Int J Clin Exp Med 2016;9(6):10364-10373
www.ijcem.com /ISSN:1940-5901/IJCEM0023853

Original Article

Early bilirubin response in acute-on-chronic hepatitis B liver failure patients treated with corticosteroids predicates a lower 3-month mortality

Juan Li[1*], Juan Wu[1,2*], Hai-Xia Liu[1], Wei Hou[1], Hong-Wei Yu[1], Yue-Ke Zhu[1], Fu-Sheng Wang[2], Qing-Hua Meng[1]

[1]Department of Critical Care Medicine of Liver Disease, Beijing You An Hospital, Capital Medical University, Beijing 100069, China; [2]Research Center for Biological Therapy, Beijing 302 Hospital, Peking University Health Science Center, Beijing 100039, China. [*]Equal contributors.

Received January 12, 2016; Accepted April 6, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Corticosteroids have been used for acute-on-chronic hepatitis B liver failure (ACHBLF) patients to inhibit overactive immunological responses. Due to the severe side effects of long-term use of corticosteroids, early identification of responders is very important for clinicians. So we conducted this study to identify efficacious indicators for response to corticosteroids. A total of 74 ACHBLF patients treated with corticosteroids were enrolled. Baseline characteristics and change of liver functions at the 3rd, 7th, 10th, 14th, 21th day during the treatment period were analyzed. Data were collected retrospectively and 3-month survival was used as the primary endpoint. 3-month survival in ACHBLF patients treated with corticosteroids was 50.0% ± 5.9%. Survival patients tended to be younger, have lower serum TBIL, creatinine and MELD score, and higher platelet than non-survival patients. After using corticosteroids, there was a significant improvement in TBIL, PTA and MELD score in survival patients compared with non-survival patients. Area under the receiver operating curve (AUROC) indicated that early improvement of bilirubin level (EIBL) at the 7th day after using corticosteroids was an efficacious predictor for response to corticosteroids. Multivariate logistic regression model identified four independent prognostic factors, including age, INR, TBIL, and EIBL, with significantly higher prognostic accuracy than MELD score. Our findings suggest that early improvement of serum bilirubin level at the 7th day after using corticosteroids in ACHBLF patients can predicate responsiveness to corticosteroid therapy and can be use as a favorable prognostic predictor for 3-month mortality in ACHBLF patients treated with corticosteroids.

Keywords: Liver failure, hepatitis B, chronic, glucocorticoids, bilirubin, prognosis

Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome of acute deterioration of hepatic function in patients with previously well-compensated chronic liver disease, manifesting as coagulopathy and jaundice, complicated within four weeks by ascites and/or hepatic encephalopathy due to the effects of one or multiple precipitating events [1, 2]. Hepatitis B virus (HBV) infection is the leading cause of ACLF in China, accounting for more than 80% of ACLF with short-term mortality as high as 50-60% [3]. Until now early use of nucleoside analogs, artificial liver support and advanced critical care management have efficiently improved the prognosis of patients with acute-on-chronic hepatitis B liver failure (ACHBLF). However, mortality is still very high without liver transplantation. Moreover, due to the shortage of liver donors and socioeconomic problems, liver transplantation cannot be widely applied in China. Thus, identifying some other efficacious therapies remains an important challenge for clinicians.

HBV is almost a non-cytopathic virus and immune-mediated inflammatory responses play an important role in the pathophysiology of ACHBLF, including exacerbation of innate immunologic responses and activation of systemic inflammatory response mediated by proinflammatory cytokines, resulting in hepatic inflammation and necrosis [4, 5]. Thus corticosteroids

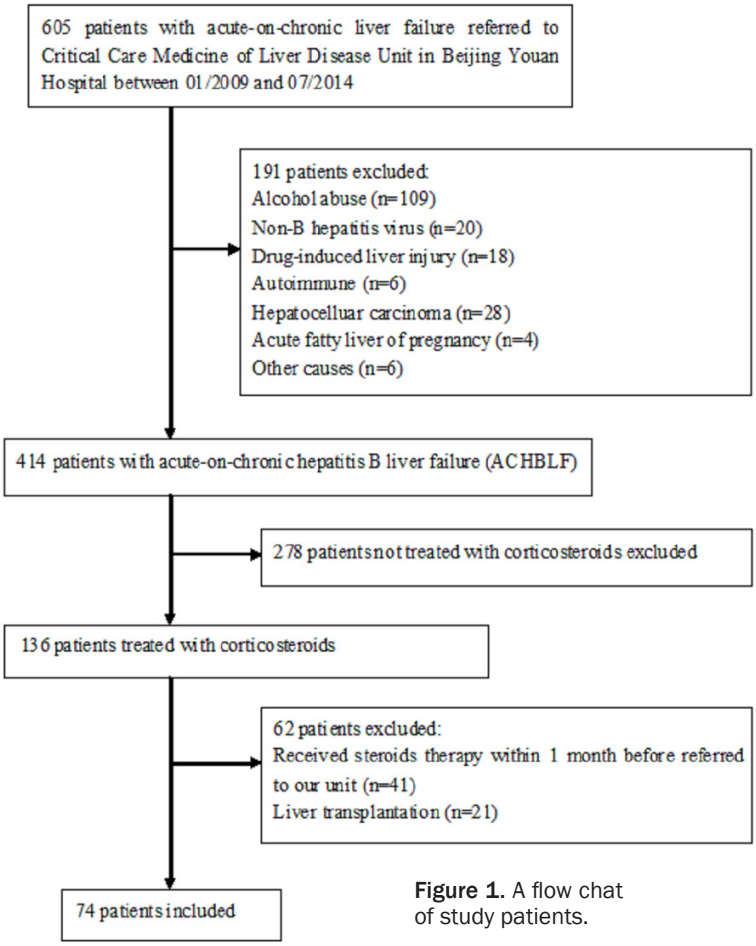

Figure 1. A flow chat of study patients.

may be used as an appropriate treatment in ACHBLF patients to restrain hepatic inflammation, due to its special effects in inhibiting immunological responses. Some studies have showed that early use of sufficient doses of corticosteroids can reverse severe acute exacerbation in chronic hepatitis B patients [6-10]. However, there remains no common consensus with regard to corticosteroid therapy in ACHBLF patients.

In clinic we observed that some ACHBLF patients may have a dramatic response to corticosteroids and obtain substantial and sustained increase in survival, whereas others appear to be nonresponsive and may have their illness aggravated if they continued corticosteroid therapy. Thus it is necessary for clinicians to identify those patients who will respond to corticosteroids and benefit from it, as well as those non responders, who can have their corticosteroids withdrawn and consider for other alternative therapeutic options such as liver transplantation. Our previous study showed that higher baseline mDC (myeloid dendritic cell) numbers or recovery of mDC numbers at the end of treatment may be a favorable predictor for response to corticosteroids treatment in ACHBLF patients [11]. However, it is not practical for all ACHBLF patients to detect peripheral mDC numbers in clinic. So we conducted this study to identify some clinical parameters as efficacious indicators for response to corticosteroids and develop a prognostic model to predicate three months mortality in ACHBLF patients treated with corticosteroids.

Patients and methods

This was an observational study. We retrospectively enrolled ACHBLF patients treated with corticosteroids in Critical Care Medicine of Liver Disease in Beijing You An Hospital, Capital Medical University from 2009 to 2014. The diagnostic criteria of ACHBLF included coagulopathy, which means international normalized ratio (INR) ≥ 1.5 or prothrombin activity (PTA) ≤ 40%, and jaundice (serum bilirubin ≥ 171 umol/L or daily increase ≥ 17.1 umol/L) with ascites and/or hepatic encephalopathy developing within 4 weeks in patients with prior history of chronic hepatitis B or compensated liver cirrhosis caused by hepatitis B virus, with either positive results of hepatitis B surface antigen and/or HBV DNA [12]. Patients with evidence of non-B hepatitis virus, alcohol abuse, drug-induced or autoimmune hepatitis and hepatocellular carcinoma were not included. ACHBLF patients with contraindications of corticosteroids therapy including recent gastrointestinal bleeding (less than 15 days), uncontrolled infection or evidence of sepsis, active peptic ulcer, and other contraindications were excluded. We also excluded patients who received corticosteroids therapy within 1 month before referred to our unit. Finally a total of 74

Table 1. Baseline Clinical and Biochemical Characteristics between the Survival and Non-survival Group in Acute-on-chronic Hepatitis B Liver Failure Patients

Variable	ACHBLF (n = 74)	Survival† (n= 33)	Non-survival† (n = 36)	*P* value
Age: mean (SD)	40.5 (13.0)	36.0 (10.3)	46.1 (13.4)	0.001
Male: n (%)	69 (93.2%)	30 (90.9%)	34 (94.4%)	0.665
MELD: mean (SD)	25.5 (5.7)	23.4 (4.8)	27.6 (6.0)	0.003
Child-Pugh score: median (range)	11 (9-13)	10 (9-12)	11 (9-13)	0.449
ALT (U/L): median (range)	315.8 (20.0-4209.0)	460.0 (20-4209.0)	231.4 (29.4-2693.6)	0.088
AST (U/L): median (range)	213.3 (37.8-5193.0)	303.6 (37.8-5193.0)	183.4 (42.7-1786.9)	0.116
TBIL (umol/L): median (range)	370.3 (172.9-810.9)	326.1 (179.4-666.9)	427.7 (172.9-810.9)	0.005
Creatinine (mmol/L): median (range)	61.0 (20.3-276.7)	58.8 (33.1-276.7)	73.4 (40.0-176.8)	0.019
Albumin(g/L): mean (SD)	32.7 (4.3)	32.6 (4.1)	32.6 (4.6)	0.968
PT: median (range)	24.8 (17.7-52.0)	23.8 (17.9-48.7)	25.3 (17.7-52.0)	0.162
PTA(%): mean (SD)	30.7 (9.5)	33.1 (9.1)	29.2 (9.9)	0.092
INR: median (range)	2.3 (1.6-4.9)	2.1 (1.6-3.8)	2.4 (1.7-4.8)	0.058
WBC (10^9/L): median (range)	7.3 (2.4-16.1)	7.1 (2.4-16.1)	8.2 (2.8-15.7)	0.273
Platelet (10^9/L): median (range)	117.0 (24.0-289.0)	122 (37.0-289.0)	100.5 (24.0-214.0)	0.013
HBV-DNA‡ ($\log_{10}$ IU/mL): mean (SD)	5.1 (1.5)	5.3 (1.6)	4.9 (1.7)	0.360
Encephalopathy: n (%)	14 (18.9%)	7 (21.2%)	6 (16.7%)	0.630
Presence of ascites: n (%)	38 (51.4%)	15 (45.5%)	21 (58.3%)	0.285
Cirrhosis n (%)	21 (28.4%)	7 (21.2%)	14 (38.9%)	0.111
Daily prednisone dose: mean (SD)	60.9 (21.6)	61.3 (24.2)	61.9 (20.4)	0.903
Days of prednisone: median (range)	7 (3-59)	7 (3-59)	7 (3-30)	0.807
Days before steroids: median (range)	17 (1-60)	14 (3-60)	21 (1-60)	0.041
3-month Survival	50.0% ± 5.9%	-	-	-

†Survival data were not available in 6 patients at the end of 3 months. ‡Data were not available in 22 patients. ACHBLF, acute-on-chronic hepatitis B liver failure; MELD, model for end-stage liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin level; PT, prothrombin time; PTA, prothrombin activity; INR, international normalized ratio; WBC, white blood cell.

ACHBLF patients treated with corticosteroids were enrolled in this study (**Figure 1**). 62 patients received intravenous methylprednisolone due to digestive symptoms, and 12 patients received oral prednisolone. In order to unify the dose of corticosteroids, we calculated 32 mg of methylprednisolone equivalent to 40 mg of prednisone and present the results using the dose of prednisone. Other conventional medical therapies and supportive care were also given according to patients' organ function. 52 patients were detected positive for HBV DNA and were treated with oral nucleoside analogs (lamivudine, enticavir or telbivudine). 10 patients had undetectable levels of HBV DNA and were not given any antiviral therapy. Another 12 patients had no available HBV DNA data due to the limit of retrospective study. Among these 12 patients, 8 patients were continued to give oral antiviral agents according to their previous treatment and 4 patients were not given any antiviral therapy.

The following variables were collected before the use of corticosteroids (0 day): age, sex, presence of encephalopathy, ascites, days between the onset of symptoms and initiation of corticosteroids (days before steroids), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum total bilirubin level (TBIL), prothrombin time (PT), INR, PTA, serum albumin level, serum creatinine, white blood cell count (WBC), platelet and HBV-DNA. MELD (model for end-stage liver disease) scores were also calculated. During the treatment period, liver functions at the 3rd, 7th, 10th, 14th, 21th day and complications were also collected. 3-month survival data were collected retrospectively, and were missing in 6 patients due to lack of accurate contacts.

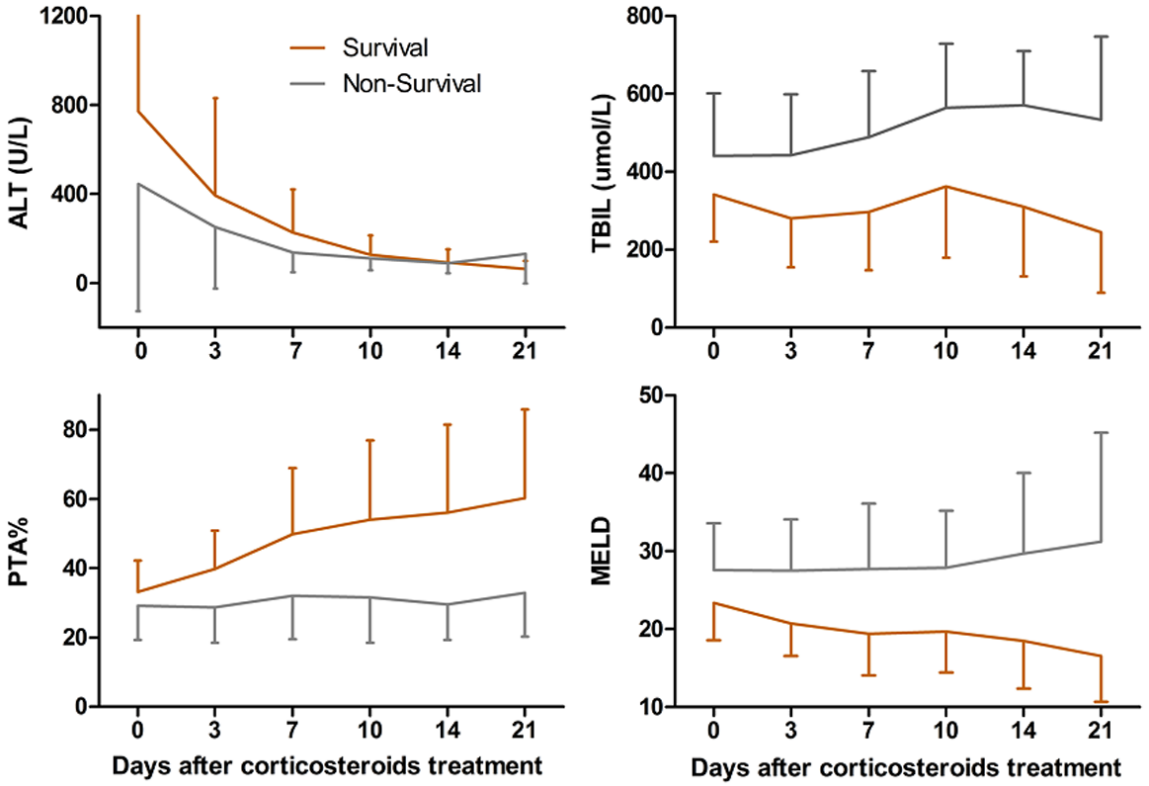

Figure 2. Improved Liver function since the use of corticosteroids treatment in the survival group compared with non-survival group in acute-on-chronic hepatitis B liver failure patients. ALT levels fell in both survival and non-survival group during the course of treatment, while in the non-survival group the mean level of ALT increased at the 21th day since the use of corticosteroids. Serum TBIL showed a declined tendency in the survival group since the use of corticosteroids, although at the 7-10th day there was a rebound, compared with continued increase in serum TBIL in the non-survival group. PTA and MELD score had dramatically improved during the treatment period in the survival group while in the non-survival group the improvements were not obvious.

Statistical analysis

All data were analyzed for normality and were reported as mean (SD) or median (range), as appropriate. Comparison of quantitative and qualitative variables was performed using t test, non-parametric analysis, chi-square and Fisher exact test. Patients' survival was estimated by the Kaplan-Meier method and expressed in percentage ± SE. In order to identify those patients who would respond to corticosteroids, we compared the baseline clinical and biological variables of the survival group and the non-survival group, as well as the dynamic changes of liver functions during the corticosteroids treatment period.

Univariate and multivariate logistic regression analyses were performed to identify independent predictors for 3-month mortality in ACHBLF patients treated with corticosteroids. All predictors with $P < 0.1$ in univariate analysis were evaluated in multivariate analysis using backward LR stepwise method. A logistic regression model (LRM) combining predictive factors of 3-month mortality was constructed. The difference of this LRM model and MELD score in terms of diagnostic accuracy was assessed by comparison of the area under the receiver operating curves (AUROC) using z test. Statistical analysis was performed using SPSS 21 (IBM, Armonk, NY). $P < 0.05$ was considered statistically significant and all P values were two-tailed.

The work described in this manuscript has been approved by the Ethics Committee of Beijing You An Hospital; all patients or their next of kins signed a written informed consent in accordance with the Institutional Review Board guidelines for the protection of human

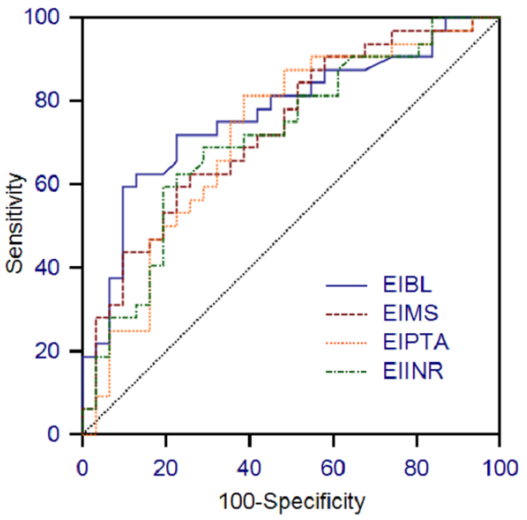

Figure 3. Receiver operating curve (ROC) analysis of EIBL, EIPTA, EIINR, and EIMS at the 7th day since the use of corticosteroids in predicting 3-month survival in ACHBLF patients. EIBL had the highest AUROC: 0.769, compared with 0.732 for EIMS, 0.718 for EIPTA, and 0.715 for EIINR. EIBL, early improvement of bilirubin level; EIINR, early improvement of INR; EIPTA, early improvement of PTA; EIMS, early improvement of MELD score.

subjects and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Comparison of baseline clinical and biochemical characteristics between the survival and non-survival group in ACHBLF patients

Baseline clinical and biochemical characteristics of the enrolled patients were described in **Table 1**. The mean age was 40.5 ± 13.0 years, and the patients were predominantly men (93.2%). The mean daily dose of prednisone was 60.9 mg and the median duration of corticosteroids therapy was 7 days. The median duration of symptoms before corticosteroids treatment was 17 days. Survival analysis indicated that 3-month survival in ACHBLF patients treated with corticosteroids was 50.0% ± 5.9%. Comparison between the survival and non-survival group showed that there were no significant differences in terms of sex, Child-Pugh score, serum levels of ALT and AST, serum albumin level, white blood cell count, HBV-DNA, presence of encephalopathy, ascites, and proportion of liver cirrhosis between the two groups. However, the survival patients tended to be younger (36.0 ± 10.3 vs 46.1 ± 13.4, p = 0.001), have lower serum TBIL (median 326.1 umol/L vs 427.7 umol/L, P = 0.005), serum creatinine (median 58.5 umol/L vs 73.4 umol/L, P = 0.019) and MELD score (23.4 ± 4.8 vs 27.6 ± 6.0, P = 0.003), and higher platelet (median 122.0*10^9/L vs 100.5*10^9/L, P = 0.013) than non-survival patients. In the survival group PT and INR tended to be lower (median 23.8 s vs 25.3 s, 2.1 vs 2.4, respectively) and PTA tended to be higher (33.1 ± 9.1% vs 29.2 ± 9.9%) than non-survival group, but differences were not statistically significant. The mean daily dose of prednisone and the median duration of corticosteroids therapy were not significantly different between the survival and non-survival group. However, the median duration of symptoms before corticosteroids treatment in the survival group was 14 days, significantly shorter than 21 days in the non-survival group (P = 0.041), indicating that early initiation of corticosteroids therapy may be beneficial for the survival.

Improved liver functions in the survival group since the use of corticosteroids treatment in ACHBLF patients

Dynamic changes of liver functions including ALT level, TBIL, PTA, and MELD score in the survival and non-survival group since the use of the corticosteroids treatment were analyzed and showed in **Figure 2**. ALT levels fell in both groups during the course of treatment, while in non-survival group the mean level of ALT increased at the 21th day, indicating that there may be some inflammatory insults occurred in the non-survival group during the treatment period. In the survival group serum TBIL showed an improved tendency after the use of corticosteroids; at the 21th day the mean level of serum TBIL decreased to 244.4 ± 154.8 umol/L, compared with the baseline: 342.4 ± 121.8 umol/L, although at the 7-10th days there was a rebound, maybe due to the cessation of corticosteroids therapy. However, in the non-survival group patients didn't have their TBIL improved after the use of corticosteroids; the mean levels of serum TBIL at baseline, the 3rd, 7th, 10th, 14th, and 21th day were 441.3 ± 159.4, 442.8 ± 156.1, 488.0 ± 170.2, 564.6 ± 163.6, 570.7 ± 139.1, 533.2 ± 213.6 umol/L respectively. Similar tendency could also be seen in the dynamic changes of PTA and MELD scores. In the survival group, the mean level of

Table 2. Univariate and Multivariate Analysis to Predicate 3-month Mortality

Variable	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (per 10 years)	1.887	1.224-2.2909	0.004	2.839	1.373-5.872	0.005
Days of prednisone	0.962	0.912-1.015	0.154			
Daily prednisone dose	1.001	0.980-1.023	0.901			
Days before steroids ≤ 14 d	0.367	0.139-0.974	0.044			
Encephalopathy	0.743	0.221-2.492	0.630			
Presence of Ascites	1.680	0.648-4.358	0.286			
ALT (per 100 U/L)	0.935	0.866-1.010	0.090			
AST (per 100 U/L)	0.917	0.832-1.011	0.083			
PTA	0.957	0.909-1.008	0.095			
INR	1.786	0.936-3.406	0.078	2.454	1.102-5.947	0.047
TBIL (mg/dL)	1.091	1.022-1.166	0.009	1.166	1.063-1.278	0.001
Creatinine (mg/dL)	2.878	0.660-12.549	0.159			
MELD score	1.154	1.044-1.277	0.005			
Child-Pugh	1.235	0.760-2.005	0.394			
WBC	1.100	0.928-1.304	0.272			
Platelet	0.988	0.979-0.998	0.019			
Patients with EIBL	0.179	0.063-0.513	0.001	0.056	0.010-0.323	0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PTA, prothrombin activity; INR, international normalized ratio; TBIL, total bilirubin level; MELD, model for end-stage liver disease; WBC, white blood cell; EIBL, early improvement of bilirubin level.

PTA had dramatically improved during the treatment period, from 33.1 ± 9.1% at baseline to 60.3 ± 25.5% at the 21th day, as well as MELD scores: from 23.4 ± 4.8 at baseline to 16.5 ± 5.8 at the 21th day after the use of corticosteroids. However, in the non-survival group, the improvements of PTA and MELD score were not obvious, from 29.2 ± 9.9%, 27.6 ± 6.0 at baseline to 32.9 ± 12.6%, 31.2 ± 14.0 at the 21th day, respectively.

Early bilirubin response to corticosteroids treatment can predicate a better survival in ACHBLF patients

We hypothesized that biological improvement of liver functions at the 7th day after the use of corticosteroids (defined as TBIL, PTA, INR or MELD scores at the 7th day better than the first day of corticosteroids treatment) might be an efficacious predictor for survival status and might be used to predict the responders to corticosteroids. So we calculated these four variables including EIBL (early improvement of bilirubin level: TBIL at day 0 minus TBIL at day 7), EIINR (early improvement of INR: INR at day 0 minus INR at day 7), EIPTA (early improvement of PTA: PTA at day 7 minus PTA at day 0), and EIMS (early improvement of MELD score: MELD score at day 0 minus MELD score at day 7). After 7 days of treatment, the evolution of liver functions was available in 63 patients and was missing in 6 patients. We used AUROC to compare the accuracy of prediction of survival for these four indicators (**Figure 3**). EIBL had the highest AUROC: 0.769 compared with 0.732 for EIMS, 0.718 for EIPTA, and 0.715 for EIINR respectively, which suggested that early improvement of TBIL at the 7th day was an efficacious predictor for survival and could be used for identifying responders to corticosteroids in ACHBLF patients.

Factors associated with 3-month mortality in ACHBLF patients treated with corticosteroids

Logistic regression was performed to identify independent predictors of mortality in ACHBLF patients treated with corticosteroids. Clinical and biological baseline variables, as well as EIBL were included in univariate analysis. As shown in **Table 2**, 10 variables reached a *P* value ≤ 0.1 as predictive factors in univariate analysis: age (OR 1.887 per 10 years, p = 0.004), days before corticosteroids less than 14 (OR 0.367, p = 0.044), ALT (OR 0.935 per

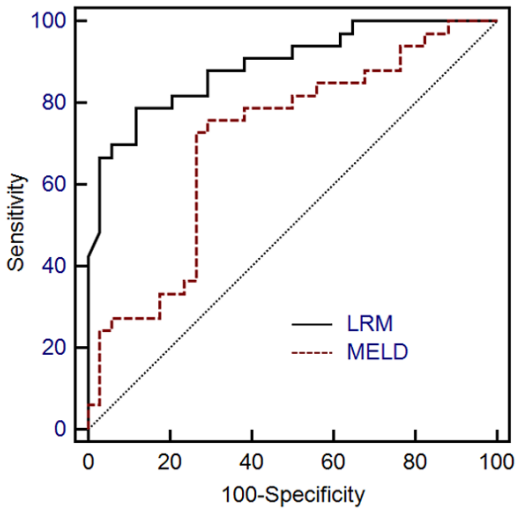

Figure 4. Receiver operating curve (ROC) analysis of conducted logistic regression model (LRM) and MELD score in predicting 3-month mortality in ACHBLF patients treated with corticosteroids. AUROC of LRM was significantly higher than MELD score (0.892, 95% CI 0.792-0.955 vs 0.708, 95% CI, 0.584-0.812, $P < 0.05$).

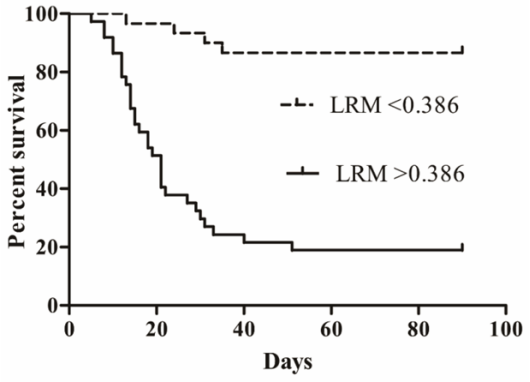

Figure 5. Survival curves at 3 months in ACHBLF patients treated with corticosteroids according to 0.386 cutoff of the conducted logistic regression model (LRM). Survival of patients with LRM < 0.386 was significantly higher than that of patients with LRM > 0.386 at 3 months (86.7 ± 6.2% vs 18.9 ± 6.4%, $P = 0.000$).

100 U/L, $P = 0.090$), AST (OR 0.917 per 100U/L, $P = 0.083$), PTA (OR 0.957, $P = 0.095$), INR (OR 1.786, $P = 0.078$), TBIL (OR 1.091 per mg/dL, $P = 0.009$), MELD scores (OR 1.154 per MELD point, $P = 0.005$), platelet (OR 0.988, $p = 0.019$), patients with EIBL (OR 0.179, $P = 0.001$). Because MELD score combined bilirubin and INR, AST level was collinear with ALT level, and PTA was collinear with INR, so MELD, AST, and PTA were excluded in multivariate analysis. In the final multivariate model, age (OR 2.839 per 10 years, 95% CI 1.373-5.872), INR (OR 2.454, 95% CI 1.102-5.947), TBIL (OR 1.166, 95% CI 1.063-1.278), patients with EIBL (OR 0.056, 95% CI 0.010-0.323) were significantly independent prognostic variables. Logistic regression model (LRM) was calculated as LRM = -7.257 + 1.043*age (per 10 years) + 0.153*TBIL (mg/dL) + 0.898*INR-2.882*(patients with EIBL). Patients with early improvement of bilirubin level was rated 1 and 0 if without. The P value of this regression model was less than 0.001 and the Hosmer-Lemeshow goodness-of-fit test was 0.924. The predicted probability was 0.806. With a cut-off value of 0.3860, LRM had an excellent sensitivity of 88.2% and specificity of 78.8%. The performance of the LRM model in predicting 3-month mortality was higher, with an AUROC of 0.892 (95% CI, 0.792-0.955), compared with MELD (AUROC 0.708, 95% CI, 0.584-0.812, $P < 0.05$) (**Figure 4**). Survival of patients with LRM < 0.386 was significantly higher than that of patients with LRM > 0.386 at 3 months (86.7 ± 6.2% vs 18.9 ± 6.4%, $P = 0.000$) (**Figure 5**).

Discussion

Corticosteroids have been used for the treatment of ACHBLF patients for a long period due to their immunosuppressive effects [6-11, 13, 14]. Some patients may be responsive to corticosteroids and have improved survival since the use of corticosteroids therapy while others may be resistant to corticosteroids therapy with a high risk of death. So it is important to find out some clinical indicators for the response to corticosteroids and generate a specific prognostic model in these patients. In ACHBLF patients treated with corticosteroids, we observed that patients with early improvement of total bilirubin level had significantly better survival than patients without any improvement of TBIL after the use of corticosteroids therapy. Multivariate logistic regression analyses indicated that before initial corticosteroids treatment, age, INR and serum TBIL were independent prognostic factors; after the initiation of corticosteroids therapy, early improvement of TBIL at the 7th day was an important predictive factor for 3-month mortality. Also we created a LRM model to predict 3-month mortality in ACHBLF patients treated

with corticosteroids and found that it had higher prediction accuracy than classical MELD scores in 3-month mortality.

ACHBLF is a severe life-threatening disease needed an early, reasonable prognostic model to accurately identify those patients with high mortality. Previous studies have explored several predictors for clinical prognosis of ACHBLF, such as age, INR, TBIL, creatinine, cirrhosis, hepatic encephalopathy, hepatorenal syndrome, et al, as well as several models including MELD scores, sequential organ failure assessment (SOFA), and so on [15-18]. However, none of these models considered the short-term influence of corticosteroids therapy on the management of ACHBLF. Since not all the ACHBLF patients will be well responsive to corticosteroids and have improved survival, it will be useful to integrate response indicators to corticosteroids therapy to predict clinical prognosis. We suggested that early improvement of serum total bilirubin level after 7 days of corticosteroids therapy is a practical and useful predictor for the response to corticosteroids and an important prognostic factor in predicting 3-month survival. The LRM integrated early improvement of TBIL at the 7th day has higher predictive accuracy for 3-month mortality than MELD scores. However, in this LRM model, we didn't validate hepatic encephalopathy and serum creatinine as independent prognostic predictors in ACHBLF patients, as investigated by other studies. For ACHBLF patients treated with corticosteroids, they should have no severe contraindications, including uncontrolled infection or evidence of sepsis, recent gastrointestinal bleeding and so on, which are all precipitating events for hepatic encephalopathy [19] and hepatorenal syndrome [20]. So the incidences of hepatic encephalopathy and hepatorenal syndrome enrolled in this study were much lower than other studies [16, 21]. Thus, this model was not designed to compete with other prognostic models of ACHBLF, but rather to predict poor survival in ACHBLF patients treated with corticosteroids.

Failure response to corticosteroids therapy is not confined to patients with ACHBLF. About 30% of steroid resistance rate has been reported in several inflammatory diseases needed to be treated with corticosteroids including asthma, rheumatoid arthritis, and glomerulonephritis. Steroid resistant can also be observed in 27-40% of severe alcoholic hepatitis patients with Maddrey's discriminant function (DF) $\geq$ 32 [22, 23]. An early change of bilirubin level at 7 days (ECBL) [22] or 25% fall in bilirubin level after 6-9 days of corticosteroid therapy [24] was proved to be an useful predictive factor for identifying responders to steroids and was the most important prognostic factor in predicting 6-month mortality in these patients. Moreover, a Lille Model composed of ECBL was created to identify nonresponders for corticosteroids and have higher prognostic prediction accuracy than Child, MELD scores, and Maddrey function for 6-month mortality in severe alcoholic hepatitis patients [23].

This observational study has clinical implications. ACHBLF patients failure to respond to corticosteroids can be early identified and can have their corticosteroids withdrawn to avoid further risks of complications, while patients who respond to corticosteroids indicate a favorable survival.

One major limitation of this study was that analyses were conducted retrospectively and the use of corticosteroids was neither randomized nor standardized. The dosage and duration of corticosteroids were at the discretion of the director of the department, which maybe bias the results. A prospective and random controlled clinical trial is ongoing in our clinical unit to further evaluate the effect of corticosteroids and investigate the most proper dosage and duration of corticosteroids for ACHBLF patients.

In conclusion, this study observed that early improvement of serum total bilirubin level at the 7th day after the start of corticosteroids is an efficacious indicator for response to corticosteroid therapy and can be use as a favorable prognostic predictor for 3-month mortality in ACHBLF patients treated with corticosteroids.

Acknowledgements

This study is supported by the Capital Health Research and Development of Special Funding Support (No. 2011-2018-09), Scientific Research Common Program of Beijing Municipal Commission of Education (No KM201310025024), and the National Key Subject Construction Project (No. WJWYA-2014-001).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qing-Hua Meng, Department of Critical Care Medicine of Liver Disease, Beijing You An Hospital, Capital Medical University, Beijing 100069, China. Tel: 86-010-83997160; Fax: 86-010-63296482; E-mail: meng_qh@126.com; Dr. Fu-Sheng Wang, Research Center for Biological Therapy, Beijing 302 Hospital, Beijing 100039, China. Tel: 86-010-63879735; Fax: 86-010-63879735; E-mail: fswang302@163.com

References

[1] Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, de Silva HJ, Hamid SS, Jalan R, Komolmit P, Lau GK, Liu Q, Madan K, Mohamed R, Ning Q, Rahman S, Rastogi A, Riordan SM, Sakhuja P, Samuel D, Shah S, Sharma BC, Sharma P, Takikawa Y, Thapa BR, Wai CT and Yuen MF. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hepatol Int 2009; 3: 269-282.

[2] Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V and Kamath PS. Acute-on chronic liver failure. J Hepatol 2012; 57: 1336-1348.

[3] You SL, Rong YH, Zhu B, Zhang AM, Zang H, Liu HL, Li DZ, Wan ZH and Xin SJ. Changing etiology of liver failure in 3,916 patients from northern China: a 10-year survey. Hepatol Int 2013; 7: 714-720.

[4] Seto WK, Lai CL and Yuen MF. Acute-on-chronic liver failure in chronic hepatitis B. J Gastroenterol Hepatol 2012; 27: 662-669.

[5] Wong VW and Chan HL. Severe acute exacerbation of chronic hepatitis B: a unique presentation of a common disease. J Gastroenterol Hepatol 2009; 24: 1179-1186.

[6] Fujiwara K, Yasui S, Okitsu K, Yonemitsu Y, Oda S and Yokosuka O. The requirement for a sufficient period of corticosteroid treatment in combination with nucleoside analogue for severe acute exacerbation of chronic hepatitis B. J Gastroenterol 2010; 45: 1255-1262.

[7] Fujiwara K, Yokosuka O, Kojima H, Kanda T, Saisho H, Hirasawa H and Suzuki H. Importance of adequate immunosuppressive therapy for the recovery of patients with "life-threatening" severe exacerbation of chronic hepatitis B. World J Gastroenterol 2005; 11: 1109-1114.

[8] Fujiwara K, Yasui S, Yonemitsu Y, Fukai K, Arai M, Imazeki F, Suzuki A, Suzuki H, Sadahiro T, Oda S and Yokosuka O. Efficacy of combination therapy of antiviral and immunosuppressive drugs for the treatment of severe acute exacerbation of chronic hepatitis B. J Gastroenterol 2008; 43: 711-719.

[9] Matsumoto K. A combination treatment of entecavir and early-phase corticosteroid in severe exacerbation of chronic hepatitis B. World J Gastroenterol 2009; 15: 1650.

[10] Zhang XQ, Jiang L, You JP, Liu YY, Peng J, Zhang HY, Xu BY and Mao Q. Efficacy of short-term dexamethasone therapy in acute-on-chronic pre-liver failure. Hepatol Res 2011; 41: 46-53.

[11] Zhao J, Zhang JY, Yu HW, He YL, Zhao JJ, Li J, Zhu YK, Yao QW, Wang JH, Liu HX, Shi SY, Zou ZS, Xu XS, Zhou CB, Wang FS and Meng QH. Improved survival ratios correlate with myeloid dendritic cell restoration in acute-on-chronic liver failure patients receiving methylprednisolone therapy. Cell Mol Immunol 2012; 9: 417-422.

[12] Liver F, Artificial Liver Group, Severe Liver D and Artificial Liver Group. Diagnostic and treatment guidelines for liver failure (2012 version). Zhonghua Gan Zang Bing Za Zhi 2013; 21: 177-183.

[13] He B, Zhang Y, Lu MH, Cao YL, Fan YH, Deng JQ and Yang SM. Glucocorticoids can increase the survival rate of patients with severe viral hepatitis B: a meta-analysis. Eur J Gastroenterol Hepatol 2013; 25: 926-934.

[14] Chen JF, Wang KW, Zhang SQ, Lei ZY, Xie JQ, Zhu JY, Weng WZ, Gao ZL and Lin BL. Dexamethasone in outcome of patients with hepatitis B virus-related acute-on-chronic liver failure. J Gastroenterol Hepatol 2014; 29: 800-806.

[15] Yan H, Wu W, Yang Y, Wu Y, Yang Q and Shi Y. A novel integrated Model for End-Stage Liver Disease model predicts short-term prognosis of hepatitis B virus-related acute-on-chronic liver failure patients. Hepatol Res 2014; 45: 405-414.

[16] Sun QF, Ding JG, Xu DZ, Chen YP, Hong L, Ye ZY, Zheng MH, Fu RQ, Wu JG, Du QW, Chen W, Wang XF and Sheng JF. Prediction of the prognosis of patients with acute-on-chronic hepatitis B liver failure using the model for end-stage liver disease scoring system and a novel logistic regression model. J Viral Hepat 2009; 16: 464-470.

[17] Zheng MH, Shi KQ, Fan YC, Li H, Ye C, Chen QQ and Chen YP. A model to determine 3-month mortality risk in patients with acute-on-chronic hepatitis B liver failure. Clin Gastroenterol Hepatol 2011; 9: 351-356.

[18] Zheng MH, Shi KQ, Lin XF, Xiao DD, Chen LL, Liu WY, Fan YC and Chen YP. A model to predict 3-month mortality risk of acute-on-chronic hepatitis B liver failure using artificial neural network. J Viral Hepat 2013; 20: 248-255.

[19] Merli M, Lucidi C, Pentassuglio I, Giannelli V, Giusto M, Di Gregorio V, Pasquale C, Nardelli S, Lattanzi B, Venditti M and Riggio O. Increased risk of cognitive impairment in cirrhotic patients with bacterial infections. J Hepatol 2013; 59: 243-250.

[20] Zhang DQ, Chen L, Gan QR, Lin QF and Pan C. Risk factors of hepatorenal syndrome in patients with acute on chronic liver failure. Zhonghua Gan Zang Bing Za Zhi 2013; 21: 743-746.

[21] Huang K, Hu JH, Wang HF, He WP, Chen J, Duan XZ, Zhang AM and Liu XY. Survival and prognostic factors in hepatitis B virus-related acute-on-chronic liver failure. World J Gastroenterol 2011; 17: 3448-3452.

[22] Mathurin P, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, Serfaty L, Valla D, Poupon R, Chaput JC and Naveau S. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatology 2003; 38: 1363-1369.

[23] Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, Texier F, Hollebecque A, Serfaty L, Boleslawski E, Deltenre P, Canva V, Pruvot FR and Mathurin P. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007; 45: 1348-1354.

[24] Morris JM and Forrest EH. Bilirubin response to corticosteroids in severe alcoholic hepatitis. Eur J Gastroenterol Hepatol 2005; 17: 759-762.