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ORIGINAL ARTICLE

New Exploration to the Clinical Classification of Liver Failure Associated with Hepatitis B Virus

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ABSTRACT

AIMS: Clinical diagnosis and classification of liver failure (LF) vary in different parts of the world. In this study, novel methods of the clinical classification of hepatitis B virus (HBV)-related LF were investigated.

METHODS: Clinical data from 153 HBV-related LF patients were analyzed by a retrospective study. Clinical classifications of LF were assigned according to the new proposal.

RESULTS: Among the 153 HBV-related LF patients, 20 (13.1%) were fulminant type, 53 (34.6%) were sub-acute type, 39 (25.5%) were acute exacerbative type, and 41 (26.7%) were slow progressive type. TBil, ALB, and PT levels were significantly different among the different types of patients with LF. Death or invalidity rate was significantly higher in acute exacerbative and fulminant type patients than in sub-acute type and slow progressive type patients.

CONCLUSION: The proposed clinical classification of LF based on the complications of hepatic encephalopathy and/or HRS is simple and practical. This scheme may help establish uniformity in diagnostic and classified criteria of LF worldwide.

Key words: Hepatitis B virus; Clinical classification; Liver failure; Liver cirrhosis

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INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most common viral diseases affecting humans[1]. The clinical spectrum of HBV infection-related diseases includes acute hepatitis, chronic hepatitis and severe hepatitis, and liver cirrhosis based on the criteria described in "The programme of prevention and cure for viral hepatitis" at the China Xi'an meeting in 2000[2]. Severe hepatitis is further divided into three types: acute type, sub-acute type, and chronic type. The basic criteria of severe hepatitis diagnosis are total bilirubin (TBil) >171 μmol/L and prothrombin activity (PTA) <40%. According to the classification criteria presented at the 2000 Xi'an meeting in China, chronic severe hepatitis accounts for approximately 90% of total severe hepatitis cases, whereas acute and sub-acute severe hepatitis account for only 10%[3,4]. Scholars proposed that at least two different populations in chronic severe hepatitis are detected, and the corresponding pathological characteristics are significantly different[5,6].

In Western countries, "liver failure (LF)" is commonly used instead of "severe hepatitis" upon diagnosis[7,8]. Scholars in the East and the West have raised their disagreements regarding classification of severe hepatitis and LF[9,10]. Severe hepatitis is based mainly on a pathological point of view, whereas LF is based on a pathophysiological point of view. These terms have different

meanings and are not interchangeable. Therefore, LF guidelines were issued in 2006 and updated in 2012 in China[11,12]. LF is divided into four categories according to the guidelines: acute LF (ALF), sub-acute LF (SALF), acute on chronic LF (ACLF), and chronic LF (CLF). However, significant differences have been observed in the diagnostic criteria used in China, Europe, and the United States. These differences may be related to various LF etiologies, complex clinical manifestations, and different expert experiences from different departments.

LF is diagnosed differently in China and in other countries because of the lack of generally accepted and evidence-based diagnostic criteria. The main problem might be attributed to varied understanding of LF diagnostic standards. We should recognize that LF is diagnosed on the basis of function rather than disease itself. LF occurs in the late stage of chronic liver diseases and manifests as hepatic encephalopathy (HE) and/or hepatorenal syndrome (HRF). Relaxations in the diagnostic criteria of LF should focus on prevention to improve patient prognosis[13]. To accurately evaluate disease prognosis and effective treatment of patients, researchers should also develop uniform diagnostic standards that can be implemented worldwide. Recently, new clinical classification of LF has been proposed that LF can be divided into two categories: acute LF(ALF) and chronic LF(CLF). The former is further divided into fulminant type and subacute type. The latter is divided into acute exacerbative type and slow-progression type[14]. In this study, data collected from patients with LF were evaluated to investigate the rationality and practicality of these clinical classifications.

MATERIALS AND METHODS

Subjects

Clinical data were collected from 153 patients admitted to Taizhou People's Hospital and Nanjing Affiliated Hospital No. 2 of the Medical School at Southeast University from 2010 to 2013. The basic data of 153 patients are shown in table 1. These diagnoses were determined according to the "Diagnostic and treatment guidelines for liver failure" (hereinafter referred to as CSIHD criterion)[12]. The diagnostic criteria of ACLF in European Society for the Study of Liver (EASL) were described in detail in a previous study[15] (hereinafter referred to as EASL criterion). All of the patients were negative to antibodies against hepatitis A virus (HAV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), and human immunodeficiency virus (HIV). Patients who showed clinical features of drug-induced liver injury, alcoholic hepatitis, steatohepatitis, or complicated disease that likely influenced survival were excluded from the study. New clinical classifications of LF are according to the reference 14. ALF is divided into fulminant and subacute types, with a four-week interval. The fulminant type must be hepatic encephalopathy, whereas the occurrence of hepatic encephalopathy does not necessarily pertain to the subacute type, which is mainly characterized by severe jaundice (TBil) >171 μmol/L) and ascites. CLF is divided into two types: acute exacerbative and slow-progressive type. The slow-progressive type is equivalent to the current slow progress of decompensated liver cirrhosis in patients with hepatic encephalopathy. The acute exacerbation type are equivalent to deterioration that occurs in decompensated cirrhosis. Clinical outcomes of patients were divided into two categories: 1) cure or improvement and 2) death or invalidity. The criteria of clinical cure and improvement were 1) loss or improvement of clinical symptoms and 2) recovery of liver function (TBil<85 μmol/L, PTA>40%). The lack of these positive measures was categorized as an invalid outcome.

Table 1 Basic data of four groups with liver failure patients.

Groups	ALF	SALF	ACLF	CLF
n	5	9	98	41
M/F	1/4	7/2	81/17	31/10
Age	42.8±11.9	44.4±10.4	46.2±12.2	50.3±13.2
TBil [1]	373.2±339.2	407.0±121.5	362.8±181.0	41.2±65.5
ALB [2]	34.3±6.3	31.1±3.0	31.4±5.8	28.4±6.9
PT [2]	48.0±12.5	26.2±7.5	4.1±12.5	19.7±8.5
HE	5	4	61	38
HRS	2	3	11	5
SBP	1	4	20	10
GB	0	2	16	8
Death or invalidity	4	4	43	9

[1]: M±QR(μmol/L); [2]: x±s(g/L, s); HE: hepatic encephalopathy; HRS: hepatorenal syndrome; SBP: spontaneous bacterial peritonitis; GB: Gastrointestinal bleeding.

Detection of the main clinical indicators

Prothrombin time (PT) was detected using an automatic blood coagulation analyzer (BE Corporation, German). HBV DNA was quantitatively detected using an ABI7300-type quantitative PCR instrument (Applied Biosystems, USA). HBV markers were detected by enzyme-linked immunosorbent assay (Beijing YuanPingHao Biological Co., Ltd., China). Biochemical indicators were determined using an automatic biochemical analyzer (Hitachi Ltd., Japan).

Statistical analysis

Normally distributed data were shown as mean ± standard deviation. ANOVA and SNK-q tests were conducted to statistically compare between groups. Skewed data were presented as median ±interquartile range. Kruskal–Wallis analysis was used to compare among groups. χ^2 test was used for statistical comparison of the counted variables. Data were analyzed using SPSS 17.0. $P<0.05$ was considered statistically significant.

RESULTS

Classification and demographic information for LF patients

A total of 153 patients with LF were re-categorized as ALF (73 cases) and CLF (80 cases). Fulminant type (20 cases, 13.1%, M/F: 12/8, Age: 43.7±12.6) and sub-acute type (53 cases, 34.6%, M/F: 46/7, Age: 44.5±11.6) were included in ALF. Acute exacerbative type (39 cases, 25.5%, M/F: 31/8, Age: 48.9±11.9) and slow progressive type (41 cases, 26.8%, M/F: 31/10, Age: 50.3±13.2) were included in CLF (Figure 1).

Comparison of TBil, ALB, PT, and prognosis among the four groups

Patients with LF were divided into four types. Significant differences were found in TBil, ALB, and PT levels among the four types (χ^2/F =59.9, 15.4, and 20.6, respectively, $p<0.01$; Table 2). The death or invalidity rates in fulminant type and acute exacerbative type patients were higher than those of sub-acute type and slow progressive type patients (χ^2= 54.3, $p<0.01$; 85% and 71.8% *vs* 37.7% and 21.6%; Figure 2).

Comparison of complications among the four groups

Complications, particularly hepatic encephalopathy (HE), hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), and gastrointestinal bleeding (GB), among the four groups were compared. Significant differences were found in HE, HRS, SBP, and GB among the four groups (χ^2= 80.3, 89.1, 54.1, and 88.0, respectively, $p<0.01$; Table 3).

Prognosis of ACLF according to the criteria in CSIHD and EASL

A total of 98 patients were diagnosed with ACLF based on the CSIHD criterion; among these patients, 62 were considered as CHB patients and 32 of these patients suffered from death or invalidity. Among 36 patients with ACLF and DLC, 26 suffered from death or invalidity. Among 49 patients with ACLF according to the EASL criterion, 29 patients were ACLF of CHB, and 23 of these 29 patients suffered from death or invalidity. Furthermore, 20 patients were diagnosed with ACLF of DLC; among these patients, 15 suffered from death or invalidity. Death or invalidity rate in ACLF of CHB patients according to the CSIHD criterion was significantly lower than that of EASL criterion (χ^2=6.34, p<0.01). No significant difference was found in ACLF of DLC patients (χ^2= 0.29, p>0.05; Table 4).

Table 2 Comparision of liver biomarkers in four groups.

Groups	*n*	TBil [1]	ALB [2]	PT [2]
FLF	20	443.9±146.9	33.4±4.3	40.8±14.4
SLF	53	378.9±200.1	33.9±4.9	30.1±10.6
CAE	39	332.4±136.5	27.3±4.7	36.2±12.7
CSP	41	41.2±65.5	28.4±6.9	19.7±8.5
χ^2/(F)		59.9	15.4	20.6
P		<0.01	<0.01	<0.01

[1]: M±QR(μmol/L); [2]: x±s(g/L, s); FLF: fulminant liver failure; SLF: subacute liver failure; CAE: chrornic acute exacerbative; CSP: chronic slow progressive.

Table 3 Complications of different types of patients with LF.

Complations	FLF	SLF	CAE	CSP	χ^2	*P*
HE	20	16	34	38	80.3	<0.01
HRS	2	6	8	5	89.1	<0.01
SBP	3	13	9	10	54.1	<0.01
GB	3	5	10	8	88.0	<0.01

HE: hepatic encephalopathy; HRS: hepatorenal syndrome; SBP: spontaneous bacterial peritonitis; GB: Gastrointestinal bleeding; FLF: fulminant liver failure; SLF: subacute liver failure; CAE: chrornic acute exacerbative; CSP: chronic slow progressive.

Table 4 Prognosis of ACLF according to the CSIHD and EASL Criterion.

Groups	Criterion in CSIHD		Criterion in EASL	
	n	death or invalidity(%)	n	death or invalidity(%)
ACLF of CHB [1]	62	32(51.6)	29	23(79.3)
ACLF of DLC [2]	36	26(72.2)	20	15(75.0)

[1] χ^2=6.34, p <0.01; [2] χ^2=0.29, p >0.05. ACLF: acute on chronic liver failure; CHB: Chronic hepatitis B; DLC: decompensated liver cirrhosis.

DISCUSSION

Complete diagnosis of a liver disease should include etiology, pathology, and pathophysiology. LF should be subjected to pathophysiology-based diagnosis and separated from the diagnosis of diseases caused by LF. Pathological changes resulting in LF are classified into two main types: one type is caused by acute severe liver necrosis and the other type is caused by chronic progressive increase in liver cell damage. The clinical manifestations of these two types of pathological changes that induce LF are different. The former is mainly characterized by acute liver dysfunction, particularly metabolic dysfunction; the latter is mainly attributed to portal hypertension[10]. In this study, the percentages of HBV-related LF according to the current classification were 3.3%, 5.9%, 64.0% and 26.8%, respectively. The percentages of HBV-related LF according to the novel classification

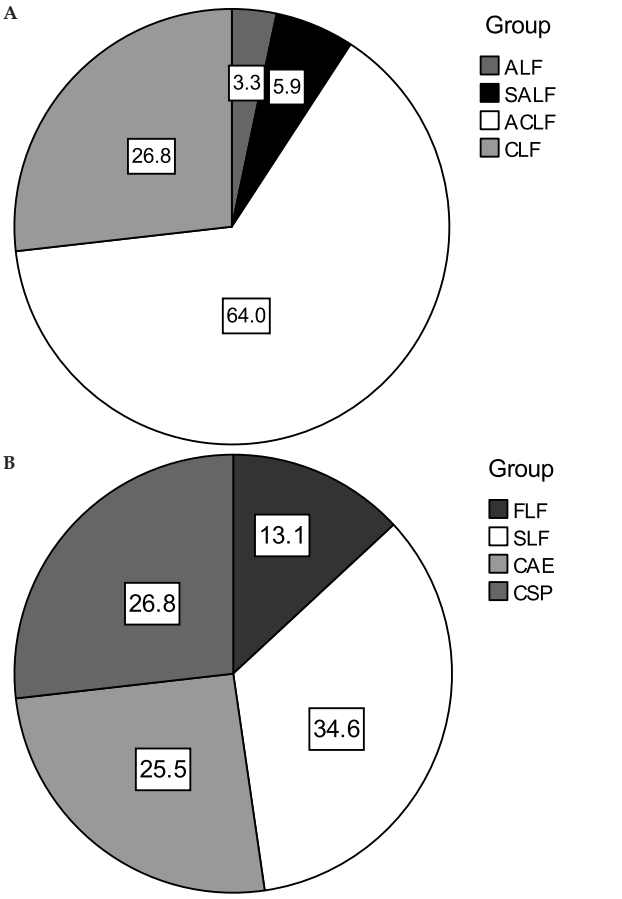

Figure 1 Constituent percent of four groups with liver failure patients. A: current classification; B: novel classification.

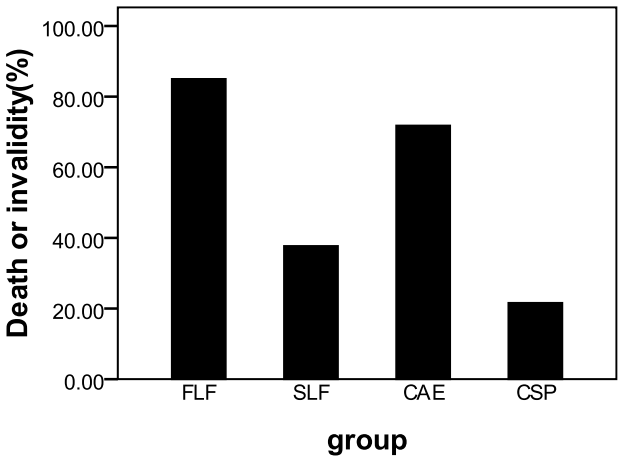

Figure 2 Prognosis of different types patients with LF(χ^2=54.3, P<0.01); FLF: fulminant liver failure; SLF: subacute liver failure; CAE: chrornic acute exacerbative; CSP: chronic slow progressive.

were 13.1%, 34.6%, 25.5% and 26.8%, respectively (Figure 1). Significant differences were found in HE, HRS, SBP, and GB among the four groups. Furthermore, clinical cure or improvement rates were 49.3% in ALF and 53.7% in CLF. Previous studies suggested that nucleoside analog treatment can reduce short-term mortality of patients with HBV-related LF[16]. However, only some of the patients in this study were treated with antiviral therapy because of very long duration of the study cycle, which might affect the clinical cure or improvement rate of the patients. In addition, our data were

obtained from two hospitals only; therefore, our results may not be representative of the general population.

According to the diagnostic criteria of ALF or SLF in China, these types should not be the basis of chronic liver disease. These types are different from ALF recommendation by the American Society for Study of Liver Diseases (AASLD)[6]. In this recommendation, ALF is defined as a condition without a previous history of cirrhosis but with liver function deterioration that occurred in 26 weeks; ALF is characterized by coagulopathy (prothrombin international normalized ratio≥1.5) and any degree of altered consciousness (encephalopathy). For HBV vertical infection, a disease may be considered as ALF even with cirrhosis if this disease was detected at 26 weeks. Considering that our common CHB patients are long-term HBV carriers, we diagnosed these patients as ACLF at the first onset of severe occurrence. In clinical practice, disease progression occurs rapidly, and prognosis is poor with or without a history of chronic liver disease for ALF patients with more than grade II hepatic encephalopathy[17]. In Asia, including China, non-hepatic encephalopathy is characterized by severe jaundice, ascites, and bleeding tendencies of patients with major conditions; this disease gradually progresses, but prognosis remains poor[18]. Therefore, ALF can be further divided into fulminant and sub-acute types with a four-week interval. Among the patients with ALF, 20 (13.1%) were fulminant type and 53 (34.6%) were sub-acute type. TBil and PT levels significantly differed between the two groups (χ^2/F=59.9, 20.6, respectively, p<0.01). The death or invalidity rates in the former were higher than those of the latter (χ^2=54.3, p<0.01).

ACLF encompasses the acute deterioration of liver function in patients with chronic liver disease; furthermore, ACLF has been recognized as a separate entity. Although no widely accepted diagnostic criteria of ACLF have been implemented, consensus definitions of the Asia-Pacific Association for the Study of the Liver in 2009 and AASLD and EASL in 2011 are commonly used[15,19]. However, these two definitions are based on fundamentally different characteristics. As such, this difference has led to confusion between ACLF and acute decompensation (AD) liver cirrhosis. Moreau *et al*[20] reported that ACLF is a syndrome that differs from AD cirrhosis. However, this conclusion cannot be extended to virus-related ACLF because ACLF in many patients in that study is induced by alcohol[21]. Liu *et al*[22] found that patients who satisfied the ACLF diagnostic criteria used in Asia can be further divided into two significantly different populations in terms of their mortality rates. In our study, death or invalidity rate in ACLF of CHB patients according to the CSIHD criterion was significantly lower than that of EASL criterion (χ^2=6.34, p<0.01). No significant difference was found in ACLF of DLC patients (χ^2=0.29, p>0.05). These results suggested that the basis of ACLF might affect prognosis similar to Liu's report. Patients with ACLF are also characterized by high short-term mortality, but those who survive acute exacerbation show longer survival rate than patients with decompensated liver cirrhosis[23]. On the basis of this finding, we proposed that DLC complicated with ACLF should be considered as acute exacerbative types to distinguish CLF of a slow progression type. Significant differences were also found in TBil and PT levels between the two groups (p< 0.01). The death or invalidity rates in the CAE group were higher than those of the CSP group (p< 0.01).

In conclusion, our classification system of LF is simple and practical. The CSIHD criterion of LF is different from EASL and AASLD criteria. This new recommendation might promote uniformity in the diagnostic criteria of LF diagnosed worldwide. However, these classification criteria should be further confirmed by prospective studies.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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