Fulminant Hepatitis in a Tropical Population: Clinical Course, Cause, and Early Predictors of Outcome

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The profiles of patients with fulminant hepatic failure (FHF) from developing countries have not been reported earlier. The current study was conducted prospectively, at a single tertiary care center in India, to document the demographic and clinical characteristics, natural course, and causative profile of patients with FHF as well as to define simple prognostic markers in these patients. Four hundred twenty-three consecutive patients with FHF admitted from January 1987 to June 1993 were included in the study. Each patient's serum was tested for various hepatotropic viruses. Univariate Cox's regression for 28 variables, multivariate Cox's proportional hazard regression, stepwise logistic regression, and Kaplan-Meier survival analysis were done to identify independent predictors of outcome at admission. All patients presented with encephalopathy within 4 weeks of onset of symptoms. Hepatotropic viruses were the likely cause in most of these patients. Hepatitis A (HAV), hepatitis B (HBV), hepatitis D (HDV) viruses, and antitubercular drugs could be implicated as the cause of FHF in 1.7% (n = 7), 28% (n = 117), 3.8% (n = 16), and 4.5% (n = 19) patients, respectively. In the remaining 62% (n = 264) of patients the serological evidence of HAV, HBV, or HDV infection was lacking, and none of them had ingested hepatotoxins. FHF was presumed to be caused by non-A, non-B virus(es) infection. Sera of 50 patients from the latter group were tested for hepatitis E virus (HEV) RNA and HCV RNA. In 31 (62%), HEV could be implicated as the causative agent, and isolated HCV RNA could be detected in 7 (19%). Two hundred eighty-eight (66%) patients died. Approximately 75% of those who died did so within 72 hours of hospitalisation. One quarter of the female patients with FHF were pregnant. Mortality among pregnant females, nonpregnant females, and male patients with FHF was similar ($P > .1$). Univariate analysis showed that age, size of the liver assessed by percussion, grade of coma, presence of clinical features of cerebral edema, presence of infection, serum bilirubin, and prothrombin time prolongation over controls at admission were related to survival ($P < .01$). The rapidity of onset of encephalopathy and cause of FHF did not influence the outcome. Cox's proportional hazard regression showed age ≥40 years, presence of cerebral edema, serum bilirubin ≥15 mg/dL, and prothrombin time prolongation of 25 seconds or more over controls were independent predictors of outcome. Ninety-three percent of the patients with three or more of the above prognostic markers died. The sensitivity, specificity, positive predictive value, and the negative predictive value of the presence of three or more of these prognostic factors for mortality was 93%, 80%, 86%, and 89.5%, respectively, with a diagnostic accuracy of 87.3%. We conclude that most of our patients with FHF might have been caused by hepatotropic viral infection, and non-A, non-B virus(es) seems to be the dominant hepatotropic viral infection among these patients. They presented with encephalopathy within 4 weeks of the onset of symptoms. Pregnancy, cause, and rapidity of onset of encephalopathy did not influence survival. The prognostic model developed in the current study is simple and can be performed at admission. (Hepatology 1996;23:1448-1455.)

Most reports on fulminant hepatic failure (FHF) have been predominantly from the West,[1-9] and particularly from three countries: the United Kingdom,[1,2] Japan,[3,4] and France.[5] Based on these geographically limited observations, a new classification of this disease entity into hyperacute, acute, and subacute liver failure has been suggested.[2] These authors also suggested the adoption of this classification universally for a uniform terminology. The latter study has not been able to consider the disease characteristics in the tropical population, presumably because of the lack of published data from the tropics.

The cause and rapidity of the onset of hepatic encephalopathy in patients with FHF have been reported as important prognostic predictors.[1-3] However, the cause of FHF may have regional differences, and the rapidity of onset of encephalopathy after the occurrence of acute hepatitis may also vary among different populations because host factors play an important role in the severity of hepatic injury.

Various other factors, including the grade of encephalopathy, serum bilirubin, prothrombin time, serum alpha-fetoprotein, liver volume estimation using ultra-

Abbreviations: FHF, fulminant hepatic failure; Ig, immunoglobulin; HAV, hepatitis A virus; HDV, hepatitis D virus; HBV, hepatitis B virus; HEV, hepatitis E virus; HCV, hepatitis C virus.

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sound, blood ammonia levels, galactose elimination capacity, and bile acid conjugation, have been suggested to distinguish survivors and nonsurvivors among patients with FHF.[1-3,6-8,10-15] The prognostic criteria for FHF developed at King's college, London,[1] and at Clichy, France,[5] when reevaluated at another center, were found to have a lower specificity and sensitivity than reported in the original studies.[16] Orthotopic liver transplantation has become an established treatment option in patients with FHF[17-21] and is gradually becoming available in developing nations. Hence, there is a need for a prognostic model in patients with FHF in these countries.

The current study on FHF therefore was conducted prospectively in a single tertiary care center in North India to identify the demographic characteristics, causative spectrum, clinical features, natural course, and predictors of outcome among patients with FHF.

PATIENTS AND METHODS

Patients

Consecutive patients with FHF admitted to the gastroenterology ward of the All India Institute of Medical Sciences, New Delhi, between January 1987 and June 1993 were included in the study.

Diagnosis of FHF. The diagnosis of FHF was made by the presence of encephalopathy within 8 weeks of onset of illness.[12] Diagnosis of FHF was confirmed by presence of submassive or massive necrosis in the postmortem liver biopsy specimen in patients who died. Consent for the postmortem liver biopsy was obtained from the nearest relative of the deceased after explaining the purpose of the biopsy. Liver biopsy in the survivors was performed whenever possible after their coagulation profile was corrected and an informed consent was obtained.

Exclusion Criteria. Patients in whom the history was unreliable or the diagnosis was not confirmed by a combination of typical clinical features, liver function tests, and viral markers with or without liver biopsy were excluded.

Chronic liver disease was excluded by liver biopsy. In patients in whom a liver biopsy was not possible because of a deranged coagulation profile, the diagnosis of chronic liver disease was made on clinical, biochemical, and imaging criteria.

Study Variables

Duration of Prodrome. Period from onset of symptoms to the onset of icterus

Icterus-Encephalopathy Interval. Interval between detection of icterus to onset of hepatic encephalopathy

Pre-encephalopathy Period. Duration from onset of symptoms to onset of encephalopathy

Duration of Coma. Time from onset of encephalopathy till complete recovery from encephalopathy or death. Complete recovery from encephalopathy was considered when the patient became conscious and was found to be oriented to time, place, and person.

Grade of Coma. Coma was classified into four grades[22]:

Grade I: Loss of sleep rhythm, presence of drowsiness, confusion, hepatic flap

Grade II: Features of grade I encephalopathy with loss of sphincter control

Grade III: Unconscious, no response to oral commands, but responds to painful external stimuli

Grade IV: Unconscious, no response to external stimuli except decerebrate posturing to painful stimuli

Cerebral Edema.[23,24] Cerebral edema was defined by the presence of spontaneous decerebrate posturing, hypertension (supine blood pressure >150/90 mm Hg), bradycardia (pulse rate <10 beats/min from the expected pulse rate for given body temperature), pupillary changes, and presence of neurogenic hyperventilation. Neurogenic hyperventilation was diagnosed by the presence of hyperventilation in the absence of any metabolic or respiratory cause for hyperventilation. Presence of decerebrate posturing alone or the presence of any two of the four features were considered as evidence of cerebral edema.

Sepsis. Sepsis was diagnosed in the presence of pyrexia (body temperature >101°F) or hypothermia (body temperature <98°F) and neutrophilic leucocytosis (total leucocyte count >15,000/mm^3 with 80% or more polymorphs) and one or more of the following: positive blood culture, positive urine culture, radiological evidence of pneumonitis.

Cause of Death. The immediate antecedent event occurring within 12 hours of death, in the absence of any other possible factor that could cause a fatal outcome, was considered as the cause of death.

Coagulopathy. Prolongation of prothrombin time by more than 4 seconds over controls was considered as evidence of abnormal clotting mechanism. This was determined from the distribution of the prothrombin time among normal subjects. Values were considered abnormal when they were beyond the mean ± 3 SD range at our laboratory. Thromboplastin was derived from rabbit brain (Biopool Inc., CA) with an international sensitivity index value of 1.8.

Treatment Schedule

All patients were given standard supportive treatment with energetic intensive care monitoring. H_2 receptor antagonists for stress ulcer prophylaxis, appropriate antibiotics for sepsis, parenteral mannitol (20%), and ventilatory support for cerebral edema, fresh frozen plasma as and when required, gut sterilization, and mantainance of fluid and electrolytes were the mainstay of therapy.

Methods

Each patient had clinical evaluation at admission and every 1 to 2 hours thereafter. History of consumption of hepatotoxic drugs or indigenous treatment such as herbal therapy was inquired of the relatives of each patient. Liver dullness by percussion at admission was assessed by at least two physicians (one resident and one consultant) at admission and subsequently twice daily.[25-27] Pregnancy was diagnosed by a history of amenorrhea, urinary human chorionic gonadotrophin assay, and bedside ultrasound. The trimesters of pregnancy were calculated from the history and sonographic assessment of fetal dimensions.

Blood was drawn at admission and subsequently every day for liver function tests and various hematologic and biochemical assays. Sera were separated and stored at −70°C for subsequent viral assays.

Viral Markers. Each patient's serum sample was screened for hepatitis B surface antigen, immunoglobulin (Ig) M anti-HBc, and IgM anti-hepatitis A virus (HAV) using commercial micro-enzyme-linked immunosorbent assay test kits (Organon, Teknika, Netherlands; and Abbott). Serum samples positive for hepatitis B surface antigen or IgM anti-HBc were also tested for the presence of anti-hepatitis D virus (HDV). Tests for both IgG and IgM anti-HDV antibody were performed using commercial enzyme-linked immunosorbent

TABLE 1. Demographic and Clinical Profile of Patients With FHF

	Survivors	Nonsurvivors	Total
Number	143 (34%)	280 (66%)	423
M:F	71:72 (1:1)	129:151 (1:1.2)	200:223 (1:1.1)
Age			
mean ± SE*	26.5 ± 0.9	31.4 ± 0.8	29.5 ± 0.6
range	(14-65)	(7-80)	(7-80)
Prodrome	128 (89.5%)	246 (89%)	374 (88%)
Duration of prodrome (d)			
mean ± SE	4.4 ± 0.6	5.2 ± 0.4	4.7 ± 0.5
range	(0-20)	(0-22)	(0-22)
Duration of preencephalopathy period (d)			
mean ± SE	5.8 ± 0.5	6.3 ± 0.4	5.7 ± 0.2
range	(0-28)	(0-28)	(0-28)
Preencephalopthy period (d)†			
0-7	117 (81.8%)	224 (80.0%)	341 (80.6%)
8-14	17 (11.9%)	37 (13.2%)	54 (12.8%)
15-21	6 (4.2%)	13 (4.6%)	19 (4.5%)
22-28	3 (2.1%)	6 (2.1%)	9 (2.1%)
Icterus-encephalopathy interval (d)			
mean ± SE	4.3 ± 0.5	4.9 ± 0.3	4.7 ± 0.3
range	(0-21)	(0-21)	(0-21)
Icterus-encephalopathy interval (d)‡			
0-7	104 (72.7%)	201 (71.8%)	305 (72.1%)
8-14	23 (16.1%)	48 (17.1%)	71 (16.8%)
15-21	16 (11.2%)	31 (11.1%)	47 (11.1%)
22-28	Nil	Nil	Nil

* $P < .0001$; only three patients were younger than 15 years. Other parameters were similar amongst survivors and nonsurvivors ($P > .1$).

† 224 of 341 (66%) patients with FHF presenting with encephalopathy within 1 week of onset of symptoms died, in comparison with 56 of 82 (68%) similar patients who had encephalopathy after 1 week of onset of symptoms ($P > .1$). Similar observations were made when mortality rate was compared amongst patients presenting with encephalopathy within 2 weeks and after 2 weeks of onset of symptoms.

‡ 201 of 305 (66%) patients who presented with encephalopathy within 1 week of onset of icterus died, in comparison with 79 of 118 (67%) patients developing FHF after 1 week of onset of icterus ($P > .1$).

assay kits (Wellcome UK). Non-A, non-B FHF was diagnosed when the serum was negative for all of the above markers in the absence of a history of intake of hepatotoxins.

Sera from 50 consecutive patients with non-A, non-B fulminant hepatitis were also tested for hepatitis B virus (HBV) DNA to detect cryptic HBV infection, hepatitis E virus (HEV) RNA by reverse-transcription nested polymerase chain reaction using primers from nonstructural region of ORF-1, and hepatitis C virus (HCV) RNA by reverse-transcription nested polymerase chain reaction, using primers from the 5′ nontranslated region.[28-30] All samples were tested in duplicate. The amplified polymerase chain reaction products were confirmed either by Southern hybridization[29] or by liquid oligomer hybridization[31] with internal oligoprobes and labeled with [^{32}P]adenosine triphosphate (New England Nuclear, Boston, MA). The detailed steps of the procedure have already been reported elsewhere.[32]

TABLE 2. Causes of FHF

Cause	Survivors (n = 143)	Nonsurvivors (n = 280)	Total (%) (n = 423)
HAV	3 (2%)	4 (1.4%)	7 (1.7%)
HBV	39 (27%)	78 (27.8%)	117 (27.6%)
HDV	5 (3.5%)	11 (3.9%)	16 (3.8%)
Non-A, non-B	89 (62.2%)	175 (63%)	264 (62.4%)*
Antitubercular drug	7 (5%)	12 (4.3%)	19 (4.5%)

NOTE. The causative profile amongst survivors and nonsurvivors was similar ($P > .1$).

* Twenty-three (8.7%) were HBV carriers (HBsAg positive but IgM anti-HBc negative).

Statistical Analysis

Among survivors and nonsurvivors, qualitative variables were compared using the χ^2 test. Quantitative variables were compared using the Student's t test. Univariate Cox's regression, multivariate Cox's regression, and multiple stepwise logistic regression were performed using the BMDP software (University of California).[33-37] This was done to identify predictive variables for prognosis in patients with FHF. Kaplan-Meier survival analysis was performed for different strata of patients.[38,39] The specificity and sensitivity for each predictor identified on multivariate analysis and the combination thereof was then assessed.

RESULTS

During the study period, 430 patients with FHF were hospitalized, which accounted for 8% of our total hospitalized patients (n = 5,354) during the above period. Diagnosis was confirmed in 423 patients who were included in the present study. One hundred forty-three (34%) patients survived, and the remaining 280 (66%) patients died. Most patients who died had histological evidence of either submassive hepatic necrosis or mas-

TABLE 3. Dichotomous Variables Influencing Outcome (Univariate Analysis)

Variables	Survivors (n = 143)	Nonsurvivors (n = 280)
Age*		
<40 yr	129	208
≥40 yr	14	72
Grade of coma†		
I	17 (11.9%)	26 (9.3%)
II	44 (30.8%)	26 (9.3%)
III	45 (31.5%)	87 (31.1%)
IV	37 (25.9%)	141 (50.4%)
Mean grade of coma‡	2.7 ± 0.1 (0-4)	3.2 ± 0.1 (0-4)
Liver size (in percussion space)*		
<2	56 (39.1%)	193 (68.9%)
≥2	87 (60.9%)	87 (31.1%)
Mean size of liver (percussion space)†	2.8 ± 0.1 (0-6)	2.0 ± 0.1 (0-5)
Cerebral edema at admission*	44 (30.8%)	201 (71.8%)
Infection at admission*	7 (4.9%)	38 (13.6%)
Serum bilirubin (mg/dL)‡		
<15	100 (69.9%)	121 (43.3%)
≥15	43 (30.1%)	159 (56.7%)
Prothombin time prolongation over controls (s)*		
<25	115 (80.4%)	154 (55%)
≥25	28 (19.6%)	126 (45%)

* $P < .0001$.
† $P < .01$.
‡ $P < .001$.

sive necrosis. Liver biopsy could be done in 83 patients who survived, within 3 weeks of recovery, and showed the presence of acute hepatitis with bridging necrosis in all. In the remaining survivors, the diagnosis was achieved by clinical and biochemical features.

Clinical and Demographic Profile

The demographic profile of the patients is shown in Table 1. Most patients (n = 334) were younger than 40 years of age, and the male-to-female ratio was 1:1.1. A prodrome of fever, anorexia, or vomiting was present in 374 (88%) patients. The presence or duration of prodrome, preencephalopathy period, icterus-encephalopathy interval, and the duration of hepatic encephalopathy among survivors and nonsurvivors were similar ($P > .1$) (Table 1). Encephalopathy developed within 14 days in 395 (93.4%) patients, and none had encephalopathy after 4 weeks of onset of symptoms of acute hepatitis (Table 1). The mean (±SE) duration between onset of symptoms and encephalopathy was 5.7 (±0.2) days.

An analysis of the icterus-encephalopathy interval showed that 376 (89%) patients in the current series developed encephalopathy within 2 weeks of onset of icterus, and all patients had encephalopathy within 3 weeks of onset of icterus. The mean (±SE) interval between detection of icterus and encephalopathy was 4.7 (±0.3) days.

There were 223 (53%) women or girls, a quarter (n = 53) of whom were pregnant. The mortality rates were similar ($P > .1$) among pregnant women (35 of 53, 66%), age-matched nonpregnant women (116 of 170, 68%), and male patients with FHF (129 of 200, 65%). The mortality rate was also similar ($P > .1$) among pregnant women during the first, second, and third trimesters.

Among the 280 patients with a fatal outcome, death occurred in 207 (74%) within 72 hours of hospitalization, and 254 (94%) died within a week of hospitalization. A Kaplan-Meier survival analysis showed that the mean (± SE) survival time was 1.03 (±0.9) days, and the median survival was 4 days. All deaths except one occurred within 1 week of onset of hepatic encephalopathy. Cerebral edema was the single most important cause of death among our patients (71.8%). The other causes of death were sepsis (23.9%), renal failure (2.9%), and gastrointestinal bleeding (1.4%).

Cause

The causes of FHF are shown in Table 2. HAV, HBV, and HDV could be incriminated in 7 (1.7%), 117 (28%), and 16 (3.8%) patients, respectively. Nineteen (4.5%) patients negative for all of these viral markers had consumed antituberculous drugs (which included rifampicin and isoniazid in optimal doses) for a mean (±SD) period of 28 (±9) days (range, 13-64 days). It was presumed that antitubercular agents caused acute hepatitis in these patients. The remaining 264 (62.4%) patients did not have any identifiable markers of acute HAV, HBV, and HDV infections in their sera. None of these patients had history of consumption of any identifiable hepatotoxins, particularly herbal drugs. Their clinical and biochemical features were suggestive of acute viral hepatitis. These patients were considered to have non-A, non-B viral infection. Sera from 50 consecutive patients with non-A, non-B FHF were ana-

TABLE 4. Variables Derived From Multiple Logistic Regression

Step No.	Term Entered	*df*	Log Likelihood	Improvement in χ^2	*P*
0			−250.03		
1	Cerebral edema at admission	1	−217.8	64.5	<.00001
2	Serum Bilirubin ≥15 mg/dL	1	−208.1	19.5	<.0001
3	Prothrombin time ≥25 s over control	1	−200.7	14.7	<.0001
4	Age ≥40 yr	1	−193.7	14.2	<.0001
5	Grade of coma III or IV	1	−191.1	5.0	.025
6	Infection	1	−188.8	4.7	.03

TABLE 5. Multiple Logistic Regression

Term	Coefficient	SE	Coefficient/SE	Exponential Coefficient	Lower Band	Upper Band
Age ≥40 yr	1.3	0.37	3.6	3.8	1.8	7.9
Grade of coma >2	0.7	0.31	2.4	2.1	1.1	3.7
Cerebral edema	1.3	0.29	4.5	3.6	2.1	6.3
Infection	1.0	0.49	2.1	2.8	1.0	7.3
Serum Bilirubin ≥ 15 mg/dL	1.1	0.26	3.9	2.8	1.7	4.6
Prothombin time (prolongation ≥ 25 s over controls)	1.2	0.29	4.1	3.3	1.9	5.7

lyzed for HEV and HCV RNA. Twenty (40%) of these had isolated HEV RNA, 7 (14%) had isolated HCV RNA, and 11 (22%) had both HEV and HCV RNA. The remaining 12 (24%) patients did not have any viral markers in their serum. Thus, HEV either in isolation or along with HCV was the causative agent in 31 (62%) of these patients with FHF. None of these 50 patients had cryptic HBV infection.[28]

Prognostic Markers

The clinical variables that influenced survival in our patients are shown in Table 3. Older age, higher grades of encephalopathy, smaller liver size on percussion, presence of overt cerebral edema, and sepsis at admission were detected in a significantly higher proportion of patients who died in comparison with those who survived ($P < .01$). The preencephalopathy period, icterus-encephalopathy interval, and cause among the survivors and nonsurvivors were similar (Tables 1, 2). Other hematologic and biochemical investigations were similar among survivors and nonsurvivors.

Univariate Cox's Analysis

Univariate Cox's regression was used to determine if the outcome and the duration of survival were influenced by these variables. It was observed that all of the variables found to be significantly associated with outcome on simple analysis were also significant on the univariate Cox's regression.

Dichotomization of Predictive Factors

Variables found significant on Cox's univariate regression were then dichotomized for best discrimination between survivors and nonsurvivors by the construction of receiver-operated curves. The best cutoff level for age was ≥40 years, grade of coma >2, liver size ≤2 intercostal spaces on percussion, serum bilirubin ≥15 mg/dL, and prothrombin time prolongation of ≥25 seconds over controls. For all other variables, it was the presence or absence of the event.

Multivariate Analysis

Multiple stepwise logistic regression was performed to discriminate survivors and nonsurvivors. The independent predictors of outcome were age ≥40 years, grade of coma >2, presence of infection, serum bilirubin ≥15 mg/dL, and prolongation of prothrombin time by ≥25 seconds over control (Tables 4 and 5). Cox's proportional hazard regression was then performed to identify the independent predictors of outcome as well as the duration of survival. This showed that four variables that independently predicted outcome were age ≥40 years, presence of cerebral edema at the time of hospitalization, serum bilirubin ≥15 mg/dL, and prothrombin time ≥25 seconds over controls (Table 6).

To identify the predictive value of one or more of the four variables on survival, five strata were constructed, depending on the number of adverse factors present. A Kaplan-Meier analysis of each of these five groups is shown Fig. 1. The pattern of survivors and nonsurvivors was significantly different in the five groups ($P < .01$). The sensitivity and specificity of each group depending on the number of adverse prognostic markers is shown in Table 7. It was seen that, with an increasing number of adverse prognostic factors, the mortality increased.

DISCUSSION

The cause and clinical spectrum of FHF at our center were different from those in the West.[1,5] In the current study, all patients had encephalopathy within 4 weeks of onset of symptoms of hepatitis. These observations are in contrast to reports from the United Kingdom,[1,2] France,[5] and Japan,[3,4] where FHF has been documented to occur up to 8 weeks after the onset of the symptoms of acute hepatitis and jaundice. Four weeks

TABLE 6. Cox's Multiple Regression Analysis

Variable	*df*	Coefficient	SE	Coefficient/SE	Global χ^2	*P*
1. Cerebral edema	1	0.87	0.14	5.95	58.8	<.0001
2. Prothrombin time prolongation ≥ 25 s over controls	2	0.43	0.13	3.31	66.8	<.0001
3. Serum bilirubin ≥ 15 mg/dL	3	0.29	0.13	2.18	73.2	<.0001
4. Age ≥40 yr	4	0.29	0.14	2.02	77.2	<.0001

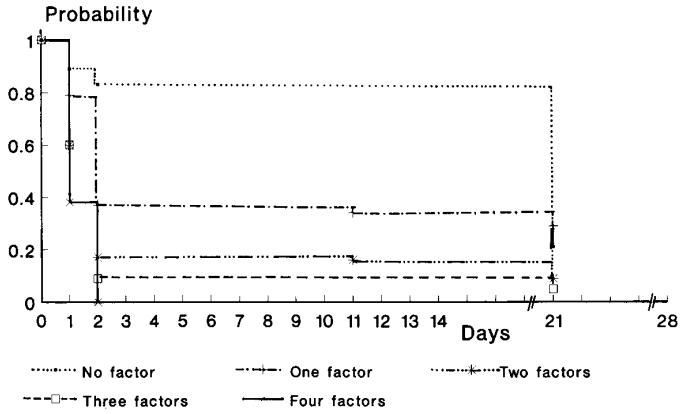

FIG. 1. Survival in patients with fulminant hepatic failure in relation to the presence of an increasing number of adverse prognostic factors. The survival in the five strata were significantly different (log rank test, $P < .0001$). Patients with three or four risk factors did not differ significantly in the duration of survival ($P = .08$).

after onset of acute hepatitis, liver failure in this country has a different clinical spectrum. It is recognized as subacute hepatic failure, a distinct clinical entity in which liver failure appears as progressive ascites, and encephalopathy is rare.[40,41] Thus, the definition of FHF for the Indian subcontinent should be the onset of hepatic encephalopathy within 4 weeks of occurrence of symptoms of acute hepatitis. The difference in the timing of clinical presentation of FHF in our patients compared with those reported from the United Kingdom may be related to the differences in causative agents and the host factors.[42]

A quarter of our female patients with FHF were pregnant, which is higher than the 3% pregnancy rate among the female population in this country.[43,44] However, pregnancy per se or the duration of the gestation did not influence the mortality in the current study. During epidemics of HEV infection, pregnant women have been reported to have a high risk of developing acute hepatitis as well as FHF compared with nonpregnant females and males.[45-51] Based on these studies, it is believed that pregnant women with FHF have higher mortality than nonpregnant females and males with FHF, which was not substantiated in the current study. Explanation for this difference is unclear. However, mortality rates among pregnant patients compared with nonpregnant females and males with FHF have not been prospectively evaluated in any of the previous studies.[45-50]

In the current study, one third of the patients had evidence of either acute HBV or HAV or HDV infection, and approximately 5% were diagnosed to have FHF subsequent to use of antitubercular drugs (Table 2). The remaining patients (n = 264) had clinical features suggestive of viral hepatitis, did not give history of consumption of any identifiable hepatotoxins, and their sera were negative for markers of acute HBV, HAV, and HDV infection. We diagnosed them as patients with presumptive acute non-A, non-B viral infection, although of course, alternative diagnosis, including toxic, drug-induced, or autoimmune hepatitis cannot be ruled out with certainty. Similar observations incriminating non-A, non-B virus as the major cause of FHF have been reported from this country.[52] Thus, most of our patients with FHF and conceivably as many as 95% were caused by hepatotropic viral infection.

HCV and HEV constitute the identifiable non-A, non-B viruses. Their role as causative agents of FHF in sporadic setup has remained unclear.[53-57] HEV could not be incriminated as a cause of sporodic fulminant hepatitis in the West.[53-55] The current study documented that HEV caused FHF in the sporadic setup in this country, which was evident by detection of HEV RNA either in isolation or along with HCV RNA in 31 (62%) of the 50 non-A, non-B fulminant hepatitis who were tested for HEV and HCV RNA. HEV being endemic in India, it may be an important causative agent among patients with non-A, non-B fulminant hepatitis.

The role of HCV in FHF has remained controversial. A study from Japan reported the presence of anti-HCV antibody or HCV RNA among most patients with FHF,[56] whereas studies from France,[57] the United States,[53,54] and the United Kingdom[55] have not been able to implicate HCV as an important cause of FHF. The documentation of HCV RNA in isolation (n = 7) or along with HEV RNA (n = 11) among 50 non-A, non-B FHF tested for these viruses indicate that either

TABLE 7. Assessment of Prognostic Indicators in Patients With FHF

Variable	No.	Death	Sensitivity	Specificity	Positive Prediction	Negative Prediction	Diagnostic Accuracy
Age ≥40 yr	86	72	83.7	38.3	25.7	90.2	47.5
Cerebral edema at admission	240	196	81.7	54.1	70	69.2	69.7
Serum bilirubin (≥15 mg/dL)	182	141	77.5	46.8	56.6	69.9	61.3
Prothrombin time (≥25 s over control)	154	126	81.8	42.8	45	80.4	57.0
Multiple adverse factors present							
Any 1 factor	146	82	56.1	79.7	86.3	44.3	63.3
Any 2 factors	115	93	80.9	79.7	87.7	69.9	80.4
Any 3 factors	86	80	93	79.7	86.0	89.5	87.3
All 4 factors*	13	12	92.3	79.7	48	98.1	81.8

* All four factors were present only in 13 patients. This resulted in an apparently lower prediction of mortality in these patients. This is attributable to the small number of patients assessed in this group.

HCV infection caused the disease or an HCV carrier state made these patients more susceptible to another hepatotropic viral infection, resulting in severe liver injury. The latter possibility seems more probable because (1) most non-A, non-B FHF with HCV RNA in their sera also had HEV RNA (11 of 18, 61%); and (2) Western reports could not incriminate HCV as an isolated cause of FHF.[53,55,57]

Thus, in contrast to Western studies, where drugs, hepatitis A, and hepatitis B viruses are the major causes of FHF, non-A, non-B presumably was the major cause of FHF in the current study.

Studies from the West have incriminated the cause of FHF and rapidity of onset of encephalopathy after occurrence of acute hepatic illness as important prognostic predictors.[1-5] In these reports, FHF due to non-A, non-B virus(es) and drugs had worse outcome than other causes of FHF,[1-3] and patients with the most rapid onset of encephalopathy had the best chance of recovery.[1,5] However in the current study, the causative distribution and rapidity of onset of encephalopathy was similar among survivors and nonsurvivors (Tables 1, 2). These differences might have been attributable to the heterogeneous cause of FHF in the West, whereas hepatotropic viruses were the predominant cause of FHF in the current study. Thus, the classification suggested by O'Grady et al.[2] may not be applicable in this country. Univariate analysis of the various other variables that were analyzed as prognostic indicators of FHF at admission (Table 3), however, showed predictors of outcome similar to those of other authors.[6,8,58] Multiple logistic regression detected two additional variables than Cox's multiple regression as independent risk factors for outcome (Tables 5 and 6). Previous studies have shown that when multivariate analysis is performed using both logistic regression and Cox's regression, the variables generated by the Cox's analysis are more reliable.[61] This is because the latter takes into account the time of the event also. Thus, the variables generated by Cox's analysis such as age $\geq$40 years, presence of cerebral edema at admission, serum bilirubin $\geq$15 mg/dL, and prolongation of prothrombin time over controls by $\geq$25 seconds were accepted finally as independent risk factors of outcome in our patients with FHF. These observations were similar to those by other authors, who found that in viral hepatitis, age, serum bilirubin, and prolongation of prothrombin time were factors that independently predicted the prognosis.[12,59,60] Earlier studies have used other measures that include factor V and α-fetoprotein.[8,10,19,58] They suffer from the disadvantage of the small number of patients studied, the complex method or expertise required for analyzing each factor, and the delay in obtaining the results.

One of the important prognostic marker in the current study was presence of overt clinical features suggestive of cerebral edema at the time of hospitalization. Cerebral edema is most often diagnosed and monitored in Western countries through the use of intracranial pressure recordings and high-resolution imaging studies. Because these were not readily available at our institution, "overt cerebral edema" was diagnosed based on clinical neurological findings (clinical diagnostic criteria are mentioned previously in Patients and Methods).[24,62] We recognize that this probably underestimates the true incidence of cerebral edema in our population with FHF. Nevertheless, given this available parameter, our data suggest that "overt cerebral edema," when recognizable clinically, carries with it a very poor prognosis.

In conclusion, the current study is the largest reported series on hepatotropic virus–induced FHF in a tropical developing region. All of the patients with FHF in this series developed hepatic encephalopathy within 4 weeks of onset of acute hepatitis. Most of the FHF were caused by presumptive non-A, non-B viral infection. HEV in the sporadic setup in its endemic region caused FHF. Mortality rate was highest within 72 hours of hospitalization. The prognostic model developed in this study was simple, reliable, rapid, and relevant to patients in developing countries for assessment for liver transplantation.

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