STUDY PROTOCOL

Chinese Chronic Liver Failure Consortium Acute-on-Chronic Liver Disease and Failure Study ——a Prospective Multi-center Study in China, the Largest Hepatitis B Virus High-endemic Region

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OUTLINE

Abbreviations:

ACLF	Acute-on Chronic Liver Failure
CLIF	Chronic Liver Failure
CLIF-C OFs	Liver-chronic liver failure-Consortium Organ Failure score
HBV	Hepatitis B Virus
CANONIC	Chronic Liver Failure (CLIF) Acute-on Chronic Liver Failure in Cirrhosis
OFs	Organ Failure
AASLD	the America Association for the Study of Liver Disease
AD	Acute Decompensation
SOFA	Sequential Organ Failure Assessment Score
INR	International Normalized Ratio

Background

Acute-on chronic liver failure (ACLF) was first described by Japanese researchers in 1995[1]. In 2011, the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) concluded that the core characteristics of ACLF were multiple organ failures and high short-term mortality[2]. In 2013, the EASL-CLIF (the European Association for the Study of The Liver-chronic liver failure) established the CLIF-SOFA[3] (chronic liver failure-sequential organ failure assessment) criteria of ACLF through a prospective multicenter study at 29 liver units in eight European countries for 1 year, with a focus on patients with alcoholic cirrhosis with acute decompensation (AD)[4]. In China, patients with acute deterioration of previously chronic liver disease were diagnosed with chronic severe hepatitis, until 2008 these patients had been termed "ACLF", due to the APASL reached a consensus of diagnostic criteria of ACLF[5, 6]. In the Asia-Pacific region, the majority of liver disease is viral hepatitis, while in western countries, it is alcoholic liver disease[7]. There is a sharp east-west divide with respect to the definition of ACLF, especially in the definition of chronic liver disease and its precipitating events[8, 9].

The investigators analyzed 6 years' data of hepatitis B virus (HBV)-related chronic liver disease in patients with AD in two affiliated hospitals of Shanghai Jiao Tong University School of Medicine. These data were also

quantified and sent to the EASL-CLIF center for analysis. 80% of whole patients were clinically diagnosed with cirrhosis, 30% of which had pathological diagnosis. Through analysis of the liver tissues of the liver transplantation (LT) patients, 95% had pseudo-lobules. The residual 5% of liver tissues were in the S3 stage of progressive liver fibrosis[10]. Compared with the CANONIC (EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis), there are many similarities between ACLF patients with alcoholic cirrhosis or HBV induced cirrhosis: (1) The age of ACLF patients is younger than that of cirrhotic patients with AD. (2) ACLF is exist at any stage of liver fibrosis. (3) The number of organ failures decides the severity of the disease and is related to mortality of the patient. (4) Predisposition to acute liver injury (ALI) does not correlate with the history of the disease and outcome of the patient. (5) The 90-day mortality rate of ACLF is 45-50%, which is obviously higher than that of non-ACLF patients (5%). (6) Eastern and western types of ACLF can have similar SOFA scores as a diagnostic criterion (CLIF-OF or CLIF-SOFA), and a similar prognostic model to predict the outcomes of ACLF and non-ACLF patients[11]. ACLF patients with cirrhosis induced by HBV or alcoholism differ in main types of organ failure. The former group is liver failure (total bilirubin ≥ 12mg/dl) and coagulation failure (international normalized ratio; INR≥2.5), whereas the latter group is renal failure (creatinine ≥ 2mg/dl or use of renal replacement therapy) and nervous system failure (hepatic encephalopathy; HE≥III grade)[4, 12].

Research on hepatic pathology in HBV-induced ACLF patients after LT in RenJi Hospital demonstrated that the pathological characteristics of ACLF may be MHN/SMHN (massive hepatic necrosis/submassive hepatic necrosis) in the background of liver pseudo-lobules. Regeneration of hepatic progenitor cells, cholestasis, and sepsis are other possible pathological features of ACLF[13].

Objective

The overall objective is to build a prospective multicenter clinical patient cohort representing Eastern-type ACLF in patients with chronic liver disease (cirrhotic and non-cirrhotic) of various etiologies, accompanied by AD or ALI, to characterize disease progression and establish appropriate diagnostic criteria.

Methods

Period I Recruitment:

The investigators plan to enroll 2000-3000 consecutive patients from January to December 2015. The research will be carried out in about 14 Chinese national wide liver centers each of whose total beds are around 500. Only chronic liver disease patients of various etiologies with AD or ALI will be enrolled. Then we will scan all of the enrolled patients and exclude those who fit our exclusion criteria.

Every patient remained will have a unique number. As soon as they are hospitalized, name, age, sex, ID (identification) number, telephone number, e-mail address, WeChat (a popular mobile phone text and voice messaging communication service) number, family address, and degree of education will be collected. The investigators will get the history and etiology of their liver disease, such as hepatitis B, alcoholic liver disease, and autoimmune liver disease. For viral hepatitis, the investigators will ask how antiviral therapy is conducted. The investigators will ascertain if the patients have a history of cirrhosis and for how long. The investigators will ascertain if the patients have any of the following predisposing factors: HBV reactivation, bacterial infection, active alcohol intake, HBV superimposed by other hepatitis viruses, gastrointestinal bleeding, portal vein thrombosis, surgery, intake of hepatotoxic drugs or herbs, or physiological exhaustion. The

investigators will establish the main cause of admission: gastrointestinal bleeding, hepatic encephalopathy, ascites, bacterial infection, jaundice or ALI. The investigators will determine whether the patients have chronic disease such as hypertension, coronary heart disease, diabetes, chronic renal disease, or connective tissue disease.

Period II 28-Days Hospitalization and Observation:

During hospitalization, data will be collected at 1, 4, 7,14, 21 and 28 days (or last visit date, if the patient is hospitalized less than 28 days), and 24h prior to death or LT (if the patient dies or has LT) and focus on the following three aspects.

The first aspect is evaluation of organ failure. The circulatory system will be evaluated by measuring heart rate and blood pressure and use of vasopressors. Renal function will be evaluated by serum creatinine or renal replacement therapy. Coagulation function will be evaluated by INR (international normalized ratio of prothrombin time). Liver function will be evaluated by serum total bilirubin. The respiratory system will be evaluated by the ratio of oxyhemoglobin saturation and fraction of inspired oxygen. The nervous system will be evaluated by the grade of hepatic encephalopathy. Bacterial infection, including pneumonia, urinary tract infection, spontaneous bacterial peritonitis, spontaneous bacteremia, and cellulitis will be evaluated by positive culture results or imaging findings.

Systemic inflammatory reactive syndrome, sepsis, severe sepsis and septic shock will also be assessed. Gastrointestinal bleeding before and after admission, treatment with diuretics, and paracentesis will be recorded. The investigators will establish whether ascites and hepatic encephalopathy can be medically controlled.

The second aspect is laboratory examinations. Tests at admission will include routine blood, urine and stool tests, liver and renal function tests, blood electrolytes, blood-gas analysis, blood glucose, coagulation test, C-reactive protein (CRP), procalcitonin (PCT), HBV antibodies and antigens, anti-hepatitis A (IgM), HBV-DNA, anti-hepatitis E (IgM), anti-hepatitis C, and immunoglobulins (IgA, IgG, IgM and IgM-4). Tests at other times will include blood, urine and stool routine tests, liver and renal function tests, blood electrolytes, blood glucose, coagulation test, CRP and PCT (procalcitonin). Tests optionally done during hospitalization will include autoantibody measurement, blood culture (if the patients have fever and shivering), sputum culture (if there is suspicion of pulmonary infection), middle urine cultivation (when there is suspicion of urinary tract infection) and ascites culture (when there is suspicion of spontaneous bacterial peritonitis).

The third aspect is imaging. During hospitalization, thoracic X ray or computed tomography (CT) will be done to diagnose pulmonary infection. Abdominal CT (enhanced when necessary), B ultrasound and Fibro-Scan or

other elastography will be done to diagnose cirrhosis (or fibrosis), portal thrombosis, esophageal and gastric varices and hepatocellular carcinoma.

Period III Clinic or Telephone Follow-up:

Patients will be followed up regularly after discharge. When the patients die during follow-up, the time of death and main cause of death will be noted. When the patients undergo LT during follow-up, the time of LT and the results of hepatic pathology will be noted.

Follow-up is by clinical visiting or telephone call depending on whether the patient can attend the clinic. Clinical follow-up is once a month for 2 years adding to 24 visits. The time of visit will be recorded. Antiviral therapy and alcohol intake will be monitored (if the patient has). Laboratory tests include routine blood tests, liver and renal function test, coagulation test, CRP and PCT. B ultrasound will be done to monitor cirrhosis (or fibrosis) and hepatocellular carcinoma. Telephone follow-up will be at 28 days, 3, 6,9, 12, 15, 18, 21 and 24 months. The investigators will determine whether there are new complications (e.g. gastrointestinal bleeding, hepatic encephalopathy, ascites, bacterial infection) and hepatocellular carcinoma.

Statistical Analysis Plan

Trial size

This is an exploratory, observational study, and anticipated size for this study is 2000-3000 patients.

Statistical methods

Refer to the CANONIC study, at the beginning we will focus on (but not limit in) the relationship between 6 parameters (TB, INR, Creatinine, SpO2/FiO2, mean arterial pressure and West-Haven grade), one for each organ/system, from CLIF-C OFs and 28-days or 90-days mortality and LT rate. Descriptive statistics, mean and standard difference, will be used to describe continuous variables, and frequency and percent will be to describe categorical variables (such as gender). Statistical significance ($P < 0.05$). In univariate statistical comparisons, the chi-square test will be used for categorical variables, T-test and Mann-Whitney test for continuous variables. Risk ratio (RR) will be used to evaluate and establish the cutoff value for each organ/system. Multivariate logistic regression, Cox' s PH models and other exploratory models would be used in the establishment of our ACLF prognostic scoring systems. The area under the ROC (AUC) will be used to compare the predictive value of ours with others. LT patients will be considered as censored and the survival function would be adjusted for the risk of liver transplantation at each study time point.

Outcome Measures

Primary Outcome Measures:

1. Short Term Mortality & Liver Transplantation Rate

Description: Mortality & Liver Transplantation Rate will be calculated and reported at 28 days,90 days,180 days,1 year ,2 year and 3 years after enrollment. Among them, the 28-day and 90-day mortality rates are the focus of our observation.

Time Frame: up to 3 years.

Secondary Outcome Measures:

2. The appearance and number of organ failure

Description: The appearance and number of organ failure（including liver, coagulation, renal, circulation, brain, respiratory system） will be evaluated and reported at 1, 4, 7, 14, 21 and 28 days (or last visit)during patients' hospitalization.

Time Frame: Up to 28 days.

3. Biochemical Parameters

Description: Serum bilirubin, international normalized ratio, serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-Glutamyltransferase, white blood cell count, neutrophil count and hemoglobin will be collected and reported at 1, 4, 7, 14, 21 and 28 days (or last visit) during patients' hospitalization.

Time Frame: Up to 28 days

4. Models for Disease Severity

Description: MELD score, MELD-Na score, CLIF-SOFA score, SOFA score and APACHE scores will be calculated and reported at 1, 4, 7, 14, 21 and 28 days (or last visit) during patients' hospitalization.

Criteria:

Inclusion Criteria:

1.Inpatient (hospitalization >1 days) (including patient in emergency observation wards);

2.Chronic liver disease patients including non-alcoholic fatty liver disease patients, chronic liver hepatitis patients without cirrhosis, compensated cirrhosis patients and decompensated cirrhosis patients;

3.Having acute liver injury [ALT (alanine aminotransferase)>3NL(normal level),AST(aspartate aminotransferase)>3NL or TB(total bilirubin)>2NL within 1 week before enrollment] or acute decompensation[having ascites, hepatic encephalopathy, bacterial infection ,gastrointestinal bleeding or jaundice(TB>5NL)within 1 month].

Exclusion Criteria:

1.pregnancy;

2.hepatocellular carcinoma or other liver malignancies;

3.malignancy of other organs;

4.severe chronic extrahepatic disease including chronic obstructive pulmonary disease combined with respiratory failure, coronary heart disease with cardiac function level 3 (NYHA), myocardial infarction in the 3 months before admission, diabetes with severe complications and chronic kidney disease with end-stage renal failure;

5.receiving immunosuppressive drugs for reasons other than chronic liver disease;

Contacts/Locations

Professor Hai Li, MD & PhD

Study Director

Digestive Department of Renji Hospital, Shanghai Jiao Tong University School of Medicine

Shanghai, China, 200001

Telephone: +86-13818525494

E-mail: haili_17@126.com

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