Plasma exchange-centered artificial liver support system in hepatitis B virus-related acute-on-chronic liver failure: a nationwide prospective multicenter study in China

Jia-Jia Chen, Jian-Rong Huang, Qian Yang, Xiao-Wei Xu, Xiao-Li Liu, Shao-Rui Hao, Hui-Fen Wang, Tao Han, Jing Zhang, Jian-He Gan, Zhi-Liang Gao, Yu-Ming Wang, Shu-Mei Lin, Qing Xie, Chen Pan and Lan-Juan Li

Hangzhou, China

BACKGROUND: Plasma exchange (PE)-centered artificial liver support system reduced the high mortality rate of hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF). But the data were diverse in different medical centers. The present prospective nationwide study was to evaluate the effects of PE on patients with HBV-ACLF at different stages.

METHODS: From December 2009 to December 2011, we evaluated 250 patients at different stages of HBV-ACLF from 10 major medical centers in China. All the laboratory parameters were collected at admission, before and after PE.

RESULTS: Among the 250 patients who underwent 661 rounds of PE, one-month survival rate was 61.6%; 141 (56.4%) showed improvement after PE. Variables such as age (*P*=0.000), levels of total bilirubin (TB, *P*=0.000), direct bilirubin (*P*=0.000), total triglycerides (*P*=0.000), low-density lipoprotein (*P*=0.022), Na^+ (*P*=0.014), Cl^- (*P*=0.038), creatinine (Cr, *P*=0.007), fibrinogen (*P*=0.000), prothrombin time (PT, *P*=0.000), white blood cell (*P*=0.000), platelet (*P*=0.003) and MELD (*P*=0.000) were significantly related to prognosis. Multivariate logistic regression analysis showed that age, disease stage, TB, Cr and PT levels were independent risk factors of mortality among HBV-ACLF patients.

CONCLUSIONS: PE can improve the clinical outcome of patients with HBV-ACLF. Levels of TB, Cr and PT, age and disease stage help to predict prognosis.

(*Hepatobiliary Pancreat Dis Int 2016;15:275-281*)

KEY WORDS: liver failure; artificial liver support; plasma exchange; acute-on-chronic liver failure

Author Affiliations: State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, and Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China (Chen JJ, Huang JR, Yang Q, Xu XW, Liu XL, Hao SR and Li LJ); Liver Failure Therapy and Research Center, 302 Hospital of People's Liberation Army, Beijing 100039, China (Wang HF); Department of Hepatology, Third Central Clinical College of Tianjin Medical University, Tianjin 300170, China (Han T); Artificial Liver Center, You'an Hospital, Capital Medical University, Beijing 100069, China (Zhang J); Department of Infectious Diseases, First Affiliated Hospital of Suzhou University, Suzhou 215006, China (Gan JH); Department of Infectious Diseases, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510630, China (Gao ZL); Institute of Infectious Diseases, Southwest Hospital, Third Military Medical University, Chongqing 400038, China (Wang YM); Department of Infectious Diseases, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China (Lin SM); Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China (Xie Q); Department of Infectious Diseases, Infectious Diseases Hospital Affiliated to Fujian Medical University, Fuzhou 350025, China (Pan C)

Corresponding Author: Lan-Juan Li, MD, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, and Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China (Tel/Fax: +86-571-87236755; Email: ljli@zju.edu.cn)

doi: 10.1016/S1499-3872(16)60084-X
Published online March 29, 2016.

Introduction

Hepatitis B virus (HBV) has a high prevalence rate worldwide; an estimated more than two billion people were infected and approximately 400 million individuals had chronic HBV infection. In China, acute exacerbation of chronic HBV is the most

common cause of acute-on-chronic liver failure (ACLF); the main etiologies in Western countries are drugs, alcohol, and hepatitis C.[1] Although the liver is scarred and distorted in compensated stage, it still performs many important functions such as synthesis, detoxification, excretion, biotransformation, etc. When insulted, the hepatocytes show necrosis underlying the original pathologic damage and that liver failure occurs. Patients with liver failure manifest as coagulopathy, jaundice, hepatic encephalopathy (HE), and ascites. Despite recent progress in antiviral therapy, liver failure remains a therapeutic challenge with a high mortality rate.[2, 3] Liver transplantation, the only effective treatment, is hampered by the shortage of organs[4, 5] and the high frequency of concomitant conditions that contraindicate the procedure. Artificial liver support system (ALSS), which originated from concept of hepatocyte regeneration, is an effective alternative treatment for liver failure. ALSS temporarily eliminates toxic substances and replaces the failed liver with an environment for the regeneration of hepatocytes or an environment that enables the patients to wait for liver transplantation.[6]

Many types of extracorporeal blood purification systems, including plasma exchange (PE), continuous hemodiafiltration, and molecular adsorbent recirculating system (MARS), have been used in the treatment of liver failure.[7-9] In China, PE has been used as the main technique in patients suffering from liver failure for approximately 20 years.[10] In liver failure, a wide range of potentially toxic substances, including bilirubin, bile acid, short chain fatty acids, aromatic amino acids, cytokines, and ammonia, accumulate in the systemic circulation and are involved in multi-organ complications. Most of these toxins are bound to protein, especially to albumin (ALB).[11, 12] The most direct method to remove toxic substances is PE, where the toxic plasma is replaced with fresh normal plasma. PE also removes stimulatory factors released because of liver injury that are responsible for the increase of complications. Many studies have shown that PE reduces mortality,[1, 13] and recently the open, prospective, randomized, controlled study carried out by Larsen et al found that exchange of plasma in acute liver failure (ALF) patients with fresh frozen plasma increases transplant-free survival after 3 months.[14] However, no multicenter study in China with a large sample size has been carried out. The present prospective multicenter study was to evaluate the effect of PE on patients with HBV-ACLF.

Methods

Ethics statement

The research protocol was approved by the Human Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine, and all enrolled participants signed a written informed consent to participate in the study. Data were entered in duplicate a computerized database and analyzed anonymously.

Patients

Data of all the patients were recorded using case report forms, and medical monitors with source documentation were used for verifying the accuracy of the data collected. Consecutive patients diagnosed with HBV-ACLF were included. Eligible patients were from 10 hospitals from December 1, 2009 to December 31, 2011. The follow-up period for enrolled patients was one month after diagnosis of ACLF. All patients received antiviral treatment and complication treatment in the intensive care unit (ICU). Other conventional treatments included energy supplements, electrolyte maintenance and acid base equilibrium.

Inclusion and exclusion criteria

HBV-ACLF was diagnosed according to the Guidelines for Diagnosis and Treatment of Liver Failure in China (2006).[15] The inclusion criteria are: (1) age ranging from 18 to 65 years; (2) acute deterioration of preexisting chronic hepatitis B; (3) extreme fatigue with severe digestive symptoms such as obvious anorexia, abdominal distension, or nausea and vomiting; (4) progressively worsening jaundice within a short period of time [serum total bilirubin (TB) level ≥171 μmol/L or a daily elevation of ≥17.1 μmol/L]; (5) an obvious hemorrhagic tendency with prothrombin activity (PTA) ≤40%.

The exclusion criteria are: co-existed hepatitis with other causes, alcohol abuse, uncontrolled diabetes and heart diseases, malignancy and previous liver transplantation.

Definition and staging of ACLF

According to the Guidelines for Diagnosis and Treatment of Liver Failure in China (2006),[15] ACLF can be classified into early, middle, and end stages based on the severity of clinical manifestations. Early stage is defined as a progressively deepening jaundice (TB level ≥171 μmol/L or a daily increase of ≥17.1 μmol/L), PTA >30% but ≤40%, and no HE or other complications. Middle-stage disease represents progression of the symptoms of the early stage, including one of the following symptoms: grades I/II HE, ascites, or a PTA of >20% but ≤30%. In the end-stage disease, the condition deteriorates further with a PTA of ≤20% and includes one of the following symptoms: hepatic-renal syndrome, severe upper gastrointestinal bleeding, serious infection, and grades III/IV HE.

Unified PE treatment

Circulatory access was established through a double lumen catheter via the patient's femoral vein. The total exchanged plasma volume was 2500-3500 mL, and the PE rate was 20-25 mL/min. Fresh-frozen plasma (FFP) was supplied by the Blood Center. Dexamethasone (5 mg) and heparin (2500 U) were injected routinely before PE. Heparin was neutralized at the end of PE by an injection of 20-50 mg protamine sulfate. PE was repeated every 2-4 days. The criteria for discontinuing PE were as follows: (1) the overall improvement in the patient's status and TB level <200 μmol/L or (2) conditions such as bleeding and circulatory abnormalities that did not allow PE implementation.

Data collection

All the laboratory data were collected at hospital admission, before and after PE. Data included patient demographics, stage of liver failure, number of rounds of PE, and laboratory parameters, including HBV DNA viral load, levels of total protein (TP), ALB, TB, direct bilirubin (DB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), potassium (K^+), sodium (Na^+), chlorine (Cl^-), glucose (Glu), fibrinogen (Fib), prothrombin time (PT), PTA, creatinine (Cr), hemoglobin (Hb), red blood cell count (RBC), white blood cell count (WBC), and platelet count (PLT).

PTA was calculated according to the formula:[16] R=(11.5×0.4)/(PT-11.5×0.6). Model for End-stage Liver Disease (MELD) scores were calculated according to the Malinchoc formula[16]: R=9.57×ln (Cr [mg/dL])+3.78× ln (bilirubin [mg/dL])+11.2×ln (INR)+6.43×1.

Therapeutic efficacy evaluation

Improvement at the end of study was defined according to guidelines for the non-bioartificial liver support system in the treatment of liver failure[17] that included a reduction in TB levels to <5 times of the normal level (85.5 μmol/L) and PTA >40%.

The patient's condition was considered to have deteriorated at the end of the study if the TB level was equal or higher than that at admission, or no improvement in PTA was observed or the patient was dead.

Statistical analysis

Continuous variables were compared using the Mann-Whitney *U* test, and categorical data were compared using the Chi-square test. Groups were compared using one-way ANOVA. *P* values <0.05 were considered statistically significant. Logistic regression was performed to identify risk factors associated with survival rate in patients with ACLF. Variables which had significant difference were included in the multivariate analysis. A software program (SPSS16.0) was used for the statistical analysis.

Results

A total of 630 patients received artificial liver support treatment, among which we identified 250 patients qualified for further analysis, including 221 males and 29 females. There was no difference in the distribution of age and gender among three stages. The selected patients underwent 661 rounds of PE: 52 patients were in the early stage and underwent 126 rounds of PE; 99 in the middle stage underwent 254 rounds of PE; and 99 in the end stage underwent 281 rounds of PE. Patients with end-stage disease had a significantly worse prognosis with PE treatment than those in the middle and early stages ($P<0.01$).

There was no difference in the serum concentrations of TP, DB, TB, ALP, TC, LDL, HDL, Cr, electrolyte, Glu and in blood cell counts at the baseline among the patients in different stages. The HBV-DNA viral load at the baseline showed significant difference among the patients in different stages ($P=0.003$). ALB levels were higher in the early stage than those in the middle ($P=0.009$) and end stages ($P=0.002$). However, there was no significant difference in ALB concentration between the patients in the middle and end stages. ALT levels were higher in the patients in the end-stage than those in the early stage ($P=0.021$), but there was no significant difference between the patients in early and middle stages or between end and middle stages. AST levels were higher in the patients in the end stage than those in the early ($P=0.02$) and middle ($P=0.012$) stages, but there was no significant difference between early and middle stages. TG levels were lower in patients in the end-stage disease than those in early ($P=0.003$) and middle ($P=0.002$) stages. However, there were no significant differences in TG level between the patients in middle and early stage diseases. MELD scores increased significantly with the severity of the ACLF stage ($P=0.000$) while the concentration of Fib decreased ($P=0.012$).

Therapeutic effect of PE

Forty-two of the 52 (80.8%) patients in the early stage, seventy-five of the 99 (75.8%) patients in the middle stage and thirty-seven of the 99 (37.4%) patients in the end stage survived for one month after diagnosis. The overall one-month survival rate was 61.6%. The improvement rates of the early, middle and end stages were 75.0% (39/52), 69.7% (69/99), 33.3% (33/99), respec-

tively. The overall improvement rate was 56.4% (141/250). The levels of ALT, AST, TB and DB were reduced after PE therapy in the early-stage patients, and these parameters as well as the levels of TP, ALB and ALP were significantly reduced after PE in the middle stage patients. Patients with end-stage disease showed significant differences be-

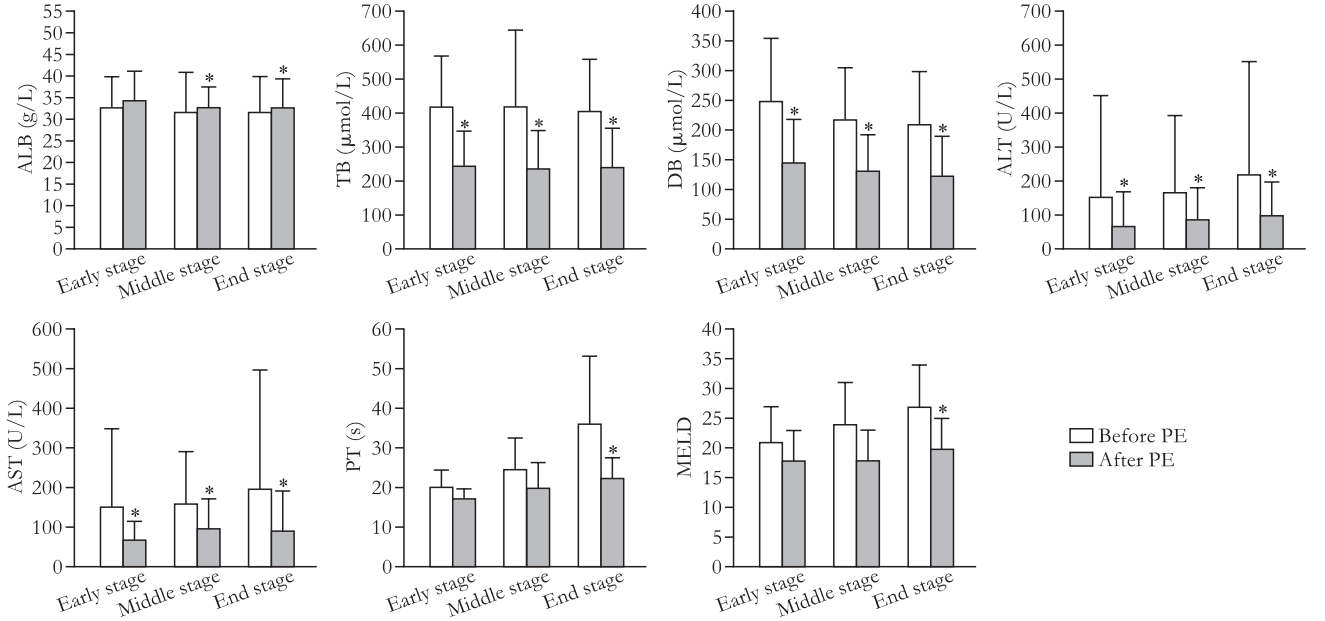

Fig. Some laboratory parameters are statistically significant between before and after PE according to the stage of HBV-ACLF. *: $P<0.05$, compared with before PE.

Table 1. Laboratory parameters before and after PE according to the stage of HBV-ACLF (n=661)

Parameters	Early stage (n=126)			Middle stage (n=254)			End stage (n=281)		
	Before PE	After PE	P value	Before PE	After PE	P value	Before PE	After PE	P value
TP (g/L)	59.9±7.0	59.2±5.6	0.078	62.4±7.7	60.5±6.1	**0.027**	61.8±7.4	59.8±9.2	0.532
ALB (g/L)	32.8±5.4	34.3±6.3	0.427	31.8±7.3	32.8±3.6	**0.028**	31.6±5.4	32.7±4.0	**0.000**
TB (μmol/L)	420.2±148.9	244.0±103.4	**0.002**	418.7±226.0	237.7±110.0	**0.000**	407.9±151.3	241.6±115.1	**0.000**
DB (μmol/L)	249.5±104.6	146.8±71.6	**0.024**	218.7±87.1	132.9±60.5	**0.000**	210.9±87.9	123.8±66.3	**0.000**
ALT (U/L)	166.2±314.1	73.4±74.1	**0.000**	178.9±243.5	94.4±138.8	**0.000**	235.1±351.1	107.5±148.5	**0.000**
AST (U/L)	152.5±194.9	69.3±44.0	**0.000**	159.9±130.9	97.3±74.1	**0.000**	196.0±300.0	91.2±99.5	**0.000**
ALP (U/L)	131.0±41.3	117.4±109.8	0.742	132.1±43.1	110.4±29.6	**0.000**	125.3±41.4	101.7±27.0	**0.000**
TG (mmol/L)	1.3±0.7	1.3±0.6	0.862	1.3±0.6	1.4±1.4	0.184	1.0±0.8	0.8±0.6	0.092
TC (mmol/L)	3.1±1.3	7.8±5.5	0.172	3.4±3.0	4.3±1.4	0.252	3.0±1.2	4.1±1.3	0.999
LDL (mmol/L)	1.6±0.8	2.3±0.9	0.849	1.7±0.8	2.4±0.9	0.841	1.4±0.7	2.1±0.7	0.29
HDL (mmol/L)	0.7±0.5	1.0±0.6	0.796	0.8±0.5	1.1±0.5	0.454	0.7±0.4	1.0±0.4	0.147
Cr (μmol/L)	78.3±55.7	80.3±52.3	0.886	75.0±36.8	71.9±30.1	0.081	73.0±31.0	72.0±23.3	**0.02**
K^+ (mmol/L)	4.1±0.6	4.1±0.5	0.372	4.0±0.7	4.0±0.9	0.836	4.1±0.6	4.0±0.7	0.181
Na^+ (mmol/L)	132.5±12.6	136.0±4.4	0.207	132.4±9.5	134.0±4.5	0.204	132.8±4.4	134.0±4.9	0.441
Cl^- (mmol/L)	97.0±8.4	97.6±5.9	0.843	96.7±7.9	96.5±5.4	0.748	98.7±5.6	98.4±6.0	0.54
Glu (mmol/L)	7.1±3.6	8.3±3.1	0.928	7.1±2.9	8.3±2.9	0.484	7.0±3.0	8.9±5.2	**0.024**
Hb (g/L)	114.8±22.3	101.5±20.9	0.645	113.9±20.2	102.5±20.9	0.417	116.0±19.2	102.4±18.5	0.603
RBC ($\times10^{12}$/L)	3.6±0.7	3.2±0.7	0.982	3.7±0.7	3.5±1.5	0.278	3.7±0.6	3.4±1.9	0.103
WBC ($\times10^9$/L)	8.9±4.4	7.7±4.2	0.877	7.5±3.7	6.7±3.6	0.268	8.4±4.0	7.3±4.0	0.392
PLT ($\times10^9$/L)	109.5±53.5	100.6±49.6	0.421	115.3±65.5	107.3±63.9	0.603	95.0±48.4	95.3±41.5	0.084
PT (s)	20.3±4.0	17.2±2.4	0.678	24.7±7.8	19.9±6.4	0.218	36.0±17.1	22.4±5.0	**0.000**
Fib (mg/L)	2.7±3.7	2.8±1.2	0.221	2.6±2.1	2.9±1.1	0.227	1.7±0.9	2.2±0.9	0.974
MELD	21±6	18±5	0.581	24±7	18±5	0.063	27±7	20±5	**0.002**

TP: total protein; ALB: albumin; TB: total bilirubin; DB: direct bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; TG: total triglyceride; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; Cr: creatinine; K^+: potassium; Na^+: sodium; Cl^-: chlorine; Glu: glucose; Hb: hemoglobin; RBC: red blood cell; WBC: white blood cell; PLT: platelet count; PT: prothrombin time; Fib: fibrinogen; MELD: Model for End-stage Liver Disease.

Table 2. Multivariate logistic regression analysis of independent risk factors for the one-month survival rate of patients with HBV-ACLF associated with PE

Parameters at admission	Consideration of stage			Without consideration of stage		
	β	HR (95% CI)	*P* value	β	HR (95% CI)	*P* value
Stage	1.079	2.940 (1.955-4.423)	0.000			
PT				0.092	1.096 (1.057-1.137)	0.000
Age	0.042	1.043 (1.016-1.071)	0.002			
TB	0.002	1.002 (1.001-1.004)	0.012	0.002	1.002 (1.000-1.004)	0.013
Cr	0.010	1.010 (1.001-1.018)	0.021	0.012	1.012 (1.057-1.137)	0.004

β: partial regression coefficient; HR: hazard ratio; CI: confidence interval; PT: prothrombin; TB: total bilirubin; Cr: creatinine.

tween the levels of ALB, TB, DB, ALT, AST, ALP, Glu, PT, and MELD scores before and after PE. Electrolyte, blood adipoprotein, and serum Cr levels remained the same after PE in the early- and middle-stages patients. PT and Cr levels were reduced after PE in the end-stage patients. Routine blood tests showed no difference in WBC or PLT count before and after PE at each stage (Table 1 and Fig.).

Factors affecting prognosis of HBV-ACLF patients with PE

The Mann-Whitney *U* test of admission parameters showed that age (*P*=0.000), TB (*P*=0.000), DB (*P*=0.000), TG (*P*=0.000), LDL (*P*=0.022), Na^+ (*P*=0.014), Cl^- (*P*=0.038), Cr (*P*=0.007), Fib (*P*=0.000), PT (*P*=0.000), WBC (*P*=0.000), PLT (*P*=0.003) and MELD score (*P*=0.000) had a significant relationship with prognosis. There was no difference of HBV-DNA viral load between improvement and deterioration groups (*P*=0.087). Logistical regression results showed that the decreases of TB (*P*=0.013), Cr levels (*P*=0.004), and PT (*P*=0.000) after PE were significant prognostic factors for improvement of patients with HBV-ACLF. Longer PT and higher TB levels indicated a significantly worse prognosis. When disease stage was taken into consideration, logical regression analysis identified stage (*P*=0.000), age (*P*=0.002), TB levels (*P*=0.012), and Cr levels (*P*=0.021) as independent prognostic factors (Table 2).

Discussion

In 2006, the study group of liver failure and artificial liver of the Society of Infectious Diseases, Chinese Medical Association published the Guidelines for Diagnosis and Treatment of Liver Failure in China.[15] ACLF was defined as a syndrome with acute or sub-acute deterioration of liver function underlying chronic liver disease including cirrhosis. It included the clinical manifestation of liver function deterioration with deepening jaundice and hemorrhagic tendency.[15] The median mortality rate associated with ACLF was high and ranged from 50% to 90%.[18] In part of patients, the traditional comprehensive internal medical treatment remains ineffective.[5] Liver transplantation is the only effective approach in these patients.[19] However, the shortage of donor liver, the complications of immune rejection after transplantation, and the high cost of treatment restrict the clinical application of liver transplantation. PE, which is an extracorporeal procedure for plasma separation and replacement of equivalent amounts of substitute fluids, is an attractive approach for the treatment of ACLF, especially in China. Patients with ACLF treated with PE can avoid liver transplantation and experience a lower mortality rate. The study of Larsen et al[14] also showed that in the patients who fulfilled criteria of ALF with poor prognosis but were not listed for transplantation because of contraindications, the survival rate demonstrated a significant increase after PE. In addition, PE combined with liver transplantation can increase the survival rate of patients with end-stage ACLF.[19]

PE involves the separation of plasma from blood and replacement with FFP. The common pore size of a plasma separator is 0.2-0.6 μm. This pore size allows passage of all plasma constituents, including electrolytes, ALB, Fib, and immunoglobulins.[20] In our study, PE helped to reduce serum bilirubin and liver enzyme levels at the different stages of the disease, but did not influence serum lipid and electrolyte levels. Renal dysfunction was also corrected in patients with end-stage ACLF. PE treatment also improved serum blood Glu and ALB levels, which function as carrier proteins and aid in maintaining biological metabolism, stabling hemodynamics, and providing energy supply. Studies on ACLF have shown that the mortality rate declined after PE treatment.[3, 6] Therefore, we found significant differences in one-month survival rates depending on the stage of the disease. In Chinese guideline of ACLF, more advanced and severe liver injury and organ dysfunction predict worse prognosis. Although there was controversy over the definition of ACLF between the European and Chinese version,[21] the predictive factors of prognosis are similar between the Chinese and European guidelines. Our study showed that

timely artificial liver treatment increased the one-month survival rate to 77.4% (117/151) in patients with early and middle stages HBV-ACLF. What's more, in patients with the end-stage disease and multiple complications such as HE, hepatic-renal syndrome, spontaneous bacterial peritonitis, electrolyte disorders and pulmonary infection, PE could eliminate toxic substances and provide blood components essential for life. However, PE could not effectively correct electrolyte and acid-base imbalance and disorder. As a result, PE can be used for only one-third of the patients with end-stage ACLF, and most of these patients require liver transplantation to prevent irreversible multiple organ function failure. In these cases, PE can only be a temporary life support which enables patients to transit successfully to liver transplantation. Following the principles of individualized treatment, we should consider the specific circumstances of each patient when choosing the most appropriate therapy. Combination with other types of artificial liver technology such as continuous hemodiafiltration and plasma perfusion can further improve treatment efficacy.[22]

Although PE can improve the prognosis, it should not be hesitated to consult the liver transplantation team. Furthermore, each round of PE requires a large volume of FFP, the lack of sufficient FFP will restrict treatment. A reasonable method of distributing plasma and adjusting the overall treatment will be required for improving prognosis and survival rates in patients with HBV-ACLF. Moreover, we performed statistical analysis for obtaining predictors of efficacy with artificial liver treatment alone. Results indicated that levels of PT, TB, and Cr at admission are independent prognostic factors, which are consistent with those reported in the literature.[23-25] In China, ACLF are divided into three stages according to the number and severity of complications and PTA. The advanced stages are associated with the worst coagulation profile and most severe complications. Logistic regression analysis of stage vs prognosis also showed that stage of disease is an independent predictive factor, and that prognosis is related to the function of liver and other organs. The later stage of ACLF has much higher mortality and requires earlier liver transplantation. Therefore, complications of patients at admission to hospital, such as infection and HE, may contribute to a poor prognosis[26] and thus be related to mortality.

Our study has several limitations. First, we analyzed the one-month survival rate in patients with HBV-ACLF who underwent PE, but we did not design a cohort or randomized study to compare mortality between patients with and without PE. Second, although we included concept of disease stage into the logistic regression analysis as an indicator of ACLF prognosis, complications that have a greater influence on mortality in liver failure require further detailed classification and analysis. Third, other potential side effects of PE, such as venous thrombosis by cathedral incubation or bleeding, were not investigated. To strengthen the overall homogeneity of the study, further randomized controlled trials and multicenter training standards will be required to validate the data of the present study.

In conclusion, PE may improve the clinical outcome of patients with HBV-ACLF, especially in early stage. The levels of TB, PT and Cr are independent prognostic factors of PE treatment for patients with HBV-ACLF. Furthermore, the stage of ACLF *per se* is an independent factor for prognosis. Timely transferring patients to liver transplantation unit may further improve the prognosis for those with more advanced stage of ACLF.

Acknowledgments: We would like to thank the following centers for support of this research: 302 Hospital of People's Liberation Army; Beijing You'an Hospital, Capital Medical University; Southwest Hospital, Third Military Medical University; Third Affiliated Hospital of Sun Yat-Sen University; Ruijin Hospital, Shanghai Jiaotong University School of Medicine; First Affiliated Hospital of Xi'an Jiaotong University; First Affiliated Hospital of Suzhou University; Third Central Clinical College of Tianjin Medical University, and Infectious Diseases Hospital Affiliated to Fujian Medical University.

Contributors: LLJ proposed the study. CJJ and LLJ wrote the first draft. CJJ collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. LLJ is the guarantor.

Funding: This work was supported by grants from the National Science and Technology Major Project (2012ZX10002004), Scientific Research Fund of Zhejiang Provincial Education Department (Y201328037) and the opening foundation of the State Key Laboratory for Diagnosis and Treatment of Infectious Diseases and Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, First Affiliated Hospital, Zhejiang University School of Medicine (2015KF04).

Ethical approval: The research protocol was approved by the Human Ethics Committee of First Affiliated Hospital, Zhejiang University School of Medicine.

Competing interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1 Bektas M, Idilman R, Soykan I, Soydan E, Arat M, Cinar K, et al. Adjuvant therapeutic plasma exchange in liver failure: assessments of clinical and laboratory parameters. J Clin Gastroenterol 2008;42:517-521.

2 Chen LB, Cao H, Zhang YF, Shu X, Chen N, Zhang K, et al. Efficacy of antiviral treatment on patients with acute-on-chronic hepatitis B liver failure with low viral load. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 2010;24:364-366.

3 Qian Y, Lanjuan L, Jianrong H, Jun L, Hongcui C, Suzhen F, et

al. Study of severe hepatitis treated with a hybrid artificial liver support system. Int J Artif Organs 2003;26:507-513.
4 Basto ST, Villela-Nogueira CA, Tura BR, Coelho HS, Ribeiro J, Fernandes ES, et al. Risk factors for long-term mortality in a large cohort of patients wait-listed for liver transplantation in Brazil. Liver Transpl 2011;17:1013-1020.
5 Wu YM, Ho MC, Hu RH, Ko WJ, Yang PM, Lai MY, et al. Liver transplantation for acute hepatic failure. Transplant Proc 2004;36:2226-2227.
6 Ichida T. Artificial liver support system for fulminant hepatic failure as bridge-use to living donor liver transplantation. Intern Med 2003;42:920-921.
7 Wang MM, Chen SJ, Ye QF, Yang YJ, Chen SB, Zhou XM, et al. Liver support therapy with molecular adsorbents recirculating system in liver failure: a summary of 252 cases from 14 centers in China. Chin Med J (Engl) 2008;121:2197-2201.
8 Nakae H, Igarashi T, Tajimi K. Selective plasma exchange with dialysis in patients with acute liver failure. Ther Apher Dial 2012;16:467-471.
9 Sugawara K, Nakayama N, Mochida S. Acute liver failure in Japan: definition, classification, and prediction of the outcome. J Gastroenterol 2012;47:849-861.
10 Li LJ. State of the art: the diagnosis and treatment of liver failure. Zhonghua Gan Zang Bing Za Zhi 2010;18:801-802.
11 Falkenhagen D, Strobl W, Vogt G, Schrefl A, Linsberger I, Gerner FJ, et al. Fractionated plasma separation and adsorption system: a novel system for blood purification to remove albumin bound substances. Artif Organs 1999;23:81-86.
12 Hughes RD. Review of methods to remove protein-bound substances in liver failure. Int J Artif Organs 2002;25:911-917.
13 Mazzoni A, Pardi C, Bortoli M, Uncini Manganelli C, Vanacore R, Urciuoli P, et al. High-volume plasma exchange: an effective tool in acute liver failure treatment. Int J Artif Organs 2002;25:814-815.
14 Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol 2016;64:69-78.
15 Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association; Severe Liver Diseases and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. Diagnostic and treatment guidelines for liver failure. Zhonghua Gan Zang Bing Za Zhi 2006;14:643-646.
16 Feng R. Shi Yong Yi Xue Jian Yan Xue. Shanghai science and Technology Press; 1996.
17 Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association. Guideline for non-bioartificial liver support system in the treatment of liver failure. Chin J Clin Infect Dis 2009;2:321-325.
18 Jalan R, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif 2002;20:252-261.
19 Xu X, Liu X, Ling Q, Wei Q, Liu Z, Xu X, et al. Artificial liver support system combined with liver transplantation in the treatment of patients with acute-on-chronic liver failure. PLoS One 2013;8:e58738.
20 Borra M, Galavotti D, Bellini C, Fumi L, Morsiani E, Bellini G. Advanced technology for extracorporeal liver support system devices. Int J Artif Organs 2002;25:939-949.
21 Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243-252.
22 Yonekawa C, Nakae H, Tajimi K, Asanuma Y. Effectiveness of combining plasma exchange and continuous hemodiafiltration in patients with postoperative liver failure. Artif Organs 2005;29:324-328.
23 Mao W, Ye B, Lin S, Fu Y, Chen Y, Chen Y. Prediction value of model for end-stage liver disease scoring system on prognosis in the acute on chronic liver failure patients with plasma exchange treatment. ASAIO J 2010;56:475-478.
24 Mori N, Suzuki F, Kawamura Y, Sezaki H, Hosaka T, Akuta N, et al. Determinants of the clinical outcome of patients with severe acute exacerbation of chronic hepatitis B virus infection. J Gastroenterol 2012;47:1022-1029.
25 Yu JW, Wang GQ, Li SC. Prediction of the prognosis in patients with acute-on-chronic hepatitis using the MELD scoring system. J Gastroenterol Hepatol 2006;21:1519-1524.
26 Huang K, Hu JH, Wang HF, He WP, Chen J, Duan XZ, et al. Survival and prognostic factors in hepatitis B virus-related acute-on-chronic liver failure. World J Gastroenterol 2011;17:3448-3452.

Received May 29, 2015
Accepted after revision December 7, 2015