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**Research Article**

# ACUTE LIVER FAILURE- RELATIONSHIP OF OUTCOME TO ETIOLOGICAL FACTORS (HBV VERSUS HEV)

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**A R T I C L E I N F O**

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**A B S T R A C T**

**Introduction** - Being an acute life threatening condition, there is very limited data about acute liver failure (ALF) from India. No study showed head to head comparison of ALF due to HBV and HEV, two main etiological factors for ALF in India.

**Aim** -The aim was to study the relationship of outcome to etiological factors, HBV versus HEV in ALF patients.

**Materials & Method** - Forty five patients of ALF with confirmed etiology (either HBV or HEV) over last 4 years at SAIMS Hospital, Indore, were studied retrospectively for various clinical and laboratory features and overall clinical outcome.

**Results - out** of total 45 patients 18 (40%) were HBV positive while 27 (60%) were HEV positive. Sixteen (59%) were female while 11 (41%) were male patients. Hepatitis E virus positive patients (25.78 ± 7.51 years) were younger than HBV positive (32.67 ± 12.02 years; p = 0.001). Five of 18 HBV positive patients died compared to 14 of 27 in HEV positive group of which maximum mortality noted in 20 - 29 year age group. None of those died in HBV positive group was pregnant compared to 7 pregnant patients in HEV positive. Duration of HE amongst HBV positive patient who died (4.20 ± 2.78 days) was significantly higher from those who died with HEV positive serology (1.93 ± 0.99 days; p = 0.015).

**Conclusion -** There was a trend towards higher mortality in HEV related ALF patients compared to HBV related ALF however it did not reach statistical significance and pregnancy did not affected mortality significantly in either group.



## INTRODUCTION

Acute liver failure (ALF) is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in individuals without known pre-existing liver disease.[1] Because of its rarity and rapid deterioration of patient's general condition, ALF has been difficult to study in detail and manier times it may become unethical too. Acute liver failure (ALF) is a life-threatening emergency, but potentially reversible condition, of varied etiology. The mortality is usually high unless aggressive and early treatment is instituted, usually in an intensive care setting. Treatment is directed at early recognition of the cause, complications, and general supportive measures, but despite advanced intensive care, mortality may be as high as 40 to 80%, which is mostly related to its complications like cerebral edema and sepsis.[2,3,4] The prognosis of these patients was very poor until the introduction of liver transplantation (LT) for the treatment of this disease in the last decades, improving their survival significantly.[5,6]

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Current results of LT are very good considering the natural history of the disease, the multiorgan involvement, the emergency context, and the lack of other effective therapies.[7] As all patient may not be the candidate of liver transplant (LT) due to various reasons like non-availability of transplant facilities at all centers, economical conditions of patients, availability of suitable donor, general condition of patients, extent of other organ involvement etc... intensive medical care become of utmost importance.

The distribution of etiologies differs around the world. Many studies on ALF have been predominantly from the West had showed various etiologies as a cause of ALF like drug toxicity as a major cause with viral hepatitis and indeterminate etiologies as other minor causes. [8,9,10] But when it comes to Indian scenario, it becomes all to gather a different story, where viral etiologies, particularly Hepatitis B Virus (HBV) and Hepatitis E Virus (HEV) usually predominates over other etiologies of ALF.[11,12,13] This difference in etiology may also result in difference in clinical course of disease as well as overall outcomes. This valid reason led to a think about comparing two main etiologies of ALF in terms of their demographic profile, clinical course and overall outcome.

There is no data weather this difference in etiology result in difference in clinical course of disease as well as overall outcomes, because treatment is available for HBV related ALF in form of antiviral drugs while no treatment is available for HEV related ALF. Therefore this study was conducted to see the relationship of outcome to etiological factors (HBV versus HEV).

## MATERIALS AND METHODS

This retrospective, hospital-based study was conducted in Sri Aurovindo Medical College and Post Graduate Institute (SAMC & PGI), INDORE, Central India. All ALF cases between January 2015 and May 2018 were identified through the review of hospital discharge cards, from the admission/discharge database. ALF is defined by three criteria: (1) rapid development of hepatocellular dysfunction (jaundice, coagulopathy), (2) encephalopathy, and (3) absence of a prior history of liver disease with an illness of <26 weeks duration.[14,15]

All adult patients who had ALF, as defined by above mentioned criteria and those with > 18 years of age were included in study. Patients with age < 18years of age, clinical/imaging/ biochemical features of chronic liver disease, patients with etiologies of ALF other than HBV and/or HEV, history of significant alcohol ingestion (>20 gm daily), malignancies, cardiac diseases and those with incomplete information were excluded from the study. The study protocol was approved by ethical committee of the institute. No informed consent was required for the study. All possible features from records like, onset of disease, onset of various decompensations like jaundice, hepatic encephalopathy etc..., history of any comorbidites, history of pregnancy and its details, findings in physical examinations, history of any kind of addictions, any significant family history, history of previous treatments were noted

The results of various biochemical parameters were recorded which included hemogram (complete blood counts), renal function test (RFT) (Serum Urea and Serum Creatinine levels), serum electrolytes, liver function test (LFT)(Bilirubin, alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT)), Serum alkaline phosphatase, prothrombin time, international normalized ratio (INR)), blood and urine for culture and sensitivity. Viral etiologies were also recorded which included anti-HAV-IgM, HBsAg, anti-HCV, and anti-HEV-IgM. Positive results of viral etiologies are cross checked twice by ELISA method. Radiological features recorded through the help of ultrasonography (USG) abdomen, chest and abdominal X-ray. Liver biopsy was not done as none of the patient's attendants gave consent for it. Electrocardiography (ECG) was also noted for any evidence of cardiac disease

***Abbreviations***

| ALF | Acute Liver Failure |
|---|---|
| ECG | Electrocardiogram |
| HBsAG | Hepatitis B Surface Antigen |
| HBV | Hepatitis B Virus |
| HE | Hepatic Encephalopathy |
| HEV | Hepatitis E Virus |
| INR | International Normalized Ratio |
| LFT | Liver Function Test |
| LT | Liver Transplant |
| RFT | Renal Function Test |
| SGOT (= AST) | Aspartate Aminotransferase |
| SGPT (= ALT) | Alanine Aminotransferase |
| USG | Ultra-Sonography |

All patients underwent standard treatment in intensive care unit with Mannitol, Frozen Plasma, IV proton pump inhibitors/blood transfusion for gastrointestinal/mucosal bleeding, IV fluids, antibiotics and intestinal decontamination as indicated.

The collected data were organized, tabulated and statistically analyzed using the SPSS 20.0 software computer package. For qualitative data, frequency and percent distribution were calculated and for comparison between groups, the chi square test was used. For quantitative data, mean and standard deviation were calculated and for comparison between two groups, student's t test was used. $P < 0.05$ was considered significant for interpretation of results.

## RESULTS

Out of total 45 total patients, 18 (40%) were HBV positive while 27 (60%) were HEV positive. Amongst HEV positive patients 16 (59%) were female while 11 (41%) were male patients while amongst HBV positive patients male and female were 9 (50%) each. Mean age of patients with HBV positive (32.67 ± 12.02 years) higher than those of HEV positive patients (25.78 ± 7.51 years) which was significant as suggested by p value of 0.001. In both HBV and HEV positive patients maximum number of patient belonged to 20 to 29 year age group (8 of 18 HBV positive vs. 18 of 27 HEV positive patients). Thirteen (28.89%) were pregnant out of total 45 patients of which 12 were HEV positive while only 1 patient had HBV positive. Various biochemical parameters has been shown in table 1. Serum urea levels were significantly higher in HBV positive patients (31.83 ± 22.9 mg/dl) compared to HEV positive patients (18.07 ± 4.15 mg/dl; p = 0.004) and globulin levels were significantly lower in HBV positive patients (3.28 ± 0.41 gm/dl) compared to HEV positive patients (3.62 ± 0.36 gm/dl; p =0.005)

**Table 1** Biochemical Parameters

| | HBV | HEV | *p* |
|---|---|---|---|
| HEMOGLOBIN (gm%) | 12.64 ± 2.67 | 12.09 ± 1.98 | 0.43 |
| TOTAL LEUKOCYTE COUNT (/mm$^3$) | 12627.78 ± 8030.00 | 13686 ± 8146.48 | 0.67 |
| PLATELETS (/µL) | 210888.9±126301.2 | 270185.2 ± 138649.5 | - |
| UREA (mg/dl) | 31.83 ± 22.9 | 18.07 ± 4.15 | 0.004 |
| CREAT (mg/dl) | 1.23 ± 1.45 | 0.77 ± 0.40 | 0.12 |
| SODIUM (mEq/L) | 136.67 ± 9.01 | 136.70 ± 5.33 | 0.99 |
| SERUM AMMONIA (µg/dL) | 215.44 ± 116.54 | 176.26 ± 100.34 | 0.23 |
| TOTAL SERUM BILLIRUBIN (mg/dl) | 13.03 ± 5.14 | 10.86 ± 4.67 | 0.15 |
| ASPARTATE AMINOTRANSFERASE (U/L) | 1694.00 ± 1361.73 | 2131.19 ± 1914.03 | 0.40 |
| ALANINA AMINOTRANSFERASE (U/L) | 3651.33 ± 2644.87 | 2683.11 ± 1159.89 | 0.10 |
| SERUM PROTEINS (g/dl) | 6.43 ± 0.70 | 6.60 ± 0.74 | 0.44 |
| ALBUMIN (g/dl) | 3.15 ± 0.6 | 2.85 ± 0.6 | 0.10 |
| GLOBULIN (g/dl) | 3.28 ± 0.41 | 3.62 ± 0.36 | 0.005 |
| ALBUMIN / GLOBULIN | 0.98 ± 0.26 | 0.79 ± 1.86 | 0.007 |
| INTERNATIONAL NORMALIZED RATIO | 3.59 ± 1.47 | 4.00 ± 1.56 | 0.37 |

Out of 18 HBV positive patients 5 patients died while 14 HEV patients died out of total 27 patients which was not statistically significant (p = 0.09) (chart 1). In both groups maximum mortality is seen in young age group of 20 to 29 years. Seven

patients out of 14 were pregnant in HEV positive group compared to no mortality in HBV positive patients.

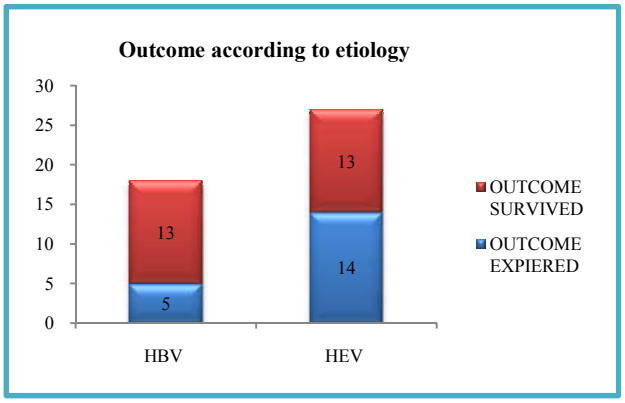


**Chart 1** Outcome According To Etiology

Duration of presenting complaints in those who died with HBV positive serology (5.00 ± 3.24 days) was not significantly different from those who died with HEV positive serology (6.71 ± 3.39 ; p = 0.34). Amongst those who died, duration of jaundice in patients with HBV positive was 7.00 ± 5.52 days compared to 6.71 ± 3.38 days in HEV positive patients, which was also not significant. Duration of HE amongst HBV positive patient who died (4.20 ± 2.78 days) was significantly different from those who died with HEV positive serology (1.93 ± 0.99 days; p = 0.015). In mortality group, duration of stay in hospital was also not significant between HBV positive patients (4.40 ± 1.14 days) and HEV positive patients (5.71 ± 1.90 days; p = 0.17). All the details has been shown in table 2.

years of age. [12] This suggest that ALF is common in young people compared to older age groups. Male to Female ratio was 1.5:1 in our study which was also comparable to 1.1:1 in study conducted by Acharya SK et. [11] Etiology of ALF in our study was HBV and HEV related ALF as they were the common etiologies amongst all detectable causes found in INDIA.[16] Most common amongst various etiologies in study done by Acharya SK [11] were HEV in 62% and HBV in 28% patients. While in study done by Das AK most common etiology was HAV (Hepatitis A virus) followed by HEV and HBV which suggest that etiologies of ALF varies amongst north - east INDIA compared to rest of the country[12].

Duration of hepatic encephalopathy (HE) in our study was 2.53 ± 1.87 days with significant difference between HBV and HEV positive patients (4.20 ± 2.78 days 1.93 ± 0.99 days respectively; p = 0.015) Duration of HE in HEV positive patients was 4 days in study done by Banait VS *et al* which is higher than our study which may suggest early presentation to tertiary care in our study. In same study by Banait VS *et al*, 54.8% mortality was noted which is similar to our study where 51.85% mortality noted in HEV positive patients. Banait VS *et al* has included all pregnant patients while present study comprises of both pregnant and non pregnant patients. This clearly suggest that even with good medical management but without liver transplant mortality in ALF remains high.[17]

Zhao RH *et al* showed that 13 of the 293 (4.43%) patients developed ALF of which 10 recovered and 3 (23.07%) died, in present study 5 of 18 (27.78%) HBV positive patients died which shows similar rates suggesting lower mortality than HEV positive patients.

**Table 2** Relationship of Outcome to Etiological Factors (Hbv Versus HEV)

| OUTCO | Clinical parameter | HBSAG | HEV | Total | *p* |
|---|---|---|---|---|---|
| Expired | Durationpresenting complaint (days) | 5.00 ± 3.24 | 6.71 ± 3.39 | 6.26 ± 3.34 | 0.34 |
| | Duration of jaundice (days) | 7.00 ± 5.52 | 6.71 ± 3.38 | 6.79 ± 3.89 | 0.89 |
| | Duration of he (days) | 4.20 ± 2.78 | 1.93 ± 0.99 | 2.53 ± 1.87 | 0.015 |
| | Total duration of stay (days) | 4.40 ± 1.14 | 5.71 ± 1.90 | 5.37 ± 1.80 | 0.17 |
| Survived | Durationpresenting complaint (days) | 9.62 ± 5.95 | 9.32 ± 6.00 | 9.42 ± 5.86 | 0.87 |
| | Duration of jaundice (days) | 9.00 ± 5.97 | 7.92 ± 5.20 | 8.46 ± 5.51 | 0.63 |
| | Duration of he (days) | 2.46 ± 1.61 | 2.85 ± 1.40 | 2.65 ± 1.50 | 0.52 |
| | Total duration of stay (days) | 8.69 ± 2.59 | 12.54 ± 5.34 | 10.62 ± 4.56 | 0.02 |

## DISCUSSION

In our study, Out of total 45 patients 18 (40%) were HBV positive while 27 (60%) were HEV positive. Sixteen (59%) were female while 11 (41%) were male patients. Hepatitis E virus positive patients (25.78 ± 7.51 years) were younger than HBV positive (32.67 ± 12.02 years; p = 0.001). Five of 18 HBV positive patients died compared to 14 of 27 in HEV positive group of which maximum mortality noted in 20 - 29 year age group. None of those died in HBV positive group was pregnant compared to 7 pregnant patients in HEV positive. Duration of HE amongst HBV positive patient who died (4.20 ± 2.78 days) was significantly higher from those who died with HEV positive serology (1.93 ± 0.99 days; p = 0.015).

In our study mean age of presentation was 29.22 ± 9.77 years, while mean age patients in a study conducted by Acharya SK [11] *et al* and Das AK [12] *et al* was 29.5 ± 0.6 years and 29.9 ± 2.1 years respectively which is similar to that noted in our study. In both HBV and HEV positive patients maximum number of patient belonged to 20 to 29 year age group. Das AK *et al* also showed that maximum number of cases of ALF were 20 - 40

Duration of symptoms from onset to hospitalization was 8 days in study by Zhao *et al* compared to mean 5 days in our study which is also similar suggest that those who develop ALF , develop it early in case of HBV positive serology.[18]

Shalimar *et al* showed average duration of stay was 7days and 4 days amongst HEV and HBV related ALF respectively compared to 9.13 days and 6.55 days respectively in present study. This suggest that ALF patient, if respond, respond quickly and adequately to the medical treatment. Survival rates in HBV and HEV positive patients were 55.1% and 35.9% respectively compared to 48.14% and 72.22% in our study. This shows survival rates were similar in HEV related ALF patients but survival rates of HBV patients were higher in our study.[19]

Our study has certain drawbacks. First number of patients in study was less, one can have different results with higher numbers of patients as some of insignificant values might become significant. Second, being retrospective study we need to drop many cases due to insufficient documentation such as details of using antiviral drugs.

In conclusion, patients with HEV related ALF tend to be younger with female predominance (1.45: 1) as compared to patients with HBV related ALF. There was a trend towards higher mortality in HEV related ALF patients, 14/27 (51.85%) compared to 5/18 (27.78%) in HBV related ALF however it did not reach statistical significance. HBV and HEV related ALF group had similar duration of presenting illness, duration of hepatic encephalopathy and hospital stay. In both HEV related and HBV related ALF, pregnancy did not affect mortality significantly.

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