison of various clinical criteria, one find that age and coagulopathy have been used in all, bilirubin level in three models, Non HEV etiology and grade of encephalopathy in two models.

In conclusion, the current study like rest of India has viral hepatitis was the common cause of FHF but a large number of patients 30 (35.7%) had indeterminate etiology. Overall mortality was 52.4%. predictors of a poor outcome were Age >60 years, bilirubin >20mg/dl, III–IV grade of encephalopathy, lactate >3.5 mmol/L, MELD score >30 and Non HEV induced FHF.

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Conflict of interest: Nil

Ethical approval: The study was approved by the Institutional Ethics Committee of Sher-i-Kashmir Institute of Medical Science (SKIMS), Soura, J&K, India

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