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BRIEF REPORT

Poor Outcomes of Acute Hepatitis E in Patients With Cirrhotic Liver Diseases Regardless of Etiology

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Background: Chronic liver diseases (CLDs) 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 hepatitis E virus (HEV) in patients with cirrhotic CLD can cause a worsen outcome, leading to exacerbation of AHE, compared with HEV-infected patients without CLD or with noncirrhotic CLD. Additional analysis revealed that the etiology of CLD is not associated with outcomes of AHE patients. These finding suggests that the overall liver status plays a predominant role in determining the outcomes of AHE.

Keywords. hepatitis E; background liver diseases; cirrhotic liver diseases; etiology.

Hepatitis E virus (HEV) infection is the most common cause of acute viral hepatitis in the world. There are an estimated 20 million HEV infections and 3.3 million symptomatic hepatitis E cases per year [1]. Four main genotypes of HEV were identified. Genotype (GT) 1 and 2 are found mainly in developing countries and are transmitted via contaminated water sources. GT 3 and 4 are prevalent in industrialized countries and are zoonotic in nature and spread mainly through eating undercooked pork or game products [2]. China is generally considered an HEV-endemic area. The seroprevalence rates of anti-HEV IgM in the general population range from 0.1% to 1.57%, and anti-HEV IgG seroprevalence rates range from 9.16% to 38.06% [3–6]. Occurrences of HEV infection in China are predominantly sporadic in pattern with occasional foodborne outbreaks. Although generally causing asymptomatic or acute hepatitis, HEV infection in patients with preexisting chronic liver diseases (CLDs), especially 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 have shown that superinfection of GT1 HEV in patients with CLD produced severe decompensation, leading to high mortality [12–15]. China is an HEV-endemic area with prevalent GT4 HEV infection. Recent evidence from Hong Kong suggested that CHB is associated with high mortality in patients with acute hepatitis E (AHE). However, whether the worse clinical features associated with HEV/CLD are due to underlying cirrhosis, which is probably a confounding factor, was not discussed. One large cohort study in hepatitis B virus (HBV)/HEV-coinfected patients suggested that the high mortality associated with HBV/HEV coinfection may be related to end-stage liver diseases, but not pure HBV infection, implying that liver status seems to play a critical role in the poor outcomes of AHE. However, CLDs vary largely in their etiology and disease stages, and the course of AHE with other CLDs is still unclear, leading to the question of whether the etiology or status of CLD may determine adverse clinical outcomes with HEV superinfections. In this study, we characterized the course of GT4 AHE in patients with various etiologies and statuses of CLD to elaborate the issue.

METHODS

Study Design

All inpatients and outpatients with suspected symptoms of acute viral hepatitis, defined as presenting with elevated liver enzymes and/or jaundice and/or nonspecific symptoms such as fatigue, itching, and nausea, who were 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 diseases in China. The numbers of outpatient and inpatient visits with liver diseases are ~1.87 million and 0.1 million per year, respectively. Patients admitted to this hospital are from all over the 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 with AHE were consecutively retrieved from January 2015 to October 2017 and interviewed to obtain demographic information, clinical symptoms, laboratory data, complications, extrahepatic manifestations, and clinical outcomes. This study was approved by the medical ethical committee of the local hospital.

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The primary outcome was incidence of liver failure. Diagnosis and classifications of liver failure were defined by international normalized ratio (INR) and prothrombin activity, according to Chinese guidelines for liver failure published in 2012. In detail, diagnosis of acute liver failure (ALF) is based on the presence of stage 2 or 3 encephalopathy with complicating end-stage disease manifestations, including profound coagulopathy (prothrombin activity ≤ 40% or INR ≥ 1.5), jaundice, and hepatic atrophy, within 2 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 disease, and shock.

CLDs were defined as the presence of 1 or more of the following diseases: chronic hepatitis B or C, alcoholic liver disease, moderate to severe fatty liver, autoimmune liver diseases, and all etiology–related cirrhosis.

a) CHB was diagnosed with positive hepatitis B surface antigen (HBsAg) for >6 months.
b) Alcoholic liver disease (ALD): The diagnosis of ALD was based on drinking history, clinical manifestation, laboratory test, imaging examination, and/or histology. Patients with ALD have excessive alcohol use for over 5 years. Excessive alcohol use is defined as drinking >20 g/d (or >140 g weekly) for women and 40 g/d (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.

Test of HEV RNA and Viral Sequence Analysis

Some of the patients in this study cohort had stored serum samples for HEV RNA testing. RNA was extracted from serum samples with a total RNA isolation kit purchased from Bioteke, Beijing, China, according to the manufacturer's instructions. 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 using genotype information from the reference sequences.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median (interquartile range [IQR]), as appropriate. Categorical variables were presented as number (percentage). The Student *t* test and Mann-Whitney *U* test were used for statistical comparisons of continuous variables between 2 groups. Analysis of variance and the Kruskal-Wallis test were performed among 3 groups. The chi-square test and Fisher exact test were utilized to compare the distribution of categorical variables as appropriate. Bonferroni correction was used for multiple comparison. Multivariate logistic analysis was used for examining the association of CLD with poor outcome in AHE patients. The estimated odds ratio (OR) and 95% confidence interval (CI) were calculated. Data were analyzed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). The results were based on 2-sided tests, and $P < .05$ was defined as statistical significance.

RESULTS

Study Population

A total of 263 patients were diagnosed with AHE based on serology and clinical presentations in our tertiary hospital during the study period. Thirty-six outpatients were excluded due to unavailable clinical information and/or laboratory data, resulting in 227 patients eligible for the study, including 56 with cirrhotic CLD, 47 with noncirrhotic CLD, and 124 with no CLD (Supplementary Figure 1). The detailed categories of CLDs are shown in Supplementary Table 1. ALD and CHB were the predominant CLDs in both the cirrhotic and noncirrhotic groups. No pregnant woman were found in all 227 subjects. Serum samples from 94 patients were available for HEV RNA test. HEV RNA was positive in 19 patients, all of whom were determined to have GT4 HEV after sequencing.

Manifestation and Outcomes of AHE With CLD

Compared with no-CLD HEV patients, HEV patients with CLD more commonly presented with ascites (37.9% vs 21.8%; $P = .008$), pleural effusion (17.5% vs 5.7%; $P = .005$), and peritonitis (14.6% vs 5.7%; $P = .024$) (Table 1). The frequency of liver failure (22.3% vs 12.1%; $P = .040$) was also significantly higher in HEV patients with CLD than HEV-only patients. Of great interest, no significant difference was apparent between HEV patients without CLD and those with noncirrhotic CLD with regard to all the liver function tests, complications, and outcomes, suggesting that noncirrhosis is unlikely to be involved in poor outcomes of AHE. An even worse but nonsignificant trend of some complications, including ascites, pulmonary infection, peritonitis renal injury, and liver failure, was observed in HEV patients without CLD compared with HEV patients with noncirrhotic 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 with AHE patients with noncirrhotic 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 were significantly different between AHE patients with cirrhotic CLD and those with noncirrhotic

Table 1. Clinical Manifestations and Outcomes Between Acute Hepatitis E Patients Without Chronic Liver Disease, Those With Noncirrhotic Chronic Liver Disease, and Those With Cirrhotic Chronic Liver Disease

Characteristic	HEV Without CLD (n = 124)	HEV With CLD (n = 103)			*P* Value
		Noncirrhotic CLD (n = 47)	Cirrhotic CLD (n = 56)	Total (n = 103)	
Age, y	55.0 ± 13.8	51.7 ± 11.6	52.7 ± 9.6	52.2 ± 10.5	.091
Male, No. (%)	94 (75.8)	42 (89.4)	53 (94.6)[a]	95 (92.2)	.001
Symptoms, No. (%)					
Jaundice	104 (83.9)	36 (76.6)	42 (75.0)	78 (75.7)	.126
Fatigue	98 (79.0)	41 (87.2)	42 (75.0)	83 (80.6)	.772
Nausea/vomiting	97 (78.2)	34 (72.3)	31 (55.4)[a]	65 (63.1)	.012
Abdominal pain/distension	26 (21.0)	14 (29.8)	23 (41.1)[a]	37 (35.9)	.012
Fever	30 (24.2)	9 (19.2)	11 (19.6)	20 (19.4)	.387
Headache	6 (4.8)	3 (6.4)	6 (10.7)	9 (8.7)	.239
Child-Pugh					
A	85 (68.5)	36 (76.6)	26 (46.5)	62 (60.2)	.222
B	31 (25)	9 (19.1)	25 (44.6)	34 (33)	
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	.362
Missing, %	1.6	0	0	0	
PLT, 10^9/L	172.0 (135.0–228.0)	177.0 (142.0–228.0)	125.0 (87.0–173.0)[a,b]	146.0 (107.0–194.0)	.006
Missing, %	1.6	0	3.6	1.9	
DBiL, umol/L	122.4 (47.7–186.9)	107.1 (35.5–147.1)	186.7 (102.8–262.8)[a,b]	132.4 (52.9–229.6)	.233
Missing, %	0	0	0	0	
TBiL, umol/L	150.2 (63.2–249.4)	140.3 (43.6–177.0)	239.6 (142.6–341.8)[a,b]	173.1 (71.8–296.3)	.182
Missing, %	0	0	0	0	
ALT, U/L	548.0 (205.0–1225.0)	666.0 (203.0–1557.0)	213.5 (99.5–716.5)[a,b]	311.0 (142.0–1042.0)	.026
Missing, %	0	0	0	0	
AST, U/L	196.5 (102.0–542.0)	302.0 (74.0–745.0)	158.5 (85.5–508.0)	222.0 (78.0–632.0)	.446
Missing, %	1.6	0	0	0	
ALP, U/L	201.00 (153.0–250.0)	167.0 (135.0–232.0)	163.0 (126.5–201.5)[a]	166.0 (130.0–217.0)	.001
Missing, %	1.6	0	0	0	
GGT, U/L	153.0 (91.0–242.0)	209.0 (142.0–406.0)	110.0 (62.0–176.0)[a,b]	151.0 (90.0–226.0)	.684
Missing, %	1.6	0	0	0	
ChE, U/L	4494.5 (3560.0–5821.0)	5371.0 (4079.0–6047.0)	2961.5 (2011.0–4381.0)[a,b]	4097.0 (2621.0–5700.0)	.056
Missing, %	1.6	0	0	0	
INR	1.06 (0.97–1.32)	1.04 (0.95–1.13)	1.23 (1.09–1.51)[a,b]	1.13 (0.98–1.35)	.162
Missing, %	2.4	0	0	0	
Blood ammonia, umol/L	31.1 (21.4–46.5)	32.0 (24.7–50.4)	45.4 (25.6–66.6)[a]	39.3 (25.4–57.1)	.060
Missing, %	29.0	14.9	14.3	14.6	
Complications/outcomes, No. (%)					
Electrolyte disturbance	40 (32.3)	11 (23.4)	31 (55.4)[a,b]	42 (40.8)	.183
Anemia	26 (21.0)	10 (21.3)	18 (32.1)	28 (27.2)	.273
Hypoproteinemia	24 (19.4)	6 (12.8)	18 (32.1)	24 (23.3)	.469
Ascites	27 (21.8)	5 (10.6)	34 (60.7)[a,b]	39 (37.9)	.008
Pleural effusion	7 (5.7)	2 (4.3)	16 (28.6)[a,b]	18 (17.5)	.005
Pulmonary infection	10 (8.1)	2 (4.3)	10 (17.9)	12 (11.7)	.363
Peritonitis	7 (5.7)	0 (–)	15 (26.8)[a,b]	15 (14.6)	.024
Renal injury	14 (11.3)	2 (4.3)	13 (23.2)[b]	15 (14.6)	.462
Heart disease	19 (15.3)	3 (6.4)	5 (8.9)	8 (7.8)	.080
Intestinal diseases	4 (3.2)	1 (2.1)	1 (1.8)	2 (1.9)	.692
Shock	1 (0.8)	0 (–)	3 (5.4)	3 (2.9)	.332
Liver failure	15 (12.1)	4 (8.5)	19 (33.9)[a,b]	23 (22.3)	.040
Duration of illness, d	18 (12–25)	16 (11–25)	24 (14–41)[a,b]	21 (12–33)	.066

Age and albumin are expressed as mean ± SD, whereas other continuous variables are expressed as median (interquartile range). Percentages are based on nonmissing data.

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

[a]HEV vs HEV without CLD.

[b]HEV vs HEV with noncirrhotic 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)	.054	2.425 (0.614–9.581)	.206
Age ≥53 y	1.474 (0.711–3.056)	.297	-	-
Cirrhosis	4.108 (1.979–8.528)	<.001	6.050 (1.814–20.179)	.003
Etiology of CLD				
No-CLD	Reference	-	Reference	-
ALD	2.255 (0.897–5.672)	.084	0.858 (0.267–2.757)	.797
CHB	2.515 (0.992–6.379)	.052	0.561 (0.135–2.325)	.426
CHB + ALD	1.817 (0.190–17.354)	.604	0.743 (0.068–8.117)	.808
Others[a]	1.384 (0.418–4.585)	.595	0.317 (0.063–1.589)	.162

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

[a]Other etiologies of CLD included nonalcoholic 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.

CLD, but comparable between AHE patients with noncirrhotic CLD and those without CLD.

Association of CLD With Poor Outcome in AHE Patients

To further characterize the role of etiology and status of CLD in the adverse clinical outcomes of AHE, patients who developed liver failure and those who did not were compared in terms of sex, age, cirrhotic status, and etiology of CLD. In multivariate analysis, cirrhosis was found to be the only independent risk factor for development of liver failure. However, etiology of CLD was not associated with liver failure (Table 2). These results support the concept that the overall status of the liver, not the specific etiology of CLD, is the more important determinant of risk of liver failure in patients with AHE.

DISCUSSION

In last decade, investigations have demonstrated that HEV infection in patients with underlying CLD may result in liver decompensation or liver failure, especially in condition of CHB/HEV superinfection [10, 16, 17]. Furthermore, previous studies have also emphasized the correspondence of progressively severe outcomes with increasing CHB stages in HEV-superinfected patients [18, 19], prompting the question of whether cirrhosis is a confounding factor. Additionally, data on the course of HEV superinfection in patients with other etiology–induced CLD are limited, and no comparative studies of patients with various CLDs and distinct CLD status are available. Our study, with a cohort of varying CLDs, revealed that superinfection with HEV in patients with cirrhotic CLD can cause a worse outcome, leading to exacerbation of AHE and liver failure, compared with HEV patients without CLD. Intriguingly, noncirrhotic CLD is unlikely to contribute to the adverse outcome. Additional analysis revealed that the etiology of CLD is not associated with the outcomes of AHE patients, at least in the setting of some common etiologies, such as CHB and ALD. These findings suggest that worse liver status plays a predominant role in severe complications and outcomes of AHE, regardless of the etiology of CLD. Our findings compare well with a recent report that HEV/HBV superinfection, rather than HBV infection alone, is responsible for the end stage of liver diseases [20]. Although some studies investigating AHE prognosis in HBV carriers without cirrhosis have also found higher mortality and live failure rates in HBV carriers than in CHB noncarriers, there was no statistical significance associated with these findings [21]. Both our and their findings highlight the overall status of background CLD, not just the etiology of CLD, in exacerbation of AHE. The interpreted mechanisms might be either due to the potentiation of cirrhotic liver upon HEV infection or due to the more aggressive immune- or inflammatory-mediated 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 a large cohort study, as well as other genotypes of HEV in endemic regions, is needed to corroborate these findings and identify the variants for predicating poor outcomes associated with HEV infection and provide recommendations for intensive surveillance of liver cirrhotic patients against HEV infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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experiments, viral sequencing and analysis; Q. P. contributed to study concept and critical revision of the manuscript; J. Z. contributed to providing clinical samples and study supervision.

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