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ORIGINAL ARTICLE

Acute Liver Failure Due to Hepatitis E Virus Infection Is Associated with Better Survival than Other Etiologies in Indian Patients

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Abstract

Background and Aim Hepatitis E virus (HEV) is a global disease and an important cause of acute liver failure (ALF) in the Indian subcontinent. The aim of this study was to assess the differences in the course of HEV-ALF as compared to other etiologies of ALF.

Methods We compared the clinical course, complications, and outcomes of HEV-ALF with other etiologies. We assessed the prognostic factors and compared existing prognostic scores in HEV-ALF patients.

Results One thousand four hundred and sixty-two ALF patients were evaluated between January 1986 and December 2015. HEV was the etiology of ALF in 419 (28.7%) cases, whereas non-A non-E hepatitis, HBV and anti-tuberculosis therapy (ATT) were the etiologies in 527 (36.0%), 128 (8.8%), and 103 (7.0%) cases, respectively. The frequency of cerebral edema in HEV-ALF (41.3%) was lower than that in non-A non-E ALF (52.9%; $P < 0.001$) and HBV-ALF (52.8%; $P = 0.024$). Infection and seizures were significantly less in patients with HEV-ALF compared to non-A non-E and HBV-ALF ($P = 0.038$ and 0.022, respectively). The survival of HEV-ALF patients was significantly better (55.1%, $P < 0.001$) than patients of other etiologies—including ATT (30.0%), non-A non-E (38.1%) and HBV (35.9%). In HEV-ALF patients, age, female sex, cerebral edema, prothrombin time >60 s, infection, and total bilirubin were observed as independent predictors of outcome on multivariate logistic regression analysis. Model for end-stage liver disease, acute liver failure study group model and King's College Hospital criteria had poor discriminative accuracy for outcome (area under receiver operator characteristic curve 0.63–0.64) in HEV-ALF.

Conclusions Hepatitis E virus-associated ALF has a better outcome than ALF of other etiologies.

Keywords ALF · Prognosis · Liver transplant · Hepatitis A virus · Cerebral edema

Abbreviations

ALF	Acute liver failure
ALFED	Acute liver failure early dynamic
ATT	Anti-tuberculosis therapy
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HEV	Hepatitis E virus
INR	International normalized ratio
KCH	King's College Hospital criteria
LT	Liver transplant
MELD	Model for end-stage liver disease

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Introduction

Acute liver failure (ALF) is a rare, potentially fatal complication of severe hepatic illness. The various causes of ALF include hepatitis virus infections (most common cause in the East), drugs like paracetamol (most common cause in the West), metabolic causes, toxins, ischemia, and rare miscellaneous causes [1–4]. Among the hepatitis viruses, HEV is reported to be a common cause of ALF from India, Pakistan, Bangladesh, and Somalia [2, 3, 5]. In contrast, HEV infection accounts for only 0.4% of ALF cases in the USA [6]. A recent report from Germany estimated 10–15% of ALF to be related to HEV [7]. A global disease burden study indicated that HEV is a major cause of ALF and also endemic in Africa, central Asia, south, and southeast Asia [8]. Annually, HEV is responsible for 20.1 million incident cases, 3.4 million symptomatic cases, 70,000 deaths, and 3000 stillbirths [8]. Furthermore, another global disease burden study highlighted the fact that the absolute burden of viral hepatitis and its related mortality have increased between 1990 and 2013 [9].

Whether etiology of ALF plays a major role in the outcome of the disease is not yet clear. A prior study did indicate that HEV-ALF may be associated with a better outcome [10], but this study was limited by a small sample size. In addition, factors influencing outcome of HEV-ALF are not clear. The definite management of ALF is liver transplantation (LT). However, shortage of organs and high procedural cost prevent the routine use of LT. Also, there is spontaneous recovery of ALF patients in 30–40% of cases. Therefore, it is important to select ALF patients judiciously for liver transplantation, to allow the allocation of the organ to patients who require it the most [11]. The present study was undertaken to evaluate the clinical course, complications, and outcomes of HEV-ALF and compare these with ALF of other etiologies. In addition, we also assessed predictors of outcome and compared prognostic scores in HEV-ALF.

Patients and Methods

Study Population

All consecutive ALF patients admitted to the All India Institute of Medical Sciences, New Delhi, India between January 1986 and December 2015 were included in this observational retrospective study. Patients with incomplete records and unclear diagnosis of ALF were excluded.

Definitions of Variables

ALF was defined as per the International Association for the Study of Liver (IASL) criteria—occurrence of encephalopathy within 4 weeks from the onset of symptoms in the absence of preexisting liver disease [2]. Grading of encephalopathy was carried out as follows [12]: *Grade 1*, loss of sleep rhythm, drowsiness, confusion, and flapping tremors; *Grade 2*, features of grade 1 encephalopathy with loss of sphincter control in addition; *Grade 3*, unconsciousness with no response to oral commands, but responding to painful stimuli; *Grade 4*, deep unconscious state, with no response to pain. Encephalopathy was categorized as "early" encephalopathy (grade 1 and 2) and "advanced" encephalopathy (grade 3 and 4). Pre-encephalopathy interval and icterus-encephalopathy interval were defined as the intervals from the onset of prodrome and jaundice, respectively, to the onset of hepatic encephalopathy [2]. Encephalopathy-admission interval was defined as the interval from onset of encephalopathy to admission to the hospital. Cerebral edema was defined clinically by the presence of spontaneous or inducible decerebrate posturing, or the presence of two or more of the following: hypertension (blood pressure $\geq$150/90 mmHg), bradycardia (heart rate, <60/min), pupillary changes, and neurogenic hyperventilation [2].

Infection was diagnosed by the presence of pyrexia (temperature >101 °F) or hypothermia (temperature <98 °F) and leucocytosis (total leukocyte count >15,000/mm^3, with $\geq$ 80% polymorphs), and one or more of the following: positive blood culture, positive urine culture, and/or radiological evidence of pneumonitis [2]. Renal failure was diagnosed if patients developed decreased urine output (<400 mL in 24 h), with serum creatinine >1.5 mg/dL and blood urea >40 mg/dL, despite hydration (objectively assessed by a central venous pressure of 10 cm of saline or more) [2].

Management Protocol

All patients were admitted to the Gastroenterology intensive care unit or ward. A uniform management protocol was followed, which included continuous, non-invasive cardiac, oxygen saturation and blood pressure monitoring, stress ulcer prophylaxis (i.v. ranitidine twice a day), inotropic support to maintain mean arterial pressure above 60 mmHg, and elective ventilation for patients with cerebral edema and/or grade 4 encephalopathy. Central venous lines were inserted in all cases. Blood sugar was monitored two hourly. Serum electrolytes, blood urea, and serum creatinine were estimated daily.

Daily microbiological surveillance was carried out in all ALF patients—blood and urine cultures were done for all patients irrespective of presence or absence of infection. Tracheal aspirates were obtained daily in ventilated patients by the catheter suction of endotracheal tubes. Prophylactic parenteral antibiotics were administered at presentation in all cases (piperacillin–tazobactam, vancomycin, and fluconazole combination during the year 2004–2010; thereafter, from the year 2011 onwards, piperacillin–tazobactam was replaced with cefoperazone and sulbactam due to increasing antibiotic resistance). This prophylactic antibiotic therapy was modified as indicated, based on the results of positive cultures. Antibiotics were administered till complete neurological recovery and absence of clinical or radiological evidence of ongoing infection. Renal replacement therapy (hemodialysis) was used whenever required.

Demographic details including age, gender, and pregnancy were obtained from our prospectively maintained database. The details of clinical presentations, including prodrome to encephalopathy interval, icterus to encephalopathy interval, encephalopathy to admission interval, grade of encephalopathy and cerebral edema were noted. In addition, the results of laboratory investigations—levels of serum bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum albumin, blood urea, and serum creatinine—were collected. The value of international normalized ratio (INR) was not available for the initial years of the study, as it was not carried out routinely at our hospital at that time. Therefore, we have described the prolongation of prothrombin time seen in these patients. Data regarding ALF etiologies and complications during hospital stay such as seizures, infection, and renal failure were obtained. King's college hospital criteria (KCH) [13], model for end-stage liver disease (MELD) [14], acute liver failure study group model (ALFSG) [15], and acute liver failure early dynamic (ALFED) scores were calculated [16]. We considered HEV as a favorable etiology for calculating the ALFSG score [15].

All patients were followed until recovery or demise, and none of these patients underwent liver transplantation or liver replacement therapy. The study was approved by the Institute ethics committee, and consent was obtained from the nearest kin of each patient.

Viral Nucleic Acid and Serological Tests

For diagnosis of hepatitis A virus (HAV) infection, we used serological testing for anti-HAV IgM by commercial ELISA (till year 2010) or automated assay (VIDAS anti-HAV IgM, Biomureix USA). For diagnosis of HEV, both qualitative nested RT-PCR (reverse transcriptase PCR) for HEV RNA and serological determination of anti-HEV IgM using commercial ELISA kit was carried out [17, 18] and the patients positive for any one or both of these tests were considered HEV positive. For hepatitis B virus (HBV) infection, patients were serologically tested for HBsAg, HbeAg, total anti-HBc, and anti-HBe by commercial ELISA and automated VIDAS assay. Nucleic acid testing for HBV DNA was performed by nested PCR (till 2008) and real-time PCR. The ALF patients who tested negative for HAV, HBV, and HEV were designated as non-A non-E patients.

Statistical Analysis

Normally distributed continuous variables were expressed as mean ± SD, and the continuous variables with skewed distribution were expressed as median (IQR). Mann–Whitney *U* test was used for continuous non-normally distributed variables, and Chi-square or Fisher's test for categorical variables. For comparison of the continuous covariates among HEV, non-A non-E hepatitis, HBV, and ATT groups, one-way analysis of variance (ANOVA) with Bonferroni correction as a post hoc test was used. Similarly, the comparisons among these groups for skewed data were performed by the Kruskal–Wallis test followed by the Mann–Whitney test with adjusted *P* values.

In the HEV-ALF cohort, univariate analysis was performed to compare survivors and non-survivors using an independent *t* test or Mann–Whitney *U* test for continuous variables, and a Chi-square test or Fisher's exact test for categorical variables, wherever applicable. P value <0.05 was taken as significant. Multivariable logistic regression analysis was carried out for identification of variables associated with mortality. Stepwise regression was used such that variables with a significance of $P \leq 0.10$ in the bivariate analysis were retained for multivariate analysis. The variables were selected by using stepwise selection procedure in the multivariable analysis with entry probability 0.05 and removal probability 0.1. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CI) were calculated. Receiver operator characteristic (ROC) curves were used to assess the performance of the various prognostic models. The threshold cutoffs of these prognostic models were identified by the ROC curve analysis. Based on these cutoff values, different diagnostic measures such as sensitivity, specificity, and predictive values were reported. The comparison of areas under ROC curves (AUROC) was performed using the Hanley and McNeil method. Statistical analysis was carried out by SPSS software (version 20, SPSS Inc. Chicago, IL).

Results

A total of 1462 ALF cases were admitted during the period 1986–2015 (30-year study period). Most of these patients were young, with median age 25 years (IQR, 21–32 years), and more females ($n = 820$, 56.1%) than males. HEV was the etiology in 419 (28.7%) cases. Non-A non-E, HBV, and ATT were the etiologies in 527 (36.0%), 128 (8.8%), and 103 (7.0%) cases, respectively. A small percentage of patients had acute viral dual-infection [60 (4%)] and HAV [23 (2%)] as the etiology. In 138 (9%), only chronic markers were positive—HbsAg in 123, anti-HCV Ab in 10,

Table 1 Comparison of baseline characteristics, laboratory parameters, complications and survival rates between patients with ALF due to hepatitis E virus (HEV), non-A non-E, hepatitis B virus (HBV), and anti-tuberculosis drugs (ATT)

Variables	HEV ($N = 419$)	Non-A, non-E ($N = 527$)	Acute HBV ($N = 128$)	ATT ($N = 103$)	P value
Mean age (years) ± SD	26.8 ± 9.3	28.8 ± 12.1	29.2 ± 13.1	31.2 ± 14.4	0.002*
Women [n (%)]	287 (68.5%)	263 (49.9%)	67 (52.3%)	72 (69.9%)	<0.001†,‡,§
Pregnancy [n (% of women)]	166 (57.8%)	81 (30.8%)	9 (13.4%)	6 (8.3%)	<0.001*,†,‡,§,¶
Prodrome-encephalopathy interval (days)	6 (4–10)	6 (3–10)	7 (4–14)	6 (4–14)	0.001†,‡
Encephalopathy-admission interval (days)	1 (1–2)	1 (1–2)	2 (1–2)	2 (1–4)	0.10
Icterus-encephalopathy interval (days)	4 (2–7)	4 (2–8)	5 (3–12)	7 (3–10)	<0.001*,‡,¶
Encephalopathy grade [n (%)]					
I–II	95 (23.6%)	110/517 (21.3%)	19/123 (15.4%)	29 (28.4%)	0.10
III–IV	308 (76.4%)	407/517 (78.7%)	104/123 (84.6%)	73 (71.6%)	
Cerebral edema at admission [n (%)]	170 (41.3%)	275 (52.9%)	66 (52.8%)	44 (43.6%)	0.002†,‡
Bilirubin level (mg/dL)	13.5 (10.5–18.3)	14.8 (9.8–22.0)	16.2 (11.8–25.2)	14 (8.5–21.5)	0.001‡
AST (IU/L)	436 (163–964)	300 (120–770)	565 (232–951)	322 (141–627)	<0.001*,†,¶,‖
ALT (IU/L)	733 (300–1522)	571 (129–1250)	983 (396–1696)	334 (132–809.5)	<0.001*,†,¶,‖
Prothrombin time prolongation [n (%)]					
<25 s	185 (44.2%)	289 (54.8%)	48 (37.5%)	42 (40.8%)	0.001†,§
25 to <60 s	156 (37.2%)	172 (32.6%)	60 (46.9%)	43 (41.7%)	
≥60 s	78 (18.6%)	66 (12.5%)	20 (15.6%)	18 (17.5%)	
Alkaline phosphatase (U/L)	259 (171–371)	205 (27–343)	266.5 (167–388)	162.5 (22–269)	<0.001*,†,¶,‖
Serum albumin (mg/dL)	2.8 (2.4–3.3)	3 (2.5–3.5)	3 (2.5–3.4)	2.9 (2.5–3.4)	0.150
Blood urea (mg/dL)	18 (14–29)	21 (15–35)	19.5 (14–30)	21 (15–38)	0.040*,†
Serum creatinine (mg/dL)	0.8 (0.5–1.1)	0.8 (0.5–1.1)	0.8 (0.6–1.2)	0.8 (0.5–1.2)	0.561
Complications during hospital stay [n (%)]					
Gastrointestinal bleed	23/413 (5.6%)	35/510 (6.9%)	5/118 (4.2%)	10/103 (9.7%)	0.649
Seizures	49 (11.9%)	49 (9.6%)	24 (20.5%)	14 (13.6%)	0.011‡,¶
Infection	148/384 (38.5%)	124/496 (25.0%)	56/112 (50.0%)	39/102 (38.2%)	<0.001‡§¶
Renal failure	55 (13.1%)	76 (14.4%)	16 (12.5%)	18 (17.5%)	0.656
Length of hospital stay (days)	7 (5–10)	6 (4–9)	4 (3–8)	5 (3–7)	0.002*,‡
Survival [n (%)]	231 (55.1%)	201 (38.1%)	46 (35.9%)	31 (30.1%)	<0.001*,†,‡

All variables are expressed as median (IQR), unless stated otherwise

* Significant between HEV and ATT

† Significant between HEV and non-A non-E

‡ Significant between HEV and HBV

§ Significant between ATT and non-A non-E

¶ Significant HBV and crypto

‖ Significant between HBV and ATT

and both HBsAg and anti-HCV Ab in 5. No serology reports were available for 64 (4%) of patients. We identified HEV, non-A non-E, HBV, and ATT as the major groups for further analysis.

Comparison of Clinical Characteristics, Laboratory Parameters, Complications, and Survival Rates Between HEV, Non-A Non-E, HBV, and ATT Induced ALF

The mean age of patients with HEV-ALF was younger than that of ATT-ALF cases (26.8 vs. 31.2; $P = 0.002$). The icterus-encephalopathy interval was shorter in HEV-ALF cases than those with HBV-ALF or ATT-ALF (4 vs. 5 and 7 days, respectively; $P < 0.001$). The frequency of cerebral edema in HEV-ALF (41.3%) was lower than that in non-A non-E ALF (52.9%; $P < 0.001$) and acute HBV-ALF (52.8%; $P = 0.024$). The proportion of patients with PT prolongation >25 s in HEV-ALF (55.8%) was significantly higher than in non-A non-E (45.2%) ($P = 0.002$). Complications like infection and seizures were significantly less in patients with HEV-ALF than in HBV-ALF ($P = 0.038$ and 0.022, respectively). The proportion of pregnant females was higher in HEV-ALF (57.9%) as compared with ALF of other etiologies such as non-A non-E (30.8%), acute HBV (13.4%) and ATT (8.3%), $P < 0.001$ for all. There were no differences in EA interval, encephalopathy grade, serum albumin, serum creatinine and renal failure among patients of different etiologies (Table 1).

The survival of ALF patients with HEV etiology (55.1%) was significantly better ($P < 0.001$) than ALF of other etiologies—ATT (30.0%), non-A non-E (38.1%), HBV (35.9%). There were no significant differences in survival between ATT, non-A non-E and HBV-ALF patients.

The median interval of hospitalization for HEV-ALF patients was 5 days (range 1–22 days), and mortality was observed in 188 (44.9%) of 419 patients. There was a trend toward improved survival over the past 3 decades (1986–1995: 50%, 1996–2005: 54.9% and 2006–2015: 61.5%), but this was not statistically significant.

Predictors of Mortality in HEV-ALF Patients

HEV-ALF non-survivors were older, and more likely to be females. The frequency of advanced HE and cerebral edema was higher in non-survivors, and parameters such as total leukocyte count, total bilirubin, frequency of infection, the proportion of patients with PT > 60 s were higher compared to survivors, whereas the hemoglobin and blood urea levels were lower (Table 2).

On multivariate logistic regression analysis, age (OR 1.04; 95% CI 1.01–1.07), female sex (OR 1.83; 95% CI 1.01–3.30), cerebral edema (OR 2.48; 95% CI 1.49–4.11), prothrombin time >60 s (OR 3.34, 95% CI 1.58–7.05), infection (OR 2.73; 95% 1.63–4.58), and total bilirubin

Table 2 Comparison of variables between survivor and non-survivor HEV-ALF patients

Variables	Survivors ($N = 231$)	Non-survivors ($N = 188$)	P value
Mean age (years) ± SD	25.5 ± 7.6	28.5 ± 10.8	0.001
Sex (men/women) [n (%)]	84 (36.4%):147 (63.6%)	48 (25.55):140 (74.5%)	0.018
Pregnancy [n (% of women)]	85/147 (57.8)	81/140 (57.8)	1.0
Icterus-encephalopathy interval (days)	4 (2–7)	4 (2–7)	0.262
Encephalopathy grade [n (%)]			
I–II	68 (31.6%)	27 (14.4%)	<0.001
III–IV	147 (68.4%)	161 (85.6%)	
Cerebral edema at admission [n (%)]	63 (28.1)	107 (56.9)	<0.001
Hemoglobin (g/dL)	12.1 (10.3–13.8)	11.3 (9.3–12.9)	0.022
Total leukocyte count (/mm^3)	12,800 (9250–17,400)	15,250 (11,200–21,150)	0.004
Platelet count ($\times 10^3$/mm^3)	192 (126–275)	194 (120–251)	0.759
Bilirubin level (mg/dL)	12.7 (9.7–16.6)	15.3 (11.8–20.7)	<0.001
AST (IU/L)	446 (149.5–1025)	420 (178–844)	0.849
ALT (IU/L)	831 (345–1749)	668 (264–1229)	0.040
Alkaline phosphatase (U/L)	266.5 (183–373)	254 (166–348)	0.629
Serum albumin (mg/dL)	2.9 (2.5–3.4)	2.7 (2.4–3.2)	0.022
Prothrombin time prolongation (s)	30 (20–45)	37 (28–60)	0.004
Blood urea (mg/dL)	19 (14–31)	17 (14–26)	0.029
Serum creatinine (mg/dL)	0.8 (0.5–1)	0.8 (0.5–1.2)	0.812
Infection [n (%)]	49/198 (24.7%)	99/186 (53.2%)	<0.001

All variables are expressed as median (IQR) unless stated otherwise

Table 3 Comparison of HEV-ALF patients evaluated between 1986 and 2000 and between 2001 and 2015

Variables	HEV-ALF between 1986 and 2000 ($N = 166$)	HEV-ALF between 2001 and 2015 ($N = 253$)	P value
Mean age (years) ± SD	26.7 ± 10.1	26.9 ± 8.8	0.709
Women [n (%)]	125 (75.3%)	162 (64.0%)	0.018
Pregnancy [n (% of women)]	81 (64.8%)	85 (52.5%)	0.041
Prodrome-encephalopathy interval (days)	6 (3–9)	6 (4–10)	0.486
Encephalopathy-admission interval (days)	1 (1–2)	1 (1–2)	0.810
Icterus-encephalopathy interval (days)	5 (2–8)	3 (2–6)	<0.001
Encephalopathy grade [n (%)]			
I–II	19/164 (11.6%)	76/239 (31.8%)	<0.001
III–IV	145/164 (88.4%)	163/239 (68.2%)	
Cerebral edema at admission [n (%)]	88 (53.7%)	82 (33.1%)	<0.001
Bilirubin level (mg/dL)	13.5 (10.7–18.3)	13.5 (10.2–18.2)	0.742
AST (IU/L)	285 (120–835)	500 (202–1070)	<0.001
ALT (IU/L)	473 (130–1131)	903 (472–1660)	<0.001
Prothrombin time prolongation [n (%)]			
<25 s	98 (59.0%)	87 (34.4%)	<0.001
25 to <60 s	41 (24.7%)	115 (45.5%)	
≥60 s	27 (16.3%)	51 (20.2%)	
Alkaline phosphatase (U/L)	231 (38–346)	275 (203–379)	<0.001
Serum albumin (mg/dL)	2.9 (2.5–3.3)	2.8 (2.4–3.3)	0.333
Blood urea (mg/dL)	18 (14–26)	18 (14–32)	0.469
Serum creatinine (mg/dL)	0.7 (0.4–0.9)	0.9 (0.6–1.25)	<0.001
Complications during hospital stay [n (%)]			
Gastrointestinal bleed	6/166 (3.6%)	17/253 (6.7%)	0.049
Seizures	15 (9.0%)	34 (13.9%)	0.163
Infection	35/163 (21.5%)	113/221 (51.1%)	<0.001
Renal failure	19 (11.4%)	36 (14.2%)	0.461
Length of hospital stay (days)	7 (5–9)	7 (5–10)	0.573
Survival [n (%)]	75 (45.2%)	156 (61.7%)	0.001

All variables are expressed as median (IQR), unless stated otherwise

(OR 1.04; 95% CI 1.01–1.08) were significant independent predictors of outcome.

Comparison of King's College Hospital Criteria, Model for End-Stage Liver Disease, Acute Liver Failure Study Group Model and Acute Liver Failure Early Dynamic Model for Predicting Outcome in HEV-ALF

The comparisons for prediction of outcomes in HEV-ALF using 4 available prognostic scores—KCH criteria, MELD, ALFSG, and ALFED model—were carried out in ALF patients admitted after 2001 with a hospital stay of more than 2 days ($n = 244$) (Prior to 2001, values of both INR and ammonia were not available in the database. INR is a component of KCH, MELD, ALFSG, and ALFED scores, whereas ammonia is required for calculation of ALFED score). Comparison of HEV-ALF patients evaluated before and after 2001 is shown in Table 3. Clinical presentations of the two cohorts were different. Patients evaluated after 2001 had higher aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and serum creatinine levels. In addition, complications like gastrointestinal bleeding and infection were higher; proportion of female patients and complications like cerebral edema were lower. The overall survival was 61.7% in patients after 2001, as compared with 45.2% in patients before 2001 ($P = 0.001$).

The ALFED score had the best discriminative accuracy (AUROC: 0.91), followed by MELD and KCH criteria, both with similar AUROC of 0.64. ALFED (with a cutoff score ≥4) had the best sensitivity (71.6%), specificity

Table 4 Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio and diagnostic accuracy of various prognostic scores for predicting mortality on day of admission in HEV-ALF ($N = 244$)

Parameter (cutoff)	AUROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+	LR−	DA (%)
MELD (≥30)	0.64 (0.57–0.71)	60.6 (47.3–72.9)	59.4 (50.7–67.7)	39.8 (29.8–50.5)	77.4 (68.2–84.9)	1.5 (1.1–2.0)	0.6 (0.5–0.9)	59.8
ALFED (≥4)	0.91 (0.86– 0.94)	71.6 (61.0–80.7)	92.9 (87.7–96.4)	85.1 (74.9–92.3)	85.3 (79.1–90.2)	10.1 (5.6–18.2)	0.31 (0.22–0.43)	85.2
King's College Hospital criteria positive (KCH)	0.64 (0.57–0.71)	42.0 (31.6–53.0)	82.7 (75.8–88.3)	57.8 (44.8–70.1)	71.7 (64.5–78.1)	2.4 (1.6–3.7)	0.7 (0.6–0.8)	68.0

MELD model for end-stage liver disease, *ALFED* acute liver failure early dynamic, *KCH* King's College Hospital

(92.9%), positive predictive value (85.1%), negative predictive value (85.3%), positive likelihood ratio (10.1), and diagnostic accuracy (85.2%). On comparison of AUROC between different scores, ALFED performed significantly better than MELD and KCH (P value <0.001, Hanley and McNeil test). There was no difference between MELD score and KCH criteria ($P = 0.95$). The sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio (positive and negative) and diagnostic accuracy of KCH, MELD, and ALFED are mentioned in Table 4. The AUROC for ALFSG score, which determines the transplant-free survival, was 0.63 (95% CI 0.56–0.71).

Discussion

In this study from the Indian subcontinent, which comprised predominantly of viral hepatitis-related ALF, HEV was responsible for one-third of all ALF cases. To the best of our knowledge, this is one of the largest studies on HEV-ALF. Clinical complications were seen less frequently in HEV-ALF patients than ALF of other causes, with better survival overall. MELD score, KCH criteria, and the ALFSG model fared poorly in prediction of outcome in HEV-ALF patients.

HEV is an important cause of ALF in both epidemic and endemic settings [10, 19–22]. The primary mode of transmission is through contaminated water. Genotypes 1 and 2 are prevalent in hyperendemic regions, where the reservoir for HEV seems to be human and causes outbreaks, sporadic acute hepatitis, acute liver failure, and acute on chronic liver failure [23–25]. Genotypes 3 and 4 infect pigs and other animal species in addition to humans. These are more prevalent in the USA, Europe, and Japan, and zoonotic transmission is thought to be the cause of infection in humans, leading to autochthonous acute HEV. In the Indian subcontinent, all human cases of HEV infection have been found to be genotype 1 [5, 26, 27]. The importance of this virus in causing morbidity and mortality was highlighted by a recent study which estimated the global burden of HEV genotypes 1 and 2 in 2005 [8]. According to this study, in the year 2005, a total of 20.1 million incident HEV cases occurred. These data reflect the magnitude of burden of this disease, which is completely preventable. A recent report of national viral hepatitis surveillance and outbreaks from India reports hepatitis cases and outbreaks by hepatitis E from most regions [28]. Recent reports from Europe indicate that 10–15% of ALF cases are related to HEV and highlight the global significance of HEV [7]. These facts suggest that patients with ALF should be screened for HEV, irrespective of their country of origin.

We would like to highlight the fact that various developments in viral diagnostic tests have occurred in the last three decades (during the study period, from 1986 to 2015). The analysis of data from our center two decades ago had shown a proportion of indeterminate cases of 62% [2]. Analysis of data in our study showed that the last 2 decades had reduced proportions of indeterminate cases—of around 33 and 37%, respectively.

Prior studies have highlighted that females develop ALF more frequently compared to males [2, 29]. Pregnant women, especially from the Indian subcontinent and Africa, are at increased risk of contracting acute HEV infection as well as developing severe complications including ALF [10, 30, 31]. In our study, approximately 60% of the female patients with HEV-ALF were pregnant. We have previously reported that the mortality in HEV-ALF is similar among pregnant as well as non-pregnant women. Also, pregnant women with ALF show similar outcomes among HEV-related and other etiologies [21]. The exact reasons why pregnant females develop ALF more frequently is not clear. Possible predisposing factors include both maternal and viral factors—maternal factors such as malnutrition, factors related to pregnancy (such as switch from Th1 to Th2 immune response), effect of hormonal changes (estrogen and progesterone), mutations in progesterone receptor gene; and viral factors such as viral load, genotypes, nucleotide, and amino acid substitutions [22].

An interesting finding in the present study was the significantly better outcome in patients with HEV-ALF. The exact reasons for this finding are not clear. Patients with HEV-ALF were younger (mean age 27 years) and had less complications including cerebral edema, seizures and infections. All of these factors have been associated with poor outcome in ALF patients. Increasing age, female sex, presence of cerebral edema, prolonged prothrombin time (>60 s), development of infection and elevated total bilirubin were independent predictors of mortality on multivariate analysis. These factors need to be taken into account while considering LT for patients with HEV-ALF.

In the present study, HEV-ALF patients between the years 2001 and 2015 had better outcomes than patients between 1986 and 2000 (Table 3). The former group had lower prevalence of cerebral edema, which is an important determinant of outcome. Major improvements in survival of ALF cases over a 35-year period have been documented in a recent large series from the UK [32].

Dynamic scores have been shown to better than static scores in predicting outcomes in diseases like alcoholic hepatitis [33]. In the present study, we found ALFED score to be better than MELD, KCH, and ALFSG for predicting the outcome (in a subset of patients from 2001 to 2015). All measures—including sensitivity, specificity, negative predictive value, positive predictive value, and diagnostic accuracy—were better (Table 4). Prior meta-analysis reported that KCH criteria had low sensitivity and high specificity for predicting outcome in non-paracetamol-induced ALF [34]. In the ALFSG model derivation, dynamic changes in variables (ammonia and INR) were not found to improve the performance [15]; therefore, this model is calculated solely from values at admission. These dynamic changes are included in the ALFED, which is a possible reason why it performs better than the ALFSG model.

Limitations of our study include its retrospective nature and associated bias. We included all patients from a prospectively maintained database, which would have limited the bias. The analysis for prediction of outcome in HEV-ALF was limited to a subset of patients, due to non-availability of parameters such as ammonia and INR prior to 2001. To define cerebral edema, we used clinical parameters and not intracranial pressure monitoring, which could have resulted in underestimation of cerebral edema. The diagnosis of infection was based on microbiology as well as clinical interpretation, which might have overestimated the frequency of infection. We could not assess other prognostic scores—such as acute physiology and chronic health evaluation; sequential organ failure assessment and Clichy criteria—as data related to the individual parameters of these scores were not available.

Conclusions

HEV is a common cause of ALF in India. Overall, HEV-ALF has a better outcome than ALF of other etiologies. KCH criteria, MELD score and ALFSG model have poor discriminative accuracy for outcome in HEV-ALF patients.

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Compliance with ethical standards

Conflict of interest None.

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