

## Predictors of the outcomes of acute-on-chronic hepatitis B liver failure

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### Abstract

**AIM:** To identify the risk factors in predicting the outcome of acute-on-chronic hepatitis B liver failure patients.

**METHODS:** We retrospectively divided 113 patients with acute-on-chronic liver failure-hepatitis B virus (ACLF-HBV) and without concurrent hepatitis C or D virus infection and hepatocellular carcinoma into two groups according to their outcomes after anti-HBV therapy. Their demographic, clinical, and biochemical data on the day of diagnosis and after the first week

of treatment were analyzed using the Mann-Whitney *U* test, Fisher's exact test, and a multiple logistic regression analysis.

**RESULTS:** The study included 113 patients (87 men and 26 women) with a mean age of 49.84 years. Fifty-two patients survived, and 61 patients died. Liver failure (85.2%), sepsis (34.4%), and multiple organ failure (39.3%) were the main causes of death. Multivariate analyses showed that Acute Physiology and Chronic Health Evaluation (APACHE) II scores  $\geq 12$  [odds ratio (OR) = 7.160, 95% CI: 2.834-18.092,  $P < 0.001$ ] and positive blood culture (OR = 13.520, 95% CI: 2.740-66.721,  $P = 0.001$ ) on the day of diagnosis and model for end-stage liver disease (MELD) scores  $\geq 28$  (OR = 8.182, 95% CI: 1.884-35.527,  $P = 0.005$ ) after the first week of treatment were independent predictors of mortality.

**CONCLUSION:** APACHE II scores on the day of diagnosis and MELD scores after the first week of anti-HBV therapy are feasible predictors of outcome in ACLF-HBV patients.

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**Key words:** Lamivudine; Liver failure; Hepatitis B virus; Acute Physiology and Chronic Health Evaluation II score; Model for end-stage liver disease scores

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## INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health problem, with higher prevalence in Asia than in the West. In Taiwan, its prevalence is estimated at more than 8%<sup>[1]</sup>. Approximately 15%-40% of the patients with HBV infection eventually develop cirrhosis, hepatocellular carcinoma, or liver failure<sup>[2]</sup>. Acute-on-chronic liver failure (ACLF) is characterized by an acute deterioration in liver function due to a precipitating event such as infection, sepsis, alcohol, or variceal bleeding, in a patient with previously chronic liver disease. The reactivation of HBV infection plays an important role in the progression of ACLF in the Asian region<sup>[3]</sup>. Therefore, the first goal of treatment is to inhibit HBV replication.

Lamivudine, an L-nucleoside analog, has good therapeutic efficacy for suppressing HBV replication<sup>[4,5]</sup>. Consciousness and coagulopathy recover within only one week of lamivudine therapy, and the response rate to treatment is 86.66%<sup>[6]</sup>. Lamivudine therapy prevents the progression from acute exacerbation of hepatitis B to liver failure<sup>[6]</sup>. However, one report has indicated that lamivudine has no overall survival benefit in the management of severe flare-ups of chronic hepatitis B (CHB) with jaundice<sup>[7]</sup>. Therefore, patients unresponsive to anti-HBV therapy require alternative and effective treatments.

Liver transplantation (LT) is widely performed in patients with fulminant hepatitis B<sup>[8,9]</sup>. Advances in the transplantation techniques have resulted in good outcomes after living donor liver transplantation (LDLT) or dual-graft LDLT in patients with ACLF-HBV<sup>[9,10]</sup>. It is important for the transplant surgeon to know the optimal timing and the criteria for LT in patients with ACLF-HBV.

Because both anti-HBV therapy and LT are suitable treatments for ACLF-HBV, hepatologists and transplant surgeons require a practical model to predict the outcomes of ACLF-HBV. The model for end-stage liver disease (MELD) is one such prognostic model<sup>[11,12]</sup>; however, MELD scores alone do not predict the prognosis accurately<sup>[13]</sup>, and their suitability as prognostic indicators is controversial. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores are widely used in intensive care units to assess the severity of disease. Although this scoring system has been investigated with respect to its utility in predicting outcomes in critically ill patients with cirrhosis, the suitability of APACHE II scores as prognostic indicators for ACLF is also controversial<sup>[14-16]</sup>. In addition, APACHE II scores have rarely been evaluated for predicting the outcomes of acute hepatic failure<sup>[17-19]</sup>.

Previous studies have focused on various risk factors of mortality on the day of diagnosis, reflecting the severity of disease only at the time of diagnosis. ACLF-HBV has a rapidly progressing clinical course. Therefore, prompt evaluation of the efficacy of anti-HBV or supportive treatment would have a great impact on the outcomes of this disease. Accordingly, we aimed to assess the applicability of MELD and APACHE II scores as

predictors of the outcomes of ACLF-HBV and develop predictive models of mortality from ACLF-HBV based on the clinical and biochemical data recorded on the day of diagnosis and after the first week of anti-HBV and supportive treatment.

## MATERIALS AND METHODS

### Patients and study design

Between January 2001 and June 2010, 113 patients were diagnosed with ACLF-HBV at these two institutions in Taiwan. ACLF-HBV was defined as the recent development of jaundice (serum total bilirubin level  $\geq 10$  mg/dL), with an international normalized ratio (INR)  $> 1.5$ , and complicated with ascites and/or encephalopathy in a patient previously diagnosed or underdiagnosed with CHB<sup>[18]</sup>. The definition of underdiagnosed CHB was that HBV tests were performed for the first time and positive in patients with cirrhosis. The exclusion criteria were concurrent hepatitis C or D virus infection, a history of alcoholic drinking, malignant jaundice, hemolytic jaundice, prolonged prothrombin time induced by blood system disease, Wilson disease, autoimmune hepatitis, and anti-HBV therapy for liver failure diagnosed at another hospital.

All the enrolled patients received 100 mg lamivudine (tablets) once daily. Their medical records were retrospectively reviewed, and they were followed up for at least 3 mo. The outcome of each patient was recorded, and the causes of death were documented.

### Observed parameters

The results of blood tests performed on the day of diagnosis and after the first week of anti-HBV therapy were recorded. The blood tests performed included white blood count (WBC), hemoglobin level, platelet count, prothrombin time (PT), INR, creatinine level, aspartate, alanine transaminase (ALT) level, total bilirubin (TBil) level, direct bilirubin (DBil) level, total cholesterol level, triglyceride level, albumin level, ammonia level, serum sodium level, serum potassium level, serum chloride level, total serum calcium level, and serum magnesium level.

MELD scores were calculated according to the following formula: MELD score =  $[3.78 \times \log_e(\text{bilirubin level in mg/dL})] + [11.2 \times \log_e(\text{INR})] + [9.6 \times \log_e(\text{creatinine level in mg/dL})] + [6.4 \times (\text{etiology: 0 if cholestatic or alcoholic, 1 otherwise})]$ <sup>[20]</sup>. APACHE II scores were calculated from 12 physiological and laboratory values: temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation (PaO<sub>2</sub> or A-aDO<sub>2</sub>), arterial pH, serum sodium level, serum potassium level, serum creatinine level, hematocrit, WBC count, and Glasgow coma score. Each value was marked from 0 to 4, where 0 = normal and 4 = most abnormal. The sum of these values was adjusted according to the patient's age and chronic health problems<sup>[21]</sup>.

**Table 1** Patient characteristics and blood tests on the day of diagnosis

	Survival	Dead	P value
Case number	52	61	
Age (yr) <sup>1</sup>	43.00 (17.00)	55.00 (19.00)	< 0.001
BMI <sup>1</sup>	25.15 (5.54)	23.41 (6.35)	0.668
Gender: Male	42 (80.8%)	45 (73.8%)	0.378
Past history: Yes			
Diabetes mellitus <sup>2</sup>	3 (5.8%)	18 (29.5%)	0.001
Hypertension <sup>2</sup>	9 (17.3%)	20 (32.8%)	0.060
Coronary artery disease <sup>3</sup>	1 (1.9%)	6 (9.8%)	0.122
Cirrhosis <sup>2</sup>	34 (65.4%)	45 (73.8%)	0.333
Blood culture: Positive <sup>2</sup>	2 (3.8%)	22 (36.1%)	< 0.001
Gastroenteric tract bleeding <sup>2</sup>	8 (15.4%)	18 (29.5%)	0.075
Laboratory investigation			
WBC count ( $\times 10^3$ /cumm) <sup>1</sup>	7.00 (3.60)	7.10 (6.55)	0.668
Hemoglobin (g/dL) <sup>1</sup>	11.80 (4.90)	10.70 (3.85)	0.879
Platelet ( $\times 10^3$ /cumm) <sup>1</sup>	91.00 (108.00)	89.50 (92.50)	0.826
Prothrombin time (s) <sup>1</sup>	18.00 (4.47)	19.90 (7.45)	0.060
INR <sup>1</sup>	2.23 (1.08)	2.66 (1.51)	0.084
Creatinine (mg/dL) <sup>1</sup>	0.80 (0.70)	0.80 (1.00)	0.109
ALT (U/L) <sup>1</sup>	71.00 (1091.00)	180.00 (833.50)	0.250
Total bilirubin (mg/dL) <sup>1</sup>	15.35 (9.65)	13.95 (12.20)	0.425
Direct bilirubin (mg/dL) <sup>1</sup>	7.50 (7.60)	7.50 (9.40)	0.642
Cholesterol (mg/dL) <sup>1</sup>	108.00 (64.50)	104.00 (52.00)	0.208
Triglyceride (mg/dL) <sup>1</sup>	99.00 (62.00)	94.00 (62.00)	0.164
Albumin (g/dL) <sup>1</sup>	2.90 (0.80)	2.60 (0.88)	0.386
Ammonia ( $\mu$ g/dL) <sup>1</sup>	124.00 (75.50)	138.00 (159.00)	0.133
Serum sodium (mmol/L) <sup>1</sup>	135.00 (6.50)	135.00 (7.50)	0.739
Serum potassium (mmol/L) <sup>1</sup>	3.70 (1.02)	4.10 (1.15)	0.008
Serum chloride (mmol/L) <sup>1</sup>	105.00 (9.00)	106.00 (9.00)	0.207
Serum calcium (mg/dL) <sup>1</sup>	8.30 (0.70)	8.10 (0.80)	0.517
Serum magnesium (mg/dL) <sup>1</sup>	2.00 (0.55)	2.00 (0.67)	0.670
MELD score <sup>2</sup>	26.00 (6.00)	29.00 (10.00)	0.091
APACHE- II score <sup>1</sup>	12.00 (5.00)	14.00 (3.00)	< 0.001

P values were derived from <sup>1</sup>the Mann-Whitney *U* test, <sup>2</sup>the  $\chi^2$  test, and <sup>3</sup>Fisher's exact test. The median (interquartile range) is presented for continuous variables and the number (percentage) is presented for categorical variables. MELD: Model for end-stage liver disease; APACHE- II: Acute Physiology and Chronic Health Evaluation II; INR: International normalized ratio; ALT: Alanine transaminase; WBC: White blood cell.

### Statistical analysis

Unless otherwise stated, continuous variables are presented as the median (interquartile range), and categorical variables are expressed as the number (percentage) of events. To detect differences between the groups, the Mann-Whitney *U* test was used for continuous variables, and the  $\chi^2$  test was used for categorical variables. If 20% of the cells had expected numbers < 5, Fisher's exact test was used instead of the  $\chi^2$  test. The cut-off value of continuous variables with a *P* value < 0.05 in the Mann-Whitney *U* test was determined by finding the point on the receiver operating characteristic curve closest to (0,1)<sup>[22]</sup>. Statistically significant variables with a *P* value < 0.05 in the univariate analysis were put into a backward multivariate analysis. New models to predict the outcomes were established based on the results of the backward multivariate analysis. All the statistical calculations were performed using SPSS version 15.0 (IBM-SPSS, Inc., Chicago, IL). Significance was defined as *P* < 0.05.

**Table 2** Univariate and multivariate analysis of clinical and biochemical data on the day of diagnosis

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age $\geq$ 45	6.912 (3.009-15.879)	< 0.001	NI	
Serum potassium $\geq$ 4.0	1.994 (0.928-4.284)	0.077	NI	
APACHE- II score $\geq$ 12	7.167 (3.072-16.724)	< 0.001	7.160 (2.834-18.092)	< 0.001
Blood culture: Positive	14.103 (3.125-63.639)	0.001	13.520 (2.740-66.721)	0.001
Past diabetes history: Positive	6.837 (1.884-24.814)	0.003	NI	

Age and history of diabetes mellitus were not included for multivariate analyses because these parameters had been calculated for the APACHE- II score. OR: Odds ratio; APACHE- II: Acute Physiology and Chronic Health Evaluation II; NI: Not included in model.

## RESULTS

### Patient characteristics

The study included 113 patients (87 men and 26 women) with a mean age of 49.84 years. The patient characteristics are summarized in Table 1. Overall, 52 (46%) patients survived the anti-HBV therapy, and 61 (54%) patients died during therapy. The patients who died were older (55 years *vs* 43 years, *P* < 0.001), more often had a history of diabetes mellitus (29.5% *vs* 5.8%, *P* = 0.004), and tended to have positive blood cultures (36.1% *vs* 3.8%, *P* < 0.001). The groups showed no significant differences in terms of gender, body mass index, history of hypertension or coronary artery disease. Liver failure (85.2%), sepsis (34.4%), and multiple organ failure (39.3%) were the main causes of death.

### Observed parameters on the day of diagnosis

The results of the blood test on the day of diagnosis are shown in Table 1. The patients who died had significantly higher values of serum potassium (*P* = 0.008) than the survivors. The groups showed no significant differences in the other observed parameters. Furthermore, the patients who died had significantly higher APACHE II scores than the survivors (14 *vs* 12, *P*  $\leq$  0.001), but no significant difference in MELD scores was detected.

A univariate analysis showed that the frequency of age  $\geq$  45 years (*P* < 0.001), history of diabetes mellitus (*P* = 0.003), positive blood culture (*P* = 0.001), and APACHE II score  $\geq$  12 (*P* < 0.001) differed significantly between the groups (Table 2). However, potassium levels  $\geq$  4.0 mmol/L were not a significant risk factor for dying based on the results from the univariate analysis. The trend (*P* = 0.077) was included in the multivariate analysis.

The multivariate analysis included all the significant parameters in the univariate analysis except for age, history of diabetes mellitus and serum potassium level,

**Table 3** Laboratory tests after the first week of anti-hepatitis B virus therapy

	Survivors ( <i>n</i> = 52)	Dead ( <i>n</i> = 61)	<i>P</i> value
White blood cell count (×10 <sup>3</sup> /cumm)	6.50 (3.40)	9.35 (6.95)	< 0.001
Hemoglobin (g/dL)	10.25 (1.95)	0.20 (3.70)	0.780
Platelet (×10 <sup>3</sup> /cumm)	92.50 (74.50)	79.50 (91.25)	0.356
Prothrombin time (s)	17.20 (4.85)	21.65 (9.35)	< 0.001
INR	1.96 (1.00)	2.87 (2.38)	< 0.001
Creatinine (mg/dL)	0.70 (0.50)	1.10 (1.35)	< 0.001
ALT (U/L)	95.50 (331.25)	115.50 (299.00)	0.238
Total bilirubin (mg/dL)	12.75 (9.60)	20.30 (15.20)	0.003
Direct bilirubin (mg/dL)	7.45 (7.85)	10.30 (8.60)	0.093
Albumin (g/dL)	3.00 (0.70)	2.80 (0.85)	0.098
Ammonia (μg/dL)	118.00 (96.00)	159.50 (223.00)	0.005
Serum sodium (mmol/L)	134.00 (8.00)	138.00 (8.00)	0.003
Serum potassium (mmol/L)	4.10 (0.90)	3.80 (1.00)	0.649
Serum chloride (mmol/L)	104.00 (14.00)	105.00 (18.00)	0.338
Serum calcium (mg/dL)	8.40 (1.25)	8.45 (1.43)	0.922
Serum magnesium (mg/dL)	1.80 (1.45)	2.30 (0.93)	0.216
MELD score	25.00 (7.00)	32.00 (12.00)	< 0.001
APACHE- II score	13.00 (10.00)	17.50 (9.00)	0.014

The median (interquartile range) is presented for continuous variables. *P* values were derived using the Mann-Whitney *U* test. MELD: Model for end-stage liver disease; APACHE- II: Acute Physiology and Chronic Health Evaluation II; INR: International normalized ratio; ALT: Alanine transaminase.

because these parameters were calculated as part of the APACHE II scores. Multivariate analysis showed that an APACHE II score  $\geq 12$  [odds ratio (OR) = 7.160, 95% CI: 2.834-18.092, *P* < 0.001] and positive blood culture (OR = 13.520, 95% CI: 2.740-66.721, *P* = 0.001) were independent predictive factors of mortality in patients with ACLF-HBV (Table 2).

#### Observed parameters after the first week of anti-HBV therapy

Table 3 shows the results of blood tests performed after the first week of anti-HBV therapy. WBC count, PT, INR, creatinine level, TBil level, ammonia level, serum sodium level, MELD score, and APACHE II score showed significant differences, and their cut-off values were determined by using the Shock index. In the univariate analysis, WBC count  $\geq 8500/\text{mm}^3$  (*P* = 0.001), PT  $\geq 19$  s (*P* < 0.002), INR  $\geq 2.5$  (*P* = 0.002), creatinine level  $\geq 0.9$  mg/dL (*P* < 0.001), TBil level  $\geq 15.5$  mg/dL (*P* = 0.001), ammonia level  $\geq 166$  μg/dL (*P* = 0.008), serum sodium level  $\geq 136$  mmol/L (*P* = 0.006), MELD score  $\geq 28$  (*P* < 0.001), and APACHE II score  $\geq 14$  (*P* = 0.0018) differed significantly between the survivors and the patients who died (Table 4).

The multivariate analysis included all the significant parameters in the univariate analysis except for WBC count and serum sodium level because these parameters were calculated as part of the APACHE II scores. INR, TBil level, and creatinine level were calculated as part of the MELD scores. Multivariate analysis showed that MELD scores  $\geq 28$  (OR = 8.182, 95% CI: 1.884-35.527, *P* = 0.005) were independent predictive factors of mor-

**Table 4** Univariate and multivariate analysis of clinical and biochemical data after the first week of anti-hepatitis B virus therapy

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
White blood cell count $\geq 8.50$	5.940 (2.129-16.571)	0.001 <sup>a</sup>	NI	
Prothrombin time $\geq 19$	4.018 (1.656-9.747)	0.002 <sup>a</sup>	1.264 (0.254-6.296)	0.775
INR $\geq 2.5$	3.960 (1.635-9.590)	0.002 <sup>a</sup>	NI	
Creatinine $\geq 0.9$	4.819 (2.090-11.112)	<0.001 <sup>a</sup>	NI	
Total bilirubin $\geq 15.5$	4.271 (1.878-9.714)	0.001 <sup>a</sup>	NI	
Ammonia $\geq 166$	4.167 (1.459-11.900)	0.008 <sup>a</sup>	3.976 (0.703-22.482)	0.118
Serum sodium $\geq 136$	3.479 (1.432-8.448)	0.006 <sup>a</sup>	NI	
MELD score $\geq 28$	13.000 (4.604-36.711)	<0.001 <sup>a</sup>	8.182 (1.884-35.527)	0.005
APACHE- II score $\geq 14$	2.941 (1.201-7.203)	0.018 <sup>a</sup>	1.597 (0.375-6.809)	0.527

The parameters of white blood cell count, serum sodium, INR, total bilirubin and creatinine were not included for multivariate analyses because these parameters had been calculated for the APACHE- II score or MELD score. OR: Odds ratio; MELD: Model for end-stage liver disease; APACHE- II: Acute Physiology and Chronic Health Evaluation II; INR: International normalized ratio; NI: Not included in model. <sup>a</sup>*P* < 0.05.

tality in patients with ACLF-HBV (Table 4).

## DISCUSSION

ACLF-HBV has a poor prognosis and is associated with high mortality. Sun *et al.*<sup>[13]</sup> reported that the 3-mo overall mortality of patients with ACLF-HBV without lamivudine treatment was 57.84%. Despite lamivudine treatment, the prognosis is unsatisfactory with a mortality rate of approximately 50.7%-75.7%<sup>[23]</sup>. We found that the 3-mo overall mortality was 54.0%, which is consistent with previous reports. These results indicate that mortality from ACLF-HBV depends on multiple factors other than HBV replication. One relevant factor may be physiological changes in these patients. In addition to liver failure (85.2%), sepsis and multiple organ failure were also important causes of death in the present study, responsible for 34.4% and 39.3% of patient deaths, respectively. Both HBV-induced primary injury and cytokine-induced secondary injury confirm that physiological change is equally important to HBV replication in the pathogenesis of ACLF-HBV. Physiological changes other than HBV replication in a patient with ACLF-HBV are highly associated with patient outcomes. HBV load and a decline in HBV DNA load are proven risk factors<sup>[23]</sup>. Other risk factors of mortality from ACLF-HBV should be investigated.

Determining which method to use for describing the severity of physiological changes or cytokine-induced secondary injury in patients with ACLF-HBV was an issue of concern in this study. APACHE II scores are widely used in intensive care units to evaluate the severity and prognosis of a disease<sup>[21]</sup>. The predictive accuracy of APACHE II scores for mortality in patients with acetaminophen-induced acute liver failure has been reported in terms of the area under the receiver operating characteristic (ROC) curve, sensitivity, and specific-

ity (0.77, 67% and 76%, respectively)<sup>[24]</sup>. We found that APACHE II scoring on the day of diagnosis does not exhibit good predictive accuracy. Through multiple logistic regression analysis, an APACHE II score  $\geq 12$  and positive blood culture on the day of diagnosis were identified as independent predictive factors of mortality. These two factors accurately predicted the outcome of ACLF-HBV patients better than the APACHE- II score alone or prior associated studies (predictive accuracy was 76.6%; area under the ROC curve was 0.804). We ignored age and history of diabetes mellitus in the multivariate analysis because they were calculated in the APACHE II scores, but we supposed that these parameters play an important role in determining APACHE II scores. The identification of positive blood culture as a predictor of mortality suggests that physicians should treat infection in patients with ACLF-HBV aggressively.

MELD scores are widely used to assess the severity of chronic liver disease and indications for LT<sup>[24]</sup>. Sun *et al.*<sup>[13]</sup> found that MELD scoring alone had lower predictive accuracy than their predictive model. Our results are consistent with those of Sun *et al.*<sup>[13]</sup> and suggest that MELD scoring on the day of diagnosis does not accurately predict mortality from ACLF-HBV. We supposed that MELD scores, which include INR, TBil level, and creatinine level, are not acute-stage indicators. However, the fact that MELD scores  $\geq 28$  after 1 wk are strongly associated with mortality implies that after the acute complications of ACLF are treated and HBV is suppressed, liver function again becomes important as a prognostic factor as it is in cirrhosis without ACLF. The change in MELD score may reflect the efficacy of anti-HBV therapy in patients with ACLF-HBV. Our findings also highlight the importance of repeated evaluations after 1 wk of anti-HBV therapy, given the fact that ACLF-HBV progresses rapidly and that disease severity and the patient's condition cannot be evaluated completely on the day of diagnosis. Furthermore, our results suggest that cytokine-induced physiological changes recover after one week of anti-HBV treatment; therefore, progressive liver injury determines the outcome of ACLF-HBV.

The English literature includes few reports on the prognostic factors of ACLF-HBV. Before the lamivudine era, the prognostic model for ACLF-HBV consisted of the presence of hepatorenal syndrome, the presence of liver cirrhosis, the presence of hepatitis B e antigen, low albumin level, and low prothrombin activity<sup>[13]</sup>. With the development of anti-HBV therapy, the HBV factor has been investigated further. Dai *et al.*<sup>[25]</sup> found that albumin level, INR, and HBV DNA level are good predictors of mortality in patients with CHB-related decompensation treated with lamivudine. Furthermore, Yu *et al.*<sup>[26]</sup> reported that MELD scores of 30 to 40, low HBV load, and rapid declines in HBV DNA load are good predictors of mortality in patients with ACLF-HBV treated with plasma exchange and lamivudine. Similarly, Sun *et al.*<sup>[23]</sup> showed that MELD scores of 20 to 30, low HBV load, and rapid declines in HBV DNA load are good predictors in patients

with ACLF-HBV treated with lamivudine. Therefore, HBV replication is the key factor for predicting mortality. We did not analyze HBV factors because of the lack of complete data.

The present study has some limitations. Because of its retrospective nature, some laboratory data, such as lactate acid level and HBV load, could not be collected and analyzed. These data are considered good predictors of the outcomes of ACLF-HBV<sup>[23]</sup>. In addition, the results need to be interpreted cautiously, given the differences in the definition of ACLF-HBV between this and previous studies. For example, the plasma TBil level ranged from  $\geq 5$  mg/dL to  $\geq 10$  mg/dL, which define the jaundice of liver failure in acute-on-chronic liver failure in previous studies; we adopted a plasma TBil level  $\geq 10$  mg/dL, which seems to be the most common criterion<sup>[13,23,25]</sup>. However, the Asian Pacific Association for the Study of Liver held a meeting in 2008, where liver failure in acute-on-chronic liver failure was defined as jaundice (serum bilirubin  $\geq 5$  mg/dL) and coagulopathy (INR  $\geq 1.5$ ). In the future, researchers must follow the above definition to help clinicians improve the identification and management of these patients<sup>[3]</sup>.

In conclusion, our logistic regression models have good predictive accuracy. APACHE II score  $\geq 12$  and positive blood culture on the day of diagnosis reflect severe liver failure. Anti-HBV medication, aggressive supportive treatment, and the control of infection are important for patients with ACLF-HBV. The need for appropriate donors among relatives, the evaluation of liver structures, and the ethical issues inherent in LT should be considered. Patients should be re-evaluated after the first week of anti-HBV treatment. MELD scores  $\geq 28$  indicate that the patient is in poor condition. These patients should undergo LT as soon as possible. This study emphasized the selection of an APACHE II score and a MELD score as predictors because these two scores are used clinically in many institutions and utilized easily by clinicians. Future research efforts should verify the outcome of liver transplantation for these ACLF-HBV patients with the risk factors described above.

## COMMENTS

### Background

Acute-on-chronic hepatitis B liver failure has a poor prognosis with high mortality. Despite lamivudine treatment, the prognosis is still unsatisfactory. Acute-on-chronic hepatitis B liver failure has a rapidly progressing clinical course. Prompt evaluation of the efficacy of anti-hepatitis B virus (HBV) treatment would have a great impact on patient outcomes.

### Research frontiers

To assess the applicability of Acute Physiology and Chronic Health Evaluation (APACHE)- II and model for end-stage liver disease (MELD) scores to predict the outcome of acute-on-chronic hepatitis B liver failure.

### Innovations and breakthroughs

The suitability of MELD scores as prognostic indicators for these patients is controversial. APACHE- II scores have rarely been evaluated among these patients. Importantly, these two scores are easily available in clinical practice.

### Applications

APACHE II scores on the day of diagnosis and MELD scores after the first

week of anti-HBV therapy are feasible predictors in determining the outcome of acute-on-chronic hepatitis B liver failure even after treatment with anti-hepatitis B virus therapy.

### Terminology

Acute-on-chronic liver failure is characterized by an acute deterioration in liver function as a result of a precipitating event such as infection, sepsis, alcohol toxicity, or variceal bleeding, in a patient with previously chronic liver disease.

### Peer review

In this article, the authors have compared various parameters to predict the outcomes of acute-on-chronic hepatitis B liver failure. The immediate message of the conclusion is that we apparently have two concrete, bedside early prognostic indicators. The authors have included the limitations of the presented study.

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