Protocol of the Predicting Acute-on-Chronic Liver Failure in Cirrhosis (PREDICT) Study on behalf of the EASL-CLIF Consortium

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REQUIREMENTS FOR PARTICIPATION (Eligible study centers and applicants):
A limited number of centers will participate in the study. In the recruitment of patients and application for ancillary study will be invited to apply:

- All participating centers of the CANONIC study
- Any EASL-CLIF-Member interested in participating that meets the criteria shown below.

Requirements for qualification of study centers (all points A-D have to be fulfilled):

A: Specialized Liver Program including:

- 1) a team of hepatologists or equivalent physicians (gastroenterologists, internist and or intensive care physicians) involved in the care of patients with liver disease (24h/day and 7 days/week)
- 2) access to ICU/ITU with experience in the management of critically ill patients with liver diseases).
- 3) an out-patient clinic allowing the structured follow-up of the patients after discharge.
- 4) Established access to a transplant-program (for centers that do not have transplantation programs on site, a formal letter of a collaboration with a transplant center is required)

B: Patients cohort and recruitment:

- At least 50 clinical contacts/visits with cirrhotic patients per month,
- Enrollment of more than 10 patients within the first three months of the study.
C: Proven expertise in the field:

- The principal investigator should have sufficient expertise in clinical studies with publications as first or last author in international journals of the field.
- The team of attending physicians must be familiar with liver disease management.

D: Research and lab facilities:

- Research nurse or research fellow in charge of the study,
- TRAINED personal with expertise in sampling biological material responsible for the sample handling, preparation, shipping, form filling, freezers and refrigerators,
- Availability of -80°C freezer and of lab near the blood extraction room, containing a centrifuge with a swinging bucket rotor (recommended refrigerated) and basic lab instruments

Applications should be submitted until 30. June 2016 and contain the following parts:

Ad A) Description of the hospital/centre and the liver program

Ad B) Description of the patients collective (visits) and commitment for sufficient recruitment

Ad C) Description of the expertise of the principal investigator and the research group including 5 pdfs of originals articles in the field of liver failure in which the PI of the applicant is PI of the studies

Ad D) Description of the research facilities

Centres that participated in the CANONIC Study, should submit only parts B) and C)
BACKGROUND

The CANONIC Study consisted in a 28-day detailed prospective observational investigation in patients admitted to hospital for the treatment of an acute decompensation of cirrhosis. The main aim of the CANONIC study was to characterize acute-on-chronic liver failure (ACLF) regarding diagnostic criteria, stages and natural history up to one year of follow up. Three quarters of the ACLF-patients (in total ca. 400) recruited in the CANONIC study presented with ACLF at enrolment. Therefore, the critical period prior to ACLF development and possible predictors could not be sufficiently analyzed in these patients due to the study aim and design. Moreover, the limited knowledge about the ACLF syndrome itself rendered the prospective and detailed analysis of predictors for the development of ACLF impossible.

The PREDICT Study is therefore designed to prospectively observe patients with Acute Decompensation (AD) at risk of developing ACLF within three months and to discover clinical, laboratory and patho-physiological (using prospective ancillary studies) predictors and mechanisms involved in the development and clinical course of ACLF, which might help to prevent and treat ACLF.

AIMS

The aim of this study is to assess prospectively the critical period prior to the development of ACLF (1), to uncover mechanistic and pathophysiological processes associated with the development and clinical course of ACLF (2) and to identify the precipitating events of ACLF (3).

Specific goals of the study:

- To identify early clinical predictors, biomarkers, mechanisms and precipitating events during the critical period prior to and involved in the development and clinical course of ACLF (with special emphasis to medical trajectory and drug history) in patients admitted/referred to study center with acute decompensation of cirrhosis (ascites, GI-hemorrhage, overt encephalopathy, new onset of non-obstructive jaundice and/or bacterial infections) and the chronological relationship of the events with occurrence and dynamics of ACLF development.

- To develop a score predicting ACLF development (CLIF-PREDICT score) and assess 28-day, 90-day, 6-month and 1-year all-cause mortality in cirrhotic patients with acute AD, but without ACLF.

- To serve as a core (hub) study for prospective ancillary studies regarding diagnosis, prognosis and pathogenesis of AD and ACLF.

STUDY TYPE, POPULATION AND DESIGN

1. This International-European, investigator-initiated, multicenter, prospective, observational study will be performed in centers that belong to the European Foundation for the Study of Chronic Liver failure (EF-CLIF foundation)-EASL-CLIF Consortium.
2. The population of patients would include ca. 1,200 cirrhotic patients over a twelve-months period. These patients will be admitted/referred to the study center because of acute decompensation of cirrhosis (ascites, overt encephalopathy, GI-hemorrhage, new onset of non-obstructive jaundice and/or bacterial infections), without ACLF (as defined according to the CANONIC study) at hospitalization.

3. After the enrolment visit, the patients will be stratified into two groups: Group 1 patients with high risk of ACLF development (CLIF-C AD score ≥ 60) and in Group 2 patients with low risk of ACLF (CLIF-C AD score <60). The whole cohort will be followed for 3 months, while Group 1 will be followed more closely. Development of ACLF is an end-point and in this case a final visit 7-10 days after ACLF development is planned. Data on liver transplantation, mortality and causes of mortality 3 months, 6 months and 12 months will be collected in the whole cohort.

4. Prospective collection of biological material and performance of ancillary studies investigating predictors for development and pathogenesis of ACLF.
STUDY OUTCOMES

1. MAIN STUDY END POINTS

• Assessment of the critical period prior to ACLF development
  - Characterization of mechanisms responsible for ACLF development
  - Predictors of clinical course dynamics of ACLF evolution and mortality.
  - Identification and role of precipitating events for ACLF development.

• To elaborate a CLIF-PREDICT score

2. SECONDARY END POINTS

• Prospective core ancillary studies to investigate the pathogenesis of ACLF.
  - Role of chronic systemic inflammation on the development and severity of ACLF
  - Role of microbiota on the development and severity of ACLF
  - Role of DILI on the development and severity of ACLF
  - Role of health trajectory and comorbidities on the development and severity of ACLF

• Prospective ancillary studies to investigate the pathogenesis of ACLF, 39 ancillary studies have been submitted which are currently under evaluation.
INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

1. The patients admitted/referred to study center with AD of cirrhosis (ascites, overt encephalopathy, new onset of non-obstructive jaundice, GI-hemorrhage and/or bacterial infections), but without ACLF (as defined according to the CANONIC study) at hospitalization.

Exclusion criteria:

1. Presence of ACLF at inclusion;
2. Pregnancy;
3. Age <18 years;
4. Patients with acute or subacute liver failure without underlying cirrhosis;
5. Patients with cirrhosis who develop decompensation in the postoperative period following partial hepatectomy;
6. Evidence of current malignancy except for non-melanocytic skin cancer and hepatocellular carcinoma within Milan criteria;
7. Presence or history of severe extra-hepatic diseases (e.g., chronic renal failure requiring hemodialysis, severe heart disease (NYHA > II); severe chronic pulmonary disease (GOLD > III), severe neurological and psychiatric disorders);
8. HIV-positive patients
9. Previous liver or other transplantation
10. Admission/referral of more than 72 hours before inclusion
11. Patients who decline to participate or who cannot provide prior written informed consent and when there is documented evidence that the patient has no legal surrogate decision maker and it appears unlikely that the patient will regain consciousness or sufficient ability to provide delayed informed consent;
12. Physician’s denial (e.g. the investigator considers that the patient will not follow the protocol scheduled).

All patients meeting the inclusion criteria will be entered in a screening log. If the patient is not enrolled, the screening log will include information explaining why enrolment did not occur.

PATIENTS’ RECRUITMENT AND SAMPLE SIZE CALCULATION

Those patients who satisfy the inclusion criteria and do not present any of the exclusion criteria will be enrolled for the study.

In the CANONIC study, among patients without ACLF (according to the definition by CANONIC study) and with a CLIF-C AD score ≥60 at study inclusion the 90-day mortality rate was about 25%. The corresponding rate among patients with a CLIF-C AD score <60 was
about 4%. On the other hand, about 50% of the observed deaths were due to ACLF, while the 90-day mortality in patients developing an ACLF was about 40%.

Based on these data, the PREDICT study will enroll around 1,200 cirrhotic patients, from which 600 consecutive patients with high-risk of ACLF-development (CLIF-C AD ≥ 60), who will undergo a close follow-up. Consequently, we expect about 350 patients developing ACLF within 90 days out of the 1,200 patients, while about 175 patients are expected to decease. In order to achieve this numbers a minimum of 10 centers must screen a minimum of 120 patients.

**DATA AND SAMPLES COLLECTION:**

**VISITS:**

At enrollment visit will collect clinical and laboratory data (D) and biological samples (S). At this visit a predefined questionnaire (Q) will interrogate potential precipitating and predisposing factors from the medical trajectory and patients history. If the interval between hospital admission and enrollment visit are longer than 24 hours, D from admission will be collected additionally. The maximal period between hospital admission and enrollment is 72 hours. 7-10 days after the enrollment visit, the second visit will take place and D/S will be collected from all patients (Group 1 and 2). The Week 12 visit (D/S) is the end of the study in both groups, if ACLF was not developed.

When the patients develop ACLF, then D/S will be collected separately at diagnosis of ACLF and 7 – 10 days thereafter. The Group 1 patients (CLIF-C AD ≥ 60) will receive two additional visits (Week 4 and 8) with data and sampling (D/S). In discharged patients a list of alarm signs will be provided, that would recommend contact to physician and/or direct hospitalization. At every new hospitalization from the patients in Group 1 D/S will be collected. If this re-admission is within 7 days prior to the scheduled visit at week 4 or 8, sampling at readmission omits the sampling and data-collection at week 4 and 8.

At 3 months (if no 12 Week visit), 6 months and 12 months data on liver transplantation, death and causes of death should be recorded.
QUESTIONNAIRE (Q), DATA (D) AND SAMPLES (S):

The major goal of the study is to explore the pre-ACLF period and to collect important data and biological samples in this critical period prior ACLF development. Therefore identification that the patient may be developing the syndrome in a particular moment is essential.

Data collection will be performed via electronic CRF similar to the CANONIC study, which will be finalized when the selection process of the ancillary studies will be finished. In general the data acquisition will include information on:

- **Health trajectory (Q):** Demographics, previous history of decompensation, precipitating factors, medication, comorbidities including the use of predefined questionnaire (Q)
- **Clinical and laboratory data (D):** Important laboratory values and clinical features in order to calculate major scores including nutritional scores and HRQoL.
- **Biological samples (S):** The following materials are required: peripheral serum, plasma, PBMC/PMN, urine, hair (in case of alcohol abuse), ascites (if any), stool, saliva.
STUDY OVERSIGHT AND PUBLICATION POLICY

Study oversight:

- The core group designs the study.
- The study will be supported by EF-CLIF, which will reward the recruiting center with a small amount for every patient included.
- In order to focus the investigations of the study, the results of the core study PREDICT will be analyzed by the core group and EF-CLIF Data Management Center.
- The respective PI of the specific ancillary study and EF-CLIF Data Management Center will analyze the ancillary studies.
- Each participating center will have full and independent access to the respective data in order to vouch for the integrity, accuracy and completeness of the analysis and its fidelity to the study protocol.
- The first draft of the protocol will be written by PIs, and the protocol and publications will adhere to the STROBE recommendations.

Publication policy:

- The first authors of the core PREDICT study will be the PIs, and senior experts from the EF-CLIF will co-review the manuscripts.
- Authors will include all 1 to 2 Investigators per center (depending on the proportion of valid patients). Authors will receive the manuscript for review and will sign the authorship form.
- In addition, the names of physicians who actively contributed to the study should be reported at the end of manuscript, with recognition of their authorship (i.e., sorting of the manuscript by PubMed by inputting their name).
- The publications deriving from the ancillary studies must include the participants who contributed with samples for the respective project, and the PI of the respective ancillary studies would serve and be listed as principal author for the manuscripts from the respective study.