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# Role of Acute Hepatitis E Virus Super Infection in Progression Stage of Liver Cirrhosis

**[1]Abdallah Mohammed Saad Zaghloul*, [1]Ibrahim Mohammed Ibrahim,**
**[1]Emad Abdel-Hamid Moustafa, [1]Salama Mohamed Shaban Elghonimy,**
**[1]Samy Eissa Abd Elwahab, [2]Ahmed Mokhtar Ahmed Ibrahim, [1]Ahmed Abou Elkhair Badawy**
[1]Tropical Medicine Department and [2]Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Abdallah Mohammed Saad Zaghloul, **Email:** zaghloulabdallah90@gmail.com, **Mobile:** 01159505293

## ABSTRACT

**Background:** Despite acute hepatitis E virus (HEV) infection is a self-limiting acute infection, it could be a cause of acute on top of chronic liver failure (ACLF) in patients with chronic liver disease. Thus, identification role of HEV superinfection in deterioration of liver cirrhosis with early treatment could save life of those patients.

**Aim:** To determine the percentage and the role of HEV infection in order to detect outcomes of patients with ACLF, to find effect of HEV infection on liver, kidney functions and coagulation profile, and to find specific clinical or laboratory characteristics of these patients if present.

**Subjects and methods:** This cross-sectional study was conducted at Tropical Medicine Department. and Clinical Pathology Department, Zagazig University Hospitals on patients with liver cirrhosis; either compensated, decompensated (who admitted for ascites for control, follow up upper GIT endoscope, spontaneous bacterial peritonitis) or in those who have chronic liver disease and experience acute hepatic decompensation, which leads to acute liver failure (jaundice, prolonged INR), as well as one or more extrahepatic organ failures. All patients had standard laboratory evaluations, including the detection of HEV IgM by ELISA technique.

**Results: The incidence of HEV was 18% in ACLF cases** and ACLF cases with positive HEV showing higher MELD score than ACLF cases with negative HEV.

**Conclusion:** ACLF cases with positive HEV have higher MELD score than ACLF cases with negative HEV (statistically significant) but regarding Child score, there was statistically non-significant difference.

**Keywords:** ACLF, MELD, HEV, cirrhosis.

## INTRODUCTION

Hepatitis E virus (HEV) is the genome of the hepatotropic virus that was discovered in 1991. It is a non-enveloped virus that is a member of the Hepeviridae family and ranges in size from 27 to 34 nm. Four different HEV genotypes have been found **(1).**

Fecal oral route via contaminated water represents major source of infection. Super infection with HEV in cirrhotic patient leads to deterioration in liver function, the abrupt deterioration of pre-existing chronic liver disorders, and higher mortality from multi-systemic organ failure **(2).**

IgM or IgG might be found during a HEV antibody test to indicate acute infection. IgM levels dramatically decrease, and this fall can only be seen for the first two to three months of recovery. In contrast, IgG lingers in infected people for a long time more than 14 years **(3).**

In 2009, the Asian Pacific Association for the Study of the Liver (APASL) established the first agreed-upon definition for ACLF: ‘‘acute liver damage manifested as jaundice (bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5), complicated in the period of 4 weeks with ascites or encephalopathy’’ in patients of chronic liver disease **(4).**

The extent of hepatic injury should be assessed after determining the source of ACLF by testing for markers of hepatic synthetic function such prothrombin time, albumin, and creatinine, as well as the nature of hepatic injury by measuring transaminases, bilirubin and alkaline phosphatase **(5).**

Early therapies are crucial for decreasing or correcting the injury, preventing further decline in liver function, maintaining failing organs, and reversing triggering causes in patients with ACLF **(2)**.

The aim of our study was to determine the percentage and the role of HEV infection in order to detect outcomes of patients with ACLF, to find effect of HEV infection on liver, kidney functions and coagulation profile, and to find specific clinical or laboratory characteristics of these patients if present.

## PATIENTS AND METHODS

This cross-sectional study was carried out at Tropical Medicine Department and the Clinical Pathology Department of the Zagazig University Hospitals between June 2021 and June 2023.

Patients with liver cirrhosis either compensated, decompensated (who admitted for ascites for control, follow up upper GIT endoscope, spontaneous bacterial peritonitis) or patients who have acute hepatic decompensation due to chronic liver disease and experience acute liver failure (jaundice, prolonged INR),



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as well as one or more extrahepatic organs failure were included in the study.

Patients with chronic kidney disease and heart failure as well as other chronic conditions other than chronic liver disease were excluded from the study.

All participants in the study were subjected to full medical history taking, general and local examination including with focusing on ascites, hepatosplenomegaly and searching for source of sepsis (UTI, pneumonia and spontaneous bacterial peritonitis).

Laboratory investigations included routine investigations as coagulation profile by Sysmex CA 1500 Roch diagnostics, **(Germany)** full liver and renal function tests, random blood sugar, procalcitonin, and CRP on Cobas integra 400 plus Roch diagnostics , complete blood count by Sysmex xn 330 Roch diagnostics, HCV Ab, HBc IgM, HBs Ag, HAV Ig M by Cobas 8000 Roch diagnostics,, urine analysis for UTI, ascetic sample analysis including chemical examination for protein, glucose and LDH, cytological examination including total WBCs count and differential count using stained films by Lishman stain, specific lab. investigation included, HEV IgM testing using ELISA. $PaO_2/FiO_2$ ration were measured. Pelviabdominal ultrasonography, CXR (searching for pneumonia in sepsis cases) and CT Brain were done if needed.

**Ethical consideration:**

**A written informed consent was taken from the patients with explanation of the procedure and possible hazards. Zagazig University Faculty of Medicine's Ethical Committee gave its approval to this work. The study followed the ethical principles set in the Declaration of Helsinki by the World Medical Association for research involving human beings.**

***Statistical analysis***

Microsoft Office Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA) was used to collect, tabulate, and statistically analyze all of the data as well as SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA). Mann-Whitney U test, Chi-square test or Fisher's exact test were used. **P value less than 0.05 was considered significant.**

## RESULTS

There was statistically significant difference between the studied groups regrading age (Table 1).

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**Table (1): Comparison between control group and ACLF group regarding demographic data and baseline characteristics**

| Demographic data and baseline characteristics | Control group (N=61) | | ACLF group (N=61) | | Test | p-value |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| **Gender** | | | | | | |
| Male | 36 | 59% | 28 | 45.9% | 2.103 | 0.147 |
| Female | 25 | 41% | 33 | 54.1% | | |
| **Age (years)** | | | | | | |
| Mean±SD | 52.77±8.37 | | 58.14±11.43 | | -2.961 | **0.004** |
| Median (Range) | 54 (39 – 70) | | 57 (35 – 75) | | | |
| **Cause of cirrhosis** | | | | | | |
| HCV | 51 | 83.6% | 42 | 68.8% | 4.111 | <0.128 |
| HBV | 8 | 13.1% | 17 | 27.8% | | |
| Other cause | 2 | 3.3% | 2 | 3.3% | | |
| **Cause of ACLF** | | | | | | |
| HEV | | | 11 | 18% | | |
| HBV | | | 12 | 19.7% | | |
| HAV | | | 4 | 6.6% | | |
| DILI | | | 8 | 13.1% | | |
| Alcohol | | | 0 | 0% | | |
| Sepsis | | | 16 | 26.2% | | |
| Other cause | | | 10 | 16.4% | | |

There was statistically significant difference between the studied groups regrading presence of jaundice, fever, ascites, lower limb edema, hepatic encephalopathy, pulse, systolic and diastolic blood pressure (Table 2).

**Table (2): Comparison between control group and ACLF group regarding clinical findings**

| Clinical findings | Control group (N=61) | | | ACLF group (N=61) | | Test | p-value |
|---|---|---|---|---|---|---|---|
| | No. | % | | No. | % | | |
| Jaundice | | | | | | | |
| Absent | 43 | 70.5% | | 0 | 0% | 66.405 | **<0.001** |
| Present | 18 | 29.5% | | 61 | 100% | | |
| Pallor | | | | | | | |
| Absent | 18 | 29.5% | | 11 | 18% | 2.217 | **0.137** |
| Present | 43 | 70% | | 50 | 82% | | |
| Lower limb edema | | | | | | | |
| Absent | 40 | 65.6% | | 4 | 6.6% | 46.070 | **<0.001** |
| Present | 21 | 34.4% | | 57 | 93.4% | | |
| Ascites | | | | | | | |
| Absent | 18 | 29.5% | | 0 | 0% | 21.115 | **<0.001** |
| Present | 43 | 70.5% | | 61 | 100% | | |
| Hepatic encephalopathy | | | | | | | |
| Absent | 49 | 80.3% | | 10 | 16.4% | 49.923 | **<0.001** |
| Present | 12 | 19.7% | | 51 | 83.6% | | |
| Fever | | | | | | | |
| Absent | 53 | 86.9% | | 41 | 67.2% | 6.678 | **0.01** |
| Present | 8 | 13.1% | | 20 | 32.8% | | |
| Pulse rate (/min) | | | | | | | |
| Mean±SD | 89.37±8.59 | | | 111.61±15.76 | | -9.671 | **<0.001** |
| SBP (mmHg) | | | | | | | |
| Mean±SD | 96.55±18.74 | | | 78.19±7.95 | | 7.042 | **<0.001** |
| DBP (mmHg) | | | | | | | |
| Mean±SD | 63.44±11.88 | | | 53.11±7.86 | | 5.66 | **<0.001** |

There was statistically significant difference between the studied groups regrading hemoglobin and WBCs and platelet count. There was also statistically significant difference between the studied groups regrading total, direct bilirubin, serum albumin, ALT, AST, ALP, GGT, PT, serum creatinine, alfa-fetoprotein, BUN and INR, chest X ray, while both did not significantly differ regarding incidence of spontaneous bacterial peritonitis, total protein or pus cell in urine. There was statistically significant difference between the studied groups regrading CRP, and procalcitonin while both did not significantly differ regarding fasting blood glucose (Table 3).

**Table (3): Comparison between control group and ACLF group regarding different investigations**

| | Control group (N=61) | | ACLF group (N=61) | | Test | p-value |
|---|---|---|---|---|---|---|
| **Hemoglobin (g/dl)** | | | | | | |
| Mean±SD | 8.22±1.3 | | 7.27±1.65 | | 3.524 | **<0.001** |
| **Platelets count (x103/mm3)** | | | | | | |
| Median (Range) | 80 (53 – 180) | | 50 (30 – 190) | | -4.303 | **<0.001** |
| **WBCs count (x$10^3$/$mm^3$)** | | | | | | |
| Median (Range) | 13 (2.7 – 27) | | 18 (8 – 37) | | -5.115 | **<0.001** |
| **T. Bilirubin (mg/dl)** | | | | | | |
| Median (Range) | 3.4(0.70 – 7) | | 9.80 (3.40 – 16.30) | | -8.807 | **<0.001** |
| **D. Bilirubin (mg/dl)** | | | | | | |
| Median (Range) | 1.20 (0.30 – 4) | | 7 (2.90 – 15) | | -8.911 | **<0.001** |
| **Protein (g/dl)** | | | | | | |
| Mean±SD | 6.35±0.47 | | 6.25±0.55 | | 1.03 | 0.305 |
| **Albumin (g/dl)** | | | | | | |
| Mean±SD | 2.84±0.30 | | 2.33±0.27 | | -9.869 | **<0.001** |
| **ALT (u/l)** | | | | | | |
| Median (Range) | 70 (16 – 1654) | | 600 (67 – 2450) | | -8.252 | **<0.001** |
| **AST (u/l)** | | | | | | |
| Median (Range) | 88 (18 – 2357) | | 900 (99 – 5640) | | -8.471 | **<0.001** |
| **ALP (u/l)** | | | | | | |
| Median (Range) | 140 (100 – 261) | | 178 (58 – 210) | | -2.867 | **0.004** |
| **GGT (u/l)** | | | | | | |
| Median (Range) | 90 (76 – 130) | | 117 (88 – 187) | | -6.184 | **<0.001** |
| **PT (sec.)** | | | | | | |
| Mean±SD | 17.03±2.27 | | 27.02±5.52 | | -7.893 | **<0.001** |
| **INR** | | | | | | |
| Mean±SD | 1.32±0.18 | | 2.09±0.42 | | -7.834 | **<0.001** |
| **BUN (mg/dl)** | | | | | | |
| Median (Range) | 45 (15 – 119) | | 76 (12 – 152) | | -2.754 | **0.006** |
| **Creatinine (mg/dl)** | | | | | | |
| Median (Range) | 1.50 (0.50 – 2.40) | | 2.90 (1.40 – 8.30) | | -7.550 | **<0.001** |
| **AFP** | | | | | | |
| Median (Range) | 19 (10 – 921) | | 440 (5 – 2350) | | -2.986 | **0.003** |
| **Spontaneous bacterial peritonitis** | 18 (29.5%) | | 7 (11.5%) | | 6.087 | **0.014** |
| Chest X **ray** **Pneumonia** | 2 (3.3%) | | 6 (9.8%) | | Fisher | **0.272** |
| **Pus cell in urine** | 4 (6.6%) | | 3 (4.92%) | | Fisher | **1.000** |
| **FBS (mg/dl)** | | | | | | |
| Median (Range) | 150 (60 – 328) | | 170 (60 – 300) | | -0.526 | **0.599** |
| **CRP (mg/L)** | | | | | | |
| Median (Range) | 5 (3 – 33) | | 46 (3 – 90) | | -6.230 | **<0.001** |
| Normal | 54 | 88.5% | 14 | 23% | 53.159 | **<0.001** |
| Elevated | 7 | 11.5% | 47 | 77% | | |
| **Procalcitonin (ng/mL)** | | | | | | |
| Median (Range) | 0.20 (0.10 – 2) | | 0.23 (0.10 – 6.1) | | -3.418 | **<0.001** |
| Normal | 56 | 91.8% | 44 | 72.1% | 7.985 | **0.005** |

b: Mann Whitney U test;

There was statistically significant difference between the studied groups regrading HEV IgM (Table 4).

**Table (4): Comparison between control group and ACLF group regarding incidence of HEV infection**

| | Control group (N=61) | | | ACLF group (N=61) | | Test | p-value |
|---|---|---|---|---|---|---|---|
| HEV IgM | No. | % | | No. | % | | |
| Negative | 61 | 100% | | 50 | 82% | 12.09 | **0.001** |
| Positive | 0 | 0% | | 11 | 18% | | |

There was statistically significant difference between the studied groups regrading mortality (Table 5).

**Table (5): Comparison between control group and ACLF group regarding mortality rate at 4 weeks**

| | Control group (N=61) | | | ACLF group (N=61) | | Test | p-value |
|---|---|---|---|---|---|---|---|
| Mortality at 4 weeks | No. | % | | No. | % | | |
| Alive | 57 | 93.4% | | 14 | 23.0% | 62.297 | <0.001 |
| Died | 4 | 6.6% | | 47 | 77.0% | | |

ACLF cases with + HEV showing higher MELD score than ACLF cases with -ve HEV. ACLF with + HEV showing high Child B score in 36.4% but ACLF cases with -ve HEV showing higher Child C score 68% (Table 6).

**Table (6): Comparison between ACLF patients with negative HEV and ACLF patients with positive HEV regarding Child and MELD scores**

| | ACLF group (N=61) | | | | | Test | p-value |
|---|---|---|---|---|---|---|---|
| | Negative HEV (N=50) | | | Positive HEV (N=11) | | | |
| Parameters | No. | % | | No. | % | | |
| MELD score | | | | | | | |
| Mean±SD | 31.96±5.90 | | | 36.36±5.04 | | -2.292 | 0.026 |
| Child score | | | | | | | |
| Median (Range) | 11 (7 – 12) | | | 11 (9 – 15) | | -1.166 | 0.244 |
| Child A | 0 | 8% | | 0 | 0% | 0.281 | 0.596 |
| Child B | 16 | 32% | | 4 | 36.4% | | |
| Child C | 34 | 68% | | 7 | 63.6% | | |
| Cause | | | | | | | |
| HCV | 34 | 68% | | 8 | 72.7% | | |
| HBV | 14 | 28% | | 3 | 27.3% | 0.471 | 0.79 |
| Other | 2 | 4% | | 0 | 0% | | |

The best cutoff of CPS in diagnosis ACLF was ≥8.5. The best cutoff of MELD in prediction of diagnosis ACLF was ≥21.5 (Table 7).

**Table (7) Performance of MELD and Child-Pugh score in diagnosis of ACLF among studied patients:**

| | **Cutoff** | **AUC** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** | **p-value** |
|---|---|---|---|---|---|---|---|---|
| **CPS** | 8.5≥ | 0.964 | 93.4% | 96.7% | 96.6% | 93.7% | 95.1% | <0.001** |
| **MELD** | ≥21.5 | 0.969 | 93.4% | 90.2% | 90.5% | 93.2% | 91.8% | <0.001** |

The best cutoff of CLLF C ACLF in prediction of mortality among ACLF patients was ≥63.5 and overall accuracy was statistically highly significant (Table 9, figure 2).

**Table (9) Performance of CLLF C ACLF in prediction of mortality of ACLF among studied patients:**

| | **Cutoff** | **AUC** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** | **p-value** |
|---|---|---|---|---|---|---|---|---|
| **CLIF** | 63.5≥ | 0.877 | 80.9% | 78.6% | 92.7% | 55% | 80.3% | <0.001** |

## DISCUSSION

In Egypt, a Mediterranean nation, HAV and HCV infections were extremely common. In patients with cirrhosis, acute hepatitis A and E are well-known to cause hepatic decompensation, notably in developing countries. HEV1, HEV2, HEV3, and HEV4 are able to infect humans **(6).**

In the current study, the majority of patients (54.1%) were female and in their middle age (58 years on average). Our study revealed that the most common causes of ACLF were sepsis 26.2 %, HBV in 19.7%, and HEV in 18 %, but DILI in 13% and no cases detected due to alcohol, this can be explained because the various causes of ACLF differ depending on the area and demographic being studied, while the bulk of acute insults in industrialized nations are caused by alcohol and drugs, infectious etiologies are more common in poorer nations, HEV super infection, sepsis and HBV super infection are major causes of ACLF in Mediterranean countries **(7).**

Regarding underlying chronic liver disease's origin in our research, HCV was connected to 68.8%, HBV in 27.8% and no cause detected in 3.3%. This is attributed to endemicity of HCV in Egypt. In contrast to **Steve *et al.* (8)**, the findings of a prospective cross-sectional study conducted in India from January 2015 to August 2016 to assess the effect of HEV in ACLF patients; HCV was 0%, cryptogenic was 10%, and alcohol was 60 %.

Regarding clinical findings in ACLF cases, jaundice was in 100 % (mean T. bilirubin 9.8 mg/dl), coagulopathy in 100% (Mean INR 2.90), ascites in 100% and encephalopathy in 83.6% of cases, this matches with the APASL definition (acute liver damage manifested as jaundice (bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5), 4 week period during which ascites or encephalopathy became complicated)**(9)**.

The most frequent causes of sepsis in our study were SBP detected in 11.5% of cases, pneumonia detected in 9.8% of cases and urinary tract infection in 4.92% of ACLF cases. This matches with **Jalan *et al.* (10) who** stated that the most frequent causes of sepsis in ACLF cases were spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI) and pneumonia.

Our study showed, biomarkers of sepsis are elevated in ACLF cases WBCS (mean 18.83±6.26), CRP (Mean 44.16±26.19**)**, procalcitonin (Mean 1.23±0.23**)** due to their common intestinal barrier damage, intestinal microbiological abnormalities, immunological activation, and ascites, ACLF patients are more likely to contract an infection and develop sepsis. **Kim and Kim (11)** said that one of the pathologic characteristics of ACLF is sepsis, which is not only one of the major causes of death in critically ill patients in the intensive care unit (ICU).

Although sepsis was implicated only in 16 ACLF cases in our study but sepsis markers were extremely elevated. This matches with **Tang *et al.* (12)** who showed that WBC, PCT and CRP were not suitable indicators for diagnosing sepsis in ACLF patients because since the majority of ACLF patients have decompensated cirrhosis and their immune systems are constantly activated, PCT may increase in non-infectious inflammation. WBC lacks sensitivity and specificity when determining whether an ACLF patient has sepsis. They also advocated that CLIF-SOFA score may be an effective way to identify sepsis in ACLF patients.

Our study revealed pattern of hepatic injury is hepatocellular pattern, as ALT was elevated with median 600 u/L and alkaline phosphatase was elevated at median of 178 u/L. This matches with **Hudu *et al.* (5) who** argued that the amount of transaminases and alkaline phosphatase should be used to assess the kind of hepatic damage.Regarding incidence of HEV superinfection, our study revealed positive HEV in **18 %** of ACLF cases (diagnosed by ELISA testing for IGM**)** versus **0 %** in control cirrhotic group and this was statistically highly significant **(HS)**. This matches with **Acharya *et al.* (13)** who stated that ACLF development in patients with cirrhosis was linked to proven HEV infection as a risk factor. There was a statistically significant correlation between HEV and platelet counts and hemoglobin, and GGT in the current investigation. In our study, underlying cause of cirrhosis in HEV positive ACLF cases was HCV 72.7**%**, HBV 27.3**%**.

Anemia was observed in ACLF patients with hemoglobin range of (7 gm/dl) as result of coagulopathy, bleeding varices, and hypersplenism and this matches with **Caldwell *et al.* (14)** who explained that hemorrhage, particularly into the gastrointestinal tract, is a key contributor to anemia in patients with chronic liver disease. Due to endothelial dysfunction, thrombocytopenia, coagulation factor deficits, and other related problems, patients with severe hepatic disease experience abnormalities in blood coagulation.

**T**here was thrombocytopenia with median of 50,000 in ACLF cases and this matches with **Pischke *et al.* (15)** who revealed that thrombocytopenia associated with HEV ACLF is generally severe, this is attributed to sepsis associated with ACLF cases and HEV infection as thrombocytopenia is one of extrahepatic manifestations of HEV infection and hypersplenism due to underlying chronic liver disease.

For chronic liver disease patients precipitating ACLF, which patients are likely to develop ACLF is the first question that needs to be resolved. Two prognostic evaluation models (CP score and MELD score) were compared in this study for predicting the development of ACLF in individuals with chronic liver disease. We discovered that patients with ACLF had higher CP and MELD scores than patients without ACLF. The most effective CPS cutoff for diagnosing ACLF is 8.5, with an area under the curve of 0.964, sensitivity of 93.4%,

specificity of 96.7%, positive predictive value of 96.6%, negative predictive value of 93.7%, and overall accuracy of 95.1%. The optimal MELD cutoff for diagnosing ACLF was 21.5 and it has an area under the curve of 0.969, sensitivity of 93.4%, specificity of 90.2%, positive predictive value of 90.5%, negative predictive value of 93.2%, and overall accuracy of 91.8%.

Our study regarding models of prognostic mortality of ACLF showed that CLIF-C ACLF was more accurate than Child and MELD scores as in CLIF-C ACLF area under curve was 0.877, but area under curve in MELD was equal 0.868 and in Child equal 0.805 and this matches with **Jalan *et al.*** [(10)] who stated that CLIF-C ACLF score predicted short-term 28 days mortality 25% better than all listed scores, and this is attributed to (The CLIF-C ACLF score) include parameters, which cover point of multi-organ failure and sepsis which are common causes of mortality in ACLF cases.

ACLF cases with positive HEV have higher MELD score than ACLF cases with negative HEV (statistically significant) but regarding Child score (statistically non-significant) regarding Child score. This matches with **Bedreli *et al.*** [(16)] who revealed that child–Pugh and MELD scores have been routinely employed to forecast how cirrhotic patients will fare. They do, however, have some shortcomings. First, 2 ascites and HE are two subjective variables that might change depending on the doctor's assessment, the use of diuretics, and the use of lactulose. Second, INR, a factor in both Child-Pugh and MELD scores, is insufficient to accurately reflect coagulopathy and, by extension, liver function in liver cirrhosis. Third, there is an interlaboratory variation in INR value.

## CONCLUSION

HEV infection is widespread in our nation in 18% of our cases that inducing an abrupt worsening of pre-existing liver disease. ACLF cases with positive HEV have higher MELD score than ACLF cases with negative HEV (statistically significant) but regarding Child score, it is statistically non-significant. SBP, pneumonia, UTI were common causes of sepsis in ACLF. WBCs, CRP, procalcitonin are not accurate markers for diagnosis of sepsis in ACLF. Higher mortality rate was observed in ACLF cases versus in control cirrhotic group with higher multi-organ failure. CLIF-C ACLF is more accurate than MELD and Child-Pugh Scores in prediction of 28 days mortality in ACLF cases.

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