Executive Summary of the PREDICT study

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

Core group:

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The study will serve as a hub for prospective mechanistic and pathophysiological ancillary studies in ACLF. Deadline for prospective ancillary study February 15, 2016. Especially younger physician-scientists and basic researchers (the last only if attached to clinical centers) are encouraged to apply for participation in the PREDICT study and propose ancillary studies using clinical data and biological samples from this study.
REQUIREMENTS FOR PARTICIPATION

Eligible study centers and applicants:

A maximum of 30 centers will participate in the study.

- In the recruitment of patients and application for ancillary study will be invited to apply:
  - All CANONIC-participants
  - Any EASL-CLIF-Member interested in participating that meets the criteria shown below.
  - Any EASL-Member, but EASL-CLIF-non-members with a) positively evaluated ancillary study (mandatory) AND b) positively evaluated qualification of the center or agreement on cooperation with a EASL-CLIF-member qualified for the study

Qualification of study centers:

- Proper and timely application,
- Fulfillment of minimal requirements:
  - Minimum visits 50 cirrhotic patients/month,
  - Research nurse or research fellow,
  - TRAINED person (with expertise in sampling biological material) responsible for the sample handling, shipping, form filling, freezers and refrigerators, sample treatment,
  - Availability of -80°C freezer,
  - Availability of lab near the blood extraction room, containing a centrifuge with a swinging bucket rotor (recommended refrigerated) and basic lab instruments
  - Scientific publications in first or second quartile IF journals in the last 5 years in the field of Hepatology or Immunology

Prospective ancillary studies:

- Any eligible applicant may apply for a prospective ancillary studies,
- Applications :
  - Applications should include the following parts: 1/ Title; 2/ Principal Investigator, research group and centre(s); 3/ Summary; 4/ Background, with proof of concept data, if available; 5/ Study design; 6/ Study population; 7/ Variables, 8/ Analytical methods; 9/ Statistical analysis and sample size calculation; 10/ Study limitations; 11/ Expertise of the PI/research group on the topic proposed; 12/ Relevance of the project and diffusion plan; 13/ Resources available to carry out the project; 14/ References.
  - Commitment for sufficient recruitment (min. 5% of patients)

A blinded and transparent review process will be performed for the scientific part, by experts in the respective fields, hepatology and other disciplines according to the application, the review results will be evaluated by the Core-Group and senior-members of
EASL-CLIF steering committee and will be made available to the all EASL-CLIF-SC-members and presented shortly in the general Assembly of EASL-CLIF during the ILC EASL 2016.
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 to hospital with acute decompensation of cirrhosis (e.g. ascites, GI-hemorrhage, encephalopathy 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-C ACLF Prediction 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 to hospital because of acute decompensation of cirrhosis (ascites, encephalopathy, GI-hemorrhage and/or bacterial infections), without ACLF (CLIF-C OF score < 11) 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 CLIF-C ACLF Prediction score

2. SECONDARY END POINTS
   - Prospective ancillary studies to investigate the pathogenesis of ACLF after proper application and evaluation (to be defined).

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

1. The patients admitted to hospital with AD of cirrhosis (ascites, encephalopathy, GI-hemorrhage and/or bacterial infections), but without ACLF (according to CLIF-C OF score < 11) 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. Diagnosis of hepatocellular carcinoma;
7. Previously known severe extra-hepatic diseases (e.g., chronic renal failure requiring hemodialysis, severe heart disease; severe chronic pulmonary disease, psychiatric disorders);
8. Patients who decline to participate or who cannot provide prior 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,

All patients meeting the inclusion criteria will be entered on 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 CLIF-C OF score < 11) 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 death 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 be admitted to the close follow-up. Consequently, we expect to observe ca. 350 patients developing ACLF within 90 days from the 1,200 patients, while 175 patients would die. 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.

At 3months (if no 12 Week visit), 6 months and 12 months data on liver transplantation, death and causes of death should be recorded.

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<th>Groups</th>
<th>Outcome</th>
<th>V1</th>
<th>V2</th>
<th>A1</th>
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<th>AD</th>
<th>V2</th>
<th>E1</th>
<th>E2</th>
<th>Follow up</th>
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<td>Group 1</td>
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<td>(CLIF-C AD ≥ 60)</td>
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<td>Group 2</td>
<td>ACLF</td>
<td>Q/D/S</td>
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V planned visits for the whole cohort
E unplanned visits in the whole cohort in case of ACLF
FU follow up data on mortality, transplant and cause of death
A additional planned visits in Group 1
AD unplanned visits in Group 1 in case of readmission
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.