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# Cohort profile: a multicentre prospective validation cohort of the Chinese Acute-on-Chronic Liver Failure (CATCH-LIFE) study

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## ABSTRACTS

**Purpose** Acute-on-chronic liver failure (ACLF) is a clinical syndrome with high short-term mortality, unclear mechanism and controversial diagnosis criteria. The Chinese Acute-on-Chronic Liver Failure (CATCH-LIFE) study has been conducted in China to fill the gaps. In the first phase (the CATCH-LIFE investigation cohort), 2600 patients were continuously recruited from 14 national nationwide liver centres from 12 different provinces of China in 2015–2016, and a series of important results were obtained. To validate the preliminary results, we designed and conducted this multicentre prospective observational cohort (the CATCH-LIFE validation cohort).

**Participants** Patients diagnosed with chronic liver disease and hospitalised for acute decompensation (AD) or acute liver injure were enrolled, received standard medical therapy. We collected the participants' demographics, medical history, laboratory data, and blood and urine samples during their hospitalisation.

**Findings to date** From September 2018 to March 2019, 1370 patients (73.4% men) aged from 15 to 79 years old were enrolled from 13 nationwide liver centres across China. Of these patients, 952 (69.5%) had chronic hepatitis B, 973 (71.1%) had cirrhosis and 1083 (79.1%) complicated with AD at admission. The numbers and proportions of enrolled patients from each participating centre and the patients' baseline characteristics are presented.

**Future plans** A total of 12 months is required for each participant to complete follow-up. Outcome information (survival, death or receiving liver transplantation) collection and data cleansing will be done before June 2020. The data in the CATCH-LIFE validation cohort will be used for comparison between the new ACLF diagnostic criteria derivated from the CATCH-LIFE investigation cohort with existing ones. Moreover, future proteomic and metabolic omics analyses will provide valuable insights into the mechanics of ACLF, which will promote the development of specific therapy that leads to decrease patients' mortality.

**Registration** NCT03641872.

## Strengths and limitations of this study

- The Chinese Acute-on-Chronic Liver Failure (CATCH-LIFE) validation cohort makes the CATCH-LIFE study the unique acute-on-chronic liver failure (ACLF) related study with two independent multicentre prospective cohorts, which provides ample statistical power to clarify certain controversial portions of the ACLF's definitions and diagnostic criteria.
- The participants in the study have typical characteristics of ACLF in hepatitis B virus high-endemic areas.
- The availability of proteomics and metabolomics may illuminate the unclear mechanism of ACLF and provides opportunities to discover novel markers for diagnosis and outcome prediction.
- The 28-day hospitalisation of participants will clarify the natural course of ACLF.
- The participating centres of this study are highly coincident with the centres that participated in the CATCH-LIFE investigation study, which could generally limit the effectiveness of the validation.

## INTRODUCTION

Patients with chronic liver disease and acute deterioration requiring hospitalisation include some potential victims of a dangerous clinical syndrome—acute-on-chronic liver failure (ACLF). ACLF is characterised by chronic liver disease and rapid progression of liver injury, culminating in multiple organ failures and high short-term mortality (over 50% in 90 days).[1–3] However, as a possible short-term fatal syndrome, up to 13 definitions[4] and several different diagnostic criteria of ACLF[1 5–7] exist, causing clinician confusion rather than guidance. Only the diagnostic criteria derived from solid evidence and representative data should be applied in clinical practice.

The first evidence-based ACLF diagnostic criterion was proposed in 2013. The European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF), through the CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study in Europe, modified the Sequential Organ Failure Assessment[8] score, showed that the failure of 6 organs/system (liver, coagulation, renal, bran, circulation and respiratory) is closely related to the short-term mortality of ACLF patients, and designed the EASL-CLIF Consortium Organ Failure score (OFs) system.[1 9 10] Nevertheless, the CANONIC study only covered aetiologies of Western-type ACLF. Alcoholism and hepatitis C virus (HCV) are the main aetiologies of Western-type ACLF,[10] while hepatitis B virus (HBV) accounts for most Eastern-type ACLF.[11 12] There are also significant differences between Eastern-type and Western-type ACLF in precipitating events, pathogenesis and clinical characteristics, OF type distribution and so on.[13 14] Therefore, in East, Southeast and Central Asia where HBV is highly endemic,[15] it is unwise to directly introduce diagnostic criteria based on data collected from HBV low-endemic regions.[15]

The Chinese HBsAg-positive population is estimated to be 86 million, accounting for 30% of HBsAg carriers worldwide and 60% of HBV high-endemic areas,[15] which makes China the optimum source of representative data for Eastern-type ACLF. In the beginning of 2015, the Chinese Acute on Chronic Liver Failure (Ch-CLIF) Consortium launched the Chinese Acute-on-Chronic Liver Failure (CATCH-LIFE) investigation study (NCT02457637). From January 2015 to December 2016, 2600 potential ACLF patients were continuously recruited into the investigation cohort from 14 nationwide liver centres across China. The detailed design and description of the study was published elsewhere.[16] Then we described the mathematical meaning of 'organ failure', established 'CATCH-LIFE OFs' for Eastern-type ACLF diagnosis, developed a prognostic prediction model for patients' stratification, and obtained other preliminary results on ACLF's mechanism via multi-omics analysis. All these results shall be milestones in the field, if being validated. Validation from an external cohort is the most convincing type of evidence. However, there is no qualified cohort available currently.

Then, we designed and conducted this CATCH-LIFE validation cohort study. The overall study aim is to validate the preliminary results of the CATCH-LIFE investigation cohort study, including possible results obtained in the future.

Details are as follows:

Initially, the two cohorts of the CATCH-LIFE study will be used to describe patients' epidemiological characteristics, discover risk factors of the mortality and evidence-based cut-off values of organ failure.

Subsequently, in clinical application:

1. To compare CATCH-LIFE OFs with existing ACLF diagnostic criteria and find the most appropriate criteria for Eastern-type ACLF.
2. To estimate the cut-off values for organ failure of ACLF in HBV high-endemic areas.
3. To validate the prognostic prediction model established for assessing patient outcomes.

The objective of this section is to ensure the authenticity, reliability and integrity of the clinical data collected.

In experimental research:

1. To explore the mechanism of ACLF via multi-omics.
2. To validate the proteomic and metabolic kits for early diagnosis and outcome prediction.

The objective of this section is to ensure the quality of bio-specimens during collection, storage and transport.

## COHORT DESCRIPTION

### Overview

The CATCH-LIFE validation study is a multicentre prospective observational cohort study conducted in 13 nationwide liver centres from different provinces of China. All participating centres met the qualifications (online supplemental appendix 1). Patients diagnosed with chronic liver disease and hospitalised for acute deterioration were enrolled. Data were collected according to the case-report forms (online supplemental appendix 2). The study had three processes: recruitment, hospitalisation follow-up and post-discharge follow-up (figure 1). All-cause death, survival and undergoing liver transplantation (LT) were considered the endpoints. Recruitment began in September 2018 and ended in January 2019. The follow-up is ongoing and will last for 12 months.

### Selection of centres

Thirteen centres from 11 different provinces (Shanghai, Beijing, Chongqing, Hunan, Hubei, Guangdong, Zhejiang, Shandong, Jilin, Henan and Xinjiang) participated the CATCH-LIFE validation cohort. Their locations, together with the population density of China, are shown in figure 2. Twelve of the 13 centres also participated in the CATCH-LIFE investigation cohort (shown as red dots in figure 2). The First Affiliated Hospital of Zhejiang University in Zhejiang province (shown as the green dot in figure 2) is accepted as a new centre. Two centres (in Tianjin and Fujian provinces) participated in the investigation cohort but are not active in this study (shown as blue dots in figure 2). Despite subtle changes, the distribution of the centres remains close to the population distribution of China; 12/13 centres are in Southeastern China, representing 94% of the Chinese population, and 1/13 centres is in Northwestern China, representing 6% of the population.

### Study population and recruitment

The study included patients with chronic liver disease (various aetiologies, including cirrhosis or non-cirrhosis conditions) and an exacerbation requiring hospitalisation, referred to as 'acute-on-chronic liver disease'. In another word, ACLF patients with high short-term mortality and other unstable chronic liver disease patients

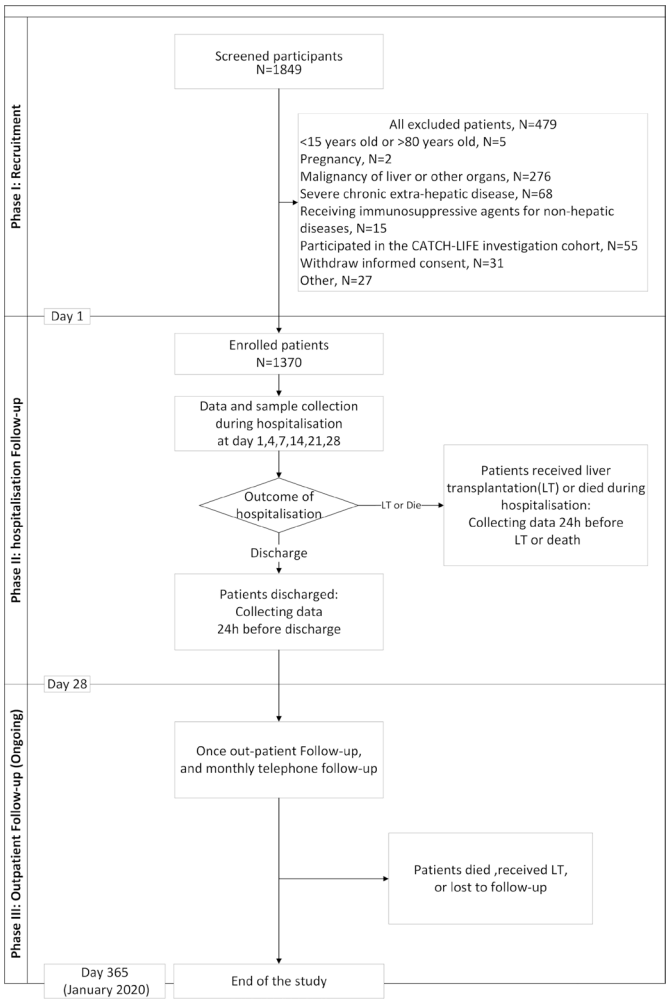


**Figure 1** Flowchart of the study procedures. CATCH-LIFE, Chinese Acute-on-Chronic Liver Failure; LT, liver transplantation.

with low risk of death are both enrolled. The following are detailed inclusion and exclusion criteria.

### Inclusion criteria

Patients who met all the following criteria were included.

1. Chronic liver disease with or without cirrhosis, including chronic viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, autoimmune liver disease, metabolic liver disease and chronic drug-induced liver disease. The duration of underlying non-cirrhotic chronic liver disease should be longer than 6 months.
2. Acute liver injury (serum alanine aminotransferase or aspartate transaminase over three times the upper limit of the normal level or total bilirubin (TB) over 2 mg/dL within 1 week before recruitment) or acute decompensation (AD) (hepatic encephalopathy, ascites, gastrointestinal bleeding, bacterial infection within 1 month before recruitment).
3. Inpatients: patients hospitalised or under emergency observation >24 hours.

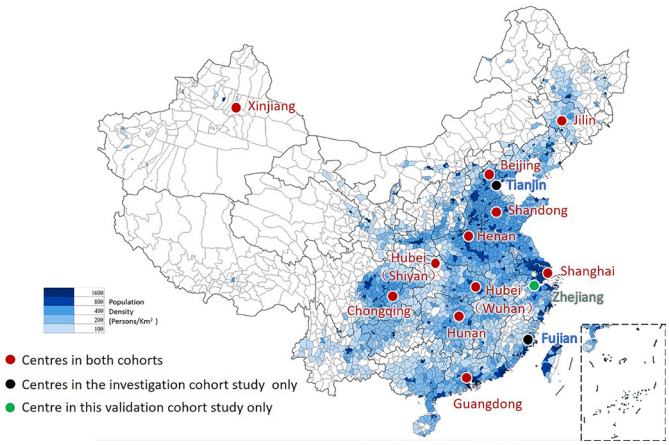


**Figure 2** The distribution of centres and the population density of China. Thirteen centres from 11 different provinces participated the Chinese Acute-on-Chronic Liver Failure (CATCH-LIFE) validation cohort. Red dots indicate the 12 of the 13 participating centres that also participated in the CATCH-LIFE investigation cohort. The green dot is the new participating centre in Zhejiang province. Blue dots are two centres in Tianjin and Fujian provinces participated in the investigation cohort but are not active in this study. The distribution of the centres accords with the population distribution of China.

### Exclusion criteria

Patients who met any of the following criteria were excluded.

(i) <15 years old or >80 years old; (ii) pregnancy; (iii) malignancy of liver or other organs (including leukaemia); (iv) chronic obstructive pulmonary disease level IV; (v) New York Heart Association (NYHA) Functional Class ≥3; (vi) myocardial infarction within 3 months before admission; (vii) diabetes with severe complications; (viii) chronic kidney disease with end-stage renal failure; (ix) receiving immunosuppressive agents for non-hepatic diseases; (x) patients who participated in the CATCH-LIFE investigation cohort study.

Every patient received standard medical therapy and was informed that the choice to participate in the study would not affect their therapeutic regimen. All consenting patients included in the study provided written informed consent. At any stage, if a patient revokes consent, he/she would be withdrawn from the study and not recruited into the study again.

### Follow-up and data collection

A total of 12 months is required for each participant to complete hospitalisation follow-up and regular post-discharge follow-up. All-cause death and 12-month survival were considered the endpoints; receiving LT was considered a competitive event versus death. Loss to follow-up was considered a censoring event.

Tables 1 and 2 show the details and schedule of data collection during the follow-up. Modularity is the main feature of our data collection schedule. All data elements were divided into 10 modules, and different combinations of modules were collected on days 1, 4, 7, 14, 21

**Table 1** Broad categories and data elements collected in the Chinese Acute-on-Chronic Liver Failure validation cohort study

| Broad categories | Data elements |
|---|---|
| Demographic data | Age, sex, ethnicity, identity number, postal code, address, mobile number, education status and insurance status |
| Medical history | Aetiology and duration of chronic liver disease, type of present and/or previous acute decompensation or acute liver injury, possible predisposition (HBV reactivation, infection, recent alcohol intake, etc) and history of other chronic disease (hypertension, diabetes, etc) |
| Basic and vital signs | Height, weight, body mass index, temperature, heart rate, blood pressure and oxygen saturation (read from pulse oximeters) |
| Laboratory tests | Routine blood test (HGB, WBC, PLT count and neutrophil/lymphocyte ratio), liver function (ALT, AST, TB, AKP, γ-GT, albumin, prealbumin), renal function test (creatinine, BUN), blood-gas analysis and electrolytes (pH, sodium, potassium), coagulation series (prothrombin time, INR, D-dimer), others (blood ammonia, C reactive protein, procalcitonin, AFP, CA199, fasting blood glucose) |
| Hepatitis virus tests | HBV (HBV-DNA, HBsAg, HBsAb, HBeAg, HBeAb, HBcAb), HCV, HAV and HEV antibodies (IgM) |
| Optional laboratory tests (if necessary ) | Thromboelastogram, cytokine, serum amyloid A, serum ferritin; ascites test (if patients take paracentesis): RBC count, WBC, count and proportion of polynuclear cell; autoimmune liver disease test; evaluation of Bacterial infection (sputum, blood, midstream urine, ascites, bile culture) |
| Imaging examination | Abdominal B ultrasound, abdominal CT/MRI scan, fibro-scan |
| Organ failure assessment | Liver, coagulation, respiratory, renal, brain, circulation failure |
| Hospitalisation summary | Medication (starting and ending times and dosage of antibiotics, glucocorticoids and proton pump inhibitor), hospitalisation duration and expenses |
| Status/outcome | Survival, liver transplantation (LT), death, lost to follow-up, re-hospitalised, malignancy detected, including the time of outcome, pathology results of the removed liver (for LT) or cause of death |

AFP, alpha-fetoprotein; AKP, alkaline phosphatase; BUN, blood urea nitrogen; CA199, carbohydrate antigen; γ-GT, gamma-glutamyl transferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HGB, haemoglobin; INR, international normalised ratio; PLT, platelet; RBC, red blood cell; WBC, white cell count.

and 28 (or the day before discharge or LT/death for patients hospitalised less than 28 days), making it easier for researchers in data collection and management.

The duration of hospitalisation follow-up depended on the patient's condition and generally did not exceed 28 days. During hospitalisation, patients' demographic data, contact details, history of disease, clinical/laboratory data, organ failure assessment (online supplemental appendix 2) and extra bio-specimens (whole blood, plasma and urine) were collected on day 1. Some data elements were retaken at days 4, 7, 14, 21 and 28 (or the day before discharge if the patient was hospitalised for less than 28 days). For patients who died

**Table 2** Data collection schedule of the Chinese Acute-on-Chronic Liver Failure validation cohort study

| Time after recruitment | Hospitalisation follow-up | | | | | | | Post-discharge follow-up (ongoing) | |
|---|---|---|---|---|---|---|---|---|---|
| Broad categories | Day 1 | Day 4 | Day 7 | Day 14 | Day 21 | Day 28 | Prior to death/LT*/ discharge | Outpatient follow-up | Monthly telephone follow-up |
| Demographic data | √ | | | | | | | | |
| Medical history | √ | | | | | | | √ | v |
| Basic and vital signs | √ | √ | √ | √ | √ | √ | √ | | t |
| Laboratory tests | √ | √ | √ | √ | √ | √ | √ | √ | |
| Hepatitis virus tests | √ | | | | | | | | |
| Optional laboratory tests | If necessary | | | | | | | | |
| Imaging examination | √ | | | | | | | | |
| Organ failure assessment | √ | √ | √ | √ | √ | √ | √ | | |
| Hospitalisation summary | | | | | | | √ | | |
| Status/outcome | | | | | | | √ | √ | √ |

LT, liver transplantation.

or underwent LT, available data 24 hours prior to death/LT were collected. At the end of hospitalisation, patient status (discharge, death or LT) was recorded. The time and the main cause of death or the time of LT and the pathology results of the removed liver were recorded as well. Other important information, particularly hospitalisation duration and expenses, and specific medications were also noted. Whether patients had cirrhosis was diagnosed by imaging examination after enrolment according to signs of dysmorphia and relation to portal hypertension.[17]

The patients' post-discharge follow-up was performed via outpatient visits and telephone calls. The time of outpatient visits was not fixed but was recommended to be 4 weeks after discharge. Telephone follow-up was performed monthly for health guidance and patient status check (survival, death or LT). If a patient was alive, the research staff would ask whether any complications (ascites growth, bacterial infection, gastrointestinal bleeding, hepatic encephalopathy and jaundice) occurred or if any malignancy was determined. If a patient died, then the time and the main cause of death was noted. If a patient underwent LT, the location and date of the procedure was recorded.

## Ascertainment of AD

According to the concepts of liver-specific complications[2] and decompensation events[18] in cirrhosis, the CATCH-LIFE study define the following five complications 'overt ascites', 'hepatic encephalopathy (HE)', 'gastrointestinal bleeding (variceal bleeding)', 'jaundice' and 'bacterial infection' within 1 month before recruitment as AD in the CATCH-LIFE study. Ascites manifested by moderate symmetrical distension of abdomen or with marked abdominal distension[19] was the criterion of overt ascites. Moreover, the most depth of ascites ≥50 mm reported by ultrasound was also was defined as overt ascites. Gastrointestinal bleeding was defined by the development of an upper and/or lower gastrointestinal variceal bleeding due to cirrhosis and portal hypertension. The criterion and severity classification of HE was referred West-Haven HE grade.[20] The criterion for jaundice was TB >5 mg/dL. Spontaneous bacterial peritonitis, pneumonia, sepsis, urinary tract infection, and cellulitis and any other type of acute bacterial infection were included in bacterial infection, which was defined by laboratory tests and imaging evidence.

## Quality control

### Electronic data capture system

All elements of the patients' clinical data were collected through the CRF and integrated into an electronic data capture (EDC) system. The functions of the system include more than electronification. In addition to data storage, security, backup and export, the system has a built-in logical verification system. The logical verification includes unfilled prompts, abnormal value prompts, contradictory prompts and hiding unnecessary parts automatically (such as automatically hiding 'microbial culture results' for non-infected patients). Moreover, any traces of the modification of the data is retained. The EDC system maintains the reliability, completeness and accuracy of the data and is helpful in audit trials, management of data-related questions and source data validation.

### Personnel training

Complete and timely training of personnel was conducted before the EDC system was implemented. The data manager (DM), principal investigator (PI) and data entry personnel were granted corresponding system rights.

### Internal verification

(i) EDC logical verification and data entry personnel self-examination was performed; (ii) the PI and DM performed inspections; (iii) a telephone check-in was conducted weekly; (iv) the PI meeting was conducted every 4 months; (v) on-site verification was conducted when recruitment was completed (March 2019), consisting of eligibility check, extreme value verification, critical case review (such as cases diagnosed with ACLF) and core data elements review.

### Raw data traceability archiving

The photographs or screen captures of medical records were taken and preserved as raw data, including medical history, progress notes, vital signs, physical examination, laboratory test results, imaging/pathology data, medication and medical orders. Participants were not identified by name, and confidentiality of the information derived from the medical records was preserved. All related raw data pictures from every centre were stored on their own hard disk, and a classified copy was sent to the responsible centre every quarter. All data had three backups. Pictures of the raw data were only used for backup and backtracking, and all centres (including the coordinating centre) did not have access to the picture data from other centres.

### Quality assessment (external verification)

1. A third-party company was responsible for data management, audit and inventory.
2. The database was sent to the data centre of the EASL-CLIF Consortium for quality verification.

### Storage and transport of bio-specimens

All biospecimens containing blood, plasma and urine samples were stored at −80°C. At the end of March 2019, all bio-specimens were transported via cold chain (−80°C) to the biological sample bank in Shanghai Renji Hospital (plasma and urine) and Chongqing Southwest Hospital (peripheral blood mononuclear cell (PMBC) DNA isolated from blood samples).

## Patient and public involvement

Participants of the CATCH-LIFE validation cohort or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## FINDINGS TO DATE

In total, 1370 patients from 13 centres were enrolled in the CATCH-LIFE validation cohort study, and the number of enrolled patients from each centre in each

month are presented in online supplemental appendix 3. The top five centres with the largest numbers of enrolled patients were Beijing Ditan Hospital (n=199), Chongqing Southwest Hospital (n=178), Hunan Xiangya Hospital (n=167), Shanghai Ren Ji Hospital (n=162) and Guangzhou Nanfang Hospital (n=125). The average monthly enrolment number was 274.

We collected the patients' plasma, PBMC DNA and urine on day 1 of admission and stored them at −80°C. Of the 1370 patients enrolled, plasma samples were obtained at least once from 1114 patients, and two or more samples were obtained from 463 patients; PMBC DNA was obtained from 977 patients. At the end of March 2019, all PBMC DNA samples were transported to Chongqing Southwest Hospital for a genome-wide association study test; other samples (plasma and urine) were sent to Renji Hospital for proteomic and metabolic tests.

Table 3 shows the patients' demographic data and the condition estimation on the first day of admission. Overall, 73.7% of the patients were men, and the mean age of the patients was 49.5 years, including 71.1% (n=973) of cirrhotic patients and 413 (28.9%) of non-cirrhotic patients; 69.5% (n=952) patients had chronic HBV-related liver diseases. The proportion of patients with AD is 79.1% (n=1083). Jaundice (44.6%) was the most common observed AD event, followed by overt ascites (40.7%), gastrointestinal bleeding (16.4%), infection (15.9 %) and HE (7.7%).

**Table 3** The baseline characteristics on the first day of admission

| Baseline characteristics | |
|---|---|
| Demographic data | |
| Male sex, n (%) | 1006 (73.4%) |
| Age (years) median (IQRs) | 49.0 (40.0–59.0) |
| HBV-related, n (%) | 952 (69.5%) |
| Cirrhosis, n (%) | 973 (71.1%) |
| Laboratory data, median (IQRs) | |
| Total bilirubin (mg/dL) | 3.9 (1.5–13.7) |
| INR | 1.41 (1.17–1.79) |
| Serum creatinine (mg/dL) | 0.78 (0.65–0.96) |
| ALT (U/L) | 82 (29–383) |
| AST (U/L) | 101 (46–265) |
| γ-GT (U/L) | 82 (38–158) |
| AKP (U/L) | 125 (92–63) |
| Albumin (g/L) | 32.3 (28.1–37.0) |
| CRP (mg/L) | 7.3 (3.1–14.6) |
| WBC (×10$^9$/L) | 4.95 (3.69–7.06) |
| Hb (g/L) | 118 (94–136) |
| Platelet count (×10$^9$/L) | 96.0 (61.0–150.0) |
| Serum sodium (mmol/L) | 138 (136–141) |
| Patients with AD | 1083 (79.1%) |
| Type of AD | |
| Overt ascites | 558 (40.7%) |
| Gastrointestinal bleeding | 224 (16.4%) |
| HE | 105 (7.7%) |
| Jaundice | 611 (44.6%) |
| Infection | 218 (15.9%) |
| **Score** | |
| MELD score | 15 (10–22) |
| Child-Pugh score | 8 (7–10) |
| Child-Pugh grade | |
| Child-Pugh A, n (%) | 261 (19.1%) |
| Child-Pugh B, n (%) | 533 (38.9%) |
| Child-Pugh C, n (%) | 576 (42.0%) |

AD, acute decompensation; AKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; γ-GT, γ-glutamyl transferase; Hb, haemoglobin; HBV, hepatitis B virus; HE, hepatic encephalopathy; INR, international standardisation ratio; MELD, the Model for End-stage Liver Disease; WBC, white cell count.

## Strengths and limitations

The CATCH-LIFE validation cohort has several strengths. First, compared with the CANONIC study (n=1343)[1] and Chinese Group on the Study of Severe Hepatitis B (n=1322)[7] from China, the study scale is a larger multicentre, prospective cohort of ACLF patients in the world. This cohort made the whole CATCH-LIFE study a unique ACLF-related study with two large independent multicentre prospective cohorts and 3970 patients. It provides plenty of data and solid evidence in related fields. Second, as the largest HBV high-endemic country, China is the optimum location for Eastern-type ACLF research. The centre distribution of this study was kept consistent with the population density distribution in China, so its data have epidemiological characteristics of patients with Eastern-type ACLF. Third, intensive quality control and quality assessment strategies were applied to ensure the authenticity, reliability and integrity of the clinical data collected. Standardised procedures were conducted in the bio-specimen's collection, storage, transport, processing and analysis to ensure the validity. Finally, we are engaged with using emerging new technologies and exploring the mechanics of ACLF, including genomics, proteomics and metabolomics. Such applications will provide insight of this fatal disease.

There are two limitations in this study. First, the centres of this study are highly coincident with the centres that participated in the CATCH-LIFE investigation study, which could generally limit the effectiveness of the external validation. Nevertheless, for these two studies, the 3-year interval in recruitment, the high internal heterogeneity in composition and no intersections in participants limited the significance of this limitation. Given that the advantages of the centres' geographical distribution and the efficiency gains from the job familiar research staff, the centre selection strategy has merits as well. Second, as a cohort in the HBV high-endemic area, the study included a few hundred non-HBV-related patients (only 30% in total), and if further stratified

by specific aetiologies, their data would be insufficient and cause potential bias. However, the aetiology of these patients (mainly alcoholic liver disease) matched Western-type ACLF; thus, they can be considered as a subgroup to compare and summarise the similarities and differences between the Western and Eastern types of ACLF, with efforts to arrive at a shared definition.

In summary, we successfully established a qualified external validation cohort for the CATCH-LIFE study in HBV high-endemic area and presented the clinical features of Eastern type ACLF through the large-scale prospective cohorts. The CATCH-LIFE study will make a considerable contribution to the exploration of ACLF mechanisms and the establishment evidence-based diagnostic criteria.

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# SUPPLEMENTAL APPENDIX

Cohort Profile: A Multi-centre Prospective Validation Cohort of the Chinese Acute-on-Chronic Liver Failure (CATCH-LIFE) Study

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## SUPPLEMENTARY APPENDIX 1

QUALIFICATIONS FOR THE SELECTION OF CENTRES

The participating centres met all the following qualifications:

1) Hepatology, gastroenterology, or infectious disease departments of tertiary university hospitals;
2) The presence of one principal investigator with a research interest in acute-on-chronic liver failure;
3) Specific staffs assigned to this study;
4) A representative geographic distribution; and
5) Monthly admittance and screening numbers if larger than 30 patients.

## **SUPPLEMENTARY APPENDIX 2** CASE-REPORT FORMS (CRF)

# TABLE OF CONTENTS

# 1 QUESTIONNAIRE FOR THE ELIGIBILITY CRITERIA

## 1 Inclusion Criteria

1. 1 Chronic liver disease: (multiple choices permitted)

- ☐ Chronic viral hepatitis
- ☐ non-alcoholic fatty liver disease (NAFLD) (via B ultrasound report)
- ☐ Alcoholic liver disease
- ☐ Autoimmune liver disease
- ☐ Hereditary liver disease (such as Wilson's disease)
- ☐ Compensated cirrhosis
- ☐ Decompensated cirrhosis
- ☐ Other Chronic liver disease [having abnormal values of serum alanine aminotransferase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (γ-GT), alkaline phosphatase (AKP), total bilirubin (TB) or pre-albumin in the past 6 months]
- ☐ None

1.2 Acute Deterioration (multiple choices permitted):

- ☐ Acute liver injury: ALT or AST > 3 times the upper limit of normal level in the past week
- ☐ Acute liver injury: TB > 2 mg/dL in the past week
- ☐ Acute decompensation (AD): gastrointestinal bleeding in the past month
- ☐ AD: Hepatic encephalopathy in the past month
- ☐ AD: Ascites in the past month

☐ AD: Defined bacterial infection in the past month

☐ None

1.3 Inpatients:

patients hospitalized or under emergency observation > 24 hours

☐ Yes ☐ No

1.4 Fulfil the criteria 1.1, 1.2, 1.3 above?

☐ Yes (continue) ☐ No (not include)

**2 Exclusion criteria**

☐ <15 years old or >80 years old

☐ Pregnancy

☐ Malignancy of liver or other organs (including leukaemia)

☐ Chronic obstructive pulmonary disease level IV

☐ New York Heart Association (NYHA) Functional Class ⩾3

☐ Myocardial infarction within 3 months before admission

☐ Diabetes with severe complications

☐ Chronic kidney disease with end-stage renal failure

☐ Receiving immunosuppressive agents for non-hepatic diseases

☐ Patients who participated the CATCH-LIFE development cohort study

Fulfilment any of the above criteria?

☐ Yes (exclude) ☐ No (continue)

# 2 (CRF) DEMOGRAPHIC INFORMATION

2.1 Multi-centre enrolment number: □□□-□□□□□□□-□

2.2 Hospitalization number：_____

2.3 Admission date：□□□□-□□-□□ (year-month-date)

2.4 Identity card number：_____

2.5 Name： _____

2.6 Gender: □male □ female

2.7 Date of birth: □□□□-□□-□□ (year-month-date)

2.8 Age: ____ (years old)

2.9 Mobile number-1(patient): _____

2.10 Mobile number-2 (family member): _____

2.11 Fixed-line Telephone number-3 (if available): _____

2.12 WeChat number (if available)：_____

2.13 Street：_____

2.14 City：_____

2.15 Province: _____

2.16 Postal code：_____

2.17 Degree of education: ☐doctor ☐master ☐bachelor ☐high school
☐primary school ☐illiteracy ☐unknown

2.18 Means of payment： ☐self-paying ☐health insurance

# 3 (CRF) HISTORY COLLECTION

## 3.1 Etiology

3.1.1 Type of chronic liver disease (multiple choices permitted)

☐ Hepatitis B virus infection (if checked, question 3.5.1 have to be answered)

☐ Hepatitis C virus infection

☐ Hepatitis E virus infection (independent or combining with another virus)

☐ Autoimmune Liver disease

☐ PBC ☐ AIH ☐ PSC ☐ unknown

☐ Alcoholic liver disease (if checked, question 3.5.2 have to be answered)

☐ Nonalcoholic steatohepatitis

☐ Schistosomiasis

☐ hereditary liver disease

☐ Chronic drug-induced liver disease

☐ Cryptogenic liver disease

3.1.2 The history of chronic liver disease: _____ months/years.

3.1.3 being diagnosed cirrhosis before： ☐ yes ☐ no

## 3.2 Present acute deterioration

3.2.1 The date of the acute deterioration this time (if more than one ADs in recent one month, then record the date of first one that occurred):
☐☐☐☐-☐☐-☐☐ (year-month-date)

## 3.3 Previous decompensation

3.3.1 Whether the patient had previous decompensation

☐Yes（to question 3.3.2） ☐No (to block 3.4)

3.3.2 Time of the first decompensation: ☐☐☐☐-☐☐ (year-month)

3.3.3 Previous types of decompensation (multiple choices permitted)

☐gastrointestinal bleeding

☐hepatic encephalopathy

☐ascites

☐pneumonia, SBP or SEPSIS

☐jaundice ( TB≥5mg/dL)

## 3.4 Predisposition of this time

3.4.1 Predispositions (multiple choices permitted)

☐HBV reactivation [in patients with 1) HBV-DNA over 500 copies/ml; 2] received nucleotide analogues (NUCs) therapy in the past 6 months; 3) ALT over 3 times the upper limit of normal level (ULN)] caused by

☐A.NUCs resistance： both HBV-DNA >1000 copies/ml and ALT (over 3 ULN) in the patients under continuous treatment with NUCs over 6 months

☐B.NUCs abandonment： both HBV-DNA >1000copies/ml and ALT (over 3 ULN) in the patients under continuous NUCs treatment but abandoning the antiviral treatment.

☐C. de novo hepatitis: HBV DNA > 10^5 copies/ml, HBsAg reappearance and ALT (over 3 ULN) in a patient previously HBsAg (-) and HBcAb (-)

☐Bacterial infection (if checked, question 3.4.2 have to be answered)

☐A. pneumonia

☐B. spontaneous bacteremia or sepsis

☐C. spontaneous bacterial peritonitis (SBP)

☐D. urinary tract infection

☐E. infection of biliary tract

☐F. cellulitis

☐G. other defined infection

☐Active alcohol intaking in the past 3 months (over 100ml hard liquor, 400ml wine or 1000ml beer per week in men and over 75% of the above volume in women)

☐Hepatitis A,C,E viruses or CMV overlap infection recently

☐Gastrointestinal bleeding in the past month before

☐Thrombogenesis in the portal vein

☐Suspicious hepatotoxic drugs or herbs intake in the past 3 months

☐Underwent invasive examination or surgery in the past 3 months

☐Defatigation in the past 3 months

☐Undefined

3.4.2 Any antibiotics treatment within the past 3 months?

☐Yes(to 3.4.3) ☐No (to block 3.5)

3.4.3 Antimicrobial usage within the past 3 months:

A. Type: _____ Date: _____ dosage: _____ duration: _____

## 3.5 Predisposition (detailed)

3.5.1 HBV infection and treatment

Whether the HBV-patient were treated with NUCs before?

☐Yes (continue) ☐No (to question 3.5.2)

A. Antiviral treatment initiation: ☐☐☐☐-☐☐ (year-month)

B. Drugs used at treatment initiation: _____

C. Whether the antiviral treatment discontinued?

☐Yes(to question D) ☐No (to question 3.5.2)

D. When was the antiviral treatment discontinued?_____

E. Why was the antiviral treatment discontinued? _____

F. Drugs in use at the time of discontinuation: _____

G. Antiviral treatment discontinuation by the patient himself/herself

☐Yes ☐No

H. NUC resistance during the course of treatment

☐Yes(to question D) ☐No (to question 3.5.2)

I. NUC resistance date: ☐☐☐☐-☐☐ (year-month)

3.5.2 Alcohol intaking

A. the type and amount of alcohol?

Beer: average amount per day ___ ml × ____years

Wine: average amount per day ___ ml × ____years

Liquor: average amount per day ___ ml × ____years

## 3.6 History of chronic disease **(multiple choices permitted)**

☐Hypertension

☐Diabetes

☐Coronary heart disease

☐Chronic renal disease

☐Rheumatism or connective tissue disease

☐Immunodeficiency diseases

☐None

# 4 (CRF) DYNAMIC DATA RECORDING DURING HOSPITALIZATION

## 4.1 Basic & Vital Sign

A. Height_____cm

B. Weight_____kg

C. BMI _____{Weight/(Height /100)$^2$}

D. Heart rate_____beats/minute

E. Temperature_____℃

F. Blood pressure_____/_____mmHg

## 4.2 Evaluation of circulatory, respiratory, central nervous systems and renal

4.2.1 Circulatory system：

A. Whether vasopressors (exclude telipressin) had been used to maintain the basic blood pressure? ☐Yes ☐No

4.2.2 Respiratory system:

A. $SpO_2$= _____%

B. $SPO_2/FiO_2$= _____{$SPO_2$/0.21}

C. Supplemental oxygen?

☐Yes (continue) ☐No (to question 4.2.3)

D. Oxygen flow rate_____L/min

E. $FiO_2$(with $O_2$) = {(21+oxygen flow rate∗4) /100}

F. $SPO_2/FIO_2$(with $O_2$) =_____ {$SPO_2/FIO_2$(with $O_2$)}

G. Whether the traumatic mechanical ventilation had been used?

4.2.3 Renal

A. Whether the renal replacement therapy (hemodialysis) had been used?

☐Yes ☐No

4.2.4 Central nervous system

A. Location identification (ask the patient: Do you know where you are?)

☐Good ☐Poor

B. Identification capacity [ask the patient: Do you know who he/she(a relative or

the doctor) is ?]

☐Good ☐Poor

C. Calculation capacity: Ask the patient: What is 100 minus 7?

☐Right answer (to question D) ☐Wrong answer (to question E)

D. Time required for the right answer: _____ seconds

E. Grades of hepatic encephalopathy (HE)

☐grade 0: Normal

☐grade 1: Minor lack of awareness, shortened attention span, sleep disturbance and altered mood. Asterixis may be present. (the patient can successfully answer the question A, B and C, but the time required for question C is long/the patient can successfully answer the question A and B but not the question C).

☐grade 2: Lethargy, disorientation to time, amnesia of recent events, impaired ability for simple computations, inappropriate behavior and slurred speech. Asterixis is present (the patient cannot successfully answer neither of the question A nor B)

☐grade 3: Somnolence, confusion, disorientation to location, bizarre behavior, clonus, nystagmus and positive Babinski sign. Asterixis is usually absent.

☐grade 4: Coma. Lack of verbal, eye, and oral response.

## 4.3 Evaluation of Bacterial infection, SIRS and Sepsis

4.3.1 Bacterial infection

A. Had the patient got defined infection?

☐Yes (to question B)

☐Suspected (to question E)

☐no (to the question 4.3.2)

B. What's the location of the infection? (multiple choices permitted)

☐Pneumonia ( via image of focus of infection on X ray or CT)

☐Spontaneous bacterial peritonitis (SBP) (positive ascites culture or absolute counting of neutrophil in ascite≥250×$10^6$/L）

☐Spontaneous bacteremia (positive blood culture) or sepsis

☐Urinary tract infection (positive middle urine culture)

☐Cellulitis

☐Infection of biliary tract

☐Others, culture result and location: _____

C. Type and name of pathogenic microorganism: _____

D. Drug susceptibility testing (you can upload the photos)

E. Had blood culture been taken?

☐Yes ☐No

4.3.2 SIRS

A. criteria（multiple choices permitted）

☐temperature > 38℃ or temperature < 36℃

☐heart rate > 90 beats per minute

☐respiratory >20 times per minute or hyperventilation ($PaCO_2$< 32mmHg)

☐WBC >12×$10^9$/L or <4×$10^9$/L

B. Were at least two of the above four criteria met?

☐Yes ☐No

4.3.3 Sepsis

A. Both bacterial infection and SIRS above are met?

☐Yes ☐No

## 4.4 Acute Decompensation (AD), Organ Failure (OF) & ACLF Evaluation

4.4.1. The number of AD（multiple choices permitted）

A. TB>5mg/dl ☐yes ☐no

B. gastrointestinal bleeding within recent 1 month ☐yes ☐no

C. Hepatic encephalopathy within recent 1 month ☐yes ☐no

D. Ascites within recent 1 month ☐yes ☐no

E. defined bacterial infection ☐yes ☐no

count the number of AD: _____ {number of YES in question 4.4.1}

4.4.2 The number of OF（multiple choices permitted）

A. Liver failure （TB>22mg/dl） ☐yes ☐no

B. Coagulation failure （INR>2.0） ☐yes ☐no

C. Renal failure （Cr>2mg/dl or hemodialysis） ☐yes ☐no

D. Respiratory failure (Artificial respiratory support) ☐yes ☐no

E. Circulatory failure （Vasopressor using） ☐yes ☐no

F. CNS failure （HE Grade≥2） ☐yes ☐no

count the number of OF: _____ {number of YES in question 4.4.2}

4.4.3 ACLF Grade= _____

{If the number of OF = 1, the ACLF Grade = 1;

if the number of OF = 2, the ACLF Grade = 2;

if the number of OF ≥ 3, the ACLF Grade = 3 }

## 4.5 Medication During Hospitalization

4.5.1 Whether thymosin has been used?

☐Yes (continue) ☐No (to question 4.5.2)

A. Type: _____ Date: _____ dosage: _____ duration: _____

4.5.2 Whether Proton-pump inhibitors (PPI) has been used?

☐Yes (continue) ☐No (to question 4.5.3)

A. Type: _____ Date: _____ dosage: _____ duration: _____

4.5.3 Whether glucocorticoids have been used?

☐Yes (continue) ☐No (to question 4.5.4)

A. Type: _____ Date: _____ dosage: _____ duration: _____

4.5.4 Whether antibiotics have been used？

☐Yes (continue) ☐No (to question 4.5.4)

A. Type: _____ Date: _____ dosage: _____ duration: _____

# 5: LABORATORY TESTS DURING HOSPITALIZATION

| 5.1 Peripheral blood cells count | | Sampling Schedule |
|---|---|---|
| 5.1.1 | Haemoglobin (HGB), g/L | Required at Day 1 / 4 / 7 / 14 / 21 / 28 |
| 5.1.2 | White blood cell count (WBC), *10^9/L | |
| 5.1.3 | Proportion of neutrophils (N%) | |
| 5.1.4 | Proportion of lymphocytes (L%) | |
| 5.1.5 | Proportion of monocytes (M%) | |
| 5.1.6 | Neutrophil lymphocyte ratio (NLR) | |
| 5.1.7 | Platelet count (PLT) , *10^9/L | |
| 5.2 Liver function test | | Required at Day 1 / 4 / 7 / 14 / 21 / 28 |
| 5.2.1 | Alanine aminotransferase (ALT), U/L | |
| 5.2.2 | Aspartate aminotransferase (AST), U/L | |
| 5.2.3 | Albumin (ALB), g/L | |
| 5.2.4 | Pre-ALB, mg/L | |
| 5.2.5 | Total bilirubin (TB), mg/dL | |
| 5.2.6 | Alkaline phosphatase (AKP), U/L | |
| 5.2.7 | Glutamyl transpeptidase (γ-GT), U/L | |
| 5.3 Renal function test | | Required at Day 1 / 4 / 7 / 14 / 21 / 28 |
| 5.3.1 | Creatinine (Cr), mg/dL | |
| 5.3.2 | Blood urea nitrogen (BUN), mmol/L | |
| 5.4 Electrolytes | | Required at Day 1 / 4 / 7 / 14 / 21 / 28 |
| 5.4.1 | Sodium (Na+), mmol/L | |
| 5.4.2 | Potassium (K+), mmol/L | |
| 5.4.3 | PH | |
| 5.5 Coagulation test | | Required at Day 1 / 4 / 7 / 14 / 21 / 28 |
| 5.5.1 | Prothrombin time (PT), seconds | |
| 5.5.2 | International normalized ratio (INR) | |
| 5.5.3 | D-dimer, μg/L | |
| 5.6 HBV-DNA, antigens and antibodies test | | Required at Day 1 only |
| 5.6.1 | HBV-DNA load, copies/ml | |
| 5.6.2 | HBsAg, IU/ml | |
| 5.6.3 | HBsAb, mIU/ml | |
| 5.6.4 | HBcAb, S/CO | |
| 5.6.5 | HBeAg, S/CO | |
| 5.6.6 | HBeAb, S/CO | |
| 5.7 Other hepatitis virus antibodies test | | Required at Day 1 only |

| | | |
|---|---|---|
| 5.7.1 | anti-HAV(IgM) | |
| 5.7.2 | anti-HEV(IgM) | |
| 5.7.3 | anti-HCV | |
| 5.8 Immunoglobulin test | | Optional |
| 5.8.1 | Immunoglobulin A (IgA), g/L | |
| 5.8.2 | Immunoglobulin M (IgM), g/L | |
| 5.8.3 | Immunoglobulin G (IgG), g/L | |
| 5.8.4 | Immunoglobulin G-4 (IgG-4), g/L | |
| 5.9 Autoantibody for autoimmune liver disease | | Optional |
| 5.9.1 | Antinuclear antibody (ANA), titer | |
| 5.9.2 | Anti-smooth muscle antibody (SMA), titer | |
| 5.9.3 | Anti-mitochondria antibody (AMA), titer | |
| 5.9.4 | AMA-M2, titer | |
| 5.10 Others test (1) | | Required at Day 1 only |
| 5.10.1 | C-reactive protein (CRP), mg/L | |
| 5.10.2 | Procalcitonin (PCT), ng/ml | |
| 5.10.3 | AFP, ng/ml | |
| 5.10.4 | CA199, U/ml | |
| 5.10.5 | Blood ammonia, umol/L | |
| 5.10.6 | Fasting blood glucose (GLU), mmol/L | |
| 5.11 Others test (2) | | Optional |
| 5.11.1 | lactic acid, mmol/L | |
| 5.11.2 | Serum ferritin, μmol/L | |
| 5.11.3 | Serum amyloid A, mg/L | |
| 5.12 Cytokine | | Optional |
| 5.12.1 | Interleukin IL-6, ng/ml | |
| 5.12.2 | Interleukin IL-8, ng/ml | |
| 5.12.3 | Interleukin IL-10, ng/ml | |
| 5.13 Bacterial culture test | | If infection is suspected |
| 5.13.1 | Blood culture | |
| 5.13.2 | Blood culture bacterial types | |
| 5.13.3 | Sputum culture | |
| 5.13.4 | Sputum culture bacterial types | |
| 5.13.5 | Middle urine culture | |
| 5.13.6 | Middle urine culture bacterial types | |
| 5.14 Ascites test | | If abdominocentesis |

| | | |
|---|---|---|
| 5.14.1 | WBC count in ascites, | is taken |
| 5.14.2 | Proportion of polynuclear cells | |
| 5.14.3 | Absolute polynuclear cell count, | |
| 5.14.4 | RBC count in ascites fluid, | |
| 5.14.5 | Lactic dehydrogenase (LDH), | |
| 5.14.6 | Adenosine deaminase (ADA), | |
| 5.14.7 | Ascites culture | |
| 5.14.8 | Ascites culture bacterial types | |

# 6: IMAGING TEST RESULTS

| | |
|---|---|
| 6.1 Abdominal ultrasound | |
| 6.1.1 | Date of test: □□□□-□□-□□ (year-month-date) |
| 6.1.2 | Ascites: □Positive □Negative |
| 6.1.3 | If ascites positive, the depth _____ mm |
| 6.2 CT/MRI scan -- cirrhosis (Preferred enhanced CT results) | |
| 6.2.1 | Test used: □ CT □ MRI |
| 6.2.2 | Date of test: □□□□-□□-□□ (year-month-date) |
| 6.2.3 | Result: □ Cirrhosis □Non-cirrhosis □Undefined |
| 6.3. CT/MRI scan -- portal thrombosis /varices/ pulmonary infection | |
| 6.3.1 | Test used: □ CT □ MRI |
| 6.3.2 | Date of test: □□□□-□□-□□ (year-month-date) |
| 6.3.3 | Whether portal thrombosis has been found?<br>□ Yes □ No □ Undefined |
| 6.3.4 | Whether esophageal and gastric varices have been found?<br>□ Yes □ No □Undefined |
| 6.3.5 | Whether pulmonary infection has been found by CT scan?<br>□ Yes □ No □Undefined |
| 6.4. Fibro-scan | |
| 6.4.1 | Test date: □□□□-□□-□□ (year-month-date) |
| 6.4.2 | Result: _____ |

# 7: (CRF) CHECK LIST FOR DATA COLLECTION COMPLETENESS DURING HOSPITALIZATION

☐Eligibility Criteria

☐Demographic Information

☐History Collection

☐Dynamic Data Recording

- ☐Basic & Vital Sign
- ☐Evaluation of circulatory, respiratory, central nervous systems and renal
- ☐Evaluation of bacterial infection/sirs/sepsis
- ☐AD, OF & ACLF evaluation
- ☐Medication during hospitalization

☐Laboratory Tests (required)

- ☐Peripheral blood cells count
- ☐Liver function test
- ☐River function test
- ☐Electrolytes
- ☐Coagulation test
- ☐Others test (1)

☐Laboratory Tests (optional)

- ☐Immunoglobulin test
- ☐Others test (2)
- ☐Cytokine
- ☐Bacterial culture test
- ☐Ascites test

☐Imaging tests

- ☐B ultrasound
- ☐CT/MRI scan -- cirrhosis
- ☐CT/MRI scan -- portal thrombosis /varices / pulmonary
- ☐Fibro-scan

☐Biospecimen collection

- ☐Whole Blood
- ☐Serum
- ☐Urine

# 8: (CRF) SUMMARY FOR THE HOSPITALIZATION

8.1 Hospitalization ending date: □□□□-□□-□□ (year-month-date)

8.2 Period of hospitalization：____days

8.3 Hospitalization Expenses: _____yuan

8.4 Outcome of hospitalization

Discharged (continue)

Died (to question 8.6)

Liver transplanted (to question 8.7)

8.5 Discharge status

Improved (regular outpatient and Tel. Follow-up)

Stable (regular outpatient and Tel. Follow-up)

Deteriorated (Tel. follow-up within 3 days after discharge)

8.6 If the patient dies, main cause of death (multiple choices permitted)

Multiple organ failure (MOF)

Septic shock

Hypovolemic shock

Other cause: _____

8.7 If the patient has LT, whether the patient is in the list of LT?

□Yes □No

A. What was the pathological result of the patient's liver? _____

B. Whether the pathological result of the patient's liver is cirrhosis?

□Yes □No

C. Whether the pathological result include “sub-massive necrosis” or “necrosis”?

□Yes □No

D. Liver transplant surgery related Expenses: _____yuan

# 9: (CRF) TELEPHONE FOLLOW-UP

9.1 Date: ☐☐☐☐-☐☐-☐☐ (year-month-date)

9.2 The patient's status

☐Alive (to question 9.3)

☐Died (to question 9.4)

☐Liver transplanted (to question 9.5)

☐Loss to follow-up

9.3 Whether there are new onset complications?

☐ Yes ☐ No

if yes, please choose

☐Gastrointestinal bleeding,

☐Hepatic encephalopathy,

☐Ascites,

☐Bacterial infection

☐Jaundice

9.4 Date of death: ☐☐☐☐-☐☐-☐☐ (year-month-date)

9.5 Date of liver transplantation: ☐☐☐☐-☐☐-☐☐ (year-month-date)

# 10: (CRF) FINAL REPORT FOR THE FOLLOW-UP

10.1 The patient's outcome

☐Death

☐LT

☐malignancy

☐Lost follow-up

☐Alive

10.2 Date of the patient's outcome: ☐☐☐☐-☐☐-☐☐ (year-month-date)

10.3 If the patient dies, main cause of death: _____

10.4 If the patient had LT, name of LT hospital: _____

10.5 If the patient lost follow-up, reasons: _____

## SUPPLEMENTARY APPENDIX 3

**Table The monthly enrolment number in each centre**

| Centre | Month of enrolment | | | | | |
|---|---|---|---|---|---|---|
| | **SUM** | SEP | OCT | NOV | DEC | JAN |
| All centres | 1370 | 127 | 250 | 316 | 375 | 302 |
| Ditan Hospital (Beijing) | 199 | 18 | 36 | 28 | 53 | 64 |
| Southwest Hospital (Chongqing) | 178 | 15 | 25 | 47 | 49 | 42 |
| Xiangya Hospital (Hunan) | 167 | 54 | 27 | 32 | 31 | 23 |
| Renji Hospital (Shanghai) | 162 | 15 | 49 | 42 | 41 | 15 |
| Guangzhou Nanfang Hospital (Guangdong) | 125 | 19 | 34 | 29 | 22 | 21 |
| Taihe Hospital (Hubei, Shiyan) | 121 | 0 | 3 | 36 | 37 | 45 |
| Wuhan Union Hospital (Hubei, Wuhan) | 115 | 1 | 12 | 20 | 38 | 44 |
| First hospital of ZU (Zhejiang) | 79 | 4 | 11 | 17 | 37 | 10 |
| SPHCC (Shanghai) | 67 | 0 | 19 | 14 | 23 | 11 |
| Second Hospital of SDU (Shandong) | 46 | 1 | 11 | 15 | 15 | 4 |
| First Hospital of JU (Jilin) | 42 | 0 | 5 | 16 | 13 | 8 |
| Henan Provincial People's Hospital (Henan) | 35 | 0 | 0 | 4 | 16 | 15 |
| First hospital of XMU (Xinjiang) | 34 | 0 | 18 | 16 | 0 | 0 |