Poor outcomes of acute hepatitis E in patients with cirrhotic liver diseases regardless of etiology

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Abstract

Background chronic liver diseases (CLD) have been documented to exacerbate clinical outcomes of acute hepatitis E (AHE). This study aimed to uncover the role of etiology and status of CLD in the adverse outcomes of AHE. We found that superinfection with HEV in patients with cirrhotic CLD can cause a worsen outcome leading to exacerbation of AHE, compared to HEV infected patients without CLD or with non-cirrhotic CLD. Additional analysis revealed that the etiology of CLD is not associated with outcomes of AHE patients. These finding suggested the overall liver status plays predominant role in determining the outcomes of AHE.

Keywords: Hepatitis E; Background liver diseases; Cirrhotic liver diseases; Etiology.
Abbreviations

HEV, hepatitis E virus; CLD, chronic liver diseases; CHB, chronic hepatitis B; GT, genotype;
AHE, acute hepatitis E; HBV, hepatitis B virus; Ig, immunoglobulin; ALB, albumin; PLT,
platelet count; DBiL, direct bilirubin; TBiL, total bilirubin; ALT, alanine aminotransferase;
GGT, $\gamma$-glutamyl transferase; ChE, cholinesterase; INR, international normalized ratio.
Introduction

Hepatitis E virus (HEV) infection is the most common cause of acute viral hepatitis worldwide. There are estimated 20 million HEV infections and 3.3 million symptomatic hepatitis E cases per year\(^1\). Four main genotypes of HEV were identified. Genotypes (GT) 1 and 2 are found mainly in developing countries and are transmitted via contaminated water sources. While GT 3 and 4 are prevalent in industrialized countries and are zoonotic nature and spread mainly through eating undercooked pork or game products\(^2\). China is generally judged to be an HEV-endemic area. The seroprevalence rates of anti-HEV IgM in general population ranged from 0.1% to 1.57% and anti-HEV IgG ranged from 9.16% to 38.06%\(^3-6\). Occurrences of HEV infection in China are predominantly as sporadic pattern with occasional food-borne outbreaks. Although generally causing asymptomatic or acute hepatitis, HEV infection in patients with pre-existing chronic liver diseases (CLD), especially for those with chronic hepatitis B (CHB), have been reported to result in severe clinical manifestations and poor outcomes\(^7-10\). Most deaths from GT3 HEV infection are caused by liver failure in patients with background CLD\(^11,12\). Studies from India showed superinfection of GT1 HEV in patients with CLD produced severe decompensation leading to high mortality\(^12-15\). China is a HEV-endemic area with predominant GT4 HEV infection. Recent evidence from Hong Kong suggested that CHB is associated with the high mortality in patients with acute hepatitis E (AHE). However, whether the worsen clinical features in HEV/CLD superimposing is due to underlying cirrhosis, which probably a confounding factor, was not unveiled. One large cohort study in the hepatitis B virus (HBV)/HEV co-infection patients suggested that the high mortality may bear the end-stage liver diseases, but not pure HBV infection, implying the liver status seems to play a critical role in deteriorative
outcomes of AHE. However, CLDs vary largely in their etiology and disease stages, the course of AHE with other CLDs is still unclear, leading to the question whether the etiology or the status of CLD determine the adverse clinical outcomes with HEV super-infections. In this study, we characterized the course of GT4 AHE in patients with various etiologies and statuses of CLD to elaborate the issue.

**Materials and Methods**

**Study design**

All the inpatients and outpatients with suspecting symptoms of acute viral hepatitis, defined as presenting elevated liver enzymes and/or jaundice and/or non-specific symptoms such as fatigue, itching and nausea, admitted to the 5th Medical Center, Chinese PLA General Hospital, were routinely tested for anti-HEV immunoglobulin (Ig) M and IgG. This medical center is the biggest tertiary hospital specialized in hepatology and infectious disease in China. The number of outpatient and inpatient visits with liver diseases are approximately 1.87 million and 0.1 million per year, respectively. Patients admitted in this hospital are from all over of country. A case of acute hepatitis E was defined by positive anti-HEV IgM and presence of typical symptoms of acute hepatitis and/or abnormal liver function tests. Patients diagnosed of AHE were consecutively retrieved from January 2015 to October 2017 and interviewed of the demographic information, clinical symptoms and laboratory data, complications, extra-hepatic manifestations and clinical outcomes. This study was approved by the medical ethical committee of local hospital.

The primary outcome is the incidence of liver failure. Diagnosis and classifications of liver failure were defined by international normalized ratio (INR) and prothrombin activity,
according to 2012 China guidelines for liver failure (PMID: 23967737). In details, diagnosis of ALF is based on presence of stage 2 or 3 encephalopathy complicating end-stage disease manifestations, including profound coagulopathy (prothrombin activity $\leq 40\%$ or INR $\geq 1.5$), jaundice and hepatic atrophy in two weeks in patients with no CLD. The secondary outcome was a series of complications, including electrolyte disturbance, anemia, hypoproteinemia, ascites, pleural effusion, pulmonary infection, peritonitis, renal injury, heart disease, intestinal diseases and shock.

CLD were defined with presence of one or more of the following diseases: chronic hepatitis B, C, alcoholic liver disease, moderate to severe fatty liver, autoimmune liver diseases, and all etiology related cirrhosis.

a) Chronic hepatitis B (CHB) was diagnosed with hepatitis B surface antigen (HBsAg) positive for more than six months (PMID: 16491521).

b) Alcoholic liver disease (ALD): The diagnosis of ALD based on drinking history, clinical manifestation, laboratory test, imaging examination and/or histology (PMID: 29804393). Patients with ALD have excessive alcohol use over five years. Excessive alcohol use is defined as drinking more than 20 g/day (or $>140$g weekly) for women and 40 g/day (or $>210$g weekly) for men.

c) Liver cirrhosis was diagnosed either by histology or by the combination of clinical, biochemical tests and imaging examinations (PMID: 28185838).

Test of HEV RNA and viral sequence analysis

Part of patients in this study cohort has stored serum samples for respective HEV RNA testing. RNA was extracted from serum samples with a total RNA isolation kit purchased from Biotek, Beijing, China, according to the manufacturer’s instruction. A fragment of the
gene encoding the capsid protein (open reading frame 2) was amplified by reverse-transcription polymerase chain reaction and sequenced to identify the genotype. Virus genotype was determined by sequencing a 348-nt fragment within the open reading frame 2 gene. Phylogenetic analyses were performed by using genotype information of reference sequences.

Statistical analysis

Continuous variables were expressed in mean ± standard deviation (SD) and median (interquartile-range [IQR]), as appropriate. Categorical variables were presented as number (percentage). Student-t test and Mann-Whitney U test were used for statistical comparisons of continuous variables between two groups. ANOVA and Kruskal-Wallis test were performed among three groups. Chi-square test and Fisher’s exact test was utilized to compare the distribution of categorical variables as appropriate. Bonferroni was used for the multiple comparison. Multivariate logistic analysis was used for examining the association of CLD and poor outcome in AHE patients. The estimated odds ratio (OR) with their 95% confidence interval (CI) were calculated. Data were analyzed using SAS software (version 9.4; SAS Institute Inc., Cary, NC). The results were based on two-sided tests and \( P < 0.05 \) was defined as statistical significance.

Results

Study population

A total of 263 patients were diagnosed of AHE based on serology and clinical presentations in our tertiary hospital during the study period. 36 outpatients were excluded for unavailable clinical information and/or laboratory data, resulting in 227 patients eligible for
the study, including 56 of cirrhotic CLD, 47 of non-cirrhotic CLD and 124 of no-CLD patients (Supplementary Fig 1). The detailed category of CLDs was show in Table S1. Alcoholic liver disease and CHB were the predominant CLDs in both cirrhotic and non-cirrhotic groups. No pregnant woman was found in all the 277 subjects. Serum samples from 94 patients were available for HEV RNA test. HEV RNA was positive in 19 patients and all of them were determined as GT4 HEV after sequencing.

**Manifestation and outcomes of AHE with CLD**

Compared with no-CLD HEV patients, HEV patients with CLD were more commonly to present ascites (37.9% vs. 21.8%, \( P = 0.008 \)), pleural effusion (17.5% vs. 5.7%, \( P = 0.005 \)) and peritonitis (14.6% vs. 5.7%, \( P = 0.024 \)) (Table 1). The frequency of liver failure (22.3% vs. 12.1%, \( P = 0.040 \)) was also significantly higher in HEV patients with CLD than solely HEV infected patients. Of great interest, there revealed no significant difference between HEV patients without CLD and with non-cirrhotic CLD in regard of all the liver function tests, complications and outcomes, suggesting that non-cirrhosis is unlikely to be involved in poor outcomes of AHE. An even worse but non-significant trend of some complications, including ascites, pulmonary infection, peritonitis renal injury and liver failure, were observed in HEV patients without CLD compared to HEV patients with non-cirrhotic CLD. In contrast, most complications and outcomes, including electrolyte disturbance, ascites, pleural effusion, renal injury and liver failure were worse in AHE patients with cirrhotic CLD, compared to AHE patients with non-cirrhotic CLD and AHE patients without CLD. Consistent with the trends of complications and outcomes, the laboratory biochemical variables including ALB (albumin), PLT (platelet count), DBil (direct bilirubin), TBil (total bilirubin), ALT (alanine aminotransferase), GGT (γ-glutamyl transferase), ChE (cholinesterase) and INR
(international normalized ratio) were significantly different between AHE patients with cirrhotic CLD and with non-cirrhotic CLD, but comparable between AHE patients with non-cirrhotic CLD and without CLD.

**Association of CLD and poor outcome in AHE patients**

To further characterize the role of etiology and status of CLD in the adverse clinical outcomes of AHE, patients developing liver failure or not were compared in respect to sex, age, cirrhotic status and etiology of CLD. In multivariate analysis, cirrhosis was found to be the only independent risk factor of development of liver failure. However, etiologies of CLD were not associated with liver failure (Table 2). These result supported the concept that the overall status of liver, other than specific etiology of CLD, is more pivotal for determinant of risk of liver failure in patients with AHE.

**Discussion**

In last decade, accumulated investigations has demonstrated that HEV infection in patients with underlying CLD may result in liver decompensation or liver failure, especially in the pattern of CHB superimpose\(^\text{10,16,17}\). Furthermore, previous studies also emphasized the correspondence of progressively severe outcomes with the increasing CHB stages in HEV superinfected patients\(^\text{18,19}\), proposing a wonder whether cirrhosis is a confounding factor. Additionally, data on course of HEV superinfection in patients with other etiologies induced CLDs is limited and no comparative studies of patients with various CLDs and distinct CLD status are available. Our study, with cohort of varying CLDs, revealed that superinfection with HEV in patients with cirrhotic CLD can cause a worsen outcome leading to exacerbation of AHE and liver failure, compared to HEV patients without CLD. Intriguingly, non-cirrhotic
CLD is unlikely to contribute to the adverse outcome. Additional analysis revealed that the etiology of CLD is not associated with outcomes of AHE patients, at least in the setting of some common etiologies, such as CHB, ALD. These findings suggested the worse liver status plays predominant role in severe complications and outcomes of AHE, regardless of the etiology of CLD. The concept of our finding compares well with recent report that the deteriorative outcomes of HEV/HBV superinfection were blamed for the end-stage of liver diseases, other than pure HBV infection. Despite some studies investigating AHE prognosis in HBV carriers without cirrhosis also found higher mortality and live failure rate in HBV carriers than in CHB non-carrier, but there was no statistical significance. Both of our and their findings highlighted the overall status of background CLD, other than pure etiology of CLD, in exacerbation of AHE. The interpreted mechanisms might be either due to the potentiation of cirrhotic liver upon HEV infection or the more aggressive immune- or inflammatory- medicated activation of cell death in cirrhotic liver status. Despite the limited number of cases in the current study, we do have statistical power to provide a glimpse into the nature and severity of HEV/CLD superimposing. Additional work with large cohort study, as well as other genotypes of HEV in endemic regions, is needed to corroborate the finding and identify the variants for predating poor outcome of HEV infection and provide recommendations for intensive surveillance of liver cirrhotic patients against HEV infection.
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Table 1. Clinical manifestations and outcomes between acute hepatitis E patients without chronic liver disease, with non-cirrhotic chronic liver disease and with cirrhotic chronic liver disease

| Characteristic                        | HEV without CLD (N = 124) | HEV with CLD (N = 103) | P value |
|---------------------------------------|---------------------------|------------------------|---------|
|                                       | Non-cirrhotic CLD (N=47)  | Cirrhotic CLD (N=56)   |         |
|                                       |                           | Total (N = 103)        |         |
| Age, years                            | 55.0 ± 13.8               | 51.7 ± 11.6            | 52.2 ±10.5 | 0.091 |
| Male, No. (%)                         | 94 (75.8)                 | 42 (89.4)              | 53 (94.6) a | 95 (92.2) | 0.001 |
| Symptoms, No. (%)                     |                           |                        |         |
| Jaundice                              | 104 (83.9)                | 36 (76.6)              | 42 (75.0) | 78 (75.7) | 0.126 |
| Fatigue                               | 98 (79.0)                 | 41 (87.2)              | 42 (75.0) | 83 (80.6) | 0.772 |
| Nausea / vomiting                     | 97 (78.2)                 | 34 (72.3)              | 31 (55.4) a | 65 (63.1) | 0.012 |
| Abdominal pain / distension           | 26 (21.0)                 | 14 (29.8)              | 23 (41.1) a | 37 (35.9) | 0.012 |
| Fever                                 | 30 (24.2)                 | 9 (19.2)               | 11 (19.6) | 20 (19.4) | 0.387 |
| Headache                              | 6 (4.8)                   | 3 (6.4)                | 6 (10.7) | 9 (8.7)  | 0.239 |
| Child-Pugh                            |                           |                        |         |
| A                                     | 85 (68.5)                 | 36 (76.6)              | 26 (46.5) | 62 (60.2) |         |
| B                                     | 31 (25)                   | 9 (19.1)               | 25 (44.6) | 34 (33)  | 0.222 |
| C                                     | 8 (6.5)                   | 2 (4.3)                | 5 (8.9)  | 7 (6.8)  |         |
| Laboratory biochemical variables      |                           |                        |         |
| ALB (g/L)                             | 33.3 ± 5.3                | 34.9 ± 4.0             | 30.7 ± 6.0 a,b | 32.7 ± 5.6 | 0.362 |

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| Parameter          | Mean (Range) | Median (Range) | Stat Value (Mean - Median) | p Value |
|--------------------|--------------|----------------|-----------------------------|---------|
| PLT (10^9/L)       | 172.0 (135.0-228.0) | 177.0 (142.0-228.0) | 125.0 (87.0-173.0) | 0.006 |
| DBiL (umol/L)      | 122.4 (47.7-186.9) | 107.1 (35.5-147.1) | 186.7 (102.8-262.8) | 0.233 |
| TBiL (umol/L)      | 150.2 (63.2-249.4) | 140.3 (43.6-177.0) | 239.6 (142.6-341.8) | 0.182 |
| ALT (U/L)          | 548.0 (205.0-1225.0) | 666.0 (203.0-1557.0) | 213.5 (99.5-716.5) | 0.026 |
| AST (U/L)          | 196.5 (102.0-542.0) | 302.0 (74.0-745.0) | 158.5 (85.5-508.0) | 0.446 |
| ALP (U/L)          | 201.00 (153.0-250.0) | 167.0 (135.0-232.0) | 163.0 (126.5-201.5) | 0.001 |
| GGT (U/L)          | 153.0 (91.0-242.0) | 209.0 (142.0-406.0) | 110.0 (62.0-176.0) | 0.684 |
| ChE (U/L)          | 4494.5 (3560.0-5821.0) | 5371.0 (4079.0-6047.0) | 2961.5 (2011.0-4381.0) | 0.056 |
| INR                | 1.06 (0.97-1.32) | 1.04 (0.95-1.13) | 1.23 (1.09-1.51) | 0.162 |
| Blood ammonia (umol/L) | 31.1 (21.4-46.5) | 32.0 (24.7-50.4) | 45.4 (25.6-66.6) | 0.060 |

**Complications/outcomes, No. (%)**

Electrolyte disturbance | 40 (32.3) | 11 (23.4) | 31 (55.4) | 42 (40.8) | 0.183
| Condition                  | HEV | HEV with CLD | HEV without CLD | HEV with non-cirrhotic CLD | P value, HEV vs. HEV with CLD total; a, vs. HEV without CLD; b, vs. HEV with non-cirrhotic CLD |
|----------------------------|-----|--------------|-----------------|---------------------------|-----------------------------------------------------------------------------------------------|
| Anemia                     | 26 (21.0) | 10 (21.3) | 18 (32.1) | 28 (27.2) | 0.273                                                                                         |
| Hypoproteinemia            | 24 (19.4) | 6 (12.8) | 18 (32.1) | 24 (23.3) | 0.469                                                                                         |
| Ascites                    | 27 (21.8) | 5 (10.6) | 34 (60.7) b | 39 (37.9) | 0.008                                                                                         |
| Pleural effusion           | 7 (5.7) | 2 (4.3) | 16 (28.6) b | 18 (17.5) | 0.005                                                                                         |
| Pulmonary infection        | 10 (8.1) | 2 (4.3) | 10 (17.9) | 12 (11.7) | 0.363                                                                                         |
| Peritonitis                | 7 (5.7) | 0 (-) | 15 (26.8) b | 15 (14.6) | 0.024                                                                                         |
| Renal injury               | 14 (11.3) | 2 (4.3) | 13 (23.2) b | 15 (14.6) | 0.462                                                                                         |
| Heart disease              | 19 (15.3) | 3 (6.4) | 5 (8.9) | 8 (7.8) | 0.080                                                                                         |
| Intestinal diseases        | 4 (3.2) | 1 (2.1) | 1 (1.8) | 2 (1.9) | 0.692                                                                                         |
| Shock                      | 1 (0.8) | 0 (-) | 3 (5.4) | 3 (2.9) | 0.332                                                                                         |
| Liver failure              | 15 (12.1) | 4 (8.5) | 19 (33.9) b | 23 (22.3) | 0.040                                                                                         |
| Duration of illness (day)  | 18 (12-25) | 16 (11-25) | 24 (14-41) b | 21 (12-33) | 0.066                                                                                         |

Age and albumin were expressed in mean ± standard deviation (SD), whereas other continuous variables were expressed in median (interquartile range). Percentages were based on nonmissing data.

Abbreviations: HEV, hepatitis E virus; CLD, chronic liver disease; ALB, albumin; PLT, platelet count; DBil, direct bilirubin; TBil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; ChE, cholinesterase; INR, international normalized ratio.

P value, HEV vs. HEV with CLD total; a, vs. HEV without CLD; b, vs. HEV with non-cirrhotic CLD.
Table 2. Univariate and multivariate analyses of liver failure in patients with hepatitis E

| Parameter       | OR (95% CI)       | P     | aOR (95% CI) | P     |
|-----------------|-------------------|-------|--------------|-------|
| Male sex        | 4.235 (0.974-18.410) | 0.054 | 2.425 (0.614-9.581) | 0.206 |
| Age ≥ 53 years  | 1.474 (0.711-3.056)  | 0.297 | -             | -     |
| Cirrhosis       | 4.108 (1.979-8.528)   | < 0.001 | 6.050 (1.814-20.179)   | 0.003 |
| Etiology of CLD |                   |       |               |       |
| No-CLD          | reference          | -     | reference     | -     |
| ALD             | 2.255 (0.897-5.672)  | 0.084 | 0.858 (0.267-2.757)  | 0.797 |
| CHB             | 2.515 (0.992-6.379)  | 0.052 | 0.561 (0.135-2.325)  | 0.426 |
| CHB+ALD         | 1.817 (0.190-17.354) | 0.604 | 0.743 (0.068-8.117)  | 0.808 |
| Others*         | 1.384 (0.418-4.585)  | 0.595 | 0.317 (0.063-1.589)  | 0.162 |

*Other etiologies of CLD included non-alcoholic fatty liver disease, combination of alcoholic liver disease and autoimmune liver disease, cryptogenic cirrhosis, combination of chronic hepatitis B related cirrhosis and hepatocellular carcinoma, drug induced liver injury related cirrhosis, primary biliary cirrhosis, hepatitis C virus related cirrhosis, and combination of primary biliary cirrhosis and autoimmune cirrhosis.

Abbreviations: OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; CLD, chronic liver disease; ALD, alcoholic liver disease; CHB, chronic hepatitis B.