Comparison of effects of hepatitis E or A viral superinfection in patients with chronic hepatitis B

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Abstract

Purpose To compare the demographics, liver function, and prognosis of Chinese patients infected with chronic hepatitis B (CHB) and superinfected with hepatitis E virus (HEV) or hepatitis A virus (HAV).

Patients and methods Among 188 patients with CHB, 136 with HEV superinfection and 52 with HAV superinfection were treated at our hospital between March 1999 and October 2007 for clinical features suggestive of acute hepatitis. The patients' age, sex, incidence of liver failure, and mortality were recorded. The tested biochemical indices and markers of liver function included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), prothrombin activity (PTA), and the serum levels of HBeAg, HBeAb, and HBV DNA.

Results There were significant differences between the age and sex distributions of the two groups ($P < 0.05$). More patients in the CHB + HEV group had complications (94.9 vs. 61.5%, $P < 0.001$), and hepatic failure (39.7 vs. 11.5%, $P = 0.002$). Additionally, the mortality among the CHB + HEV group was significantly higher (33.8 vs. 1.9%, $P < 0.001$).

Conclusions The comparison of clinical outcomes revealed that patients with HBV + HEV had more advanced baseline liver disease and a poorer prognosis than those with HBV + HAV. Because there is no vaccine against HEV, patients with CHB should take appropriate precautions against superinfection with HEV, such as consumption of

boiled water and well-cooked food, in regions where it is endemic.

Keywords Chronic hepatitis B · Hepatic failure · Hepatitis A · Hepatitis E · Mortality · Superinfection

Introduction

Infection by hepatitis B virus (HBV) is a serious public health problem worldwide. The national seroepidemiologic survey of diseases carried out by the Chinese Ministry of Public Health in 2006 among persons between 1 and 50 years of age found 7.18% prevalence of HBsAg carriers [1]. Most of the carriers are asymptomatic and go unrecognized; and, during the long course of chronic hepatitis B (CHB), there is a chance that the patients might be sporadically superinfected by other viruses. Studies of serum epidemiology in China found that in patients with viral hepatitis, the superinfection rate with 2 or more viral types was 32.4%; and HAV superinfection in patients with CHB accounted for 41.2%, while HEV superinfection in patients with CHB accounted for 17.6% [2].

HAV and HEV are endemic in China and South Asia, and are the most common causes of acute hepatitis in this region. Both viruses generally cause an acute, self-limiting illness followed by a complete recovery. Recent studies have shown that both HAV and HEV can result in severe disease and a poor outcome in patients with underlying chronic liver disease (CLD), especially for those with chronic hepatitis C [3, 4]. Data on the course of these infections in patients with underlying CHB is limited and no previous comparative studies of patients with the two superinfections are available. However, some evidence has suggested that coinfection with HBV + HEV is more

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likely to be fatal than with HBV + HAV [5]. The aim of our study was to compare the clinical manifestations, liver function, and prognosis of patients with CHB who were superinfected with either HAV or HEV.

Patients and methods

Patients

Among 2,104 patients infected with HBV and seen at our hospital from March 1999 to October 2007, all were tested for superinfection by HEV and HAV. A total of 253 patients (221 men and 32 women) were selected for this study on the basis of the following inclusion criteria: hospitalization from March 1999 to October 2007 for clinical features suggestive of acute hepatitis, underlying CHB, and superinfection by HEV or HAV as determined serologically. Patients who were known to have liver disorders other than CHB were excluded. All the patients originated from the Guangdong Province in south China.

Diagnostic methods and criteria

The diagnostic standards used to classify CHB, HAV, and HEV infections were obtained from the program of prevention and cure for viral hepatitis of the Chinese Society of Infectious Diseases and Parasitology, and the Chinese Society of Hepatology of the Chinese Medical Association, established in Xian in September of 2000 [6]. The diagnostic criteria and definitions of terms applied in describing the patient histories were as follows. Patients whose conditions were diagnosed as HBeAg-positive chronic hepatitis B had positive results for serum HBsAg, HBV DNA, and HBeAg, negative results for anti-HBe, elevated levels of serum ALT continuously or repeatedly, or results of a histologic examination of the liver that indicated hepatitis. Patients whose conditions were diagnosed as HBeAg-negative chronic hepatitis B had positive results for serum HBsAg and HBV DNA, continuously negative results for HBeAg, positive or negative results for anti-HBe, continuously or repeatedly abnormal levels of serum ALT, or results of a histologic examination of the liver that indicated hepatitis. Patients who had compensated cirrhosis (corresponding to Child–Pugh grade A) showed slight hypodynamia, poor appetite or abdominal distension, and abnormal levels of ALT and AST; however, they showed no hepatic decompensation. There may have been signs of portal hypertension, such as hypersplenism and mild esophageal and gastric varices; however, there was neither esophagogastric variceal bleeding, ascites, nor hepatic encephalopathy. Patients who had decompensated cirrhosis (corresponding to Child–Pugh grade B and grade C) often

had serious complications, such as esophagogastric variceal bleeding, hepatic encephalopathy, or ascites. Most of these patients had significant signs of hepatic decompensation such as serum albumin <35 g/L, bilirubin >35 $\mu\text{mol/L}$, increased levels of ALT and AST, and prothrombin activity (PTA) <60%.

Chronic hepatitis B carriers were patients in whom the serum HBsAg and HBV DNA results were positive and the HBeAg or anti-HBe result was positive; however, the levels of ALT and AST were normal during follow-up examinations performed three times in less than a year, and no abnormalities were found during histologic examination of the liver. Aspiration liver biopsy was recommended in patients with positive HBV DNA results for further diagnosis and treatment.

Inactive HBsAg carriers were patients in whom the serum HBsAg result was positive, the HBeAg result was negative, the anti-HBe result was positive or negative, the HBV DNA was lower than the limit of detection by PCR, and the levels of ALT were normal during follow-up examinations performed three times in less than a year. The result of the histologic examination of the liver in these patients indicated that the Knodell Histological Activity Index (HAI) was <4, or only slight lesions could be detected by other semiquantitative scoring systems.

For the purposes of this study, patients in Group CHB + HAV, all had positive results for anti-HAV-IgM, with negative results for markers of hepatitis C virus (HCV), hepatitis D virus (HDV), or HEV; thereby excluding superinfection with these viruses. Patients in Group CHB + HEV had positive results for both anti-HEV-IgM and anti-HEV-IgG and negative results for markers of infection with HAV, HCV, or HDV. The presence of HEV-IgG is sometimes used in China to diagnose acute hepatitis E infection because some patients do not seek medical care in the early stages of their illness; therefore, HEV-IgM may not be detected in these patients. However, only 136 patients with positive results for both anti-HEV-IgM and anti-HEV-IgG were included in the Group CHB + HEV.

The patients' histories are summarized in Table 1. Among them, 52 patients had HAV superinfection [Group A, 39 men and 13 women, median age, 37.0 (23.0–48.5) years]; and 136 patients had HEV superinfection [Group B, 124 men and 12 women, median age, 40.0 (33.0, 51.5) years]. Informed consent was obtained from each patient included in the study, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected a priori in approval by the institution's human research committee.

Diagnostic kits targeting the anti-hepatitis A virus (HAV) IgM were commercially supplied by the Beijing Kewei Clinical Diagnostic Reagent Company, Ltd. (Beijing,

Table 1 Characteristics of patients with CHB

	CHB + HAV superinfection (<i>n</i> = 52)	CHB + HEV superinfection (<i>n</i> = 136)	<i>P</i> value ^a
Age (years) ^b	37.0 (23.0, 48.5)	40.0 (33.0, 51.5)	0.022*
Sex ^c			0.004*
Male	39 (75.0)	124 (91.2)	
Female	13 (25.0)	12 (8.8)	
Family history of hepatitis B ^c	19 (36.5)	58 (42.7)	0.446
Chronic hepatitis B carrier ^c	13 (25.0)	24 (17.7)	0.257
Chronic hepatitis ^c	20 (38.5)	73 (53.7)	0.062
Compensated cirrhosis ^d	2 (3.9)	16 (11.8)	0.099
Decompensated cirrhosis ^d	4 (7.7)	10 (7.4)	1.000
Inactive HBsAg carrier ^c	13 (25.0)	12 (8.8)	0.004*
Alcoholic hepatitis ^d	3 (5.8)	3 (2.2)	0.350
Alcoholic cirrhosis ^c	6 (11.5)	19 (14.0)	0.660
Complications ^c	32 (61.5)	129 (94.9)	<0.001*
Liver fluke ^d	2 (3.9)	7 (5.2)	1.000
Chronic gastrointestinal disease ^d	5 (9.6)	12 (8.8)	1.000
G6PD deficiency ^d	3 (5.8)	7 (5.2)	1.000
Hepatic failure ^c	6 (11.5)	54 (39.7)	0.002*
Other diseases ^{c,e}	4 (7.69)	15 (11.0)	0.497
Death ^c	1 (1.9)	46 (33.8)	<0.001*

Median (interquartile range) for age and number (percentage) for other variables are shown

HAV hepatitis A virus, CHB chronic hepatitis B, HEV hepatitis E virus, G6PD glucose-6-phosphate dehydrogenase

* Significantly different, *P* < 0.05

^a The *P* values were derived from ^b Mann–Whitney *U* test, ^c Chi-square test, or ^d Fisher's exact test, ^e Other diseases included hypertension, diabetes, hyperthyroidism, tuberculosis, and asthma

China); HBsAg, anti-HBs, HBV_e antigen (HBeAg), anti-HBe, and anti-HBc were supplied by the Hepatitis Institute of Beijing (Beijing, China). The diagnostic kits for anti-HEV-IgM and anti-HEV-IgG were commercially supplied by Genelabs Technologies (Singapore). Markers for hepatotropic viruses were detected by enzyme-linked immunosorbent assay (ELISA).

Indices of liver function and biochemistry

The collection and storage of serum, detection procedures, and analysis of results were performed in accordance with the kit manufacturers' instructions. Serum samples for the determination of the indices of liver function and biochemistry were obtained weekly. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), and serum albumin were analyzed by an automated filter photometric chemistry analyzer (Technicon RA-1000, USA). A French STAGO automatic blood coagulation analyzer was used for the determination of prothrombin activity (PTA).

Statistical analysis

As continuous variables fell into abnormal distributions, the median and interquartile ranges are shown. The difference in age between groups A and B was evaluated by the Mann–Whitney *U* test. For the biochemical indices, the

differences were examined by multiple linear regression to adjust for the difference in baseline characteristics (i.e., age and sex) between the two groups. Categorical variables were expressed as number (frequency). The differences in sex, family history of hepatitis B, and disease histories were examined by the chi-square test. The differences in HBeAg and HBeAb antigens were tested by multiple logistic regression analysis to adjust for the effects of age and sex. The level of significance was defined as *P* ≤ 0.05. All two-sided statistical analyses were performed with SAS statistical software (version 9.1.3, SAS Inc., Cary, NC, USA).

Results

A total of 188 patients, 163 men and 25 women, with a mean age of 40.5 ± 14.2 years were included in the analysis. The differences in baseline characteristics between the CHB + HAV and CHB + HEV groups are shown in Table 1. Although patients with known liver disorders other than CHB had been excluded from the study, some patients were found to have alcoholic hepatitis, cirrhosis, and other disorders after they were enrolled. Among the 188 patients, 10.1% had other diseases including hypertension, diabetes, hyperthyroidism or tuberculosis; and about half of the patients had chronic hepatitis (49.5%) or a family history of hepatitis B (41.0%).

Some of the patients were hepatitis B carriers (19.7%). All the patients were tested for anti-HBc IgM, and none had positive results (data not shown).

The differences in age, sex, inactive HBsAg carrier status, complications, and hepatic failure were significant. The patients in the CHB + HEV group were older (40.0 years of age vs. 37.0 years of age, $P = 0.022$), more were men (91.2 vs. 75.0%, $P = 0.004$), and fewer were inactive HBsAg carriers (8.8 vs. 25.0%, $P = 0.004$) when compared with the patients in the CHB + HAV group. More patients in the CHB + HEV group had complications (94.9 vs. 61.5%, $P < 0.001$), and hepatic failure (39.7 vs. 11.5%, $P = 0.002$). Finally, the mortality among the CHB + HEV group was significantly higher (33.8 vs. 1.9%, $P < 0.001$).

The results of laboratory tests for liver function, biochemistry, HBV serology, and the levels of HBV DNA for 128 patients with HBV DNA levels greater than 2.69 log₁₀ copies/mL are shown in Table 2. The CHB + HEV group had higher peak levels of ALT (1,425.5 vs. 903.0 U/L, $P = 0.003$), AST (1,118.5 vs. 446.5 U/L, $P < 0.001$), and TBil (389.5 vs 123.5 μmol/L, $P < 0.001$), but lower peak prothrombin activity (PTA, 45.0 vs. 84.0%, $P < 0.001$) as compared with the CHB + HAV group. There was no significant difference in the level of HBV DNA between the two groups.

The causes of death and disease histories for the 47 patients who died are summarized in Table 3. More than 80% of the patients who died in the CHB + HEV group succumbed to hepatic failure, as did the only patient who died from the CHB + HAV group. Also, a majority of the patients who died experienced complications (97.8% in the CHB + HEV group and the single patient from the

CHB + HAV group). Among the patients who died in the CHB + HEV group, fewer than 50% had chronic hepatitis (41.3%), compensated cirrhosis (28.3%), alcoholic cirrhosis (21.7%) or decompensated cirrhosis (19.6%). A few of the patients were chronic hepatitis B carriers (6.5%) or suffered from liver flukes (4.4%) or chronic diseases of the gastrointestinal tract (4.4%).

Discussion

The People's Republic of China is one of the endemic areas in the world for HBV. According to the national investigation of 2002, the rate of HBsAg-positivity was 9.09% in persons older than 3 years of age in China [7]. The national seroepidemiologic survey of diseases carried out by the Chinese Ministry of Public Health in 2006 among persons between 1 and 50 years of age found 7.18% prevalence of HBsAg carriers [1]. It is common to find patients with CHB who have acquired HAV or HEV superinfections in the PR of China. Domestic and foreign studies have reported that hepatitis E superinfection can produce severe damage to the liver in patients with chronic liver disease [8–10]. The exacerbation of liver problems in patients coinfecting with HBV + HAV has been widely reviewed [11].

Ours is the first study to focus on a comparison of various clinical markers related to liver function between patients hospitalized with acute hepatitis who were infected with HBV and coinfecting with HEV or HAV. A previous study had examined the rates of coinfection as a cause of fatal liver failure in patients with HBV in China [5]. These authors found that 28.4% of the patients who died were coinfecting with HBV + HEV, while only 1.4% were

Table 2 Comparisons of peak levels of biochemical indices, markers of liver function, HBeAg (+), and HBeAb (+)

	CHB + HAV superinfection ($n = 52$)	CHB + HEV superinfection ($n = 136$)	P value
ALT (U/L)	903.0 (429.5, 1,267.5)	1,425.5 (911.5, 2,014.0)	0.003*
AST (U/L)	446.5 (197, 859.5)	1,118.5 (550.0, 1,624.0)	<0.001*
PTA (%) ^a	84.0 (57.0, 100.0)	45.0 (24.0, 76.0)	<0.001*
Serum albumin (g/L)	34.8 (32.0, 39.3)	34.0 (31.0, 37.3)	0.590
Total serum bilirubin (μmol/L)	123.5 (50.6, 242.0)	389.5 (126.0, 597.5)	<0.001*
HBV DNA (log ₁₀ copies/mL) ^b	5.5 (4.9, 6.8)	6.4 (4.7, 7.6)	0.176
HBeAg (+)	33 (63.5)	98 (72.1)	0.54
HBeAb (+)	24 (46.2)	51 (37.5)	0.665

Continuous variables are presented as median (interquartile range) and tested by multiple linear regression; categorical variables are presented as number (percentage) and tested by multiple logistic regression analysis

HAV hepatitis A virus, CHB chronic hepatitis B, HEV hepatitis E virus, HBV hepatitis B virus, ALT alanine aminotransferase, AST aspartate aminotransferase, PTA prothrombin activity

* Significantly different between two groups, $P < 0.05$

^a $PTA = \{(0.4 \times PT \text{ of control group}) / [PT \text{ in case group} - (0.6 \times PT \text{ in control group})]\} \times 100\%$

^b Only the 128 patients with HBV DNA greater than 2.69 log₁₀ copies/mL are reported

Table 3 Cause of death and disease history of 47 deceased patients with CHB

	CHB + HAV superinfection (<i>n</i> = 1) <i>N</i> (%)	CHB + HEV superinfection (<i>n</i> = 46) <i>N</i> (%)
Cause of death		
Hepatic failure	1 (100.0)	38 (82.6)
Hepatic failure plus other causes	0 (0.0)	6 (13.0)
Other causes	0 (0.0)	2 (4.4)
Family history of hepatitis B	1 (100.0)	15 (32.6)
Chronic hepatitis B carrier	0 (0.0)	3 (6.5)
Chronic hepatitis	0 (0.0)	19 (41.3)
Compensated cirrhosis	0 (0.0)	13 (28.3)
Decompensated cirrhosis	1 (100.0)	9 (19.6)
Inactive HBsAg carrier	0 (0.0)	1 (2.2)
Alcoholic cirrhosis	0 (0.0)	10 (21.7)
Complications	1 (100.0)	45 (97.8)
Liver fluke	0 (0.0)	2 (4.4)
Chronic gastrointestinal disease	0 (0.0)	2 (4.4)

HAV hepatitis A virus,
CHB chronic hepatitis B,
HEV hepatitis E virus

coinfected with HBV + HAV. We also found that the vast majority of deaths occurred among the patients coinfecting with HBV + HEV. Our results demonstrated that, in general, the patients coinfecting with HEV had more serious liver disease with higher rates of compensated cirrhosis, hepatic failure, and complications, and higher levels of ALT, AST, and TBil. The patients with HBV + HEV also had lower peak prothrombin activity. The reason for the increased severity of the HBV + HEV coinfection remains unclear. Our results indicate that there was no significant difference in the level of HBV DNA between the two groups, which suggests that the HEV superinfection neither stimulated nor suppressed the replication of HBV.

We had previously evaluated the characteristics and prognoses of 276 patients aged 26.53 ± 11.24 years who were treated in our hospital for single infection of HAV and 144 patients aged 50.39 ± 14.66 years who had single infection of HEV [12, 13]. Among the patients with HAV infection, the average ALT level was $1,454.53 \pm 1,114.6$ U/L; the TBil concentration was 132.08 ± 109.56 $\mu\text{mol/L}$; and the PTA was 92% (78–100). Among the patients with HEV infection, the ALT level was $1,008.32 \pm 929.71$ U/L; the TBil concentration was 231.25 ± 193.41 $\mu\text{mol/L}$; and the PTA was 86% (67–100). None of the patients with single infections of either HAV or HEV developed liver failure, and none died. Although these data are not directly comparable with those in the current study, they do provide a glimpse into the nature and severity of the HAV and HEV infections typically observed in this region.

A previous study had shown that sporadic HAV infection mainly affected teenagers, and sporadic HEV infection mainly affected middle-aged and older people [14].

However, that study took place in Japan, a country where HEV is not endemic; and the source of infection was thought to be exposure to farm animals, which the authors noted might have caused an age bias. In contrast, in our previous study exploring liver functions of patients infected only with HAV or HEV, the results indicated that the patients infected with HAV were younger than those infected with HEV [12, 13]. Similarly, in the present study comparing the ages of patients coinfecting with HBV + HAV and those coinfecting with HBV + HEV in a country in which these diseases are endemic, we observed a small but significant difference in age between the two groups ($P < 0.05$), with slightly younger patients coinfecting with HBV + HAV. The age of death in both groups was over 30 years of age for those who suffered from liver failure, which indicates that middle-aged and older patients with chronic HBV infection should pay strict attention to diet to prevent superinfection with hepatic viruses such as HAV or HEV that may enter the body via the alimentary tract [15]. The importance of screening those who are susceptible to HAV and administering the HA vaccine in middle-aged and older patients with chronic HBV infection in order to decrease the incidence of HAV superinfection in the population has been discussed [10]. Unfortunately, there is no vaccine to prevent HEV infection; therefore, the development and application of an HEV vaccine would be especially important for older patients with chronic HBV.

This study compares the differences in clinical course and outcome for patients who are infected with HBV and have superinfections with HAV versus HEV. One limitation of the study was that, although they are commonly used in clinical practice [15], several of the diagnostic

assays are not approved internationally. Also, the two groups differed significantly in age and sex, although the statistical analysis was adjusted for these baseline differences. Because only one patient with HBV + HAV died during the study, conclusions are limited as to the major causes of death in this group. Finally, the genetic characteristics of the hepatitis A and E viruses and the levels of HAV and HEV RNA were neither monitored nor compared in this study. Therefore, we were unable to estimate the contribution of the viral load or genetic markers to the severity of the liver disease in the coinfecting patients. Further studies are warranted to explore in depth the associations among the severity of hepatitis virus coinfection, viral titer or load, the patient's immune status, and the genetic characteristics of the coinfecting viruses.

In summary, patients with HBV + HEV had more advanced baseline liver disease and a poorer prognosis than those with HBV + HAV. During the long course of chronic hepatitis B infection, emphasis should be placed on reducing the chance that patients might be sporadically infected with HAV or HEV by taking appropriate precautions, such as vaccination against HAV and consumption of boiled water and well-cooked food.

References

1. Chinese Center for Disease Control and Prevention website: <http://www.chinacdc.net>.
2. Xiong LS, Cui SF, Zhou JG, Xing Y. Detection and analysis of HAV-HEV, HGV infection in patients with viral hepatitis. *Zhonghua Gan Zang Bing Za Zhi* 2004;12:395–396 (in Chinese, with English abstract)
3. Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, Ferraro T, Concia E. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998;338:286–290
4. Hamid SS, Atiq M, Shehzad F, Yasmeen A, Nissa T, Salam A, Siddiqui A, Jafri W. Hepatitis E superinfection in patients with chronic liver disease. *Hepatology* 2002;36:474–478
5. Ke WM, Li XJ, Yu LN, Lai J, Li XH, Gao ZL, Chen PJ. Etiological investigation of fatal liver failure during the course of chronic hepatitis B in southeast China. *J Gastroenterol* 2006;41:347–351
6. Protocol of prevention and treatment in viral hepatitis. *Chin J Hepatol (Chinese)* 2000; 8: 324–333
7. Liang XF, Chen YS, Wang XJ, He X, Chen LJ, Wang J, Lin CY, Bai HQ, Yan J, Cui G, Yu JJ. A study on the sero-epidemiology of hepatitis B in Chinese population aged over 3-years old. *Chin J Epidemiol* 2005;26:655–658
8. Zhang GS, Feng FM, Li YL, Yuan JX, Shang H. A study of chronic hepatitis B infection superinfected with hepatitis E infection. *Zhonghua Gan Zang Bing Za Zhi* 2006;14:906–908 (in Chinese, with English abstract)
9. Kumar M, Sharma BC, Sarin SK. Hepatitis E virus as an etiology of acute exacerbation of previously unrecognized asymptomatic patients with hepatitis B virus-related chronic liver disease. *J Gastroenterol Hepatol* 2008;23:883–887
10. Kumar Acharya S, Kumar Sharma P, Singh R, Kumar Mohanty S, Madan K, Kumar Jha J, Kumar Panda S. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. *J Hepatol* 2007;46:387–394
11. Keefe EB. Hepatitis A and B superimposed on chronic liver disease: vaccine-preventable diseases. *Trans Am Clin Climatol Assoc* 2006;117:227–268
12. Xiaodan Z, Weimin K, Hong C, Ying Z, Yangsu H. Clinical disease features of sporadic hepatitis A affected by chronic infection of hepatitis B virus. *Chin J Coal Ind Med* 2003;6:100–101
13. Xiangming X, Hong C, Hong D, Yangsu H, Weimin K. Effect of basis on chronic infection of hepatitis B virus on clinical features of sporadic hepatitis E. *Pract Prevent Med* 2000;7:247–249
14. Sainokami S, Abe K, Kumagai I, Miyasaka A, Endo R, Takikawa Y. Epidemiological and clinical study of sporadic acute hepatitis E caused by indigenous strains of hepatitis E virus in Japan compared with acute hepatitis A. *J Gastroenterol* 2004;39:640–648
15. Mahtab MA, Rahman S, Khan M, Mamun AA, Afroz S. Etiology of fulminant hepatic failure: experience from a tertiary hospitals in Bangladesh. *Hepatobiliary Pancreat Dis Int* 2008;7:161–164