Epidemiological and clinical features of hepatitis B virus related liver failure in China

Chen Liu, Yu-Ming Wang, Ke Fan

Chen Liu, Yu-Ming Wang, Department of Infectious Diseases, Southwest Hospital, Third Military Medical University, Chongqing 400038, China

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Correspondence to: Yu-Ming Wang, Professor, Department of Infectious Diseases, Southwest Hospital, Third Military Medical University, Chongqing 400038, China. wym417@163.com Telephone: +86-23-68754141 Fax: +86-23-65334998 Received: September 28, 2010 Revised: June 20, 2011 Accepted: June 27, 2011 Published online: July 7, 2011

Abstract

AIM: To examine the epidemiologic and clinical characteristics of hepatitis B virus (HBV) related liver failure in patients in China.

METHODS: This study was conducted with a retrospective design to examine 1066 patients with HBV-related liver failure in the southwest of China.

RESULTS: There were more male than female patients. Young and middle-aged people comprised most of the patients. Farmers and laborers comprised the largest proportion (63.09%). Han Chinese accounted for 98.12%, while minority ethnic groups only accounted for 0.88% of patients. A total of 43.47% patients had a family history of HBV-related liver failure and 56.66% patients had a history of drinking alcohol. A total of 42.59% patients with HBV-related liver failure had definite causes. With regard to the clinical manifestation of HBV-related liver failure, the symptoms were: hypodynamia, anorexia and abdominal distension. Total bilirubin (TBIL) and alanine aminotransferase (ALT) levels were altered in 46.23% of patients with evident damage of the liver. Univariate logistic regression analysis showed that the patients’ prognoses were correlated with ALT, aspartate aminotransferase, albumin, TBIL, prothrombin activity (PTA), and alpha-fetoprotein levels, and drinking alcohol, ascites, hepatorenal syndrome, infection and ≥ 2 complications. Multifactor logistic regression analysis showed that the activity of thrombinogen and the number of complications were related to the prognosis.

CONCLUSION: Alcohol influences the patients’ prognosis and condition. PTA and complications are independent factors that can be used for estimating the prognosis of HBV-related liver failure.

Peer reviewer: Qin Su, Professor, Department of Pathology, Cancer Hospital and Cancer Institute, Chinese Academy of Medical Sciences and Peking Medical College, PO Box 2258, Beijing 100021, China

INTRODUCTION

Hepatitis B virus (HBV) infection is a severe threat of public health worldwide. Two billion people have been infected with HBV out of a total population of 6 billion, including chronic HBV infection in 350 million people[1,2]. One million people have died of liver disease related to HBV, 75% of which are distributed in the Asian-Pacific area[3]. China has a high occurrence of HBV infection. A survey of national epidemiology announced in April 2008 by the Ministry of Health showed that 93 million people in China have been infected with HBV.
The features of HBV-related liver failure include a lot of complications in patients, difficulty of treatment and a high fatality rate. Therefore, a large sample investigation about the natural history and the clinical process of HBV-related liver failure are required. This study analyzed the epidemiologic and clinical characteristics of HBV-related liver failure, based on a sample of 1066 cases in the southwest region of China.

MATERIALS AND METHODS

Case selection
All the 1066 cases were chosen from inpatients of the General Infectious Disease Institute of Southwest Hospital, the Third Military Medical University of China PLA, from February 2003 to December 2009. The patients were mostly from Chongqing and Sichuan, including the southwest regions in Guizhou and Yunnan.

The selection criteria included: (1) patients with chronic hepatitis B; (2) serum total bilirubin (TBIL) ≥ 171 μmol/L, prothrombin activity (PTA) ≤ 40% and complete data. The exclusion criteria were: (1) liver transplanted patients; (2) a short time of hospitalization (< 72 h); (3) patients with missing clinical and laboratory data; and (4) patients with associated tumors and other major diseases.

Methods

Epidemiologic survey: A questionnaire was given to the patients, which required information such as age, sex, ethnic group, career, family history, history of drinking alcohol, inducement of HBV-related failure, symptoms, physical signs, laboratory examinations, and complications. Questions that were not properly answered were not included in the statistical analysis. The daily alcohol intake (g) is equal to: alcohol intake × 0.8 × spirit (%), which was classified into low, medium, and high degrees (Table 1).

Laboratory examinations: Serum biochemical tests of alanine aminotransferase (ALT), AST, total bilirubin and albumin levels were measured by a Hitachi 7060 full-automatic chemical analyzer. α-fetoprotein (AFP), hepatitis B surface antigen (HbsAg), hepatitis B core antibody (HbcAb), hepatitis B e antigen (HbeAg) and hepatitis B e antibody (HbeAb) were measured using a German Roche Elecsys 2010 full-automatic electrochemiluminescence analyzer.

Serum HBV DNA was measured by a PE5700 instrument (ABI) and the reagent kits were from Cloning Biological High-tech Co., Ltd. (Shanghai, China). HBV DNA ≥ 1000 copy/mL (3.0 log10) was positive.

Statistical analysis
SAS V8.0 statistical software was used for analysis. Data were shown as means ± SD. Potential factors that may have influenced the prognosis were examined by logistic analysis. \( P < 0.05 \) indicates statistical significance.

RESULTS

Epidemiology

Among the 1066 patients with HBV-related liver failure, there were 901 males (84.52%) and 165 females (15.48%), with a male: female ratio of 5.46:1.

The mean age was 39.76 ± 11.69 years (range, 12-75 years). The highest morbidity was in the age group of 30-39 years (31.71%, Table 2). The age group with the second highest morbidity was between 40 and 49 years (28.61%), followed by 20-29 years (18.01%), 50-59 years (14.26%), > 60 years (6.19%) and < 20 years (1.22%) (Table 2).

With regard to the occupation structure of the patients with HBV-related liver failure, farmers comprised the highest proportion, followed by laborers, cadres, teachers, students, businessmen, drivers, doctors, nurses and a painter and a policeman (Table 2).

A total of 1046 (98.12%) patients belonged to the Han ethnic group, followed by the Tuja minority ethnic group (1.50%), the Miao minority ethnic group (0.28%), and the Gelao minority ethnic group (0.09%) (Table 2).

Family history and history of alcohol drinking

A total of 463 patients (43.47%) had a family history of HBV-related liver failure and 56.66% of patients had a history of drinking alcohol. Two hundred patients seldom drank alcohol (18.76%), 171 patients drank alcohol lightly (28.61%), 13 patients drank alcohol moderately (1.22%) and 2 patients drank alcohol heavily (0.28%).
108 patients drank alcohol moderately (10.13%) and 125 patients drank alcohol heavily (11.73%).

**Induction of chronic hepatitis B into severe hepatitis/liver failure**

The incidence rate of HBV-related liver failure was highest in the presence of other contagious viruses that infect the liver. Among 192 cases (18.01%), 109 cases were also infected by HDV (Table 3). The second highest cause of induction of disease was drinking alcohol, followed by fatigue and other infections. Over half of the patients had no ascertainable cause of disease. In those patients in whom the cause of disease was known, most only had 1 factor that induced the disease. None of the patients had more than 3 types of inducement of disease.

**Clinical manifestations**

On admission, the patients’ main clinical manifestations were hypodynamia, loss of appetite and abdominal distension (Table 4).

**Laboratory data in patients with hepatitis B virus related liver failure**

Table 5

| Laboratory indexes | Mean |
|--------------------|------|
| ALT (IU/L)          | 272.51 ± 541.51 |
| AST (IU/L)          | 262.13 ± 440.55 |
| Glutamyltranspeptidase (IU/L) | 91.24 ± 55.74 |
| Alkaline phosphatase (IU/L) | 187.41 ± 96.01 |
| ALB (g/L)           | 32.08 ± 7.95    |
| TBIL (μmol/L)       | 396.56 ± 190.52 |
| Direct bilirubin (μmol/L) | 234.48 ± 100.75 |
| PTA (%)             | 15.62 ± 12.98   |
| Glucose (mmol/L)    | 5.35 ± 3.86     |
| Blood urea nitrogen (mmol/L) | 59.45 ± 970.09 |
| Creatinine (μmol/L) | 204.40 ± 613.78 |
| AFP (ng/mL)         | 191.26 ± 221.36 |
| HBV DNA (copies/mL) | 4.3 ± 8.8 × 10^7 |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; TBIL: Total bilirubin; PTA: Prothrombin activity; AFP: α-fetoprotein; HBV: Hepatitis B virus.

**Complications in patients with hepatitis B virus related liver failure**

Table 6

| Complications                                      | n (cases) | Percentage (%) |
|----------------------------------------------------|-----------|----------------|
| Ascites                                            | 509       | 47.83          |
| Hepatic encephalopathy                             | 506       | 47.48          |
| I level                                            | 34        | 3.86           |
| II level                                           | 178       | 20.23          |
| III level                                          | 122       | 13.86          |
| IV level                                           | 172       | 19.55          |
| Hernia of brain                                    | 29        | 2.72           |
| Hydrocephalus                                      | 78        | 7.32           |
| Hemorrhage of digestive tract                      | 234       | 21.95          |
| Hepatorenal syndrome                               | 210       | 19.70          |
| Spontaneous bacterial peritonitis                  | 103       | 9.66           |
| Infection                                          | 417       | 39.12          |
| Electrlyte imbalance                               | 141       | 13.23          |

The laboratory data of the patients are shown in Table 5. A total of 11.54% (123 cases) of the cases were HBeAg positive, 22.52% (240 cases) were HBeAb positive, 78.30% (834 cases) were HBV DNA positive, and the mean value was 4.3 ± 8.8 × 10^7 copies/mL.

**Complications**

The most common complications were ascites, hepatic encephalopathy, and infection. Hemorrhage of the digestive tract and electrolyte imbalance were the next most common complications (Table 6).

**Prognosis**

The patients were divided into 2 groups: the improved group and the deteriorated group (including exacerbation and death). The description “improved” was used...
to define those patients who were able to be discharged from hospital because clinical symptoms improved and liver function recovered. The description of “deteriorated” was defined as patients who died or deteriorated when they were voluntarily discharged from the hospital, except for those who died or further deteriorated because of other diseases or accidents. Three hundred and forty-five cases improved (34.36%) and 721 cases were deteriorated (67.64%) (369 cases died and 352 cases were exacerbated). The rate of death due to the disease was 34.62%.

Logistic single factor regression analysis
Logistic regression analysis was performed for 42 factors that might have influenced the prognosis, using prognosis (improvement and unsuccessfully treated) as the dependent variable. The result showed that the patients’ prognoses were related to ALT, AST, ALB, TBIL, PTA, and AFP levels, and drinking alcohol, ascites, hepatorenal syndrome, infection and ≥ 2 complications.

Logistic multifactor regression analysis
Logistic multifactor regression analysis was performed for prognostic factors that were screened out by single factor regression analysis. We found that PTA ($P = 0.03$) and the number of complications ($P = 0.01$) were independently related to the prognosis of HBV-related liver failure.

DISCUSSION
In China, the main transmission route of HBV is vertical transmission and the secondary way is by blood products. Among the patients in our study, there were more males than females, while the number of males with HBV-related liver failure is increasing. With regard to profession, farmers and laborers comprised the largest proportion at 63.09%, with farmers occupying even larger proportion than laborers. The cause of the illness might be related to people’s life style and working environment, inaccurate comprehension of the disease due to poor medical conditions and minimal schooling, and missing the best time for treatment because of not visiting a doctor in time. Among the ethnic groups, the Han accounted for 98.12% of patients, while minority ethnic groups only accounted for 0.88%. This finding could be because economic conditions are better and the population of the Han is higher compared with the ethnic minorities in the southwest of China. The result of single factor analysis showed that the patients’ prognosis was not related to sex, age, occupation and ethnic groups.

The recurrence and aggravation of chronic HBV are due to various inducements during the long repetitive chronic process. Based on our data analysis, illness conditions deteriorated in 42.59% of patients in whom the cause of disease was known. The main factors responsible for inducing the illness were as follows: superinfection with other contagious viruses that infected the liver, drinking alcohol, fatigue and being complicated with other infections. With regard to superinfection with other contagious viruses that infect the liver, internationally, it is regarded that HGV virus infection does not cause liver failure, but it is rather found in patients co-infected with HBV. In China, drinking alcohol is common because of the rich “alcohol culture” and gradually enriched material conditions. Young and middle-aged people are busy with work and are under great social pressure. These factors, which have resulted in a trend for a lower average age for HBV-related liver failure, are the reasons for inducing and exacerbating the illness. Infection was found to be another cause of HBV-related liver failure, with 10 cases having liver failure due to an unclean diet history. Eight of these 10 cases had diarrhea and the patients may have been complicated with gastrointestinal infection. If the inducement of HBV-related liver failure is fatigue, it is related to damage of the patient’s immune system. In 57.41% of patients, their illness deteriorated and there did not appear to be any definite cause of HBV-related liver failure. This may be related to several factors such as social environment, job competition, mental stress and emotional factors. In summary, infection (including being complicated with other hepatitis virus infections and other infections) is the biggest inducement of the disease, which is similar to the findings in other reports[6-8]. In addition, the factor of alcohol further increased the possibility of HBV-related liver failure.

Our data showed that the characteristics of severe hepatitis in the southwest of China are similar to acute liver failure and acute-on-chronic liver failure abroad, and these included acute onset, inducement for initiating or worsening of the disease, superinfection by hepatitis B and D viruses, and being complicated by infection and fatigue. Clinical manifestations of HBV-related liver failure involve two main types: alimentary tract symptoms, such as yellowing of the skin and sclera, hypodynamia, anorexia, abdominal distension, and physical signs of hepatitis such as liver palms, hepatic face, and spider nevus. Some of the patients did not have encephalopathy at the early stage of the disease, and this occurred after hospitalization. Some of the patients had ascites as the main clinical manifestation at admission, and most of them had secondary onset of hepatic encephalopathy. The prognosis of patients with hepatic encephalopathy greater than stage II was worse.

According to the laboratory data, liver function indicated damage to the liver and PTA was decreased. In the early stage of the disease, ALT and AST levels were increased. TBIL was also increased. The results of single factor analysis showed that patients’ prognoses were related to ALT, AST, ALB, TBIL, PTA and AFP levels, which is consistent with other studies in China and in other countries[9-11]. Multifactor logistic regression analysis showed that PTA was independently related to the prognosis. PTA is the most important biochemical index used to determine the aggravation of chronic hepatitis B[9]. The lower the level of PTA, the higher the rates of hemorrhage and fatality[9]. The prognosis is bad if PTA is < 30%, and if this
is the case, the majority of patients die\textsuperscript{10}. The quantity of serum bilirubin reflects the degree of damage to liver cells. TBIL appeared to be related to HBV-related liver failure, but multifactor analysis showed that TBIL was not a factor that affected the prognosis. It is generally acknowledged that the higher the level of AFP, the better the prognosis of patients with liver failure. The US Acute Liver Failure Study Group has shown that a 1-fold higher level of AFP is not related to a good prognosis; however, patients’ prognoses are relatively good when AFP levels are increased 3 days after hospitalization\textsuperscript{34}. 

HBV-related liver failure/severe hepatitis B is a serious disease. The incidence rate of complications is high. It is critical to prevent complications to improve the survival rate\textsuperscript{11}. Our study results showed that 70.73% of patients had up to several complications. A total of 48.78% of patients had 2 or more complications. The type, quantity and the degree of severity of complications are important factors that can influence the outcome of HBV-related liver failure/severe hepatitis B. In our study, single factor analysis showed that the patients’ prognoses were related to ascites, hepatorenal syndrome, infection and $\geq 2$ complications. Multifactor analysis showed that the number of complications was an independent risk factor of HBV-related liver failure. In the USA and European countries, the first manifestation of hepatic failure is often hepatic encephalopathy. However, according to our data, ascites is the main manifestation in China. Infection is usually the earliest complication occurring in the middle stage of the disease. Our data showed that infection was a complication that occurred in the early stage of HBV-related liver failure. Infection was related to the prognosis and it also aggravated the disease. Previous studies have shown that 60% to 80% of liver failure patients have secondary bacterial or fungal infection\textsuperscript{12,13}. Riordan and Williams demonstrated that approximately 80% of patients with severe HBV are complicated with infection, which is difficultly controlled\textsuperscript{14}. Because of the complexity of the pathogenesis of liver failure, the present system for estimating the prognosis cannot predict the results, although there is a great deal of patients’ data available.

Liver failure is severe liver damage caused by various factors, which cause obstruction or compensation of function, such as composition, detoxification, drainage and biotransformation\textsuperscript{15}. Various clinical syndromes can appear, including the obstruction of coagulation mechanisms, icterus, hepatic encephalopathy and ascites\textsuperscript{16}. According to the speed of pathological development, histology of liver failure and the patient’s condition, liver failure can be classified into 3 types: acute liver failure (ALF), acute-on-chronic liver failure (ACLF) and chronic liver failure (CLF)\textsuperscript{17,18}. According to morbid physiology, liver failure is mainly divided into two types that separately result in necrosis caused by the inflammation of liver cells and the decompensation of liver cells. ALF belongs to the type of liver failure that results in necrosis caused by inflammation of liver cells\textsuperscript{19}. ACLF and CLF belong to the type of liver failure with decompensation of liver cells\textsuperscript{20}. Patients with ALF have symptoms such as abnormal crur (usually an international normalized ratio $\geq 1.5$), a change in consciousness to varying degrees (encephalopathy), and the duration of disease is less than 26 wk\textsuperscript{21,22}. Patients with ACLF have acute decompensation on the basis of chronic liver disease (TBIL $\geq 171 \mu \text{mol/L}$)\textsuperscript{23}. Patients with CLF have chronic decompensation of liver function (TBIL $< 171 \mu \text{mol/L}$) caused by a decrease in liver function on the basis of the final phase of hepatitis\textsuperscript{19}. According to the diagnostic standard discussed above\textsuperscript{19-23}, in our study, 654 cases had ACLF, 296 cases had CLF, and 116 cases had ALF.

The term “liver failure” is used in European countries and the USA because it is associated with function, whereas it is called severe chronic hepatitis in China and Japan because it is associated with inflammation. Hepatitis virus that appears to be acute liver failure is called severe hepatitis\textsuperscript{24}. The main difference between the terms “liver failure” used in the USA and European countries and “severe hepatitis” used in China is whether to include hepatic encephalopathy in the diagnosis. Some patients with liver failure do not have hepatic encephalopathy\textsuperscript{25}. Severe damage of the liver may develop into liver failure before hepatic encephalopathy occurs.

Although there are differences, liver failure has been divided into ALF, including the acute and sub-acute types, and CLF, including the chronic acute and chronic decompensated types, and this point of view gradually becomes consistent among international academic communities. Because of the large amount of etiologies of liver failure, physicians use a combination of clinical diagnoses (e.g. chronic severe hepatitis) and morbid physiology diagnoses (e.g. CLF). Liver decompensation is the main manifestation of chronic liver failure. Patients with this disease may not have hepatic encephalopathy, but patients with acute liver failure must have hepatic encephalopathy\textsuperscript{26-34}.

In conclusion, the morbidity of chronic HBV is steadily increasing. Once chronic HBV develops into HBV-related liver failure/chronic severe hepatitis, the liver is seriously damaged with complex symptoms, it develops rapidly, it has many complications, it is difficult to treat and it has a high death rate. We advise patients with hepatitis to enhance self-protection and prevent bad life-style habits, so that they can be diagnosed in the early stage and be cured in a timely manner with positive results and treatment of complications, so as to ultimately reduce the death rate.

\textbf{COMMENTS}

\textbf{Background}

Hepatitis B virus (HBV) infection becomes a severe threat for public health worldwide. The features of HBV-related liver failure include: a serious condition (e.g. encephalopathies), and the duration of disease is usually less than 26 wk\textsuperscript{21,22}. Patients with ACLF have acute decompensation on the basis of chronic liver disease (TBIL $\geq 171 \mu \text{mol/L}$)\textsuperscript{23}. Patients with CLF have chronic decompensation of liver function (TBIL $< 171 \mu \text{mol/L}$) caused by a decrease in liver function on the basis of the final phase of hepatitis\textsuperscript{19}. According to the diagnostic standard discussed above\textsuperscript{19-23}, in our study, 654 cases had ACLF, 296 cases had CLF, and 116 cases had ALF.

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\textbf{BACKGROUND}
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Hepatitis B virus (HBV) infection becomes a severe threat for public health worldwide. The features of HBV-related liver failure include: a serious condition (e.g. encephalopathies), and the duration of disease is usually less than 26 wk\textsuperscript{21,22}. Patients with ACLF have acute decompensation on the basis of chronic liver disease (TBIL $\geq 171 \mu \text{mol/L}$)\textsuperscript{23}. Patients with CLF have chronic decompensation of liver function (TBIL $< 171 \mu \text{mol/L}$) caused by a decrease in liver function on the basis of the final phase of hepatitis\textsuperscript{19}. According to the diagnostic standard discussed above\textsuperscript{19-23}, in our study, 654 cases had ACLF, 296 cases had CLF, and 116 cases had ALF.

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\textbf{RESEARCH FRONTIERS}

This study investigated the inducement of liver failure/severe hepatitis B and the independent risk factors associated with its prognosis.

\textbf{INNOVATIONS AND BREAKTHROUGHS}

This study explored the inducement and prognosis of hepatitis B virus related liver failure as well as the diagnostic classification of liver failure.
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